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Is Acetyl-L- Carnitine effective and safe in treating children with ADHD?

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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 systematic review is to see how effective and safe is Acetyl-L-Carnitine in treating children with ADHD.

Study Design: This systematic review evaluated 3 randomized, controlled and double blind articles all published in English, which were published in peer-reviewed journals. The articles were found on PubMed through PCOM's library website.

Outcomes measured: This review assessed how safe and effective ALC would be in treating children with ADHD. The outcomes were measured using the Parent and Teacher ADHD Scale IV, Conners' Global Index-Parents Scale, Conners' Global Index – Teachers Scale and the Vineland scores as well. These scales measure the behavior and attention of the child. This study also measured side effects such as psychic, neurologic, autonomic and other side effects to determine how safe this medication was.

Results: Based on all three studies conducted, it was determined that ALC combined with methylphenidate was ineffective in treating children with ADHD but it did prove to be safe and help to prevent side effects such irritability and headache. It was also determined that ALC alone without any other medications, was not effective and did not have a great impact on treating the behavior and attention of the children as well. The only significant finding showed that the children being treated with ALC alone were more prone to headaches compared to the group being treated with the placebo alone. However, ALC worked better in children with the inattentive type of ADHD compared to how it worked in children with the combined type of inattention and hyperactivity. ALC also worked very well to improve the symptoms of children with not only ADHD but also Fragile X Syndrome.

Conclusion: In the end, it was determined that combined with methylphenidate, ALC would not be considered an effective treatment to help improve the behavior of children with ADHD. ALC used alone without any other medication was also determined to be ineffective in treating the behavior symptoms of ADHD. It was found that ALC actually might be more beneficial for treatment for a certain type of ADHD, like the inattentive type. ALC was proven to also have great improvement in the inattention and social skills of children, not only with ADHD, but also with Fragile X Syndrome and more studies could be done to see how well this would work in children with Autism.

Key Words: "ADHD", "attention-deficit hyperactive disorder", "ALC", "Acetyl-L-Carnitine"

Introduction

Attention deficit hyperactivity disorder contains 3 categories, which include an inattentive type, an impulsive type and a hyperactive type.⁴ The inattentive type is used mostly to describe children who have trouble staying focused and are easily distracted.⁴ The inattentive type might just walk away from responsibilities and tasks and they lack perseverance.⁵ Their work ethic may be all over the place due to the fact that they are disorganized. These children may also have behavior issues and may be defiant. They may also show a lack of comprehension of academics in school or a lack of comprehension of general things dealt with in life.⁵ Children with the inattentive type may also be forgetful and lose things very easily, especially when they place something down because they may not be able to remember where they placed that item.⁴ The impulsive type is used to describe children who make careless decisions without putting much thought into those decisions. They can act on a whim, in a way that is careless and may seem impatient at times. They may also find it hard to wait their turn in school or when playing games with other people at school.⁴ The hyperactive type describes children who cannot sit still such as children who always fidget while seating down or who are restless.⁴ Restless behaviors can be displayed in ways such as tapping on the desk at school or talking during quiet time in school or climbing furniture at home.⁵

In adults this can be displayed as the constant need to move or swing the legs back and forth.⁵ This may not allow the child to be able to sit still during class long enough to be beneficial.⁵ They always feel the need to move or walk around and these symptoms can manifest at home, school or anywhere else.⁴ They always feel the need to move even if the place and time is not appropriate.⁵ The impulsive type will make quick

decisions in the moment without thinking about the consequences affecting them or people around them. They may not even realize that some decisions they make carry a lot of harm that make impact their lives or the lives of others.⁴ They also assume if they make quick and fast decisions they will be rewarded and will receive instant gratification.⁵

Teenagers with ADHD are more likely to have conflict with their friends, and tend to be more aggressive.⁴ They are more likely to become involved in crime, drink, smoke and use other drugs, which would further impact their decision making skills.⁴ These children are not only impulsive in their actions but they also can be impulsive in their social interactions and conversations. These children may find that when conversing with other people, they tend to interrupt others while they are talking and they can also be intrusive.⁵

People with ADHD may present with all of these types but may also present with one or two of these types.⁴ Some people may be affected by the inattentive type of ADHD, due to fact that they can't stop daydreaming.⁴ The most common presentation of this condition is the inattentive type combined with the hyperactive behavior in older children.⁴ In younger children, such as preschool age, the hyperactive type may present first.⁴ It is expected that sometimes people may not be able to focus all the time or stop moving around, but if these behaviors get to the point where they interact with your quality of life, especially at home and at school, then it may be ADHD.⁵ Most people have this condition starting from a very young age but symptoms can change as people age and become older. Teenagers and adults with ADHD will be less hyperactive but will often feel restless.⁵

Scientists are unsure of what exactly causes this disorder and its symptoms but it has been proven that many things can lead to the development of this condition. In children with this condition, research has shown that low dopamine levels also affects the child and their learning abilities.⁷ The chemical is transported between the nerves of the cells in the brain, and is more used in the regions of the brain that deal with learning and memory.⁷ It has also been proven that our social environment can affect children too as well. ADHD can sometimes manifest from lack of exercise, huge emphasis on achievement and any change in the child's family situation at home.⁷ Certain foods can play a role too in developing this, such as in children who eat many food containing artificial flavoring and preservatives.⁷

Genes have proven to play a part in the development of this condition because ADHD can be hereditary.⁷ Any substance used during pregnancy can lead to an increased risk of the child developing ADHD such as cigarette smoking, alcohol use or controlled substance use. Any risk to fetus causing low birth weight, lack of oxygen at birth or brain injuries might cause this condition too.⁷ Exposure to environmental toxins such as high levels of lead, at a young age, can lead to this development as well.⁷ It has been shown that this condition is more common in males than females but this does not exclude the fact that females can get this condition too.⁴ If it does present in a female, they tend to have more issues with attention compared to being hyperactive.⁴ Many people with ADHD can also have other conditions associated with them such as various other type of learning disabilities, anxiety disorders, conduct disorders due to the impulsive behavior, depression, and substance abuse.⁴

Unfortunately, the economic cost of ADHD is very high due to the fact that 9.5 % of children that are between the ages 4-17 years old have been diagnosed with ADHD.⁶ 27% of all the costs of ADHD are due to education and the healthcare associated with this condition.⁶ Children with ADHD need more attention in school, which leads to more education costs for programs such as special education, occupation and speech therapy and school counseling.⁶ These children also need more healthcare visits to adjust medications and monitor progress, which can cost up to 18.04 billion dollars total per year.⁶ First line medications are usually considered to be psychostimulants for this disorder.⁸ These stimulants include amphetamine-based drugs such as Dexedrine, Adderall and Vyvanse.⁸ Stimulants also include methylphenidate-based medications such as Ritalin (methylphenidate), Biphentin and Concerta.⁸ Non-stimulant drugs can be used as well such as Strattera (atomoxetine) and Intuniv (guanfacine) for patients that do not want to use stimulants or when stimulants fail.⁸

Objective

The objective of this systematic review is to see how effective and safe is Acetyl-L-Carnitine in treating children with ADHD.

Methods

This systematic review evaluated 3 randomized, controlled and double blind articles all published in English, which were published in peer-reviewed journals. The articles were found on PubMed through PCOM's library website. The articles were selected based on their time frame and how much the information in the articles could help answer my question. They were also selected on whether they discussed patient oriented evidence that matters (POEMs). The articles were found using the key words

“ADHD” and “Acetyl-L-Carnitine”. All patients in all 3 of the studies were over the age of 5 and under the age of 13 years, previously diagnosed with ADHD. The intervention used was Acetyl-L-Carnitine in weight based doses from 500 to 1500 mg b.i.d.

In study conducted by Abbasi et al. from 2011, the first group was treated with acetyl-l-carnitine plus methylphenidate at a dose of 20 -30 mg/day depending on their weight. The second group was treated with just acetyl-l-carnitine at a dose of 20-30 mg/day depending on their weight.

In study conducted by Arnold et al. from 2007, the first group was treated with acetyl-l-carnitine at a dose of 500-1500 mg/day depending on weight while the second group was being treated with the placebo at a dose of 500-1500 mg/day depending on the weight.

In study conducted by Torrioli et al. from 2008, the first group contained only boys aged 6 to 13 years old that had ADHD but also had Fragile X syndrome. They were treated with Acetyl –l- Carnitine at 500 mg twice daily while the second group had the same conditions but they were treated with a placebo at the same dose. P-values, ANOVA, t-values, standard deviations were used in the following articles.

Table 1 –Demographics and characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Intervention
Abbasi ¹ (2011)	Double blind RCT	40	Between the ages of 7-13	40 outpatients, which included 28 boys and 12 girls, between the ages of 7-13 who met the DSM-IV-TR diagnostic criteria for ADHD	Were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia, or other psychiatric	2	Methylphenidate plus Acetyl –l- Carnitine

					disorders.		
Arnold ² (2007)	Double blind RCT	112	Ages 5 to 12	Confirmed by the Diagnostic Interview Schedule for children (DISC-IV); an item mean on either the 18 DSM-IV ADHD symptoms	Severe medical, surgical or neurological problems; anything that would interfere with treatment or assessment; a prior history of Carnitine therapy in the past three months prior to baseline	31	Acetyl –l- Carnitine
Torrioli ³ (2008)	Double blind RCT	63	Ages 6 – 13 years	Patients were recruited through genetic clinics and were included when their FXS diagnosis was confirmed by southern blot and they had ADHD	Were not included in the study if they had disorders of central nervous system other than FXS, excluding epilepsy	7	Acetyl –l- Carnitine

Outcomes

In study conducted by Abbasi et al. from 2011, the outcomes were measured using the Parent and Teacher ADHD Scale IV that has been used in Iran in school-age children. This scale measures the behavior and attention of the child and determines if it is abnormal. In this study, the behavior and attention of patients were assessed at baseline and then again at 21 days and then at 42 days after the medications were started. This study also measured side effects such as psychic, neurologic, autonomic and other side effects to determine how safe this medication was. The side effects were measured using the mean decrease in ADHD-RS-IV score that evaluates 18 symptoms of ADHD.

In the study conducted by Arnold et al. from 2007, a clinical evaluation was performed using the placebo or acetyl-l-carnitine for 16 weeks total. The children were evaluated at baseline, then at 8 weeks, then at 12 weeks and then again at 16 weeks using the Parent and Teacher Rated Scales. The behavior and attention was recorded as well as the safety measures including adverse reactions at 8, 12 and 16 weeks.

In the study conducted by Torrioli et al. from 2008, an evaluation of the behavior and attention of boys with ADHD and Fragile X syndrome, was performed and they were treated with either the placebo or acetyl-l-carnitine. In this study, the assessment used to evaluate the boys was the Conners' Global Index-Parents and Conners' Global Index – Teachers Scale. Results were also recorded from the Vineland scores as well. The boys that remained in the study were evaluated at baseline, then at 1 week, then at 6 weeks and then again at 12 weeks.

Results

In study conducted by Abbasi et al. 2011, a trial was conducted using children and adolescents aged 7 to 13 years old. The total number of people in the study was 40 patients, which included 28 boys and 12 girls, all of whom had ADHD.¹ The dose of the methylphenidate and the Acetyl-L-Carnitine that the children were receiving was dependent on their weight. The doses of these medications ranged from 20 to 30 mg a day for the methylphenidate medication.¹ In the first group, which was the group being treated with ALC and methylphenidate, one patient dropped out. In the second group, being treated with methylphenidate and the placebo, one patient also dropped out as well. In this study the principal measure that evaluated the behavior of the children was the Teacher and Parent attention deficit and hyperactivity disorder rating scale –IV.¹ It was

proven in this study that overall the Acetyl – L- Carnitine did not make a difference in the behavior and attention of these children.¹ It was shown that there was no difference between the two groups on the following scales. The side effects of ALC was also evaluated and it was shown that the group taking methylphenidate plus the placebo had more headaches and irritability than the group taking methylphenidate and ALC. The mean standard deviations scales were recorded and evaluated at baseline, and there was no difference between the two groups.¹ As time went on, according to a one way repeated measures of analysis, the treatment that both groups were receiving did seem to greatly impact their behavior and attention on the Parent ADHD Rating Scale scores but the behavior between both groups was not that different.¹ At the end of the study, the standard deviation for the Parent ADHD Rating Scale for the group receiving ALC and methylphenidate was -12.25 ± 9.86 and it was -10.35 ± 9.62 for the group receiving methylphenidate plus the placebo.¹ The children were again evaluated at 6 weeks and it was determined that there was no difference in the behavior between the two groups again. It was also determined that there was no major difference in attention on the Teacher ADHD Rating Scale at baseline or at week 6 as well.¹ Throughout the whole study, the behavior and the attention of both groups was very similar and did not change much between both groups, which lead to the results of the ALC not being effective.¹ At the end of the study, the standard deviation for the Teacher ADHD Rating Scale scores for the group receiving ALC and methylphenidate was -7.90 ± 10.13 and it was -6.00 ± 7.84 for the group receiving methylphenidate plus the placebo.¹ This study did not only evaluate the effectiveness of the drug but also the side effects and safety. This study evaluated side effects such as abdominal pain, anxiety, decreased appetite, depression,

insomnia, weight loss, nausea, dry mouth, irritability, headaches, vomiting, fatigue, diarrhea, and dizziness. It was determined that the group receiving the methylphenidate and the placebo experienced more headaches and irritability.¹ The group receiving methylphenidate and the placebo contained 19 people total and out of 19 patients, 18 of them experienced irritability, while 12 of them experienced headaches.¹ The value here was small. The NNH for the side effects, such as headaches was -3. That means for every 3 patients treated with ALC, 1 fewer patient experienced side effects, such as headaches. At the end of this study, it was determined that ALC plus methylphenidate helped to prevent side effects such as headaches and irritability.

In the study conducted by Arnold et al. 2007, the total number of participants was 112 children, which contained 83 boys and 29 girls, aged 5 to 12 years old diagnosed with ADHD.² The intent to treat analysis, 9 DSM-IV Teacher Rated Inattentive Symptoms Scale, determined that using ALC alone without any other medications, was not effective and did not have a great impact on the behavior and attention of the children in this study.² Out of the 112 children that entered the study, only 92 children completed the assessment that took 8 weeks and 81 children completed the whole study.² The primary outcome measure showed that ALC does help to improve the behavior and attention of the child but the results were not significant enough to consider this treatment successful. The primary outcome measure was the ITT outcome, which was the Teacher Rated Inattention Scale.² Data from this primary outcome measure showed that there was no significant difference between the group taking the ALC and the group taking just the placebo. ITT analyses of secondary measure also reported finding the same results stating that there was not much of a difference between both groups as well. Another primary

outcome measure, known as the ADHD Inattentive Symptoms Scale, showed significant effects of ALC working well in children. According to these primary outcome measures, the ALC worked better in children with the inattentive type of ADHD compared to how it worked in children with the combined type of inattention and hyperactivity.² This primary outcome measure reported a p-value of 0.02 for the group of children being treated with the ALC, which proved the data to be significant.² This article also reported on the side effects of the ALC compared to the placebo. The side effects observed in the group being treated with ALC compared to the group being treated with the placebo, were not significant and were not different between the two groups.² This article reported on side effects such as gastrointestinal disorders, headache, infections, cough, musculoskeletal disorders, metabolism and nutrition disorders, psychiatric disorders, poisoning, nasal congestion and skin disorders. In the group of children being treated with ALC there was a total of 58 children but only 42 completed the trial out of this group.² In the group being treated with the placebo, there were 60 children and only 39 completed the trial.² The NNH calculated was 10 patients. That means for every 10 patients treated with ALC, 1 more patient experienced side effects, such as headaches. The value here is large. The only significant finding from the study showed that the children being treated with ALC were more prone to headaches compared to the group being treated with the placebo, which was the opposite of what was found in the study conducted by Abbasi et al. 2011.²

In the study conducted by Torrioli et al. 2008, the objective of the results was to see if ALC would be effective in treating young boys with not only ADHD but also Fragile X Syndrome. 63 males entered the study and the study eventually ended with 7

patients dropping out leaving 56 patients to complete one year worth of treatment.³ The patients were evaluated at baseline, then at 1 month, then at 6 months and then again in 12 months. In this study, according to the physicians' ratings, it was determined that the ALC was safe to use in this population with a very low number of side effects being reported.³ This study used mean values and confidence intervals to record the data of both groups. According to the Conners' Parents Scale, responsible for measuring inattentiveness, socialization and behavior, the score decreased 8 points in the group of children being treated with the ALC and 4.4 points in the group being treated with the placebo.³ The p-value recorded for this difference was 0.05, which was considered to be significant. Due to the fact that these scores decreased, this proved that the behavior and the inattentiveness of these young boys greatly improved.³ According to the Conners' Teachers' Scale, the score decreased as well by -6.2 points in the group being treated with ALC and -5.6 points in the group being treated with the placebo, in a 12 month period.³ This difference was considered insignificant due to the fact that this difference produced a p-value of 0.041.³ This insignificant finding was probably due to the fact that fewer teachers were able to respond to the questionnaires. The Vineland ABC and the Vineland Socialization Scales were also used as well and these scales help determine that the boys treated with ALC, had great improvements in their attention and socialization skills compared to the group of boys treated with just the placebo.³ The scores of the Vineland ABC and the Vineland Socialization Scales both increased but it increased more in the group being treated with ALC by +2.3 and +6.6 points respectively.³ In the group that contained the boys being treated with the placebo, they ended up losing all of their improved skills and actually fell well below their starting points.³

Discussion

ADHD is a disorder that is becoming more common but also is more recognized today as a condition that really affects a child's ability to learn. Research suggest that one of the things that could lead to ADHD is the child's ability to metabolize fatty acids and phospholipids, which are needed for brain development.¹ It was shown that in children with ADHD, the levels of fatty acids are decreased in the plasma.¹ ADHD is usually treated with stimulants, which are the first line medications but it is not guaranteed that these medications will always work. This urged scientists to find a different type of medication that can treat the problem instead of only treating the symptoms. Studies also show that diet and exercise play a big part in the development of ADHD and that needs to be addressed as well. It was proven that ALC can effect neurotransmitter metabolism by decreasing the glutamate dehydrogenase activity and increasing cytochrome oxidase activity.¹ Because of this reason, the goal of study conducted by Abbasi et al. from 2011, was to prove that ALC can improve the metabolization of methylphenidate in children with ADHD. Unfortunately, according to the results of this study, it was proven that giving ALC along with methylphenidate was not helpful. But on the other hand, it was shown that children in the group treated with methylphenidate and ALC, were shown to have fewer side effects such as headaches and irritability than the group treated with the placebo and methylphenidate.¹ Although, results in other studies were quite different showing that ALC decreased impulsive and hyperactive behavior in children.

According to the study by Torrioli et al. 2008, the results showed that the ALC was effective towards improving the inattentive and social behavior in the male children with FXS.³ Although, it was proven that the ALC did not actually improve or increase the

intelligence of these boys.³ The children treated with the placebo also showed improvement but not nearly as much as the group treated with the ALC. Other therapies seem to help improve behavior too, along with the ALC, such as physical, speech and occupational therapy and support from teachers and parents.³ In this study, the ALC treatment helped to improve the hyperactive behavior but not enough to produce positive results and one reason for this could be due to the fact that only 34 patients were scored out of the 51.³ Since most of this study took place during the summer holiday months, some appointments to assess the children were missed. It was noticed that in the Vineland scores, the hyperactive group of children did well with the placebo during the first month but then afterwards the behavior started to worsen, probably due to the placebo effect.³ The children, parents and teachers probably over estimated how well the drug would work in the first month and then started to notice that afterwards it just was not working at all.³

According to study by Arnold et al. 2007, different malfunctions located in the brain can cause different types of ADHD. For example, research shows that the inattentive type is caused increased activation of the anterior cingulate and the middle frontal gyrus, which means there is a delay in the function of the thalamus.² In other words, another study can be performed testing the ALC treatment with just children who have the inattentive type and this may produce better results. Other research shows the combined type is caused by the activation of the thalamus, putamen and insula, which would not benefit from ALC treatment.² According to study by Torrioli et al. 2008, research shows that ALC can increase the synthesis of acetylcholine, which would also increase dopamine levels and various other amino acids needed for brain development.³

There are several factors that come into play that could have affected the results, such as short duration, small sample size, and doses of the medications used.^{1,2,3} These results are very similar to the results of study by Arnold et al. 2007. In study by Arnold et al. 2007, it was proven that ALC was not effective in treating children with ADHD because it showed no difference in behavior in these children compared to the children being treated with the placebo.² There are several factors that could play into the outcomes and one of them being which type of ADHD does the child have. It was proven that overall ALC was not an effective for ADHD treatment, however it was also proven that the ALC worked better in children with the inattentive type of ADHD and was more ineffective for children with the combined type.^{2,3} This study only included children of upper and middle class families, but it probably would have been beneficial to include children of lower class families as well to have better rounded results.² Dosage of medications in this study could have affected the results as well. Patients could have been noncompliant with taking their medications, some medications could have been defective or there could have been miscalculation in the initial dosing.^{1,2,3}

There are also others factors that could have affected the results but not counted for in this study such as season, diet, culture and geographic location. Three sites located near the Eastern part of the Central Plains showed that the children being treated with the ALC showed improvement in behavior compared to the group being treated with the placebo.² The other sites that were also included in this study showed results only opposite of this. In the group of children being treated with the ALC, it contained more children in the inattentive group compared to the combined group. In the group being treated with the placebo, it had an equal number of children in both the inattentive group

and the combined group.² This variable in the number of children being treated with the ALC definitely could have played a part in the failure of this study, leading to an unfair advantage for the placebo.²

Conclusion

In the end, it was determined that combined with methylphenidate, ALC would not be considered an effective treatment to help improve the behavior of children with ADHD. ALC, however, was found to have beneficial effects in reducing side effects such as headaches and irritability. ALC used alone without any other medication was also determined to be ineffective in treating the behavior symptoms of ADHD. ALC was proven to have great improvement in the inattention and social skills of children, not only with ADHD, but also with Fragile X Syndrome.

Further research can and should be explored, evaluating the effects ALC treatment in children with autism, who cannot tolerate stimulants. It was also determined that ALC is safe to use for treatment of ADHD without harmful side effects. In two out of the three articles discussed, it was found that ALC actually might be more beneficial for treatment for a certain type of ADHD, like the inattentive type. Further research should also be done exploring ALC as a potential treatment for children and adolescents, who only have the inattentive ADHD. There are many factors that could have played a role in this failure in two out of the three studies, such as the sample size, location, economic status, dosage of medications, compliancy, and the measuring analysis.

Research supports that one of the main reasons that cause inattentive ADHD was a decrease in the levels of fatty acids being produced and absorbed. This research

supports the theory that ALC can be used to help increase energy levels of these children that have the inattentive type of ADHD by stimulating lipid production or increasing the absorption of the lipids in different portions of the brain. It has also been found that this supplement can help increase levels of acetylcholine by increasing the cytochrome oxidase activity. With further research, ALC may be proven to improve the lives of children with the inattentive type of ADHD and other conditions such as autism.

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