Systematic review of clinical trials of aripiprazole for treating attention deficit hyperactivity disorder

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ABSTRACT

تقيم هذه المراجعة المنهجية سلامة وفعالية استخدام الأريبيبرازول لعلاج اضطراب نقص الانتباه وفرط النشاط. وتمت مراجعتها في قواعد بيانات مثل الباحث العلمي من قوقل والمكتبة الأمريكية. وقد ادرجت جميع التجارب الضابطة والغير ضابطة للأريبيبرازول لعلاج اضطراب نقص الانتباه وفرط النشاط. وقد أجري آخر بحث لها في مارس 2013م. وحكمت جودة الدراسات وتم تقييم كفاءتها وانعكاس آثارها. من بين العناوين 34 المستردة ذات الصلة أفادت مقالتين فقط استخدم فيها تجارب سريرية ضابطة عشوائية مزدوجة التعمية ولم تذكر أي من التجارب أن الأريبيبرازول كانت فعالة. ومع ذلك، فقد تم الإبلاغ عن وجود نسبة عالية من الآثار السلبية مثل زيادة الوزن، والخمول والصداع. ولم يتم العثور على التجارب السريرية. و خلافاً للدارسات الغير ضابطة للتجارب ،فإن نتائج التجارب الضابطة لم تدعم فعالية الأريبيبرازول علاج اضطراب نقص الانتباه وفرط النشاط. وبالإضافة إلى ذلك، يشير لنا معدل ارتفاع الآثار السلبية الحاجة إلى إجراء المزيد من التجارب الضابطة للوصول إلى نتيجة.

This systematic review assesses the effectiveness and safety of aripiprazole for treating attention deficit hyperactivity disorder (ADHD). The databases of PubMed/MEDLINE and Google Scholar were searched. All the controlled and non-controlled trials of aripiprazole for the treatment of ADHD were included. The latest search was conducted in March 2013. The quality of studies was assessed, and the efficacy and adverse effects were evaluated. Out of 34 relevant retrieved titles, only 2 articles reported randomized double blind controlled clinical trials. None of the controlled trials reported that aripiprazole was effective. However, a very high rate of adverse effects such as weight gain, sedation, and headache were reported. No well-controlled clinical trial was found. In contrary to non-controlled studies, the findings of controlled trials do not support the effectiveness of aripiprazole for treating ADHD. In addition, the high rate of adverse effects suggests that more controlled trials require to be conducted to reach a conclusion.

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Attention deficit hyperactivity disorder. Attention deficit hyperactivity disorder (ADHD) is a very common psychiatric disorder in children and adolescents.[1] The main characteristic symptoms of ADHD are inattentiveness, hyperactivity, and impulsivity. Stimulants, tricyclics,[2] and some noradrenergics are usually administered for its management. However, some patients may not tolerate these medications or the patients do not respond to these medications. Therefore, alternative medications are needed for managing this sample of children with ADHD.

Aripiprazole. Aripiprazole is one of the atypical antipsychotic medications. The United States Food and Drug Administration (FDA) approved it for treating schizophrenia in 2002. Aripiprazole is effective and generally without serious adverse effect for treating children and adolescents with autism spectrum disorders,[3] tic disorders,[4] schizophrenia,[5] and bipolar mania.[6] Aripiprazole is a partial agonist of dopamine D2 and serotonin 5-HT1A receptors.[7] Aripiprazole has a distinctive effect on the dopaminergic system in comparison with other atypical antipsychotics, so it is called a dopamine system stabilizer.[8] In addition, aripiprazole's affinity for dopamine receptors is higher than that of endogenous dopamine.[9] This provides an explanation for the lower rate of aripiprazole-related extrapyramidal symptoms (EPS).[9] Moreover, aripiprazole increases serum prolactin levels less than other atypical antipsychotics.[9] Additionally, aripiprazole is a 5HT2C receptor partial antagonist. This partial antagonist

effect is associated with the lower rate of aripiprazole-related weight gain in comparison with other atypical antipsychotics.[9] The affinity of aripiprazole to histamine H1, alpha1-adrenergic, and muscaline M1 receptors is moderate.[10] Tremor, sedation, and minimal weight gain is reported with aripiprazole.[11] Aripiprazole is less likely to increase prolactin levels in pediatric psychosis and bipolar disorder.[12] Furthermore, aripiprazole does not significantly interact with co-administered lithium and valproate.[13] Aripiprazole co-administered with clomipramine seems to be effective and safe in drug resistant depressed patients.[14] Furthermore, aripiprazole does not markedly change the pharmacokinetics of venlafaxine, escitalopram, fluoxetine, paroxetine, and sertraline in either healthy subjects or patients with major depressive disorder.[15] Moreover, the pharmacokinetics of aripiprazole are not meaningfully affected by hepatic or renal function.[16] Aripiprazole temporarily worsened the ADHD symptoms in the short-term in 2 young children with ADHD and Tourette disorder.[17] These 2 children were administered aripiprazole 15 mg/day, and some of the symptoms of ADHD decreased with time.

This systematic review aims to summarize and review non-controlled and controlled trials (RCTs) on the effects of aripiprazole for treating children and adolescents with ADHD. This study also summarizes aripiprazole's related adverse effects in patients with ADHD. Performing this systematic review is justified as there is evidence of the treatment of ADHD with aripiprazole; however, there is a lack of published systematic reviews on the role of aripiprazole in treating ADHD.

Literature search. This systematic review was conducted using the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol.[18] The 2 electronic databases of PubMed/MEDLINE and Google Scholar were searched. In addition, the references of the included articles were manually searched to find possible relevant articles. The latest search was conducted in March, 2013. The terms "aripiprazole", "ADHD", and "attention deficit hyperactivity disorder" were used to find possible relevant titles. The time period was from the inception of databases to March 2013. The inclusion criteria for this review were: a) Design of the study: Both controlled and non-controlled trials were included. b) Population: children, adolescents, and adults with ADHD diagnosed according to DMS-IV diagnostic criteria.[19] c) Intervention: aripiprazole at any dose with any other medications or placebo in the treatment of patients with ADHD. d) Outcome: some objective tests were used to evaluate the clinical symptoms of ADHD in the short or long term. Language and date of publication were not considered as an exclusion criterion. Moreover, trials with co-administered psychotropic medications were not excluded. The titles and abstract of the identified studies were screened. In addition, a data extraction form was designed to record the characteristics of studies, including design characteristics, participants' characteristics and their flow into and during the trial, interventions, dose of aripiprazole, primary outcomes to assess ADHD symptoms, and secondary outcomes or adverse effects were evaluated. A statistical analysis was planned, however, there was an insufficient number of studies to perform this.

Literature review. Thirty-four relevant titles were retrieved. Seventeen out of these 34 abstracts were irrelevant. Two other articles did not assess the clinical symptoms of ADHD as an outcome,[20,21] and 3 other articles were not interventional studies.[22-24] Out of 12 articles reporting an intervention with aripiprazole, 3 articles were case reports,[17,25,26] and 7 studies were open label without a control group.[27-33] There was one commentary.[34] Only 2 articles reported randomized double blind placebo-controlled clinical trials (**Figure 1**).[6,35]

Table 1 outlines the characteristics of the 2 randomized controlled clinical trials.[6,35] One of these 2 trials was a 6-week double blind, placebo-controlled trial[6] that included 43 children and adolescents with bipolar disorder and ADHD. The diagnoses were made according to DSM-IV diagnostic criteria. This trial reported that aripiprazole no more than placebo decreased ADHD symptoms measured by the Swanson, Nolan, and Pelham Scale-Version IV. However, aripiprazole was not associated with serious adverse effects.[6]

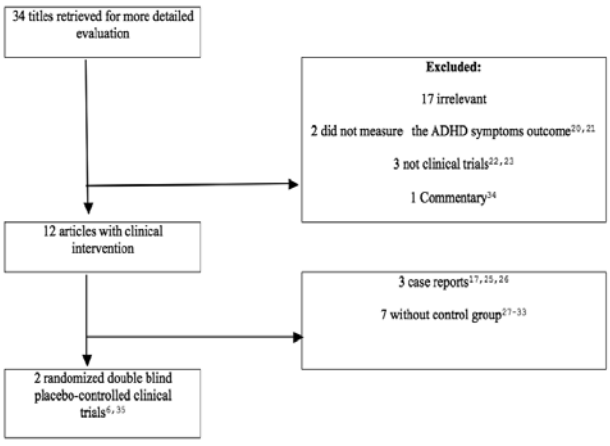

Figure 1 - Flowchart of trial selection process.

The other trial was a crossover designed trial that included 16 children diagnosed with juvenile bipolar disorder and ADHD. The patients were stabilized by administering aripiprazole. The patients were then co-administered methylphenidate or placebo.[35] Adding methylphenidate to aripiprazole did not aggravate the mania symptoms. In addition, methylphenidate no more than placebo improved ADHD symptoms in the patients stabilized with aripiprazole.[35] Co-morbid psychiatric disorders were very common in their sample. For example, the rate of anxiety disorders was 57.1%, conduct disorder 57.1%, oppositional defiant disorder 78.6%, and psychotic disorders 50%.

Masi et al[27] performed an open label study including 28 outpatients with ADHD and Tourette's disorder. Aripiprazole effectively decreased ADHD symptoms. In addition, no serious adverse effect was reported. Mild sedation was the most common adverse effect (21.4%), and no significant laboratory change was reported (**Table 2**). Another open label study was conducted by Ercan et al.[28] They administered aripiprazole (8.2 mg/day) to 20 children and adolescents for 8 weeks. The patients were diagnosed with ADHD plus severe conduct disorder, and 18 patients were resistant to previous administered medications. Aripiprazole improved the patients' attention and decreased their hyperactivity. Again, aripiprazole had no significant adverse effects. However, nearly all of the patients significantly gained weight. Aripiprazole decreased prolactin levels.[28] Murphy et al[29] conducted a study on 16 children with tic disorder. Aripiprazole decreased ADHD symptoms as recorded by the parent-reported Conners' Abbreviated Symptom Questionnaire. However, 11 out of 16 patients experienced adverse effects. The most common adverse effects were weight gain, nausea, and irritability. Four other non-controlled open label studies reported that aripiprazole significantly decreased ADHD symptoms, and aripiprazole had no marked adverse effect.[30,32,33,36] Weight gain and sedation were among common adverse effects (**Table 2**).

This systematic review aimed to gather current evidence regarding the efficacy and safety of aripiprazole for treating children and adolescents with ADHD. One of the main findings of this review is that most evidence comes from case reports and non-controlled open label studies. A well-controlled published clinical trial investigating this matter was not found, and only 2 published controlled trials were found. Both of the controlled trials reported that aripiprazole did not significantly decrease ADHD symptoms, while all of the 6 non-controlled studies reported that aripiprazole significantly decreased ADHD symptoms. However, there are some limitations regarding the 2 controlled trials.[6,35] Both of these trials administered aripiprazole to children and adolescents with bipolar disorder and ADHD symptoms. In addition, the patients in one of the studies were administered aripiprazole to treat their mania symptoms. Then, a small sample of children was administered methylphenidate or placebo as an adjuvant medication.[35] In other words, all the children had taken

Table 1 - Summary of randomized controlled clinical trials of aripiprazole for patients with attention deficit hyperactivity disorder.

First author (year)	Sample size	Diagnosis	Design of study	Intervention	Main outcome measure	Main outcomes	Main adverse effects
Tramontina et al, 2009[6]	Children and adolescents	Bipolar disorder co-morbid with ADHD according to DSM-IV criteria	6-week double blind, placebo-controlled trial	Aripiprazole (n=18) or placebo (n=25)	Young Mania Rating Scale, the SNAP-IV, weight	While aripiprazole decreased mania symptoms more than placebo, aripiprazole no more than placebo decreased ADHD symptoms	Well tolerated and without serious adverse effects or weight gain
Zeni et al, 2009[35]	16 children and adolescents aged 8-17 years	Juvenile bipolar disorder and ADHD according to DSM-IV criteria, their manic symptoms responded to aripiprazole, but the ADHD symptoms were significant	Randomized crossover trial (2 weeks for each medication)	MPH and placebo (2 weeks each) combined with aripiprazole	Brazilian versions of the SNAP-IV Young Mania Rating Scale	There was no significant difference between MPH and placebo effects on ADHD and manic symptoms	Addition of stimulants to aripiprazole did not significantly increase the rate of aripiprazole-related adverse effects

ADHD - attention deficit hyperactivity disorder, DSM - Diagnostic and Statistical Manual of Mental Disorders, MPH - Methylphenidate, SNAP-IV - Swanson, Nolan, and Pelham Scale version IV

Table 2 - Summary of randomized controlled clinical trials of aripiprazole for patients with attention deficit hyperactivity disorder.

First author (year)	Sample size	Diagnosis	Design of study	Intervention	Main outcome measure	Statistical analysis	Main outcomes	Main adverse effects
Masi 2012[27]	A consecutive group of 28 children and adolescents aged 8 to 16 years	A primary diagnosis of Tourette's disorder and co-morbid ADHD combined subtype according to DSM-IV criteria	12-week, open label, without control group	Aripiprazole (10.0±4.8mg/day)	ADHD-RS-IV		Effective to decrease 22.5% of ADHD symptoms. Co-morbidity of ADHD with OCD was a risk factor for better response	Well tolerated, no dropout due to adverse effects. Mild sedation (21.4%), mild to moderate agitation (14.3%) (usually in the first 2 weeks), mild and transient nausea (14.3%), increased appetite (2.6%). Its dose decreased from 7.5 to 5 mg/day in one patient in week 12 due hand tremor. No extrapyramidal symptoms. No effects in blood parameters, prolactin levels, ECG, weight, height, blood pressure, and cardiac frequency during the follow-up period. No negative effect on school performance of children
Ercan 2012[28]	20 children and adolescents aged 6 to 16 years	ADHD and early-onset severe CD according to DSM-IV using K-SADS-PL. Those with mental retardation or co-morbid with other psychiatric disorders were excluded	8-week, open label study without control group	Aripiprazole dose at the end of 8 weeks: 8.55 mg (SD=1.73). Except for 2 patients, all other patients were resistant to previous administered medications	T-DSM-IV, CGI-S, CGI-I, CBCL, TRF, ESRS, laboratory assessments	19 patients completed	Effective and well-tolerated treatment for ADHD and CD symptoms. 63.1% of responders categorized as very much or much improved. Aripiprazole decreased inattention, hyperactivity/impulsivity, ODD, and CD subscales of the T-DSMIV (both parent, teacher and clinician forms)	No dropout due to adverse effects. Statistically significant (p<0.005) weight gain in 18 out of 19 patients. No significant change in complete blood cell counts, liver or thyroid function, urine toxicology, fasting glucose, lipid, and prolactin levels, or ECGs. A significant decrease in prolactin level and an increase in alkaline phosphatase, free T3, and urea levels at week 12. Irritability (4), sedation (3), and anxiety (2). No significant increase in extrapyramidal symptoms
Murphy 2009[29]	16 children and adolescents aged 8-17 years	A primary diagnosis of a chronic tic disorder with/without co-morbid disorder(s)	6-week open label, flexible-dose study	Aripiprazole dose was 3.3 mg (range 1.25-7.5 mg)	Yale Global Tic Severity Scale, CGI-S, CGI-I, ASQ-P		Significant improvement in ADHD	Well tolerated but significantly increased weight. Half of the patients experienced at least 2.5 kg weight gain. 11 patients reported side effects. (one headache, 3 with mild nausea, 4 with increased irritability, 5 with excitability/restlessness, 3 with inattention, 2 with frequent urination). The severities of adverse effects were mild to moderate. No changes in metabolic test results (lipid and cholesterol levels) or ECG. Increased T3 levels in 11 of 16 patients

ADHD - attention deficit hyperactivity disorder, DSM - Diagnostic and Statistical Manual of Mental Disorders, OCD - obsessive-compulsive disorder, CD - conduct disorder, K-SADS-PL - Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version, ADHD-RS-IV - ADHD-Rating Scale, T-DSM-IV - Turgay DSM-IV based child and adolescent behavior disorders screening rating scale, CGI-S - Clinical Global Impression - Severity scale, CGI-I - Clinical Global Impression - Improvement scale, CBCL - child behavior checklist, TRF - teachers report form, ESRS - extrapyramidal symptom rating scale, ASQ-P - Conners Abbreviated Symptom Questionnaire for Parents, CGAS - Children's Global Assessment Scale, LOCF - Last observation carried forward, SNAP-IV - Swanson, Nolan and Pelham version IV, CPT - Continuous Performance Test, ODD - oppositional defiant disorder

Table 2 - Summary of randomized controlled clinical trial of aripiprazole for patients with attention deficit hyperactivity disorder cont'd.

First author (year)	Sample size	Diagnosis	Design of study	Intervention	Main outcome measure	Statistical analysis	Main outcomes	Main adverse effects
Findling 2008[30]	23 children aged 8 to 12 years	ADHD patients with co-morbid disorders were excluded if they had co-morbid diagnoses (such as a pervasive developmental disorder, CD, generalized anxiety disorder. Six patients had oppositional defiant disorder	6-week, open label pilot trial	Aripiprazole 6.7 mg/day. The mean dose at the end of the study was 0.18 mg/kg/day. No concurrent other psycho-therapeutic drug was permitted	ADHD-RS-IV, CGI, CGAS, weight, blood pressure, pulse rate and prolactin level	Intent-to-treat using LOCF	Effective	Common adverse effects: sedation (n=18; 78.3%), headache (n=11; 47.8%), nausea (30.4%). Two patients discontinued due to weight gain. Significant increase in weight and decrease in blood pressure. Significant decrease in prolactin
Tramontina 2007[31]	10 children and adolescents	Juvenile bipolar disorder with ADHD	6-week open trial	Aripiprazole up to 20 mg/day	Young Mania Rating Scale, SNAP, Global functioning (CGI-S)	8 patients completed – LOCF	Effective	Well tolerated but with significant weight gain
Lyon 2009[33]	11 children aged 7 to 18 years	Tourette's disorder, 9 had ADHD	10-week open label	Aripiprazole 4.5-3.0 mg/day	ADHD-RS-parent version	One patient dropped out due to akathisia and muscle cramp	Effective: inattention scores (p<0.035), hyperactivity-impulsivity scores (p<0.007), ADHD-RS total scores (p<0.007)	Well tolerated but adverse effects were very common: extrapyramidal symptoms in 10 patients, weight gain in 7 patients, headache in all the patients, and tiredness in 8 patients
Chaichan, 2011[32]	29 children aged 6 to 15 years	ADHD	10 weeks	Aripiprazole	SNAP-IV, CGI-S, CPT		Effectively decreased inattentiveness and hyperactivity	No serious adverse effect. The most common adverse effect was weight gain

ADHD - attention deficit hyperactivity disorder, DSM - Diagnostic and Statistical Manual of Mental Disorders, OCD - obsessive-compulsive disorder, CD - conduct disorder, K-SADS-PL - Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version, ADHD-RS-IV - ADHD-Rating Scale, T-DSM-IV - Turgay DSM-IV based child and adolescent behavior disorders screening rating scale, CGI-S - Clinical Global Impression - Severity scale, CGI-I - Clinical Global Impression - Improvement scale, CBCL - child behavior checklist, TRF - teachers report form, ESRS - extrapyramidal symptom rating scale, ASQ-P - Conners Abbreviated Symptom Questionnaire for Parents, CGAS - Children's Global Assessment Scale, LOCF - Last observation carried forward, SNAP-IV - Swanson, Nolan and Pelham version IV, CPT - Continuous Performance Test, ODD - oppositional defiant disorder

aripiprazole before co-administering methylphenidate or placebo. The ADHD symptoms were not assessed during the period in which the patients were taking only aripiprazole. In addition, high rates of co-morbid psychiatric disorders were a possible covariate factor. Under-recognized ADHD symptoms in the patients with bipolar disorders can be another explanation for these results.

Stimulants and norepinephrine reuptake inhibitors, such as atomoxetine, are administered to treat ADHD. These 2 categories of medications increase dopamine levels in the brain.[37] However, aripiprazole is an atypical antipsychotic with partial agonist activity at dopamine D(2) receptors. The opposite effects of stimulants and aripiprazole might not support the assumption that aripiprazole improves ADHD symptoms. This

explanation is in accordance with the findings of the controlled clinical trials. Both trials administered high doses of aripiprazole. Further studies may administer lower doses of aripiprazole. It is expected that a lower dose of aripiprazole is associated with a higher dopamine agonist effect.[27]

Nevertheless, all of the non-controlled studies reported that aripiprazole improved ADHD symptoms. It should be noticed that these studies were open label and non-controlled. Moreover, these studies included children with ADHD and excluded those with bipolar disorder. Besides, some of the studies excluded those with other co-morbid psychiatric disorders.[28-30] Therefore, generalization of their results to other samples should be carried out with caution. The duration of these studies was from 2 to 12 weeks, and all the studies included small sample sizes.

All the controlled and non-controlled studies reported that aripiprazole was without serious adverse effects. However, sedation was a commonly reported adverse effect. Therefore, it is possible that the improvements reported by non-controlled studies are secondary to tranquilization or sedation. Weight gain was also a commonly reported adverse effect. In one study,[28] 18 out of 19 patients significantly gained weight. Another study[29] also reported that half of the 16 patients experienced weight gain of 2.5kg during the 6 weeks. Controlled studies are needed to investigate whether weight gain is associated with aripiprazole or is due to growth of the children. Meanwhile, the numbers of reported extrapyramidal adverse effects were very low. This is similar to other studies reporting that aripiprazole is associated with low risks of extrapyramidal adverse effects.[9] The short duration of the studies might be an explanation for the low rate of adverse effects. Some adverse effects, such as weight gain and extrapyramidal symptoms may need a longer time to appear.

In conclusion, there is a lack of well-controlled trials investigating the efficacy of aripiprazole on ADHD. Therefore, the current evidence is not sufficient to recommend aripiprazole for the treatment of ADHD in children and adolescents. However, the results of non-controlled studies encourage conducting further well-controlled trials with a rigorous methodology. Further studies should consider co-morbid psychiatric disorders and co-administered medications as covariate factors.

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