

5-Hydroxytryptophan: A Clinically-Effective Serotonin Precursor

by Timothy C. Birdsall, N.D.

Abstract

5-Hydroxytryptophan (5- HTP) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin. Intestinal absorption of 5-HTP does not require the presence of a transport molecule, and is not affected by the presence of other amino acids; therefore it may be taken with meals without reducing its effectiveness. Unlike LT, 5-HTP cannot be shunted into niacin or protein production. Therapeutic use of 5-HTP bypasses the conversion of LT into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. 5-HTP is well absorbed from an oral dose, with about 70 percent ending up in the bloodstream. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin. In the CNS, serotonin levels have been implicated in the regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behavior, and pain sensation. Therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions, including depression, fibromyalgia, insomnia, binge eating associated with obesity, chronic headaches, and insomnia.

(*Altern Med Rev* 1998;3(4):271-280)

Introduction

5-Hydroxytryptophan (5-HTP) (see Figure 1) is an aromatic amino acid naturally produced by the body from the essential amino acid L-tryptophan (LT). Produced commercially by extraction from the seeds of the African plant, *Griffonia simplicifolia*, 5-HTP has been used clinically for over 30 years. The clinical efficacy of 5-HTP is due to its ability to increase production of serotonin in the brain.

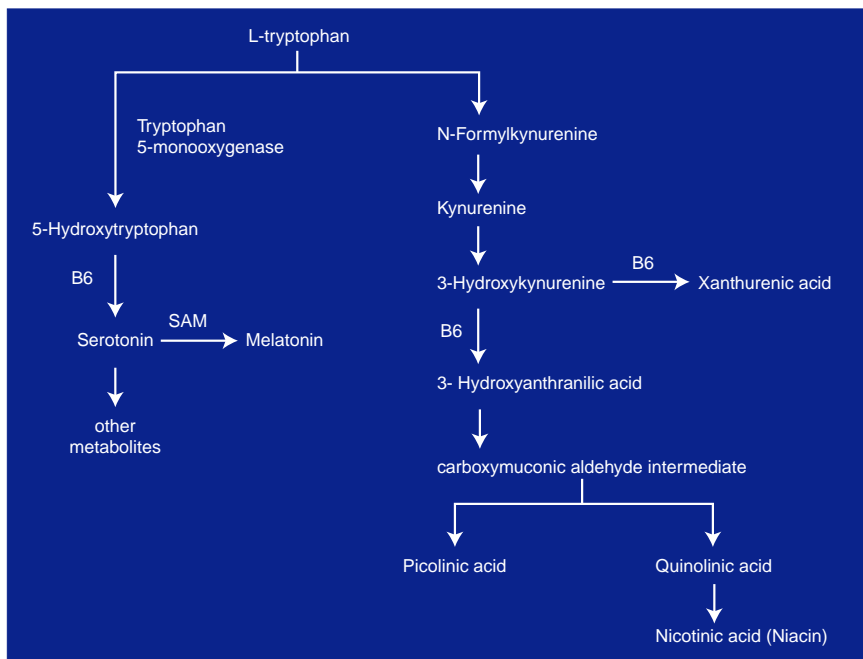
Metabolism of Tryptophan and Serotonin

Serotonin (5-hydroxytryptamine), dopamine, and norepinephrine are the three main “monoamine” neurotransmitters, each produced endogenously from one specific amino acid. Tryptophan is converted into serotonin, while dopamine and norepinephrine are made from tyrosine. In the central nervous system (CNS), serotonin has been implicated in regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behavior, and pain sensation.

Timothy C. Birdsall, N.D.

Correspondence address: e-mail: 73541.2166@compuserve.com or altmedrev@thorne.com

Figure 1. Tryptophan metabolism



as one percent of dietary LT may be transported into the CNS.

4) LT is used by the body for other metabolic purposes in addition to serotonin production, including protein synthesis and the creation of niacin.

Biochemistry and Metabolism of 5-HTP

5- HTP is the intermediate metabolite of LT in the production of serotonin (see Figure 2). Therapeutic use of 5-HTP bypasses the conversion of LT into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. Tryptophan hydroxylase can be inhibited by numerous factors, including stress, insulin resistance, vitamin B6 deficiency, and insufficient magnesium. In addition, these same factors can increase the conversion of LT to kynurenine via tryptophan 2,3-dioxygenase, making LT unavailable for serotonin production.

5-HTP is well absorbed from an oral dose, with about 70 percent ending up in the bloodstream.^{5,6} Absorption of 5-HTP is not affected by the presence of other amino acids; therefore, it may be taken with meals without reducing its effectiveness. Unlike LT, 5-HTP cannot be shunted into niacin or protein production.

Serotonin levels in the brain are highly dependent on levels of 5-HTP and LT in the central nervous system (CNS). 5-HTP easily crosses the blood-brain barrier, not requiring the presence of a transport molecule. LT, on the other hand, requires use of a transport molecule to gain access to the CNS. Since LT shares this transport molecule with several other amino acids, the presence of these

While other cells outside the brain, such as blood platelets and some enterocytes, make and/or use serotonin, all serotonin used by brain cells must be made within the neurons, since serotonin cannot cross the blood-brain barrier. Therefore, the synthesis of serotonin is heavily dependent upon the availability of LT within the CNS. The production and subsequent transport of LT from the bloodstream into the CNS can be compromised by several factors:

1) Stress, elevated cortisol levels, vitamin B6 deficiency, and even high dosages (above 2,000 mg) of LT, which all stimulate the conversion of LT to kynurenine, lowering serum LT levels.¹⁻³ (See Figure 2)

2) Elevated serum levels of kynurenine inhibit transport of LT into the CNS, and reduce CNS serotonin levels.⁴

3) Transport of LT across the blood-brain barrier requires binding to a transport molecule, which LT shares with five other amino acids (tyrosine, phenylalanine, valine, leucine and isoleucine). Since LT is present in foods in relatively small amounts in comparison to these other amino acids, as little

competing amino acids can inhibit LT transport into the brain.

Mechanisms of Action

5-HTP acts primarily by increasing levels of serotonin within the central nervous system. Other neurotransmitters and CNS chemicals, such as melatonin, dopamine, norepinephrine, and beta-endorphin have also been shown to increase following oral administration of 5-HTP.⁷⁻¹⁰ This ability to increase not only serotonin levels in the brain, but also dopamine and norepinephrine, allows 5-HTP to produce some significant and unique effects on brain chemistry and on serotonin-related conditions which other substances, including LT, cannot duplicate.

Clinical Studies Using 5-HTP

Depression: Much of the published research on 5-HTP has to do with its use in the treatment of depression. Since the early 1970s, at least 15 studies have evaluated the clinical effects of 5-HTP on depression.¹¹⁻²⁵ These are summarized in Table 1. Taken together, these studies examined a total of 511 patients with different types of depression. Of these 511 subjects, 285 (56%) showed significant improvement while taking 5-HTP.

In addition, biochemical studies show 5-HTP is closely involved in depressive disorders. In a study employing positron-emission tomography (PET) scanning, eight healthy volunteers and six people diagnosed with major depression received infusions of radiolabelled 5-HTP. The researchers found significantly less 5-HTP crossed the blood-brain barrier into the brains of the depressed subjects than into the brains of the normal controls. The authors suggested the transport of 5-HTP across the blood-brain barrier may be compromised in major depression,²⁶ which might make the brain dependent on LT to 5-HTP conversion in the brain.

Some concern has arisen regarding whether 5-HTP should be used only in conjunction with a peripheral decarboxylase inhibitor (PDI) such as carbidopa. The argument is essentially that without a PDI, 5-HTP will be converted into serotonin in the peripheral circulation, negating any potential CNS benefit from 5-HTP.^{13,22-24} However, this argument ignores scores of clinical studies in which 5-HTP was given alone and in which significant clinical benefit was seen, with no significant adverse effects.

The first large clinical trial using 5-HTP in depression was conducted by Sano in 1972. Using an open trial design, a total of 107 patients with endogenous unipolar or bipolar depression were given daily oral dosages of 5-HTP from 50 to 300 mg. Significant improvement was observed in 74 of the patients (69%), and no significant side effects were reported. The response rate in most of these patients was quite rapid (less than two weeks).¹¹

The issue of speed of response was subsequently addressed in a study of 59 patients with eight different types of depression. 5-HTP was administered orally in dosages from 150 to 300 mg daily for a period of three weeks. Thirteen patients (22%) were markedly improved, and another 27 patients (45.8%) showed moderate improvement. Of these 40 patients who improved, 20 (50%) began to show improvement within three days, and 32 patients (80%) improved within two weeks of beginning treatment with 5-HTP.¹⁵ In contrast to many conventional antidepressants which may take 4 weeks or longer to achieve therapeutic response in most patients, those taking 5-HTP appear to have a significantly more rapid response.

Japanese researchers administered 5-HTP to 24 patients hospitalized for depression. After two weeks of treatment, a "marked amelioration of depressive symptoms" was observed in seven patients diagnosed with unipolar depression. The administration of

Table 1. Clinical trials of 5-HTP use in depression

Reference	Number of Patients	Diagnosis	Study Design	5-HTP Dosage (mg/day)	Duration of treatment (days)	Results
Sano ¹¹	107	Endogenous depression	Open Trial	50-300	7-35	74/107 markedly improved
Fujiwara ¹²	20	Endogenous depression	Open Trial	50-200	7-28	10/20 markedly improved
Matussek ¹³	23	Unipolar depression (13); bipolar depression (1); involuntional depression (8); schizoaffective depression (1)	Open Trial	100-300	4-20	7/23 markedly improved
Takahashi ¹⁴	24	Unipolar depression (20); involuntional depression (2); neurotic depression (1); psychotic depression (1)	Open Trial	300	14	7/20 in the unipolar group markedly improved
Nakajima ¹⁵	59	Mixed group; 8 different types of depression	Open Trial	150-300	21+	13/59 markedly improved; 27/59 moderately improved
van Hiele ¹⁶	99	Endogenous depression (44); depression with endogenous features (24); personal depression (31)	Open Trial	50-600 a	14+	37/68 in the endogenous group and 6/31 in the personal group markedly improved
Kaneko ¹⁷	18	Endogenous depression	Open Trial	150-300	10-28	10/18 markedly improved
van Praag ¹⁸	5	Endogenous depression (unipolar and bipolar)	Double-blind; 5-HTP vs. placebo	200-3,000	21	3/5 markedly improved
Brodie ¹⁹	7	Psychotic depression (6); schizoaffective psychosis (1)	Double-blind; 5-HTP vs. placebo	250-3,250	1-15	1/7 moderately improved
Barlet ²⁰	25	Melancholia (4); involuntional depression (7); reactive depression (8); neurotic depression (6)	Double-blind; 5-HTP vs. placebo	200-800	10-240	19/25 improved
Lopez ²¹	14	Endogenous depression	Double-blind; 5-HTP vs. nialamide	50-300	15-20	12/15 markedly improved
van Praag ²²	20	Endogenous depression (unipolar and bipolar)	Double-blind; 5-HTP vs. clomipramine vs. placebo	200 ^a	21	11/20 markedly improved; 5-HTP and clomipramine equally effective
van Praag ²³	15	Endogenous depression (unipolar and bipolar)	Double-blind; 5-HTP vs. tryptophan vs. placebo	200 ^a	28	8/15 markedly improved; 5-HTP more effective than tryptophan or placebo
Mendlewicz ²⁴	39	Bipolar (24); unipolar(15)	Double-blind; 5-HTP vs. 5-HTP +deprenyl vs. placebo	300 ^a	32	13/21 responded to 5-HTP alone
Poldinger ²⁵	36	Endogenous depression (10); reactive depression (16); situational depression (9); involuntional depression (1);	Double blind; 5-HTP vs. fluvoxamine	300	42	27/36 improved
Total	511					285/511 improved
Total — Double blind studies only	161					94/161 improved

Adapted from van Praag and Lemus.⁷

^a 5-HTP was given in combination with a peripheral decarboxylase inhibitor.

5-HTP was also associated with a 30 percent increase in the levels of 5-hydroxyindolacetic acid, the primary metabolite of serotonin, in the patients' cerebrospinal fluid. This suggested the exogenous 5-HTP was being converted to serotonin within the CNS.¹⁴

5-HTP vs. Conventional Anti-depressants: The current conventional therapies of choice for depression are the selective serotonin reuptake inhibitors (SSRIs). A 1991 Swiss study evaluated 5-HTP in comparison to an SSRI drug in a double-blind, multicenter study design. A total of 36 subjects, all of whom were diagnosed with some form of depression, received either 100 mg of 5-HTP three times per day, or 150 mg of fluvoxamine (an SSRI) three times daily. The subjects were evaluated at 0, 2, 4, and 6 weeks, using four evaluation tools: the Hamilton Rating Scale for Depression (HRSD), a standard depression rating scale; a patient-performed self-assessment; the investigator's assessment of severity; and a global clinical impression.²⁵

Both treatment groups showed significant and nearly equal reductions in depression beginning at week two and continuing through week six. After four weeks, 15 of the 36 patients treated with 5-HTP, and 18 of the 33 patients treated with fluvoxamine had improved by at least 50 percent, according to the HRSD scores. By week six, the two groups had about equal numbers showing 50 percent improvement. When the numbers were totaled at the end of the study, the researchers found the mean percentage improvement from baseline to the final assessment was slightly greater for patients treated with 5-HTP. The number of treatment failures was higher in the fluvoxamine group (5/29, 17%) than in the 5-HTP group (2/34, 6%), although neither of these differences were statistically significant. All four evaluation tools yielded similar results.

The study also looked at the incidence of adverse effects from both treatments, which

were found to be rare and generally mild, usually occurring during the first few days of treatment and then disappearing. Overall, 5-HTP appeared to be slightly better tolerated than fluvoxamine, although the results did not reach the level of statistical significance. Tolerance was assessed as being "good to very good" in 34/36 patients receiving 5-HTP (94.5%), compared to 28/33 in the fluvoxamine group (84.8%).²⁵

5-HTP has also been compared in a few studies with conventional tricyclic antidepressants (chloripramine and imipramine) - the most effective drugs for treating depression until the development of the SSRIs. The studies found 5-HTP to be at least as effective as these drugs in treating severe depression, while displaying fewer side effects. In severe cases, 5-HTP dosages as high as 1200 mg daily were used.^{22,27-29}

Fibromyalgia: Primary fibromyalgia syndrome is characterized by general musculoskeletal aching, multiple tender points, fatigue, morning stiffness, and sleep disturbances. Fibromyalgia patients have been found to have low serotonin^{30,31} and tryptophan^{32,33} levels, and some studies have shown symptomatic improvement with the use of tricyclic and SSRI antidepressants.^{34,35} These findings suggest 5-HTP might be useful in the treatment of fibromyalgia, and three clinical trials have demonstrated significant improvement in symptoms, including pain, morning stiffness, anxiety, and fatigue.³⁶⁻³⁸

Caruso et al conducted a double-blind, placebo-controlled study in 50 fibromyalgia patients, administering 100 mg of 5-HTP three times daily for a period of 30 days. Significant improvements were seen in number of tender points ($p < 0.001$), subjective pain severity ($p < 0.001$), morning stiffness ($p = 0.017$), sleep patterns ($p < 0.001$), anxiety ratings ($p < 0.001$), and fatigue ratings ($p = 0.003$). The incidence of side effects in the 5-HTP group was low (6/25 patients), and no significant

laboratory abnormalities were reported during the study.³⁸

In a longer-term study, a total of 50 patients diagnosed with primary fibromyalgia syndrome were given 100 mg 5-HTP three times per day for 90 days in an open study. Patients were assessed at the beginning of the study and after 15, 30, 60, and 90 days of treatment. The clinical variables evaluated included: total number of tender points, pain intensity, sleep quality, morning stiffness, anxiety, and fatigue. All of these measures showed significant improvement throughout the length of the study ($p < 0.001$). A total of 15 patients (30%) reported side effects from the 5-HTP, but in only one case were they severe enough for the patient to be withdrawn from the study.³⁷

In a randomized, placebo-controlled study of 200 fibromyalgia patients who were also migraine sufferers, 5-HTP (400 mg/day) was compared to a tricyclic drug (amitriptyline) and a monoamine oxidase inhibitor (MAOI) drug (pargyline or phenelzine). The combination of 5-HTP (200 mg/day) with an MAOI was also evaluated. Patients were treated for a total of 12 months and kept a daily pain diary by means of a visual analogic scale. At the end of the twelve-month trial period, all treatment regimens showed significant improvement over placebo ($p < 0.0001$), although the combination of 5-HTP with the MAOI was the most effective. 5-HTP alone was as effective as the tricyclic or MAOI drugs. No patients withdrew from the study due to side effects; eight percent of the patients taking 5-HTP alone reported some degree of stomach upset.³⁶

Obesity: During dieting, serum tryptophan levels and CNS serotonin levels drop dramatically.³⁹⁻⁴¹ These low serotonin levels in obese patients have been associated with carbohydrate cravings and resultant binge eating. It has been theorized that 5-HTP can help prevent this dieting-associated decline in

serotonin, thus enhancing weight loss. Three clinical trials in obese patients have demonstrated decreased food intake and subsequent weight loss with 5-HTP supplementation.⁴²⁻⁴⁴

Using a placebo-controlled, double-blind protocol, researchers at the University of Rome evaluated the effects of 5-HTP (300 mg three times daily) on the eating habits and weight loss of 20 obese female patients. All patients had a body mass index between 30 and 40, and were determined to consume an excess of food daily, based on calculated energy needs. The twelve-week study period was divided into two six-week sections. During the first six weeks, the patients took either 5-HTP or placebo, but no dietary restrictions were placed on them. In the second six-week period, the patients were placed on a 1200 calorie per day diet, while continuing to take either the 5-HTP or placebo. Subjects compiled detailed 3-day food diaries once every two weeks.⁴²

Those in the placebo group did not experience significant weight loss in either of the two periods (94.3 ± 5.6 kg vs. 93.2 ± 5.3 kg), while the subjects in the 5-HTP group showed significant weight loss in both the first period (99.7 ± 5.9 kg vs. 98.0 ± 5.0 kg, $p < 0.03$) and the second period (98.0 ± 5.0 vs. 94.7 ± 5.1 kg, $p < 0.02$). The placebo group also did not show significant change in their calorie intake, even in the second period when instructed to reduce food intake, while the 5-HTP group had a significant spontaneous dietary intake reduction during the first period, from 3220 calories/day to 1879 calories/day ($p < 0.001$), with carbohydrate intake falling by 50 percent. During the second period, the calorie intake of the 5-HTP group decreased further, to 1268 calories/day ($p < 0.01$), with further reductions in carbohydrates. The researchers interpreted these findings as supporting the theory that 5-HTP decreased carbohydrate cravings and binge eating, even in the absence of a structured diet.⁴²

At this high dosage of 5-HTP (900 mg/day), about 80 percent of the subjects initially reported experiencing some nausea. However, this side effect was not severe enough to cause any of the subjects to drop out of the study, and was less frequent during the second six-week period, suggesting that this symptom may be a transitory effect of 5-HTP administration.⁴²

Chronic Headaches: Chronic headaches, especially migraines, are considered by some researchers to be the result of low serotonin levels, probably as the result of increased breakdown of serotonin by the enzyme monoamine oxidase.^{45,46} Low serotonin levels are thought to lower pain thresholds in chronic headache sufferers, allowing other headache triggers to more easily “set off” a headache.

5-HTP has been used successfully in the prevention of chronic headaches of various types, including migraine, tension headaches, and juvenile headaches.^{36,47-52} In a large study of 124 subjects, the ability of 5-HTP to prevent migraines was compared to methysergide, one of the most commonly used migraine drugs. At a dosage of 600 mg daily for six months, 5-HTP totally prevented or substantially decreased the number of migraine attacks in 75 percent of the subjects. However, this difference was not determined to be statistically significant.⁴⁹ In a study of 48 elementary and junior high school students, 5-HTP (4.5 mg/kg/day) produced a 70 percent decrease in headache frequency, compared to an 11 percent decrease in the placebo group.⁴⁸

Insomnia: 5-HTP has been shown to be beneficial in treating insomnia, especially in improving sleep quality by increasing REM sleep.⁵³⁻⁵⁵ Eight normal subjects were monitored to determine the effect of 5-HTP on rapid eye movement (REM) sleep. A total of 600 mg 5-HTP was administered to the subjects in the following manner: 200 mg at 9:15 pm, followed by 400 mg at 11:15 pm. A significant increase in the amount of REM

sleep was observed while the subjects were taking 5-HTP (118 ± 14 mins vs. 98 ± 11 mins, p<0.005). A smaller study using a 200 mg dose also showed increases in REM sleep, but to a lesser degree.⁵⁵ The smaller dose is probably preferable, since, according to anecdotal reports, higher doses may have a tendency to cause very vivid dreams or nightmares.

Dosage

Initial dosage for 5-HTP is usually 50 mg three times per day with meals. If the clinical response is inadequate after two weeks, dosage may be increased to 100 mg three times per day. For insomnia, the dosage is usually 100-300 mg before bedtime. Because some patients may experience mild nausea when initiating treatment with 5-HTP, it is advisable to begin with 50 mg doses and titrate upward.

Drug-Nutrient Interactions

Although no specific reports have been published, it is possible that 5-HTP, when taken in combination with either a selective serotonin reuptake inhibitor (SSRI) antidepressant such as fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), or fluvoxamine (Luvox), or an MAOI antidepressant such as phenelzine (Nardil) or tranylcypromine (Parnate) may cause a condition known as serotonin syndrome.⁵⁶ This syndrome has been reported in patients taking LT at doses above 1200 mg/day along with MAOIs, but was not identified in a 12-month study with 5-HTP (200 mg/day) taken in conjunction with an MAOI drug.³⁶

Serotonin syndrome is characterized by agitation, confusion, delirium, tachycardia, diaphoresis, and blood pressure fluctuations. Should serotonin syndrome be suspected, 5-HTP and any other precipitating drug (SSRI or MAOI) should be discontinued immediately. Because of the possibility of serotonin syndrome, 5-HTP should probably not be used in patients currently being treated with either

an SSRI or MAOI antidepressant. If it is used in conjunction with either of these prescription drugs, e.g. short-term dual therapy while changing over from an SSRI to 5-HTP, the practitioner and patient should be aware of the potential symptoms of this condition.

Contraindications

One additional concern regarding 5-HTP is the possibility of an eosinophilia-myalgia syndrome (EMS) similar to the illness linked to contaminated LT. The contamination identified in certain batches of LT has been related to production methods using bacterial fermentation and subsequent inadequate filtration. This is unlikely to occur with 5-HTP, since it is produced by extraction from plant sources. Two cases of EMS-like symptoms have been described in patients taking 5-HTP. One case reported in 1980 involved the use of very high doses (1400 mg daily).⁵⁷ Because contamination of LT was not identified as a factor in EMS until 1990, the product consumed by this patient was not tested for contamination. The second case involved a mother and two children who were confirmed to have taken contaminated 5-HTP.⁵⁸

Because of the possibility of serotonin syndrome (see above), 5-HTP should be used with caution in patients currently being treated or who have recently been treated with either an SSRI or an MAOI antidepressant.

There are no adequate, well-controlled studies on the use of 5-HTP in pregnancy, therefore, it should not be used while pregnant.

Side Effects

Some patients may initially experience mild nausea when taking 5-HTP. This effect is usually transitory, and is best dealt with by initiating therapy at low doses (50 mg three times daily) and increasing the dosage gradually if necessary.

References

1. Maes M, Jacobs MP, Suy E, et al. Effects of dexamethasone on the availability of L-tryptophan and on the insulin and FFA concentrations in unipolar depressed patients. *Biol Psychiatry* 1990;27:854-862.
2. Krieger IE. Acrodermatitis enteropathica and the relationship to pellagra. *Med Hypothesis* 1981;7:539-547.
3. Green AR, Aronson JK, Curzon G, Woods HF. Metabolism of an oral tryptophan load. I: Effects of dose and pretreatment with tryptophan. *Br J Clin Pharmacol* 1980;10:603-610.
4. Gal EM, Sherman AD. L-kynurenine: its synthesis and possible regulatory function in brain. *Neurochem Res* 1980;5:223-239.
5. Magnussen IE, Nielsen-Kudsk F. Bioavailability and related pharmacokinetics in man of orally administered L-5-hydroxytryptophan in a steady state. *Acta Pharmacol Toxicol* 1980;46:257-262.
6. Magnussen I, Jensen TS, Rand JH, Van Woert MH. Plasma accumulation of metabolism of orally administered single dose L-5-hydroxytryptophan in man. *Acta Pharmacol Toxicol* 1981;49:184-189.
7. van Praag HM, Lemus C. Monoamine precursors in the treatment of psychiatric disorders. In: Wurtman RJ, Wurtman JJ, eds. *Nutrition and the Brain*. New York: Raven Press; 1986:89-139.
8. den Boer JA, Westenberg HG. Behavioral, neuroendocrine, and biochemical effects of 5-hydroxytryptophan administration in panic disorder. *Psychiatry Res* 1990;31:267-278.
9. Chadwick D, Jenner P, Harris R, et al. Manipulation of brain serotonin in the treatment of myoclonus. *Lancet* 1975;2:434-435.
10. Guilleminault C, Tharp BR, Cousin D. HVA and 5HIAA CSF measurements and 5HTP trials in some patients with involuntary movements. *J Neurol Sci* 1973;18:435-441.
11. Sano I. L-5-hydroxytryptophan-(L-5-HTP) therapy. *Folia Psychiatr Neurol Jpn* 1972;26:7-17.
12. Fujiwara J, Otsuki S. Subtype of affective psychoses classified by response on amineprecursors and monoamine metabolism. *J Oral Pathol* 1973;2:93-100.

13. Matussek N, Angst J, Benkert O, et al. The effect of L-5-hydroxytryptophan alone and in combination with a decarboxylase inhibitor (Ro-4-4602) in depressive patients. *Adv Biochem Psychopharmacol* 1974;11:399-404.
14. Takahashi S, Kondo H, Kato N. Effect of L-5-hydroxytryptophan on brain monoamine metabolism and evaluation of its clinical effect in depressed patients. *J Psychiatr Res* 1975;12:177-187.
15. Nakajima T, Kudo Y, Kaneko Z. Clinical evaluation of 5-hydroxy-L-tryptophan as an antidepressant drug. *Folia Psychiatr Neurol Jpn* 1978;32:223-230.
16. van Hiele LJ. L-5-Hydroxytryptophan in depression: the first substitution therapy in psychiatry? The treatment of 99 out-patients with 'therapy-resistant' depressions. *Neuropsychobiology* 1980;6:230-240.
17. Kaneko M, Kumashiro H, Takahashi Y, Hoshino Y. L-5HTP treatment and serum 5-HT level after L-5-HTP loading on depressed patients. *Neuropsychobiology* 1979;5:232-240.
18. van Praag HM, Korf J, Dols LCW, Schut T. A pilot study of the predictive value of the probenecid test in the application of 5-hydroxytryptophan as an antidepressant. *Psychopharmacologia* 1972;25:14-21.
19. Brodie HKH, Sack R, Siever L. Clinical studies of L-5-hydroxytryptophan in depression. In: Barchas J, Usdin E, eds. *Serotonin and Behavior*. New York: Academic Press; 1973:549-559.
20. Barlet P, Pailard P. Etude clinique du 5-hydroxytryptophane dans les états dépressifs du troisième âge. *Cah Med Lyon* 1973;50:1985-1901. [Article in French]
21. Lopez-Ibor Alino JJ, Ayuso Guitierrez JL, Montejo Iglesias ML. 5-Hydroxytryptophan (5-HTP) and a MAOI (Nialamide) in the treatment of depressions. *Int Pharmacopsychiat* 1976;11:8-15.
22. van Praag HM. Central serotonin: Its relation to depression vulnerability and depression prophylaxis. In: Obiols J, Ballus C, Gonzalez Monclus E, Pujol J, eds. *Biological Psychiatry Today*. Amsterdam: Elsevier/North-Holland; 1979:485-498.
23. van Praag HM. Precursors of serotonin, dopamine and norepinephrine in the treatment of depression. In: Lemberger L, Reidenberg MM, eds. *Proceedings of the Second World Conference on Clinical Pharmacology and Therapeutics*. Maryland: American Society for Pharmacology and Experimental Therapeutics; 1984:541.
24. Mendlewicz J, Youdim MB. Antidepressant potentiation of 5-hydroxytryptophan by L-depre-nil in affective illness. *J Affect Disord* 1980;2:137-146.
25. Poldinger W, Calanchini B, Schwarz W. A functional-dimensional approach to depression: serotonin deficiency as a target syndrome in a comparison of 5-hydroxytryptophan and fluvoxamine. *Psychopathology* 1991;24:53-81.
26. Agren H, Reibring L, Hartvig P, et al. Low brain uptake of L-(11C)5-hydroxytryptophan in major depression: A positron emission tomography study on patients and healthy volunteers. *Acta Psychiatr Scand*. 1991;83:449-455.
27. van Praag HM, Van Den Burg W, Bos ERH, Dols LCA. 5-hydroxytryptophan in combination with clomipramine in "therapy-resistant" depression. *Psychopharmacology*. 1974;38:267-269.
28. Nardini M, DeStefano R, Ianuccelli M, et al. Treatment of depression with L-5-hydroxytryptophan combined with clomipramine: A double-blind study. *J Clin Pharmacol Res* 1983;3:239-250.
29. Angst J, Woggon B, Schoepf J. The treatment of depression with L-5-hydroxytryptophan versus imipramine. Results of two open and one double-blind study. *Arch Psychiatr Nervenkr* 1977;224:175-186.
30. Wolfe F, Russell IJ, Vipraio G, et al. Serotonin levels, pain threshold, and fibromyalgia symptoms in the general population. *J Rheumatol* 1997;24:555-559.
31. Startz T, Samborski W, Hrycaj P, et al. Serotonin concentration in serum of patients with generalized tendomyopathy (fibromyalgia) and chronic polyarthritis. *Med Klin* 1993;88:458-462.
32. Yunus MB, Dailey JW, Aldag JC, et al. Plasma tryptophan and other amino acids in primary fibromyalgia: a controlled study. *J Rheumatol* 1992;19:90-94.
33. Russell IJ, Michalek JE, Vipraio GA, et al. Serum amino acids in fibrositis/fibromyalgia syndrome. *J Rheumatol Suppl* 1989;19:158-163.
34. Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996;39:1852-1859.

35. Bryson HM, Wilde MI. Amitriptyline. A review of its pharmacological properties and therapeutic use in chronic pain states. *Drugs Aging* 1996;8:459-476.
36. Nicolodi M, Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. Serotonin as the common clue for pathogenesis and therapy. *Adv Exp Med Biol* 1996;398:373-379.
37. Puttini PS, Caruso I. Primary fibromyalgia syndrome and 5-hydroxy-L-tryptophan: a 90-day open study. *J Int Med Res* 1992;20:182-189.
38. Caruso I, Puttini PS, Cazzola M, Azzolini V. Double-blind study of 5-hydroxytryptophan versus placebo in the treatment of primary fibromyalgia syndrome. *J Int Med Res* 1990;18:201-209.
39. Goodwin GM, Cowen PJ, Fairburn CG, et al. Plasma concentrations of tryptophan and dieting. *BMJ* 1990;300:1499-1500.
40. Schweiger U, Laessle R, Kittl S, et al. Macronutrient intake, plasma large neutral amino acids and mood during weight-reducing diets. *J Neural Transm* 1986;67:77-86.
41. Anderson IM, Parry-Billings M, Newsholme EA, et al. Dieting reduces plasma tryptophan and alters brain 5-HT function in women. *Psychol Med* 1990;20:785-791.
42. Cangiano C, Ceci F, Cascino A, et al. Eating behavior and adherence to dietary prescriptions in obese adult subjects treated with 5-hydroxytryptophan. *Am J Clin Nutr* 1992;56:863-867.
43. Cangiano C, Ceci F, Cairella M, et al. Effects of 5-hydroxytryptophan on eating behavior and adherence to dietary prescriptions in obese adult subjects. *Adv Exp Med Biol* 1991;294:591-593.
44. Ceci F, Cangiano C, Cairella M, et al. The effects of oral 5-hydroxytryptophan administration on feeding behavior in obese adult female subjects. *J Neural Transm* 1989;76:109-117.
45. Fioroni L, Andrea GD, Alecci M, et al. Platelet serotonin pathway in menstrual migraine. *Cephalalgia* 1996;16:427-430.
46. Lance JW. 5-Hydroxytryptamine and its role in migraine. *Eur Neurol* 1991;31:279-281.
47. Maissen CP, Ludin HP. Comparison of the effect of 5-hydroxytryptophan and propranolol in the interval treatment of migraine. *Schweiz Med Wochenschr* 1991;121:1585-1590.
48. De Giorgis G, Miletto R, Iannuccelli M, et al. Headache in association with sleep disorders in children: a psychodiagnostic evaluation and controlled clinical study—L-5-HTP versus placebo. *Drugs Exp Clin Res* 1987;13:425-433.
49. Titus F, Davalos A, Alom J, Codina A. 5-Hydroxytryptophan versus methysergide in the prophylaxis of migraine. Randomized clinical trial. *Eur Neurol* 1986;25:327-329.
50. De Benedittis G, Massei R. Serotonin precursors in chronic primary headache. A double-blind cross-over study with L-5-hydroxytryptophan vs. placebo. *J Neurosurg Sci* 1985;29:239-248.
51. Longo G, Rudoi I, Iannuccelli M, et al. Treatment of essential headache in developmental age with L-5-HTP (cross over double-blind study versus placebo). *Pediatr Med Chir* 1984;6:241-245.
52. Bono G, Criscuoli M, Martignoni E, et al. Serotonin precursors in migraine prophylaxis. *Adv Neurol* 1982;33:357-363.
53. Soulairac A, Lambinet H. Effect of 5-hydroxytryptophan, a serotonin precursor, on sleep disorders. *Ann Med Psychol* 1977;1:792-798.
54. Guilleminault C, Cathala JP, Castaigne P. Effects of 5-hydroxytryptophan on sleep of a patient with a brain-stem lesion. *Electroencephalogr Clin Neurophysiol* 1973;34:177-184.
55. Wyatt RJ, Zarcone V, Engelman K, et al. Effects of 5-hydroxytryptophan on the sleep of normal human subjects. *Electroencephalogr Clin Neurophysiol* 1971;30:505-509.
56. Martin TG. Serotonin Syndrome. *Ann Emerg Med* 1996;28:520-526.
57. Sternberg EM, Van Woert MH, Young SN, et al. Development of a scleroderma-like illness during therapy with L-5-hydroxytryptophan and carbidopa. *N Engl J Med* 1980;303:782-787.
58. Michelson D, Page SW, Casey R, et al. An eosinophilia-myalgia syndrome related disorder associated with exposure to L-5-hydroxytryptophan. *J Rheumatol* 1994;21:2261-2265.