

Comparison of Risperidone and Aripiprazole in the Treatment of Children with Attention-Deficit/Hyperactivity Disorder: A Systematic Review

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ABSTRACT

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Background and Objective: Attention-deficit/hyperactivity disorder (ADHD) is a disorder of childhood and adolescence characterized by persistent symptoms of increased activity and impulsive behavior. Totally, 2-5% of schoolchildren exhibit specific and comprehensive symptoms of ADHD. The aim of the present study was to investigate the comparison of risperidone and aripiprazole in the treatment of ADHD children.

Methods: A literature search was performed in the electronic databases of Embase, PubMed, Web of Science, Scopus, and Google Scholar for articles published from inception between 2005 and 2022. Persian keywords and their English equivalents in Mesh were used to search all domestic and foreign articles in all databases. This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines and the quality of articles was assessed using the risk of bias checklist.

Findings: Of the 320 articles initially identified, 8 were eventually included, with 4 articles published from Iran and 4 articles from other countries. Totally, 50% of the studies were related to Iran. The age of the studied subjects ranged from 3 to 18 years, and 283 children were studied and investigated. In 90% of the studies, with $p>0.05$, there was no significant difference in the efficacy of the two drugs, risperidone and aripiprazole.

Conclusion: In general, both risperidone and aripiprazole are effective for the treatment of ADHD and can be used according to the clinical conditions and medical history of the child.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a disorder of childhood and adolescence characterized by persistent symptoms of increased activity and impulsive behavior [1, 2]. Children with this disorder have more academic problems than other peers, they are excluded from the community or show antisocial behavior in school, and they also have many problems afterward [3].

In the classification of neurodevelopmental disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, ADHD was introduced as one of the most common disorders in childhood with features such as inattention, hyperactivity, and impulsivity [4]. Reports indicate that approximately 50% of patients in child psychiatric clinics are children with ADHD [5].

In 2007, a meta-analysis of more than 100 studies estimated the prevalence of ADHD in children and adolescents to be 5.3% worldwide [6]. Studies in Iran and the United States in children aged 6 to 18 years found that ADHD was diagnosed in 4% of Iranian children and 8.2% of American children [7].

The prevalence of ADHD in children is not related to gender differences. Thus, 3 to 10 times more boys than girls suffer from this disorder [8]. The exact cause of this disorder is not known, but some biological and environmental factors are involved in its development. Norepinephrine and dopamine play an important role in the regulation of attention in ADHD.

Norepinephrine plays a role in executive function and dopamine plays a role in maintaining attention [9, 10]. ADHD is associated with a high rate of psychiatric disorders. Treating behavioral disorders at an early age may help prevent long-term disability [11].

Drug treatment of ADHD is primarily with sympathomimetics. Methylphenidate is one of the most commonly used psychiatric medications for the treatment of ADHD [12].

Half of clinical patients suffer from disruptive behavior disorders (DBDs), and smoking, alcohol and illicit drug use, physical aggression, risky sexual

behavior, frequent or serious offending, and involvement in destructive crime have been associated with this disorder [4, 11].

Due to the association of ADHD with behavioral disorders, the use of atypical antipsychotics has increased [13]. Risperidone and aripiprazole are atypical antipsychotics. Risperidone is a safe and effective treatment for ADHD in children.

Aripiprazole is an agonist of D2 dopamine and serotonin 5HT1A receptors and an antagonist of serotonin 5HT2A receptors. Extrapyramidal side effects, hyperprolactinemia, weight gain, metabolic disturbances, and sedation common with other antipsychotics are less with this drug.

The efficacy and tolerability of aripiprazole in children and adolescents have been well-established in numerous clinical trials [11]. To date, no meta-analysis has comprehensively evaluated the comparison of risperidone and aripiprazole in the treatment of children with attention-deficit/hyperactivity disorder. There is also a knowledge gap in the assessment of predictors of response that needs to be addressed.

Considering the consequences of untimely treatment of ADHD and the existence of various drug therapies for the treatment of this disorder, a review of the studies comparing the two drugs risperidone and aripiprazole in the treatment of ADHD can be conducted by revealing and comparing the side effects of these two drugs, and the degree of tolerance of the drug in children and its efficacy should be useful in choosing the more appropriate drug. The aim of the current study was to investigate the comparison of risperidone and aripiprazole in the treatment of ADHD children in 8 articles.

Methods

Study design

This systematic review and meta-analysis were conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Figure 1) [14].

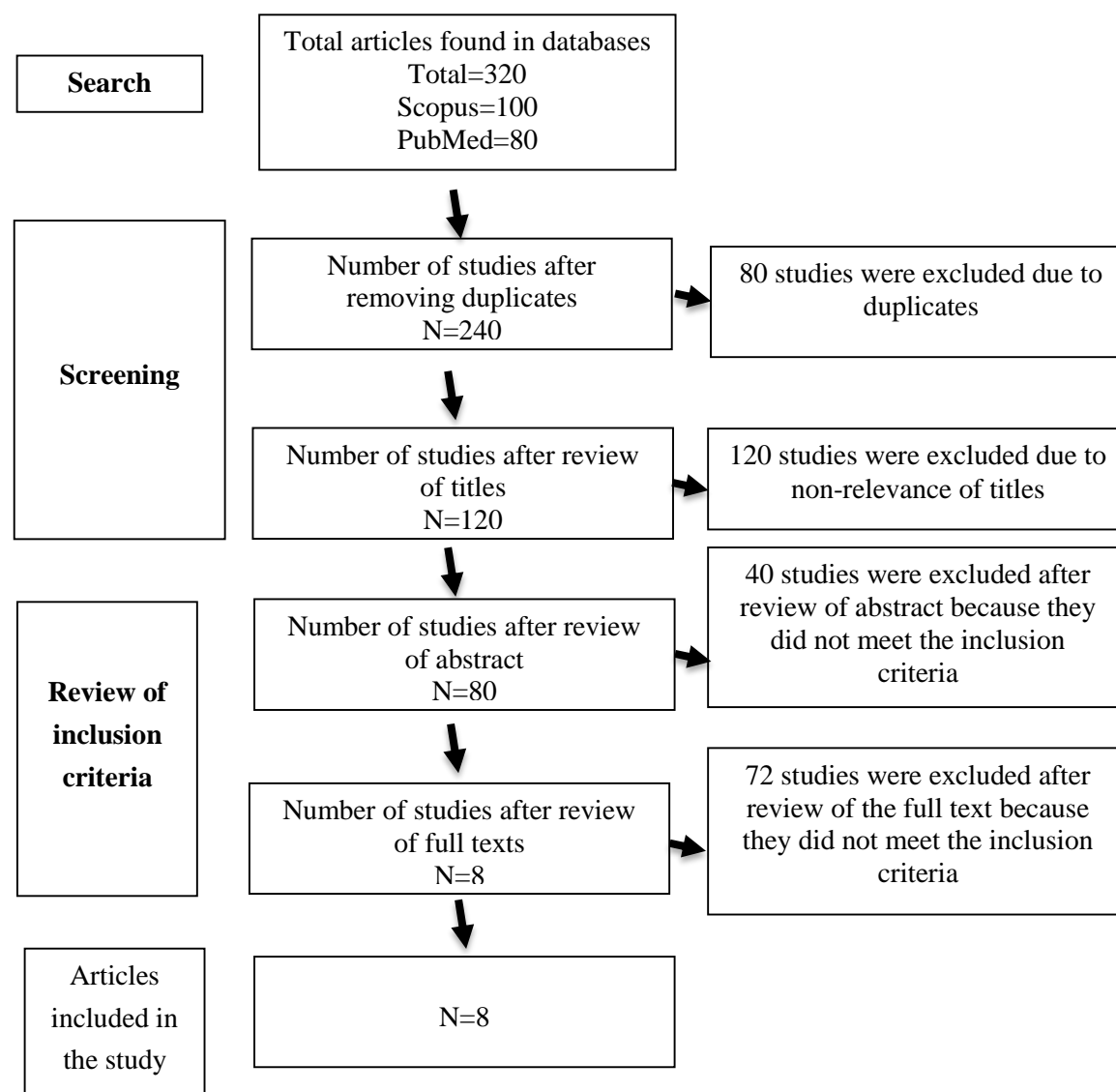


Figure 1: PRISMA flowchart and the steps for entering articles into the study

Inclusion and exclusion criteria

Studies were included if they: (1) were published between 2005 and 2022, (2) were written in English, (3) focused on children aged 3 to 18 years with a diagnosis of ADHD, (4) were peer-reviewed, and (5) were available in full text. Studies were excluded if they: (1) were case studies, (2) involved individuals diagnosed with ADHD in adulthood, or (3) focused on the cognitive treatment of ADHD. Case studies were excluded because they could not be generalized to the experiences of children with ADHD in adulthood. Studies with adult diagnoses were

excluded as the review aimed to compare risperidone and aripiprazole in the treatment of children with attention-deficit/hyperactivity disorder. Furthermore, ADHD treatment was not the focus of this review.

Search strategy and selection of articles

With the help of a digital college library, five databases were searched for relevant abstracts: Embase, PubMed, Web of Sciences, Scopus and Google Scholar. Articles published between 2005 and 2022. After searching for related terms in the

Medical Subject Headings (MeSH) database, the following keywords finally were selected: ["risperidone"] or ["aripiprazole"] or ["risperidone" and "aripiprazole"] and ["attention deficit disorder with hyperactivity" or "ADHD"] and ["children" or "child"].

Two authors independently assessed the eligibility of titles and abstracts. They then reviewed the full texts of the selected articles. All discrepancies were resolved by consensus with a third author. Additionally, two authors independently extracted data, including the first author's name, study period, publication date, study site, and total population size (disaggregated by gender) and treatment of risperidone and aripiprazole in children with attention-deficit/hyperactivity disorder. Duplicate articles were excluded, with preference given to those providing more detailed information or a larger sample size.

Quality assessment

The risk of bias was assessed using the checklist formulated by Hoy et al. ^[15], which comprises nine questions, each with two possible answers (yes/no). The score ranged from 0 to 9, with a higher score indicating an increased risk of bias.

Results

This study examined a total of 8 articles, all in English, published between 2005 and 2022. Of these, four studies were conducted abroad and four studies in Iran. In total, 50% of the studies were related to Iran. The subjects studied in all articles were children.

In 30% of the studies, the age range of the children was 3-6 years, and overall, the subjects were between 3 and 18 years old. All samples of 7 studies suffered from ADHD. One study included children who suffered from neurological and psychological disorders. A total of 283 children were examined in the above studies.

Eight studies reviewed were clinical trials. In the studies in this review, the dose of risperidone was started at a minimum dose of 0.25 to 0.5 mg per day and increased to a maximum dose of 1 to 4 mg per day.

The dose of aripiprazole began with a minimum dose of 1.25 to 2.5 mg per day and was increased to a maximum dose of 5 to 15 mg per day. In these studies, the efficacy of methylphenidate was compared with the efficacy of two medications, aripiprazole and risperidone. A number of these studies also examined combined treatment with methylphenidate and each of the two medications mentioned. The summary of the research results can be found in Table 1.

In 90 percent of the studies, no significant difference was found between the two drugs, risperidone and aripiprazole, in terms of efficacy and tolerability in children ($p > 0.05$). In one study, the Conners scale score at 12 weeks was lower in the aripiprazole group than in the risperidone group, which was also statistically significant. Side effects were reported in 40% of studies for risperidone alone or in combination with methylphenidate. In one study, aripiprazole in combination with methylphenidate was found to be more effective than risperidone. In contrast, in another study, aripiprazole in combination with methylphenidate was not effective in reducing ADHD symptoms.

Discussion

The aim of the ongoing study was to investigate the comparison of risperidone and aripiprazole in the treatment of ADHD children. In 90% of studies comparing risperidone and aripiprazole in ADHD children, there was no statistically significant difference between the two medications in efficacy and tolerability.

All studies in this review article concluded that the efficacy of these two medications in treating ADHD in children is the same. Dreakhshanpour et al. ^[12] found that risperidone reduced emotional symptoms in addition to treating ADHD.

They also found that the aripiprazole group had a lower Conners scale score than the risperidone group after 12 weeks, which was also statistically significant, which may be the reason for the greater efficacy of aripiprazole over risperidone. Lamberti et al. ^[16] mentioned no side effects for these two medications, but prolactin levels were reduced in the aripiprazole group.

Table 1. The summary of the research results

| N | Authors' names & year | Diagnosis of children | mean age /subjects | Study method/ subjects | Study tool | Method in the intervention group | Side effects | Results | risk of bias |
|---|---------------------------|-----------------------|---|--|---|--|---|--|--------------|
| 1 | Marco Lamberti [15], 2016 | ADHD-autism | 8.4 ± 2.9 & 7.8 ± 2.3 in two different groups / 44 subjects | randomized clinical trial | (K-SADS-PL ¹) CGI-S ² , C-GAS ³ Conners scale (K-SADS-PL) CGI-S and C-GAS Clinical Global Scale | Risperidone 0.25-3 mg per day Aripiprazole 1.25-15 mg per day | No | After 24 weeks, there was no statistically significant difference between the two drugs in efficacy and tolerability (p > 0.05). | 1 |
| 2 | Pei-Yin Pan [25], 2021 | ADHD-mood disorder | 10.67 & 10.45 in two different groups/43 subjects | Double-blind clinical trial | Conners' scale Barkley's side-effect rating scale Weight CGI-S | Aripiprazole 5-20 mg per day Methylphenidate 0.3 to 0.7 mg per kilogram per day | No | After 4 weeks, methylphenidate had no effect on improving ADHD symptoms compared with placebo. In combination with aripiprazole, it was not effective in children with ADHD and mood disorders (p>0.05). | 1 |
| 3 | Safavi [21], 2015 | ADHD | 4.52±1.24 & 4.47±1.16 in two different groups/47 subjects | Single-blind randomized clinical trial | Checklist for measuring weight and side effects of medicines Conners' scale CGI-S and C-GAS | Risperidone 0.25-2 mg per day Methylphenidate 5- 30 mg per day | Methylphenidate in combination with risperidone; side effects: anorexia and somnolence in 21.7% and 17.4%, respectively | After 6 weeks, there was no statistically significant difference between the two drugs in efficacy and tolerability (p > 0.05). | 2 |

¹ Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version² Clinical Global Impressions Scale³ Children's Global Assessment Scale

| | | | | | | | | | |
|---|--|--|---|---|--|--|--|--|---|
| 4 | Yousefi [24], 2018 | ADHD | 8.57 ± 1.89 , 8.23 ± 1.78 & 8.70 ± 1.99 in three different group /60 subjects | Randomi zed clinical trial | Parent's ADHD Rating Scale Checklist of drug side effects CGI-S | Aripiprazole 2.5-10 mg per day Risperidone 0. 5-2 mg per day Methylpheni date 5- 20 mg per day | NO | After 3 weeks, there was no statistically significant difference between the two drugs in efficacy and tolerability (p > 0.03). | 1 |
| 5 | Razjouyan [20], 2018 | ADHD | 3 - 6 /34 subjects | Double- blind randomiz ed clinical trial | CGAS Conners' scale Checklist of drug side effects | Risperidone 0.25-1 mg per day Aripiprazole 0.25-1 mg per day | anxiety in 20%, nausea and vomitin g in 20%, polyph agia in 25%, and somnia lence in 15% of risperid one users | After 12 weeks, there was no statistically significant difference between the two drugs in efficacy and tolerability (p > 0.05). | 0 |
| 6 | Dreakhshan pour [12], 2015 | ADHD | 4.18 ±0.98 & 3.77 ± 0.88 in two different groups/5 5 subjects | Double- blind randomiz ed clinical trial | CGAS Conners scale Checklist of drug side effects | Risperidone 0.25-1.25 mg per day Aripiprazole 2.5-6.25 mg per day | NO | At 12 weeks, the Conners scale score was significantly lower in the aripiprazole group than in the risperidone group (p=0.019). | 1 |
| 7 | ALCEU GOMES CORREIA FILHO [26], 2005 | ADHD- mental retardation | 11.4 & 12.1 in two different groups/4 5 subjects | Randomi zed clinical trial | Swanson's ADHD scale (SNAP) Barkley's side effects rating scale | Risperidone 0. 5-4 mg per day | NO | Risperidone is more effective than methylphenidate in the treatment of ADHD (p < 0.05). | 1 |
| 8 | Eva Germanò [23], 2014 | Psycholog ical and neurologic al diseases | 10.2 + 2.6 /60 subjects | Randomi zed clinical trial | Compariso n with standard 12-lead ECG | Risperidone 0.25-4 mg per day Aripiprazole 0.25-15 mg per day | Both risperid one and aripipra zole increas e QTd | Risperidone QT increase (p<0.05) and (p<0.001) QTd increase (p<0.001) (p<0.01) Aripiprazole QTd increase (p<0.01) | 0 |

In the study by Kelly et al. and Shalbafan et al., second-generation antipsychotics such as risperidone and aripiprazole are mentioned, and it is noted that risperidone, as one of the drugs in this category, causes the most sexual side effects and galactorrhea by blocking the dopamine receptor. Another drug in this category, aripiprazole, is known as a partial dopamine agonist and causes a decrease in galactorrhea and a decrease in prolactin levels [17, 18].

The effect of risperidone on hyperprolactinemia in children is stronger than in adults by blocking dopamine receptors because children have more dopamine receptors than adults. Hyperprolactinemia can cause galactorrhea, gynecomastia, irregular menstruation and amenorrhea, sexual dysfunction, and decreased fertility. Hypogonadotropic hypogonadism, caused by hyperprolactinemia along with low estrogen and testosterone levels, results in low bone density and osteoporosis. This is particularly important in children who are at the age of puberty and reaching their maximum bone mass [19].

In the study by Houghton et al. [20], fracture risk was found to be 40% lower in children taking aripiprazole compared with risperidone. This may be related to the reduction in bone mass caused by risperidone use.

Razjouyan et al. [21] reported side effects such as anxiety in 20%, nausea and vomiting in 20%, and somnolence in 15% of risperidone users. According to the study by Safavi et al. [22], side effects such as anorexia and somnolence occurred in 21.7% and 17.4% of users, respectively, when methylphenidate was used in combination with risperidone.

In the study by Gadow et al. [23], the most common side effects of risperidone were somnolence and anorexia during the day. In the studies reviewed in this review article, no side effects were reported for aripiprazole, but side effects such as somnolence, nausea and vomiting, anorexia, osteoporosis, and anxiety were mentioned for risperidone.

Germanò et al. [24] investigated the effect of risperidone and aripiprazole on electrocardiographic changes and ventricular repolarization. They suggested that these two medications have a mild effect on ventricular repolarization, and risperidone increases QT interval duration (QTc) and QT dispersion (QTd) of interval values (the difference

between the highest QT and the lowest QT), whereas aripiprazole increases only QTd.

In their study, it was mentioned that each of these two drugs normalized the QT interval more than normal, but this mild effect may have clinically relevant results and should be prescribed with caution, especially in children who have a genetic history of arrhythmias. Some studies have investigated the combined effects of methylphenidate and two medications, aripiprazole and risperidone.

The results of these studies are contradictory, showing the need for further studies in this area. Yousefi et al. [25] found that there was no difference in the efficacy of the two medications, risperidone and aripiprazole alone, in the treatment of ADHD, but in combination with methylphenidate, aripiprazole had a greater effect in the treatment of ADHD, while Pan et al. [26] did not consider aripiprazole in combination with methylphenidate to be effective in the treatment of ADHD and ADHD symptoms did not improve in these children after four weeks.

Correia et al. [27] consider risperidone more effective than methylphenidate in the treatment of ADHD. In general, both risperidone and aripiprazole are effective for the treatment of ADHD and can be used depending on the child's clinical conditions and history and taking into account the side effects mentioned for risperidone.

Conclusion

It seems that using the results of the mentioned studies and referring to similar studies, two drugs, risperidone and aripiprazole, can be considered useful and effective in the treatment of ADHD, and no difference in the efficacy and tolerability of these two drugs was found in the results.

According to the studies mentioned, aripiprazole may be considered beneficial in some respects, as some studies mentioned side effects for risperidone alone or in combination with methylphenidate. Regarding the greater efficacy of the aripiprazole compared to risperidone cannot be concluded based on the result of one article and further studies are recommended.

Finally, it is important to consider the child's condition, clinical symptoms, and medical history when choosing a medication. However, choosing the best drug with the least side effects or combining several drugs to achieve the best treatment results requires further and more detailed studies in this area. One of the limitations of this study was that there were not enough articles comparing the two medications mentioned above in children with ADHD. It should be noted that most of the available studies examined the efficacy of each of these two medications alone.

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