The Effects of L-Theanine (Suntheanine®) on Objective Sleep Quality in Boys with Attention Deficit Hyperactivity Disorder (ADHD): a Randomized, Double-blind, Placebo-controlled Clinical Trial

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Abstract
INTRODUCTION: The purpose of this study was to investigate the efficacy and safety of L-theanine as an aid to the improvement of objectively measured sleep quality in a population of 98 male children formally diagnosed with attention-deficit/hyperactivity disorder (ADHD). METHODS: A randomized, double-blind, placebo-controlled trial was conducted involving boys, ages 8-12 years, who had been previously diagnosed with ADHD. An experienced physician confirmed the diagnosis of ADHD in each subject. Randomization was stratified based upon current use of stimulant medication to ensure an equal distribution of stimulant/non-stimulant treated subjects into active and placebo treated groups. Participants consumed two chewable tablets twice daily (at breakfast and after school), with each tablet containing 100 mg of L-theanine (total 400 mg daily Suntheanine®, Taiyo Kagaku, Yokkaichi, Japan) or identical tasting chewable placebo for six weeks. Subjects were evaluated for five consecutive nights using wrist actigraphy at baseline, and again at the end of the six-week treatment period. The Pediatric Sleep Questionnaire (PSQ) was completed by parents at baseline and at the end of the treatment period. RESULTS: Actigraph watch data findings indicated that boys who consumed L-theanine obtained significantly higher sleep percentage and sleep efficiency scores, along with a non-significant trend for less activity during sleep (defined as less time awake after sleep onset) compared to those in the placebo group. Sleep latency and other sleep parameters were unchanged. The PSQ data did not correlate significantly to the objective data gathered from actigraphy, suggesting that parents were not particularly aware of their children's sleep quality. L-theanine at relatively high doses was well tolerated with no significant adverse events. CONCLUSIONS: This study demonstrates that 400 mg daily of L-theanine is safe and effective in improving some aspects of sleep quality in boys diagnosed with ADHD. Since sleep problems are a common co-morbidity associated with ADHD, and because disturbed sleep may be linked etiologically to this disorder, L-theanine may represent a safe and important adjunctive therapy in childhood ADHD. Larger, long-term studies looking at the wider therapeutic role of this agent in this population are warranted.
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Introduction

Attention-deficit/hyperactivity disorder (ADHD) occurs in approximately 3-7 percent of the childhood population and approximately 2-5 percent of the adult population.[1-3] Boys are three times more likely than girls to have ADHD and are 6-9 times more likely to be seen with ADHD among clinic-referred children.[3] Early detection and treatment is considered important in improving the long-term prognosis.[2]

Characteristic ADHD symptoms comprise inattention, hyperactivity, and impulsivity.[1-3] Current research also indicates that ADHD is commonly associated with a number of co-morbidities, including sleep disturbances. An estimated 25-50 percent of children and adolescents with ADHD experience some type of sleep problem. The most common complaints include delayed sleep onset (prolonged sleep latency), bedtime resistance (i.e., resist parents efforts to get them to go to bed), nighttime awakenings, unsettled sleep, difficulty waking in the morning, prolonged tiredness upon waking in the morning, and daytime sleepiness. There is also a higher incidence of sleep disorders,

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such as restless legs syndrome, periodic limb movement disorder, and sleep-disordered breathing (e.g., snoring and sleep apnea) in children with ADHD.[4-11] Difficulties with duration of time to fall asleep (sleep latency) may be seen in as much as 56 percent of children who have been diagnosed with ADHD, compared with 23 percent of children without a diagnosis of ADHD. Up to 39 percent of children with ADHD exhibit difficulties associated with frequent nighttime awakening.[10] In one study, over 55 percent of children diagnosed with ADHD were described by their parents as being tired upon awakening, compared with 27 percent of children without an ADHD diagnosis.[11]

Typically, stimulant medications such as Ritalin® (methylphenidate), Dexedrine® (dextroamphetamine), and Adderall® (various amphetamine salts/dextroamphetamine) are used to mitigate ADHD symptoms. The non-amphetamine medication Strattera® (atomoxetine) is also used to treat ADHD. Concerns exist regarding the potential for short- and long-term negative side effects of ADHD medications.[11-13] An estimated 10-30 percent of ADHD patients either do not respond to stimulant medications, or do not tolerate them because of a side effect.[14] Sleep problems, including reduced sleep time and delayed sleep latency, are among the more common side effects of stimulant medications.[11,13,15-17] Because sleep problems might potentially exacerbate ADHD symptoms,[11,18] and because interventions targeted at improving sleep might help manage some symptoms associated with ADHD,[11] there is a need for treatments that positively impact subjective and objective sleep in persons with ADHD.

L-theanine is a non-protein amino acid (gamma glutamylethylamide) that occurs naturally in green tea leaves (*Camellia sinensis*). It is produced in a purified form (L-theanine isomer >99%) using a patented enzymatic process to synthesize L-theanine from a mixture of glutamine with an ethylamine derivative (Suntheanine®; Taiyo Kagaku, Japan[19]). This patented L-theanine product has been the subject of human research for its effects on stress reduction,[20] mood,[21] brain waves,[22,23] alertness,[24] and cognitive/mental performance.[25-27] Effects on attention and cognitive performance appear to be particularly pronounced when it is combined with caffeine.[28-31] L-theanine in combination with caffeine significantly activates brain attentional circuitry and improves cognitive performance. The effects of the combination of caffeine and L-theanine are greater than either caffeine or L-theanine alone. Some of the effects of L-theanine on brain state modulation appear to be via the release or reduction of the brain chemicals gamma aminobutyric acid (GABA), dopamine, and serotonin.[32]

One study suggested a positive effect of L-theanine on sleep. Ozeki et al indicated that L-theanine significantly improved sleep quality in a select male population using actigraphy as a physiological indicator.[33] Despite this positive impact on sleep, L-theanine does not appear to be sedating. In a study that investigated the effect of L-theanine on daytime drowsiness using a psychomotor vigilance task (PVT) and the visual analog scale, there was no indication that L-theanine promoted daytime drowsiness.[34]

Brain waves (assessed by electroencephalogram [EEG]) shift toward a predominance of alpha waves in the occipital and parietal parts of the brain within 40 minutes of ingestion of L-theanine, at dosages ranging from 50 to 200 mg, with effects lasting up to eight hours.[19,34,35] Alpha-wave predominance is associated with a state of relaxation. Mason reported that the intensity of increase in alpha waves was dose-dependent, with a 200 mg dose eliciting a significant increase over the control group, which remained detectable after 30 minutes.[35]

The purpose of the present study was to investigate whether L-theanine improved objective and subjective aspects of sleep quality in boys with ADHD. It was hypothesized that treatment with L-theanine, relative to placebo, would result in a significant change from baseline in actigraph measured objective sleep quality.

Methods

Participants

This randomized, 10-week, double-blind, placebo-controlled trial was conducted at the Canadian Centre for Functional Medicine in conjunction with the Food, Nutrition & Health Program at the University of British Columbia. Approval for the study was received from the Therapeutics Products Division and the Natural Health Products Directorate of Health Canada, as well as the Clinical Research Ethics Board at the University of British Columbia. The study was registered with the U.S. National Institutes of Health (ClinicalTrials.gov).

Over 100 boys, ranging from age 8-12 years, were invited to participate in the study after meeting criteria for the diagnosis of ADHD by physician evaluation as defined by the *Diagnostic*

and Statistical Manual of Mental Disorders: DSM-IV-TM, Fourth Edition,[1] using the methodology outlined by the American Academy of Pediatrics *Clinical Practice Guideline: Diagnosis and Evaluation of the Child with ADHD*.[2] Ninety-eight participants were enrolled in the study, with 93 completing all requirements.

During recruitment, parents/guardians were required to assess their child's symptoms using the DSM-IV criteria list, the Conner's Short Form for Parents, a developmental and environmental health questionnaire, and the Pediatric Sleep Questionnaire (PSQ). This information was screened by the investigator-physician, and prospective participants were invited to engage in a thorough medical, developmental, and environmental history, as assessed and approved by that same physician. Psychiatric and medical conditions were ruled out that: (1) could possibly result in an inappropriate diagnosis of ADHD, or (2) were not congruent with the exclusion criteria – other psychiatric diagnoses, any chronic medical conditions, serious learning disabilities, or attendance in a behavior modification program.

Ultimately, 98 boys were recruited and randomized to placebo or treatment groups. The following information was collected from each participant: age, ethnicity, whether or not the subject was taking a stimulant medication or a sleep aid (e.g., melatonin or a pharmaceutical sleep medication). Subjects were stratified separately, depending upon whether or not they were on stimulant medications, to ensure equal distribution of stimulant and non-stimulant treated children into the active treatment and placebo groups.

Materials

Participants were required to take a total of four chewable tablets of L-theanine (two 100-mg tablets in the morning and two 100-mg tablets in the late afternoon after school [total of 400 mg L-theanine]) or placebo daily. All participants were given a sufficient quantity of the product to complete the six-week treatment period. For emergency purposes, all participants had 24-hour access to the investigator-physician, who also kept a set of codes in sealed opaque envelopes.

The formulation was produced as a chewable tablet, because it was thought that the children might have greater difficulty swallowing pills or tablets. The placebo and L-theanine chewable tablets were available in two flavors (wild berry and tropical fruit). Both flavors were agreeable with the majority of participants, thereby ensuring a high level of compliance. The placebo chewable tablets looked and tasted identical to the active treatment tablets. The placebo tablets contained all of the same non-medicinal ingredients used for color, flavor, sweetener, and tablet manufacture, as well as 100 mg of lactose in place of L-theanine.

Sleep Quality Measures

Both objective (actigraphy) and subjective (PSQ) measures were used to assess sleep quality in participants.

Actigraph Watch Data (Objective Measure)

Actigraphy is an activity-based sleep monitor that employs the use of a wristwatch-like recording accelerometer device worn during sleep to measure movement frequency, amplitude, and patterns typical of deep sleep, REM sleep, wakefulness, periodic limb movements, and disordered breathing. Actigraphy has been established to reliably record sleep activity levels, sleep efficiency, sleep duration, sleep latency, the number of nocturnal awakenings, and sleep patterns.[36,37] Actigraphy has an established place in the assessment of disordered sleep in children with ADHD and has been used to demonstrate the high rate and variety of sleep problems in this population.[17,38-42]

In this study, actigraph wristwatches were chosen to provide an objective measure of sleep patterns. Each subject was required to wear the actigraph watch on his non-dominant wrist for five consecutive nights during the pre-treatment period and for five consecutive nights near the end of the treatment period, for a total of 10 nights of actigraph data.

In order to minimize artifactual data, parents were required to keep an actigraph log regarding their child's activities, including externally imposed movements from any sports, riding in vehicles, swimming, and periods of actigraph removal. The actigraphic sleep measures considered in this study included sleep efficiency (percentage of night spent sleeping restfully), number of discreet bouts of nocturnal activity, number of minutes of wakefulness after onset of sleep (wake after sleep onset [WASO]), sleep latency (time to fall asleep), and sleep duration (total sleep time).

Pediatric Sleep Questionnaire (Subjective Measure)

For screening purposes, parents initially completed a validated pre-treatment PSQ, which subjectively evaluated the child's past and current sleep problems based upon parent observations. Parents repeated this evaluation three more times:

Figure 1. Sleep Efficiency (Percentage of Night Spent Sleeping Restfully)

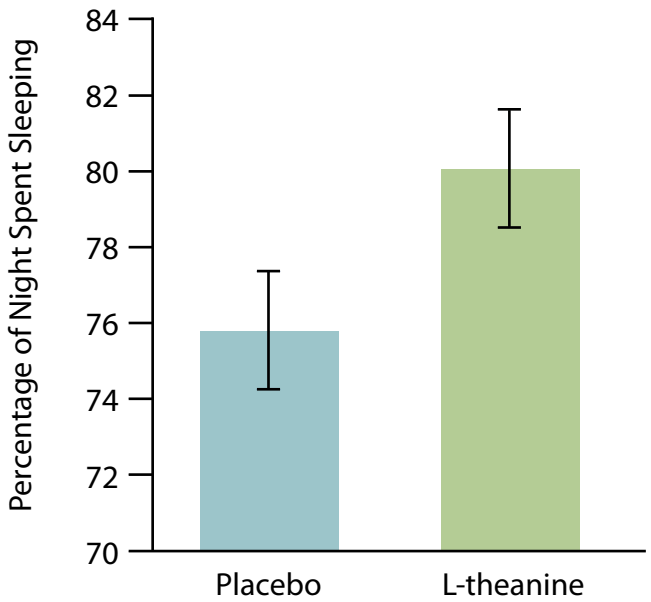
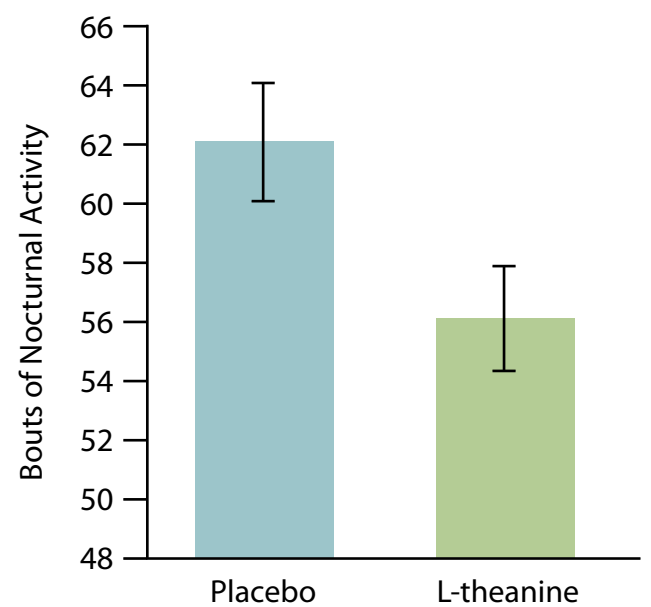


Figure 2. Number of Discreet Bouts of Nocturnal Activity



twice during treatment and once immediately post-treatment (i.e., at the end of the six-week trial period).

PSQ questions focused primarily on the following eight indicators: WASO, restless legs, head banging, waking up on more than two occasions during the night, feeling unrefreshed, and difficulty waking up in the morning, as well as child's and teacher's perception of daytime sleepiness.

Statistical Analysis

A mixed between-within participant analysis of variance (ANOVA) was used to test differences between placebo and treatment groups, with consideration also given to whether participants were taking stimulant medications. The ANOVA F-test in one-way analysis of variance is used to assess whether the expected values of a quantitative variable within several pre-defined groups differ from each other. As such, the independent variables were: (1) placebo vs. L-theanine treatment, and (2) stimulant medicated vs. non-medicated, whereas the dependent variable was pre-treatment vs. during treatment. Given that there are a large number of comparisons, an alpha of 0.01 was employed. However, results close to an alpha of 0.05 are reported.

Results

Ninety-eight participants finished the trial, with 93 completing all requirements of the study. Data were analyzed for the 93 participants. Forty-six of the participants who completed all requirements received L-theanine (mean age=9.45 years) and 47 received the placebo (mean age=9.74 years). A total of 27 of the participants were on stimulant medication during the study, 13 in the treatment group and 14 in the placebo group. The remaining 64 participants were not taking stimulant medications. One boy in the treatment group and two boys in the placebo group were taking melatonin for sleep.

Results are depicted in Figures 1-3. Statistically significant differences in favor of L-theanine were found for actigraphic-measured sleep efficiency (increased percent of time spent in restful sleep in L-theanine compared to placebo group, $p<0.05$ [Figure 1]) and sleep activity (fewer bouts of nocturnal activity in L-theanine compared to placebo group, $p<0.05$ [Figure 2]). Although not statistically significant, a strong trend toward significance was detected for WASO, with a lower number of minutes spent awake after onset of sleep in the L-theanine compared to the placebo group ($p<0.058$ [Figure 3]). There was no

significant difference between groups for sleep latency or sleep duration (p>0.05).

PSQ data did not correlate significantly to the objective data gathered from actigraphy. In essence, it appeared that parents were not well aware of their child's sleep patterns at baseline, nor were they able to detect changes that occurred during the study interval that were apparent using actigraphy. This finding is consistent with other studies indicating parental reports of sleep problems in their children with ADHD do not always agree with objective sleep patterns, and that parents of children with ADHD may not be accurate reporters of their children's sleep pattern and/or sleep disturbances.[41,43,44]

Although placebo and active agents demonstrated excellent tolerability, one minor adverse event was reported in the L-theanine group within four days of beginning ingestion. The participant's mother reported that the child developed a new, very subtle facial tic, although the child had exhibited a variety of tics in the past and had a variety of facial tics on an ongoing basis. The participant was immediately excused from the study and the new tic purportedly ceased. The supervising physician/principle investigator noted that the mother was very anxious, even before starting the study, and judged that it was unlikely that the small change in existing symptoms was related to the L-theanine treatment. No other adverse events were reported.

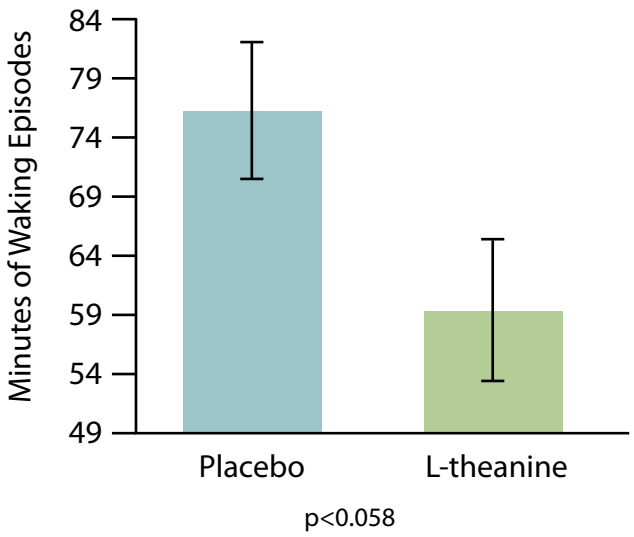
Discussion

This study was aimed at examining the potential efficacy of L-theanine, a non-protein amino acid found in the leaves of green tea (*Camellia sinensis*), in improving sleep quality in boys with ADHD. Improvements in several objective sleep quality measures were compelling and significant. Actigraph watch data findings indicated that children who had taken L-theanine obtained significantly higher sleep percentage (sleep efficiency) and reduced nocturnal motor activity scores compared to boys in the placebo group. Children who were administered L-theanine also exhibited less wakefulness after sleep onset (WASO) than those receiving the placebo; however, this finding did not reach statistical significance. No benefits were detected for sleep latency or sleep duration.

Poor correlations between objective sleep data obtained by actigraphy and parents' subjective ratings (measured by the completion of the PSQ) were found in this study. Findings from previous sleep studies have revealed that parents of children with ADHD are not always accurate reporters of their children's sleep patterns. As an example, a study by Corkum and Tannock comparing actigraphy and parental sleep ratings in children with ADHD found that the parents' subjective views were not consistent with objective measures (such as actigraphy and sleep diary data), with the exception of longer sleep duration ratings.[41] A study by Wiggs et al reported poor correspondence between parent ratings and actigraphy.[43] Parental inaccuracy is particularly evident when sleep questionnaires are compared with the objective measures of actigraphy.[43,44]

Regardless of whether parents are clearly aware of their children's sleep quality, actigraph watch data findings indicate that L-theanine does indeed appear to be an effective agent in positively influencing the quality of sleep among male children who have been diagnosed with ADHD, including both children taking stimulant medication and those not taking medication. Given the importance of sleep in assisting children in regulating cognition (e.g., attention, memory), emotion, and behavior during the daytime, particularly children for whom such regulation is problematic (i.e., those diagnosed with ADHD), L-theanine

Figure 3. Wake After Sleep Onset (Number of Minutes of Wakefulness After Onset of Sleep)



warrants investigation to determine whether its effects on sleep are long-term, and whether they translate into measurable positive changes in symptoms of ADHD. A longer duration study with robust measures of mood, cognition, and behavioral change should be undertaken.

While L-theanine has been studied for its effects on stress, mood, and cognition in non-ADHD subjects, this is the first report of its effects in children with ADHD. L-theanine might be reasonably expected to improve some aspects of sleep (a common co-morbidity found in persons with ADHD) over a period of six weeks, and so would seem to be most suited to persons with ADHD and co-morbid sleep problems. Its effects on the characteristic symptoms of ADHD and other co-morbidities associated with ADHD have yet to be established. Since it did not improve sleep latency (time to fall asleep) or sleep duration, it does not appear to be warranted for these particular sleep complaints in boys with ADHD.

L-theanine is found in high concentrations only in the small, immature leaves of shade grown tea plants. Because of the high cost to grow and harvest tea with the highest levels of L-theanine, and because the flavor and effects of this kind of tea are desirable to consumers, the concentration of L-theanine in tea is generally positively related to its price in the Asian marketplace. The lower priced tea (both green and black), as well as most of the powdered tea (Matcha) sold into the European and North American marketplace, is typically low in L-theanine. In addition to the low concentrations of L-theanine in most commercially available teas, clinicians should also be wary of recommending tea consumption as a means of increasing L-theanine intake in children with ADHD, since tea with higher amounts of L-theanine generally also has higher amounts of caffeine.

Although L-theanine can be extracted from green tea, the amount of L-theanine in mass produced tea is probably too low to make this commercially viable. Because of this, clinicians should be wary of lower cost products claiming to be composed of L-theanine extracted from tea. It is possible that such products could be composed of a racemic mixture of L- and D-theanine (Lekh R. Juneja, Ph.D., Taiyo, Kagaku Corp., In House Analytical Data, personal communication, May 28, 2011). In an analysis of six commercially available products labeled as L-theanine, five of the six products contained significant amounts of D-theanine. Only Suntheanine contained pure L-theanine enantiomer (>99% L-isomer purity).[45] The active product used in this study was pure L-theanine (Suntheanine®). The safety and effectiveness of racemic mixtures of theanine have not been determined.

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