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Is L-theanine an Effective Treatment for Reducing Anxiety in Patients Ages 18-25?

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A Selective Evidence Based Medicine Review

In Partial Fulfillments of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not L-theanine, an amino acid analogue found in green tea leaves, is an effective treatment for reducing anxiety in patients ages 18-25.

Study design: Review of two double-blind, randomized controlled studies and one single-blind, randomized controlled study published in 2007, 2012 and 2013 respectively.

Data sources: PubMed

Outcome(s) measured: Each study measured L-theanine's ability to reduce acute anxiety with a series of self-report measures assessing acute anxiety and stress, including the Profile of Mood States (POMS), the visual analogue scales (VAS), State-Trait Anxiety Inventory (STAI) and achievement emotion measurement.

Results: Kimura and colleagues found that state-trait anxiety inventory scores were significantly lower in the L-theanine group compared to placebo, Yoto and colleagues found that L-theanine significantly decreased tension-anxiety scores compared to placebo and Unno and colleagues found that scores of subjective stress were significantly lower in the L-theanine group compared to placebo.

Conclusion: Each reviewed study provides convincing and statistically significant evidence that L-theanine has the potential to reduce symptoms of anxiety. However, there were inconsistencies. All three studies used VAS as a self-report measure, but only Unno and colleagues found VAS scores to be significantly reduced. Similarly, STAI scores were only significantly lowered in the study by Kimura and colleagues. Despite these discrepancies, the studies demonstrate a likely benefit of L-theanine reducing anxiety-related symptoms.

Key words: L-theanine, anxiety

INTRODUCTION

Anxiety affects millions of people worldwide with devastating, life altering consequences. It is defined as an individual's emotional and physical fear response to a perceived threat¹. When symptoms are excessive, irrational, out of proportion to the trigger or are without an identifiable trigger, it is considered to be pathologic¹. Anxiety can hugely impact a patient's day to day life as it can lead to excessive stress, sleep disturbance and fatigue. With the ever growing fitness crazes, approaches to living a more "clean," healthy lifestyle, and the growing popularity of alternative therapies, there is a market for treating anxiety with alternative approaches. Consequently, it is relevant to see whether L-theanine, a natural element of green tea, can effectively reduce anxiety in patients.

Physician Assistants have been working in the field of psychiatry since 1975². With approximately 100,000 PAs practicing in the United States, approximately 1,500 work in psychiatry. Although psychiatry is a specialty with few PAs, there is a huge demand according to the AAPA². PAs can work in behavioral health facilities, psychiatry units of hospitals and private practice where they can conduct initial assessments and perform maintenance check ups.

Generalized anxiety disorder (GAD) in patients has an estimated lifetime prevalence of 5% and a 1-year prevalence of 3%³. Furthermore, patients with anxiety disorders are three to five times more likely to go to the doctor and six times more likely to be hospitalized for psychiatric disorders than those who do not suffer from anxiety disorders. With 3% of the U.S. diagnosed with generalized anxiety disorder, it is undeniable that PAs will encounter GAD not just in the field of psychiatry, but in family medicine and other specialties as well³. As the most common form of psychopathology, it is not surprising that anxiety makes up 1/3 of the cost to treat mental health disorders in the U.S at \$42 million per year. Walmart, the most popular store in the United

States, sells a package of 20 green tea bags for \$2.42⁴. At .12¢ per bag, L-theanine could serve as an inexpensive and accessible alternative for treatment.

Despite the fact that 3% of the U.S. population has anxiety, there is no single etiology that is known to exist. It proposed that the origin of anxiety is multifactorial, such as an increase in stressors, physical and or emotional trauma and genetic factors¹. Although the pathophysiology is not well understood either, neurotransmitter receptors of serotonin, NMDA, and glutamate are thought to play a role. In order to be diagnosed, patients must have excessive worry for at least 6 months, in addition to three of the following: restlessness, fatigue, impaired concentration, irritability, muscle tension and insomnia¹. Traditionally, anxiety is treated with antidepressants such as SSRIs (ie sertraline, escitalopram) and SNRIs. An additional option is a benzodiazepine. To enhance the effectiveness of drug therapy, cognitive behavioral therapy is crucial in helping patients learn how to cope with their worry habits. Other options include relaxation, meditation, exercise and reading self-help books. Despite the effectiveness of SSRIs, there are numerous side effects, such as sexual dysfunction, drowsiness, headache and stomach upset¹. Therefore, L-theanine could serve as a potential alternative and or an additional option for patients dealing with side effects, or who want to avoid the addictive component of benzodiazepines.

Similar to benzodiazepines which exert their effects by interacting with GABA receptors, L-theanine blocks the binding of L-glutamic acid to glutamate receptors in the brain⁵. Exposure to acute or chronic stress results in glutamate increase. An increase in glutamate also results in hyper-activation of the sympathetic nervous system (SNS). MRI studies have shown that the brain regions associated with anxiety such as the amygdala and hippocampus are glutamate rich and hyperactive in patients with anxiety disorders⁶. Therefore, because L-theanine blocks

glutamate receptors, it is being proposed as a potential method to reduce anxiety. It is important to note that although anxiety does not directly cause hypertension, repeated elevations in blood pressure can lead to hypertension over time. This is because constant stress and worry can stimulate the nervous system to produce vasoconstricting hormones. Consequently, because glutamate stimulates the SNS, L-theanine has the potential to not only reduce psychological symptoms of anxiety, but the physiological symptoms as well.

OBJECTIVE

The objective of this systematic review is to determine whether or not L-theanine, an amino acid analogue found in green tea leaves, is an effective treatment for reducing anxiety in patients ages 18-25. Three scholarly articles were selected for this systematic review, each meeting the same specific criteria. Each article consisted of a study pool between the ages of 18 and 25 and used 200mg L-theanine PO as the intervention. The articles used the same comparisons: a treatment group receiving L-theanine compared to the experimental group who received a visually matched placebo. Two of the articles were randomized, double-blind placebo controlled studies, while one was a randomized, single-blind placebo controlled study. In order to measure L-theanine's ability to alleviate stress and anxiety, the studies used a visual analog scale (VAS), profile of mood states (POMS) and the state-trait anxiety inventory (STAI).

METHODS

The articles that compose this systemic review were accessed through PubMed. In order to obtain the articles, key words searched were "anxiety" and "L-theanine." All three articles were published in English within the last 10 years and were selected because they met the criteria discussed above, in addition to measuring patient oriented outcomes (POEMS). Inclusion criteria included participants between ages 18-25 with no mental health history and articles published in

English between the year 2000 and present. Exclusion criteria included participants under 18 or over 25, participants with a mental health history, and articles published before year 2000 and not published in English. Among the three articles, statistic reports used were p-value, fischer's z-test, one-way ANOVA, two-way ANOVA, x^2 , F-score and post hoc analysis with Least Significant Difference (LSD) tests and Tukey's honestly significant difference (HSD) tests.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Unno (2013)	Randomized, single-blind study	20	Intervention=22.5 +/- .2yrs Control=22/2 +/- .1 yrs	Healthy, 5 th year university students	If students had consumed caffeinated beverages throughout the experiment.	0	200mg L-Theanine
Kimura (2007)	Double-blind, randomized study	12	21.5	Healthy undergraduate students who weren't suffering from chronic or oral illnesses	If students had taken any medication that could influence results	0	200mg L-Theanine dissolved in water
Yoto (2012)	Double-blind, randomized study	16	22.8 +/- 2.1 years	Healthy students who weren't suffering from chronic or oral illnesses	If students had drank or eaten anything but water prior to the start of each trial	2	200mg L-Theanine

OUTCOMES MEASURED

A variety of outcomes were measured among the three trials. In the study conducted by Yoto and colleagues⁵, the following measurements were used: participants completed a

subjective assessment with The Profile of Mood States (POMS) and the visual analogue scales (VAS). POMS measured six identifiable moods such as tension-anxiety and depression, while VAS measured feelings of fatigue, relaxation, arousal, pleasure and tension. In the study conducted by Kimura and colleagues⁷, the VAS and State-Trait Anxiety Inventory (STAI) were used. The STAI had 20 items for assessing trait anxiety (i.e. “I worry too much over something that really doesn’t matter”) and 20 items for assessing state anxiety (i.e. “I am worried,” “I feel calm”). In Uno and colleagues study⁸, participants completed the STAI, VAS and an achievement emotion measurement before the administration of L-theanine.

RESULTS

In the study conducted by Yoto and colleagues⁵, 16 healthy participants averaging 22.8 years old were originally enrolled and 2 participants withdrew due to temporary illness. The patients were randomized to receive 200mg of L-theanine, placebo or caffeine (caffeine will not be discussed as it is not relevant to objective) on 3 study days, 7 days apart. Participants were instructed to not eat or drink anything but water prior to the task. Participants were placed in a quiet room and relaxed for 15 minutes. They completed VAS and POMS before the task and taking L-theanine, and after the task and taking L-theanine. Prior to the initial statistical analysis, separate, one-way, repeated measures ANOVAs of baseline data were conducted to account for any baseline differences across “study days prior to the treatments.” A Tukey’s honestly significant difference (HSD) post hoc test was then applied to data groups with significant main effect. The POMS score indicated significant scores: tension-anxiety and anger-hostility scores showed treatment effects over the two groups together ($\chi^2=6.000, 6.048, P=0.05, 0.049$) and L-theanine intake decreased tension-anxiety score below that in the placebo condition ($P=0.004$).

No differences were obtained among treatments through VAS assessments. All of the data was continuous and not convertible to dichotomous format.

Table 2: Changes in POMS scores from base line

	Tension- Anxiety	Depression- Dejection	Anger- Hostility	Vigor- Activity	Fatigue	Confusion- bewilderment
Placebo	6.1	5.2	5.6	.7	6.9	7.4
L- Theanine	.98	.5	2.8	.98	1	1.6

In the study conducted by Unno and colleagues⁸, 20 healthy 5th year pharmacy students composed the participant pool (no participants withdrew). The students were assigned to practice in a hospital or drug store setting for 11 weeks. Because the first 10 days of practice were assumed to be the most stressful and anxiety-provoking, these days were analyzed. The participants were randomly divided and began taking 200mg L-theanine or placebo (twice a day, after breakfast and lunch) 7 days prior to beginning clinical practice, and then an additional 10 days once beginning clinical practice. The patients were instructed to avoid caffeinated beverages throughout the experiment. The STAI, subjective stress (VAS) and achievement emotion measurement were completed each of the 17 days. There was no significant difference found in STAI values between the control and L-theanine group. However, the average VAS score was significantly lower in the L-theanine group than in the placebo group ($p=.020$; one-way ANOVA). There were no statistically significant achievement emotion results. All of the data was continuous and not convertible to dichotomous format.

Table 3: Characteristics of the placebo-group and the L-theanine-group

	Age	Men/women	STAI value	Subjective stress (VAS 0-10)	Achievement emotion (score: 1-5)
Placebo	22/2 +/- .1 yrs	7/3	41 +/- 2.9	4.07 +/- .33	3.26 +/- .07
Theanine	22.5 +/- .2yrs	7/3	41.9 +/- 2.4	3.10 +/- .25	3.19 +/- .06
P-value			Not significant	p=.020	Not significant

In the study conducted by Kimura and colleagues⁷, the participant pool consisted of 12 healthy undergraduate students averaging the age of 21.5 not suffering from chronic illnesses. Each participant was randomly assigned to participate in four experimental conditions on four separate occasions: oral administration of L-theanine at the start of the session, oral administration of L-theanine after the first stress task, no administration of any treatment, and placebo administration at the start of the session. The order in which the participants were assigned to each condition was formed using a Latin square design. Psychological measures used were the STAI and VAS. Participants were asked to consume no food or beverages but water the morning of and began the task after a 20 minute rest period in an experimental chamber. VAS and STAI measures were completed after the arithmetic task, then 10 and 20 minutes post task. Two-way ANOVAs revealed significant interactions between the condition and period in perception of stress ($F(6,83)=3.91, p<.01$) and state of anxiety ($F(6, 80)=4.29, p<.01$). It was also found that change of scores in subjective stress in both L-theanine conditions were significantly lower than the two control conditions. Furthermore, the STAI state anxiety score was significantly higher under the placebo condition compared to the L-theanine conditions. Overall, no differences were found with taking L-theanine at different times. All of the data was

continuous and not convertible to dichotomous format. The data was analyzed using ANOVAs and any significant interactions found underwent post hoc analysis using LSD tests ($p < .05$).

Table 5: Means (S.D.s) of change scores from baseline scores in state anxiety score

Condition	Task	Rest 1	Rest 2
Control	1.83 (4.15)	.82 (4.13)	.08 (4.98)
Placebo	11.58	0.00 (3.9)	-1.67 (4.54)
L-theanine 1	1.58 (7.32)	-1 (3.98)	-1.92 (5.66)
L-theanine 2	3.17 (10.06)	.33 (5.14)	-1.08 (4.10)

DISCUSSION

In 2006, the FDA approved L-theanine as GRAS (Generally Recognized as Safe)⁹. This includes the approved use as a food product in fruit juices, tea, chewing gum, specialty bottled waters, etc. According to the FDA, there is 153-382mg of L-theanine per 12 oz of tea, corresponding to the 200mg of L-theanine used in the discussed studies. The FDA also reviewed a series of toxicity studies that found L-theanine to be non-toxic and safe at levels up to 4000mg per kg of body weight. Presently, L-theanine is most commonly marketed for its ability to promote relaxation in 200mg supplement form¹⁰. However, there is no research that definitively supports these claims, and experts recommend that patients consume L-theanine through tea rather than supplements. Despite L-theanine's potential to treat anxiety, a condition that affects up to 40 million people in the US alone, few are aware of its existence. This is especially ironic as L-theanine is inexpensive and easily accessible on the shelves of all grocery stores across America and free of the burdens of insurance and expensive prices.

Although not pertinent to the objective, it is important to note that two of the studies measured physiologic responses to anxiety. Unno and colleagues⁸ measured salivary amylase activity levels (sAA) as markers of sympathetic nervous system activity (a higher sAA value represents higher stress and anxiety levels). They found that the placebo-group showed a tendency of higher sAA levels than the L-theanine group ($p=.049$). Additionally, Kimura and colleagues⁷ found that the placebo group had higher heart rates and sAA levels than the L-theanine group. Since increased heart rate and salivary production are associated with heightened anxiety¹, these findings further support the proposed objective.

Each study has limitations that must be acknowledged. First, each study utilized self report measures, which makes the results susceptible to reactivity and subjectivity. Each participant could have their own interpretation or understanding of anxiety, introducing a participant bias. For instance, a participant who was a math major may have found the arithmetic tasks less anxiety provoking than a participant who was an art major. Each study also took place over an extended period of time, so participants grew familiar with the anxiety questions and stressful arithmetic tasks. The participants could have inferred the study's objective, falling subject to demand characteristics. Internal validity is also compromised as the same tasks were completed by the same participants on multiple days. Furthermore, participants could have reported improvements in anxiety level simply because they knew they were receiving some type of treatment, introducing a response bias. Next, the small sample size compromises the external validity of the study. Further weakening the generalizability is the fact that the limited participants used were all students. Additionally, Kimura and colleagues only used male participants, calling into question the external validity of their results. External validity is also compromised in the study by Unno and colleagues because all of the participants were pharmacy

students. Pharmacy students could be more biased toward the efficacy of drugs compared to the general public due to their specialized medical background.

CONCLUSION

The studies reviewed provide convincing and statistically significant evidence that L-theanine has the potential to reduce symptoms of anxiety. Kimura and colleagues⁷ found that state-trait anxiety inventory scores were significantly lower in the theanine group compared to placebo, Yoto and colleagues⁶ found that L-theanine significantly decreased tension-anxiety scores compared to placebo and Unno and colleagues⁸ found that scores of subjective stress were significantly lower in the L-theanine group compared to placebo. Furthermore, L-theanine significantly reduced HR and salivary production compared to placebo in two of the studies, further bolstering L-theanine's ability to not just reduce psychological symptoms of anxiety, but physical. Nonetheless, it can only be said that L-theanine has the "potential" to reduce symptoms of anxiety as there were discrepancies among the studies. All three studies used VAS as a self-report measure. However, only Unno and colleagues⁸ found that L-theanine significantly reduced VAS scores. Additionally, two studies used STAI as a measurement, but only Kimura and colleagues⁷ found that L-theanine significantly reduced STAI scores. Although each study found results favoring L-theanine's ability modify anxiety, these inconsistencies makes it difficult to arrive at a definitive conclusion.

It is important to conduct future studies that account for the limitations in the discussed articles. None of the participants used were diagnosed with GAD. Therefore, it can only be said that L-theanine may reduce symptoms of anxiety in healthy patients. It would be helpful and beneficial for future studies to use participants diagnosed with GAD, that way a conclusion can be drawn about pathologic anxiety. Additionally, two of the three studies did not have

participants take L-theanine daily, only when they underwent acute stress tasks. It is possible that L-theanine may work similarly to a benzodiazepine and treat sudden, acute symptoms of anxiety. It would be curious to see whether L-theanine can work like an SSRI and provide daily maintenance therapy. To answer this question, future experiments should utilize a longitudinal study and require a large simple of participants diagnosed with GAD to take L-theanine daily for an extended period of time. Aside from anxiety, research with L-theanine is being explored in PTSD, schizophrenia, hypertension, attention and insomnia to name a few. As a cost-effective and easily accessible supplement in a time where clean-living is more popular than ever, it is clear that L-theanine has the potential to become highly utilized in not just anxiety, but a variety of conditions.

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