L-Tryptophan

It's Back, It's Safe & It's Effective

By Gene Bruno, MS, MHS

If I say the word "tryptophan", what's the first thing that comes to your mind? Maybe you're thinking it's the amino acid in turkey that makes people sleepy after Thanksgiving. Or, if you're over the age of 40 and know something about dietary supplements, you might be thinking of it as the amino acid that made some people sick, resulted in several deaths, and was removed from the market almost 20 years ago.

If you made the latter association, then pay close attention because as you read this article you're going to find out that L-tryptophan (LT) was unfairly convicted, and is actually a safe dietary supplement. In addition, you'll learn that it's quite effective for inducing sleep, reducing symptoms associated with premenstrual disorder and depression, working as an adjunct to smoking cessation therapy, reducing appetite and promoting weight loss, and also promoting growth hormone release. But now, let's begin by answering the question, "What is it and how does it work?"

What is it and how does it work?

LT is an essential amino acid, which means that it must be consumed from food since the body cannot make it using other amino acids. It is present in virtually all plant and animal proteins. Once the body absorbs LT, it converts it into 5-hyrdoxytryptophan (5-HTP), and then into the neurotransmitter serotonin. It is primarily the serotonin which then does all the wonderful things attributed to LT. For example, serotonin is the precursor to the sleep hormone, melatonin.[1]

Now let's take a look at what really happened when LT was removed from the market.

Eosinophilia-myalgia syndrome and L-tryptophan

In 1989 and 1990, two reports of a new disease labeled the eosinophilia-myalgia syndrome (EMS) were published, and were attributed to LT.[2] [3] As a result, the FDA took action to limit the availability of dietary supplements containing LT. In all, more than 1500 cases of EMS, including at least 37 deaths, were reported to the national Centers for Disease Control and Prevention (CDC).[4]

In certain epidemiological studies, more than 95 percent of the cases of EMS were traced to LT supplied by Showa Denko K.K. of Japan.[5] With regard to Showa Denko LT, analysis of case-associated lots revealed several chemical impurities. One of these, labeled "peak E," is an unusual dimeric form of LT (1,1'-ethylidenebis[tryptophan]), and its presence is considered to be associated with EMS.[6]

Did LT really cause EMS?

It should be noted that LT was sold as a dietary supplement since the 1970s, and no incidences of LT-associated EMS were reported in the literature prior to 1989. It should also be noted that people who did not consume LT still developed EMS[7], while national surveillance in the U.S. indicated that on average 10% of consumers of Showa Denko EMS-implicated LT were diagnosed with EMS and there was no dose-risk relationship[8]; and cases of EMS and a related disease, eosinophilic fascitis, have occurred prior to and after the 1989 epidemic.[9]

Additionally, according to Shapiro[10] the possibility has not been ruled out that early symptoms of EMS could have resulted in the subjects using LT for relief, rather than the LT being an actual causative factor. Shapiro further indicated that the apparent epidemic "could have been an artifact of waxing and waning enthusiasm for reporting exposed cases to an EMS registry, corresponding with the timing and the amount of publicity given to the topic. The questionable validity of these studies considerably weakens the claim that LT or a contaminant caused EMS." [11]

The bottom line is that there are still questions as to LT role in EMS. In any case, since the association was with LT from a specific supplier, all LT should not have been portrayed as being equally culpable in the development of EMS.

Legality of L-tryptophan

Although the FDA has enunciated concern about the safety of dietary supplements containing LT in 1989, this does not mean that the FDA prohibits the marketing of such supplements today. This is quite interesting since the FDA does have the power to prohibit the sales of a supplement that it deems unsafe. However, the FDA has taken the position that under the Food, Drug and Cosmetic Act (the Act), as amended by the Dietary Supplement Health and Education Act of 1994 (DSHEA), the manufacturer is responsible for ensuring that its products are safe. A firm is not required to obtain pre-market review or approval from the FDA of its products before marketing them as dietary supplements. If a firm has information that it believes establishes that a product containing LT is safe within the meaning of the Act, it could market such a product as a dietary supplement.[12]

Furthermore, the FDA previously had an import alert ("Detention without physical examination of L-tryptophan") which limited the importation of LT into the United States.[13] However, as of May 2, 2005, the FDA cancelled the import alert on LT. The cancellation stated, "There is insufficient evidence at this time to support detention without physical examination of involving foreign sources of l-tryptophan. Therefore, this alert is cancelled."[14]

Safety of LT

The U.S. FDA's Center for Food Safety and Applied Nutrition has a food additive database called EAFUS (http://www.cfsan.fda.gov/~dms/eafus.html). The site states "The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS." If you scroll down you will see that L-Tryptophan is listed. The FDA itself on its own website has indicated that L-Tryptophan is Generally Recognized As Safe. There is no other safety certification more valued or used than GRAS status.

Furthermore, Gormley[15] quoted FDA spokesperson Arthur Whitmore as recently stating: "The agency has not concluded that any particular product is adulterated under the ACT; therefore the FDA has taken no steps to limit the availability of dietary supplements containing L-Tryptophan produced in the U.S." Again, if the FDA does not have safety concerns, then LT is considered safe.

To quote again from the FDA's import alert recall, "There is insufficient evidence at this time to support detention…." The FDA released it to the general public (not just infants) because there is insufficient evidence (i.e. safety) to support detention.

For the reasons previously expressed, LT that has been submitted to proper quality control testing should be considered safe for inclusion in dietary supplements. Of course, you might wonder what constitutes a proper quality control test for LT. If so, you are wise for doing so. Consider that the USP, FCC, EP, and JP assay methods for L-Tryptophan are titration methods. These titration methods only give you the percent of L-Tryptophan present. They are purity tests; they do not measure impurities. The minimum assay is 98.5%, but as we found in 1989, the other 1.5% is critical to test for.

Therefore, I believe that it is important that L-Tryptophan be tested using an HPLC method, run for at least 50 minutes. The reason for this is that the L-Tryptophan peak appears on the HPLC chromatogram at about 16-20 minutes, which is where some labs would cut off the test. However, what was found after 1989 was the impurities implicated in the EMS cases were found by HPLC runs from 35 to 50 minutes.

Hence the importance of running the test for at least 50 minutes. In addition, endotoxin testing should also be performed at the lowest detection limit currently known.*

Now, let's look at LT's benefits.

Inducing sleep

First and foremost, LT is an effective sleep aid. Certainly LT has significant sedative-like properties, although unlike other sedatives it does not appear to impair performance.[16] Specifically, LT is not associated with impairment of visuomotor, cognitive, or memory performance, nor does it elevate threshold for arousal from sleep.[17]

At least 20 years worth of research (including 40 controlled studies)[18] has demonstrated that LT can help induce sleepiness in humans. The weight of the evidence suggests that doses of 1 gram or more is effective. In younger insomniacs, LT is effective in inducing sleep the first night of administration, while in more chronic, well established insomnia or in more severe insomnias, repeated administration of low doses of L-tryptophan over time may be required for therapeutic improvement.[19]

One particular study[20] found that LT may be effective in doses lower than 1 gram. In 15 mild insomniacs 1 gram of LT helped reduce the amount of time it took to fall asleep, although lower doses of 1/4 g and 1/2 g produced a trend in the same direction. Stage IV sleep was significantly increased by 1/4 g of L-tryptophan.

Reducing PMS symptoms

Although the precise cause of premenstrual syndrome (PMS) is still unknown, but it is increasingly believed that there is an alteration in serotonin activity.[21] [22] [23] Furthermore, considering the fact that LT is a precursor to serotonin, and LT depletion increases aggression in women during the premenstrual phase[24], as well as aggravating PMS[25], it's not surprising that research shows supplementation with LT is effective in treating premenstrual dysphoric disorder, a severe form of PMS. In a double-blind, randomized, controlled clinical trial[26], 37 patients with premenstrual dysphoric disorder were treated with 6 grams LT daily for 17 days from the time of ovulation to the third day of menstruation, during three consecutive cycles. In addition, 34 patients were given a placebo. Compared to the placebo group, the women receiving the LT experienced significant ($p = 0.004$) therapeutic effect for the cluster of mood symptoms comprising the items dysphoria, mood swings, tension and irritability.

In an earlier study[27] on 13 patients, similar results were demonstrated with 6 grams LT significantly improving symptoms. Other research[28] has shown that as little as 2 grams daily (1 gram, twice daily), every other day for 10 days premenstrually for two consecutive menstrual cycles, was also effective at relieving PMS symptoms, and might reduce associated excessive food intake. On a personal note, LT is the single most effective supplement that my wife ever used for PMS.

Treating depression

Selective serotonin reuptake inhibitors (SSRIs) are a category of drugs commonly used for the treatment of depression. SSRIs work by blocking serotonin transporters so serotonin remains for a longer time and is more available to brain neurons. So does LT have value in the treatment of depression since it is the precursor to LT? The answer seems to be yes; at least when used in combination with other antidepressant medications.

In a randomized, double-blind, placebo-controlled trial[29], 30 patients with major depressive disorder were treated for over 8 weeks with 20 mg of fluoxetine (Prozac) per day and either tryptophan (2 to 4 grams per day) or a placebo. The results were a significantly greater decrease in depression scores in the tryptophan/fluoxetine group than in the placebo/fluoxetine group. Since 4 grams of LT seemed to cause some daytime drowsiness, 2 grams of LT appeared to be the optimal amount. The authors concluded that "Combining 20 mg of fluoxetine with 2 g of tryptophan daily at the outset of treatment for major depressive disorder appears to be a safe protocol that may have both a rapid antidepressant effect and a protective effect on slow-wave sleep." [Note: Due to the risk of serotonin syndrome (a rare, but potentially life-threatening adverse drug reaction from excess serotonergic activity at central nervous system and peripheral serotonin

* There may be others, but at least one laboratory that I know of, Compound Solutions, Inc., the raw-material supplier for LT-ONE™ Ultra-Premium L-Tryptophan, conducts their L-Tryptophan testing according the methods I described.

receptors), do not take LT with an SSRI medication without the prior approval from your physician.]

In addition, work done in the 1960s and 1970s demonstrated that tryptophan effectively augmented the effect of older category antidepressants called monoamine oxidase inhibitors.[30] [31] [32] In a large, 12-week, double-blind study[33], LT (3 grams per day) alone was compared to the tricyclic antidepressant amitriptyline, as well as amitriptyline plus LT, and a placebo alone in patients with mild to moderate depression. The LT alone and LT plus amitriptyline were equally effective, and significantly better than placebo.

Seasonal affective disorder (also called SAD) is another type of depression. The most common type of SAD is called winter depression; and it usually begins in late fall or early winter and goes away by summer. Since winter depression is probably caused by the body's reaction to a lack of sunlight, light therapy is often used in treating this disorder. Research[34] has shown that serotonin levels are lowest in the winter, and serotonin product rises in response to light; which may explain the value of light therapy for winter SAD. However, not all SAD patients respond to light therapy, and require alternative therapy. LT is one such therapy. In a study[35] of 13 SAD patients, there were significant therapeutic effects of both light and tryptophan; although relapse back to SAD-related depression occurred more slowly after LT was withdrawn compared to light therapy.

Adjunct to smoking cessation therapy
Cigarettes are as addictive as heroin or cocaine.[36] Quitting is not easy, but LT may be able to help. In one research project, LT (50 mg/kg/day) and high-carbohydrate diets, together with more traditional smoking cessation treatment techniques, were used to help reduce the effects of smoking withdrawal and improve abstinence rates. Subjects were randomly assigned to receive either tryptophan or a placebo. The results were that reported anxiety and other withdrawal symptoms were lower in the LT group compared with placebo subjects. Furthermore, LT-treated subjects who could not fully abstain were able to smoke fewer daily cigarettes. This data suggests that LT shows promise for use as an adjunct to existing smoking cessation programs.

Reducing appetite and promoting weight loss
Since serotonin is involved in the regulation of appetite[37], it shouldn't be too much of a stretch to think that LT might have value for reducing appetite. One mechanism by which this may take place is inhibiting stomach emptying. Consider that the longer food remains in the stomach, the less likely a person is to feel hungry. Consequently, if gastric (stomach) emptying is inhibited, hunger is reduced. Research[38] has shown that when taken in doses of 3 grams, LT is a potent inhibitor of gastric emptying in humans, resulting in a significant reduction of hunger.

Since LT can help reduce hunger, it seems likely that it might also be able to aid in weight loss. In fact, drugs thought to enhance serotonin-mediated neurotransmission have been shown to diminish appetite (particularly for carbohydrates) and promote weight loss. Along these lines of thinking, researchers conducted a placebo-controlled, double blind study[39] comparing the ability of LT or a placebo to influence weight loss among 62 obese outpatients who were on the Protein-Sparing Modified Fast (PSMF); a reducing diet which can be associated with a severe craving for carbohydrates, as well as a reduction in brain LT and serotonin levels (other types of weight loss diets have also been associated with a decrease in LT concentrations[40]). LT (750 mg, twice daily, orally, for 3 months) was given to 30 subjects, while the remainder were given the placebo. The results were that the LT significantly enhanced weight loss among moderately obese subjects. This took place significantly during both the first treatment month, but also during the total 3-month test period.

Now let's shift gears for a moment and consider the relationship between sleep and weight gain (don't worry, this does relate to our discussion). Research has shown that when people are deprived of sleep, certain biochemical changes take place that result in increased hunger and appetite.[41] Other research has shown that overweight and obese people get less sleep than normal weight people.[42] Given the fact that LT can induce sleep and reduce hunger, is it possible that supplementation with LT can

address both of these issues at one fell swoop? It certainly seems likely.

Promoting growth hormone release

For years, many people have been looking for ways to increase their levels of human growth hormone (HGH). The value of increasing HGH can be understood by examining this hormone's functions, which include maintaining the immune system, stimulating muscle growth through amino acid sparing and promotion of amino acid transport into muscle cells, and burning fat from fat cells.[43] As it turns out, LT is capable of increasing HGH. This was demonstrated in various studies of human subjects back in the 1970s.[44] [45] [46] [47] [48] [49] In one particular study[50] of 8 healthy male volunteers, LT was given to each of them at different times in doses of 2, 5, and 8 grams (or a placebo) to determine the most effective dose for stimulating HGH release. The results were that all three doses stimulated HGH release compared to placebo; although HGH release from the 8 gram dose was somewhat reduced. It should also be noted that 2 subjects failed to respond to the 2 gram dose, and 5 subjects failed to respond to the 5 gram dose; so LT may not work for everyone as a HGH releaser.

Conclusion

LT is a safe and effective amino acid. Research demonstrates that it has value for inducing sleep, reducing symptoms associated with premenstrual disorder and depression, working as an adjunct to smoking cessation therapy, reducing appetite and promoting weight loss, and also promoting growth hormone release.

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