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The treatment characteristics of oral antipsychotics in treatment of adolescents with schizophrenia in China

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Abstract

Background Evidence on treatment for adolescent with schizophrenia in China is limited. Understanding the current practice of antipsychotics utilization is imperative to inform appropriate use in this population.

Methods This retrospective cohort study used electronic medical records (2018–2022) from two hospitals in China. Adolescents (12-17y) with schizophrenia (ICD-10: F20.x) who were prescribed oral antipsychotics during the study period were included. Index date was the date of the first antipsychotics prescription. Patients were followed up until the earliest of last antipsychotics prescription, 18y, or study end. Antipsychotic utilization was described by commonly prescribed antipsychotics, polypharmacy, dosage and medication adherence (indicated by proportion of days covered [PDC]). Dosage was converted using defined daily dose(DDD) for unified measurement.

Results Overall, 869 (mean age: 15.6y, male 50.6%) and 618 (mean age: 16.1y, male 50.7%) patients were included in PKU6H and XJH, respectively. Most patients (99.65% and 100.00%) had ever used second-generation antipsychotics (SGAs), while relatively few (4.14% and 4.21%) had ever used first-generation antipsychotics (FGAs). The top three ever-prescribed SGAs were aripiprazole (50.46%), olanzapine (38.45%), risperidone (34.41%) in PKU6H, and aripiprazole (35.76%), risperidone (28.96%), paliperidone (27.83%) in XJH, 32.34% and 11.49% patients had polypharmacy, respectively. The average daily dose was 0.77(SD 0.40) DDDs and 1.00(SD 0.52) DDDs, respectively, with most (81.59% and 63.27%) ≤ 1 DDD. Medication adherence was both around 0.8 and observed with a steady trend over long-term.

Conclusions In Chinese adolescent patients, SGA is the mainstream mostly prescribed as monotherapy. Polypharmacy is observed with a steady pattern. Antipsychotics were prescribed with equal or reduced dose compared to adults DDD, and good adherence observed.

Clinical trial number Not applicable.

Keywords Antipsychotics, Schizophrenia, Adolescent, China

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Introduction

Schizophrenia affects 24 million people worldwide (2019) and ranks as the 12th most disabling disorder [1, 2]. Early-onset schizophrenia (EOS), variably defined as onset before the age of 17 to 21 years, occurs in fewer than 5% of patients and has been associated with a higher disease burden than adult-onset schizophrenia due to the disruptions that occurs to pubertal development [3–5]. Adolescents with schizophrenia have larger deficits in several cognitive measures such as executive function, memory, and cognitive functioning as compared to those with disease onset in later in life [4, 6]. Thus, early diagnosis and treatment for schizophrenia is particularly important in adolescents, with implications for prognosis during adulthood [3, 7, 8]. Antipsychotics are the cornerstone of treatment for schizophrenia, although nonadherence represents one of the most challenging aspects of schizophrenia management in all age-groups [9–11].

Few guidelines exist for the treatment of EOS, largely because pediatric populations are rarely included in clinical trials during drug development due to ethical challenges [12]. Only limited evidence supports the use of individual antipsychotics in patients with EOS, which lags significantly behind the quality and quantity of evidence in adult populations [13]. Treatment guidelines, when available, highlight the paucity of long-term efficacy and safety data in pediatric populations [14, 15]. Accordingly, much of clinical practice in adolescents with EOS is not evidence-based but extrapolated from adult data [16, 17].

In China, the lifetime prevalence of schizophrenia is approximately 0.6%, affecting around 7 million individuals over their lifetime [18, 19]. As with many other countries, there are currently no established guidelines for the management of EOS, and drug labels often lack information regarding their use in adolescents, and age-appropriate dosage are often missing. Consequently, the treatment of children and adolescents heavily relies on the clinical experience of their physicians, in conjunction with input from patients and their families. To fulfill the unmet medical needs in treatment for pediatric diseases, the Center for Drug Evaluation of China's National Medical Products Association released the *List of Priority Drugs for Pediatric Population* in 2017 to support pediatric drug development in China. Subsequently, several antipsychotics have been approved for use in adolescent populations based on global clinical data, including Paliperidone, Risperidone and Aripiprazole. However, evidence regarding the utilization of antipsychotics in adolescent patients with schizophrenia is limited. Only a few studies have reported on commonly used antipsychotics in this population [20, 21], while evidence on other important aspects, such as dosage, polypharmacy and medication adherence, remains lacking. More research involving Chinese patients will help guide practical utilization in this context.

In light of this, real-world data are critical to understand current drug utilization patterns to inform appropriate use in the future. We used real-world data from two Chinese hospitals to generate insights into the current landscape of antipsychotic utilization and treatment characteristics in adolescents with EOS, aiming to supplement the current knowledge gap and provide additional evidence on the utilization of antipsychotics among Chinese adolescent patients with schizophrenia.

Methods

Data sources

This study utilized electronic medical record (EMR) databases from two major regional mental health institutions in China; Peking University affiliated 6th Hospital (PKU6H) which is a specialized psychiatric hospital, and the Xijing Hospital - the First Affiliated Hospital of Air Force Military Medical University (XJH) psychiatry department. Both hospitals are first-class tier III teaching and research hospitals providing tertiary medical services to patients with mental disorders from all over China. The standardization process and content of the two databases were described in detail in previous published studies [22, 23].

The study was approved by the Institutional Review Boards of PKU6H and XJH. Written informed consent from patients was waived given the de-identification of patient information in the databases.

Study population

Eligible patients had at least one visit record in the hospital database during the study period from 1 January 2018 to 31 December 2022, had a diagnosis code for schizophrenia (ICD10: F20.X) recorded in the study hospital, had received at least one prescription for an oral antipsychotic between 1 January 2018 and 31 December 2022, and were between 12 and 17 years of age on the date of the first antipsychotic prescription (index date). A baseline period of 1 year prior to the index date was used to capture baseline clinical characteristics and comorbidities. Patients were followed up until the last record available, 18 years of age, or the end of study period (31 December 2022), whichever occurred the earliest (Figure S1).

Exposures and outcomes

The primary exposure in this study was the use of oral antipsychotics. A treatment episode was defined as a continuous period of oral antipsychotic usage, consistent with the concept of treatment episode described in previous studies [24, 25]. For analysis, we allowed a gap of up to 60 days between the end of the days of supply

from a previous prescription and the start of the next prescription [26]. All oral antipsychotic prescriptions were included for analysis, and the cumulative treatment duration was calculated as the sum of all treatment episodes during the follow-up period (Figure S2). The study assessed the following treatment characteristics of antipsychotics utilization:

Frequently prescribed antipsychotics and polypharmacy

Frequently prescribed antipsychotics refers to the antipsychotics most commonly prescribed (ever-used) during the study period. Frequency was calculated as the total number of patients who ever-prescribed antipsychotics divided by the total number of patients. Patients prescribed two or more antipsychotics with overlapping treatment for more than 60 days were categorized as receiving polypharmacy [27]. This definition aligns with clinical recommendations that a transition between antipsychotics should typically occur within a maximum of 60 days.

Dosage

Doses of antipsychotics were converted to the defined daily dose (DDD) to offer a unified measurement of the dose prescribed. The DDD is a theoretical unit of measurement produced by WHO, defined as an assumed average maintenance dose per day for a drug used for its main indication in adults [28] and is frequently employed in antipsychotic drug research [29, 30]. The number of DDDs was calculated by dividing the prescribed daily dose by the DDD. For example, the DDD for oral paliperidone is 6 mg daily, and a daily dose of 3 mg coverts to 0.5 DDDs. For antipsychotics without a published DDD (for example, blonanserin), the DDD was defined as the mean value of the minimum and maximum doses specified in the label for maintenance treatment. The raw value of dosage in mg/day is also reported in supplementary material.

Medication adherence

The medication adherence was assessed using the proportion of days covered (PDC), which was calculated as the proportion of non-overlapping days covered by the antipsychotic prescription divided by the treatment duration.

Other variables of interest were demographic characteristics at index, presence of mental health comorbidities and comedications during baseline and follow-up period.

Statistical analysis

The analysis was descriptive. Categorical variables, such as antipsychotic utilization (e.g., first-generation antipsychotics [FGA] versus second-generation antipsychotics [SGA], proportion of ever-users, polypharmacy, and frequent combinations), were described with counts and percentages. Continuous variables, such as dosage (Defined Daily Dose [DDD]) and adherence (Proportion of Days Covered [PDC]), were described with means (standard deviations, SD) and quartiles (25th, median, 75th).

To account for differences in follow-up duration across patients, person-years were calculated as the total duration of follow-up in the study population. Adherence (PDC) was further analyzed by patient subgroups (e.g., patients with polypharmacy, those with at least 30 or 60 days of total treatment duration, and subgroups based on age and sex) to explore variation between demographic groups and treatment characteristics. All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Patient population

In PKU6H and XJH, 869 and 618 eligible adolescent patients who had at least one oral antipsychotics during the study period were included in the analysis (Figure S3), with follow-up of 841.38 person-years and 433.87 person-years respectively. Patients in both hospitals were similar in terms of age (approximately 16 years) and sex distribution (51% male) at the index date (Table 1). Mental health comorbidity was present in 66.63% of patients treated at PKU6H and 59.22% treated at XJH during baseline and follow-up period. The most frequent co-diagnoses were other schizotypal and delusional disorders (81.87%) followed by major depressive disorder (38.51%) at PKU6H, and major depressive disorder (52.19%) and bipolar disorder (47.54%) at XJH. For co-medication, 76.52% at PKU6H and 61.65% at XJH used other mental health comedication, most frequently anti-depressants (63.91% and 77.95%, respectively), and anxiolytics (73.23% and 49.61%, respectively).

During follow-up period, patients at PKU6H had total treatment duration (sum duration of episodes) of 245.31 days (SD 272.99) and patients at XJH had treatment duration of 180.16 days (SD 191.62) (Table 1). Most patients had only one treatment episode (67.32% at PKU6H and 74.11% at XJH), and follow-up characters on episodes is present in Table S1.

Frequently prescribed antipsychotics and polypharmacy

Almost all patients (99.65% at PKU6H and all at XJH) received SGAs during the study period, while only a few patients (around 4% in both hospitals) received FGAs. On average, patients were prescribed 2.04 (SD 1.16) SGAs at PKU6H, and 1.59 (SD 0.87) SGAs at XJH (Table S2), Among the SGAs, the percentage of ever users varied across individual antipsychotics. The most commonly

Table 1 Demographic and clinical characteristics of the study population

	PKU6H *N* = 869	XJH *N* = 618
Age (years)		
Mean ± SD	15.56 ± 1.76	16.06 ± 1.4
Median (Q1–Q3)	15.93 (14.24–17.09)	16.34 (15.19–17.19)
Sex (n, %)		
Male	440 (50.63)	313 (50.65)
Female	429 (49.37)	305 (49.35)
Mental health comorbidity at baseline and follow-up, (n, %)		
No	290 (33.37)	252 (40.78)
Yes	579 (66.63)	366 (59.22)
Other schizotypal and delusional disorder	474 (81.87)	89 (24.32)
Major depressive disorder	223 (38.51)	191 (52.19)
Bipolar disorder	156 (26.94)	174 (47.54)
Seizure disorder	30 (5.18)	6 (1.64)
Attention deficit hyperactivity disorder	43 (7.43)	3 (0.82)
Mental retardation	24 (4.15)	20 (5.46)
Autistic disorder	0 (0.00)	2 (0.55)
Comedication of mental health drug at baseline and follow-up (n, %)		
No	204 (23.48)	237 (38.35)
Yes	665 (76.52)	381 (61.65)
Antidepressants	425 (63.91)	297 (77.95)
Anxiolytics	487 (73.23)	189 (49.61)
Antiepileptics	225 (33.83)	104 (27.30)
Hypnotics and sedatives	88 (13.23)	29 (7.61)
Lithium	17 (2.56)	51 (13.39)
Psychostimulants	19 (2.86)	0 (0.00%)
Treatment duration (total days of episodes) (days)		
Mean ± SD	245.31 ± 272.99	180.16 ± 191.62
Median (Q1–Q3)	147 (49–357)	109 (35–255)

PKU6H, Peking University affiliated 6th Hospital; XJH, Xijing Hospital - the First Affiliated Hospital of Air Force Military Medical University

Table 2 Frequently used antipsychotics and combination of polypharmacy

	PKU6H *N* = 869	XJH *N* = 618
Proportion of antipsychotics used (ever-used) (*n*, %)		
First-generation (FGA)	36 (4.14)	26 (4.21)
Chlorpromazine	2 (5.56)	6 (23.08)
Haloperidol	9 (25.00)	2 (7.69)
Penfluridol	9 (25.00)	0 (0.00)
Perphenazine	5 (13.89)	15 (57.69)
Sulpiride	5 (13.89)	4 (15.38)
Tiapride	10 (27.78)	0 (0.00)
Second-generation (SGA)	866 (99.65)	618 (100.00)
Amisulpride	173 (19.98)	126 (20.39)
Aripiprazole	437 (50.46)	221 (35.76)
Blonanserin	48 (5.54)	0 (0.00)
Clozapine	58 (6.70)	9 (1.46)
Lurasidone	15 (1.73)	28 (4.53)
Olanzapine	333 (38.45)	153 (24.76)
Paliperidone	211 (24.36)	172 (27.83)
Quetiapine fumarate	169 (19.52)	82 (13.27)
Risperidone	298 (34.41)	179 (28.96)
Ziprasidone	22 (2.54)	10 (1.62)
Frequent combinations of polypharmacy (n, %)		
No	588 (67.66)	547 (88.51)
Yes	281 (32.34)	71 (11.49)
Aripiprazole + risperidone	44 (15.66)	15 (21.13)
Amisulpride + olanzapine	40 (14.23)	/
Aripiprazole + paliperidone	39 (13.88)	17 (23.94)
Olanzapine + paliperidone	38 (13.52)	2 (2.82)
Olanzapine + risperidone	37 (13.17)	7 (9.86)
Aripiprazole + amisulpride	/	8 (11.27)
Aripiprazole + olanzapine	/	8 (11.27)

PKU6H, Peking University affiliated 6th Hospital; SD, standard deviation; Q1-Q3, first and third quartiles; XJH, Xijing Hospital - the First Affiliated Hospital of Air Force Military Medical University

prescribed SGAs in both hospitals included aripiprazole (50.46% at PKU6H and 35.76% at XJH), olanzapine (38.45% at PKU6H and 24.76% at XJH), risperidone (34.41% at PKU6H and 28.96% at XJH), and paliperidone (24.36% at PKU6H and 27.83% at XJH), albeit in somewhat different rankings. Among the few patients who received FGAs, the average number prescribed was 1.11 (SD 0.32) at PKU6H and 1.04 (SD 0.20) at XJH. Most patients at PKU6H were prescribed tiapride, haloperidol, and penfluridol, while those at XJH primarily received perphenazine and chlorpromazine (Table 2 and Table S2).

During the treatment duration, antipsychotic polypharmacy was observed in 32.34% of patients at PKU6H and 11.49% at XJH. Among those with polypharmacy, the most frequently prescribed antipsychotic combinations included aripiprazole + risperidone and aripiprazole + paliperidone at both hospitals, along with amisulpride + olanzapine (PKU6H only), and aripiprazole + amisulpride and aripiprazole + olanzapine (XJH only) (Table 2).

Patients experienced an average of 1.25 (SD 0.55) and 1.17 (SD 0.45) times of polypharmacy, with the mean duration of polypharmacy being 265.87 days (SD 249.51) at PKU6H and 212.93 days (SD 174.00) at XJH, representing 67% and 54% of the overall treatment duration for those with polypharmacy at each hospital (Table S3).

When further assessed by mental health comorbidity status, a higher proportion of patients with comorbidities experienced polypharmacy compared to those without,

in both hospitals (PKU6H: 43.70% vs. 9.66%; XJH: 13.39% vs.8.73%) (Table S4).

Antipsychotic dosage

Overall, the mean daily dose of antipsychotics was 0.77 DDDs (SD 0.40) at PKU6H and 1.00 DDDs (SD 0.52) at XJH. During the follow-up period, the mean maximum daily dose was 1.22 DDDs (SD 0.71) at PKU6H and 1.34 DDDs (SD 0.72) at XJH (Table 3). The prescribed daily doses and maximum daily doses of all individual antipsychotics (both FGAs and SGAs) were presented in Fig. 1, with raw dosages calculated in mg/day detailed in Table S5.

In this adolescent population, most patients (81.59% in PKU6H and 63.27% in XJH) received doses of ≤1 DDD, with the majority falling under 1 DDD. Approximately 20–30% of patients were prescribed doses higher than 1 DDD, and the percentages of patients receiving doses > 1.5 DDDs did not exceed 5% at PKU6H and 15% at XJH (Table 3). For individual antipsychotics, the mean daily doses for most drugs were below 1 DDD, except for penfluridol at PKU6H. At XJH, the mean daily doses of four drugs (ziprasidone, amisulpride, lurasidone and olanzapine) exceeded 1 DDD while the doses for the other medications remained below 1 DDD (Fig. 1).

Medication adherence

Over the treatment duration, the mean PDC was 0.82 (SD 0.17) at PKU6H and 0.84 (SD 0.19) at XJH. The percentage of patients with PDC greater than 0.80 was 56.96% and 65.53%, respectively (Table 4). Patients had polypharmacy of antipsychotics also demonstrated a similar PDC of around 0.80, at both hospitals. Among patients treated for at least 30 or 60 days, the PDC decreased slightly but remained above 0.75, indicating a steady trend over longer terms (Table 4). Subgroup analyses shown in Table S6 reveal similar results across different sex (male vs. female) and age groups (< 15 years vs. >=15 years).

Table 3 Antipsychotic doses prescribed during the treatment duration as a function of defined daily dose (DDD)

	PKU6H *N* = 869	XJH *N* = 618
Dailly dose in DDDs		
Mean ± SD	0.77 ± 0.40	1.00 ± 0.52
Median (Q1–Q3)	0.69 (0.50–0.95)	0.98 (0.60–1.25)
% of DDDs (n, %)		
< 1	668 (76.87)	313 (50.65)
= 1	41 (4.72)	78 (12.62)
> 1 to ≤ 1.5	117 (13.46)	138 (22.33)
> 1.5	43 (4.95)	89 (14.40)
Maximum daily dose in DDDs		
Mean ± SD	1.22 ± 0.71	1.34 ± 0.72
Median (Q1–Q3)	1.00 (0.67-2.00)	1.20 (0.80-2.00)

DDD defined daily dose; PKU6H, Peking University affiliated 6th Hospital; SD, standard deviation; Q1-Q3, first and third quartiles; XJH, Xijing Hospital - the First Affiliated Hospital of Air Force Military Medical University

Discussion

This real-world study demonstrated antipsychotic drug utilization patterns and treatment characteristics in nearly 1,500 adolescents with schizophrenia treated in two major hospitals in China. Our findings indicate that SGAs constituted the majority of antipsychotics use, with commonly prescribed medications including aripiprazole, olanzapine, risperidone, and paliperidone. Antipsychotic monotherapy predominated over polypharmacy, although the latter was observed consistently. The doses of antipsychotics were generally comparable to or below 1 DDD, and treatment adherence was good, with proportion of days covered during treatment exceeding 75% in current practice.

Our results indicate that SGAs were overwhelmingly preferred over FGAs in the treatment of adolescents with schizophrenia. These findings are consistent with prior studies in pediatric populations. For instance, Zhang et al. conducted a study including over 700 pediatrics with schizophrenia from China and reported that 99.3% of EOS patients were prescribed SGAs, with only 5.5% receiving FGAs [20]. Other studies [31–33] on antipsychotics utilization in Chinese pediatric populations have similarly highlighted the increasing dominance of SGAs over FGAs in the use of antipsychotics in a broader sense, despite the limited evidence in this age group. Our study further confirmed this trend using data from two major hospitals. The observed preference for SGAs may be attributable to their improved side-effect profile, particularly the reduced risk of extrapyramidal symptoms compared to FGAs [34–36]. This safety advantage is particularly relevant for pediatric patients, who are at a critical stage of psychological and neuronal development. Adolescents with schizophrenia often require treatments that minimize adverse effects while addressing the fluctuating severity of their condition. Therefore, the safety profile of antipsychotics remains a key consideration in treatment strategies for this vulnerable population.

Further, the ranking of the most frequently prescribed SGAs in pediatrics has varied across different studies, but common SGAs include aripiprazole, risperidone, paliperidone, quetiapine and olanzapine [20, 31, 33]. Our findings are generally consistent with the existing literature that the top 5 commonly used SGAs at both hospitals are mostly overlapped with these reported drugs. However, the individual antipsychotics commonly used in adolescents differ somewhat from those prescribed to adults. According to a recent national survey from China, the most frequently prescribed SGAs in adults are risperidone (35.1%), olanzapine (31.3%), clozapine (24.6%), and aripiprazole (16.9%) [37]. In comparison, while

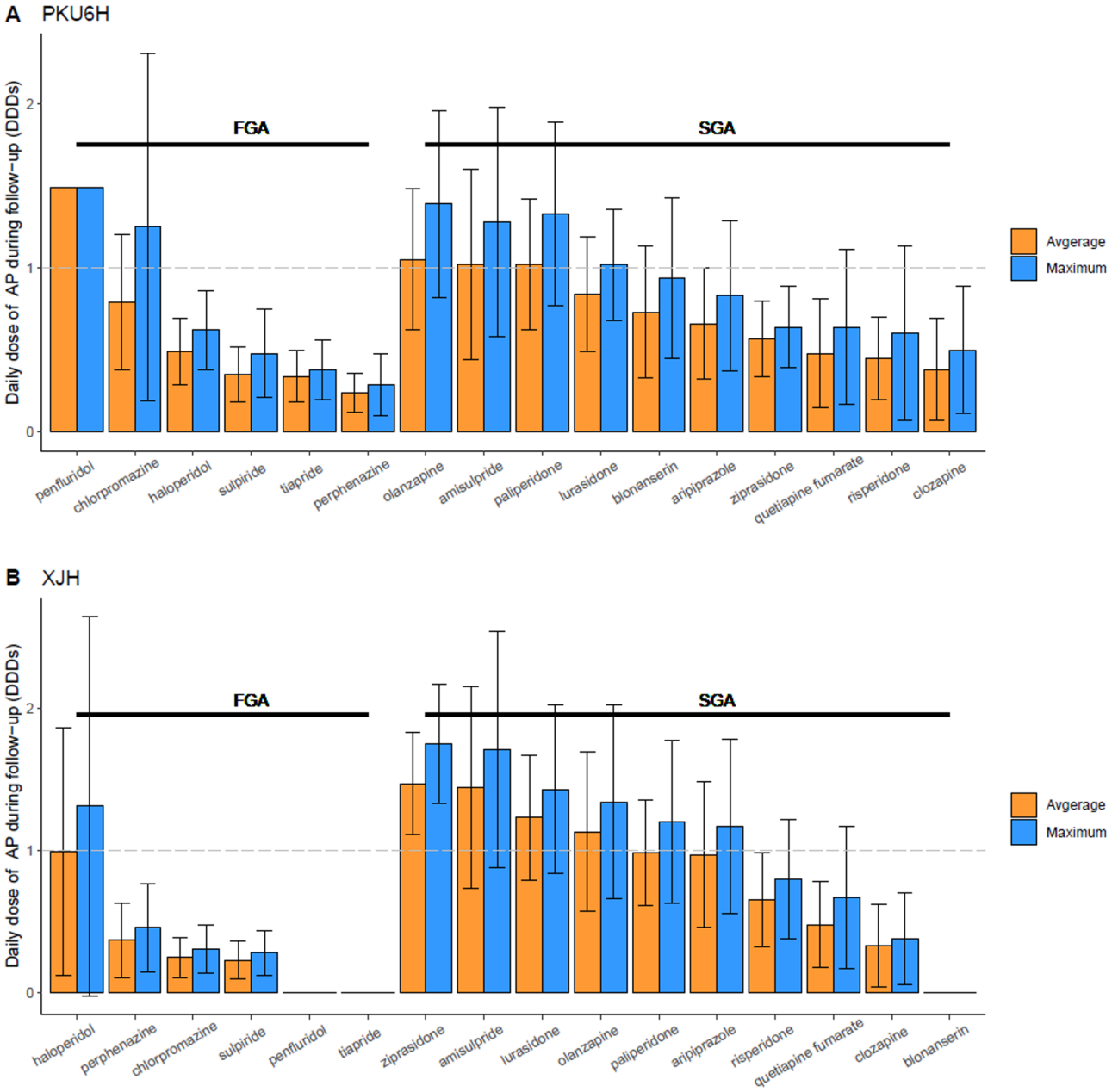

Fig. 1 Dosage of individual antipsychotics in DDD FGA, first-generation antipsychotic; PKU6H, Peking University affiliated 6th Hospital; SGA, second-generation antipsychotic; XJH, Xijing Hospital - the First Affiliated Hospital of Air Force Military Medical University. Data are provided in Table S5. Note: the mean dose of penfluridol in PKU6H is truncated at 1.5 DDDs

risperidone and olanzapine were commonly prescribed in both adolescents and adults, our results also indicated that the use of aripiprazole (35.8% in PKU6H and 50.5% in XJH versus 16.9% in the national survey) and paliperidone (24.4% and 27.8% versus 2.4%) were substantially higher in adolescents, and the use of clozapine (6.7% and 1.5% versus 24.6%) was substantially lower. Such difference could likely be attributed to the indication approval that paliperidone, aripiprazole and risperidone are the first three antipsychotics approved for treatment in adolescents in the Chinese context. This potentially highlights the impact of regulatory frameworks on prescribing trends in this vulnerable age group. Besides, clozapine is usually used for treatment-refractory schizophrenia due to its superior efficacy relative to other antipsychotics in adults, it is seldomly used in pediatric population largely due to lack of clarity on its benefit in this population and no solid evidence established so far [38].

On the other hand, in this study, we observed that most patients remained on monotherapy throughout

Table 4 Medication adherence (PDC) of antipsychotics during treatment duration

	PKU6H	XJH
Medication adherence (PDC) over the treatment duration		
N	869	618
Mean ± SD	0.82 ± 0.17	0.84 ± 0.19
Median (Q1–Q3)	0.85 (0.71–1)	0.92 (0.73–1)
PDC > 0.80 (n, %)	495 (56.96)	405 (65.53)
Medication adherence (PDC) in patients had polypharmacy		
N	281	71
Mean ± SD	0.78 ± 0.12	0.81 ± 0.11
Median (Q1–Q3)	0.79 (0.71–0.87)	0.81 (0.72–0.90)
PDC > 0.80 (n, %)	126 (44.84)	40 (56.34)
Medication adherence (PDC) in patients had at least 30 days of treatment duration		
N	709	509
Mean ± SD	0.78 ± 0.17	0.81 ± 0.19
Median (Q1–Q3)	0.79 (0.68–0.92)	0.84 (0.70-1.00)
PDC > 0.80 (n, %)	336 (47.39)	297 (58.35)
Medication adherence (PDC) in patients had at least 60 days of treatment duration		
N	616	386
Mean ± SD	0.76 ± 0.16	0.76 ± 0.19
Median (Q1–Q3)	0.77 (0.66–0.87)	0.78 (0.66–0.90)
PDC > 0.80 (n, %)	251 (40.75%)	178 (46.11)

PDC, proportion of days covered; PKU6H, Peking University affiliated 6th Hospital; SD, standard deviation; Q1-Q3, first and third quartiles; XJH, Xijing Hospital - the First Affiliated Hospital of Air Force Military Medical University

the treatment duration, consistent with previous studies reporting that 50–80% of patients with EOS were on antipsychotic monotherapy [20, 31]. This finding reiterates the general preference for monotherapy in managing EOS, aligning with adult schizophrenia treatment guidelines that recommend it as the standard approach [39]. However, younger age has been identified as a potential risk factor for polypharmacy [40, 41], and our findings show that antipsychotic polypharmacy was more prevalent among patients with comorbid mental health disorders. While the intent may be to optimize symptoms, the routine use of multiple antipsychotics raises concerns about increased risks of adverse effects, nonadherence, and higher treatment cost [42]. These risks, couples with the limited clarity on clinical evidence, underscore the need for evidence-based guidance on polypharmacy in this vulnerable population.

In addition to antipsychotic polypharmacy, we also observed a high prevalence of mental health comorbidity (including major depressive disorder, bipolar disorder as well as other schizotypal and delusional disorder as the most frequently observed comorbidities) during baseline and follow-up. Correspondingly, there was a notable prevalence of comedications (including antidepressants, anxiolytics and antiepileptics emerged as the most frequently prescribed alongside with antipsychotics), reflecting the complex pharmacological needs of adolescent patients with schizophrenia. These findings are consistent with the observations that this vulnerable population often experience various psychotics symptoms and frequently present with comorbid mental health disorders [43]. This dynamic nature of the illness course makes the treatment of schizophrenia in adolescence more complex and particularly challenging, which further underscores the importance of carefully evaluating the necessity, safety and effectiveness of co-medications in the management of comorbidities in young patients with schizophrenia [44].

While much of the existing research has emphasized commonly prescribed antipsychotics and the prevalence of polypharmacy, other important aspects of antipsychotic utilization remain underexplored. Our findings contribute to this gap by demonstrating that the prescribed doses for adolescents were generally equal to or less than the DDD for adults, and over half are less than 1 DDD. In the national survey comprised mostly of adults, 17.2% patients received doses defined as "high" (defined as ≥ 600 mg chlorpromazine equivalent which equates to ≥ 2 DDDs), whereas doses more than 1.5 DDDs were only prescribed for about 5% at PKU6H, and for 14.4% at XJH [37]. Moreover, the mean chlorpromazine equivalent dose was about 450 mg/day (or 1.5 DDDs) while in our study, the mean doses of antipsychotics prescribed was 0.77- 1 DDD at two hospitals. This suggests that clinicians may be more cautious and have different strategy for dosage in their prescribing practices for this population.

Another notable contribution of our study lies in adherence patterns. In our study, adherence in adolescent patients was notably high, with approximately 60% of patients achieving a PDC over 80%, which is a widely accepted benchmark for good adherence [45, 46]. It is widely accepted that treatment adherence is crucial in the management of schizophrenia, as it significantly affects treatment outcomes and impact patients' prognosis and functional recovery. Poor medication adherence has been associated with increased rates of relapse, hospitalization, and overall worsened prognosis [39, 47]. Furthermore, patients on polypharmacy also demonstrated good adherence, maintaining a consistent long-term pattern. Notably, the PDC remained stable when patients with short treatment duration were excluded. Our findings are among the few to document treatment adherence in

adolescents, this contrasts with studies in adults showing that polypharmacy is often associated with poor adherence. The finding is particularly evident when compare to a previous study under similar settings [48], which reports a considerably lower adherence to oral antipsychotics among adult patient with schizophrenia, suggesting that specific family or clinical dynamics may support adherence in this younger population. Our results are encouraging, but more studies are needed to validate our findings.

Potential limitations of this study include those that apply to all prescription-based drug utilization studies where it is assumed that the medication dispensed was consumed as prescribed. Patients who received healthcare in settings other than the two hospitals were not captured. This limitation may lead to over- or underestimation of adherence for those who stopped and resumed treatment or seek care elsewhere, which cannot be reliably identified based on available data. The study follow-up was therefore designed to stop upon the last known prescription, however, this approach may not capture longer-term adherence and medication-taking behavior beyond this period. Additionally, the PDC method employed, while a common proxy for adherence in real-world studies, may not fully capture actual medication-taking behavior, dose adjustments, or early discontinuation, the PDC findings should be interpreted in this context. On the other hand, the reasons underlying clinical decision-making including choice of antipsychotic and rationale for dose selection and modification were not recorded. This restricts our ability to evaluate the appropriateness of prescriptions, their safety, as well as effectiveness implication. To achieve a fuller spectrum of understanding, future studies should prioritize these key areas for this vulnerable population, where evidence remains significantly behind that available for adults. The DDD method for comparing doses is widely applied and enables the comparison of results across different studies from different regions under a unified measurement [49]. However, DDDs are normally assigned based on use in adults and DDDs are not currently available for pediatrics [50]. In this study, we applied DDD conversion to create a standardized reference for assessing antipsychotic doses in the pediatric population, allowing for reasonable comparisons with recommended adult practices. However, it is important to acknowledge the potential bias involved, we also provide the original values without DDD conversion for further context. Moreover, in clinical practice, doses vary widely based on individual needs and responses, rather than conforming to a single DDD value. This limitation should be considered when interpreting our study's comparisons. Lastly, our study focuses solely on adolescent patients, primarily because most antipsychotic drugs approved for pediatric use are indicated for adolescents, with limited evidence available for younger children. As treatment in children is often more complex, our findings may not fully capture the nuances of antipsychotic use in the broader pediatric population. Future studies are needed to explore treatment strategies in younger children to better understand the challenges and potential differences in this age group.

Overall, our study contributes to the limited body of evidence on antipsychotic utilization in adolescents with schizophrenia, providing valuable insights into current landscape of antipsychotic utilization pattern in practice. Our findings demonstrated the treatment characteristics in adolescents and indicated that adolescent treatment practices may exhibit unique features when compared to adults. Key aspects include their choices of antipsychotics, the prevalence of polypharmacy, dosing approaches, and medication adherence. These peculiarities help to contextualize treatment practices in the absence of pediatric-specific schizophrenia guidelines. Given these insights, future research is crucial for developing specialized treatment guidelines and optimizing treatment strategies for this vulnerable population. By addressing these needs, treatment outcomes can be improved and the quality of care for adolescents with schizophrenia can be enhanced.

Supplementary Information

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Supplementary Material 1

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Author contributions

HW and YZ: Conceptualization, Methodology, Writing- Original Draft TW: Conceptualization, Interpretation, Formal Analysis, Validation. SD: Methodology, Investigation, Formal Analysis, Visualization, Writing– Review & Editing. RC and KJ: Resources, Data curation. HQ: Conceptualization, Methodology, Writing– Review & Editing, Supervision, Project administration. HQ and WD: Methodology, Validation, Data curation, Resources. TS: Conceptualization, Writing– Review & Editing, Supervision. All authors contributed to editing and commenting on the final manuscript.

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Data availability

The original contributions presented in th estudy are included in the article/supplementary material, further inquires can be directed to the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Yongjing Zhang, Tao Wu, Sijia Dong, and Hong Qiu are employees of Johnson and Johnson. Yongjing Zhang and Hong Qiu report stock ownership in Johnson and Johnson. Other authors declared no conflicts of interest to this work.

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