

Comparative Study of Treatments of Children with ADHD with Medication Alone Vs Medication with Cognitive Behavioral Therapy

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Abstract

This study is important due to the long terms negative effects of using stimulants for ADHD therapy as they manifest negative side effects. The amphetamine stimulants are neurotoxic with long-terms use and it's imperative to use it in lower dosages while at the same time yielding the maximum affects to treat ADHD symptoms. This narrative review is conducted to explore the professional literature between 2000-2015. The trials conducted to explore the efficacy of adjunctive therapy with stimulants demonstrated various results. The supplementation of combined magnesium and vitamin B6 yielded positive results with significant improvement in ADHD, specifically in hyperactivity, aggression, and low attention span. Zinc supplementation, with 30 mg or more, with amphetamine aided in lowering the dosage of amphetamine use by at least 20% while yielding the same results compared to higher amphetamine use without zinc. Zinc+methylphenidate combination yielded positive results to lower ADHD symptoms; however the results are not conclusive due to more trials are needed in different dosages of zinc. Based on the clinical studies, dietary supplements are useful in treating ADHD symptoms. Clinical trials with zinc and magnesium+B6 have shown to yield positive results in lowering the ADHD symptoms. With current ADHD therapy, continued stimulant use leads to tolerance and increases with continued use; hence the stimulant dosage also needs to be increased to reach efficacy. Adding adjunctive dietary supplements have demonstrated that the

stimulant dosages can be lowered. However, further study is needed to factor in bioavailability, efficacy of other dosages, diet, and any other factors that could hinder the function of the dietary supplements internally.

Keywords: Attention deficient hyperactivity disorder; Magnesium; Zinc; Magnesium b6 adhd; Vitamin b6 ADHD; Hyperactivity; Stimulant therapy; ADHD brain; Adderal; Ritalin; Amphetamines; Methylphenidate

1. Introduction

Attention deficit hyperactivity disorder (ADHD) in childhood is a dominant, stressful, and impairing disorder that is not fully treated by pharmacotherapy alone and lacks evidence-based psychosocial treatments. ADHD is an illness that has grown steadily over the years in the childhood population, which is later carried on to the adolescent and adult years, but with less severity. The diagnosis has probably increased in the population due to parents and teachers becoming more aware with the disorder. According to the Center for the Disease Control and Prevention, in the United States alone, approximately 11% of children 4-17 years of age (6.4 million) have been diagnosed with ADHD as of 2011. For individuals 17 years of age or older, ADHD severity is reduced; ADHD symptoms are reduced with increasing age but not completely gone. Those who have ADHD and are not diagnosed or treated are affected negatively throughout their day, especially during activities that require constant mental focus. ADHD individuals, without medications, cannot fully reach their maximum potential to conduct their daily activities and the disorder places a burden on them mentally and emotionally. At the moment there is no cure for ADHD, currently the symptoms are treated, such as hyperactivity and lack of attention.

Stimulants play an important role in today's therapy of treating the symptoms of ADHD. Stimulant therapy has proven to show alleviation of ADHD symptoms for patients to have normal functioning daily activity [1]. However, there is also the issue of side effects from long-term therapy with stimulant use. The popular drug Adderall, an amphetamine salt, is used widely for the treatment of ADHD symptoms. Unfortunately, Adderall can cause neurotoxicity with continued use; "heavy use of stimulants may also be neurotoxic in humans and that alterations may persist over prolonged periods of time" [2]. Amphetamine salts have demonstrated to hinder the height and weight growth development in children. Other side effects of amphetamines are, but not limited to, increased arousal or wakefulness, anorexia, hyperactivity, state of pleasurable affect, and euphoria, which can further lead to the abuse of the drug [3]. However, the use of Ritalin, or the generic name methylphenidate, another popular ADHD drug, has shown to be neuroprotective. Research has shown that methylphenidate is better option in terms of stimulant use; "the neuroprotective effects of methylphenidate are due, at least in part, to its ability to attenuate or prevent this abnormal cytoplasmic dopamine accumulation through several possible neuropharmacological mechanisms" [4]. However, methylphenidate therapy does not respond to all individuals; the response varies from person to person. It's important to explore other treatments that cause the least side effects yet yield the maximum benefits. The focus of the paper will revolve around exploring ways to reduce the degree of ADHD symptoms and reduce the dosages of stimulants.

Dopamine is the neurotransmitter of focus when using stimulants. Dopamine is responsible for the brain's feeling of reward, incentive motivation, and focus. Berman reported that stimulant use increases dopaminergic activity and in

doing so it down regulates the dopamine receptors over time [3]. The down regulation of dopamine receptors is one of the reasons the dose of the stimulant must be increased in order to reach its efficacy. Increasing dosage use of neurotoxin stimulants, in the long run, will harm the brain causing psychosis and seizures as research demonstrates [1].

ADHD is not an illness that can be treated temporarily; it has to be treated life long, because it is associated with a defect of the brain's anatomy. "Relative to controls, the fractional anisotropy (FA) values were significantly smaller in both regions of interest in the right hemisphere, in contrast to a control region (the fornix), indicating an alteration of anatomical connections within the attention and EF cerebral systems in adults with childhood ADHD" [5].

Since ADHD is a life-long disorder, the therapy recommended to be used should be have minimal negative effects to the brain, which is issue in the case of use with amphetamine salts. According to serum studies, mineral deficiencies may contribute significantly to ADHD symptoms. "Low levels of copper, iron, zinc, magnesium, and omega-3 fatty acids have been reported in children with ADHD" [6]. This thesis will focus on zinc and magnesium as alternative treatment for ADHD.

This research will be a narrative review in which past clinical studies of alternative therapies will be investigated. The research will investigate clinical studies to provide evidence in treating without stimulant use and/or aiding lowering dosages of stimulant use. The main reason for this study is due to the fact that children with ADHD grow up with internal emotional and mental stress. They fall back behind their peers in academics, or anything that requires consistent mental focus, and they become overwhelmed and it leads to depression, which is a catastrophic illness. Through observation in school-aged children, ADHD is seen as a major growing problem that needs more investigation to lower the epidemic. If the causes of the rise of number ADHD diagnosis or finding alternative treatment are not investigated then children with the disorder will grow up with psychological issues, which perhaps could affect society negatively. Stimulants does not provide 100% response, therefore, other therapies must be investigated.

Stimulant use does benefit individuals who are diagnosed with ADHD, but it does manifest side effects. The uses of stimulants have short-term as well as long-term negative side effects on the user. Short-term side effects are but not limited to are: insomnia, increased heart rate, increased blood pressure, loss of appetite, sometimes violent behavior, hyperexcitability, and possible death from overdosing. The long-term side effects include but not limited to: malnutrition and weight loss, psychological dependence, depression, permanent damage to blood vessels of heart and brain.

The research will focus on answering certain questions: do dietary supplements give an advantage in the treatment and management of ADHD not provided by traditional amphetamine treatment and management approaches? do specific dietary supplements magnesium, zinc, vitamin B6 specifically offer an advantage in the treatment of ADHD? do dietary supplements augment the efficacy of amphetamine-based treatment of ADHD? The goal of this paper is to answer the questions mentioned, to explore dietary supplements in treating the symptoms of ADHD, and

discuss the outcomes that manifested from it. Furthermore, the paper will also discuss the trials conducted by adding non-stimulant supplements in addition to the stimulant use in individuals diagnosed with attention deficient hyperactivity disorder.

2. Methods

This research review documentations of clinical trials conducted to alleviate ADHD symptoms with non-stimulant treatment, specifically with magnesium, vitamin B6, and zinc between the years 2000-2015. The research will also include assessment of ions in the blood serum. The age ranges of the subjects are from 17-years-old and younger. Key words and key phrases used in this research were: attention deficient hyperactivity disorder, magnesium, zinc, magnesium b6 adhd, vitamin b6 adhd, hyperactivity, stimulant therapy, adhd brain, Adderall, Ritalin, amphetamines, methylphenidate. Science journals were searched with the keywords in such as Google Scholar, PubMed, Eurotext, Wiley Online Library, Molecular Psychiatry, along with Diagnostic and Statistical Manual 4 and 5, and other minor scholarly websites.

The inclusion criteria for the research include clinical trials with children 17 or younger who were diagnosed with ADHD. The children cannot have any underlying medical conditions that are diagnosed prior to participating in the trials such as absorption problems or dietary restrictions. The children must also not have consumed zinc, magnesium, or vitamin B6 prior to the trials. The children must also have prior ratings of significant symptoms of ADHD based on objective assessments by their parents and teachers.

Since ADHD is a multifactorial disorder, multiple studies were taken in consideration to focus on what alleviated the symptoms. The results of clinical studies are organized in a table format.

3. Results

Initial electronic search yielded 76 articles, but secondary search yielded 24 articles. The secondary search included the criteria of children 17 years old or younger, who were diagnosed with attention deficient hyperactivity disorder prior to participating in the clinical trials. Inclusion criteria also includes the subjects must not take any dietary supplements that is associated with magnesium, zinc, or vitamin B6. From the articles found in electronic search, the three main articles chosen are:

- “Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: A double blind and randomized trial” by Akhondzadeh S et al. [7].
- “Zinc for Attention-Deficit/Hyperactivity Disorder: Placebo-Controlled Double-Blind Pilot Trial Alone and Combined with Amphetamine” by Arnold LE et al. [8]
- "Improvement of Neurobehavioral Disorders in Children Supplemented with Magnesium-vitamin B6." by Mousain-Bosc et al. [9].

Magnesium/B6 Clinical Trial

The results demonstrated significant improvement in the ADHD symptoms, more specifically aggression, lack of attention, and hyperactivity were all reduced in the test group. The combined supplementation also leads to the ERC-Mg concentration levels to increase in the test group [9].

Zinc Supplementation Clinical Trial

According to the results, there were no significant changes with 15 mg/day.

However, there was a reduction of 37% amphetamine use with b.i.d. zinc supplementation (30mg/day) yielding optimal results when compared to placebo. The clinical outcomes sometimes favored zinc and other times favored placebo [8].

Zinc/Methylphenidate Clinical Trial

There was no initial difference with zinc therapy. However, the test subjects demonstrated improvement of their behavior based on the ratings by parents and teachers over the 6-week double-blind, placebo control trial. Also in each group there was a drop out of 2 subjects [7].

The following table summarizes each clinical trial:

Therapy:	Magnesium/B6	Zinc+Amphetamine	Zinc+Methylphenidate
No. of Test Subjects:	40	28	22
No. of Placebo Subjects:	36	24	22
Age Range:	Mean age: 6.49	6-14 years of age	5-11 years of age
Duration:	6 months	13 weeks	6 weeks
Outcomes:	Erc-Mg was lower in ADHD subjects that the control group before treatment. A significant rise in Erc-Mg level in ADHD patient in which it correlated with the lowering of the ADHD symptoms. The significant improvement appeared after 8 weeks of therapy.	Single dose of 15 mg/day of zinc did not show significant effect. However, 15 mg BID showed significant improvement with 37% decrease in AMPH dosage for optimal effect.	No improvement from baseline in week 1, but the therapy showed significant improvement at week 6 from both the parent and teacher ADHD rating scales.
Authors:	Mousain-Bosc, M., Roche, M., Polge, A., et al.	Arnold, L. E., DiSilvestro, R. A., Bozzolo, D., et al.	<ul style="list-style-type: none"> • Shahin Akhondzadeh • Mohammad-Reza Mohammadi • Mojgan Khademi
Year:	March 2006	February 2011	January 2004

Table 1: Clinical trials.

- Do dietary supplements provide an advantage in the treatment and management of ADHD not provided by traditional amphetamine treatment and management approaches? Yes
- Do specific dietary supplements magnesium, zinc, vitamin B6 specifically offer an advantage in the treatment of ADHD? Yes
- Do dietary supplements augment the efficacy of amphetamine based treatment of ADHD? Yes

4. Discussion

Magnesium/B6

Children, diagnosed with ADHD presented with low ERC-Mg concentration, presented with hyper-excitability behavior, such as aggression, hyperactivity, and lack of attention. Erythrocyte measurements demonstrated healthy children with a ERC-Mg level of 2.76 mmol/L, and ADHD children with 2.04 mmol/L before Mg-B6 treatment. However, after the Mg-B6 supplementation, the test group's ERC-Mg concentration increases to 2.35 mmol/L, still below the ERC-Mg level of healthy children, there were clinical improvement of reduced hyperactivity and increased attention capacity. Based on the trial, the improvement in ADHD symptoms is reached around 8 weeks. When the Mg-B6 as stopped, the ADHD symptoms returned in 2 weeks, along with measurements of reduced serum concentration of ERC-Mg. This outcome confirms that the ADHD symptoms are directly related to the low magnesium level in erythrocytes. These findings demonstrate magnesium to be significantly deficient in ADHD individuals and with magnesium deficiency ADHD symptoms, specifically hyperactivity and lack of focus, are manifested. Magnesium+B6 aids in lowering the major ADHD symptoms and therefore can treat the disorder even without stimulant use. The trial was conducted without adjunctive stimulant use due to the reluctance of the children's parents agreeing to give stimulants to their children [9].

Zinc+Amphetamine

According to L. Eugene Arnold et al. [8], the clinical trial conducted of supplementation of zinc with amphetamines demonstrated significant help in treating ADHD symptoms. Zinc glycinate form was selected for the trial due to the minimal gastrointestinal symptoms. The goal of the trial was to see if any effect would manifest with zinc supplementation and so it did; it lowered the dosage of amphetamine by 37%. This outcome demonstrated that zinc does play a role in treating the ADHD symptoms. There was non-consistent outcome in some subjects and it was probably due to interaction with prior medication use in those individuals, which possibly imposed an inhibiting effect on zinc or hindered zinc absorption [8]. This narrative research was to investigate if zinc can be used as an alternative therapy in helping to treat ADHD symptoms, and from this study the evidence demonstrates that zinc can help, but as an adjunctive therapy to amphetamine. As mentioned earlier, amphetamines are neurotoxic in the long-term and keeping the dosages low while yielding the same therapeutic effect is beneficial for those who use the drug. This study demonstrated that zinc is possibly deficient in ADHD individuals and supplementing them with dietary zinc will treat their ADHD symptoms.

Zinc+Methylphenidate

In this study the goal was to aid in treating ADHD symptoms due to that fact that stimulants have less that favorable profile with negative side effects; stimulant response varies from individual to individual. Therefore, exploring alternative therapies was conducted to expand treatment options. In the 6-week double-blind, placebo-controlled study, zinc+methylphenidate demonstrated positive results. The clinical trial demonstrated that zinc does play a positive role in lowering ADHD symptoms. Zinc is responsible for the production of melatonin, which regulates dopamine production. As mentioned earlier, dopamine is the main neurotransmitter associated with ADHD, in which dysregulation of it manifests ADHD. In the experiment, there was no improvement in the first week but there was significant improvement of ADHD symptoms after the 6th week. The measurements of the outcome were only from the ratings of ADHD symptoms from the teachers' and parents' observations, but not serum zinc level. These results surely demonstrate zinc could possibly be deficient in ADHD individuals and supplementing dietary zinc can lower ADHD symptoms but serum zinc level should've been measured to confirm the results [7].

Overall the clinical research that was conducted demonstrated enough evidence that ADHD symptoms can be treated with alternative therapy proving this research thesis. The clinical studies have demonstrated alternative therapy can be used alone such as with magnesium/B6 supplement or it can aid in adjunctive therapy with zinc+stimulants to lower the stimulant dosages. However, more research must be conducted in order to have a solid conclusion. The limitations of this narrative study includes: there is not enough meta-analysis data are there to decrease any errors that could possibly come about; there are not enough clinical studies investigated in why the dietary supplements did yield positive results consistently. Also, another limitation of this narrative research is the data investigated may not be 100% accurate; the data collected is based on the studies by other authors.

5. Conclusion

The clinical studies investigated supported the thesis of this narrative research. Dietary supplements do help in treating the symptoms of ADHD. One of the most significant findings of this research is ADHD individuals have deficiencies in zinc and magnesium in their serum, which contributes to their disorder, and improved with supplementation. Stimulants may or may not help everyone due to different neurobiochemistry that varies from person to person. However, zinc and magnesium+B6 shown to help majority of the test subjects, and it has proven to be alternative therapy for ADHD.

A negative side effect with pharmaceutical grade stimulants is the issue of dependence; ADHD individuals will constantly be dependent on medications and the dosages would have to be increased as the tolerance increases in order to reach optimal effects. Clinical trials with non-stimulants, brain imaging, and blood serum assessments have presented researchers that the disorders cannot be corrected with surgery, and it must be treated lifelong with medications.

From the clinical trials discussed, Magnesium/B6 combination demonstrated consistent positive results. Unlike adjunctive therapy with zinc supplementation with amphetamine therapy and methylphenidate therapy, magnesium+B6 by itself did demonstrate that it could treat ADHD symptoms solely.

Clinicians can take the information presented from this thesis and create protocol to systematically treat their ADHD diagnosed patients. Stimulant use does not give positive response to all ADHD individuals so it's recommended to initiate treatment with dietary non-stimulants.

They can follow the following protocol, starting from non-stimulants to stimulants:

1. First initiate treatment with magnesium+b6 and titrate it until Erc-Mg reaches the close to the level as healthy individuals, which is 2.76, and maintain the therapy for at least 8 weeks for optimal results.
2. If the ADHD symptoms are not subsided, then zinc (15mg)+methylphenidate (1mg/kg/day) should be tried.
3. If zinc+methylphenidate does not yield any significant positive results then zinc (15 mg BID)+amphetamine (≤ 25 kg weight: 5mg/day; 25-45kg weight: 10mg/day; >45 kg weight: 15mg/day) should be tried.

Further studies must be conducted to be fully conclusive in improving ADHD symptoms with non-stimulant use in adjunction to stimulant use. The current experiments did show positive results but the data did not demonstrate homogenous results with zinc+amphetamine use. It's noted that different diets and difference in absorption rate could have contributed to inaccurate results for zinc trials. Prospective future studies should consider the following points in order to avoid similar errors:

1. There must be more participants in the trials in order to have a conclusive statement; $n > 100$. A high number is chosen due to the possibility of children dropping out from the trials. A low number can alter the results significantly which can possibly lead to selection bias.
2. There must be a standardized diet in which all participants consume. As the ions from the supplements may not be fully absorbed based on the different diets consumed by the participants.
3. Age range from the participants should be narrowed and the trials should be conducted. For example, a 6-year-old child's ADHD behavior should not be compared to the ADHD behavior to a 17-year-old because the ADHD symptoms improve with age.
4. The absorption rate for each test subject and control subject must be measured before including the individual in the clinical studies.
5. Finally, there must be consistent measurement of zinc, magnesium, and vitamin B6 frequently throughout the duration of the clinical studies to confirm if there is proper absorption of the ions and vitamins.

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