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ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Methylphenidate and Atomoxetine in Medication-Naive Children with Attention-Deficit Hyperactivity Disorder in a Real-World Setting

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Abstract

Background and Objective Methylphenidate (MPH) and atomoxetine (ATX) are the most common medications used to treat attention-deficit hyperactivity disorder (ADHD) in China; however, despite this, there is still a paucity of studies comparing their efficacy and safety, particularly for different characteristics. To address the lack of research, a real-world prospective cohort study was conducted to examine these properties of MPH and ATX, and to analyze correlations associated with age, sex, and different ADHD presentation.

Methods Children with ADHD meeting the eligibility criteria were recruited from January 2016 to July 2021. Study participants were treated with either MPH or ATX prescribed in the real-world setting, and were followed up for 26 weeks. Clinical efficacy response and adverse events (AEs) were recorded and measured. Subgroup analysis was performed to examine the efficacy response and AEs associated with age, sex, and different ADHD presentation.

Results A total of 1050 children were recruited and 29 children were lost to follow-up. Of the 1021 children remaining, 533 were treated with MPH and 488 were treated with ATX. No significant differences were found in intelligence quotient, age, sex, or ADHD presentation between the MPH- and ATX-treated groups ($p > 0.05$). The response rates were 84.6% in the MPH-treated group and 63.3% in the ATX-treated group. Subgroup analysis of response rate demonstrated that the treatment effect of MPH over ATX was consistent across subgroups except in the girls (odds ratio [OR] 2.09, 95% confidence interval [CI] 0.97–4.7) and the hyperactive/impulsive presentation group (OR 2.88, 95% CI 0.77–12.76). A total of 47.8% of children experienced AEs during MPH treatment, significantly lower than the rate of 56.8% during ATX treatment ($p < 0.05$). The incidence of AEs in the MPH-treated group was higher in young children (<8 years: 56.8%; 8–10 years: 47.2%) and lower in children over 10 years of age (29.0%).

Conclusions Overall, MPH was more effective and better tolerated than ATX. The incidence of AEs in children treated with MPH varied with age, and was higher in young children and lower in children over 10 years of age.

Key Summary Points

This study allows for an understanding of differences in response rates and adverse events (AEs) of methylphenidate (MPH) and atomoxetine (ATX) in a real-world clinical context.

Overall, MPH was found to be more effective and better tolerated than ATX.

The rate of AEs during MPH treatment was higher in young children and lower in those over 10 years of age.

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1 Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattention, hyperactivity/impulsivity, or both. Symptoms of ADHD typically first occur in childhood and most children with ADHD will continue to experience symptoms throughout adolescence and sometimes even into adulthood [1]. ADHD often impacts many aspects of an individual's well-being, including physical health, emotional development, and academic, social, and occupational performance. Meta-analysis found the worldwide ADHD prevalence to be 7.2% [2]. In 2022, a prevalence of ADHD among Chinese children and adolescents aged 6–16 years was reported as 6.4% in a large sample study [3].

Treatment for patients with ADHD can either be pharmacological, non-pharmacological, or both. Pharmacological treatments have been proven to be effective, and a number of medications are available, recommended, and widely used [4–6]. Medications for ADHD are categorized into stimulants and non-stimulants. Stimulants include methylphenidate (MPH) and amphetamine products, while non-stimulant medications include the norepinephrine transporter inhibitor atomoxetine (ATX) and the α2 agonists guanfacine and clonidine. Although international guidelines vary in their recommendations for the treatment of ADHD, there is a general consensus that first-line pharmacologic treatment has typically involved the use of stimulants [5]. According to the National Institute for Health and Care Excellence (NICE) guidelines [7], pharmacological therapy should begin with MPH for children older than 5 years of age and be switched to amphetamine with inadequate response. NICE also suggests that if the response to amphetamine is also poor, the patient should be switched to ATX or guanfacine [7]. In contrast to NICE guidelines, the Chinese official guidelines list MPH and ATX as the first-line drugs in the treatment of ADHD, and these have become the most prescribed psychotropic medications for ADHD [8, 9]. Although MPH experienced a downward trend in popularity in the past decade, it is still more frequently prescribed than ATX in clinical practice [9].

MPH acts as a dopamine-norepinephrine reuptake inhibitor, modulating the patient's dopamine levels and, to a lesser extent, norepinephrine levels. ATX is classified as a norepinephrine reuptake inhibitor, which increases extracellular synaptic levels of norepinephrine and dopamine by obstructing norepinephrine presynaptic reuptake [5]. The benefits, tolerability, and safety of the two ADHD medications are of significant concern to clinicians, patients, and their families. Although a large number of studies and meta-analyses have confirmed the effectiveness of both medications, inconsistencies were found in their response rates and safety profiles, and there is wide variability between studies [6, 10–15]. The most common adverse events (AEs) of MPH include decreased appetite, insomnia, abdominal pain, and headaches [16–18]. ATX has a longer list of AEs, including decreased appetite, headaches, somnolence, abdominal pain, nausea, vomiting, constipation, dizziness, irritability, and mood swings [8, 16, 19, 20]. We do not yet have a sufficient understanding of the neurobiology of ADHD to accurately inform medication choice. Currently, medications are selected on a trial-and-error basis, meaning that if one medication does not work well, it is replaced with another medication [5]. It is important for clinicians and patients to facilitate risk assessments in clinical practice to more accurately estimate the frequency of known medication adverse effects and efficacy. Despite the fact that MPH and ATX are the most common medications used to treat ADHD in China, there is still a paucity of studies comparing their efficacy and safety, particularly for different subgroups.

To address these issues, we conducted a real-world, head-to-head, prospective cohort study to examine the efficacy and safety of MPH and ATX in previously medication-naive children with ADHD, and to analyze correlations associated with age, sex, and different ADHD presentation.

2 Methods

2.1 Participants

The present study was conducted at the Children's Hospital of Fudan University (CHFU), a National Children's Medical Center for patients with ADHD and other neurodevelopmental disorders. The study was approved by the Ethical Committee of CHFU. All participants were recruited at the Child Healthcare and Developmental-Behavioral Clinic of CHFU from 1 January 2016 to 31 July 2021. A diagnosis of ADHD was based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Inclusion criteria included (1) patients aged 6–14 years and ethnically Chinese Han; (2) patients were ADHD medication treatment-naive prior to participation in the study; and (3) medication treatments had been deemed necessary by a clinical specialist and had been approved by the children's parents. 'Necessary' means that the effect of behavioral training or environmental adjustment is not obvious, and the symptoms greatly affect learning and daily functioning, thus requiring medication in accordance with the guidelines for managing ADHD.

To analyze correlations associated with sex, age, and ADHD presentations, we categorized participants into

different subgroups: two gender groups, i.e. boys and girls; three age groups, i.e. early school age (< 8 years), middle school age (8–10 years), and late school age (≥ 10 years); and three ADHD presentations according to the DSM-5 diagnostic criteria: (1) primarily hyperactive/impulsive presentation: patients have six or more hyperactive/impulsive symptoms and five or fewer inattentive symptoms; (2) primarily inattentive presentation: patients have six or more inattentive symptoms and five or fewer hyperactive/impulsive symptoms; and (3) combined presentation: patients have six or more inattentive and hyperactive/impulsive symptoms.

2.2 Treatment and Follow-Up Procedure

All participants were treated with either osmotic release oral system MPH (OROS MPH, Concerta) or ATX (Strattera) in a real-world setting without any intervention from the study team. Prescriptions were dispensed by a clinical specialist, mainly based on a patient's clinical symptoms, the urgency of treatment, parents' and patients' preference, and compliance. Once the participants had been recruited, they were followed up for 6 months—twice monthly for the first 2 months and then once monthly for the remaining 4 months. The OROS MPH formulation is an extended-release formulation of MPH that has an active duration of approximately 12 h after administration [21]. Two forms of OROS MPH tablets are available—Concerta 18 mg and Concerta 36 mg. Patients were prescribed a starting dose of 18 mg/day; however, if this dosage was found to be ineffective after 2–3 weeks of treatment, it was increased to 36 mg/day. In the event that a dosage of 18 or 36 mg/day proved effective, the subjects' treatment was continued during the follow-up period. For some older children, the dosage may increase to 54 mg/day due to weight gain over the long-term follow-up period. Meanwhile, ATX was initiated at a total daily dose of 0.5 mg/kg during the first 2 weeks, followed by 0.8–1.0 mg/kg around week 3, and then titrated to a maximum dose of 1.2–1.4 mg/kg.

2.3 Clinical Assessments

Each participant's intelligence quotient (IQ) was evaluated using the Wechsler Intelligence Scale for Children-Revised (WISC-R) at baseline. Clinical laboratory assessments, which included renal and hepatic function, electrolytes, cholesterol, complete blood count, and electrocardiography (12-lead), were carried out at the beginning of the study and after approximately 26 weeks. A simple clinical questionnaire was developed to investigate the efficacy and safety of the two drugs. Parents completed the questionnaire and confirmed that the completed information was correct. The 'response' was defined as the core symptoms of ADHD (inattention, hyperactivity, and impulsivity) being significantly improved because of medication in both the school and home settings. If symptoms had not improved after 6 weeks of medication, this was considered as no response. Treatment-related AEs were proactively and comprehensively recorded throughout.

2.4 Statistical Analyses

The statistical software R version 4.2.0 for Windows was used to perform data analysis. Descriptive analyses were performed for continuous measurements such as age (mean ± SD [X±S]), and categorical variables were presented as numbers and percentages. Independent sample *t*-tests were used to compare the mean values, and proportions were compared between groups using the Chi-square test. The R Stats Package 'stats' version 4.2.0 was employed to calculate the odds ratios (ORs) and 95% confidence interval (CIs). *P*-values <0.05 were considered statistically significant for all tests.

3 Results

3.1 Participant Characteristics

A total of 1050 children were recruited from 1 January 2016 to 31 July 2021. After receiving medication treatment over the first half of the month, 29 participants were lost to follow up and could not be contacted. Of the 1021 children remaining, a total of 533 were treated with MPH (465 boys and 68 girls) and 488 were treated with ATX (416 boys and 72 girls). No significant differences were found in IQ, age, sex, or ADHD presentation between the MPH-treated group and the ATX-treated group at baseline (all *p*-values >0.05) (Table 1).

3.2 Efficacy of Methylphenidate and Atomoxetine

Of the 533 children who received MPH treatment, 451 (84.6%) responded, from the 6-week measurement period until the end of follow-up, of whom 338 (74.9%) children were administered a dose of 18 mg, while 113 (25.1%) children were administered a dose of 36 mg. On average, these children received a dose of 22.5 mg. According to their parents' reports, these children had a marked improvement in the clinical symptoms of ADHD during treatment. In addition, 76 (14.2%) children did not respond to treatment and 6 (1.1%) children discontinued treatment due to AEs; efficacy for the children who discontinued treatment was unknown owing to the short treatment duration. A total of 309 children responded to ATX treatment, from the 6-week measurement period until the end of follow-up. The response rate in the ATX-treated group was 63.3% (309/488), which was significantly lower than that in the MPH-treated group (63.3%

Table 1 Demographic and baseline characteristics of the methylphenidate and atomoxetine groups

	Methylphenidate [$n = 533$]	Atomoxetine [$n = 488$]	t/Chi-square	p-value
Age at the start of medication, years	8.6 ± 1.66	8.4 ± 1.47	1.705	0.0885
Intelligence quotient	86.6 ± 20.67	84.8 ± 18.90	1.4516	0.1469
Sex			0.6975	0.4036
Male	465 (87.2)	416 (85.2)		
Female	68 (12.8)	72 (14.8)		
Age, years			3.332	0.189
< 8	222 (41.7)	215 (44.1)		
8–10	218 (40.9)	208 (42.6)		
≥ 10	93 (17.4)	65 (13.3)		
ADHD presentation			1.4765	0.478
Combined	265 (49.7)	226 (46.3)		
Inattentive	246 (46.2)	237 (48.6)		
Hyperactive/impulsive	22 (4.1)	25 (5.1)		

Data are expressed as *n* (%) unless otherwise specified

ADHD attention-deficit hyperactivity disorder

vs. 84.6%; $p < 0.05$). In the ATX-treated group, a total of 163 (33.4%) children did not respond to treatment, and 16 (3.3%) children discontinued treatment due to AEs with an unknown efficacy (Fig. 1).

3.3 Subgroup Analysis of Efficacy

3.3.1 Sex

In boys, the response rate was 85.2% (396/465) for children treated with MPH and 62.7% (261/416) for children treated with ATX. It can be observed that in boys, the response rate for MPH treatment was higher than that for ATX treatment ($p < 0.01$). Regarding girls, the response rate was 80.9% (55/68) for children treated with MPH and 66.7% (48/72) for children treated with ATX; however, no significant difference was observed ($p = 0.06$) (Table 2).

3.3.2 Age

For children age <8 years, the response rate was 83.3% (185/222) in children treated with MPH and 60.9% (131/215) in children treated with ATX. For children aged 8–10 years, the response rate was 85.8% (187/218) in children treated with MPH and 65.4% (136/208) in children treated with ATX, and for children age ≥10 years, the response rate was

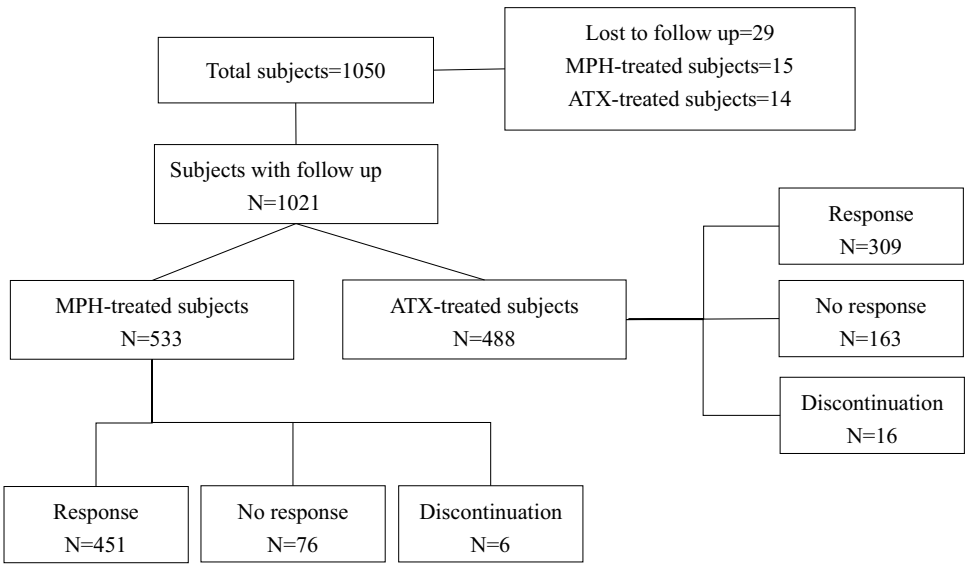

Fig. 1 Flow diagram of enrollment and the response to treatment

Table 2 Results of response rates in subgroup subjects treated with methylphenidate and atomoxetine

	Methylphenidate [% (*n/N*)]	Atomoxetine [% (*n/N*)]	OR (95% CI)	*p*-Value
Sex				
Male	85.2 (396/465)	62.7 (261/416)	3.40 (2.47–4.72)	< 0.01
Female	80.9 (55/68)	66.7 (48/72)	2.09 (0.97–4.70)	0.060
Age, years				
< 8	83.3 (185/222)	60.9 (131/215)	3.19 (2.05–5.04)	< 0.01
8–10	85.8 (187/218)	65.4 (136/208)	3.18 (1.99–5.17)	< 0.01
≥ 10	84.9 (79/93)	64.6 (42/65)	3.06 (1.43–6.72)	< 0.01
ADHD presentation				
Combined	85.3 (226/265)	64.6 (146/226)	2.87 (1.88–4.42)	< 0.01
Inattentive	84.1 (207/246)	62.4 (148/237)	3.18 (2.08–4.94)	< 0.01
Hyperactive/impulsive	81.8 (18/22)	60.0 (15/25)	2.88 (0.77–12.76)	0.118

OR odds ratio, *CI* confidence interval, *ADHD* attention-deficit hyperactivity disorder

84.9% (79/93) and 64.6% (42/65), respectively. The response rates in the MPH-treated group were significantly higher than that in the ATX-treated group ($p < 0.05$) (Table 2).

3.3.3 Attention-Deficit Hyperactivity Disorder (ADHD) Presentation

For combined presentation children, the response rate was 85.3% (226/265) in children treated with MPH and 64.6% (146/226) in children treated with ATX. For inattentive presentation children, the response rate was 84.1% (207/246) in children treated with MPH and 62.4% (148/237) in children treated with ATX, and for hyperactive/impulsive presentation children, the response rate was 81.8% (18/22) and 60.0% (15/25), respectively. Among the three presentations, there was no statistically significant difference in the response rate between the two drugs for hyperactive/impulsive presentation (Table 2).

Overall, subgroup analysis by sex, age and ADHD presentations demonstrated that the treatment effect of MPH

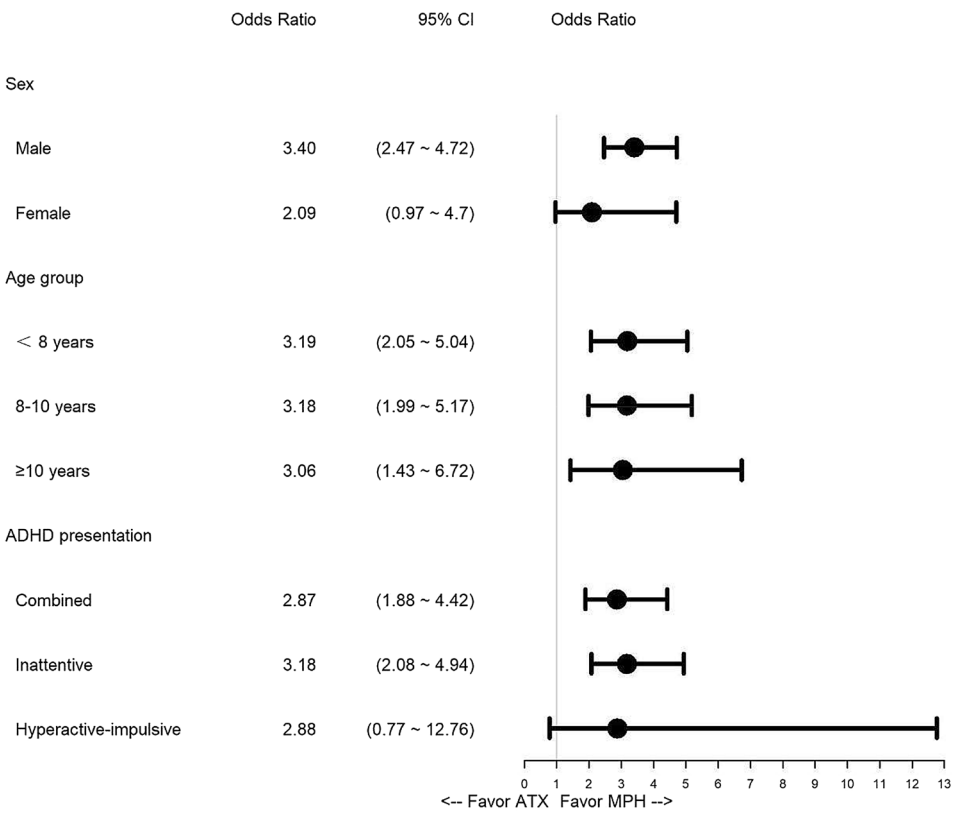

Fig. 2 Forest plots of response rate by sex, age and ADHD subtype

over ATX was consistent across subgroups except in girls (OR 2.09, 95% CI 0.97–4.7) and the hyperactive/impulsive presentation group (OR 2.88, 95% CI 0.77–12.76) (Fig. 2). However, the sample size of the girls and children with hyperactive/impulsive presentation was significantly smaller compared with the other subgroups, which may result in a larger variance in the statistical results and thus may not reach a statistically significant level.

3.4 Adverse Events of Methylphenidate and Atomoxetine

Within the MPH-treated group, 255 (47.8%) children experienced at least one treatment-related AE. Among these patients, 154 experienced only one AE, 83 experienced two AEs, and 18 experienced three or more AEs. The very common (≥ 10%) AEs during MPH treatment included decreased appetite (32.6%) and sleep disturbances consisting of insomnia and fractured sleep (12.0%). Common (≥ 1%) AEs were psychiatric problems, tics, weight loss, abnormal electrocardiogram (ECG), abdominal pain, headaches, nausea, vomiting, chest tightness/palpitations, transient transaminase elevation, and dizziness. Psychiatric problems associated with MPH treatment mainly included irritability, aggression, and emotional instability. Rare (≤0.5%) AEs included hair pulling, eyelash pulling, frequent micturition, oral ulcer, rash, lip cracking, and fever. Furthermore, less frequent AEs have also been observed, including dry mouth and fatigue (for details, see Table 3).

Table 3 Results of adverse events in the methylphenidate and atomoxetine groups

	Methylphenidate [*n* (%)]	Atomoxetine [*n* (%)]
Total number of subjects with AEs	255 (47.8)	277 (56.8)
Decreased appetite	174 (32.6)	177 (36.3)
Abdominal pain	12 (2.3)	18 (3.7)
Vomiting	8 (1.5)	10 (2.0)
Nausea	8 (1.5)	12 (2.5)
Constipation	2 (0.4)	9 (1.8)
Weight loss	20 (3.8)	19 (3.9)
Sleep disturbances (insomnia/fractured sleep)	64 (12.0)	24 (4.9)
Somnolence	0	61 (12.5)
Tics	20 (3.8)	7 (1.4)
Headache	9 (1.7)	10 (2.0)
Dizziness	6 (1.1)	10 (2.0)
Fatigue	0	3 (0.6)
Psychiatric problems (irritability, aggression, emotional instability, depression, crying, anxiety, sadness, etc.)	24 (4.5)	71 (14.5)
Chest tightness/palpitation	7 (1.3)	3 (0.6)
Abnormal ECG	15 (2.8)	10 (2.0)
Transient transaminase elevation	7 (1.3)	3 (0.6)
Dry mouth	3 (0.6)	3 (0.6)
Hair pulling	2 (0.4)	0
Eyelash pulling	1 (0.2)	0
Eyebrow alopecia	0	1 (0.2)
Frequent micturition	1 (0.2)	1 (0.2)
Oral ulcer	1 (0.2)	0
Rash	1 (0.2)	7 (1.4)
Lip cracking	1 (0.2)	1 (0.2)
Skin itch	0	2 (0.4)
Fever	1 (0.2)	1 (0.2)
Enuresis	0	2 (0.4)
Urinary hesitancy	0	1 (0.2)
Tinnitus	0	1 (0.2)
Earache	0	1 (0.2)
Hand trembling	0	1 (0.2)

AEs adverse events, *ECG* electrocardiogram

Within the ATX-treated group, 277 children (56.8%) experienced at least one treatment-related AE. The incidence of AEs in the ATX-treated group was higher than that in the MPH-treated group (56.8% vs. 47.8%; $p < 0.05$). Of the 277 children who experienced AEs, 136 experienced just one, 98 experienced two, and 43 experienced at least three AEs. The very common AEs noted during ATX treatment included decreased appetite (36.3%), psychiatric problems (14.5%), and somnolence (12.5%). Psychiatric problems associated with ATX treatment mainly consisted of irritability, aggression, emotional instability, depression, crying, anxiety, and sadness. Common AEs were sleep disturbances, abdominal pain, weight loss, nausea, vomiting, dizziness, abnormal ECG, constipation, headache, rash, and tics. Rare AEs such as eyebrow alopecia, frequent micturition, lip cracking, skin itch, fever, enuresis, urinary hesitancy, tinnitus, earache, and hand trembling were observed (Table 3).

Moreover, MPH treatment had higher risks of sleep disturbances and tics than ATX treatment (sleep disturbances: OR 2.76, 95% CI 1.71–4.61; tics: OR 2.68, 95% CI 1.17–6.88). Somnolence was more common in ATX-treated children than in MPH-treated children (12.5% for ATX vs. 0% for MPH). The risk of psychiatric AEs associated with ATX treatment was higher than those associated with MPH treatment (OR 3.61, 95% CI 2.27–5.95).

3.5 Subgroup Analysis of Adverse Events

3.5.1 Sex

In the MPH-treated group, AEs were experienced by 49.2% (229/465) of boys and 38.2% (26/68) of girls. No statistically significant differences were observed between boys and girls ($p > 0.05$). In the ATX-treated group, the rates of AEs were 56.4% (235/416) and 58.3% (42/72) for boys and girls, respectively, also with no statistically significant difference between boys and girls ($p > 0.05$).

3.5.2 Age

The rates of MPH-related AEs were 56.8% (126/222), 47.2% (103/218), and 29.0% (27/93) in the <8 years, 8–10 years, and ≥10 years age groups, respectively. Statistically significant differences were found between the three age groups ($p < 0.05$). The Chi-square test was used to compare the groups and a statistically significant difference in the frequency of MPH-related AEs was identified for the ≥10 years age group, compared with the < 8 years and 8–10 years age groups ($p < 0.05$). The rates of ATX-related AEs were 54.9% (118/215), 62.0% (129/208), and 46.2% (30/65) in the <8 years, 8–10 years, and ≥ 10 years age groups, respectively. There was no significant difference between the three age subgroups ($p > 0.05$).

3.5.3 ADHD Presentation

In the MPH-treated group, the rates of AEs were 50.2% (133/265) for the combined presentation, 43.9% (108/247) for the inattentive presentation, and 63.6% (14/22) for the hyperactive/impulsive presentation. Although the incidence of AEs in the hyperactive/impulsive presentation was the highest, there was no significant difference between different presentations. In the ATX-treated group, the rates of AEs were 59.3% (134/226) for the combined presentation, 54.8% (130/237) for the inattentive presentation, and 52.0% (13/25) for the hyperactive/impulsive presentation. In this dataset, the combined presentation had the highest incidence of AEs; however, this was not statistically significant.

4 Discussion

The present study reported the results of a real-world comparison of the efficacy and safety of OROS MPH and ATX in a large sample of Chinese children and adolescents with ADHD. To our knowledge, this is the largest prospective cohort of children with ADHD undergoing pharmacologic treatment in a real-world clinical setting. We studied a total of 1021 previously medication treatment-naive patients with ADHD, for a period of 26 weeks. We not only compared the efficacy and safety of the two drugs as a whole but also analyzed the different subgroups.

In this study, the response rates of MPH and ATX were 84.6% and 63.6%, respectively. Due to differences in the definitions of 'response' and heterogeneity in study populations, there are certain differences in 'response rates' between different studies [12].

Many previous studies have found that compared with ATX, MPH showed a higher response rate and had greater improvement in improving ADHD symptoms [11, 12, 22–25]. The results of our study were in agreement with these researches. We found that, overall, MPH was more effective than ATX. In particular, we compared the differences in the subgroups (sex, age, and ADHD presentation) and found that the treatment effect of MPH over ATX was consistent across subgroups except in girls and children with hyperactive/impulsive presentation. It is worth noting that the sample size of the girls and children with hyperactive/impulsive presentation was significantly smaller compared with the other subgroups, and due to the smaller sample size, it may be difficult to detect statistically significant differences between them and other subgroups.

With regard to AEs, a meta-analysis reported that the overall AE rate during MPH treatment was 66% [26], and a Chinese study reported 42.3% of patients receiving MPH treatment had AEs [27]. In a meta-analysis, the AE rate in ATX-treated children was reported to be 70.4% [11].

However, in a real-world study, only 28.0% of ATX-treated children and 25.9% of MPH-treated children were reported to experience AEs [28]. In the present study, the rates of AEs were 47.8% and 56.8% in MPH-treated and ATX-treated subjects, respectively. The incidence of AEs reported here is slightly lower than in many studies from other countries [11, 22, 26], which may be related to differences in age, sex, race, or other demographic characteristics of study subjects. It was reported that AEs were significantly more frequent in ATX-treated participants than in MPH-treated participants [28], with this study showing the same result; compared with ATX, MPH treatment resulted in a low frequency of AEs. For MPH-treated subjects, no statistical difference was found between the different sexes or ADHD presentations, and similar findings were found in the ATX-treated group. It is noteworthy that the incidence of AEs in the MPH-treated group was higher in young children and lower in children over 10 years of age; however, this age-related difference was not found in the ATX-treated group.

The specific AEs observed in our study are consistent with previous literature; however, the proportion of AEs varies between studies. Decreased appetite was the most common AE in our study, in both MPH- and ATX-treated children, and occurred in approximately one-third of subjects. This rate is in agreement with several previous studies and slightly higher than reported in other studies [26, 29]. During the 26-week follow-up period, 3.8% of the MPH-treated children and 3.9% of the ATX-treated children experienced weight loss as a result of decreased appetite. To manage decreased appetite and weight loss, guidelines suggest administering medication after meals, rather than before, as well as encouraging the consumption of high-calorific snacks and late-evening meals [29].

In addition to decreased appetite, sleep disturbances, somnolence, and psychiatric AEs were also common. Twelve percent of subjects treated with MPH experienced sleep disturbances, which was higher than the rate in subjects receiving ATX treatment. This may suggest that children with ADHD who experience comorbid sleep disturbances should choose ATX treatment over MPH. Conversely, somnolence was more common in ATX-treated children (12.5%) than MPH-treated children. If ATX-treated children experience serious somnolence, it is recommended administering the medication once daily, in the evening [29]. Previous studies have reported that some psychiatric problems were seen in MPH- or ATX-treated children, such as irritability, anxiety, depression, sadness, crying, nervousness, emotional lability, aggression, tension, etc. [11, 28, 30–32]. In this study, psychiatric AEs associated with MPH treatment consisted of irritability, aggression, and emotional instability. ATX-treated subjects also experienced these as well as several other AEs, including depression, crying, anxiety, and sadness. The risk of psychiatric AEs associated with ATX treatment was higher than that with MPH, and MPH has a better safety profile for psychiatric symptoms.

Tics are common in childhood and approximately 20% of children with ADHD go on to develop a chronic tic disorder [33]. When ADHD and tics co-occur in an individual, the onset of ADHD typically precedes that of tic symptoms [34]. Therefore, it is difficult to determine the relationship between the two—whether the tics are an adverse effect of pharmacological treatment or they would likely occur anyway. Although there is no statistically significant relationship between stimulant use and the onset or worsening of tics in children with ADHD, stimulants may nonetheless exacerbate tics in individual cases [33, 35]. The notion that MPH may aggravate tics is still unexplored, and this is a key area for future research. In the present study, we observed that 3.8% and 1.4% of subjects developed tics or worsening tic symptoms during MPH and ATX treatments, respectively. Overall, MPH-treated children had a higher incidence of tics than ATX-treated children.

Rare AEs such as eyebrow alopecia, eyelash pulling, hair pulling, urinary hesitancy, frequent micturition, enuresis, tinnitus, earache, fever, rash, skin itch, oral ulcer, lip cracking, and hand trembling may also occur to a lesser extent during ATX and MPH treatment. During the follow-up period, we excluded other factors that could cause such adverse effects and found that these AEs were related to ATX or MPH treatment. These AEs are usually transient and disappear soon after medication withdrawal. It is perhaps worthwhile to mention that there were more rare adverse reactions (including quantity and type) during ATX treatment than during MPH treatment (Table 3). We found that these rare adverse reactions mainly involved skin mucosa and the urinary system. Eyebrow alopecia, hair loss, oral ulcer, and lip cracking occurred in the skin and mucous membranes. Frequent micturition, enuresis and urinary hesitancy was related to urinary system. The mechanism of these adverse effects may be related to excessive extracellular or synaptic dopamine and norepinephrine, which can regulate the sympathetic and parasympathetic pathways [36]. Although these AEs are rare and have only been reported as individual cases in previous literature [37–41], clinicians should be aware and pay attention to these adverse reactions.

A few limitations of this study should be considered. First, although the use of an instrument such as the Swanson, Nolan and Pelham version IV (SNAP-IV) scale or the ADHD Rating Scale (ADHD-RS) to assess the improvement of ADHD symptoms would have resulted in greater accuracy and objectivity, we did not use any of these scales. We developed a simpler clinical questionnaire to investigate the efficacy of the two drugs. The 'response'-related items include whether the core symptoms of ADHD (inattention, hyperactivity, and impulsivity) were significantly improved because of medication,

i.e. concentrates better on schoolwork, is less easily distracted, and interrupt others less often, whether the improvement occurred in either the school or home setting. Second, in this study, if symptoms had not improved after 6 weeks of medication, this was categorized as a 'no response'; however, a small number of patients may not respond to ATX during the 6-week treatment period. The reason why we chose 6 weeks as the treatment period is because in a real-world clinical setting, 6 weeks is the length of a conventional course of treatment. Thus, in the event a 6-week treatment period yielded no appreciable effect, treatment with the drug in question was halted and the patient was transferred to another treatment. Throughout our research, in most cases of unresponsiveness to medication, a change of medication was accepted, i.e. ATX to MPH, or MPH to ATX). However, within a practical setting, no washout period was used, a fact that may affect the results. Consequently, the results after a change of dressing were not analyzed. Third, although ADHD medications are known to be associated with statistically significant increases in blood pressure and heart rate, we did not routinely measure these in participants. ECG examinations were only arranged at baseline, around week 26 and when cardiovascular symptoms occurred. Fourth, the present study was a real-world study and not a randomized study. The prescriptions were prescribed by a specialist, mainly based on a patient's clinical symptoms, the urgency of treatment, parents and patients' preference, and compliance, which may introduce some bias. However, when we compared the demographic characteristics of the MPH and ATX treatment groups, we found no significant differences in sex, age, IQ, or ADHD presentation. Although the lack of randomization could be viewed as a limitation, our naturalistic study design is also a strength because it allows for an understanding of differences in response rates and AEs in a real-world clinical context. Fifth, AEs are related to drug dose, which is usually determined by body weight in children. Information about dose and body weight was not analyzed in this study, and as a result, the AE incidence was not adjusted by dose or body weight, which is a potential confounder. Sixth, we did not address the issues of comorbidity in both ADHD groups. ADHD is associated with high rates of comorbidities, ranging from 40% to nearly 90% [8, 42–45]. Common comorbidities include learning disorders (LDs), oppositional defiant disorders (ODDs), conduct disorder (CD), sleep disorders, anxiety /depression disorders, and tic disorders [42–44]. Children who have ADHD and who also have psychiatric comorbidities may experience poorer outcomes compared with those without. Additionally, treating these children is generally more challenging [42, 46]. However, studies showed that ATX plays an important role in the treatment of ADHD patients with various types of comorbidities [8, 47]. We envisage future work should address these limitations to expand this work.

5 Conclusions

In the present real-world study, MPH was found to be more effective and better tolerated than ATX overall. The incidence of AEs during MPH treatment was higher in young children and lower in those over 10 years of age. Decreased appetite and sleep disturbances were the most frequent AEs in children taking MPH, while decreased appetite, somnolence, and psychiatric problems were the most frequent AEs in ATX-treated children. A higher incidence of tics and sleep disturbances was observed in MPH-treated children than in ATX-treated children. However, ATX-treated children had a higher incidence of psychiatric problems and somnolence than their MPH-treated counterparts. Psychiatric problems mainly included irritability, aggression, emotional instability, depression, crying, anxiety, and sadness. In addition, rare AEs such as eyebrow alopecia, eyelash pulling, hair pulling, urinary hesitancy, frequent micturition, enuresis, tinnitus, earache, fever, rash, skin itch, oral ulcer, lip cracking, etc. may also occur during ATX and MPH treatment, and clinicians and prescribers need to monitor patients for these adverse effects.

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Declarations

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Conflicts of Interest Ying Zhang, Li Yin, Cun You, Chunxue Liu, Ping Dong, Xiu Xu, and Kaifeng Zhang declare no relevant conflicts of interest.

Ethics Approval This study was approved by the Ethical Committee of CHFU.

Informed Consent Written informed consent to participate in this study was provided by the participants' parents and/or legal guardian.

Availability of Data and Material The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions All authors contributed to the article and approved the submitted version. Kaifeng Zhang, Ying Zhang, and Xiu Xu designed the study and performed the research; Li Yin, Cun You, Ying Zhang, Ping Dong, and Chunxue Liu contributed to follow-up and data collection; Ying Zhang and Kaifeng Zhang analyzed the data; Ying Zhang wrote the draft manuscript; and Xiu Xu

and Kaifeng Zhang revised the manuscript. All authors have read and approved the final article.

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