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Editorial Perspective: Psychosis risk in adolescence – outcomes, comorbidity, and antipsychotics

Introduction

Although childhood and adolescence are clearly central years for the timely identification of emergent mental disorders, their strategic importance for psychosis prevention has been acknowledged only recently by mainstream research in the area of Clinical High-Risk for Psychosis (CHR-P). This is partly due to the unfortunate consequences of the two-tier system imported from somatic medicine which perpetrates the gap between child–adolescent and adult mental health services as well as a certain conceptual amblyopia in a parallel segmentation of research (see Raballo, Poletti, & McGorry, 2017).

In this respect, the Annual Research Review on psychosis risk in adolescents (Catalan et al., 2020) provides a much needed systematic and meta-analytic map of the field and aligns with recent meta-analytic evidence of the extensibility of CHR-P criteria to child and adolescent help-seekers (Raballo, Poletti, Preti, & McGorry, 2020). These meta-analyses cover complementary developmental phases (i.e. childhood–adolescence (Raballo, Poletti, Preti, & McGorry, 2020) and adolescence–youth (Catalan et al., 2020)) and jointly corroborate the applicability of CHR-P criteria from childhood and adolescence to young adulthood. Furthermore, they pave the way toward a more developmentally oriented reformulation of current staging models for early detection of vulnerability to psychosis. However, the central issue of age-appropriate assessment remains critical. Indeed, with the exception of the schizophrenia proneness instrument–child and youth version (SPI–CY) for the assessment of basic symptoms in children and adolescents (age 8–17) (Schultze-Lutter & Koch, 2010), the other existing tools currently adopted to explore at-risk criteria in children and adolescents (e.g. SIPS or CAARMS) were mainly developed for young adults and not specifically adapted for children and adolescents. As most studies on young adults included also some adolescents (≥ age 15), it is probably safe to use SIPS or CAARMS in this age group; nonetheless, some aspects require further refinement. In particular, it is unclear (a) at what age children are able to provide reliable account of at-risk symptoms, (b) when and how parental reports should be considered, and (c) how a differential diagnosis to relevant child and adolescent psychiatric disorders should be made (e.g. autism spectrum disorders).

Given this overall background, in this editorial perspective, we further expand the discussion of the most important meta-analytical findings in relation to central aspects of the CHR-P construct and its application in childhood and adolescence. We will specifically address the following key issues:

1. age effects on transition rates from CHR-P stages to psychosis;
2. pathogenetic trajectories to CHR-P stages as suggested by comorbidity patterns; and
3. implications of pharmacological treatments with antipsychotics.

CHR-P in developmental years: transition prevalences, age-effect, and model scalability for 'transition psychiatry'

It is interesting to observe that the meta-analytical transition rates from CHR-P states to psychosis (20% at 12 months, 23% at 24 months, and 23.3% at 36 months) reported in the study of Catalan et al. (2020) are slightly higher than the overall more conservative transition rate (from 16.0% in the fixed-effect model to the 17.5% in the random-effects model) found in Raballo, Poletti, & Preti (2020). This difference may be related to the less stringent age-related inclusion criteria (i.e. enrolled subjects between 12 and 25 years vs. <18 years, respectively), given that age has been reported to exert a modest yet significant effect in increasing transition risks (Fusar-Poli et al., 2012). While these findings are helpful when considering group level prognosis (which is obviously a far cry for an individual level one), they nonetheless indicate that CHR-P is a relevant prognostic construct to assess help-seeking and mental health needs experienced across developmental periods from late childhood to early adulthood. This is a well-known point of weakness of our mental health institutional organization (i.e. the historical gap inherited from the model of somatic medicine (see Raballo et al., 2017). This gap can only be partially mitigated by optimizing the transition from adolescent-centered to adult-oriented psychiatric care, since it suggests a deeper, developmentally oriented revision of our concepts of biopsychosocial pathogenesis and care.

Indeed, since it is well known that childhood and adolescence are high-risk periods for developing mental health problems which gradually accumulate to emerge more markedly in later years (in parallel with major biopsychosocial disruptions), it is obvious that the true epicenter of the preventive approach in mental health should be child–adolescent-centric. In this respect, CHR-P applicability in childhood and adolescence has also the additional value of representing a kind of proof of concept for the suitability of a staging model

approach that could be useful when considering a broad spectrum of emergent mental illness.

Trajectories and mental health comorbidity: deconstructing intra-CHR-P heterogeneity

Meta-analytical evidence confirms that CHR-P adolescents present substantial comorbidity with other mental disorders, such as mood disorder (46%), anxiety disorders (31%), attention deficit/hyperactivity disorder (ADHD) (22%), bipolar disorder (19%), and pervasive developmental disorder (PDD) (14%). This indicates first that a nontrivial fraction of help-seeking CHR-P youth, independently of whether they develop or not an overt psychotic episode, fulfills DSM-IV/V's general criteria for a mental disorder (i.e. a clinically significant syndrome associated with disability and/or severe distress). Therefore, they present a substantial need for care (with the annexed issue of timely differential diagnosis), given the concomitant developmental challenges of their age. Second, it is worth noting that the spectrum of comorbidities appears broadly polarized around two meta-clusters, that is, affective disturbances, including mood (unipolar and bipolar) and anxiety disorders, and neurodevelopmental conditions with childhood diagnosis, limited to ADHD and PDD. This pattern suggests that comorbid mental disorders associated with CHR-P states may have different psychopathological and developmental origins, which might explain some of the heterogeneity within CHR-P or at least provide further risk stratification. For example, the comorbidity with affective disorders might intercept three clinically relevant sub-populations. Those could be (a) a fraction of subjects at later risk of affective psychosis (associated with unipolar or bipolar mood disorders); (b) a fraction of subjects at risk of nonaffective psychosis, but with predominant affective features of depression and demoralization potentially obscuring background negative symptoms (such as anhedonia, anergia, and avolition). This latter subgroup could be more associated with progressive disability, enduring negative symptoms and functional decline, thereby being less visible in terms of positive symptoms (i.e. the classical 'transition to psychosis' outcome); (c) a group of help-seekers with primarily affective/anxiety spectrum disorders and contingent, strictly state-like stress-induced subclinical positive symptoms but unlikely progression to psychosis.

In contrast, the comorbidity with childhood-onset disorders such as ADHD and PDD might point to a CHR-P subgroup with more pronounced neurodevelopmental vulnerability. Childhood ADHD, for example, is a well-known risk factor for subsequent psychotic experiences and schizophrenia, with the use of stimulant medications as a potential amplifier of such risk (Björkenstam, Pierce, Björkenstam, Dalman, & Kosidou, 2020). Similarly, childhood PDD is an acknowledged risk factor for subsequent nonaffective psychotic disorder in adolescence and young adulthood (Selten, Lundberg, Rai, & Magnusson, 2015).

Overall, findings on comorbidity suggest that in a fraction of adolescents, CHR-P states are part of a complex clinical pictures also characterized by concurrent affective disturbance, while in another fraction of adolescents, CHR-P states are preceded by premorbid stages characterized by neurodevelopmental conditions as ADHD and PDD. The latter implies that, on the basis of cumulative ADHD + PDD prevalences, at least one third of CHR-P adolescents experienced previous childhood diagnoses before CHR-P assessment and, presumably, may already have been referred to child and adolescent mental health services. This aspect should be carefully considered when developing improved service design and efforts to increase treatment accessibility. Indeed, it has been repeatedly emphasized that specialized CHR-P services only detect and follow a small proportion of individuals who will develop psychosis; therefore, an obvious move to improve the early detection of psychotic risk would be to focus on childhood early premorbid stages. This is an achievable goal which could be attained through a strategic integration of child and adolescent mental health services (CAMHS) with adult ones (AMH) to optimize the continuity of care in the transition across the two (Raballo et al., 2017).

Antipsychotics treatment

Catalan et al. (2020) reported that 30.4% of adolescents at CHR-P were prescribed antipsychotics at baseline. Interestingly, this is higher than the 20.6%–23.6% meta-analytically reported in adults with CHR-P (Raballo, Poletti, & Preti, 2020) and in ostensible tension (if not explicit contradiction) with treatment guidelines for CHR-P, especially for children and adolescents: see, for example, the Recommendation 4 of European Psychiatric Association guidelines (Schmidt et al., 2015: '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').

Therefore, treatment guidelines indicate a cautious, staged approach to CHR-P treatment,

especially in children and adolescents, and exclude AP as a first-choice treatment for prevention purposes. Indeed, low-dose antipsychotic prescription is conditional on the failure of psychological interventions and concomitant progressive clinical deterioration. In contrast, real-world data meta-analytically collected by Catalan et al. (2020) reveal an inconvenient (and dramatically unspoken) truth: children and adolescent at CHR-P may be substantially exposed to antipsychotics.

Over and above intuitive concerns on treatment appropriateness (Schmidt et al., 2015), it is worth noting that ongoing AP treatment in CHR-P could possibly mitigate the initial clinical presentation and modulate the later outcome trajectory thereby blurring prognostic estimates and predictive modeling. Indeed, CHR-P adolescents being already treated with antipsychotics at baseline might surreptitiously be equated to all other antipsychotics-naive CHR-P, while they are actually an antipsychotic-attenuated first-episode psychosis (Raballo, Poletti, & Preti, 2020). Conversely, CHR-P undergoing incident AP treatment may not reach the formal psychometric threshold for psychosis at follow-up (because of the ongoing treatment), yet their ascription to the 'non-converters' group together with medication-naive CHR-P individuals is questionable for the same reason why the same body temperature (e.g. 98.6 F or 37 C) has a different clinical meaning depending on whether or not they are undergoing anti-pyretic treatment (e.g. paracetamol). The magnitude of this systematically overlooked confounder in mainstream CHR-P literature (Raballo, Poletti, & Preti, 2020) reverberates in current prognostic estimates of longitudinal trajectories and reduces the precision of contemporary prediction models. Indeed, in the original UHR model (i.e. the conceptual and operational precursor of CHR-P), the prescription of antipsychotics was considered a functional equivalent of transition to psychosis. This is because, in common clinical practice, such therapeutic decision in individuals at putative risk for psychosis indicates that the treating staff has identified a mental state in urgent need of AP treatment (Yung et al., 2003). Precisely for the same reason, the start of the first antipsychotic treatment is typically considered the end point of the duration of untreated psychosis (DUP).

From this perspective, to make a necessary step forward toward precision psychiatry in the field of early detection in child and adolescent psychiatry, we suggest that (a) those individuals already under ongoing antipsychotic medication at the moment of CHR-P evaluation should be considered as a separate risk group from AP-naïve ones; (b) antipsychotic medication after CHR-P diagnosis should be regarded as a functional equivalent of transition to psychosis (i.e. a mental state requiring urgent AP treatment) even when positive symptoms remain below the psychometric severity threshold. Finally, a more detailed reporting about antipsychotic treatment at baseline and follow-up is recommendable to increase transparency in the field.

Conclusions

The CHR-P construct and its overarching clinical staging framework are embracing the childhood and adolescent years as well as early adulthood; however, the majority of empirical research (and service implementation) has been relatively circumscribed to adult populations. In recent years, child and adolescent psychiatry has gradually accumulated sufficient evidence for implementing appropriate early detection strategies in this age group and to gain the primary recognition it deserves within the broader field of early detection in psychiatry. Indeed, psychosis generally does not arise out of the blue but involves progressive changes in personality, interpersonal functioning, and quality of life deeply intertwined with developmental milestones. Therefore, age-appropriate early detection strategies are essential to minimize unmet need, correct idiosyncratic referral pathways, and mitigate delayed, inappropriate treatment and duration of untreated psychosis with associated biopsychosocial consequences. CHR-P adolescents (as well as their parents) suffer from a comprehensive and pervasive reduction of their psychosocial well-being which requires appropriate individual and family support independently of the risk of developing overt positive symptoms (i.e. the current standard definition for first-episode psychosis).

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