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Joshua Meir Alge

Philadelphia College of Osteopathic Medicine

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**Is Ginkgo Biloba Effective In Managing The Symptoms Of ADHD
And Does It Exhibit Lower Adverse Side Effects As Compared To
The Current Standard Of Treatment?**

Joshua Meir Alge, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective evidence based medicine review is to determine whether or not ginkgo biloba is effective in managing the symptoms of ADHD and if it exhibits lower adverse side effects as compared to the current standard of treatment.

Study Design: Systematic review of three English language studies, two of which were randomized, double blind, controlled trials (one positive controlled, one placebo controlled), and one open prospective cohort study, published between 2009-2015.

Data Source: Two randomized, double blind, controlled trials (one positive controlled, one placebo controlled), and one open prospective cohort study. In one study the group received only ginkgo biloba as tolerated with no comparison group. In another study, one group received methylphenidate and ginkgo biloba while the comparison group received methylphenidate and a placebo. In the final study one group received ginkgo biloba while the comparison group received methylphenidate. All studies were published in peer reviewed journals and were found via Medline and Pubmed.

Outcomes Measured: The efficacy and tolerability of ginkgo biloba in the treatment of ADHD symptoms as well as its side effects. This was measured by an ADHD Rating Scale IV and FBB-HKS (a German DSM-IV-oriented rating scale for ADHD problems) performed by the subjects' parents and teachers, CGAS by the subjects' parents, and side effects by parents, subjects, and psychiatrists using a rating scale.

Results: The positive controlled study showed methylphenidate to be significantly more efficacious than ginkgo biloba, however ginkgo biloba showed fewer adverse side effects. The placebo controlled study showed ginkgo biloba was effective as an add on therapy to methylphenidate as compared to methylphenidate and a placebo. The open prospective study showed that with ginkgo biloba, there was improvement in ADHD symptoms as compared to baseline, with minimal adverse side effects.

Conclusions: From the studies conducted, ginkgo biloba showed to be inferior to methylphenidate. However, it was an effective alternative or adjunctive treatment for ADHD symptoms as compared to no treatment or a placebo. Furthermore, it exhibited minimal adverse side effects.

Keywords: ADHD; Ginkgo biloba

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neuropsychiatric disorders found in children.¹ Patients with ADHD are believed to have a deficit in their executive functions, skills that help people focus, organize, and perform tasks.² The frontal lobe of the brain is responsible for these executive functions.² Symptoms of ADHD remain constant, however some children grow out of it as the brain develops into adulthood.² For others though, the symptoms remain in adulthood.

The prevalence of ADHD is on the rise, with the CDC recently reporting that amongst the general population, 10.2% of children and adolescents in the US have ADHD.³ This means that practitioners should expect to see this disorder more often amongst their patients. It is believed that there were an average of 9 million office visits with ADHD as the primary diagnosis in 2009-10.³ By seeing how frequently patients present with this disorder, it makes sense that more money and resources are being invested in managing ADHD. \$38–72 billion is believed to have been spent on children ages 4-17 in the US with ADHD, most of which was used for education and healthcare.⁴ The total cost of all US cases of ADHD is estimated to be between \$143 billion to \$266 billion.⁴

There is still much to be discovered and understood about ADHD. The exact cause is unknown although ADHD seems to have a genetic component. Strong familial connections have been shown, in that a child has a 50% chance of having the disorder if one parent has it, and a 30% chance if an older sibling has it.⁵ It also has been associated with pregnancy issues like low birth weight, premature birth, and difficult pregnancies as well as mothers who drink alcohol or smoke tobacco when pregnant.⁵ It also has been connected with physical trauma of the frontal lobe of the brain.⁵ Neurochemical studies have shown that deviations from the normal activity of

dopaminergic and noradrenergic transmitter function can be found in those with ADHD.⁶ The key symptoms of ADHD are inattention, hyperactivity, and impulsivity.¹

Currently there are many different choices to help curb the symptoms of ADHD. Lessening the severity of its symptoms is always the goal, as there is no way to treat or eradicate ADHD. The first line therapy for the disorder continues to be stimulants like Methylphenidate and amphetamines.⁷ These have always been shown to be the most effective treatment option.⁷ However, stimulants have shown to have adverse side effects like headaches, insomnia, decreased appetite, mood changes, and weight loss.⁷ Non-stimulants like atomoxetine and tricyclic antidepressants have also been used to treat ADHD, and have shown to exhibit fewer side effects.⁷ Dietary changes as well as vitamins and supplements have also been used by those who would like to avoid taking medications.⁸ Behavior therapy has also been an important treatment option often used in conjunction with medical treatment, to help increase organization and help patients understand what environments help them cope better.⁷

The biggest issue in treating ADHD is finding a treatment that effectively curbs the symptoms, while exhibiting the fewest adverse side effects. This has pushed patients and practitioners to research alternative treatment options. One alternative that has become more popular is ginkgo biloba. Ginkgo biloba is a supplement that is used to help manage the symptoms of many different disorders and illnesses, including those that effect the brain.

Objective

The objective of this selective evidence based medicine review is to determine whether or not ginkgo biloba is effective in managing the symptoms of ADHD and if it exhibits lower adverse side effects as compared to the current standard of treatment.

Methods

This review assessed three studies, two double blind randomized controlled trials, and one open prospective cohort study, which recorded and compared the side effects and efficacy of ginkgo biloba as an oral medication in treating the symptoms of ADHD. In each of these studies, children between the ages of 6 and 14, that had been previously diagnosed with ADHD, were included. Ginkgo biloba was the intervention that was evaluated in each of these studies. The supplement was administered orally and the dosage ranged from 80-240 mg. In one study the group received only ginkgo biloba as tolerated with no comparison group. In another study, one group was administered methylphenidate and ginkgo biloba while the comparison group received methylphenidate and a placebo. In the final study one group received ginkgo biloba while the comparison group was given methylphenidate. The outcomes measured were the efficacy and tolerability of ginkgo biloba in the treatment of ADHD symptoms, as well as the side effects exhibited by ginkgo biloba.

The keywords used in the searches were ADHD and ginkgo biloba. All articles were published in English in peer reviewed journals between 2009-2015. These studies were searched and found via Medline and Pubmed. The articles were selected based on their relevance to this review's clinical question and if they included patient oriented outcomes. Inclusion criteria for the participants in the studies were older than 6 and younger than 14, diagnosed with ADHD according to DSM-IV. Exclusion criteria for the studies were other psychiatric disorders, comorbidities like hypertension, and other neurologic disorders like seizures. The studies utilized various statistics including RRI, ARI, NNH, and p-value.

Table 1: Demographics & characteristics of included studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	w/d	Interventions
Salehi ⁶ (2010)	Double blind RCT	50	6-14	Newly diagnosed with ADHD as per DSM-IV-TR, who scored at least 1.5 standard deviations above the norm based on their age and gender on the ADHD-RS-IV School Version.	History/current pervasive developmental disorders, schizophrenia, other psych disorders/comorbidities, suicide risk, MR (IQ<70), significant chronic medical conditions, organic brain disorders, seizures, drug use, or hyper/hypotension.	4	Regimen of ginkgo T.D. at a dose of 80-120mg per day depending on weight.
Shakibaei ¹ (2015)	Double blind RCT	66	6-12	Diagnosed with ADHD based on the DSM-IV-TR, Children's Global Assessment Scale (CGAS) score<80.	Mental retardation (IQ≤70), Type I Bipolar disorder, psychosis, pervasive developmental disorder, organic brain disease, seizures, CVD.	6	Regimen of methylphenidate at a dose of 20-30mg + ginkgo biloba 80-120mg per day depending on weight
Uebel-von Sandersleben ⁸ (2014)	Open prospective cohort study	20	6-13	Diagnosed with ADHD according to DSM-IV, who were unwilling or could not tolerate methylphenidate. All subjects attended regular school and had an IQ>80.	Pharmacological treatment within the previous 2 weeks, seizure disorders, other ADHD-like disorders, and other medical conditions such as hypertension.	0	Regimen of ginkgo biloba EGb 761 at a dose of 80-240mg a day based on tolerability

Outcomes Measured

Between the three studies the outcomes measured were the symptoms of ADHD as defined in the DSM-IV-TR via rating scales, the Children's Global Assessment Scale (CGAS), and side effects of the intervention via rating scales. In one study, the participants' parents measured their children's symptoms of ADHD through the ADHD Rating Scale IV. In this study, side effects were assessed by a psychiatrist. In another study, the participants' parents and teachers gauged their children's symptoms of ADHD via the ADHD Rating Scale IV, CGAS was performed by the subjects' parents, and side effects were assessed by a psychiatrist. In the last study, the participants' attentiveness was assessed by their parents through the FBB-HKS (part of the Diagnostic System of Mental Disorders in Children and Adolescents [DISYPS-KJ], a German DSM-IV-oriented rating scale for ADHD problems). Hyperactivity and impulsiveness were measured by DISYPS-KJ FBB-HKS and FBB-SSV which was performed by the subjects' parents. Changes in strains on family life were assessed by the FaBel, and changes in the children's perceived quality of life were obtained with the KINDL questionnaire. The general psychopathological profile of the patients was assessed using the German version of the children's strengths and difficulties questionnaire (SDQ-D). Side effects were gauged by both parents and subjects via the Side Effects Rating Scale (SERS-D).

Results

The study by Salehi was a six-week, parallel group, double blind randomized control trial performed in an outpatient child and adolescent clinic. It was composed of 50 participants diagnosed with ADHD ages 6-14, of which 39 were males and 11 were females. Subjects were randomly assigned to either an experimental group (one) or a comparison group (two). Group one received a ginkgo biloba tablet at a dose of 80–120 mg/day. Dosage was based on weight, 80

mg/day for those under 30 kg and 120 mg/ day for those over 30 kg. Group two received methylphenidate at a dose of 20–30 mg/day based on weight, 20 mg/day for those under 30 kg and 30 mg/day for those over 30kg. No significant difference was found between the two groups in regards to basic demographic data including gender, age, and ethnicity. Four patients dropped out, two from each group. Patients were evaluated at days 0, 21, and 42 using the Teacher and Parent ADHD Rating Scale- IV, which was the primary outcome assessed. Subscales were used to differentiate change in inattentive and hyperactive-impulsive symptoms. A one-way two-tailed post-hoc Tukey mean comparison test was performed on the change in Parent and Teacher ADHD Rating Scale scores from baseline. Results are presented as mean \pm SD, and differences were considered significant with $P \leq 0.05$. A Fisher's exact test was used to compare the frequency of side effects found during the study.

At day zero there was no significant difference between the two groups. At the end of the six weeks, the parents reported there was a significant change in both the inattentive symptoms as well as the hyperactive-impulsive symptoms for the experimental and the comparison group -6.52 ± 11.43 and -15.92 ± 11.44 , respectively. The teachers also reported a significant change in all symptoms for both groups at the six week mark: -0.84 ± 6.79 for the experimental group and -14.04 ± 8.67 for the comparison group. Ten side effects were noted over the trial, all of which were deemed mild to moderate and tolerable. All the side effects were found to be more prevalent in the methylphenidate group. Of those, decreased appetite, insomnia, and headaches were the only side effects to have showed a significant difference in occurrence between the two groups. Table 2 shows the incidence of decreased appetite with ginkgo biloba (experimental event rate of 20%) as compared to Methylphenidate (control event rate of 76%). P-value was .0002, relative risk increase (RRI) was -74% and absolute risk increase (ARI) was -56%. The

number needed to harm (NNH) was -17 meaning for every 17 people on ginkgo biloba instead of methylphenidate, one less patient will suffer from decreased appetite.

Table 2: Incidence of negative outcomes with intervention

CER	EER	RRI	ARI	NNH	P-value
76%	20%	-74%	-56%	-17	0.0002

The study by Shakibaei was a six week randomized, double-blinded, placebo-controlled, clinical trial with children and adolescents from the ages of 6-12. 66 children were distributed equally between two groups, with two dropouts coming from the experimental group (due to side effects) and four coming from the placebo group (one from side effects, two from refusal to continue, one from lack of response). The dropouts were not significantly different than the other participants. The experimental group had 19 males and 12 females, and the placebo group had 20 males and 9 females. All participants were given 20-30 mg/day of methylphenidate. Subjects over 30 kg were given 30 mg, and subjects under 30 were given 20 mg. Dosage was increased each week by 10 mg up to the assigned dose. Participants in the experimental group received 80-120 mg/day of enteric coated tablets of ginkgo biloba. 80 mg/day was given to those with a body weight of less than 30 kg, and 120 mg/day for those over 30 kg. Dosage was increased each week by 40 mg up to the assigned dose. Participants in the placebo group received placebo tablets which were identical in color and size to the ginkgo biloba tablets and were composed of lactose and starch. No significant difference was found between the two groups in regards to demographics. Participants were assessed prior to the study and at weeks four and six by parents and teachers using the ADHD Rating Scale-IV, with subscales for inattention and hyperactivity-impulsivity. Parents completed the CGAS at baseline and at week six, measuring the participants general psychosocial functioning. Finally, side effects were gauged by a psychiatrist at weeks two and six. The primary outcome assessed was change in ADHD Rating Scale-IV scores, which

was considered significant if there was at least a 27% change in baseline, which was derived from previous studies using this scale. Information was reported as mean \pm SD or %. Normal distribution of quantitative data was checked with the Kolmogorov-Smirnov Test. Group comparisons were assessed using the Independent Sample t-Test, Manne-Whitney U Test, and Fisher's Exact Test. A p-value of <0.05 was considered significant in all analyses.

At baseline, no significant difference was found between the two groups in regards to their disorder. However, significant decreases in both inattentive and hyperactivity-impulsivity scores were noted for both groups on the ADHD Rating Scale-IV. The parents reported a total change of -13.1 ± 3.36 and -10.2 ± 3.01 for the experimental and placebo groups, respectively, with a p-value of .001. The teachers reported a total change of -12.80 ± 5.02 and -11.13 ± 3.43 for the experimental and placebo groups, respectively, with a p-value of .141. There was significant change in both groups in CGAS, with the experimental increasing by 8.92 ± 7.37 , and the placebo changing by 8.51 ± 5.33 . However, there was not a significant difference between the groups. Several side effects were monitored in both groups, including loss of appetite. Table 3 shows the incidence of decreased appetite in both groups, with it occurring in 24.1% of the participants in the placebo group and 6.4% of the time in the experimental group. RRI was -73% and ARI was -17.7%. The NNH was -5 and the P-value was .075. This difference was not considered significant, and there was no significant difference between any of the side effects in either group.

Table 3: Incidence of negative outcomes with intervention

CER	EER	RRI	ARI	NNH	P-value
24.1%	6.4%	-73%	-17.7%	-5	.075

The study by Uebel-von Sandersleben was an open prospective clinical cohort study, that lasted four to five weeks depending on the participant. The study was comprised of 20 subjects,

15 male and 5 female, ages 6-13. Every subject was started on a dose of 80mg/day of ginkgo biloba. If attention issues remained present after the first week, then the dose was raised to 120mg/day. For two of the subjects this second dose was effective. The other 18 were raised again for the third week to 240mg/day. This was an effective dose for the remaining subjects. All subjects stayed on the determined effective dose for three total weeks, meaning for two patients the study lasted four weeks total, and for the remaining 18 the study lasted five weeks. No patients dropped out during the study. The primary outcome of this study was attentiveness of the patients before and after the intervention. This was assessed through the subjects' parents and the use of the FBB-HKS questionnaire, which is a German oriented DSM-IV rating scale for ADHD problems. This questionnaire was also used to gauge hyperactivity-impulsivity. Aggressive behavior was evaluated via the FBB-SSV, family life strain was assessed by the FaBel and the subjects' quality of life was gauged by the KINDL questionnaire. Each participant's psychopathological profile was assessed by the German version of the SDQ-D questionnaire. Each patient was evaluated before and after the intervention, with pre and posttreatment behavioral scores being analyzed with a one-sided nonparametric Wilcoxon sign rank test. Information was reported as mean \pm SD.

After the intervention, there proved to be a significant decrease in total symptoms. Table 4 shows the patients' FBB-HKS Total Score changed -0.4 ± 0.6 , from 1.9 ± 0.04 before the intervention, to 1.5 ± 0.7 post treatment. The SDQ-D showed improvement in the subscale of prosocial behavior ($p < .01$), but the other subscales of hyperactivity, emotional problems, conduct problems, and peer problems (all $p > .14$) remained unchanged. The FBB-SSV showed improvement in Oppositional-Aggressive symptoms ($p < .01$), but Dissocial-Aggressive symptoms were unchanged ($p = .25$). FaBel showed improvement in family life ($p < .01$), but the

KINDL questionnaire showed quality of life remained unchanged ($p=.72$). The SERS-D showed lower symptom burden from both parent and participant ratings ($p=.05$). No serious adverse reactions were noted during the study, although three mild adverse events were observed in three patients. These were eosinophilia, allergic dermatitis, and prolonged thrombin time. Each of these was thought to be unrelated to the ginkgo biloba. In total, the incidence of adverse events was 0.004 per observation.

Table 4: Efficacy of ginkgo biloba

Study	Pretreatment Score	Posttreatment Score	Total Change	P- Value
FBB-HKS Total Score	1.9±.04	1.5±.7	-.4±.6	<.01

Discussion

As with any study, there are always limitations. Each study tested the efficacy of ginkgo biloba in a different way, so each individual study had its own unique shortcomings. For each study, they could have lasted longer and used a larger sample size. This would have provided a firmer understanding of the effects of the drugs, and could have answered questions about the drug's efficacy over an extended period of time. Another issue was that the subjects were only children and adolescents. It would be interesting to see if the population sample could have been compared by age to see if there were any changes in efficacy or side effects.

Currently ginkgo biloba is classified as a supplement in the US, is regulated by the Food and Drug Administration (FDA), and is available for purchase.⁹ More often than not, people pay out of pocket for supplements, as insurance companies avoid covering alternative medicines when possible.¹⁰ Usually, a supplement needs to have been proven efficacious and safe before an insurance company will cover it.¹⁰ Currently, ginkgo biloba is most commonly used by people who want to help increase their brain function or memory.⁹ Though at this time, the FDA has not approved ginkgo biloba for treatment of any medical condition.⁹

Conclusions

In conclusion, the goal of this review was to discern if ginkgo biloba is effective in managing the symptoms of ADHD and if it exhibited lower adverse side effects as compared to the current standard of treatment. While the evidence brought from these studies is far from conclusive, it appears that ginkgo biloba is not as effective as the current standard of treatment. Despite this, there is still some benefit to be had by it, as well as the fact that the patients who took ginkgo biloba often suffered less side effects. A new area to expand this research would be to compare ginkgo biloba to some of the second or third line treatment options, specifically the non-stimulants. It might be there that we find both interventions to be at a similar level of efficacy.

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