

2015

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Genevieve Asante-Odame

*Philadelphia College of Osteopathic Medicine, Genevieveas@pcom.edu*

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## Recommended Citation

Asante-Odame, Genevieve, "How Safe and Effective Is Tryptophan in Improving Sleep in Healthy Individuals With Mild Sleep Disorders?" (2015). *PCOM Physician Assistant Studies Student Scholarship*. 207.  
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# **How safe and effective is Tryptophan in improving sleep in healthy individuals with mild sleep disorders?**

Genevieve Asante-Odame, 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

December 19, 2014

## ABSTRACT

**OBJECTIVE:** The objective of this selective EBM review is to determine whether or not tryptophan is effective in improving sleep in healthy individuals with mild sleep disorders.

**STUDY DESIGN:** Systematic review of three published, randomized controlled trials (double-blind, placebo-controlled) between 2005-2010, all English language.

**DATA SOURCES:** Three randomized controlled trials published between 2005 and 2010 were found using PubMed/MEDLINE and Cochrane databases.

**OUTCOMES MEASURED:** Improved sleep quality and duration of sleep, which were measured using sleep diaries and sleep study questionnaires.

**RESULTS:** The first study, Cubero et al showed that administration of diet containing high levels of tryptophan reflected more hours of sleep (~7.68 h) as compared to the control (~6.77 h). Hudson et al report a 13.3% increase in total sleep time with pharmaceutical tryptophan added to carbohydrates as compared to 5.5% increase in total sleep time with foods that have naturally high content of tryptophan. The duration of sleep measured in the Shell et al study showed an increase of 6.83 h as compared to 5 h in the control group. No serious adverse events were noted in any of the three studies.

**CONCLUSIONS:** All three studies reported increases in the duration of sleep and improved sleep quality when tryptophan was included in each trial. This suggests that indeed tryptophan is effective in improving sleep in healthy individuals with mild sleep disorders with little adverse reactions from the added tryptophan.

**KEY WORDS:** Tryptophan, sleep

## INTRODUCTION

Sleep disorder is characterized by an interruption in one's sleep pattern in which an individual gets little to no sleep (less than 7-8 hours) due to the difficulty in initiating or staying asleep – specifically insomnia.<sup>1</sup> Those with mild sleep problems are those categorized as “short-term” where symptoms last 1-3 weeks.<sup>2</sup> This paper evaluates three randomized control trials (RCTs) comparing the efficacy of tryptophan in improving sleep in healthy individuals with mild sleep disorders.

Sleep disorders are relevant to patients because about 70 million people have some form of sleep disorder which affects their functional daily activities.<sup>1</sup> As a result, they become sleepy during the daytime, which leads to loss of productivity at school, work, home, increased risk of getting into accidents while on the road, and increased risk of other chronic health problems.<sup>3</sup> Studies show that close to 20 percent of motor vehicle accidents are due to drivers who have not had adequate sleep.<sup>3</sup> Others experience work-related injuries due to day-time sleepiness and significant fatigue.<sup>3</sup>

Its relevance to the Physician Assistant is due to the increasing number of health care visits each year for sleep problems – about 137 percent increase in those who suffer from insomnia. A significant number of physicians have reported an increase in health conditions with those who complain of sleep problems, mainly “hypertension; diabetes; depression; and obesity”.<sup>4</sup> And since many of these clinicians do not have certification to bill for pertinent sleep studies in their offices or lack the necessary training to interpret the results, they are unable to provide a continuum of care even after these patients have seen specialists. There is an increase need to include sleep testing in the offices and appropriate certification or training to physicians

and Physician Assistants since it is affordable, efficient and has shown to improve follow-up time with patients who present with sleep problems.<sup>4</sup>

The exact cost of sleep disorders is unknown; however studies suggest that about “billions of dollars are spent each year in the United States on the direct costs of sleep loss and sleep disorders.”<sup>3</sup> This is partly due to increase use of healthcare facilities for hospital procedures, prescriptions, and office visits. On average, laboratory sleep-tests for those with sleep problems may cost about “\$17.5 billion to test and \$3 billion to treat every person in the United States”.<sup>3</sup> Studies show that close to \$1.2 billion was attributed to sleep aids for insomnia in 2002 and there is a significant increase in cost for elderly patients seeking care for their sleep problems. Other indirect costs include absent from work or school, incapacity, health conditions, late work schedules, medication abuse, accidents at work or on the road, and much more. All of these factors affect total expenditure in the US and is concerning to both the consumer and producer.<sup>3</sup>

Though the main cause of sleep disorders is unknown, it is believed to be “multifactorial” where individuals have medical, mental or physical problems.<sup>2</sup> Some of the medical problems include obesity, hypertension, chronic obstructive pulmonary disease, and iron deficiency.<sup>1</sup> Mental problems include anxiety disorders, depression, bipolar or psychosis.<sup>2</sup> Some physical problems include irregular bed times, activities around bedtime, and other daytime activities.<sup>2</sup> Some usual methods used to treat sleep disorders include “benzodiazepines (triazolam, estazolam, lorazepam), nonbenzodiazepine sedatives (zaleplon, zolpidem, eszopiclone), melatonin agonists (ramelteon), and antidepressants (doxepin, amitriptyline and trazodone).”<sup>5</sup> Other nonpharmacologic ways include modified sleep actions, relaxation techniques, cognitive therapy and cognitive behavioral therapy.<sup>5</sup>

Tryptophan is an amino acid that is found in most foods rich in protein and some plants. Once metabolized in our bodies, it is converted to serotonin and melatonin and this shortens the time to fall asleep and prolongs sleep duration.<sup>6</sup> The treatment options mentioned above all play an effective role in treating sleep disorders. However, as with all medications, each option will have a different effect on each patient. The use of foods containing tryptophan or incorporating pharmaceutical tryptophan into foods can be effective in improving sleep in healthy individuals with mild sleep disorders.

## OBJECTIVE

The objective of this systemic review is to determine whether or not “tryptophan is effective in improving sleep in healthy individuals with mild sleep disorders.”

## METHODS

Three double-blind randomized controlled trials were used in this review. The population was limited to pre-weaning infants of 4-20 weeks in age; and males and females older than 18 but younger than 65 years of age, all showing some sleep problems related to insomnia. The intervention for the first two RCTs included food containing varying amount of tryptophan in them and the last one was with amino acid capsules filled with 5-hydroxytryptophan. The specific concentration and sources of tryptophan intake varied across studies, as did the structure of each control group. Comparisons were made between the treatment groups and an experimental group who received a visually matched placebo or control. Outcomes measured included quality of sleep and duration of sleep.

Key words used in the search included Tryptophan and sleep. The chosen articles were all written in English and published between 2005 and 2010. Each was found through PubMed and Medline databases and selected based on their relevance to my clinical question and whether

they included Patient-Oriented Evidence that Matters (POEMS). The inclusion criteria consisted of randomized controlled trials and a population of healthy individuals 4-20 weeks of age and 18-65 years old, all with mild sleep disorders. Those excluded from the studies were infants older than 20 weeks, adults with heart disease, mental health disease, diabetes, sleep apnea, food allergies, endocrine disease, implanted pacemakers or electrical devices, those taking prescription sleeping medication or have taken Gabadone, pregnant women or lactating mothers, and shift workers. Summary of statistics reported include p values, analysis of variance (ANOVA) with Scheffe F-test scores, multivariate analysis of variance F-score (MANOVA), RRR, ARR and NNT values. Table 1 summaries the demographics included in each study.

**Table 1: Demographics & Characteristics of included studies**

Study	Type	# of pts	Age(yrs)	Inclusion criteria	Exclusion criteria	W/D	Intervention
Cubero, (2007) <sup>7</sup>	Double blind RCT	30	4-20 weeks	Patients were at least 5 months of age with sleep problems (more than three nocturnal awakenings)	Infants > 20 weeks	0	Diet C: Blemil Plus 1 Day (low L-tryptophan levels) and Blemil Plus 1 Night (high L-tryptophan levels)
Hudson, (2005) <sup>6</sup>	Double blind RCT	57	>18	Patients with difficulty initiating or maintaining sleep three or more nights/week for a duration of three months or more	Heart disease, mental health disease, pregnancy, food allergies, diabetes, sleep apnea and shift workers	8	Protein source tryptophan and pharmaceutical grade tryptophan in combination with carbohydrate
Shell, (2010) <sup>8</sup>	Double blind RCT	18	18-65	Patients with a history of intermittent nonrestorative sleep	Patients currently taking prescription sleeping medication, those who have previously taken Gabadone, those with known endocrine disease, pregnant or lactating females and those with implanted pacemakers or implanted electrical devices.	0	Gabadone ( a combination of 5-hydroxytryptophan, GABA and choline in low dose)

## OUTCOMES MEASURED

The outcomes measures in all three studies were POEMS using daily sleep diaries or sleep evaluation questionnaire. In Cubero et al.'s study, the children in the treatment group were fed with Diet C, which was made of Blemil Plus 1 Night – 3.4 g of tryptophan in 100 g of protein and Blemil Plus 1 Day – 1.5 g of tryptophan in 100 g of protein.”<sup>7</sup> The parents of the children undergoing the experiment were instructed to log their children’s sleep pattern over 24 hours, the number of bottles they had, and any occurrence that ensued that night in daily sleep diaries. Also, actimeters were put on the children’s ankles to quantify their movement while asleep in order to correlate them with their parents’ sleep diaries. These actimeters stored any change the child made every two minutes and were analyzed immediately after it came off by the “Sleep analysis software” based on “actual time of nocturnal sleep, minutes of immobility of the infant in its cradle during the night, sleep latency, percentage of nocturnal awakenings and sleep efficiency.”<sup>7</sup> Hudson et al. experimental group received food containing “250mg of pharmaceutical tryptophan with 25 g of dextrose and 25 g of rolled oats (Food 2)” and food containing “25 mg of deaired butternut squash seed meal and 25 mg of dextrose (Food 1).”<sup>6</sup> Subjects in this group utilized sleep diaries as well, where the total sleep time; sleep efficiency (time asleep/total time in bed X 100); time awake during night; time awake during middle of night was recorded. Sleep quality index, which included perception of rejuvenation in morning (1 = Exhausted, 2 = Fair, 3 = Refreshed) and perception of sleep quality (1 = Restless, 2 = Fair, 3 = Very sound) were averaged out using the aforementioned subjective measures to create scores to help with consistency.<sup>6</sup> Lastly, Shell et al.’s treatment group received capsules with Gabadone in it, which included 5-hydroxytryptophan among other substances in a capsule. Subjects completed both the Pittsburgh sleep quality index (PSQI) and the Leeds Sleep Evaluation Visual

Analog Scale (LSEQ). The LSEQ questionnaire included “1) falling asleep; 2) quality of sleep; 3) ease of waking from sleep; and 4) behavior after awakening”.<sup>8</sup> The PSQI included subjective information like “bedtime, rising time, minutes to fall asleep, and actual hours slept.”<sup>8</sup>

## RESULTS

Three double-blind randomized controlled trials compared the effects of sleep in individuals that showed some sleep problems with varying amounts of tryptophan in their food and one trial was with capsules. Cubero et al. studied children 5 months old or younger with some sleep difficulties in their own respective homes. Compared to the treatment group, the control group received normal initiation milk (Blemil Plus 1 Forte – Diet A) without any addition of tryptophan. All thirty enrolled children were followed for 3 weeks and both clinician and subjects were kept blind to the study. Data from this trial was reported as continuous data that was later converted into dichotomous format to evaluate tolerability and treatment effects. It was noted that the children who received Diet C showed major improvement in their total time asleep as compared to the control – Diet A ( $p < 0.05$ ). When evaluating the treatment effect of Diet A versus Diet C the RRR was 3.42, ARR was 0.41 and NNT 2.439. No side effects were reported by the parents of children who were involved in this experiment.

**Table 2: Cubero et al. treatment v. control ANOVA with Scheffe F test at 3 weeks ( $X \pm SD$ )**

	Daily hours of actual sleep	Nocturnal sleep latency (hours)	Sleep improvement % as reflected in the responses to the questionnaire given by parents of infants
Diet A (control)	$6.77 \pm 0.12$	$0.60 \pm 0.08$	12
Diet C (high tryptophan)	$7.68 \pm 0.54$	$0.44 \pm 0.04$	53

Hudson et al. studied 57 male and females older than 18 years of age who showed symptoms of primary insomnia and could complete the protocol for 3 weeks. Subjects met with

the nurses at the various hospitals to turn in their sleep diaries and review side effects. Data from this trial were reported as continuous data and could not be converted into a dichotomous format; therefore calculations evaluating tolerability and treatment effects could not be computed. Hudson et al. reported that eight subjects dropped out of the study due to “failure to attend weekly interviews, death of close family member, relationship stress, and nausea”.<sup>6</sup> These subjects’ data were not included in the final data analysis. Compared to the treatment group, the control group received Food 3 which only had 50 g of rolled oats. Subjects who had either Food 1 or Food 2 showed increase in total sleep time (5.5% with a  $p < 0.10$  and 13.3% with a  $p < 0.01$ , respectively) as compared to Food 3, which was insignificant. Pairwise comparisons were reported between weeks using the MANOVA test and are listed in Table 3. Also, only three patients out of the 57 individuals who enrolled in the trial reported having nausea mainly from Food 1 and Food 3.

**Table 3: Hudson et al. Pairwise Measurements for Treatment v. Control groups**

	Total sleep time in minutes (baseline week)	Total sleep time in minutes (treatment week)	Sleep efficiency (time asleep/time in bed)%	Sleep quality index (1-low, 2-average, 3-high)
Food 1	339 ± 15.1	358 ± 15.1	74.0 ± 2.77	2.02 ± 0.096
Food 2	314 ± 16.0	356 ± 16.0	74.7 ± 2.94	2.08 ± 0.102
Food 3	359 ± 16.6	376 ± 16.5	76.9 ± 3.03	1.78 ± 0.106

Shell et al. studied patients between 18 to 65 years of age with a history of intermittent nonrestorative sleep for a week. All the data from the trial was continuous data that could not be converted to dichotomous data. Eighteen patients were randomly selected and baseline electrocardiographic measurements were recorded. Half were assigned to either take two capsules of Gabadone before bed or two capsule of placebo before bedtime. Sleep study questionnaires and electrocardiographic analysis were created from the results after day 7. A significant improvement in time to fall asleep was achieved in subjects who took Gabadone, about 41% with

a  $p=0.01$ . Also, subjects in the treatment group had about one extra hour of sleep ( $p=0.01$ ) as compared to the control group who did not see any significant change in the duration of sleep ( $p=0.46$ ). Shell et al. reported that none of the subjects complained of side effects from either taking placebo or Gabadone. Table 4 summaries the variables imperative to this review paper.

**Table 4: Shell et al. treatment v. placebo LSEQ and PSQI computed data**

	Gabadone		Placebo	
	Baseline	Day 7	Baseline	Day 7
Time to sleep (mins)	32.32	19.11	34.83	33.11
Hours slept	5.00	6.83	7.17	7.11
Am grogginess (mins)	30.56	11.11	67.78	65.00
Perceived snoring reduction, %	25		Not significant	

## DISCUSSION

Using three double-blind RCT's, this meta-analysis reviewed the effect of tryptophan in improving the sleep in children between 4-20weeks of age and adults between 18 and 65 years old with mild sleep disorders. The blinding and validity of each RCT was without error, with very few drop-out rates, however sample sizes were relatively small as were follow up duration. In addition, the effects of tryptophan on sleep were only assessed via computed data from subjects' responses in the different questions, however many other options exist. Though Cubero et al.'s trial focused on children less than 5 months of age, the other two studies mentioned in this review have shown benefit to using tryptophan in individuals older than 18 but younger than 65.

Tryptophan (mainly known as L-tryptophan) is an essential amino acid that is relatively safe when used as directed. Its supplementation is contraindicated in patients taking antidepressants or other sedatives as this may cause profound drowsiness. The Food and Drug Administration (FDA) regulates the sale of tryptophan since it was reported to have caused a deadly condition called eosinophilia-myalgia syndrome (EMS) in 1989. And though there have not been any significant incidences of this condition since, many pharmaceutical companies are required to label all ingredients on their packaging. There are not enough studies to determine the appropriate dose for tryptophan and no black box warning exists.<sup>9</sup>

Tryptophan supplementation has other uses: premenstrual dysphoric disorder (PMDD), smoking cessation, bruxism, facial pain, depression, seasonal affective disorder and anxiety. Nevertheless, more research is needed to validate this aforementioned uses.<sup>10</sup> Not only is it necessary that sample sizes be large or longer research trials be conducted; it is also important to determine the appropriate length of time to take this supplement as there is very little research about dependence or withdrawal syndromes. Also, certain criteria should be in place to identify reliable pharmaceutical companies who do not genetically engineer L-tryptophan because this can pose a risk to the development of EMS.

## CONCLUSION

Based on the three studies above, it can be concluded that tryptophan is effective in improving sleep in healthy individuals with mild sleep disorders. When added to various food as a supplement or taken in a capsule form, tryptophan consistently lower the time to fall asleep and lengthen duration of sleep in people who present with sleep problems as compared to the group who did not take it.

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