Systematic Review

# A Systematic Review of Magnesium Therapy for Treating Attention Deficit Hyperactivity Disorder

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**Abstract**

There are contradictory reports about the association of magnesium and attention- deficit hyperactivity disorder (ADHD). Moreover, some studies reported that magnesium is effective for treating ADHD. This is the first systematic review evaluating the effectiveness of magnesium to treat patients with ADHD.

The two databases of MEDLINE/ PubMedline and Google Scholar were electronically searched using the search items and considering inclusion and exclusion criteria.

Out of the 37 titles, only six studies were experimental interventional studies. However, three of these studies were without any control group. The other three studies were controlled clinical trials. Nevertheless, none of the studies was a randomized double- blind controlled clinical trial. These studies supported that magnesium is effective for treating ADHD.

Magnesium monotherapy studies were not found. There is no well- controlled clinical trial investigating the efficacy and safety of magnesium for treating ADHD. In addition, the safety of magnesium in ADHD is ignored. Therefore, until further strong evidences for its efficacy and safety are provided, magnesium is not recommended for treating ADHD.

**Keywords:** Attention Deficit Hyperactivity Disorder (ADHD), drug therapy, magnesium, review, trace elements

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## Introduction

Attention- deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in clinical samples of children and adolescents referring to child psychiatric clinics.[1] About 10% to 30% of patients are not satisfied with stimulants and they do not tolerate stimulants which are widely used for treating ADHD.[2] Moreover, some patients are unresponsive to medications.[2] Therefore, providing better and safer alternative treatments for managing ADHD is highly needed.

The function of more than 325 enzymes is dependent to magnesium.[3] Magnesium interacts with the serotonergic (5-HT(1A) and 5-HT(2A/2C) receptors), noradrenergic (alpa(1)- and alpha(2)- receptors), and dopaminergic (dopamine D(1) and D(2) receptors) systems in the mouse.[4] The role of noradrenergic and dopaminergic receptors in the pathophysiology of ADHD has been extensively studied.[5,6] In addition, current treatments, such as stimulants and atomoxetine, act through adrenergic and dopaminergic receptors.[7]

Moreover, N-methyl-D-aspartate (NMDA)-induced norepinephrine release[8] is inhibited by magnesium. Nevertheless, atomoxetine is a NMDA receptor blocker,[9] the blockade of NMDA receptors in the prefrontal cortex causes attention deficit.[10] In addition to these contradictory findings, there is a serious concern about the possible cytotoxic effects of chronic manganese exposure leading to Parkinson's disease symptoms.[11]

In addition, there is a controversy about the serum level of magnesium in patients with ADHD. While many studies reported that the serum level of magnesium in ADHD is lower than the controls,[12–14] others reported that its level in ADHD is higher than the controls.[15,16] In addition, a double-blind, placebo-controlled trial compared the effect of methylphenidate and dextroamphetamine in hyperactive boys on magnesium level.[17] The study showed that dextroamphetamine treatment increased the magnesium plasma level after three weeks of taking the medication.[17]

Considering the contradictory findings about the serum level of magnesium in ADHD,[12–15] the effects of magnesium on the ADHD-related neurotransmitters,[4] the effects of some stimulants on magnesium in ADHD children,[17] and some concerns about the possible cytotoxic effects of magnesium,[11] it is highly required to investigate the role of magnesium for treating ADHD.

There is no published systematic review about the possible role of magnesium for treating ADHD. Therefore, the aim of the current review was to systematically summarize and critically assess the data from controlled clinical trials of magnesium treatment for patients with ADHD.

## Methods

The guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol were employed to conduct this recent systematic review.[18]

### Data sources

The two electronic databases of Medline/PubMed and Google Scholar were searched up to 5th April 2012.

### Search strategy

The search terms included the terms for "ADHD", "attention-deficit hyperactivity disorder", and "magnesium". The search was

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not limited to any publication time. Non-English language was not considered as an exclusion criterion. The retrieved titles and abstracts were studied to select relevant articles.

### Inclusion and exclusion criteria

The inclusion criteria were as follow: the study design was an interventional study conducted in humans with no restrictions in the study design; the effect of magnesium for treating the symptoms of ADHD was assessed; the participants were children, adolescents, and adults (from early childhood to elderly); and a validated instrument was used to evaluate the clinical efficacy outcomes.

Trials were included if they were conducted on patients with ADHD and studied the efficacy of magnesium on the clinical symptoms of ADHD. Studies which employed magnesium as the only treatment or as an adjunct to other treatments were included. The articles which did not report the findings of an experimental trial were excluded. Language and publication time were not considered as exclusion criteria.

The following criteria were considered in order to evaluate the methodologic quality of randomized controlled clinical trials: random sequence generation, allocation concealment, patient blinding, assessor blinding, reporting of dropout or withdrawal, intention-to-treat analysis, selective outcome reporting, and other potential biases. A data sheet was used to record the extracted data.

### Statistical analysis

It was aimed to conduct a statistical analysis. However, it was not practical, because no randomized controlled clinical trial was found.

## Results

Seventy- four relevant titles were screened. Thirty- seven were duplicated, fifteen were irrelevant, and four were without any intervention. Overall, six articles reported interventions by administering magnesium supplements.[19–24] From these six articles, one was an open study without any control group,[19] one was a case report,[22] and one article did not report unique data.[24] There were only three studies with a control group design.[20,21,23] Two of these three articles were not in English.[21,23] Both of these two non-English articles provided English abstracts with some details about the studies (Table 2). No double- blind randomized controlled clinical trial was found (Figure 1).

Key data from these interventional studies are reported in Tables 1 and 2. Magnesium monotherapy studies were not found. Therefore, the studies which included multicomponent formulas with magnesium were reviewed. The observational study prescribed polyunsaturated fatty acids (PUFA) in combination with zinc and magnesium for three months. The study reported that this

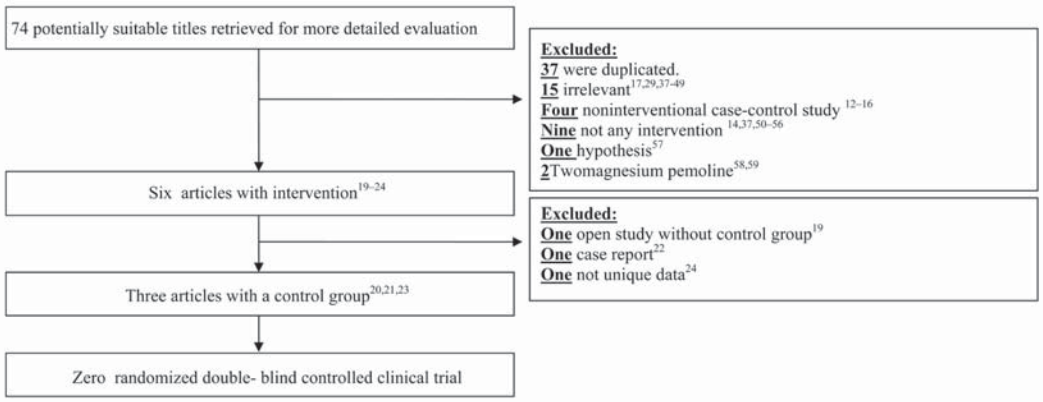


**Figure 1.** Flowchart of study selection process.

**Table 1.** Summary of noncontrolled clinical studies of magnesium 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 |
|---|---|---|---|---|---|---|---|
| Huss, 2010 [19] | 810 children aged five to 12 years | ADHD symptoms | Observational study | Polyunsaturated fatty acids (PUFA) in combination with zinc and magnesium for three months; seven patients took stimulants concurrently. | SNAP-IV (Swanson, Nolan, and Pelham (SNAP) Strengths and Difficulties Questionnaire (SDQ) | Reduction in symptoms of attention- deficit and hyperactivity/ impulsivity | No serious adverse events, parent-reported tolerability was poor in 20 children (2.5%) |
| Mousain-Bosc, 2004 [22] | 52 children with ADHD, aged zero to 15 years from a nursery school | ADHD according to DSM-IV | Open trial without controlled group | Magnesium preparations (Uvimag_ or Magne-B6) at a dose of 6 mg/kg/day for a period of one to six months | The “Connor’s Rating Scale for Parents and Teachers”. | Mg level reached near to normal level after taking Mg regimen for two months. ADHD clinical symptoms improved after two to four months taking Mg regimen. | Not reported |

**Table 2.** Summary of controlled clinical trials of magnesium for treating patients with attention- deficit hyperactivity disorder

| First author (year) | Sample size | Diagnosis | Design of study | Intervention | Main outcome measure | Main outcomes | Main adverse effects |
|---|---|---|---|---|---|---|---|
| Mousain-Bosc, 2006[20] | 76 children including 40 children (mean age: 6.49 years; 13 girls and 27 boys) with ADHD symptoms and 36 children (mean age: 4.37 years, 14 girls and 22 boys) | ADHD symptoms | Open controlled trial | Magnesium-vitamin B6 (Mg-B6) regimen (6 mg/kg/d Mg, 0.6 mg/kg/d vit-B6) for at least eight weeks. No other con-current medication was allowed. | Symptoms of ADHD (hyperactivity, hyperemotivity/ aggressive-ness, lack of attention at school) were scored | Hyperactivity and (hyperactivity, hyperemotivity/ aggressiveness were decreased. Attention increased. Intraerythrocyte Mg (Erc-Mg) values significantly increased in ADHD (2.32 ± 0.41 mmol/L versus 2.05 ± 0.3 mmol/L, P = 0.004) while these values were still lower than for control. Erc-Mg level returned to lower level when Mg-B6 supply was discontinued. Changes in Erc-Mg values were not statistically correlated with changes in clinical symptoms. | Not reported. |
| Nogovitsina, 2006[21] | 31 children aged from six to 12 years, and 20 children with similar manifestations as control group | Attention-deficiency and hyperactivity syndrome | Controlled clinical trial | A polyvitamin complex Magnesium-vitamin B6 (Mg-B6) for 30 days | Not reported | Decreased the level of synkinesis, increased the characteristics of attention | Not reported |
| Starobrat-Hermelin, 1998[23] | 75 children with ADHD and deficiency of magnesium | ADHD according to DSM-IV | Controlled clinical trial | 50 patients received standard treatment and magnesium supplement for six months, 25 patient were left with standard treatment without magnesium supplement. | The "Connor's Rating Scale for Parents and Teachers". | Hyperactivity was decreased in magnesium group while hyperactivity increased in the group which received standard treatment | Not reported |

supplementation decreased both inattentiveness and hyperactivity/impulsivity in both genders and all age groups (Table 1).[19]

The other study by Mousain-Bosc, et al. was an open label study without any control group.[22] They reported that magnesium regimen decreased scholar inattention after four months while it did not change scholar inattention after two months of taking the regimen. The intraerythrocyte magnesium level of reached near to normal level after taking magnesium regimen in the 30 out of 52 children who were followed up.[22]

Mousain-Bosc, et al's study was an open controlled trial. Magnesium-vitamin B6 increased the magnesium plasma level and decreased hyperactivity. In addition, the supplement decreased inattentiveness.[20]

### Safety of magnesium supplement

Except one study,[19] safety issues were not reported in other trials. The study reported that the supplement was tolerated well and the rate of adverse effects was 2.5%.[19]

## Discussion

This is the first systematic review of the efficacy and safety of magnesium supplement for treating patients with ADHD. The most striking finding of this systematic review is that there was not any randomized double- blind controlled clinical trial investigateing the possible efficacy and safety of magnesium supplement for treating ADHD. Few interventional studies regarding the possible treating role of magnesium for ADHD are conducted. All of them can be considered as preliminary reports because they have methodologic limitations as follow:

Regarding the large study conducted by Huss, et al. it was not a controlled clinical trial.[19] In addition, the children were not formally diagnosed with ADHD using DSM-IV diagnostic criteria.[25] Moreover, the samples were prescribed a combination of supplements that one of them was magnesium. Therefore, it cannot be warranted that the findings are related to magnesium supplementation. Furthermore, socioeconomic status was not considered as a covariate factor. Finally, psychiatric comorbidities are very frequent in children with ADHD.[26,27] For example, more than 50% of them suffer from oppositional defiant disorder.[27] It needs to be noticed that the children were not assessed for possible zinc or magnesium or PUFA deficiency at baseline. Meanwhile, the concentrations of fatty acid[28] and zinc[29] in some children with ADHD are lower than controls.

The other open label study without control group reported the effectiveness of magnesium for treating ADHD symptoms.[22] However, there are some points which need to be considered before the interpretation and generalization of its results. The sample was a group of children from a nursery school. Moreover, their age range was from zero to 15 years. It is not clear whether the diagnosis is valid and reliable for children as young as infants. In addition, as in other open trials, the results can be biased. Moreover, no statistical report was provided regarding whether the regimen affected on hyperactivity/impulsivity. Besides, nothing is mentioned about other possible psychiatric disorders comorbidities.[22]

The open clinical trial by Mousain-Bosc, et al. was not a randomized double- blind trial.[20] In addition, magnesium was administered in combination with vitamin B6. Moreover, the main outcome measurewas not familiar and it was not reported about its validity and reliability. The questionnaire which was used in that study consisted of three questions. There was one question for each of hyperexcitability, hyperemotivity/aggressiveness, and lack of school attention domains. While it is mentioned that the children in the treatment group were with ADHD clinical symptoms according to DSM-IV, it does not seem that they were with ADHD as a disorder. However, the study reported that there was no association between the increases in the magnesium level and improvement of ADHD clinical symptoms.[20]

The other controlled clinical trial included 75 patients with ADHD and magnesium deficiency.[23] The English abstract of this trial reported that standard treatment and magnesium supplement decreased hyperactivity while standard treatment without magnesium supplement increased hyperactivity.[23]

Overall, the preliminary reports are promising that magnesium is effective for treating ADHD. This effect may be due to magnesium deficiency in children.[30] However, further studies with consideration of the following recommendations are suggested:

a. Stimulants may impact magnesium plasma level.[17] Meanwhile, in some studies magnesium was not administered concurrently with stimulants.[19,20] Further studies should consider stimulants as a covariate factor.
b. The level of magnesium in plasma is lower than cerebrospinal fluid in which an active transport process maintains this gradient. Its concentration in extracellular space is four times less than intracellular space.[3] Chronic hypermagnesemia does not alter its level in whole brain in animals.[31] Moreover, acute hypermagnesemia weakly increases total and ionized cerebrospinal fluid magnesium.[32] Moreover, only 1% of magnesium is not intracellular.[3] Therefore, the peripheral level of magnesium may not represent the actual level of magnesium in the brain and nerve cells. Phosphorus nuclear magnetic resonance (NMR) spectroscopy is suggested for assessment of magnesium in the brain.[3]
   Vitamin B6 deficiency negatively impact on magnesium balance.[33] Therefore, vitamin B6 deficiency and synergy of trace nutrients and zinc [60] should be screened in further studies.
c. Since kidney and liver functions are associated with magnesium level, healthy kidney and liver functions need to be included as well.
d. ADHD is a psychiatric disorder which its clinical symptoms can occur in many other disorders. For example, inattentiveness is a clinical symptom of ADHD. Meanwhile, lack of concentration is a symptom of major depressive disorder. Therefore, future studies should consider rigorous methodology to examine the effect of magnesium on ADHD as disorder rather than only symptoms.
e. Oppositional defiant disorder comorbidity in ADHD increases the risk of limited variety of food and these children usually do not try new food.[34]
f. All the trial studied the short-term effect of magnesium supplementation. In addition, safety of magnesium supplementation in children with ADHD is an ignored area in all of the studies except one.[19]
g. In some of the studies, magnesium was administered in combination with stimulants or other standard treatments. Meanwhile, there is a speculation that some stimulants may affect on magnesium serum level.[17] Moreover, we do not know whether negative trials were not published yet and this has distorted the overall picture about this matter.
h. Besides, depression and anxiety are not uncommon in ADHD. Meanwhile, magnesium improved both anxiety and depression in a study on animals.[35]
i. Furthermore, ADHD is very common in children with autistic disorders. Its prevalence in autistic disorders is more than 50%.[36]
j. Dietary intake of magnesium influences study outcomes. Therefore, dietary intake of magnesium needs to be considered.

In addition to the points mentioned above, the current review suffers from some other limitations. The first one is lack of a well-controlled magnesium monotherapy trial for treating ADHD. Therefore, magnesium monotherapy is not studied yet. Secondly, only one author reviewed current evidences. Third, current results cannot be generalized to other age groups. Since there was no double- blind controlled clinical trial, no statistical analysis could be performed.

In conclusion, there was not any well-controlled clinical trial investigating the efficacy and safety of magnesium supplement for treating ADHD. The limited evidences about magnesium efficacy reported by preliminary studies should be examined in long-term double- blind randomized controlled clinical trials with enough sample sizes. In addition, covariate factors, such as comorbidities and concurrent medications should be considered. Therefore, till enough strong evidence is provided and safety concerns are removed, administering magnesium in children with ADHD and without hypomagnesium is not recommended.

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