A head-to-head randomized clinical trial of methylphenidate and atomoxetine treatment for executive function in adults with attention-deficit hyperactivity disorder

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Abstract

Results regarding the effects of methylphenidate and atomoxetine on executive functions were inconsistent and no study has directly compared the efficacy of these two medications in improving executive functions in adults with attention-deficit hyperactivity disorder (ADHD). We conducted an 8–10 wk, open-label, head-to-head, randomized clinical trial involving adults with a clinical diagnosis of ADHD confirmed by psychiatric interview. The two treatment arms were immediate-release methylphenidate (IR-methylphenidate) (n=31) and atomoxetine once daily (n=32). Executive functions were assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB), including spatial working memory, spatial short-term memory, sustained attention and spatial planning at visit 3 (60.4±6.3 d). Compared to baseline, adults treated with atomoxetine showed significant improvement in spatial working memory, spatial short-term memory, sustained attention and spatial planning at visit 3; adults treated with IR-methylphenidate showed significant improvement in spatial working memory at visit 3. Comparing the magnitude of improvement in executive functions between these two medications, the effect was generally similar for the two groups, although atomoxetine might have significantly greater efficacy than IR-methylphenidate in terms of improving spatial planning (SOC). Our results provide evidence to support that both IR-methylphenidate and atomoxetine improved various executive functions in adults with ADHD with greater improvement in atomoxetine than IR-methylphenidate in spatial planning.

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Key words: Adult ADHD, atomoxetine, executive function, methylphenidate.

Introduction

Attention deficit hyperactivity disorder (ADHD) is a lifelong neuropsychiatric disorder (Biederman and Faraone, 2005; Gau et al., 2005; Polanczyk et al., 2007) with long-term academic and social impairments that may be mediated by impaired executive function (Diamantopoulou et al., 2007). The literature documents executive function deficits in ADHD (Seidman, 2006), with the most consistent results for planning, working memory and inhibition, followed by set-shifting tasks (Pennington and Ozonoff, 1996). Executive function deficits tend to persist into adolescence and young
adulthood (Biederman et al., 2007, 2008a; Hinshaw et al., 2007).

Executive functions, regulated by catecholamine systems (Arnsten and Li, 2005), involve distinctive brain areas, including the prefrontal cortex, thalamus, basal ganglia, cerebellum and parietal and temporal lobes (Middleton and Strick, 2001, 2002; Collette and Van der Linden, 2002; Willcutt et al., 2005). Executive dysfunctions have been suggested as independent targets for ADHD treatment (Faraone et al., 2005; Arnsten and Pliszka, 2011).

Among the psychostimulants, methylphenidate is the most commonly prescribed agent and widely studied (Greenhill et al., 2002; Faraone et al., 2004). Both immediate-release methylphenidate (IR-methylphenidate) and osmotic release oral system methylphenidate (OROS-methylphenidate) are effective in treating children (Gau et al., 2006, 2008; Wilens et al., 2006) and adults (Kessler et al., 2005; Adler et al., 2009a) with ADHD without significant difference between the two regimens (Faraone and Glatt, 2010). Methylphenidate not only reduces core symptoms of ADHD, but also improves many functional domains via blockage of the transporter for dopamine (DA) and norepinephrine (NE; Hechtman et al., 2004; Coghill, 2010). Moreover, some studies have demonstrated that methylphenidate can improve executive function deficits, including sustained attention (Bouffard et al., 2003; Turner et al., 2005; Wilson et al., 2006; Biederman et al., 2008b), verbal learning (Biederman et al., 2008b), verbal memory (Kurscheidt et al., 2008) and response inhibition (Aron et al., 2003; Boonstra et al., 2005) in adults with ADHD. Moreover, in a head-to-head comparison study in healthy adults, Marquand et al. (2011) found that the effects of methylphenidate and atomoxetine on working memory were context-dependent. However, other studies failed to demonstrate the efficacy of methylphenidate in organization (Biederman et al., 2008b), working memory (Biederman et al., 2008b), set shifting (Biederman et al., 2008b; Advokat, 2010) and problem solving (Muller et al., 2007). In summary, the findings regarding the efficacy of methylphenidate in improving executive function are inconsistent in adult ADHD.

Atomoxetine, a potent inhibitor of the presynaptic NE transporter, has been approved by the United States Food and Drug Administration as the first non-stimulant agent for the treatment of ADHD in children, adolescents and adults. Atomoxetine is efficacious in reducing ADHD symptoms (Spencer et al., 1998; Michelson et al., 2003) and improving social and family functioning (Adler et al., 2009b) among adults with ADHD. Moreover, atomoxetine can improve inhibitory control (Chamberlain et al., 2007) and inhibitory capacity (Faraone et al., 2005) of adults with ADHD. A recent randomized, double-blind clinical trial using the Brown Attention-Deficit Disorder Scale, the proxy data of ecological executive function assessments, demonstrated that atomoxetine was associated with improvement in five clusters (organization and activating for work; focusing on tasks; regulating alertness and effort; modulating emotion; utilizing working memory) during a 6-month period (Brown et al., 2011). However, other studies failed to demonstrate its efficacy in sustained attention (Spencer et al., 1998), attentional set shifting (Spencer et al., 1998), visual memory (Spencer et al., 1998) and spatial working memory (SWM; Chamberlain et al., 2007) among adults with ADHD. In summary, the findings regarding the efficacy of atomoxetine in improving executive functions are also quite limited and inconsistent for adults with ADHD.

Dysregulated dopaminergic and noradrenergic neurotransmission has been widely implicated in the pathophysiology of ADHD (Arnsten, 2006a). Previous studies have confirmed the mechanisms of pharmacotherapy dependent on a mixture of dopaminergic and noradrenergic actions cortically and dopaminergic effects subcortically (basal ganglia; Arnsten, 2011; Del Campo et al., 2011). However, the impact of DA and NE on executive function may be somewhat different. For example, DA is associated with improving working memory by suppressing inputs to the cell irrelevant to current demands (Vijayraghavan et al., 2007) and NE can improve working memory and inhibitory control by strengthening appropriate network connections and allowing networks to maintain their firing for long periods (Arnsten, 2009; Robbins and Arnsten, 2009; Chamberlain et al., 2011). Taking the above neurobiological evidence into account, DA and NE, operating from different directions, may increase the signal: noise ratio of prefrontal neurons.

Despite preliminary results demonstrating the potential therapeutic effects of methylphenidate and atomoxetine on executive function performance (Del Campo et al., 2011), very few studies have compared these two medications directly in children with ADHD (Yang et al., 2011; Schulz et al., 2012) and in healthy adults (Marquand et al., 2011; Nandam et al., 2011). To the best of our knowledge, there has been no head-to-head comparison study of methylphenidate and atomoxetine in adults with ADHD. Since the psychopharmacological mechanisms of methylphenidate and atomoxetine are somewhat different, there may be different effects on executive function in adults.
with ADHD. Hence, we directly compared the long-term efficacy of methylphenidate and atomoxetine in improving executive functions in drug-naive adults with ADHD.

Method

Participants

We recruited participants, aged 18–50 yr, by advertisements at an out-patient clinic of the Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan, and in the newspaper. Those adults interested in our study were first assessed by a board-certified child psychiatrist (first author) through telephone interview for around 30–40 min and screened by the screener(s) using the Chinese-language version of the Adult ADHD Self-Report Scale-v1.1 (Kessler et al., 2005; Yeh et al., 2008). Those identified as probable cases of ADHD by telephone interview would be invited for further clinical assessment by the board-certified child psychiatrists. Those who met the diagnostic criteria of DSM-IV for ADHD and whose clinical diagnosis of ADHD was confirmed by the modified adult version of the ADHD supplement of the Chinese version of the Schedule for Affective Disorders and Schizophrenia–Epidemiological Version (K-SADS-E; Chang, 2012) for childhood and current diagnosis of ADHD would be enrolled. The Chinese K-SADS-E, as a reliable and valid instrument to assess child and adolescent psychiatric disorders, has been extensively used in a variety of clinical (Gau and Chiang, 2009; Gau et al., 2010) and epidemiological (Gau et al., 2005, 2007) studies in Taiwan. All participants were assessed by the Wechsler Adult Intelligence Scale – Revised to confirm their IQ >80.

Participants were excluded if they had any systemic medical illness, such as cardiovascular disease, a history of bipolar disorder, psychosis, major depression, substance use disorder, learning disability, pervasive developmental disorder or mental retardation. Participants who currently had depressive or anxiety symptoms or suicidal ideation or who had been treated with any psychotropic agent, including medications for ADHD, were also excluded.

Study design and procedures

The Research Ethics Committee of National Taiwan University Hospital, Taiwan (ID: 200705065R; ClinicalTrials.gov no. NCT00550667) approved this study prior to its implementation. The potential subjects received a comprehensive explanation of the purpose and procedure of this study as well as a reassurance of confidentiality. Written informed consent was obtained from all participants.

This was an 8–10 wk open-label, randomized, head-to-head clinical trial with the IR-methylphenidate and atomoxetine groups at a 1:1 ratio, determined by computer-generated random sequencing. The participants received three assessments and medication administration at baseline (visit 1), weeks 4–5 (visit 2) and weeks 8–10 (visit 3) after an initial clinical assessment. Participants started taking medication, either IR-methylphenidate (an initial daily dosage of 30 mg, at 10 mg thrice daily) or atomoxetine (an initial dosage of 0.5 mg/kg in the first week and 1.2 mg/kg from the second week) at visit 1. Drug dosage was titrated at visit 2, depending on clinical response and adverse effects (maximum daily dosage of IR-methylphenidate = 60 mg, 20 mg thrice daily; maximum daily dosage of atomoxetine = 1.2 mg/kg).

The peak plasma concentration of IR-methylphenidate is reached approximately 1–2 h after ingestion and the half-life of the drug in plasma is 2–4 h (Gualtieri et al., 1982).

Therefore, cognitive testing was started 90 min after ingestion of the drug to maximize drug levels during the test session (Gualtieri et al., 1982).

Efficacy measures

Executive functions were assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline and visit 3. The validity of the CANTAB has been confirmed by demonstrations of comparable effects following manipulations of homologous neural regions and of common effects of pharmacological agents often used in the treatment of ADHD (Rhodes et al., 2006; Chamberlain et al., 2007, 2011). The psychometric properties of CANTAB established in Western populations (Luciana, 2003) and in Taiwan (Gau et al., 2009; Gau and Shang, 2010a) are good. Five CANTAB tasks involving executive abilities were employed.

Spatial span (SSP)

The SSP measured spatial short-term memory. Similar to the Corsi blocks task (Milner, 1971), this task required the ability to remember the order in which visual stimuli were presented. At the beginning, nine white boxes were presented in fixed locations on the screen. Next, the boxes changed colour, one after the other, in a pre-determined sequence. The participants were then asked to point to the boxes in the order in which they had changed colour. The test
began with two-box problems and went up to nine-box problems. Two indices were reported: (1) span length: the longest sequence successfully recalled; (2) total errors: the number of times an incorrect box was selected.

SWM
The SWM, based on a self-ordered search test (Petrides and Milner, 1982) and adapted from Olton’s radial arm maze (Olton, 1987), assessed non-verbal working memory. First, a number of coloured boxes were displayed on the screen. The subject had to touch the coloured boxes one at a time to find the token inside. Once a token was found, there would never be another token inside the same square. To avoid repeatedly searching in previously targeted locations, the subject had to remember where he/she had searched and found a token. The order of searching was self-determined and the number of boxes started at two. The subject ultimately completed four trials each with two boxes, three boxes, four boxes, six boxes and eight boxes. Two major indices included: (1) strategy utilization: the number of search sequences starting with a novel box in the difficult problems (both six- and eight-box problems); (2) errors in the total and three different levels of difficulty (four-, six- and eight-box problems): the total errors for four-, six- and eight-box problems were calculated based on the between-errors, within-errors and double errors of particular box problems.

Intra-extra-dimensional set shifts (IED)
The IED assessed a subject’s ability to selectively maintain his/her attention on the specific attribute of compound stimuli across different examples, or intra-dimensional shift, and then to shift their attention to a previously irrelevant attribute of stimuli or extra-dimensional shift (EDS; Downes et al., 1989). The test comprised nine stages with increasing difficulty. Throughout the IED task, the subject was required to discover rules, initially through trial and error. Once the rule was achieved on six consecutive occasions, the computer established a new rule. Despite these changes, the subject had to try to make as many correct choices as possible. Four target indices were included: (1) pre-EDS errors: the number of errors made prior to the EDS stage; (2) EDS errors: errors made in the EDS stage; (3) completed stages: the number of stages successfully completed; (4) adjusted total trials: the adjustment adds 50 for each stage not attempted due to failure at an earlier stage.

Rapid visual information processing (RVIP)
The RVIP, a 4-min visual continuous performance test (CPT) modified and simplified from Wesnes and Warburton’s task (Wesnes and Warburton, 1984) was designed to assess sustained attention capacity (Sahakian et al., 1989). Digits (ranging from 2 to 9) appear one at a time (100 digits/min) in a random order. The subject had to detect three target sequences (3–5–7, 2–4–6, 4–6–8) and respond (within 1800 ms after the onset of the last number) when they saw the last number (7, 6 and 8, respectively). The subject was instructed to detect as many target sequences (27 in total) as possible. The total hit score represented the number of occasions upon which the target sequence was correctly responded to. The score of total misses represented the number of occasions the participant failed to respond to a target sequence within the response window. The score of total false alarms represented the number of times the participant responded outside the response window of a target sequence. The score of total correct rejections represented the number of stimuli that were correctly rejected. Five indices were presented: (1) probability of hits (h, the participant responding correctly): total hits divided by the sum of total hits and total misses; (2) probability of false alarms (f, the participant responding inappropriately): total false alarms divided by the sum of total false alarms and total correct rejections; (3) A’ (calculated as \(0.5 + \frac{(h-f)+(h-f)^2}{4*}\text{h}^* (1-f))\): a signal detection measure of sensitivity to the target, regardless of response tendency (Sahgal, 1987); (4) mean latency: mean time taken to respond with correct responses.

Stockings of Cambridge (SOC)
The SOC assessed spatial planning based on the Tower of London test (Shallice, 1982) and requires participants to move balls according to a goal position with given orders and locations. Three balls were distributed in both the upper and lower stocking displays. The placement in the upper display was the template for the lower display. Thus, the subject was required to move the balls in the lower display until the three balls were located in the same place, respectively, indicated in the upper display. Before moving the balls, the subject was asked to plan the moves and to use as few moves as possible in order to copy the upper display. The starting position of the balls was varied so that the solution could be reached after a minimum of two, three, four or five moves. For each trial, the subject also completed a yoked control condition in order to provide baseline measures of motor
initiation and executive times. Four major indices were presented: (1) problems solved in the specified minimum number of moves: the number of occasions that were successfully completed in the minimum possible number of moves; (2) mean moves: the number of moves taken in excess of the specified minimum number, but within the maximum allowed; (3) initial thinking time: the difference in reaction time taken to select the first ball for the same problem under the two conditions; (4) subsequent thinking time: the difference in time between selecting the first ball and completing the problem for the same problem under the two conditions.

**Adherence**

We used subjective and objective assessments to determine the adherence of IR-methylphenidate and atomoxetine. The subjective assessment was based on retrospective feedback from the participants themselves. The objective assessment of the daily missed doses was based on pill count and a standard interview conducted by the investigators. We compared adherence between the two treatment groups based on average days of taking medication per week.

**Statistical analyses**

SAS version 9.2 (SAS Institute Inc., USA) was used to conduct data analysis. The α value was pre-selected at the level of $p<0.05$ and the intent-to-treat principle was used in the statistical analysis. The mean scores and S.D. were presented for continuous variables and percentage was used for categorical variables for the demographics and baseline assessments. Because of the repeated measures of the same subject, we used a linear multi-level model to test the executive functions measured by CANTAB at weeks 8–10, compared to baseline (week 0) and to test the visits × drugs interactions. In addition, Cohen’s $d$ was used to compute the effect size on the inter-session variance for the comparisons between baseline and weeks 8–10, with small, medium and large effect sizes as Cohen’s $d \geq 0.2$ to $<0.5$, $\geq 0.5$ to $<0.8$ and $\geq 0.8$, respectively.

**Results**

**Sample description and medication**

A total of 71 screen-positive participants were eligible subjects with a clinical diagnosis of ADHD based on the DSM-IV. Two of them were excluded because their current symptom severity did not reach the DSM-IV criteria based on modified ADHD supplement of the K-SADS-E interview and another six were excluded due to personal reasons ($n=3$), being a psychologist ($n=1$) and having some autistic traits ($n=2$). Finally, 63 participants entered our study and were randomly assigned to the IR-methylphenidate ($n=31$) and atomoxetine ($n=32$) groups. At baseline, the two groups did not differ in demographics, including gender, age, intelligence and symptom severity (Table 1). They did not differ in the CANTAB performance involving executive function (Supplementary Table S1).

In the IR-methylphenidate group, 26 participants (81.2%) completed the visit 2 assessment and 21 (67.7%) completed the visit 3 assessment. Patient drop-out was due to personal reasons ($n=6$), loss of contact ($n=3$) and medication change ($n=1$). In the atomoxetine group, 29 participants (90.6%) completed the visit 2 assessment and 24 (75.0%) completed the visit 3 assessment. Patient drop-out was due to personal reasons ($n=5$), traffic issues ($n=1$) and loss of contact ($n=2$) (Fig. 1). Fisher’s Exact tests revealed no significant difference in follow-up compliance between the two groups at visit 2 ($p=0.474$) and visit 3 ($p=0.585$). In addition, there were no group differences in number of days taking medications at visit 2 ($p=0.26$) and visit 3 ($p=0.10$; Ni et al., 2013).

The mean daily dosages were 28.8 and 34.8 mg for the IR-methylphenidate group and 82.0 and 83.0 mg for the atomoxetine group at visit 2 and visit 3, respectively. The most common adverse effects (methylphenidate, atomoxetine) reported at visit 2 were decreased appetite (46.2%, 41.1%), followed by vomiting (35.0%, 32.0%) and palpitation (19.2%, 17.9%), which may prevent further dosage adjustment at visit 2. However, there was no statistically significant difference of adverse effects between the two groups at visit 2 ($p$ values ranging from 0.100 to 0.937) and at visit 3 ($p$ values ranging from 0.109 to 1.00; Ni et al., 2013).

**Comparison of executive functions**

The atomoxetine (60.1±6.6 d) and IR-methylphenidate (60.6±6.2 d) groups did not significantly differ in the days of visit 3 when they received the CANTAB ($p=0.807$) from the baseline. In addition, there was no statistically significant difference of baseline executive functions performance between these two groups (all $p$ values $\geq 0.05$; Supplementary Table S1).

**SWM**

In the atomoxetine group, we found significantly better strategy utilization (lower strategy scores) and fewer errors (four-box, eight-box and total) at weeks...
8–10 than at baseline with medium effect sizes (Cohen’s $d$ ranging from 0.49 to 0.71). In the IR-methylphenidate group, we found significantly fewer total errors at weeks 8–10 than at baseline with a medium effect size (Cohen’s $d$, 0.51). Comparing the extent of improvement directly, the atomoxetine group significantly had greater improvement than the IR-methylphenidate group in errors of four-box problems (Table 2).

SSP

In the atomoxetine group, we found significantly longer span sequences successively recalled at weeks 8–10 than at baseline with a small effect size (Cohen’s $d$, 0.44), suggesting improved spatial short-term memory with atomoxetine after 8–10 wk of treatment. There was no significant improvement in SSP in the IR-methylphenidate group. When comparing two treatments directly, there was no significant difference in span length or total errors (Table 2).

IED

In the IR-methylphenidate group, adjusted total trials significantly decreased at weeks 8–10 from baseline with a medium effect size (Cohen’s $d$, 0.59). In the atomoxetine group, there was no significant difference between weeks 8–10 and baseline. When comparing the two groups directly, there was also no significant difference in terms of IED (Table 2).

RVIP

In the atomoxetine group, there were higher probability of hits and better sensitivity to the target

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Table 1. Demographics and baseline characteristics of participants with ADHD

<table>
<thead>
<tr>
<th></th>
<th>Methylphenidate $(n=31)$</th>
<th>Atomoxetine $(n=32)$</th>
<th>Overall $(n=63)$</th>
<th>$F_{(1, 61)}$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, $n$ (%)</td>
<td>18 (58.1)</td>
<td>19 (59.4)</td>
<td>37 (58.7)</td>
<td>$\chi^2_{(1)}=0.01$</td>
<td>0.916</td>
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<tr>
<td>Age, mean (S.D.)</td>
<td>31.4 (7.2)</td>
<td>31.2 (8.4)</td>
<td>31.3 (7.8)</td>
<td>$F=0.01$</td>
<td>0.904</td>
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<td>Educational level, $n$ (%)</td>
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<td></td>
<td>$\chi^2_{(1)}=0.40$</td>
<td>0.526</td>
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<tr>
<td>College or higher</td>
<td>27 (87.1)</td>
<td>26 (81.3)</td>
<td>535 (84.1)</td>
<td></td>
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</tr>
<tr>
<td>Senior high or below</td>
<td>4 (12.9)</td>
<td>6 (18.8)</td>
<td>10 (15.9)</td>
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<tr>
<td>Employment status, $n$ (%)</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2_{(2)}=1.35$</td>
<td>0.508</td>
</tr>
<tr>
<td>Professional</td>
<td>6 (19.4)</td>
<td>3 (9.4)</td>
<td>9 (14.3)</td>
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</tr>
<tr>
<td>Technical personnel</td>
<td>12 (38.7)</td>
<td>15 (46.9)</td>
<td>27 (42.9)</td>
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</tr>
<tr>
<td>Non-technical personnel</td>
<td>13 (41.9)</td>
<td>14 (43.8)</td>
<td>27 (42.9)</td>
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</tr>
<tr>
<td>DSM-IV ADHD Subtype</td>
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<td></td>
<td>$\chi^2_{(2)}=2.41$</td>
<td>0.300</td>
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<td>Combined type</td>
<td>14 (45.2)</td>
<td>16 (50.0)</td>
<td>30 (47.6)</td>
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<tr>
<td>Inattentive type</td>
<td>17 (54.8)</td>
<td>14 (43.8)</td>
<td>31 (49.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity type</td>
<td>0 (0)</td>
<td>2 (6.3)</td>
<td>2 (3.2)</td>
<td></td>
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</tr>
<tr>
<td>Symptom counts based on the ADHD supplement, mean (S.D.)</td>
<td></td>
<td></td>
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<tr>
<td>Inattention</td>
<td>7.6 (1.5)</td>
<td>7.2 (1.7)</td>
<td>7.4 (1.6)</td>
<td>$F=0.81$</td>
<td>0.371</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>3.2 (1.6)</td>
<td>3.4 (1.7)</td>
<td>3.3 (1.7)</td>
<td>$F=0.25$</td>
<td>0.617</td>
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<tr>
<td>Impulsivity</td>
<td>2.0 (1.0)</td>
<td>1.9 (1.0)</td>
<td>2.0 (1.0)</td>
<td>$F=0.23$</td>
<td>0.632</td>
</tr>
<tr>
<td>Adult Self-Report Scale, mean (S.D.)</td>
<td></td>
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<tr>
<td>Inattention</td>
<td>26.6 (5.2)</td>
<td>25.7 (5.9)</td>
<td>26.1 (5.6)</td>
<td>$F=0.40$</td>
<td>0.532</td>
</tr>
<tr>
<td>Hyperactivity-impulsivity</td>
<td>20.3 (7.4)</td>
<td>20.3 (7.7)</td>
<td>20.3 (7.6)</td>
<td>$F=0.00$</td>
<td>0.999</td>
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<tr>
<td>Intelligence quotient (IQ)</td>
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<tr>
<td>Full-scale IQ</td>
<td>112.1 (9.3)</td>
<td>112.3 (12.8)</td>
<td>112.2 (11.3)</td>
<td>$F=0.00$</td>
<td>0.955</td>
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<tr>
<td>Performance IQ</td>
<td>110.2 (8.9)</td>
<td>109.9 (13.3)</td>
<td>110.1 (11.4)</td>
<td>$F=0.01$</td>
<td>0.933</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>112.3 (11.7)</td>
<td>112.6 (13.5)</td>
<td>112.4 (12.7)</td>
<td>$F=0.01$</td>
<td>0.923</td>
</tr>
</tbody>
</table>

ADHD, Attention-deficit hyperactivity disorder.
sequences at weeks 8–10 than at baseline, with medium to large effect sizes (Cohen’s $d$ ranging from 0.86 to 0.95). In the IR-methylphenidate group, there was no significant improvement in RVIP after 8–10 wk of treatment. When comparing the two treatments directly, there was no significant difference in RVIP (Table 2).

SOC

Both treatment groups had significantly shorter subsequent thinking time in four move problems at weeks 8–10 than at baseline, with medium effect sizes (Cohen’s $d$, 0.68 and 0.79, respectively). Comparing the two medications directly, the atomoxetine group had significantly fewer moves (five problems and total) from baseline to weeks 8–10 than the IR-methylphenidate group (Table 2).

Discussion

As the first head-to-head randomized clinical trial in adults with ADHD, we directly compared the efficacy of IR-methylphenidate and atomoxetine in a wide range of executive functions over 8–10 wk. We found that IR-methylphenidate was associated with improvement in SWM, attentional set shifting (IED) and spatial planning/problem solving (SOC). Atomoxetine was associated with improvement in SSP, SWM, sustained attention (RVIP), inhibitory ability (RVIP) and spatial planning/problem solving (SOC).

IR-methylphenidate effect on executive functions

Despite a past report of no effect of methylphenidate on SWM in drug-naive boys with ADHD (Rhodes et al., 2006) and on verbal working memory in young adults with ADHD (Biederman et al., 2008b), our results lend evidence to support the association of IR-methylphenidate with improving SWM in adults with ADHD, consistent with findings in healthy adults (Elliott et al., 1997; Mehta et al., 2000; Clatworthy et al., 2009) and in uncontrolled (Kempton et al., 1999; Barnett et al., 2001) and controlled (Bedard et al., 2004; Mehta et al., 2004) studies of children with ADHD. For example, Mehta first demonstrated that methylphenidate-induced improvements in working
Table 2. Comparison of performances in CANTAB

<table>
<thead>
<tr>
<th></th>
<th>IR-methylphenidate (n=21)</th>
<th>Atomoxetine (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (S.D.)</td>
<td>Week 8–10 Mean (S.D.)</td>
</tr>
<tr>
<td>Spatial working memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strategy utilization</td>
<td>32.42 (4.45)</td>
<td>31.67 (5.62)</td>
</tr>
<tr>
<td>Total errors</td>
<td>25.69 (13.70)</td>
<td>18.57 (14.31)</td>
</tr>
<tr>
<td>4-box problems†</td>
<td>1.46 (1.94)</td>
<td>0.95 (1.36)</td>
</tr>
<tr>
<td>6-box problems</td>
<td>6.81 (5.08)</td>
<td>4.43 (4.64)</td>
</tr>
<tr>
<td>8-box problems</td>
<td>17.42 (10.75)</td>
<td>13.19 (11.77)</td>
</tr>
<tr>
<td>Spatial span</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Span length</td>
<td>7.00 (1.23)</td>
<td>7.14 (1.24)</td>
</tr>
<tr>
<td>Total errors</td>
<td>14.81 (6.72)</td>
<td>14.05 (7.70)</td>
</tr>
<tr>
<td>Intra-extra dimensional set shift</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed stages</td>
<td>8.52 (1.66)</td>
<td>9.00 (0.00)</td>
</tr>
<tr>
<td>Extra-dimensional shift errors</td>
<td>5.96 (7.35)</td>
<td>3.29 (4.17)</td>
</tr>
<tr>
<td>Pre-extra-dimensional shift errors</td>
<td>7.40 (4.04)</td>
<td>6.48 (3.36)</td>
</tr>
<tr>
<td>Total trials (adjusted)</td>
<td>82.04 (25.61)</td>
<td>70.67 (9.02)</td>
</tr>
<tr>
<td>Rapid visual information processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of hits</td>
<td>0.74 (0.13)</td>
<td>0.78 (0.16)</td>
</tr>
<tr>
<td>Probability of false alarm</td>
<td>0.04 (0.006)</td>
<td>0.03 (0.004)</td>
</tr>
<tr>
<td>A*</td>
<td>0.93 (0.03)</td>
<td>0.94 (0.04)</td>
</tr>
<tr>
<td>Mean latency (ms)</td>
<td>430 (65.68)</td>
<td>410 (81.93)</td>
</tr>
<tr>
<td>Stocking of Cambridge Problems solved in minimum moves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total moves†</td>
<td>16.81 (1.69)</td>
<td>16.74 (1.35)</td>
</tr>
<tr>
<td>2-move problem</td>
<td>2.04 (0.20)</td>
<td>2.14 (0.36)</td>
</tr>
</tbody>
</table>
Memory occurs with task-related reductions in regional cerebral blood flow in the dorsolateral prefrontal cortex and posterior parietal cortex in healthy adults (Mehta et al., 2000). In a positron emission tomography study, Clatworthy et al. (2009) reported direct evidence that methylphenidate had significant effects on SWM, as predicted by changes in D2/D3 receptor availability in the ventral striatum in healthy adults.

Previous uncontrolled (Kempton et al., 1999) and controlled (Bedard et al., 2004) studies reported that IR-methylphenidate was effective in improving SSP in children with ADHD, but we did not find the same results in adults with ADHD after 8–10 wk of IR-methylphenidate treatment. Similar to previous findings in children (Rhodes et al., 2006) and adults (Biederman et al., 2008b; Advokat, 2010) with ADHD, our results did not provide evidence to support the efficacy of 8–10 wk IR-methylphenidate over attentional set-shifting in adults with ADHD. Our negative finding is not consistent with that of a double-blind, placebo-controlled, cross-over study investigating the effect of an acute dose of methylphenidate (0.5 mg/kg) over set-shifting in children with ADHD (Mehta et al., 2004), which supported the efficacy of methylphenidate over set-shifting. Such discrepant results can be explained by different age groups and task difficulties. A previous study demonstrated that age may be an important factor in interpreting performance of the attention-set shifting test (Luciana and Nelson, 1998). Adults with ADHD may have better task performance assessing set-shifting than children with ADHD.

Since our previous studies demonstrated that the magnitude of differences in the SWM and SOC increased with increased task difficulties (Gau and Shang, 2010a), it is possible that the inconsistent finding of methylphenidate over set-shifting in children and adults with ADHD just comes from a different status of difficulties between the two populations. Some studies have reported the efficacy of IR-methylphenidate in improving sustained attention in adults with ADHD (Bouffard et al., 2003; Turner et al., 2005; Vaidya et al., 2005; Wilson et al., 2006; Biederman et al., 2008b) and in healthy adults (Nandam et al., 2011), but our findings did not support such findings in adults with ADHD.

<table>
<thead>
<tr>
<th>3-move problem</th>
<th>4-move problem</th>
<th>5-move problem†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean initial thinking time (ms)</td>
<td>6356 (3099)</td>
<td>7367 (5090)</td>
</tr>
<tr>
<td>Mean subsequent thinking time (ms)</td>
<td>771 (536)</td>
<td>594 (528)</td>
</tr>
</tbody>
</table>

CANTAB, Cambridge Neuropsychological Test Automated Battery; IR-methylphenidate, immediate-release methylphenidate; β, parameter estimate of slope of changes over time.

* p<0.05; b p<0.01; c p<0.001.
† Significant difference between methylphenidate and atomoxetine group after 8–10 wk of treatment.
its efficacy in improving sustained attention as assessed by the RVIP.

Although previous studies did not find that IR-methylphenidate was effective in improving organization planning as measured by the Rey-Osterrieth complex figure (Biederman et al., 2008b) and Tower of London tasks (Muller et al., 2007) in adults with ADHD, consistent with child study (Rhodes et al., 2006), we found that IR-methylphenidate was efficacious in spatial planning as measured by the SOC test.

**Atomoxetine effect on executive functions**

In animal studies, NE efflux in the prefrontal cortex was selectively increased during a SWM task (Rossetti and Carboni, 2005), suggesting that NE may be involved in the active maintenance of spatial information (Rossetti and Carboni, 2005) and influence the working memory process (Arnsten and Li, 2005).

Although a single dose of atomoxetine had no effect on SWM in adults with ADHD (Chamberlain et al., 2007), treatment with atomoxetine for 8–10 wk improved SWM in adults with ADHD. Such finding is in line with the findings for children with ADHD after 12 wk of treatment (Gau and Shang, 2010b).

Like the past findings among adults with ADHD (Spencer et al., 1998; Chamberlain et al., 2007), we did not find that atomoxetine improved cognitive flexibility. Therefore, this study did not lend evidence to support the findings of improving attentional set-shifting in animals (Newman et al., 2008) and in children with ADHD (Gau and Shang, 2010b).

Corresponding to previous findings in healthy adults (Chamberlain et al., 2006) and in adults with ADHD (Chamberlain et al., 2007), we also found that atomoxetine was efficacious in sustained attention assessed by the RVIP. Although atomoxetine may not improve sustained attention in auditory CPT in adults with ADHD (Spencer et al., 1998), we found that atomoxetine was efficacious in improving sustained attention in adults with ADHD. Our findings are consistent with those for children with ADHD (Gau and Shang, 2010b) and in line with the NE hypothesis on the regulation of attention (Coull et al., 2004; De Martino et al., 2008).

Our finding of the effectiveness of atomoxetine in improving spatial planning and problem solving in adult ADHD corresponds to our previous child ADHD study (Gau and Shang, 2010b) and similar to a recent adult ADHD study via the Brown Attention-Deficit Disorder Scale (Brown et al., 2011).

**IR-methylphenidate vs. atomoxetine**

Methylphenidate has been shown to preferentially increase the extracellular levels of NE more than DA in the prefrontal cortex and subcortical regions and simultaneously improved sustained attention and working memory (Arnsten and Li, 2005; Berridge et al., 2006). On the other hand, by increasing cortical NE and DA levels without putative effects on the subcortical DA system (Bymaster et al., 2002), atomoxetine can improve many aspects of executive function in ADHD (Faraone et al., 2005; Chamberlain et al., 2007; Brown et al., 2011). Since there is very sparse innervation of the striatum by NE, atomoxetine, as a selective inhibitor of presynaptic NE, may not exert such a wide range of effects (Del Campo et al., 2011). With regard to the different psychopharmacological mechanisms, there may be differential effects in executive function improvements. Recently, Schulz and colleagues found that symptomatic improvement was associated with common reductions in bilateral motor activation for 6–8-wk OROS-methylphenidate and atomoxetine in children with ADHD. However, symptomatic improvement was divergently associated with the level of brain activation in the right inferior frontal gyrus, left anterior cingulate/supplementary motor area and bilateral posterior cingulate cortex for OROS-methylphenidate and atomoxetine (Schulz et al., 2012).

Limited studies were found to directly compare the efficacy of IR-methylphenidate and atomoxetine in improving executive function in children with ADHD (Yang et al., 2011) and in healthy adults (Marquand et al., 2011; Nandam et al., 2011). In a randomized, double-blind, placebo-controlled, cross-over study examining the effect of an acute dose of methylphenidate and atomoxetine on the stop signal inhibition task in 24 healthy adults, Nandam et al. (2011) found that methylphenidate was superior to atomoxetine in enhancing response inhibition and reducing response time variability. In a randomized, double-blind, placebo-controlled and cross-over study examining the effect of acute dose of methylphenidate and atomoxetine on working memory in 15 healthy adults, Marquand found no significant difference for both groups in non-rewarded working memory test (Marquand et al., 2011). In another 4–6-wk randomized controlled trial, Yang et al. found that both OROS-methylphenidate and atomoxetine improved executive functions in children and adolescents with ADHD. However, in a further direct comparison, Yang et al. found no obvious significant difference between the two medications with regard to executive
functions, no matter whether in laboratory-based neuropsychological tests or behaviour rating scales (Yang et al., 2011).

However, with longer treatment duration, we found that atomoxetine was probably superior to IR-methylphenidate in spatial planning in adults with ADHD, although the two medication groups were comparable in spatial short-term memory, SWM, sustained attention and attentional set shifting after treatment. The superiority of atomoxetine should be taken more conservatively because of a significant difference in the magnitude of improvement but no statistically significant interaction terms from group and visit. It appears that the results of our present study regarding executive functions are inconsistent with previous findings (Marquand et al., 2011; Nandam et al., 2011; Yang et al., 2011). Since previous studies demonstrated that catecholaminergic signalling has been associated with an 'inverted-U' dose-response relationship in the prefrontal cortex (Arnsten, 2006b; Levy, 2009) with optimal prefrontal cortex function at intermediate concentrations and too much or too little DA or NE resulting in impaired prefrontal cortex function, our findings may be explained by differential drug dosage. Previous meta-analysis studies of adults with ADHD confirmed a larger effect size under higher methylphenidate doses (Faraone et al., 2004). Although the IR-methylphenidate dosage in our study (10–20 mg thrice/d, 0.4–0.5 mg/kg.d) was similar to Bouffard's design (10–15 mg thrice/d), it was lower than that in the Nandam et al.'s study (30 mg once) of healthy adults and those in previous Western studies (0.6–1.1 mg/kg.d; Mattes et al., 1984; Guatierri et al., 1985; Wender et al., 1985; Bouffard et al., 2003; Kessler et al., 2005). The lower dosage in our study can be explained by clinical practice in Taiwan (Ni et al., 2013). The suggested initial dosage of IR-methylphenidate for adult ADHD is 30 mg/d and the maximum dosage is 60 mg/d. The daily dose of IR-methylphenidate is actually higher than that of methylphenidate, based on Taiwan's National Health Insurance Dataset analysis (17.81±8.95 mg for adults aged 18–30 yr) in the same year as the study conducted in 2009 (Ni et al., 2013). Although dosage titration was scheduled at weeks 4–5, most participants were satisfied with the efficacy of 30 mg/d IR-methylphenidate and decided to maintain the same dosage.

**Strength and limitations**

The major strengths of this study are, first, that this is the first head-to-head study comparing IR-methylphenidate and atomoxetine directly in adults with ADHD. Second, a wide range of executive functions were assessed comprehensively by standardized and well-validated neuropsychological tests. A lack of significant differences in baseline demographics, clinical variables and executive functions indicated a successful randomization.

However, there are several methodological limitations in our study. First, the results in our exploratory study should be regarded as preliminary because of multiple comparisons, small sample size and lack of a healthy comparison group. It needs replication in further studies including a healthy comparison group and a placebo control group in addition to two treatment groups using larger samples to address the issue of type I errors and to reduce bias from placebo effect or regression to the mean. Second, IR-methylphenidate is a controlled drug in Taiwan, which prevents us from conducting a double-blind, randomized clinical trial as an investigator-initiated clinical trial. Although executive functions were assessed by the CANTAB rather than by behavioural rating, the bias caused by non-blind design cannot be ignored and the potential placebo or experimental effect must be taken into consideration while interpreting our results. Third, the limited sample size may not have enough power to demonstrate the superiority of atomoxetine over IR-methylphenidate in spatial short-term memory, sustained attention and response inhibition. Fourth, generalization of the study results to broader ethnic Chinese populations with ADHD and adults with ADHD who have other psychiatric co-morbid conditions as usually seen in clinical practice may be questionable because of selection bias derived from sample recruitment only from one medical centre in Taipei and the exclusion of some psychiatric co-morbidities. Like many clinical trials, the selection bias generated due to the inclusion and exclusion criteria adopted in the study is not generally preventable. Fifth, the relatively lower dosage of IR-methylphenidate in our study than Western studies (Turner et al., 2005; Nandam et al., 2011), but higher than Taiwan's clinical practice should be taken into account while interpreting our findings. Finally, previous studies state that it can take 4–6 wk from the time a patient reaches their target dose of atomoxetine before ADHD symptoms begin to improve (Michelson et al., 2002). Since we may adjust dosage of atomoxetine at weeks 4–5, there may not have been adequate time at weeks 8–10 to see complete symptom improvement with atomoxetine.
Conclusions

Our findings strongly indicate that, similar to Western findings, both IR-methylphenidate and atomoxetine are associated with a significant improvement in various executive functions in adults with ADHD. Atomoxetine may be superior to IR-methylphenidate in spatial planning after 8–10 wk of treatment. Our findings not only expand the understanding of the relationship of catecholamines and executive function, but may also be of help in clinical practice in choosing the appropriate drug for ADHD adults with different executive function deficits. In the future, our findings should be linked to functional brain images to explore the precise effects of medications on the neural circuitry of executive function.

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Statement of Interest

None.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145713000357.

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