Attention deficit hyperactivity disorder (ADHD) is a common psychiatric disorder, affecting about 3% of adults and 5% of children and adolescents (1,2). ADHD is associated with a broad range of negative outcomes for affected subjects and puts a serious burden on families and the society. As a result, early identification and treatment of symptoms of ADHD is essential to effective management of this disorder.

ADHD implicates a challenge for social and academic development of affected children and leads to more life events in adulthood and developmental comorbidities (3,4). Spencer et al. (5) found that about 65% of the patients had one or more of concomitant diseases in addition to ADHD, which hampered the treatment efficacy in clinical settings. Effective treatment often includes pharmacotherapy with agents influencing neurotransmission (6). In recent years, concerns have been raised about available drugs for the treatment of ADHD including methylphenidate immediate-release tablets (IR-MPH), methylphenidate controlled-release tablets (OROS-MPH) and atomoxetine (AHC). MPH is recommended as the first-choice drug, while AHC is preferred in case of MPH-related side effects or the presence of comorbid tics, anxiety or substance abuse (7).

For school-aged children, stimulant agents are well-established as first-line pharmacotherapy. IR-MPH is the most commonly prescribed and best-studied stimulant...
medication and has been proved effective for treating ADHD (8). And OROS-MPH is a once-daily controlled-release formulation developed to overcome some of the limitations associated with IR-MPH (9) and has demonstrated efficacy and safety in reducing the core symptoms of ADHD (9,10). However, although MPH and AHC can effectively manage ADHD symptoms in most pediatric patients, many patients still fail to respond optimally to either.

A number of foreign studies have shown that IR-MPH, OROS-MPH and AHC are effective and well tolerated in children and adolescents with ADHD (11-13). Chinese studies have focused on the effectiveness and safety of IR-MPH, OROS-MPH and AHC for the treatment of ADHD in children and adolescents, particularly IR-MPH. However, it is still controversial as to which of them is the most safe and effective option for ADHD children and adolescents in China. Therefore, the urgent need is to collect the data from clinical setting for comparing the effectiveness and safety of IR-MPH, OROS-MPH and AHC and then provide more supportive evidence for their usage in the clinic practice.

In view of this, this systematic review summarized domestic and international published literatures on IR-MPH, OROS-MPH and AHC for Chinese children and adolescents with ADHD to evaluate their effectiveness and safety for informing the administration of these drugs.

**Subjects and methods**

**Search strategy**

Relevant publications were retrieved from CNKI, VIP and CBMDICS online using the following keywords or subject terms: Attention deficit hyperactivity disorder or ADHD, Ritalin or methylphenidate or immediate-release methylphenidate hydrochloride, methylphenidate hydrochloride controlled-release or controlled-release methylphenidate, and hydrochloride atomoxetine or atomoxetine. Literature related to Chinese children and adolescents were retrieved from PubMed, Embase and MEDLINE databases using the following subject terms: Methylphenidate, atomoxetine, and attention deficit disorder with hyperactivity. Relevant references were traced. Qualified articles from the earliest to those recorded in September 2010 in each database were used in this study.

**Inclusion criteria**

An eligible article should: (I) be designed as a randomized controlled trial or controlled clinical trial; (II) enroll Chinese children between 6 and 18 years of old who were diagnosed with ADHD according to the 4th Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (14), ICD-10, CCMD-3 or CCMD-II-R; (III) aim to compare the effectiveness and safety of IR-MPH, OROS-MPH and AHC, or any two of them; and (IV) have a clear description of the outcomes.

**Literature data extraction and quality assessment**

Relevant data were extracted from the articles using Epidata 3.1 software. These included the age, sex, baseline comparability, diagnostic criteria, interventions, follow-up time, sample size, outcome assessment indicators, outcome values, types, number and severity of adverse events, Symptom Rating Scale (TEES) scores during treatment, randomization scheme, allocation concealment, whether double-blind, patients lost to follow-up and approaches to outcome analysis.

The quality of an article was assessed in terms of its randomization method, allocation concealment, double-blind design, number of patients lost to follow-up and methods of outcome analysis. The assessment was completed by two independent reviewers. In the case of discrepancies unresolved through discussion, a third reviewer's opinion was sought.

**Statistical analysis**

The definition of the total incidence of adverse events in this study was different from the typical incidence. The numerator of the total incidence was the adverse events frequency (one patients would be count twice if he suffered two kinds adverse events) and the denominator was the number of patients. Analysis of included literature was completed in EXCEL 4.0 software.

**Results**

**Characteristics of included literature**

Of 89 retrieved articles, eight were included in the final analysis based on the inclusion criteria. Four articles compared IR-MPH and OROS-MPH in terms of their effectiveness and safety while the other four compared IR-MPH and AHC. None of the included articles described
Table 1: The basic characteristics of the included literatures

<table>
<thead>
<tr>
<th>Authors</th>
<th>Diagnostic criteria</th>
<th>Co-morbidities</th>
<th>Sample size and gender distribution (persons)</th>
<th>Age (years)</th>
<th>Contrast agents</th>
<th>Dosages</th>
<th>Follow-up (weeks)</th>
<th>Outcome assessment indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gau et al.</td>
<td>K-SADS-E Not mentioned</td>
<td>IR-MPH group: 32 (male: 29; females: 3) OROS-MPH group 32 (male: 29; females: 3)</td>
<td>6-15</td>
<td>IR-MPH OROS-MPH</td>
<td>IR-MPH group: 26.7±7.6 mg/d; OROS-MPH group: 27.7±13.5 mg/d</td>
<td>4</td>
<td>GTRS-R:S; GPRS-R:S; SKAMP; SAICA; PSQ; CGI-I</td>
<td></td>
</tr>
<tr>
<td>Bo et al.</td>
<td>CCMD-3 Not mentioned</td>
<td>IR-MPH group 39, OROS-MPH group 41 (all males)</td>
<td>6-13</td>
<td>IR-MPH OROS-MPH</td>
<td>In the IR-MPH group, the loading dose was 10 mg/d, which was increased to 20-40 mg/d within two weeks; In the OROS-MPH group, the loading dose was 18 mg/d, which was increased to 18-36 mg/d within two weeks</td>
<td>12</td>
<td>PSQ Conners Restless Index C-WISC effectiveness rate</td>
<td></td>
</tr>
<tr>
<td>Jiang et al.</td>
<td>DSM-IV Not mentioned</td>
<td>IR-MPH group 28 (male: 24; females: 4) OROS-MPH group 48 (male: 43; females: 5)</td>
<td>6-18</td>
<td>IR-MPH OROS-MPH</td>
<td>IR-MPH group: 10-20 mg/d; OROS-MPH group: 18 mg/d</td>
<td>4</td>
<td>PSQ</td>
<td></td>
</tr>
<tr>
<td>Pan et al.</td>
<td>DSM-IV Not mentioned</td>
<td>IR-MPH group 20 (male: 17; females: 3) OROS-MPH group 30 (male: 27; females: 3)</td>
<td>6-12</td>
<td>IR-MPH OROS-MPH</td>
<td>In the IR-MPH group, the loading dose was 10 mg/d and 18 mg/d, respectively in IR-MPH group and OROS-MPH group, which were optimized based on the therapeutic outcomes</td>
<td>6</td>
<td>SNAP-IV scale integrated visual and audio continuous performance test (IVA-CPT)</td>
<td></td>
</tr>
<tr>
<td>Li et al.</td>
<td>DSM-IV Not mentioned</td>
<td>AHC group 18 (male: 16; female: 2) IR-MPH group 17 (male: 14; females: 3)</td>
<td>6-16</td>
<td>AHC IR-MPH</td>
<td>The daily loading dose was 0.8 mg/kg for AHC group and 0.2 mg/kg for IR-MPH group, which were further adjusted based on clinical response and tolerance.</td>
<td>8</td>
<td>ADHDRS-IV-Parent:Inv CPRS-R:SCGI-S</td>
<td></td>
</tr>
<tr>
<td>Xu et al.</td>
<td>DSM-IV Not mentioned</td>
<td>AHC group 23; IR-MPH group 23 (No significant difference in terms of gender)</td>
<td>6-16</td>
<td>AHC IR-MPH</td>
<td>The daily loading dose was 0.8 mg/kg for AHC group and 0.2 mg/kg for IR-MPH group, which were adjusted on the first and second weekend based on the clinical response and tolerance.</td>
<td>8</td>
<td>ADHDRS-IV-Parent:Inv CPRS-R:SCGI-S</td>
<td></td>
</tr>
<tr>
<td>Zhan et al.</td>
<td>CCMD-3 Not mentioned</td>
<td>AHC group 35 (male: 25; female: 10) IR-MPH group 34 (male: 24; females: 10)</td>
<td>6-12</td>
<td>AHC IR-MPH</td>
<td>AHC group: 0.5-1.2 mg/kg daily; IR-MPH group: 5-10 mg/d</td>
<td>12</td>
<td>Conners Restless Index</td>
<td></td>
</tr>
<tr>
<td>Ding et al.</td>
<td>DSM-IV Not mentioned</td>
<td>AHC group 29 (male: 21; female: 8) IR-MPH group 29 (male: 20; females: 10)</td>
<td>6-18</td>
<td>AHC IR-MPH</td>
<td>AHC group: 0.5-1.2 mg/kg daily; IR-MPH group: 5-11 mg/d</td>
<td>12</td>
<td>Conners Restless Index</td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Assessment of the quality of the included literatures

<table>
<thead>
<tr>
<th>Authors</th>
<th>Randomization</th>
<th>Allocation concealment</th>
<th>Double blindness</th>
<th>Loss to follow-up</th>
<th>Outcome analysis methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gau et al. (7)</td>
<td>Mentioned randomization but without explaining the specific method</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>No</td>
<td>ITT</td>
</tr>
<tr>
<td>Bo et al. (8)</td>
<td>The visit sequences were randomized</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>No</td>
<td>ITT</td>
</tr>
<tr>
<td>Jiang et al. (9)</td>
<td>Not randomized</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Some loss to follow-up, but no reason was elucidated</td>
<td>per-protocol PI</td>
</tr>
<tr>
<td>Pan et al. (10)</td>
<td>Randomized by drawing lots</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Some loss to follow-up, and the reasons were elucidated</td>
<td>per-protocol PI</td>
</tr>
<tr>
<td>Li et al. (11)</td>
<td>Randomized using random number table</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>ITT</td>
</tr>
<tr>
<td>Xu et al. (12)</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>Yes</td>
<td>No</td>
<td>ITT</td>
</tr>
<tr>
<td>Zhan et al. (13)</td>
<td>Mentioned randomization but without explaining the specific method</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>No</td>
<td>ITT</td>
</tr>
<tr>
<td>Ding et al. (14)</td>
<td>Mentioned randomization but without explaining the specific method</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
<td>No</td>
<td>ITT</td>
</tr>
</tbody>
</table>

the therapeutic effect on comorbid conditions associated with ADHD. They had a small sample size (35 to 80 cases) with good baseline comparability in common, despite different medication doses, follow-up periods and indicators used in outcome evaluation (Table 1).

Quality evaluation of the articles

Of the eight studies, six had randomization but only one of them used allocation concealment and two were double-blind designs. Six studies did not have patients lost to follow-up, while the other two had such subjects but failed to provide the reasons. Six of them conducted intention-to-treat analysis (ITT) and the other two carried out per-protocol analysis (Table 2).

Evaluation of therapeutic efficacy

OROS-MPH versus IR-MPH

Three out of four studies used PSQ as an outcome indicator, though one of them (15) did not provide the specific values of PSQ. In view of the small number of included articles and discrepancies in outcome indicators (Table 1), only the results of those studies would be described in this section.

In the study conducted by Gau et al. (16), no statistical difference in the decrease of CTRS-R:S, CPRS-R:S and SKAMP scores was observed between the two groups on day 6, 13, 20 and 27 of treatment, though OROS-MPH was associated with faster reduction in the scores of all behavior dimensions than IR-MPH; the SAICA score suggested that OROS-MPH was significantly more effective in improving peer relations than IR-MPH; and the CGI-I score and mother satisfaction were also noticeably higher in the OROS-MPH group than in IR-MPH group. The study by Bo et al. (17) showed no difference in the Conners hyperactivity index score between the two groups. In their study, patients in both groups had significant improvement in all aspects of PSQ scores except the psychosomatic factor in the IR-MPH group. Both groups had a higher C-WISC score after treatment, though the difference was not compared. The difference in the efficacy between the two groups was not significant. Jiang et al. (15) showed PSQ scores in both groups significantly decreased compared with before treatment but did not compare the difference between groups. Pan et al. (18) showed significant differences in the SNAP total scores and sub-scores, and the IVA-CPT scores (except vision control quotient), of
both groups compared with before treatment, though the
difference in such improvement was not significant between
the two groups. However, any mean difference between
each value before and after 6-week treatment in the OROS-
MPH group was higher than that in the IR-MPH group.

In summary, IR-MPH and OROS-MPH were effective
treatment for ADHD. Compared with IR-MPH, OROS-
MPH might be better in improving peer relationships,
CGI-I score and mother satisfaction, psychosomatic factors,
SNAP scale score and the IVA-CPT Rating Scale scores.

AHC versus IR-MPH

Two out of four studies used ADHDRS-IV-Parent:Inv,
CGI-S, CPRS-R:S and other indicators for outcome
evaluation, and the other two used the Conners hyperactivity index scale. In view of the small number of
included articles and discrepancies in outcome indicators,
only the results of those studies would be described in this
section.

The study of Xu et al. (19) showed significant difference
in the ADHDRS-IV-Parent:Inv, CGI-S and CPRS-R:S scores in both groups before and after treatment. Zhan et al.
(20) and Ding Airu et al. (21) also showed difference in the
Conners hyperactivity index.

In summary, AHC and IR-MPH were effective for
ADHD, but there was no difference between them in terms
of ADHDRS-IV-Parent:Inv, CGI-S, CPRS-R:S and the
Conners hyperactivity index.

Safety evaluation

OROS-MPH versus IR-MPH

Apart from the study of Bu et al. (17) that compared adverse
reactions between groups using the TESS score table, the
other three (15,16,18) studies reported the number of cases
with adverse events in the two groups. As a result, adverse
events of those three reports were analyzed in combination.

Among 139 patients treated with OROS-MPH, 108 cases
of adverse events were reported and the total incidence was
77.7%. For the 131 patients receiving IP-MPH treatment, 110 cases of adverse events occurred and the total incidence was
84.0%. Adverse events associated with OROS-MPH,
in descending order of frequency, were loss of appetite, sleep disorders and stomach pain. As with IR-MPH, the
three most common adverse reactions were loss of appetite, dizziness and abdominal pain. As shown by the four studies, the
adverse events were mild and the incidence frequency were
not significantly different between the two groups.

Gau et al. (16) showed that anxiety, onychophagy and appetite
improved more quickly in the OROS-MPH group than in
IR-MPH group.

AHC versus IR-MPH

Among 105 patients treated with AHC, 54 cases of adverse
reactions were reported and the total incidence was 51.4%.
For the 103 patients receiving IP-MPH treatment, 51 cases
of adverse reactions occurred and the total incidence was
49.5%. Adverse events associated with AHC, in descending
order of frequency, included loss of appetite, sleep disorders
and stomach pain. As with IR-MPH, the three most
common adverse reactions were loss of appetite, dizziness
and abdominal pain. As shown by the four studies, the
adverse events were mild and the incidence frequency were
not significantly different between the two groups.

Discussion

Due to inconsistent diagnostic criteria, medication dose,
follow-up time and other factors that might affect the
outcome evaluation, as well as varying indicators for
outcome analysis, the included studies were not perfectly
eligible for pooled analysis. The small number of included
articles also limited the value of the pooled analysis. Hence,
this review only provided qualitative description of the
study results. The poor quality of a study would affect the
validity and reliability of the outcomes when included in
a pooled analysis. In this review, the study results were
of certain significance because they had good intergroup
comparability as shown in Table 1, though the quality and
compliance with report standards of related clinical studies
should be further improved.

This review suggested that IR-MPH, OROS-MPH
and AHC were effective for children and adolescents with
ADHD in China. There was no difference in the efficacy
ratings across different scales and dimensions between
OROS-MPH versus IR-MPH and AHC versus IR-MPH.
Compared with IR-MPH, OROS-MPH might be better
in improving peer relationships, CGI-I score and mother
satisfaction, psychosomatic factors, SNAP scale score
and the IVA-CPT Rating Scale. No clinical research comparing
the efficacy between OROS-MPH and AHC was found.

Steele et al. (22) conducted a study to compare OROS-
MPH and IR-MPH, which found that OROS-MPH
was superior to IR-MPH in terms of a variety of clinical
outcome measures, including the complete remission
rate. Xu et al. (23) carried out a meta-analysis of domestic
and international randomized, controlled studies on IR-MPH and AHC for ADHD children, finding that they had equivalent total scores regarding the improvement of ADHD conditions, though IR-MPH had better subscores than AHC. This review showed no difference between IR-MPH versus OROS-MPH and IR-MPH versus AHC, which might be due to a small number of included studies, inconsistent follow-up period (mostly not long enough), low quality of included studies and varying definition of adverse events.

As revealed in the two pair of comparisons, the incidence rates of adverse events were similar across groups without significant difference. Since all adverse reactions were mild, the three drugs could be considered safe and well tolerated. Loss of appetite was the most common adverse reaction with the three drugs.

The treatment for ADHD comorbid tic disorder was challenging as 15-30% children with ADHD presented tic symptoms or worsened underlying conditions after administration of stimulants (24). Overseas research showed that AHC not only improved the core symptoms of ADHD remarkably but also reduced the severity of tics in ADHD children with comorbid tic disorders (25,26). Zhang et al. (24) also reported that AHC was significantly effective for hyperactivity, attention deficit, motor tics, vocal tics in ADHD children with comorbid tic disorders. Foreign studies suggested that AHC could be useful for treating ADHD comorbid anxiety (27). However, few studies were done on the treatment of ADHD comorbidity with AHC in China. None of the included studies in this review identified comorbid conditions in their subjects. Hence, well-designed randomized, controlled trials would be needed to compare the effectiveness and safety of AHC, as well as IR-MPH and OROS-MPH for Chinese children and adolescents with ADHD and comorbid conditions.

**Acknowledgements**

None.

**Footnote**

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**References**
