Antipsychotic Exposure in Clinical High Risk of Psychosis: Empirical Insights From a Large Cohort Study

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ABSTRACT

Objective: Current treatment guidelines for individuals at clinical high risk (CHR) for psychosis do not recommend the prescription of antipsychotics (not even second-generation ones) as the first treatment option for preventing psychosis. Yet, recent meta-analytic evidence indicates that antipsychotic exposure in CHR is relatively widespread and associated with a higher imminent risk of transition to psychosis. Therefore, we undertook this study to better delineate which clinical characteristics of CHR individuals may lead to the choice of antipsychotic prescription and whether it identifies a subgroup at higher risk for conversion to psychosis.

Methods: Consecutively referred CHR individuals (N = 717) were assessed for demographic and clinical characteristics and followed up for 3 years (200 did not reach the end of the follow-up time) from 2016 to 2021. The sample was then dichotomized, on the basis of antipsychotic prescription, to prescribed (CHRAP+, n = 492) or not-prescribed (CHRAP–, n = 225) groups, which were subsequently compared for sociodemographic and clinical characteristics. The risks of conversion to psychosis in CHRAP+ versus CHRAP– groups were tested via survival analysis.

Results: Of the 717 CHR individuals, 492 (68.62%) were prescribed antipsychotics; among these antipsychotics, the highest proportion used was for aripiprazole (n = 152), followed by olanzapine (n = 106), amisulpride (n = 76), and risperidone (n = 64). The CHRAP+ group had younger age ($t = 2.138$, $P = .033$), higher proportion of female individuals ($\chi^2 = 5.084$, $P = .024$), psychotic symptoms of greater severity ($t = 7.910$, $P < .001$), and more impaired general function ($t = 5.846$, $P < .001$) than the CHRAP– group. The CHRAP+ group had greater risk for conversion to psychosis (27.0% in the CHRAP+ group vs 10.9% in the CHRAP– group, $P < .001$). Factors related to positive symptoms were the most likely to influence doctors' decision-making regarding prescripton of antipsychotics, without influence of age, sex, and education levels.

Conclusions: Clinicians may prescribe antipsychotics mainly based on the severity of positive and disorganization symptoms of CHR individuals. The CHRAP+ group was associated with a higher risk of conversion to psychosis. In pragmatic terms, this finding indicates that baseline antipsychotic prescription in CHR cohorts is a warning flag for higher incipient risk of psychosis and designates as hyper-CHR subgroup as compared to antipsychotic-naive CHR.

Trial Registration: ClinicalTrials.gov identifier: NCT04010864

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Despite increasing evidence of the significant importance of early identification and intervention for individuals with clinical high risk (CHR) of psychosis,[1–5] there are still several gray areas (if not misunderstandings) in real-world preventive strategies. For instance, antipsychotics, as the traditional, classical, and more accessible form of treatment for patients with post-onset psychosis,[6,7] have been proven to be effective in reducing, or at least delaying, the possibility of progression to psychosis.[8–10] However, there is no evidence that any specific antipsychotic should be taken to prevent the conversion from CHR to psychosis.[11] On the contrary, many guidelines[12,13] do not recommend the use of an antipsychotic as the first treatment choice to prevent psychosis, yet clinicians often deviate from guidelines and prescriptive indications, resulting in a higher-than-expected baseline exposure to antipsychotics in CHR individuals.[11,14]

For example, a recent meta-analysis[15] revealed that at least 1 of every 4 to 5 enrolled CHR individuals already has an ongoing exposure to antipsychotics at baseline. This apparent deviation in compliance with the guidelines (which is nonetheless an off-label prescription of antipsychotic medication) is presumably supported by clinicians' impressions and experiences and motivated by the major goal of obtaining a rapid symptom alleviation in the CHR phase of psychosis. As a matter of fact, antipsychotic prescription—especially in a clinical group considered to be at higher risk of developing a first psychotic episode such as CHR individuals—is generally motivated by the impression of a rapidly deteriorating clinical picture and/or by a symptom severity profile that is perceived to be likely to develop fully into psychosis.[16] Should this be the case, the reason for choosing antipsychotics becomes sufficient.[17] However, why is a specific subgroup of CHR prescribed antipsychotics? Is there any specific, common symptom profile identifying this subgroup? Is clinician evaluation of higher risk of

Clinical Points

- There is increasing evidence of the significant importance of early intervention for individuals with clinical high risk of psychosis, but many gray areas exist in real-world preventive strategies.
- Antipsychotics were commonly prescribed in routine clinical care for individuals with clinical high risk at their first visits to mental health services.
- Antipsychotic prescription in individuals with clinical high risk is to be considered as a warning flag for higher incipient risk of conversion to psychosis.

conversion to psychosis accurate? All of these questions remain unsolved and are to date not supported by precise empirical data.

Therefore, we decided to perform a thorough investigation of the tendencies and preferences of clinicians in prescribing antipsychotics for CHR individuals, capitalizing on the ShangHai At Risk for Psychosis program-extended (SHARP-extended) cohort. To our knowledge, indeed, this is a unique dataset that would allow a real-world investigation of antipsychotic prescription in a large CHR sample (N > 300) and with long-term follow-up data (> 2 years).

In the current study, we hypothesized that CHR with AP prescription (CHRAP+) differs from CHR without AP prescription (CHRAP–) in terms of symptom profile and that such a difference would refer to symptom dimensions expected to be amenable to antipsychotic treatment. In addition, we hypothesized that those patients with CHR who were prescribed an antipsychotic may be more likely to convert to psychosis than those without antipsychotic prescription, assuming that antipsychotic prescription is a proxy for the overall perceived severity of the clinical picture.

METHODS

Sample and Procedures

This observational study included 717 patients who were confirmed as CHR by face-to-face interview. Data are from the SHARP-extended, the sample for which was recruited between 2016 and 2021 at the Shanghai Mental Health Center (SMHC) in China (Clinical trials.gov identifier NCT04010864).[18] The Research Ethics Committees at the SMHC approved this study. All participants agreed to participate in the study. Adult subjects gave informed consent; subjects younger than 18 years of age had their consent forms signed by their parents, and the youths gave informed assent and agreed to participate in the study. 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 as follows: (i) under age of 45 years; (ii) for individuals younger than 18 years, accompanied by either a parent or a legal guardian; (iii) capable of providing informed consent (or assent if under 18 years); (iv) completed at least 6 years of primary education; and (v) psychotropically naive. 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. Zhang and colleagues[13–15] provide further details regarding the SHARP methodology.

The research procedure was independent of the routine clinical treatment procedure at the SMHC. For the present study, of the total 717 CHR individuals who completed the baseline assessment, 200 individuals did not reach the end of follow-up; 67 of the remaining 517 were lost to follow-up, leaving 450 individuals who completed both baseline and 3-year follow-up assessments. Recruited CHR individuals were followed up every 6 months until the end of 36 months, with reassessment by telephone or by face-to-face interview every 6 months using the Structured Interview for Prodromal Syndromes (SIPS).[19,20]

Measurement

The SIPS was used to identify individuals with CHR. It consists of 19 items that assess 4 symptom domains: positive symptoms (scales P1–P5: P1, unusual thought content; P2, suspiciousness; P3, grandiosity; P4, perceptual abnormalities; and P5, disorganized communication), negative symptoms (scales N1–N6: N1, social anhedonia; N2, avolition; N3, expression of emotion; N4, experience of emotions and self; N5, ideational richness; and N6, occupational functioning), disorganization symptoms (scales D1–D4: D1, odd behavior or appearance; D2, bizarre thinking; D3, trouble with focus and attention; and D4, impaired personal hygiene), and general symptoms (scales G1–G4: G1, sleep disturbance; G2, dysphoric mood; G3, motor disturbances; and G4, impaired tolerance to normal stress). During the SIPS interview, the Global Assessment of Functioning (GAF)[21] was used to measure the participants' global psychological, social, and occupational functioning. The drop in GAF scores (ie, the GAF score relative to 12 months prior) was used for assessing functional deterioration in the SIPS interview.

Conversion to Psychosis

Conversion to psychosis was the major outcome in the SHARP study. The present study explores the potential relationship between baseline antipsychotic prescription and conversion to psychosis. Of the remaining 450 CHR individuals, 101 (22.4%) had converted to full psychosis at 3 years of follow-up. Conversion to psychosis was defined using the POPS (Presence of Psychotic Symptoms in SIPS)[16] criteria. The conversion was defined as the development of at least 1 psychotic-level symptom (rated "6" on the SIPS positive symptoms scale) with either sufficient frequency or sufficient duration or occurring at least an hour a day on average for at least 4 days a week for a total duration of at least 16 hours during the week.

Medication Prescription

The antipsychotic treatment at baseline was prescribed either after or at the same time as CHR evaluation. All

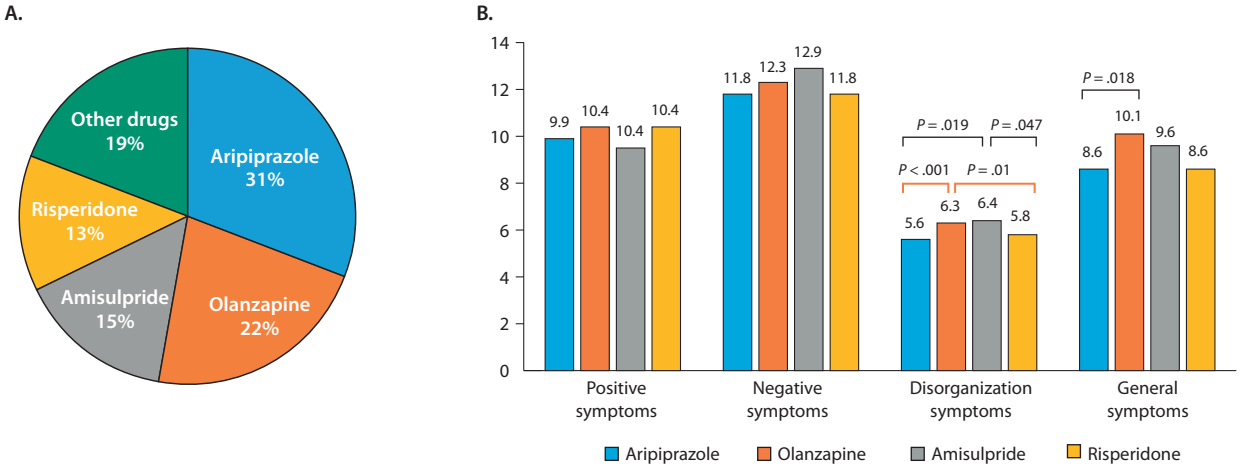
Table 1. Comparison of Baseline Demographic and SIPS Variables Between the CHRAP+ and CHRAP– Groups[a]

Variables	Total Sample (n = 717)	CHRAP+ (n = 492)	CHRAP– (n = 225)	Comparison $t/\chi^2/Z$[b]	Comparison *P* Value
Demographic Variables					
Age, mean (SD), y	20.23 (6.1)	19.91 (5.9)	20.95 (6.5)	$t = 2.138$	**.033**
Sex, n (%)				$\chi^2 = 5.084$	**.024**
Male	341 (47.6)	220 (64.5)[c]	121 (35.5)[c]		
Female	376 (52.4)	272 (72.3)[c]	104 (27.7)[c]		
Education, mean (SD), y	11.25 (3.1)	11.06 (3.0)[c]	11.66 (3.2)[c]	$t = 2.382$	**.018**
Family history, n (%)[d]				$\chi^2 = 0.932$	.628
None	574 (80.1)	392 (68.3)[c]	182 (31.7)[c]		
Low risk	78 (10.9)	57 (73.1)[c]	21 (26.9)[c]		
High risk)	65 (9.1)	43 (66.2)[c]	22 (33.8)[c]		
SIPS Variables					
Prodromal syndrome, n (%)				$\chi^2 = 6.053$	**.048**
APSS	660 (92.1)	460 (69.7)[c]	200 (30.3)[c]		
GRDS	66 (9.2)	37 (56.1)[c]	29 (43.9)[c]		
BIPS	37 (5.2)	28 (75.7)[c]	9 (24.3)[c]		
Single category, n (%)	672 (93.7)	459 (68.3)	213 (31.7)	$\chi^2 = 0.496$	.481
Combined categories, n (%)	45 (6.3)	33 (73.3)	12 (26.7)		
GAF score, mean (SD)					
12 months before current time	78.6 (4.4)	78.53 (4.170)	78.70 (4.754)	$t = 0.478$	.633
Current	56.3 (7.3)	55.21 (6.746)	58.58 (8.030)	$t = 5.846$	**<.001**
Drop (from 12 months before baseline to baseline)	22.3 (7.2)	23.33 (6.684)	20.12 (7.901)	$t = 5.623$	**<.001**
No. of positive symptoms, median, mean (SD)					
P1 unusual thought content	4, 2.9 (1.9)	4, 3.1 (1.9)	3, 2.61 (1.9)	$Z = 2.135$	**.033**
P2 suspiciousness	4, 3.1 (1.9)	4, 3.4 (1.8)	3, 2.4 (1.9)	$Z = 5.381$	**<.001**
P3 grandiosity	0, 0.2 (0.7)	0, 0.2 (0.7)	0, 0.2 (0.7)	$Z = 1.822$	.068
P4 perceptual abnormalities	3, 2.5 (2.1)	4, 2.8 (2.1)	2, 1.8 (1.9)	$Z = 3.955$	**<.001**
P5 disorganized communication	0, 0.5 (1.1)	0, 0.4 (1.0)	0, 0.6 (1.2)	$Z = 0.459$	.646
Total	9, 9.2 (3.9)	10, 9.9 (3.6)	7, 7.6 (4.0)	$t = 7.910$	**<.001**
No. of negative symptoms, median, mean (SD)					
N1 social anhedonia	3, 2.6 (1.4)	3, 2.7 (1.3)	3, 2.4 (1.3)	$Z = 3.742$	**<.001**
N2 avolition	3, 2.5 (1.3)	3, 2.6 (1.2)	2, 2.5 (1.4)	$Z = 1.649$	.099
N3 expression of emotion	1, 1.4 (1.4)	1, 1.5 (1.4)	1, 1.3 (1.4)	$Z = 1.801$	.072
N4 experience of emotions and self	1, 1.4 (1.3)	1, 1.4 (1.3)	1, 1.4 (1.4)	$Z = 0.417$	.677
N5 ideational richness	0, 0.6 (1.0)	0, 0.5 (0.9)	0, 0.6 (1.1)	$Z = 0.887$	.375
N6 occupational functioning	3, 3.4 (1.5)	3, 3.5 (1.5)	3, 3.0 (1.6)	$Z = 3.603$	**<.001**
Total	11, 11.8 (5.9)	12, 12.1 (5. 8)	10, 11.0 (6.2)	$t = 2.265$	**.024**
No. of disorganization symptoms, median, mean (SD)					
D1 odd behavior or appearance	0, 0.7 (1.1)	0, 0.7 (1.1)	0, 0.7 (1.1)	$Z = 0.423$	.672
D2 bizarre thinking	2, 2.0 (1.9)	2, 2.2 (2.0)	1, 1.7 (1.8)	$Z = 3.930$	**<.001**
D3 trouble with focus and attention	0, 2.4 (1.0)	2, 2.5 (1.0)	2, 2.2 (1.0)	$Z = 2.009$	**.045**
D4 impaired personal hygiene	4 ,0.4 (0.7)	0, 0.4 (0.7)	0, 0.3 (0.6)	$Z = 2.366$	**.018**
Total	5, 5.6 (3.2)	6, 5.9 (3.2)	4, 4.8 (3.0)	$t = 4.481$	**<.001**
No. of general symptoms, median, mean (SD)					
G1 sleep disturbance	3, 2.3 (1.3)	3, 3.2 (1.2)	2, 2.2 (1.3)	$Z = 2.262$	**.024**
G2 dysphoric mood	3, 3.0 (1.3)	3, 3.0 (1.3)	3, 2.9 (1.4)	$Z = 1.330$	.184
G3 motor disturbances	0, 0.2 (0.6)	0, 0.3 (0.7)	0, 0.2 (0.5)	$Z = 1.700$	.089
G4 impaired tolerance to normal stress	4, 3.4 (1.5)	4, 3.6 (1.4)	3, 3.0 (1.6)	$Z = 1.874$	.061
Total	9, 8.9 (3.2)	10, 9.2 (3.1)	9, 8.2 (3.4)	$t = 4.072$	**<.001**
SOPSTAL, median, mean (SD)	36, 35.4 (11.4)	37, 37.2 (10.7)	31, 31.6 (11.9)	$t = 6.276$	**<.001**

[a]**Bold** type indicates statistical significance ($P < .05$).
[b]*t* for independent *t* test, *Z* for Mann-Whitney U Test (nonparametric test), χ^2 for κ test.
[c]Percentages are of the total sample with that variable.
[d]High-risk family history = having at least 1 first-degree relative with psychosis, low-risk family history = having any family members with mental disorders or a first-degree relative with non-psychotic disorders.
Abbreviations: APSS = attenuated positive symptom syndrome, BIPS = brief intermittent psychotic syndrome, CHRAP+ = at clinical high risk for psychosis and prescribed an antipsychotic, CHRAP– = at clinical high risk for psychosis and not prescribed an antipsychotic, GAF = Global Assessment of Functioning, GRDS = genetic risk and deterioration syndrome, SIPS = Structured Interview for Prodromal Symptoms, SOPSTAL= total score on the Scale of Prodromal Symptoms.

participants initially sought mental health services and had no previous drug treatment for psychiatric disorders. The information regarding antipsychotic prescription was collected from the patients' medical records, which were stored in the hospital's electronic information system. Individuals with CHR were informed that this study is not a treatment study and that it involves naturalistic follow-up with no extra intervention or financial remuneration. They would first visit their own clinicians and follow those clinicians' diagnosis and treatment plan as routine clinical procedure. After that, CHR individuals would complete baseline assessments in this study. Individuals with CHR were placed in the CHRAP+ group (age range, 9–45 years) if they were prescribed an antipsychotic by their clinicians

Figure 1. (A) Proportion of Antipsychotic Drugs in CHR Patients With Prescription and (B) Clinical Symptom Profiles Across Different Types of Antipsychotics



Abbreviation: CHR = clinical high risk (for psychosis).

at baseline, and those without prescription were placed in the CHRAP– group (age range, 11–39 years). It should be noted that antipsychotic prescription is not equal to enduring or continued antipsychotic treatment during the follow-up period. Indeed, among 492 CHRAP+ individuals, 374 (76.0%) were treated with an antipsychotic at follow-up, whereas among 225 CHRAP– individuals, 48 (21.3%) were later treated with an antipsychotic during the follow-up.

Statistical Analysis

Demographic and baseline clinical features are presented separately. Quantitative variables are expressed as mean (SD), while qualitative variables are presented as frequencies (%). The two groups were compared using χ^2 tests for comparisons of categorical variables, rank sum tests for comparisons of individual SIPS item scores, and independent *t* tests for comparisons of continuous variables. In the prescription group, CHR individuals were further grouped by the antipsychotic types. The demographic and clinical characteristics among different antipsychotic prescription groups were compared by 1-way analysis of variance and Fisher least significant difference post hoc test. Binary logistic regression analysis (in the general multivariable model) was used to evaluate the effects of demographic and clinical variables on antipsychotic prescription, and a Hosmer-Lemeshow goodness-of-fit test was performed to assess the calibration of the predictive logistic regression model. The χ^2 statistic was used to test the significance of individual factors in the model. The exploratory factor analysis procedure was performed using the principal components analysis and varimax rotation with Kaiser normalization. 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 antipsychotic prescription using age, sex, education, and estimated factor scores as predictors. Survival analysis (Kaplan-Meier) methods and log rank tests were performed to illustrate the relationship of baseline with or without prescription to either conversion or non-conversion over time. Converters were classified with certainty and non-converters were "censored."

RESULTS

Sample Characteristics

Of the 717 CHR individuals, 492 (68.62%) were prescribed antipsychotics at baseline (CHRAP+ group). Individuals with CHR had younger age and lower education level, were more often female, and were more likely to be prescribed an antipsychotic. Individuals with CHR who met the criteria for BIPS and APSS were more likely to be prescribed an antipsychotic than those met the criteria for GRDS. The scores for Scale of Prodromal Symptoms (SOPS) positive, negative, disorganization, and general symptoms were higher for the CHRAP+ group than for the CHRAP– group at baseline (Table 1).

Frequency and Characteristics of Prescription Drugs

In prescription group, the highest proportion of drugs used was for aripiprazole (n = 152) with mean (SD) dose of 7.06 (2.955) mg, followed by olanzapine (n = 106) with mean (SD) dose of 6.44 (3.181) mg, amisulpride (n = 76) with mean (SD) dose of 218.09 (147.966) mg, and risperidone (n = 64) with mean (SD) dose of 1.79 (0.653) mg (Figure 1A). The clinical symptoms measured by the SOPS subscales (Figure 1B) were compared among patients with different types of antipsychotics. Patients with prescription of aripiprazole seemed to have lower severity level of disorganization and general symptoms than those prescribed olanzapine and amisulpride.

Table 2. Binary Logistic Regression for Predicting Antipsychotic Prescription[a]

Predictor Factor	β	SE	OR	95% CI for OR	Wald Statistic	*P* Value
Overall Regression Model						
Age	0.017	0.014	0.983	0.956–1.011	1.482	.223
Sex	0.249	0.178	0.779	0.550–1.104	1.969	.161
GAF score	0.036	0.022	0.965	0.923–1.008	2.517	.113
GAF drop[b]	0.062	0.016	1.064	1.031–1.098	14.621	**<.001**
Positive symptoms	0.139	0.027	1.149	1.091–1.211	27.419	**<.001**
Negative symptoms	0.038	0.019	0.963	0.927–1.000	3.840	**.050**
Disorganization symptoms	0.018	0.036	1.018	0.949–1.092	0.250	.617
General symptoms	0.036	0.029	1.037	0.979–1.099	1.522	.217
Regression Model for SOPS Items						
P1 unusual thought content	0.099	0.063	1.104	0.976–1.25	2.475	.116
P2 suspiciousness	0.233	0.049	1.262	1.146–1.389	22.604	**<.001**
P3 grandiosity	0.153	0.128	0.858	0.667–1.104	1.418	.234
P4 perceptual abnormalities	0.192	0.044	1.212	1.111–1.322	18.691	**<.001**
P5 disorganized communication	0.105	0.102	0.9	0.738–1.099	1.066	.302
N1 social anhedonia	0.222	0.093	1.248	1.041–1.496	5.733	**.017**
N2 avolition	0.247	0.101	0.781	0.641–0.953	5.937	**.015**
N3 expression of emotion	0.117	0.108	1.124	0.91–1.39	1.179	.278
N4 experience of emotions and self	0.174	0.107	0.84	0.681–1.037	2.621	.105
N5 ideational richness	0.219	0.136	0.804	0.615–1.05	2.576	.108
N6 occupational functioning	0.190	0.075	1.209	1.043–1.401	6.344	**.012**
D1 odd behavior or appearance	0.125	0.101	0.882	0.723–1.076	1.526	.217
D2 bizarre thinking	0.050	0.065	1.051	0.926–1.193	0.589	.443
D3 trouble with focus and attention	0.121	0.098	1.129	0.931–1.369	1.516	.218
D4 impaired personal hygiene	0.134	0.158	1.144	0.839–1.56	0.718	.397
G1 sleep disturbance	0.097	0.08	1.102	0.943–1.289	1.489	.222
G2 dysphoric mood	0.146	0.082	0.864	0.736–1.015	3.166	.075
G3 motor disturbances	0.396	0.189	1.486	1.026–2.152	4.386	**.036**
G4 impaired tolerance to normal stress	0.121	0.078	1.128	0.968–1.315	2.378	.123

[a]**Bold** type indicates statistical significance ($P < .05$).
[b]GAF drop = GAF score decrease from 12 months before current time to current time.
Abbreviations: GAF = Global Assessment of Functioning, OR = odds ratio, SE = standard error, SOPS = Scale of Prodromal Symptoms.

Table 3. Logistic Regression on Demographic and Factorial Variables for Predicting the Prescription of Antipsychotics[a]

Predictor Factor	β	SE	OR	95% CI for OR	Wald Statistic	*P* Value
Age	0.010	0.019	1.010	0.973–1.049	0.276	.599
Sex	−0.243	0.178	0.784	0.553–1.111	1.868	.172
Education	−0.018	0.038	0.982	0.912–1.008	0.221	.638
Factor 1: Negative symptoms	0.217	0.089	1.243	1.043–1.481	5.893	**.015**
Factor 2: Speech and behavior disorganization	−0.213	0.087	0.808	0.682–0.958	6.044	**.014**
Factor 3: General symptoms	0.144	0.086	1.154	0.975–1.366	2.788	.095
Factor 4: Unusual thought symptoms	0.333	0.088	1.395	1.174–1.659	14.255	**<.001**
Factor 5: Distorted cognition and perception symptoms	0.659	0.098	1.933	1.596–2.340	45.555	**<.001**

[a]**Bold** type indicates statistical significance ($P < .05$).
Abbreviations: OR = odds ratio, SE = standard error.

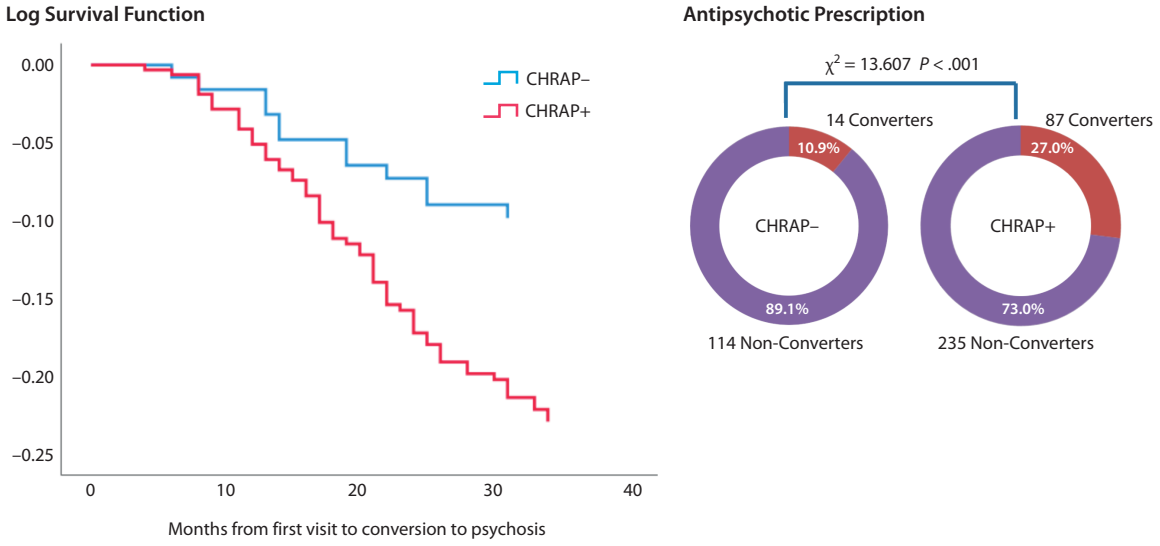
Prediction Analyses

Binary logistic regression analysis was applied to evaluate the effect of demographic and clinical variables on antipsychotic prescription, including age, sex, education, GAF scores, and SOPS subscale scores (ie, scores for positive, negative, disorganization, and general symptoms). The SOPS items were further analyzed in regression analysis. Table 2 shows that the risk factors associated with antipsychotic prescription included GAF drop (ie, decrease in GAF score from 12 months before the present time to the present time), positive symptoms (total score and P2 and P4 scores), negative symptoms (total score and N1, N2, N6 scores), and G3 score of general symptoms; these were found to be significant predictors of antipsychotic prescription.

Exploratory Factor Analysis

To get a more fine grained picture of the dimensional features of prodromal symptomatology[22,23] and uncover its underlying structure, we performed an exploratory factor analysis of the 19 SOPS items, which resulted in 5 factors (Supplementary Appendix 1 and Supplementary Table 1). The first factor, with high loading coefficients for all 6 items of negative symptoms and item 4 (impairment in personal hygiene) of disorganization symptoms, was labeled *negative symptoms*. The second factor, with loading for item

Figure 2. Kaplan-Meyer Survival Curves for Transitions to Psychosis for CHRAP+ Versus CHRAP– Groups and Conversion Rates for Each Group



Abbreviations: CHRAP+ = at clinical high risk for psychosis and prescribed an antipsychotic, CHRAP– = at clinical high risk for psychosis and not prescribed an antipsychotic.

5 (disorganized communication) of positive symptoms, item 5 (ideational richness) of negative symptoms, item 1 (odd behavior of appearance) of disorganization symptoms, and item 1 (motor disturbances) of general symptoms, was labeled *speech and behavior disorganization*. The third factor, with loading for 3 general symptoms (sleep disturbance, dysphoric mood, and impaired tolerance to normal stress), was labeled *general symptoms*. The fourth factor, with loading for item 1 (delusional ideas) of positive symptoms and item 2 (bizarre thinking) of disorganization symptoms, was labeled *unusual thought symptoms*. The fifth factor, with loading for 3 positive symptoms (suspiciousness, grandiose ideas, and hallucinations), was labeled *distorted cognition and perception symptoms*.

Predicting Antipsychotic Prescription With the 5-Factor Model of Prodromal Symptoms

Binary logistic regression analysis was applied to evaluate the effect of demographic and factorial variables on antipsychotic prescription, including age, sex, education, and the aforementioned 5 factors. Table 3 shows that factors 1, 2, 4, and 5 (ie, negative symptoms, speech and behavior disorganization, unusual thought symptoms, and distorted cognition and perception symptoms) were found to be significant predictors of antipsychotic prescription.

Survival Analysis

The Kaplan-Meier survival analysis, applied for 517 CHR individuals (101 converters and 349 non-converters, with 67 having been lost to follow-up), estimated the probability of conversion in CHRAP+ and CHRAP– individuals. The results of statistical testing were $P = .006$ (log rank test, $\chi^2 = 7.569$), $P = .007$ (generalized Wilcoxon test, $\chi^2 = 7.383$), and $P = .006$ (Tarone-Ware test, $\chi^2 = 7.481$) for the comparison between CHRAP+ and CHRAP– individuals. Figure 2 shows that the conversion rate in the CHRAP+ group (87 [27.0%] of 322 were converted) was significantly higher than that in the CHRAP– group (14 [10.9%] of 128 were converted).

DISCUSSION

Summary of Findings

Although available evidence shows that clinicians tend to overprescribe antipsychotics for individuals with CHR,[15] there is relatively little study of the determinants of such prescribing behavior. Using a large-scale clinical cohort sample, we demonstrated a number of important findings. First, antipsychotics were commonly prescribed in routine clinical care. Nearly 2 in 3 CHR individuals were prescribed antipsychotics at their first visits to a mental health service in Shanghai. Second, CHRAP+ individuals were more likely to have serious positive symptoms and impaired general function, although the level of severity was still within the operational thresholds defined by CHR criteria. Third, the risk for conversion to psychosis was higher in CHRAP+ than in CHRAP– individuals at baseline. To our best knowledge, this CHR cohort analysis is the largest of antipsychotic prescription practices and related baseline symptomatic features. Furthermore, this study also included the largest empirical field test confirming that antipsychotic prescription in CHR cohorts is to be considered as a warning flag for higher incipient risk of conversion to psychosis.[24]

Exposure to Antipsychotic Prescription

Antipsychotics, mostly second-generation, were the primary psychiatric treatment for patients with CHR in the present cohort. Consistently, our previous studies[11,25] found that a large proportion of individuals with CHR had

initiation of antipsychotic treatment in the CHR phase. While the preference for antipsychotics as a first-choice treatment has been previously reported in other countries,[26–28] the prescribing rate in this cohort is high by comparison. The main reason antipsychotics were widely prescribed might be that clinicians follow a dimensional approach targeting more prominent psychopathological dimensions, which, in CHR, tend to be positive psychotic symptoms. Most individuals with CHR reported positive psychotic symptoms, although the severity of these symptoms was mild and attenuated. As for the choice of different types of antipsychotics, we found that clinicians preferred to prescribe amisulpride or olanzapine to treat patients with more serious disorganization symptoms. Current results suggested that guidelines issued in the National Institute for Health and Care Excellence (NICE),[29] which specifically do not recommend the early use of antipsychotics in CHR phase, or the Patient Outcome Research Team (PORT) guidelines,[30] which specifically do not recommend olanzapine as an initial choice of agent, do not appear to have had an impact on real-world prescribing patterns. In the current study, we found that CHR individuals with high severity level of disorganized and general symptoms were more likely to be prescribed olanzapine. The sedative effect of olanzapine is prominent in the clinical practice of psychiatry. Clinicians sometimes use olanzapine in the treatment of patients with early psychosis to pursue the short-term or fast clinical effect on disorganization symptoms. However, adolescents are often susceptible to metabolic syndrome[31] associated to olanzapine, and such an adverse effect should be paid special attention to when prescribing antipsychotic in the CHR population. Notably, antipsychotic treatment is not totally excluded from treatment guidelines, and what we propose in the current study is to prescribe antipsychotics more accurately and individually and to use a stricter antipsychotic prescription strategy targeting those CHR individuals with severe positive and general symptoms, but mild negative symptoms.[11]

Demographic Characteristics

Individuals with CHR who were of younger age, female sex, and lower level of education were more represented in the subgroup prescribed antipsychotics. Previous studies[32] have found that those with younger age[33,34] (and fewer educational years accordingly) and female sex[35] were more likely to report psychotic symptoms, which in turn may lead to an increase in the probability of clinicians' prescribing antipsychotics. In addition, we had reported that the younger individuals with CHR had a significantly higher conversion risk than the older ones.[36] Therefore, those early-onset psychotic symptoms in adolescence may be more severe than adult-onset ones, thereby justifying the clinician decision to prescribe antipsychotics. Interestingly, those demographic variables were not significant in the logistic model after adjusting for clinical symptoms and factors, thus implying that the antipsychotic prescriptions were mainly based on the severity of symptoms rather than demographic characteristics themselves. However, the distribution of these clinical features has demographic differences.

Clinical Characteristics and Conversion to Psychosis

Although all the enrolled CHR individuals fall within the established CHR severity thresholds, we found significant quantitative differences in clinical characteristics between CHRAP+ and CHRAP– individuals. Those differences were particularly prominent in positive psychotic symptoms and disorganized symptoms, both of which are associated with increased risk of conversion to psychosis.[23,37] These results support our hypothesis that antipsychotic prescription is a proxy for overall perceived severity. Our results also suggest that previous findings showing that use of an antipsychotic in CHR individuals might lead to higher risk of developing psychosis may be a possible result of confounding by severity or confounding by indication.

The 5 principal components of the SOPS in current exploratory factor analysis closely resemble the 4-factor structure implied by the SOPS itself: positive symptoms, negative symptoms, disorganization symptoms, and general symptoms. This 5-factor solution also consisted mostly of items from a previous study by Tso et al,[38] which yielded 4 latent factors: positive symptoms, distress, negative symptoms, and deteriorated thought process. However, we noted major differences compared with Tso and colleagues' 4-factor structure. In their study, positive symptoms were found to be the most prominent factor explaining the highest proportion (18.7%) of total variance, followed by distress (9.1%), negative symptoms (5.3%), and deteriorated thought process (3.0%) factors. However, our results showed that negative symptoms were the most prominent factor. This was not surprising, given that negative symptoms were always the significant predictor in our previous SHARP studies. Increasing evidence supports negative symptoms as a key characteristic in the CHR population[39,40] and in patients with schizophrenia.[41]

With respect to conversion outcome, consistent with previous studies,[11,15,36] our results confirmed that individuals with CHR who were prescribed antipsychotics at their first visit had higher risk for developing into full psychosis than those who were not. It seems that clinicians correctly perceived a higher imminent risk of transition to psychosis, motivating the prescription of antipsychotics. What is interesting is that the effect is quite robust and has been replicated across different international settings.[24] Considering the high clinical heterogeneity of CHR populations,[42] the rationale for following a precision medicine approach that is tailored to patients' characteristics appears reasonable and feasible for antipsychotic prescription.[43] Therefore, providing systematic and standardized evaluation methods and criteria for guiding antipsychotic prescription in the CHR population should be recommended.

Limitations

The present study is subject to some limitations. First, characteristics of clinicians, such as sex, clinical experiences,

and training background, may affect their prescribing behavior for individuals with CHR. This study lacks a systematic evaluation of the characteristics of the treating clinicians (eg, sociodemographic, experience, and seniority). Second, for intuitive size reasons, the data may not be representative of the entire Chinese population (about 1.41 billion) since recruitment and follow-up were conducted only at a single site. Indeed, although the SMHC is the largest psychiatric service center in China (serving over 800,000 outpatients per year) and provides professional treatment for patients throughout the country, only about half of the current samples were not Shanghai natives. Therefore, even if a single-site design may increase sample homogeneity and continuity, it could also limit the generalizability of the findings. Third, in the exploratory factor analysis, an eigenvalue greater than 1 was applied to decide whether or not to retain a factor. That criterion is rather liberal, which may lead to inclusion of some statistically weak factors that could be nonetheless clinically informative (factor 4: unusual thought symptoms; factor 5: distorted cognition and perception symptoms). By using strict criterion such as the Horn parallel analysis or Velicer minimum average partial test, only 3 factors remained and the factors related to attenuated positive symptoms (factors 4 and 5) were no longer significant. The factors related to attenuated positive symptoms were retained in current study due to these symptoms' having important clinical significance in the identification of CHR individuals. Furthermore, we limited the analysis to antipsychotic prescription with no possibility of ascertaining actual compliance, which may affect the conversion outcome

CONCLUSION

This study confirms the reality of widespread prescription of antipsychotics in CHR individuals. The results indicate that this happens already at the baseline assessment and corroborates emerging reports[11,15,24] indicating that antipsychotic-exposed CHR individuals are a separate subgroup with enhanced imminent risk of transition to psychosis. Therefore, they require more intensive treatment monitoring and support at follow-up. Ultimately, the study demonstrates that antipsychotic prescription in CHR, although formally off-label, is not a random event but reflects the comprehensive psychopathological pattern at presentation. Such a pattern, although categorically fitting CHR criteria, can be better characterized through a dimensional approach.[22] Indeed, it is the dimensional structure of the exhibited psychopathology at baseline (which includes negative symptoms, speech and behavior disorganization, unusual thought symptoms, and distorted cognition and perception as well as drop in functioning) that is associated with the decision by the treating clinicians to prescribe antipsychotics. Besides reiterating the importance of a more sophisticated stratification within CHR individuals, this study opens important pragmatic avenues to improve precision in early treatment choices for CHR.

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Supplementary Material

Article Title: Antipsychotic Exposure in Clinical High Risk of Psychosis: Empirical Insights From a Large Cohort Study

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List of Supplementary Material for the article

1. Appendix 1 Exploratory factor analysis
2. Table 1 Principal components analyses with orthogonal rotation of items from the SIPS (total sample, N=717)

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Supplementary Appendix 1. Exploratory factor analysis

The exploratory factor analysis of 19 SIPS variables of full sample(N=717) resulted in five factors is presented in sTable-1. The Kaiser–Meyer–Olkin index of sampling adequacy was 0.809, indicating that the correlation matrix was suitable for factor analysis. The initial principal components were rotated orthogonally (Varimax with Kaiser Normalization). Five factors had eigenvalues greater than one. The first factor, with an eigenvalue of 4.690 and high loading coefficients (>0.45) for N1, N2, N3, N4, N5, N6 and D4 was labeled 'Factor-1: Negative symptoms'. The second factor, with an eigenvalue of 2.290 and high loading coefficients for P5, N5, D1 and G3 was labeled 'Factor-2: Speech and behavior disorganization'. The third factor, with an eigenvalue of 1.706 and high loading factors for G1, G2 and G4, was labeled 'Factor-3: General symptoms'. The fourth factor, with an eigenvalue of 1.18 and high loading factors for P1 and D2, was labeled 'Factor-4: Unusual thought symptoms'. Finally, the fifth factor, with an eigenvalue of 1.090 and high loading factors for P2, P3 and P4, was labeled 'Factor-5: Distorted cognition and perception symptoms'. One item (D3 Trouble with Focus and Attention) did not load on to any factor with a loading higher than 0.45.

Supplementary Table 1. Principal components analyses

Supplementary Table 1. Principal components analyses with orthogonal rotation of items from the SIPS (total sample, N=717)

Variables	Factor 1	Factor2	Factor3	Factor4	Factor5
P1 unusual thought content	0.023	0.124	0.031	**0.855**	0.053
P2 suspiciousness	0.158	-0.369	0.044	0.057	**0.489**
P3 grandiosity	-0.194	0.353	-0.005	-0.159	**0.542**
P4 perceptual abnormalities	0.033	-0.036	0.012	0.119	**0.610**
P5 disorganized communication	0.132	**0.652**	-0.042	0.144	-0.156
N1 social anhedonia	**0.793**	0.078	0.082	-0.040	0.021
N2 avolition	**0.766**	0.050	0.285	-0.034	0.084
N3 expression of emotion	**0.792**	0.275	-0.046	0.056	0.006
N4 experience of emotions & self	**0.789**	0.256	-0.044	0.055	-0.069
N5 ideational richness	**0.475**	**0.614**	-0.044	0.142	-0.121
N6 occupational functioning	**0.555**	0.054	0.248	0.187	0.286
D1 odd behavior or appearance	0.271	**0.582**	-0.144	0.241	0.181
D2 bizarre thinking	0.057	0.118	0.077	**0.881**	0.075
D3 trouble with focus & attention	0.288	0.165	0.320	0.071	0.439
D4 impaired personal hygiene	**0.482**	0.393	-0.082	0.099	0.175
G1 sleep disturbance	-0.066	0.093	**0.785**	-0.008	0.046

G2 dysphoric mood	0.105	-0.154	**0.800**	-0.023	-0.090
G3 motor disturbances	0.202	**0.609**	0.086	-0.034	0.117
G4 impaired tolerance to normal stress	0.239	-0.109	**0.654**	0.229	0.289