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ARTICLE

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Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: a randomized controlled trial

Li Yang[1], Qingjiu Cao[1], Lan Shuai[1], Haimei Li[1], Raymond C. K. Chan[2] and Yufeng Wang[1]

[1] *Institute of Mental Health, Peking University, Beijing, China*
[2] *Neuropsychology and Applied Cognitive Neuroscience Laboratory; Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China*

Abstract

This study aimed to compare the effects of osmotic release oral system-methylphenidate (OROS-MPH) and atomoxetine (ATX) on executive function in children and adolescents with attention deficit hyperactivity disorder (ADHD) by a randomized controlled trial. Subjects who met DSM-IV ADHD criteria were randomized to receive either OROS-MPH or ATX treatment. The doses were titrated to achieve optimal response and then maintained for 4–6 wk. A battery of executive function tests and the Behavior Rating Inventory of Executive Function (BRIEF) were administered to subjects who completed the dose titration (OROS-MPH, $n=85$; ATX, $n=57$) at the pre- and post-treatment periods. Forty-six children without ADHD were recruited as controls. Both OROS-MPH and ATX significantly improved scores in the Rey Complex Figure Test (RCFT), digit span, and Stroop color-word task. The scores in RCFT and the reverse digit span were not significantly different from the control group at post-treatment assessment (OROS-MPH = ATX = control, $p>0.05$), whereas the word interference time of the Stroop test was still more than that of the control group (OROS-MPH = ATX > control, $p>0.05$). OROS-MPH also significantly improved the total correct response in the verbal fluency test to normal level, and the shifting time in the trail-making test to subnormal level. The current findings suggest both OROS-MPH and ATX improved executive function generally in children and adolescents with ADHD, and could return working memory back to normative performance level.

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Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most prominent neurodevelopmental disorders in childhood, affecting about 3–5% school-aged children (APA, 1994). It is characterized by developmental inappropriate inattention, hyperactivity and impulsivity. Neuropsychological research has associated ADHD with a wide range of neurocognitive deficits (Carter *et al.* 1995; Sergeant *et al.* 1999), particularly executive function (EF) (Barkley *et al.* 1992; Halperin *et al.* 2008; Pennington & Ozonoff, 1996; Schachar *et al.* 1995).

EF generally refers to a product of the coordinated operation of various processes to accomplish a particular goal in a flexible manner (Funahashi, 2001). It consists of at least five factors: (1) inhibition, (2) working memory, (3) planning, (4) set-shifting, and (5) fluency (Pennington, 1997; Pennington *et al.* 1996; Welsh *et al.* 1991). For inhibition, Walshaw *et al.* (2010) reviewed studies examining errors of commission on the Continuous Performance Test (CPT) and suggested moderate effect size (0.56) for ADHD samples compared to controls exhibiting a more impulsive response style. Nigg and colleagues found deficits in stop-signal reaction time (SSRT) for children and

Address for correspondence: Professor Y. Wang, 51, Huayuan Bei Road, Beijing 100191, China.
Tel.: 86-10-82802907 *Fax*: 86-10-62070258
Email: wangyf@bjmu.edu.cn

adolescents with ADHD compared to control groups (Nigg, 1999, 2002; Rucklidge & Tannock, 2002; Schachar *et al.* 2000) while Barkley and colleagues found a significant difference in Stroop interference (Barkley *et al.* 1992; Berlin *et al.* 2004; Grodzinsky & Diamond, 1992; Lufi *et al.* 1990; Seidman *et al.* 1997). For working memory, Karatekin & Asarnow (1998) reporting performance on the digit span subtest of the Wechsler intelligence scales indicated that children with ADHD perform significantly worse than controls. Rhodes *et al.* (2004) found significant deficits in spatial working memory (SWM) on the Cambridge Neuropsychological Test Automated Battery (CANTAB) for children with ADHD. For planning, Nigg *et al.* (2002) found children with ADHD-combined type to have a lower total score on the Tower of London task than controls. Similar findings have been reported in two other studies (Kempton *et al.* 1999; Marzoochi *et al.* 2008). For set-shifting, Gorenstein *et al.* (1989) found that children with ADHD made significantly more perseverative errors on the Wisconsin Card Sorting Test than controls. For verbal fluency, individuals with ADHD appear to have deficits with regard to phonemic fluency (Barkley *et al.* 1992; Marzoochi *et al.* 2008; Mataró *et al.* 1997; Pineda *et al.* 1999). One study also reported deficits in semantic categories for children with ADHD (Geurts *et al.* 2004). Since EF is associated with academic performance and behavioural regulation, intervention is required for deficits in EF.

One of the most commonly used medications for the treatment of ADHD are stimulants (AACAP Work Group, 2007), of which methylphenidate (MPH) is among the most widely used. Immediate-release MPH needs to be taken three times a day to maintain the therapeutic effect, whereas osmotic release oral system-MPH (OROS-MPH) can be taken only once a day to maintain the effect for 12 h by a gradually ascending release of the drug. Such drug regimens are convenient for children attending schools. The pharmacological mechanism of MPH is known to block the dopamine transporter and increase dopamine level in the synaptic cleft. Its clinical effect is improvement of attention, classroom performance and decrease of hyperactivity, impulsivity, defiant and disruptive behaviours (Greenhill, 1995). MPH was also found to improve SWM, inhibition, set-shifting, planning, and other EFs in children and adults with ADHD. The medicated children with ADHD were found to be improved and comparable with controls on CANTAB Spatial Span, SWM, intra-extra dimensional set shifting (IED), Stockings of Cambridge (SOC) and delayed matching-to-sample tasks (Kempton *et al.* 1999; Mehta *et al.* 2004; Turner *et al.* 2005). SSRT and variability of response execution were significantly ameliorated by MPH (Aron *et al.* 2003; Bedard *et al.* 2003). With MPH medication, Tower of Hanoi rule-breaking errors decreased, and planning time increased particularly for incorrect solutions (Hazel-Fernandez *et al.* 2006). MPH also significantly improved performance in the interference score of Stroop color-word task (Langleben *et al.* 2006).

Atomoxetine (ATX) is a new non-stimulant drug for the treatment of ADHD in children and adolescents. It is a highly specific inhibitor of the norepinephrine transporter. Its efficacy and tolerance has been approved through many open-label and randomized placebo-controlled trials (Kelsey *et al.* 2004; Michelson *et al.* 2001, 2003; Spencer *et al.* 1998, 2001, 2002; Weiss *et al.* 2005). Only a few studies have investigated its effect on EF, including a study in a small sample ($n = 9$) and another one using the Stroop test in adults (Barton *et al.* 2005; Faraone *et al.* 2005), which suggested ATX might also improve EF. A recent study showed ATX improvement on almost all of the proxy data of ecological EF assessments [Behavior Rating Inventory of Executive Function (BRIEF); Brown Attention Deficit Disorder Scale (BADDS)], particularly working memory, planning, organization and monitoring, activating to work, focusing for tasks, regulating alertness and effort, and modulating emotions (Brown *et al.* 2009; Maziade *et al.* 2009; Wilens *et al.* 2009). The performance-based EF tests (Working Memory Test Battery for Children and CANTAB) also showed significant improvement in shifting and flexibility of attention, spatial short-term memory, sustained attention and response inhibition, SWM, and spatial planning and problem solving after treatment with ATX for 4 wk or 12 wk (Gau & Shang, 2010; Sumner *et al.* 2009).

According to the theory of attentional network (Posner, 2008), dopamine is associated with executive network as measured by the working memory task (Goldman-Rakic, 1992), Stroop and Attentional Network Test (ANT; Posner *et al.* 2007), and norepinephrine are associated with alertness, a state important for the accomplishment of all kinds of cognitive functions. Although preliminary studies have demonstrated potential therapeutic effects for both MPH and ATX on EF performances in children with ADHD, very few studies have been performed to compare these two drugs directly. Regarding the different psychopharmacological mechanisms, there may be differential effects in EF improvements, which remain unclear. The present study is a head-to-head comparison study on improvement of EF between OROS-MPH and ATX. The findings of this study may

shed light on the choice of drug for ADHD patients with different deficits in EF in clinical practice and promote individualized therapy.

Methods

Children and adolescents meeting the ADHD criteria in DSM-IV by clinical and structured interview were recruited from the Child and Adolescent Psychiatric Outpatient Department of Peking University Sixth Hospital. The subjects were unmedicated or had been effectively medicated with immediate-release MPH but had not used medication in the last 6 months since the symptoms relapsed. Those with a history of no response or intolerance to either MPH preparations or ATX were excluded for ethical reasons. Other exclusion criteria were: (1) diagnosis of bipolar I or II disorder, psychosis, anxiety disorder, depression disorder, tic disorder, pervasive developmental disorder or mental retardation with IQ $\leqslant$70 [The Chinese-Wechsler Intelligence Scale for Children (C-WISC; Gong & Cai, 1993) was used to assess the IQ. It is a revised version of the Wechsler Intelligence Scale for Children – third edition (WISC-III; Wechsler, 1991)]; (2) any seizure disorder or abnormal electroencephalogram (EEG) associated with epilepsy, or currently taking anticonvulsive drugs; (3) some medical conditions not appropriate to receive medications such as narrow-angle glaucoma, cardiovascular diseases, or any diseases which may deteriorate when the pulse or blood pressure is increased, including hypertension or those taking antihypertensive drugs; (4) using other psychotropic drugs including health food with central nervous system (CNS) activity in the past 30 d or during the course of the study. The study was approved by the Peking University Sixth Hospital Institutional Review Board. Parents signed written informed consent and the children provided their assent. There were 262 patients recruited and randomized into either OROS-MPH or ATX treatment groups.

This was a single-blind randomized controlled trial study with only blind raters because of the different appearance of the medications. The study adopted a randomized block design, which was generated by the Clinical Epidemiology Research Centre of Peking University Third Hospital. The random allocation was concealed in envelopes until a medication group was assigned. On the basis of manufacturer's instructions and published pharmacological data, this study used flexible doses which imitated clinical practice as far as possible. Dose was titrated to achieve optimal clinical response for both groups. OROS-MPH started with 18 mg/d. The dose could be increased each week to 36 mg/d and then 54 mg/d according to the patient's response. ATX was initiated using a weight-based milligram at 0.5 mg/kg.d provided after breakfast. The dose could be increased to 0.8 mg/kg.d for week 2 and then 1.2 mg/kg.d for weeks 3 and 4. If the therapeutic effect was not satisfactory and the side-effects were tolerable, 1.4 mg/kg.d (or 100 mg maximum) could be used in week 5. For both drugs, when an optimal dose (with optimal effects and minimal side-effects) was achieved it was not increased any further, and that dose was continued with for 4–6 wk before EF measurement.

One hundred forty-two patients, aged 7–14 yr (mean $\pm$ S.D. 9.64 $\pm$ 1.95 yr), completed the drug titration and EF test–retest. Eighty-five subjects were in the OROS-MPH group, and 57 in ATX group (Fig. 1). For patients who completed the study, there were no significant differences found between the OROS-MPH- and ATX-treated groups at baseline in terms of sex, age, IQ, clinical subtypes, and comorbidities (Table 1). One hundred and twenty (45.8%) patients dropped out. The two most common reasons for dropping out were adverse event (decreased appetite, etc.) and parental withdrawal of consent (see Fig. 1). There were no significant differences between those patients who completed titration and those who dropped out in terms of sex, age, IQ, clinical subtypes, comorbidities, baseline symptom ratings and EFs ($p > 0.05$). The dropout rate was higher in the ATX group (56.2%) than in the OROS-MPH group (35.6%). Discontinuation due to adverse events and inefficacy in ATX group was higher than in OROS-MPH group (20.8%, 6.9% *vs.* 11.4%, 1.5%). Forty-six (35 boys, 11 girls) gender- and age-matched children and adolescents without ADHD from primary and middle schools voluntarily participated in the study as normal controls. The controls were administered the same cognitive function battery at baseline and at a 4–6 wk interval without receiving any drug treatment. Both subjects and caregivers gave their informed consent. The mean age and IQ of the control group was 10.40 $\pm$ 1.77 yr, and 117.43 $\pm$ 14.64, respectively. The control group showed a significantly higher IQ level than the two medication groups ($p > 0.01$), which was reasonable as ADHD children always showed subnormal IQs. Given the significant difference in IQ between the two groups, IQ was controlled as a covariate in subsequent analysis described in the statistical analysis.

During the medication titration course, children and their parents were interviewed weekly. ADHD symptoms were assessed by parents and teachers who

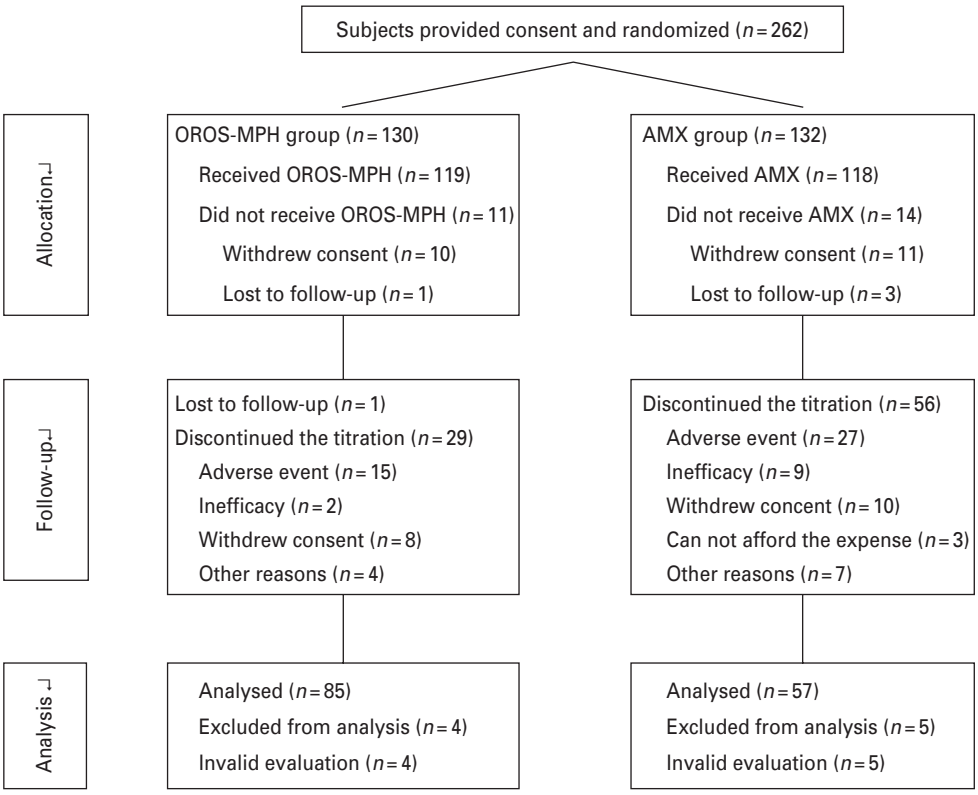

Fig. 1. Flow diagram of the randomization procedure and outcome of all recruited subjects.

completed the ADHD Rating Scale-IV (DuPaul *et al.* 1998). This scale consists of 18 items according to DSM-IV criteria for ADHD. The total symptom score as well as inattention and hyperactivity-impulsivity subscale scores were used to evaluate therapeutic effect. This scale has been translated into Chinese. The validity and reliability of the Chinese version were tested by Su *et al.* (2006). The Clinical Global Impression – Severity scale (CGI-S; Wu, 1984) was used to assess the severity of ADHD symptoms. The CGI-S is a 7-point scale (1 = not at all ill, 7 = maximal impairment).

EF was assessed at baseline and after 4–6 wk optimal dose treatment, using multiple assessment measures as performance-based tests and ecological rating scales. The rater of the performance-based tests was blind to the medication group. Performance-based EF tests were the primary outcome measures, which included: (1) the Stroop color-word interference task (Ji & Jiao, 1987; Stroop, 1935), which included four sessions. The color interference time and word interference time reflect interference inhibition. (2) RCFT (Verf, 1993; Zhao, 2002): this test assesses visual working memory. The subject was asked to observe a complex figure for 30 s, then draw from memory immediately, and draw again 20–30 min later. The scores were rated according to the structure and detail accuracy. (3) Digit span (Gong & Cai, 1993; Wechsler, 1991): this is a subtest of the C-WISC which assesses verbal working memory. It includes order digit span and reverse digit span. (4) Tower of Hanoi (Simon, 1975): this test was used to assess the function of planning. The task uses three columns and four discs. The subject was asked to move the discs to a specified column according to the test's rules. The total time and steps reflect the ability of planning to achieve the objective. (5) Trail-making test (Spreen & Strauss, 1998): this test assesses the ability of set shifting. It includes tests A and B. In test A, the subject is asked to accurately and quickly make trails following the number order. In test B, the subject is asked to accurately and quickly make trails following cross-order between number and letter. The shifting time is equal to the time difference between tests B and A. (6) Verbal fluency test (Spreen & Strauss, 1998): in this test the subject is asked to name as many animals as possible in 2 min. The number of correct responses, repeat responses and error responses was recorded. Ecological

Table 1. Comparison of demographic features, subtype and comorbidity of OROS-MPH and ATX-treated group ($N=142$)

	OROS-MPH ($n=85$)	ATX ($n=57$)		
	Mean ± S.D. or n (%)	Mean ± S.D. or n (%)	t or χ^2	p
Age (yr)	9.47 ± 1.94	9.90 ± 1.95	−1.318	0.190
Sex				
Male	69 (81.2%)	50 (87.7%)	1.076	0.300
Female	16 (18.8%)	7 (12.3%)		
IQ	102.99 ± 15.01	105.72 ± 13.03	−1.119	0.265
ADHD subtype				
Inattentive	36 (42.4%)	31 (54.4%)	4.843	0.089
Combined	48 (56.5%)	23 (40.4%)		
Hyperactive/impulsive	1 (1.2%)	3 (5.3%)		
Comorbidity				
ODD	31 (36.5%)	13 (22.8%)	2.979	0.084
CD	2 (2.4%)	0 (0.0%)	1.360	0.243

ODD, Oppositional defiant disorder; CD, conduct disorder.

EF was assessed by the BRIEF, which is the secondary outcome measure. The BRIEF is an 86-item questionnaire for parents and teachers of children aged 5–18 yr, which assesses EF behaviours in the home and school environments. The items constitute two domains and eight factors. It is a reliable and valid behavioural rating scale of EF in children and adolescents (Gioia *et al.* 2002*a*, *b*; Mahone & Hoffman, 2007; Qian & Wang, 2007, 2009; Vriezen & Pigott, 2002).

Sample size was estimated with regard to the parameters from previous studies (Qian *et al.* 2007; Shuai *et al.* 2007) with 80% power and a 0.05 significance level. The number ranged from 17 to 67 cases in each treatment group according to multiple test parameters. The study is intended to recruit an estimated maximum sample size of 67 cases for each group. Due to the relatively high dropout rate in the ATX group, and the small trend of difference detected between the two treatment groups, the study closed before the ATX group achieved the designed sample size.

Analyses were performed among patients who completed the dose titration and EF test. The score changes of the performance-based EF tests and the BRIEF after treatment were tested within each medication group, and the differences at baseline and study endpoint were compared between groups and also with the control group. The data with normal distribution were analysed by t test. Those with non-normal distribution were analysed by non-parametric Wilcoxon signed-ranks test. The mismatched baseline measures were corrected by analysis of covariance or two-factor analysis of variance. All statistical tests were two-tailed. An α-level of 0.05 was used to assert statistical significance. For those measures with a significant p value, the effect size was calculated to show the superior effect of one drug over the other. We calculated all statistics using SPSS 13.0 (SPSS Inc., USA).

Results

Both OROS-MPH and ATX significantly improved scores in RCFT, digit span, Tower of Hanoi and Stroop color-word tasks ($p>0.05$) (see Table 2). Although the scores in RCFT and the reverse digit span of the two medication groups were less than those of the control group at baseline (OROS-MPH > ATX > control for immediate structure and detail score of RCFT, OROS-MPH = ATX > control for other measures), there was no significant difference among the three groups at study endpoint (OROS-MPH = ATX = control, $p>0.05$). Nevertheless, the word interference time of the Stroop test for the two medication groups was still more than that of the control group at endpoint (OROS-MPH = ATX > control) after correction by baseline scores ($p>0.05$).

OROS-MPH also significantly improved the shifting time (baseline 137.03 ± 81.90 *vs.* endpoint 113.33 ± 75.48, $p=0.005$) in the trail-making test, and the total correct response (baseline 19.36 ± 5.62 *vs.* endpoint 20.46 ± 6.13, $p=0.048$) in the verbal fluency test. The latter was comparable with control (OROS-MPH = control, $p=0.355$), but for the former shifting time was still longer ($p=0.049$) than that of the control group

Table 2. Performance-based executive function between OROS-MPH and ATX treatment groups

Test	OROS-MPH ($n=85$)		ATX ($n=57$)				Control ($n=46$)			
	Baseline Mean ± S.D. (median)	Endpoint Mean ± S.D. (median)	Baseline Mean ± S.D. (median)	Endpoint Mean ± S.D. (median)	t, Z or χ^2	p	Baseline Mean ± S.D. (median)	Endpoint Mean ± S.D. (median)	F	p
RCFT										
Immediate structure	2.15 ± 2.18 (1.00)	3.58 ± 1.97*** (4.00)	2.95 ± 2.23 (4.00)	3.71 ± 2.19*** (4.00)	0.246	0.621†	4.09 ± 1.40 (4.00)	4.41 ± 1.68* (5.00)	0.338	0.714†‡
Immediate detail	7.81 ± 6.66 (6.00)	13.92 ± 7.29*** (13.00)	10.93 ± 7.67 (11.00)	14.89 ± 7.67*** (15.50)	0.784	0.377†‡	14.20 ± 5.73 (14.00)	17.67 ± 6.00*** (17.5)	1.173	0.313†
Recall structure	2.33 ± 2.22 (2.00)	3.62 ± 2.02*** (4.00)	2.93 ± 2.26 (3.00)	3.71 ± 2.03*** (4.00)	0.068	0.795	4.11 ± 1.35 (4.00)	4.46 ± 1.63* (5.00)	1.002	0.370†‡
Recall detail	7.88 ± 6.75 (5.00)	13.92 ± 6.83*** (14.00)	10.05 ± 7.34 (10.00)	15.11 ± 7.30*** (15.00)	0.970	0.326	13.85 ± 5.35 (13.00)	17.24 ± 5.63*** (17.00)	0.461	0.632†
Digit span										
Order digit span	7.66 ± 1.31	7.51 ± 0.88	8.15 ± 1.16	7.61 ± 0.90**	1.051	0.307†	8.33 ± 1.10	8.13 ± 1.70	2.128	0.132†
Reverse digit span	3.98 ± 1.42 (3.00)	4.29 ± 1.33** (4.00)	4.48 ± 1.66 (4.00)	4.61 ± 1.30* (4.00)	2.133	0.147‡	5.54 ± 1.57 (5.00)	5.07 ± 1.54* (5.00)	1.154	0.319†‡
TMT										
Shifting time (s)	137.03 ± 81.90 (117.00)	113.33 ± 75.48** (102.00)	126.11 ± 85.15 (107.00)	106.96 ± 80.99 (88.00)	0.956	0.341‡	76.00 ± 70.95 (52.50)	60.72 ± 37.14 (49.00)	5.733	0.004**†‡
Tower of Hanoi										
Completion	55.3%	83.5%	78.9%	84.2%	4.678	0.044*§	80.4%	87.0%	0.566	0.754
Total steps	35.83 ± 20.17 (30.00)	33.37 ± 14.54 (31.00)	28.44 ± 10.06 (26.00)	33.11 ± 16.36 (33.00)	0.365	0.716‡	32.35 ± 17.33 (26.00)	31.30 ± 14.54 (25.00)	0.674	0.515†‡
Verbal fluency test										
Correct responses	19.36 ± 5.62	20.46 ± 6.13*	20.58 ± 5.74	20.98 ± 6.68	0.229	0.633	23.59 ± 5.86	23.83 ± 5.42	1.043	0.355†
Stroop test										
Color interference (s)	8.06 ± 10.33 (5.00)	8.64 ± 7.88 (7.00)	10.02 ± 1.55 (6.00)	7.21 ± 8.21 (5.50)	−1.528	0.126	3.13 ± 5.93 (3.00)	4.93 ± 5.98 (3.00)	2.143	0.233†
Word interference (s)	30.65 ± 15.83 (29.00)	25.09 ± 14.43** (21.00)	31.25 ± 19.24 (28.00)	25.21 ± 11.34* (25.00)	−0.175	0.862	20.04 ± 7.74 (19.00)	18.00 ± 8.42* (16.50)	6.150	0.003**†‡

RCFT, Rey Complex Figure Test; TMT, trail-making test.

† Due to mismatch of the baseline score or IQ, analysis of covariance was used to correct the p value.

‡ Non-normal distribution data were transformed to normal distribution by square root(x) or ln(x).

§ Due to mismatch of the baseline rate, the completion rate at endpoint of the study was stratified and analysed between two medication groups in subjects failing to complete the test at baseline. Comparison with controls was performed among 46 patients medicated with OROS-MPH and 46 with ATX, who were matched for gender and age.

* $p>0.05$, ** $p>0.01$, *** $p>0.001$.

Table 3. Behavior Rating Inventory of Executive Function (BRIEF) between OROS-MPH and ATX treatment groups

	OROS-MPH		ATX			
Subscales	Baseline Mean ± S.D.	Endpoint Mean ± S.D.	Baseline Mean ± S.D.	Endpoint Mean ± S.D.	*F* or *Z*	*p*
Parent ratings						
Inhibition	19.16 ± 4.35	15.73 ± 4.32***	18.50 ± 4.52	15.82 ± 3.74***	0.016	0.899
Shift	12.64 ± 2.54	11.47 ± 2.61***	12.31 ± 2.30	11.38 ± 2.43*	0.043	0.835
Emotional control	16.52 ± 4.29	14.46 ± 3.89***	16.16 ± 4.15	14.56 ± 3.73***	−0.350	0.726
Initiate	15.49 ± 2.68	14.02 ± 3.20***	15.14 ± 2.54	14.33 ± 3.16	0.318	0.573
Working memory	23.52 ± 3.14	19.52 ± 4.16***	22.79 ± 2.96	19.56 ± 3.92***	0.004	0.951
Plan	28.81 ± 3.61	24.46 ± 5.37***	28.16 ± 3.97	24.53 ± 5.01***	0.006	0.939
Organize	14.40 ± 2.67	12.35 ± 3.29***	14.78 ± 2.60	12.63 ± 3.24***	0.252	0.617
Monitor	20.65 ± 2.69	17.29 ± 3.66***	20.38 ± 2.76	17.86 ± 3.54***	0.841	0.361
BRI	48.32 ± 9.09	41.66 ± 9.41***	46.97 ± 8.83	41.63 ± 8.01***	0.000	0.984
MI	102.88 ± 11.33	87.64 ± 16.57***	101.35 ± 11.68	88.91 ± 16.01***	0.205	0.651
Global executive composite	151.20 ± 17.57	129.30 ± 24.05***	148.53 ± 17.20	130.54 ± 22.21***	0.096	0.757
Teacher ratings						
Inhibition	22.17 ± 5.49	17.34 ± 4.60***	21.75 ± 5.61	17.18 ± 5.58***	0.018	0.892
Shift	17.00 ± 3.45	14.74 ± 3.57***	16.50 ± 4.98	13.68 ± 3.10**	1.719	0.194
Emotional control	15.64 ± 4.87	13.19 ± 4.00***	15.89 ± 5.57	12.68 ± 3.88**		
Initiate	16.57 ± 2.75	13.64 ± 3.40***	15.04 ± 3.28	13.29 ± 4.16***	0.159	0.691
Working memory	23.51 ± 3.71	18.87 ± 4.35***	22.36 ± 4.10	18.46 ± 5.08***	0.136	0.713
Plan	23.62 ± 3.35	19.55 ± 4.64***	21.39 ± 4.12	18.25 ± 5.81***	1.143	0.288
Organize	15.53 ± 3.55	12.13 ± 3.27***	15.64 ± 4.40	12.82 ± 4.35***	0.616	0.435
Monitor	24.45 ± 4.32	20.15 ± 5.00***	23.32 ± 4.98	19.71 ± 5.35***	0.126	0.724
BRI	54.81 ± 11.93	45.28 ± 11.13***	54.14 ± 14.66	43.54 ± 11.09***	0.430	0.514
MI	103.68 ± 14.57	84.34 ± 18.03***	97.75 ± 16.94	82.54 ± 22.76***	0.144	0.705
Global executive composite	158.49 ± 23.78	129.62 ± 27.68***	151.89 ± 27.87	126.07 ± 31.85***	0.257	0.614

BRI, Behaviour Regulation Index; MI, Metacognition Index.
The sample size for teacher's ratings was 75, with 47 for OROS-MPH and 28 for ATX.
* $p > 0.05$, ** $p > 0.01$, *** $p > 0.001$.

(OROS-MPH > control). ATX showed improvement trends on the above measures, but not significantly. The test scores at endpoint were better for the OROS-MPH group than for the ATX group, but not statistically significant.

The completion rate of Tower of Hanoi increased more for the OROS-MPH group than for the ATX group [those failing to complete the task at baseline (68.4% in OROS-MPH group *vs.* 33.3% in ATX group) completed the task at endpoint ($p = 0.044$, OR 4.3)].

Both OROS-MPH and ATX significantly improved the parent- and teacher-rated BRIEF (except for the parent-rated initiate factor in the ATX group, which showed an improved trend but still not statistically significant). However, the two groups did not differ significantly for the total score and subscale scores (Table 3).

Discussion

This study adopted two types of EF measures, performance-based neuropsychological tests and ecological behavioural rating scales. The laboratory-based neuropsychological tests were more specific for the components of EF, although they might not reflect EF in real life, while the rating scales had good ecological validity. Brown (2006) and Barkley & Fischer (2011) suggested a behavioural rating scale might be a more sensitive indicator. The combination use of laboratory-based neuropsychological tests and rating scales for EF can provide a more comprehensive view of medication effects on EF performance at various levels.

The results imply that both OROS-MPH and ATX could improve EF in ADHD children. OROS-MPH significantly improved the scores of all the

performance-based neuropsychological EF tests including working memory, inhibition, set shifting, planning, and verbal fluency. For ATX, performance-based working memory and inhibition improved significantly. The two medication groups were comparable after treatment on all the tests which reflected the functions of the so-called prefrontal cortex executive system. In regard to the behavioural rating scales, both OROS-MPH and ATX comparably improved all of the eight factors of the BRIEF whether it was rated by parents or by teachers. (Although the improvement on initiate for the ATX group was not statistically significant, the rating scores showed a decreasing trend and did not differ significantly from the OROS-MPH group.) The results from BRIEF suggested the two medications enhanced not only meta-cognition processes but also behavioural regulation at a higher hierarchy as the essential deficit of ADHD. The study of Barkley & Fischer (2011) concluded that EF ratings were better predictors of impairment in major life activities generally and occupational functioning specifically at adult follow-up. Therefore the present study suggests both OROS-MPH and ATX might improve the prognosis of ADHD through optimized everyday life performances.

Preliminary findings of improvement of EF were also reported in previous studies in stimulant-medicated children, including SWM, visual memory, set-shifting, planning, response and executive inhibition (Aron *et al.* 2003; Hazel-Fernandez *et al.* 2006; Kempton *et al.* 1999; Langleben *et al.* 2006; Rhodes *et al.* 2004; Vance *et al.* 2003). Our results concerning OROS-MPH are in accord with the above studies. We also found significant improvement on the verbal fluency test. But the treatment did not normalize all EFs. According to the view of Gualtieri & Johnson (2008), there might be three possible reasons: sub-optimal response, irrelevance between cognitive performance and symptom response, and necessary but not sufficient for medication.

There has been a growing literature on the effects of ATX on EF in recent years. Both neuropsychological tests such as the working memory test and behavioural rating scales have been reported to be improved (Brown *et al.* 2009; Maziade *et al.* 2009; Sumner *et al.* 2009). Our results were consistent with these findings. Using CANTAB IED shifts and SOC, Gau & Shang (2010) reported improvement of shifting and planning in an open-label follow-up study with ATX. Despite the different tasks used, our results show similar trends to Gau & Shang's study, and are supplementary evidence for the improvement of executive inhibition in the Stroop test.

There was no head-to-head comparison study between OROS-MPH and ATX on EF in ADHD patients before the present study. Despite some slight differences found, the effect of the two drugs were comparable on many measures such as scores on RCFT, reverse digit span, Tower of Hanoi total time, Stroop word interference time, and most scores on the BRIEF. Parts of EF, such as working memory, were improved to within the deviation of controls suggesting 'normalization'. Since the control group was also tested twice at an interval of 4–6 wk as was the optimal dose treatment phase in the medication group, the observed improvement in the latter is beyond the practice effect.

Newcorn *et al.* (2008) compared the clinical response in ADHD symptoms between ATX and OROS-MPH, reporting superior response rates for MPH (56%) than for ATX (45%). MPH was also significantly superior to ATX in the mean change of the ADHD Rating Scale scores. It appears that the results of our study regarding EF are inconsistent with those of Newcorn *et al.* The inconsistency might come from analysis of a different population, as Newcorn *et al.*'s study analysed all patients at baseline and at least a follow-up measurement by using a last-observation-carried-forward approach, while analysis in our study was performed in patients who completed the titration protocol, excluding those that dropped out due to inefficacy. This also reflects the individual variance of the medication response.

Studies in rats have shown that stimulants might suppress delay-related firing for non-preferred stimulations (like 'noise'), enhancing signal-to-noise ratio through facilitated transmission by dopamine D_1 receptors, which are essential for working memory and attention regulation processes of the prefrontal cortex (Arnsten & Dudley, 2005; Goldman-Rakic, 1995; Granon *et al.* 2000; Vijayraghavan *et al.* 2007; Williams & Goldman-Rakic, 1995; Zahrt *et al.* 1997). However, ATX inhibited post-synaptic spontaneous firing of prefrontal neurons in order to increase delay-related firing ('signals') for the preferred stimulation (Li *et al.* 1999; Sawaguchi, 1998) through α_{2A} receptors (Arnsten & Goldman-Rakic, 1985; Cai *et al.* 1993). A similar effect was also seen for the α_{2A} agonist, guanfacine, which improves many aspects of prefrontal cortical function, including working memory, attention regulation, behavioural inhibition, and planning in rats (Ramos *et al.* 2006; Tanila *et al.* 1996), monkeys (Arnsten *et al.* 1988; Mao *et al.* 1999), and humans (Jakala *et al.* 1999). Taking the above neuropsychopharmacological evidence into account, both OROS-MPH and ATX increase the signal-to-noise ratio of prefrontal neurons from different directions. The

cognitive effect may be dose-dependent but not drug-specific.

There are a number of methodological limitations in the current study. First, we did not include a group who received placebo; therefore, there might have been bias in results for the potential placebo effect when we estimated the effect of each medication. The relatively small sample size in the ATX group may have underestimated its therapeutic effect. Further, the slight differential effect between the OROS-MPH and ATX treatment groups might also be a type I error. We excluded youths with significant current psychiatric comorbidity, restricting the generalization of the findings to more comorbid, clinically relevant populations. These limitations indicate that further studies with better design and larger sample size are required.

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[Trial registration: ClinicalTrials.gov, Identifier: NCT01065259. Concerta and Strattera on the executive function in attention deficit hyperactivity disorder (ADHD) children (http://clinicaltrials.gov/ct2/show/NCT01065259?term=NCT01065259&rank=1).]

Statement of Interest

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