JOURNAL OF PSYCHOPATHOLOGY 2023;29:110-116
DOI: 10.36148/2284-0249-N331

Review

Antipsychotic medication in individuals at Clinical High Risk for Psychosis: what recommendations for clinicians?

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SUMMARY

The "Early Intervention in Psychosis" (EIP) paradigm resulted in relevant promise for preventing the onset of severe mental disorders. International guidelines on early treatment of young people at Clinical High Risk for Psychosis (CHR-P) (not updated in the last 5 years) recommend individual psychotherapy as first-line treatment, while Antipsychotics (AP) should be used only when psychosocial interventions has shown to be ineffective. However, the use of APs in people at CHR-P still remains a complex, often divisive issue, where official guidelines and real-world prescription habits seldom correspond, especially in adolescence. Indeed, it has been reported baseline AP exposure rates ranging from 25% to 75% in different studies. Why these findings in ostensible tension (if not in open contradiction) with current treatment guidelines for CHR-P individuals? Moreover, recent evidence notably showed that people at CHR-P with AP exposure at the recruitment in EIP services, have higher rates of psychosis transition compared to CHR-P subjects without AP prescription in different follow-ups. Is it an iatrogenic effect of AP drug? Should AP prescription to CHR-P people be halted? In the current paper, we reviewed international guidelines on AP treatment in CHR-P individuals, with the purpose of updating mental health clinicians on an ongoing debated topic and encouraging prescribing habits aligned with expert advice and evidence.

Key words: antipsychotic, clinical high risk, ultra-high risk, early psychosis, early intervention in psychosis, treatment

Received: August 22, 2023
Accepted: December 11, 2023

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How to cite this article: Di Lisi A, Pelizza L. Antipsychotic medication in individuals at Clinical High Risk for Psychosis: what recommendations for clinicians? Journal of Psychopathology 2023;29:110-116. https://doi.org/10.36148/2284-0249-N331

Introduction

Prevention is crucial in medicine and remains a global healthcare priority [1]. In mental health, McGorry and his team [2] pioneered prevention interventions in early psychosis. Specifically, their clinical staging model carefully defined "Clinical High Risk for Psychosis" (***CHR-P***) mental states, with the purpose of better understanding psychosis's developmental trajectories and early detecting young individuals potentially at risk for developing a full-blown psychotic disorder over the next 12 months [3]. Indeed, patients with First-Episode Psychosis (FEP) often had earlier, attenuated psychiatric symptoms up to 5-10 years before the onset of their overt psychosis [4]. Therefore, early intervention on CHR-P individuals has been mainly designed to avoid psychosis transition and reduce the duration of untreated psychosis (DUP), so as to improve outcomes and prognosis in this young population [5,6].

There are two current approaches to identify CHR-P individuals: (1) the "Ultra-High Risk" (UHR) paradigm and (2) the "Basic Symptoms" (BS) theory.

In accordance with the McGorry's model [7], three ***UHR*** subgroups are defined: (1) Attenuated Psychotic Symptoms (APS), (2) Brief, Limited, Intermittent Psychotic Symptoms (BLIPS), and (3) Genetic Risk and Functioning Deterioration (GRFD) syndrome. These UHR status may be reliably assessed using specific clinical interviews, such as the "Comprehensive Assessment of At-Risk Mental States" (CAARMS) [8,9].

APS are the most common UHR mental state, with an approximately 80% prevalence rate [10]. Individuals with APS show mild, attenuated positive/disorganized symptoms that must be of sufficient severity/frequency to warrant clinical attention, must have been present at least once per week for the past month, and must have begun/worsened in the last year. APS also are not better explained by other mental disorders (e.g., affective disorders with psychotic features) and are not attributable to physiological effects of a substance or another medical condition. Finally, criteria for any psychotic disorder have never been met [11]. *BLIPS* subjects have criteria for overt psychosis met for less than a week and ceased spontaneously (i.e., without antipsychotic medication) [12]. The *GRFD* syndrome is a state-trait condition combining a family history of psychosis in first-degree relatives or schizotypal personality disorder in the patient with 30% drop in functioning or chronic low functioning in the past year.

Another historical approach for identifying CHR-P individuals (especially those at risk for schizophrenia) is the *BS theory* [13]. It is based on the identification of BS, i.e. subtle, self-experienced disturbances in cognitive, perceptual and affective mental processes that anticipate and may transit to full-blown psychotic symptoms, especially the positive ones [14]. In particular, specific cognitive and perceptual BS (known as *COPER* and *COGDIS*) showed to effectively detect CHR-P individuals and to predict psychosis conversion in the next 12 month [15] (although they are not necessarily confined to the prodromal phase, but also occur during and after an acute psychotic episode) [16]. Reliable assessment of BS includes the "Schizophrenia Proneness Instrument, Adult (SPI-A) or Child & Youth" (SPI-CY) version [17].

Antipsychotic prescription in people at CHR-P

The use of *antipsychotic* (AP) in young people at CHR-P is a delicate, complex, and often divisive issue [18], where real-world prescription habits and official guidelines' recommendations seldom correspond, especially in adolescence [19]. Indeed, AP prescription in CHR-P subjects is common in clinical practice (with reported baseline prevalence rates ranging from 23% to 77% in different studies) [20], despite this overall is in ostensible tension (if not in open contradiction) with current official guidelines on treatment for CHR-P individuals, indicating a more cautious approach [21]. In this respect, real-world results meta-analytically examined by Catalan and colleagues [22] showed an "inconvenient truth": i.e., approximately a third of CHR-P adolescents are exposed to AP medication already at entry into specialized "Early Intervention in Psychosis" (EIP) services [23].

It was reported that the most likely factors influencing clinicians' decision-making regarding AP prescription in people at CHR-P are related to global functioning decline and clinical severity of positive/disorganized symptoms, with the primary aims of reducing patient's distress, improving daily functioning and delaying psychosis transition [24,25]. However, to date, evidence on beneficial effects of AP treatment in preventing psychosis and improving long-term outcomes in CHR-P individuals remains inconsistent. Additionally, official guidelines on early psychosis intervention partially differ, with some experts recommending against a primary use of AP drug, while others being more optimistic, particularly in adults with severe psychopathology and high functioning decline [26].

Therefore, the main aim of this paper was to compare international guidelines' recommendations on AP prescription in CHR-P individuals, because of updating mental health professionals on an ongoing debated topic and encouraging prescribing habits aligned with expert advice and current evidence. In our opinion, given recent empirical advances, there's a need to bridge the gap between the cautious prescription approach recommended by official guidelines (not updated for at least 5 years) and "real-world" clinical practices. Indeed, in the current CHR-P paradigm, baseline AP exposure is too often neglected, despite its relevant impact on initial psychopathology, clinical trajectories and psychosis transition assessment [27].

Official guidelines' recommendations on AP prescription in CHR-P people

The "National Institute for health and Care Excellence" (*NICE*) guidelines on recognition and management of psychosis and schizophrenia in children and young people [28] indicate psychological intervention (i.e., Cognitive-Behavioral Therapy [CBT]) as first-line treatment. They specifically recommend not to offer AP drug in any case.

The "European Psychiatric Association" (*EPA*) guidance on early intervention in clinical high risk states of psychoses [29,30] first suggests that in CHR-P adults it should be applied the least restrictive service approach, using CBT as first-line therapy. Where psychotherapy has shown to be ineffective, it should be complemented by a low-dose second-generation AP medication, especially if progressive and severe symptoms occur, with the main aim to reach clinical stabilization. Any long-term AP treatment with preventive goal is not recommended. The EPA guidance also indicates that any intervention in CHR individuals should also address current individual unmet needs and other co-morbid mental condition (especially anxiety and depression). Furthermore, the

EPA emphatically states that evidence on the psychosis predictive value of CHR criteria and effectiveness of psychosocial and pharmacological treatments in CHR-P children and adolescents is still not sufficient to justify primarily preventive interventions. In children and adolescents, specific psychological therapies aimed at improving functioning should be provided as part of an overall intervention plan and complemented by treatments for other psychosocial problems and co-morbid mental disorders. Indeed, an early intervention in people at CHR-P should not only aim at preventing a FEP, but also the development/persistence of functioning deficits (i.e., social, educational or vocational).

The Australian Clinical Guidelines (***ACG***) for early psychosis [31] (Orygen, 2016) recommend CBT as first-choice intervention for young people at CHR-P. CBT is primarily advised to alleviate CHR-P psychopathology (so potentially delaying/preventing psychosis transition). Individual CBT and supportive counseling may also improve pre-onset social functioning. According to the ACG, AP drug is avoided unless a week of full-blown positive symptoms occurs. Exception involves brief or mild positive symptoms associated with self-harm or aggression risk, substance-related psychotic symptoms, or subthreshold psychotic features persisting despite CBT and/or other psychosocial interventions and causing distress or functioning inability. The ACG also indicate that omega-3 fatty acids in CHR-P subjects may aid in delaying/preventing psychosis transition.

The Canadian Treatment Guidelines (***CTG***) for individuals at CHR-P [32] recommend offering individual CBT (with/without family intervention) as first-line therapy in the least restrictive service approach. If psychotherapy has shown to be ineffective and severe, progressive attenuated psychotic symptoms persist, a low-dose second-generation AP drug can be added only for CHR-P adults. However, long-term preventive AP therapy is discouraged. After treatment, if symptoms or impaired functioning persist without full-blown psychosis diagnosis, the CTG indicate a 3-year monitoring using structured, validated assessment tools.

As for ***Italy***, the first official guidelines (authored by the "Istituto Superiore di Sanità" (ISS) in 2007) [33] were specifically focused on early schizophrenia and recommended using targeted psychological treatments (specifically CBT) in CHR-P individuals. The primary clinical goal was to decrease symptoms, improve social skills, identify dysfunctional thoughts, and reduce anxiety and depression. However, these treatments were not recommended for preventing the onset of schizophrenia or for improving its clinical progression, due to insufficient supporting evidence. AP treatment was recommended for CHR-P individuals since the existing evidence did not sufficiently support the use of preventive drug treatment.

More recently, the Emilia-Romagna region (ER) developed specific regional recommendations on early detection/intervention in young people at CHR-P (last updated in August 2023) [34]. In particular, it recommends against prescribing AP medication for subthreshold symptoms and/or to reduce psychosis transition risk. However, a careful clinical assessment for a possible

TABLE I. *International guidelines' recommendations on AP prescription in CHR-P.*

	Year	First Line Treatment	AP-Medication
NICE	2016	CBT	Do not offer AP medication
EPA	2015	CBT	Use low-dose second-generation AP if psychological treatment has proved ineffective or CHR-P symptoms get worse
ACG	2016	CBT	AP only if there's evidence of at least 1 week of frank positive psychotic symptoms, or if positive symptoms are milder or briefer, but are directly associated with risk of self-harm or aggression
CTG	2017	Individual CBT with or without family intervention; Treat comorbid disorders	Use low-dose second- generation AP for short-term period only if previous psychological interventions have proven ineffective
ISS	2007	CBT	Do not offer AP medication
ER Recommendation	2023	CBT	AP only if functional impairment, a high risk of self-healing, and ineffectiveness of first-line psychosocial interventions

Legend - NICE: National Institute for Health and Care Excellence; EPA: European Psychiatry Association; ACG: Australian Clinical Guidielinea; CTG: Canadian Treatment Guidelines; ISS: Istituto Superiore di Sanità. ER: Emilia-Romagna region.

AP prescription in CHR-P subjects should take into consideration the presence of accelerated functioning impairment, a high risk of self-harm behaviors, and ineffectiveness of first-line psychosocial interventions. In any case, APs should be prescribed for a short time and primarily aimed at alleviating psychological distress.
In ***summary***, as shown in the Table I official guidelines align in prioritizing CBT as first-line approach for managing at-risk mental states. In this respect, CBT seems to be helpful in addressing different therapeutic needs (such as decreasing psychological distress; enhancing symptom understanding, coping strategies, positive thought patterns, self-monitoring and engagement with treatment) [35]. Additionally, integrating social support interventions and family psychoeducation can further enhance long-term outcomes in CHR-P people [36].

However, the usefulness of AP medication in preventing psychosis transition in CHR-P individuals is still doubtful. Indeed, while some official guidelines advocate short-term AP use to mitigate CHR-P symptoms (so potentially reducing the risk of transition to overt psychotic features), particularly if psychosocial treatment are ineffective, other international guidelines recommend against AP use in CHR-P populations, mainly due to their potential side effects (such as weight gain and sexual dysfunction) and self-stigmatization [37]. So while CBT is widely endorsed, the role of AP drug remains debated, at least requiring a careful consideration of potential risks and benefits for CHR-P individuals [38]. In this respect, a recent umbrella review on 20 randomized controlled trials comparing various treatments in CHR-P samples (i.e., needs-based interventions, omega-3, different AP medications, integrated psychosocial interventions, family therapy) [39] showed no evidence on higher effectiveness of any current preventive treatment in avoiding/delaying psychosis conversion risk. Moreover, specifics about the duration of AP prescription are still undefined, although its long-term use is not generally recommended [40].

Open questions and future direction

As for prevention goal, some general ***questions*** remain unanswered. First, if there is no evidence that APs are really effective in preventing psychosis onset in high-risk subjects, why continue to prescribe them for that purpose in clinical practice? Moreover, recent studies paradoxically reported that CHR-P individuals with baseline AP exposure showed higher incidence rates of psychosis transition compared to those CHR-P individuals without AP prescription across different follow-ups [41].
Based on these unexpected results, other relevant questions arise. How should we consider AP treatment not effective and harmful in attenuated clinical pictures and at the same time beneficial (especially for positive symptoms) in more severe ones (i.e., FEP or chronic psychosis)? Why AP therapy should work with difficulty in CHR-P people experiencing similar but attenuated psychotic features, so as not to prevent psychosis conversion? Raballo and co-workers [42] solved this paradox inverting the order of causality. They suggested that subjects with baseline AP exposure had higher psychosis transition rate because mental health clinicians, in real word settings, frequently recommend AP medication to those patients who experience more severe CHR symptoms. In this sense, the AP prescription would be a need-based option motivated by the perception of increasing severity by the treating staff, and reflect a global apprehension of a mental state requiring not deferable AP therapy [43]. This increasing severity could thus plausibly enhance the risk of symptomatically transition to overt psychosis despite the pharmacological prescription [44]. If this is the case, the AP prescription pattern rather than an iatrogenic harm factor (favoring conversion to psychosis in CHR-P people) could be better considered as a severity indicator ("warning flag") of the ongoing psychopathological process (i.e., the more severe the process, the less likely to obtain symptom stabilization) [45]. This interpretation also avoids the clinical optic illusion that AP-exposed CHR-P individuals presenting attenuated psychotic symptoms have the same prognostic risk of (symptom-based) conversion to psychosis than AP-naïve ones [46]. Indeed, the ongoing AP treatment could mitigate the initial presentation of their clinical picture and modulate the later outcome trajectories thereby blurring predictive modeling and prognostic estimates [47]. In other words, CHR-P subjects with baseline AP exposure might surreptitiously be equated to all other AP-naive CHR-P, while they are actually experienced an AP-attenuated first episode psychosis [48]. Indeed, they may not reach the formal psychometric threshold for psychosis at follow-up (because of the ongoing treatment), yet their ascription to the "non-converter" CHR-P subgroup together with AP-naive individuals is highly questionable [49]. In summary, AP treatment can also be considered as a systematically overlooked confounder that clearly influences our current prognostic estimates of longitudinal outcomes and reduces the precision of contemporary prediction models in early psychosis [50].
Finally, if clinicians want to prescribe AP medication, as there is no evidence in patients with psychosis for higher beneficial effects of one AP drug compared to another, what AP treatment should be preferred and when is it best to use APs?
In ***conclusion***, prescribing AP medication in CHR-P people is never an easy choice, although in "real-world" clinical practice it is quite common. In our opinion, a

definitive judgment on the clinical benefits of AP prescription in CHR-P individuals cannot be primarily based on the psychosis risk prevention. Indeed, current CHR-P criteria are substantially psychometric in nature and predominantly assess positive symptoms without considering other relevant clinical, social and personal characteristics and outcomes. The literature in this field generally over-focused symptom-based criteria for transition to psychosis, neglecting the original CHR-P criteria on "functional equivalents" of such transition (i.e., the threshold at which antipsychotic treatment would be probably be commenced in common clinical practice) [51,52]. Within this psychometric supremacy of positive symptoms, we believe that the CHR-P population as currently defined is too clinically heterogeneous. Mental health clinicians and researchers should make an effort to identify specific CHR-P subgroups with different functioning and outcomes because these subgroups might respond differently to AP treatment. In particular, for better understand CHR-P individuals and their prognosis, it is necessary to take into consideration other important clinical variables beyond positive symptoms, such as role and socio-occupational functioning, quality of life, presence of psychiatric comorbidity (including substance use disorder and past traumatic events), persistent negative symptoms, longitudinal diagnostic trajectories, subjective sense of well-being, personal and social recovery, sense of belonging to the local community, and individual experience of patient's own lived world. In line with this, Zhang and co-workers [53] observed various prognostic trajectories for different CHR-P subtypes, indicating potential prediction of treatment response. By using a personal risk assessment, the authors recommended restricting AP prescription to CHR subjects with predominant positive symptoms and functional decline [54]. This insight advocates a stringent AP prescription strategy to curtail inappropriate use [55]. However, future studies investigating which different CHR-P subgroups might have benefits from AP prescription are needed.

Conflict of interest statement

The authors declare to have no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

ADL and LP: conceptualization and paper design, literature search, writing the first draft of the manuscript; writing the final draft of the manuscript; review and editing.

Ethical consideration

Ethical approval and inform consent were not sought for the present paper because it is not a research study involving humans.

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