Antipsychotic prescription, assumption and conversion to psychosis: resolving missing clinical links to optimize prevention through precision

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The current concept of clinical high-risk (CHR) of psychosis relies heavily on “below-threshold” (i.e. attenuated or limited and intermittent) psychotic positive phenomena as predictors of the risk for future progression to “above-threshold” positive symptoms (aka “transition” or “conversion”). Positive symptoms, even at attenuated levels are often treated with antipsychotics (AP) to achieve clinical stabilization and mitigate the psychopathological severity. The goal of this study is to contextually examine clinicians’ decision to prescribe AP, CHR individuals’ decision to take AP and psychosis conversion risk in relation to prodromal symptoms profiles. CHR individuals (n = 600) were recruited and followed up for 2 years between 2016 and 2021. CHR individuals were referred to the participating the naturalistic follow-up study, which research procedure was independent of the routine clinical treatment. Clinical factors from the Structured Interview for Prodromal Syndromes (SIPS) and global assessment of function (GAF) were profiled via exploratory factor analysis (EFA), then the extracted factor structure was used to investigate the relationship of prodromal psychopathology with clinicians’ decisions to AP-prescription, CHR individuals’ decisions to AP-taking and conversion to psychosis. A total of 427(71.2%) CHR individuals were prescribed AP at baseline, 532(88.7%) completed the 2-year follow-up, 377(377/532, 70.9%) were taken AP at least for 2 weeks during the follow-up. EFA identified six factors (Factor-1-Negative symptoms, Factor-2-Global functions, Factor-3-Disorganized communication & behavior, Factor-4-General symptoms, Factor-5-Odd thoughts, and Factor-6-Distorted cognition & perception). Positive symptoms (Factor-5 and 6) and global functions (Factor-2) factors were significant predictors for clinicians’ decisions to AP-prescription and CHR individuals’ decisions to assume AP, whereas negative symptoms (Factor-1) and global functions (Factor-2) factors predicted conversion. While decisions to AP-prescription, decisions to AP-taking were associated to the same factors (positive symptoms and global functions), only one of those was predictive of conversion, i.e. global functions. The other predictor of conversion, i.e. negative symptoms, did not seem to be contemplated both on the clinician and patients’ sides. Overall, the findings indicated that a realignment in the understanding of AP usage is warranted.

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INTRODUCTION

Operational criteria Clinical high risk (CHR) for psychosis and the related major outcome, i.e. “conversion” or “transition” to psychosis, are the central compass of contemporary early detection strategies and have progressively spread around the world. Despite CHR concept provides a golden window for early prevention and intervention for psychosis, achieving timely, optimal and effective intervention for CHR individuals is still a problematic target. For example, although only less than 30% of CHR convert to psychosis within the following 2 years1,2 (and even less among children and adolescents3,4), and AP exposure already at inception is relatively common in this clinical population5,6,7.

Conceptual analysis and empirical questions

Rather than an erratic phenomenon, AP prescription in this population is presumably guided by pondered clinical decisions, yet it is not clear what are the main reasons for such a choice given that CHR are by definition below the clinical threshold for psychosis and related indicated pharmacological treatment8. One of the most plausible reasons is that clinicians and treating staff ascribe to these individuals a higher likelihood to convert to psychosis in the near future. A recent meta-analysis, indeed, revealed that AP prescription since baseline in CHR samples is associated with a higher imminent risk of conversion to psychosis, and therefore should be regarded as a non-negligible red flag for clinical risk management9. Thus the next logical question is whether these CHR individuals with ongoing AP prescription at enrollment exhibit specific features that make clinicians feel that they are at greater risk. On the other side, i.e. from the perspective of CHR individuals, what are the main reasons to begin AP assumption? Even more importantly, if clinicians or CHR individuals both opt for AP treatment as a necessary therapeutic step

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psycosites? If these problematic issues are not clarified, they are likely to lead to the repeated occurrence of some empirical errors, and ultimately affect the effect of early intervention.

**Aim of the study**

The current study examined whether the factors that are associated to clinicians to prescribe AP to CHR individuals, the factors that are associated to CHR individuals to decide to take AP, and the factors that predict the onset of psychosis are similar. According to our previous findings, which suggest that AP may not be effective in preventing psychosis among CHR youth, we speculate that there may be a misplacement of targets in clinicians’ decisions on prescribing AP, CHR individuals’ decisions on taking AP and determining the progression of psychosis.

**RESULTS**

**Sample characteristics**

Baseline sample characteristics are summarized in Table 1. There were significant differences between those who did and did not convert on gender, GAF scores, positive, negative and disorganization symptoms.

**Factor extraction**

The exploratory factor analysis of 19 SIPS items and two GAF variables of full sample (N = 600) resulted in six factors is presented in Table 2. Six factors had eigenvalues > 1. The first factor, with an eigenvalue of 5.327 and high loading coefficients (>0.4) for N1-5 was labeled ‘Factor-1: Negative symptoms’. The second factor, with an eigenvalue of 2.249 and high loading coefficients for N6, Current and Drop GAF scores was labeled ‘Factor-2: Global functions’. The third factor, with an eigenvalue of 1.727 and high loading factors for P5, N5, D1, D4, and G3, was labeled ‘Factor-3: Disorganized communication and behavior’. The fourth factor, with an eigenvalue of 1.268 and high loading factors for G1, G2, and G4, was labeled ‘Factor-4: General symptoms’. The fifth factor, with an eigenvalue of 1.158 and high loading factors for P1 and D2, was labeled ‘Factor-5: Odd thoughts’. The sixth factor, with an eigenvalue of 1.092 and high loading factors for P2 and P4, was labeled ‘Factor-6: Distorted cognition and perception’. Two items (P3-Grandiosity and D3-Trouble with Focus and Attention) did not load on to any factor with a loading higher than 0.4.

**Effect size comparison on 6 factors**

The effect sizes across the 6 factorial scores from comparisons of Prescribed-CHR and Not-Prescribed-CHR, With-AP-CHR and Without-AP-CHR, Converted-CHR and Not-Converted-CHR are presented in Fig. 1. The effect sizes on the factor-5 and 6 (related to positive psychotic symptoms) were greater and significant for comparison of prescribed-CHR and Not-Prescribed-CHR, With-AP-CHR and Without-AP-CHR. However, the effect sizes on the factor-1 (related to negative symptoms) were greater and significant for comparison of Converted-CHR and Not-Converted-CHR. Factor 2 (related to global functions) was significant in all comparisons.
Second, CHR individuals with severe baseline positive symptoms such as thought and communication and behavior (D1 odd behavior or appearance; D4 impaired personal hygiene; G3 motor disturbances). Factor-4: General symptoms (G1 sleep disturbance; G2 dysphoric mood; G4 impaired tolerance to normal stress). Factor-5: Odd thoughts (P1 unusual thought content; D2 bizarre thinking). Factor-6: Distorted cognition and perception (P2 suspiciousness; P4 perceptual abnormalities).

Table 2. Standardized factor loadings obtained from exploratory factor analysis, using varimax rotation, of 14 clinical items and two GAF (Global Assessment of Functioning) scores from the SIPS (N = 600).

| Variables | Factor-1 | Factor-2 | Factor-3 | Factor-4 | Factor-5 | Factor-5 |
|-----------|----------|----------|----------|----------|----------|----------|
| P1        | 0.011    | 0.111    | 0.084    | −0.03    | 0.851    | 0.03     |
| P2        | 0.023    | 0.167    | −0.141   | 0.016    | 0.025    | 0.594    |
| P3        | −0.247   | 0.252    | 0.352    | −0.153   | −0.186   | 0.24     |
| P4        | 0.02     | −0.021   | 0.148    | 0.059    | 0.117    | 0.688    |
| P5        | 0.078    | 0.204    | 0.579    | −0.128   | 0.141    | −0.387   |
| N1        | 0.762    | 0.262    | 0.121    | 0.051    | −0.059   | 0.038    |
| N2        | 0.701    | 0.357    | 0.053    | 0.237    | −0.027   | 0.027    |
| N3        | 0.834    | 0.089    | 0.284    | −0.034   | 0.093    | 0.046    |
| N4        | 0.828    | 0.1      | 0.207    | −0.052   | 0.063    | −0.043   |
| N5        | 0.432    | 0.137    | 0.568    | −0.05    | 0.181    | −0.291   |
| N6        | 0.294    | 0.734    | 0.065    | 0.069    | 0.157    | 0.062    |
| D1        | 0.291    | 0.07     | 0.622    | −0.12    | 0.225    | 0.151    |
| D2        | 0.047    | 0.108    | 0.108    | 0.066    | 0.886    | 0.101    |
| D3        | 0.051    | 0.34     | 0.318    | 0.245    | 0.031    | 0.259    |
| D4        | 0.355    | 0.235    | 0.463    | −0.113   | 0.046    | 0.029    |
| G1        | −0.049   | 0.049    | 0.073    | 0.798    | −0.023   | 0.047    |
| G2        | 0.073    | 0.074    | −0.134   | 0.799    | −0.054   | −0.065   |
| G3        | 0.177    | −0.008   | 0.712    | 0.137    | −0.029   | 0.03     |
| G4        | 0.065    | 0.321    | −0.061   | 0.618    | 0.228    | 0.252    |
| Current-GAF | −0.295  | −0.829  | −0.12    | −0.132   | −0.097   | −0.069   |
| Drop-GAF  | 0.133    | 0.836    | 0.119    | 0.123    | 0.052    | 0.019    |

Notes: Factor-1: Negative symptoms (N1 social anhedonia; N2 avolition; N3 expression of emotion; N4 experience of emotions and self; N5 ideational richness). Factor-2: Global functions (N6 occupational functioning; Current-GAF; GAF drop, GAF score baseline from highest in the past year). Factor-3: Disorganized communication and behavior (P5 disorganized communication; N5 ideational richness; D1 odd behavior or appearance; D4 impaired personal hygiene; G3 motor disturbances). Factor-4: General symptoms (G1 sleep disturbance; G2 dysphoric mood; G4 impaired tolerance to normal stress). Factor-5: Odd thoughts (P1 unusual thought content; D2 bizarre thinking). Factor-6: Distorted cognition and perception (P2 suspiciousness; P4 perceptual abnormalities).

Inferencing on AP prescription from the six-factorial model
We used logistic regression to evaluate the effect of demographic (i.e. age, gender, education), and six factorial psychopathological variables on clinicians’ decisions of AP-prescription. Table 3 showed that the factor 2,5,6 (i.e. Global functions, Odd thoughts and Distorted cognition and perception) were found to be significant predictors in AP-prescription. The same factors also predicted CHR individuals’ decisions of AP-taking (Table 4). Conversion, was predicted by factor 1,2,4 (i.e. Negative symptoms, communication and behavior and General symptoms) (Table 5). Notably, the general symptoms (factor-4) was appeared as a protective factor in the model, meaning that the higher is the level of general symptoms the lower is the risk for conversion.

DISCUSSION
Summary of findings
This paper aims at investigating the complex, yet clinically central, interconnection of clinicians’ intention of antipsychotic prescription, CHR individuals’ intention of assuming antipsychotic therapy and the psychopathological risk factors for conversion to psychosis in a large cohort. Four major findings were obtained: First, severe baseline positive symptoms such as thought and perception abnormality and impairments of global functions predicted the AP prescriptions by clinicians for CHR individuals. Second, CHR individuals’ decision of AP-taking is associated to the same factors motivating clinicians’ AP prescription (i.e. positive symptoms and global functions). Third, CHR individuals exhibiting more severe negative symptoms (such as social anhedonia and impairments of global functions) at baseline were more likely to convert to psychosis in the following 2 years. Finally, while both clinicians and CHR individuals appear focused on global functions and the management of positive symptoms by AP treatment already in the very early phase of psychosis, an important empirical predictor of conversion, i.e. negative symptoms, is less likely to be improved by AP treatment and requires specific treatment attention.

In sum, while clinicians’ prescription and patients’ assumption largely cohere with respect in the target psychopathological features, namely positive symptoms and global functions, these overlap only partially with respect to the prevention aim. Indeed, besides global functions also negative symptoms were found to play an important role in determining the actual risk of transition to psychosis in our CHR sample and they are allegedly only marginally affected by AP treatment. Therefore, the specific area of prodromal negative symptoms would require sustained therapeutic attention if we want to improve outcomes.

Clinicians’ considerations of AP prescriptions
We found that baseline positive symptoms were the significant predictors of AP prescriptions by clinicians. Specifically, CHR individuals with the higher severity level of symptoms of distorted cognition and perception (suspiciousness and perceptual abnormalities) and odd thoughts (unusual thought content and bizarre thinking) were more likely to be treated with AP. It’s not surprising since the essence of the CHR identification was based on attenuated positive symptoms, such as delusions and hallucinations. The effectiveness of AP on positive symptoms in patients with psychosis and CHR individuals had been
widely reported. Our results suggest that clinicians follow a rational, symptom oriented clinical strategy, which becomes fully visible adopting a dimensional perspective (such as the one derived from EFA factors) beyond the canonical categorical stratification of CHR subgroups. Our results suggest that clinicians should adopt a longer-term vision, beyond the purely on-demand symptomatic treatment. There is increasing evidence that non drug treatments such as cognitive-behavioral therapy. 

Fig. 1 Effect sizes (Cohen d) for 6 factorial scores compared between prescribed-CHR and Not-Prescribed-CHR (A), With-AP-CHR and Without-AP-CHR (B), Converted-CHR and Not-Converted-CHR (C).
for psychosis may be effective for individuals with attenuated positive symptoms. There is another realistic reason why AP is widely prescribed by our clinicians is the lack of non-drug treatment for CHR populations. Therefore, the development of diversified early interventions may help to improve the widespread use of AP.

**Table 3.** Logistic regression for predicting the clinicians’ decision of antipsychotics prescription on demographic and factorial variables (n = 600).

| Predictor factor                          | Beta  | S.E.  | β   | 95%CI for β | Wald statistic | P value |
|------------------------------------------|-------|-------|-----|-------------|----------------|---------|
| Age                                      | 0.011 | 0.021 | 1.011 | 0.970      | 1.054          | 0.262   | 0.609 |
| Gender                                   | −0.149| 0.198 | 0.861 | 0.585      | 1.268          | 0.572   | 0.449 |
| Education                                 | −0.012| 0.042 | 0.988 | 0.910      | 1.072          | 0.089   | 0.765 |
| Factor-1: Negative symptoms              | −0.011| 0.100 | 0.989 | 0.814      | 1.203          | 0.012   | 0.914 |
| Factor-2: Global functions                | 0.305 | 0.097 | 1.356 | 1.122      | 1.640          | 9.921   | 0.002 |
| Factor-3: Disorganized communication and behavior | 0.046 | 0.099 | 1.047 | 0.863      | 1.271          | 0.216   | 0.642 |
| Factor-4: General symptoms                | 0.023 | 0.095 | 1.024 | 0.849      | 1.233          | 0.060   | 0.806 |
| Factor-5: Odd thoughts                    | 0.328 | 0.097 | 1.388 | 1.147      | 1.680          | 11.350  | 0.001 |
| Factor-6: Distorted cognition and perception | 0.647 | 0.107 | 1.910 | 1.550      | 2.354          | 36.869  | <0.001 |

Notes: Beta is the regression coefficient. S.E. is the standard error. 95% CI is the estimated 95% confidence interval for the corresponding parameter. β is the standardized regression coefficient. p values that are statistically significant are shown in bold.

**Table 4.** Logistic regression for predicting the CHR individuals’ decision of antipsychotics assumption on demographic and factorial variables (n = 532).

| Predictor factor                          | Beta  | S.E.  | β   | 95%CI for β | Wald statistic | P value |
|------------------------------------------|-------|-------|-----|-------------|----------------|---------|
| Age                                      | −0.014| 0.023 | 0.986 | 0.942      | 1.031          | 0.391   | 0.532 |
| Gender                                   | 0.029 | 0.205 | 1.030 | 0.689      | 1.538          | 0.021   | 0.886 |
| Education                                 | 0.007 | 0.045 | 1.007 | 0.923      | 1.099          | 0.022   | 0.881 |
| Factor-1: Negative symptoms              | −0.011| 0.102 | 0.989 | 0.810      | 1.208          | 0.011   | 0.916 |
| Factor-2: Global functions                | 0.308 | 0.105 | 1.360 | 1.107      | 1.672          | 8.564   | 0.003 |
| Factor-3: Disorganized communication and behavior | 0.147 | 0.108 | 1.158 | 0.938      | 1.431          | 1.863   | 0.172 |
| Factor-4: General symptoms                | 0.167 | 0.100 | 1.182 | 0.971      | 1.438          | 2.783   | 0.095 |
| Factor-5: Odd thoughts                    | 0.227 | 0.101 | 1.255 | 1.030      | 1.529          | 5.058   | 0.025 |
| Factor-6: Distorted cognition and perception | 0.433 | 0.109 | 1.542 | 1.246      | 1.908          | 15.841  | <0.001 |

Notes: Beta is the regression coefficient. S.E. is the standard error. 95% CI is the estimated 95% confidence interval for the corresponding parameter. β is the standardized regression coefficient. p values that are statistically significant are shown in bold.

**Table 5.** Logistic regression for predicting the conversion to psychosis on demographic and factorial variables (n = 532).

| Predictor factor                          | Beta  | S.E.  | β   | 95%CI for β | Wald statistic | P value |
|------------------------------------------|-------|-------|-----|-------------|----------------|---------|
| Age                                      | −0.041| 0.027 | 0.960 | 0.911      | 1.011          | 2.390   | 0.122 |
| Gender                                   | −0.291| 0.229 | 0.747 | 0.477      | 1.171          | 1.617   | 0.203 |
| Education                                 | 0.082 | 0.052 | 1.085 | 0.980      | 1.201          | 2.472   | 0.116 |
| Factor-1: Negative symptoms              | −0.326| 0.110 | 0.722 | 0.582      | 0.895          | 8.825   | 0.003 |
| Factor-2: Global functions                | −0.333| 0.117 | 0.717 | 0.570      | 0.902          | 8.075   | 0.004 |
| Factor-3: Disorganized communication and behavior | −0.176| 0.099 | 0.839 | 0.690      | 1.019          | 3.140   | 0.076 |
| Factor-4: General symptoms                | 0.260 | 0.116 | 1.297 | 1.034      | 1.627          | 5.062   | 0.024 |
| Factor-5: Odd thoughts                    | −0.140| 0.113 | 0.870 | 0.697      | 1.085          | 1.530   | 0.216 |
| Factor-6: Distorted cognition and perception | −0.119| 0.114 | 0.888 | 0.710      | 1.111          | 1.081   | 0.299 |

Notes: Beta is the regression coefficient. S.E. is the standard error. 95% CI is the estimated 95% confidence interval for the corresponding parameter. β is the standardized regression coefficient. p values that are statistically significant are shown in bold.

**CHR individuals’ considerations of AP taken**

The decision from CHR individuals (or their family members) to take AP seems consistent with the clinicians’ prescriptions. The assumption of AP was most significantly predicted by the suspiciousness and perceptual abnormalities symptoms (factor-6, see Fig. 1). Previous studies17,18 found that perceptual abnormalities...
can lead to the increase of anxiety and depression symptoms of CHR individuals, which is more likely to attract the attention of patients and their families. On the other hand, perceptual abnormalities symptoms are easier for clinicians and patients to identify as relatively abnormal. Also, when perceptual abnormalities occur, people often think that the psychosis has begun, which makes the use of antipsychotics a reasonable option. However, perceptual abnormalities such as hallucinations, especially isolated perceptual symptoms may play a role of “nonspecific/clinical noise” for predicting psychosis in CHR phase and normal variations among the general population. Whether it is suitable for use as an indication of AP has not been determined.

Slightly different from clinicians’ second reason for clinicians’ decisions of AP-prescription (odd thoughts), CHR individuals’ decisions of AP-taking is also predicted by global functions. This might be related to the fact that usually thought symptoms are relatively ego-syntonic and less worrisome for patients that for clinicians. For CHR individuals as well as for their caregiver, on the contrary, changes in functioning, such as academic and inter-peer performance, is of obvious impact and immediately perceivable. Deflections in Global functions is typically the driving force for the CHR individuals and their caregivers to seek for professional help to recover, and AP taken might be mostly motivated by the hope of gaining previous functional levels back again. On the other side, negative symptoms such as observed withdrawal or pro-active isolation are more easily attributed to relatively typical adolescent behavior, and might be perceived as less relevant for treatment seeking as well as for need-based treatment.

## Risk factors for conversion to psychosis

A growing body of research has demonstrated that negative symptoms are significant predictor of conversion to psychosis in CHR population. In current study, CHR individuals with severe negative symptoms at baseline were more likely to convert to psychosis. In contrast, the positive symptoms that had been targeted and treated by AP were not even significant in our prediction model. While much effort has been dedicated to positive symptoms in the prospective of CHR identification and conversion, negative symptoms (and partly global functions), on the other side, may be largely neglected in clinical practice and research. Bearing in mind the little effectiveness of AP on negative symptoms and the risk that some of their side effects may aggravate the negative symptoms, the early use of AP for the purpose of effective prevention of psychosis should be particularly cautious. Future study of new approaches in targeting negative symptoms in CHR, such as N-methyl-D-aspartate receptor modulator interventions (glycine and o-serine), cognitive remediation therapy, and family therapy should be undertaken.

Interestingly, in this study, the functional impairment is not only the focus of the three parties, but also the contradiction. This may be related to the special status that function is related to both positive and negative symptoms. From the perspective of CHR individuals, the most important concern is to restore the function. From the perspective of clinicians, they hope to improve the function by controlling the positive symptoms with AP prescriptions. However, in the process of early psychosis, on the one hand, the function improves with the improvement of positive symptoms by AP treatments, on the other hand, it deteriorates with the deterioration of negative symptoms and the influence of AP treatment itself. Consistent with previous findings, poor function in CHR individuals was associated with an increased risk of conversion to psychosis. On the other hand, there is research evidence that CHR individuals with lower levels of negative symptoms and higher levels of social functioning are more likely to recover symptomatically.

Notably, the general symptom factor revealed a protective effect with respect to the conversion to psychosis. Specifically, CHR individuals with higher severity of general symptoms had a significantly lower conversion risk compared with CHR individuals with lower levels of general symptoms. However, the mechanism behind such apparent protective role is not entirely clear. Indeed, first there are inconsistencies in the literature, which found that baseline mood disturbance is associated with poor prognosis but had no effect on risk of transition to full psychosis. Also, previous studies had not included other variables, such as dysphoric mood, as a potentially relevant factor for predicting psychosis, although dysphoric mood has been found to be related to clinical caseness in CHR cohorts rather than to progression towards psychosis. On a clinical level, however, general symptoms are better understood as a cloud of relatively unspecified symptoms that certainly motivate referral but are not specifically predictive of the progression towards psychosis.

### Strengths and limitations

The main strengths of this study are its longitudinal, prospective design with determined clinical outcome, stratified clinicians’ decision (AP-prescription) and CHR individuals’ decision (AP-taking) in the analysis, large sample size of drug naïve CHR individuals, and examination of the SIPS factor structure. Furthermore, all included participants were AP-naïve prior to the moment of CHR assessment as per inclusion criteria, which substantially mitigates some potential, AP-related prognostic confounders (e.g. the risk of including pharmacologically-attenuated first episode psychosis within the CHR sample). Some limitations of our study, however, merit comment. First, this CHR cohort was surveyed naturalistically, and various medications other than AP (such as antidepressants) that CHR individuals might have assumed with varying compliance during the follow-up period may have an impact the clinical outcomes. However, a major focus of this study is the decisions of CHR individuals on AP-taking rather than the process of AP usage. The information of decision making on AP-taking from CHR individuals is accurate which had been carefully recorded according to CHR individuals and their caregivers during multiple follow-up. A second limitation is the lack of more detailed information on the background of our prescribing clinicians, including career seniority, educational background, field of expertise, familiarity with CHR assessment and treatment standards, etc. Those variables may impact their decision of AP prescriptions. A third limitation is the lack of data on the compliance of CHR individuals, the inferences of their caregivers, even their financial situation and medical insurance situation may influence the CHR individuals’ decision on AP taken. Although we performed tripartite checks-involving the CHR individuals, their family members, and clinician reports plus medical records to confirm and quantify the AP treatment details, our approach was less accurate than other strict methods, such as pill counts and self-report.

### CONCLUSIONS

There are intuitive gaps between the focus of clinicians’ AP prescriptions, expectations of CHR individuals’ taking AP, and the clinical symptom-related risk factors predicting conversion to psychosis. With the exception of global functions are recognized as central by clinicians and CHR individuals and play a clear role in increasing the transition risk, clinicians and CHR individuals’ perspectives converge on positive symptoms (which in our sample did not seem to pay a central role in predicting later conversion) and pay definitely less attention to negative symptoms (which proved a robust predictor of conversion to psychosis). It is clear that a realignment in the understanding of AP usage is necessary, and that important risk predictors of
conversion, such as negative symptoms, largely fall outside the therapeutic spectrum of AP. However, treating negative symptoms in CHR remains an important yet elusive target: indeed, a recent network meta-analysis which reviewed 11 treatment approaches for negative symptoms in CHR, found that effectiveness did not reach statistical significance for any of the treatments at stake. Thus developing novel interventions to decrease the burden of negative symptoms in CHR youth is a clear priority for preventive purposes. On pragmatic side, although our result confirms that AP prescription in CHR is rationally associated with specific psychopathological profiles, further education and training on rational use of AP may help improving prescriptive appropriateness and ultimately improve care and management of CHR individuals. Furthermore, the results indirectly suggest that going beyond CHR categorical strata towards a more detailed dimensional approach (such as the current factorial decomposition of SIPS/SOPS) is feasible and could be an important move for a more personalized and precise treatment decision making.

METHODS

Sample, design and setting

The data used for this study was derived from the ShangHai At Risk for Psychosis-eXtended (SHARP-extended) program. The methodology and study design of the SHARP-extended have been described in detail elsewhere. Six hundred CHR individuals were recruited between 2016-2019 year at the Shanghai Mental Health Center (SMHC) in China. The Research Ethics Committees at the SMHC approved this study. All participants gave written informed consent at the recruitment stage of the study. Subjects younger than 18 years of age had their consent forms signed by their parents, but they also gave written informed consent themselves. Patients had to fulfill at least one of the prodromal syndrome criteria: (1) brief intermittent psychotic syndrome (BIPS), (2) attenuated positive symptom syndrome (APSS), or (3) genetic risk and deterioration syndrome (GRDS). Inclusion criteria were: (i) under age of 45 years old; (ii) individuals younger than 18 years old had to be accompanied by either a parent or legal guardian; (iii) capacity to provide informed consent or assent if under 18; (iv) must have completed at least 6 years of primary education; and (v) be psychotropically naïve at the moment of CHR assessment. Exclusion criteria were: (i) severe somatic diseases, for example, pneumonia, cancer or heart failure, (ii) intellectual disability, or (iii) a history of drug (such as methamphetamine) abuse or dependence.

The referral medical system does not exist in China, so patients are generally free to choose hospitals and doctors. In the first visiting, CHR individuals were referred to the participating the naturalistic follow-up study, which research procedure was independent of the routine clinical treatment. The study does not interfere with clinicians’ prescription decisions and CHR individuals’ decisions of AP-taking. Of the total of 600 CHR individuals completed the baseline assessment, 68 individuals have not reached the end of follow-up, remained 532 individuals who completed 2-year follow-up, reassessed by telephone or by face-to-face interview every 6 months using the Structured Interview for Prodomal Syndromes (SIPS) or POPS.

The SMHC is the largest outpatient mental health clinic that offers medication management and psychotherapy in China. The SMHC is a comprehensive psychiatric hospital in Shanghai that sees more than 1,000,000 outpatients per year. The participants were recruited from the department of the Shanghai Psychotherapy and Psychological Counseling Center (SPCC) at the SMHC. There are approximately 1000 professional staff who provide care for the patients at the SMHC. Among them, 258 are psychiatrists and psychologists and 541 are psychiatric nurses, along with other support staff. The SPCC provides comprehensive clinical services, including psychological assessment and counseling as well as medical management. Patients come seeking help for issues ranging from general psychological problems (e.g., interpersonal adaptation, marriage and learning difficulties) to more severe psychological disorders and mental illnesses (e.g., schizophrenia and bipolar disorder).

Statistical analysis

CHR individuals were grouped according to baseline AP-prescription (reflecting clinicians’ decision, Prescribed-CHR vs. Not-Prescribed-CHR), AP-taking during the follow-up (reflecting CHR individuals’ decision, With-AP-CHR vs. Without-AP-CHR) and conversion to psychosis (reflecting the natural process of psychosis, Converted-CHR vs. Not-Converted-CHR). Quantitative variables are expressed as mean ±S.D., while qualitative variables are presented as frequencies (%). The two groups were compared using χ² tests for comparisons of categorical variables and independent t tests for comparisons of continuous variables. Comparisons between Prescribed-CHR and Not-Prescribed-CHR groups, With-AP-CHR and Without-AP-CHR groups, Converted-CHR and Not-Converted-CHR groups were conducted separately. Effect sizes were calculated using Cohen’s d for mean comparisons. The exploratory factor analysis was applied using the principal components analysis and varimax rotation. The number of factors retained in the analysis was based on retaining factors that accounted for >10% of the common variance as well as interpretability. Then, using the factor loading coefficients, we calculated the estimated factor scores for each factor for all CHR individuals. A multiple logistic regression analysis was conducted to predict clinicians’ decisions of AP-prescription, CHR individuals’ decisions of AP-taking, and conversion to psychosis using age, gender, education, and estimated factor scores as predictors.

DATA AVAILABILITY

All relevant data are available from the authors upon reasonable request.
REFERENCES

1. Fusar-Poli, P. et al. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70, 107–120 (2013).
2. Fusar-Poli, P. et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry 69, 220–229 (2012).
3. Raballo, A., Poletti, M. & Preti, A. Editorial perspective: psychosis risk in adolescence—outcomes, comorbidity, and antipsychotics. J. Child Psychol. Psychiatry, https://doi.org/10.1111/jcpp.13438 (2021).
4. Raballo, A., Poletti, M., Preti, A. & McGorry, P. Clinical high risk for psychosis in children and adolescents: a meta-analysis of transition prevalences. Schizophr. Res. https://doi.org/10.1016/j.schres.2020.03.063 (2020).
5. Raballo, A. & Poletti, M. Overlooking the transition elephant in the ultra-high-risk room: are we missing functional equivalents of transition to psychosis? Psychol. Med. 1–4, https://doi.org/10.1017/S0033291719003337 (2019).
6. Zhang, T. et al. Real-world effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the SHARP (Shanghai At Risk for Psychosis). Aust. N. Z. J. Psychiatry 54, 696–706 (2020).
7. Raballo, A., Poletti, M. & Preti, A. Meta-analyzing the prevalence and prognostic effect of antipsychotic exposure in clinical high-risk (CHR): when things are not what they seem. Psychol. Med. 50, 2673–2681 (2020).
8. Yung, A. R. et al. Psychiatry prediction: 12-month follow up of a high-risk (“prodromal”) group. Schizophr. Res. 60, 21–32 (2003).
9. McGorry, P. D., Hartmann, J. A., Spooner, R. & Nelson, B. Beyond the “at risk mental state” concept: transitioning to transdiagnostic psychiatry. World Psychiatry 17, 133–142 (2018).
10. Yung, A. R. et al. Monitoring and care of young people at incipient risk of psychosis. Schizophr. Bull. 22, 383–393 (1996).
11. Leucht, S. et al. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. Am. J. Psychiatry 177, 342–353 (2020).
12. McCutcheon, R. A. et al. The efficacy and heterogeneity of antipsychotic response in schizophrenia: a meta-analysis. Mol. Psychiatry 26, 1310–1320 (2021).
13. McGorry, P. D. et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch. Gen. Psychiatry 59, 921–928 (2002).
14. Woods, S. W. et al. Randomized trial of olanzapine versus placebo in the symptomatic acute treatment of the schizophrenic prodrome. Biol. Psychiatry 54, 453–464 (2003).
15. McGlashan, T. H. et al. Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. Am. J. Psychiatry 163, 790–799 (2006).
16. Zheng, Y. et al. Cognitive behavioral therapy for prodromal stage of psychosis: outcomes for transition, functioning, distress, and quality of life: a systematic review and meta-analysis. Schizophr. Bull. https://doi.org/10.1093/schbul/sbab044 (2021).
17. Hillaertala, S. A. & McCellan, J. Phenomenology and diagnostic stability of youths with atypical psychotic symptoms. J. Child Adolesc. Psychopharmacol. 15, 497–509 (2005).
18. Zhang, T. et al. Isolated hallucination is less predictive than thought disorder in psychosis: Insight from a longitudinal study in a clinical population at high risk for psychosis. Sci. Rep. 8, 13962 (2018).
19. Nelson, B. et al. Long-term follow-up of a group at ultra high risk (“prodromal”) for psychosis: the PACE 400 study. JAMA Psychiatry 70, 793–802 (2013).
20. Bartels-Velthuis, A. A., van de Willige, G., Jenner, J. A., van Os, J. & Wiersma, D. Course of auditory vocal hallucinations in childhood: 5-year follow-up study. Br. J. Psychiatry 199, 296–302 (2011).
21. Bartels-Velthuis, A. A., Wigman, J. T., Jenner, J. A., Bruggeman, R. & van Os, J. Course of auditory vocal hallucinations in childhood: 11-year follow-up study. Acta Psychiatr. Scand. 134, 6–15 (2016).
22. Zhang, T. et al. Using ‘WeChat’ online social networking in a real-world needs analysis of family members of youths at clinical high risk of psychosis. Aust. N. Z. J. Psychiatry 52, 375–382 (2018).
23. Falkenberg, I. et al. Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? Psychiatry Res. 228, 808–815 (2015).
24. Yarborough, B. J., Yarborough, M. T. & Cavee, J. C. Factors that hindered care seeking among people with a first diagnosis of psychosis. Early Interv. Psychiatry 13, 1220–1226 (2019).
25. Healey, K. M. et al. Latent profile analysis and conversion to psychosis: characterizing subgroups to enhance risk prediction. Schizophr. Bull. 44, 286–296 (2018).

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AUTHOR CONTRIBUTIONS
T.H.Z., A.R. and J.J.W. conceptualized the study, wrote the first draft of manuscript and conducted the statistical analyses. J.H.Z., R.P.G., G.S.W., L.H.X. and Y.Y.W. interviewed participants and collected and organized the primary data. Y.Y.T., Y.G.H., H.C.L., T.C. and X.C.T. managed the literature searches, statistical analyses and edited the manuscript. J.J.W. and C.B.L. designed the study and provided supervision in the implementation of the study. All authors have approved the final manuscript.

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The authors declare no competing interests.

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