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Serotonin a la carte: Supplementation with the serotonin precursor 5-hydroxytryptophan

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Abstract

This paper reviews the preclinical and clinical evidence regarding the use of the dietary supplement 5-hydroxytryptophan (5-HTP) for the treatment of depression. In the absence of supplementation with exogenous 5-HTP, the amount of endogenous 5-HTP available for serotonin synthesis depends on the availability of tryptophan and on the activity of various enzymes, especially tryptophan hydroxylase, indoleamine 2,3-dioxygenase, and tryptophan 2,3-dioxygenase (TDO). Factors affecting each of these are reviewed. The amount of 5-HTP reaching the central nervous system (CNS) is affected by the extent to which 5-HTP is converted to serotonin in the periphery. This conversion is controlled by the enzyme amino acid decarboxylase, which, in the periphery, can be blocked by peripheral decarboxylase inhibitors (PDIs) such as carbidopa. Preclinical and clinical evidence for the efficacy of 5-HTP for depression is reviewed, with emphasis on double-blind, placebo-controlled (DB-PC) trials. Safety issues with 5-HTP are also reviewed, with emphasis on eosinophilia myalgia syndrome (EMS) and serotonin syndrome.
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Keywords: Serotonin; Antidepressants; 5-HTP; Tryptophan; Depression; Selective serotonin re-uptake inhibitor

Abbreviations: 5-HIAA, 5-hydroxyindole acetic acid; 5-HTP, L-5-hydroxytryptophan; AADC, aromatic L-amino acid decarboxylase; BH$_4$, L-erythro-tetrahydrobiopterin; BID, twice per day; CNS, central nervous system; EMS, eosinophilia myalgia syndrome; FDA, Food and Drug Administration; HAM-D, Hamilton Depression Rating scale; HPLC, high-performance liquid chromatography; IDO, indolamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; MAOI, monoamine oxidase inhibitor; PDI, peripheral decarboxylase inhibitor; PET, positron emission tomography; QID, 4 times per day; SNP, single-nucleotide polymorphism; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant; TDO, tryptophan 2,3-dioxygenase; TID, 3 times per day; TNF, tumor necrosis factor; TPH1 and TPH2, tryptophan hydroxylase genes.

Contents

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1. Introduction

The synthesis of serotonin from tryptophan proceeds via the intermediary L-5-hydroxytryptophan (5-HTP; Fig. 1). The purpose of this paper is to review the preclinical and clinical evidence for the use of the dietary supplement 5-HTP in the treatment of depression.

5-HTP is an aromatic amino acid naturally produced by the body from the essential amino acid L-tryptophan. Produced commercially by extraction from the seeds of the African plant *Griffonia simplicifolia*, 5-HTP has been used clinically for over 30 years. In addition to depression, the therapeutic administration of 5-HTP has been shown to be effective in treating a wide variety of conditions, including fibromyalgia, insomnia, binge eating associated with obesity, cerebellar ataxia, and chronic headaches (reviewed by Birdsall, 1998). 5-HTP easily crosses the blood–brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin (Birdsall, 1998). Supplementation with 5-HTP is hypothesized to normalize serotonin synthesis, which is putatively related to its antidepressant properties (see Section 2.1). However, most of the studies involving the use of 5-HTP for depression were conducted 20 or more years ago. At that time, there was a high level of interest in the serotonin hypothesis of depression. In December of 1987, the first selective

serotonin re-uptake inhibitor (SSRI)–fluoxetine (Prozac)–was approved in the United States. Other SSRIs quickly followed. This new class of antidepressants became widely prescribed, as they were found to be both generally effective and safe. It is possible that this series of events led to a loss of interest in 5-HTP.

2. Rationale for use of 5-hydroxytryptophan in depression

2.1. Serotonin hypothesis of depression

The serotonin hypothesis of major depression has been formulated in several different ways. One version of this hypothesis is that a deficit in serotonergic activity is related to the etiology of depression. Based on this hypothesis, the goal of antidepressant treatment is to increase synaptic serotonin levels. Serotonin re-uptake inhibitors increase synaptic serotonin levels by inhibiting re-uptake. However, many, if not most, antidepressants have serotonin re-uptake inhibition as part of their mechanisms—not just SSRIs. Many tricyclic antidepressants (TCAs) are nonselective serotonin re-uptake inhibitors (Richelson, 1994). Monoamine oxidase inhibitors (MAOIs), another type of antidepressant medication,
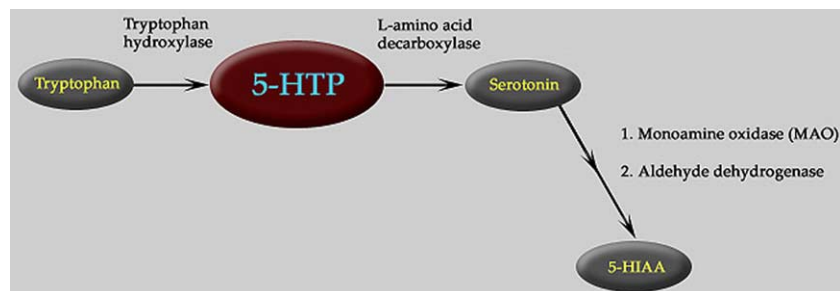

Fig. 1. Flow chart illustrating the biosynthesis and metabolism of 5-HTP. The enzymes involved in the process are shown to the right of the arrows. Abbreviations: 5-HTP: L-5-hydroxytryptophan; 5-HIAA: 5-hydroxyindoleacetic acid.

increase synaptic serotonin by decreasing the catabolism of serotonin (Fig. 1).

2.1.1. Factors affecting 5-hydroxytryptophan availability for serotonin synthesis

The amount of synaptic serotonin can also be affected by the availability of substrate for serotonin synthesis. Although other neurotransmitters, notably catecholamines, are involved in mood regulation, the studies reviewed in this section suggest that normal mood depends in large part on normal serotonin stores.

2.1.1.1. Tryptophan. Tryptophan is the amino acid precursor to 5-HTP and serotonin (Fig. 1). There are several reports that plasma tryptophan is significantly lower in patients with major depression than in normal controls or in patients with only minor symptoms of depression (Coppen et al., 1973; Cowen et al., 1989). Furthermore, administration of tryptophan has been used as an antidepressant (reviewed by Shaw et al., 2002).

Tryptophan depletion is a widely used paradigm to study the role of the serotonergic system in the pathophysiology and treatment of depression (Neumeister, 2003). The administration of a tryptophan-free mixture of essential amino acids produces a significant decrease in plasma tryptophan, associated with a decrease in brain tryptophan, brain serotonin, and 5-hydroxyindole acetic acid (5-HIAA) levels in rats (Gessa et al., 1974). In humans, several studies have shown that reducing serotonin synthesis (by depriving the brain of tryptophan) can induce depression within hours (Neumeister et al., 1998; Delgado et al., 1990; Lam et al., 1996). Similarly, after oral administration of an amino acid mixture without tryptophan, significant decreases of plasma tryptophan and cerebrospinal fluid levels of 5-HIAA have been reported (Young et al., 1985; Williams et al., 1999). It has also been shown that increases in brain tryptophan concentration raise serotonin release (Carboni et al., 1989). Taken together, these data suggest that the concentration of 5-HTP and serotonin depend upon the availability of its precursor tryptophan.

2.1.1.2. Tryptophan 2,3-dioxygenase/Indolamine 2,3-dioxygenase. Tryptophan availability and, therefore, 5-HTP and serotonin synthesis are also influenced by the enzymes indolamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO; Fig. 2). IDO is the first enzyme in the kynurenine pathway, which degrades and converts tryptophan to kynurenine; it is found in various tissues such as lung, brain, and placenta (Sun, 1989; Saito et al., 1991; Heyes et al., 1992). TDO is a cytosolic enzyme analogous to IDO, with the exception that TDO is believed to be specific to the liver; TDO also plays a critical role in the regulation of circulating levels of tryptophan (Smith & Pogson, 1980).

Stimulation of these enzymes by proinflammatory cytokines, in particular interferon-γ (IFN-γ), enhances the catabolism of tryptophan, making less tryptophan available for conversion to 5-HTP and serotonin (Taylor & Feng, 1991; Myint & Kim, 2003). Corticoids have also been shown to induce TDO activity (Salter & Pogson, 1985), which is important given that a number of patients with depression have elevated cortisol levels (Porter et al., 2004). 680C91 and 709W92 are competitive inhibitors of TDO ($K_i = 42 \pm 3$ and 40 ± 2 nM, respectively; Salter et al., 1995). Using these novel compounds, the authors found that TDO inhibition increased CSF serotonin levels in rats (Salter et al., 1995). These findings suggest an important role for TDO and IDO in the regulation of 5-HTP and serotonin synthesis.

2.1.1.2.1. Tryptophan's effect on tryptophan 2,3-dioxygenase and indolamine 2,3-dioxygenase. Tryptophan can also regulate its own catabolism via the induction of TDO or IDO. At supraphysiologic concentrations, tryptophan increases the activity of TDO 5- to 6-fold in rat hepatocytes (Smith & Pogson, 1980). Thus, increased dietary intake of tryptophan may not ultimately lead to increased 5-HTP and serotonin levels.
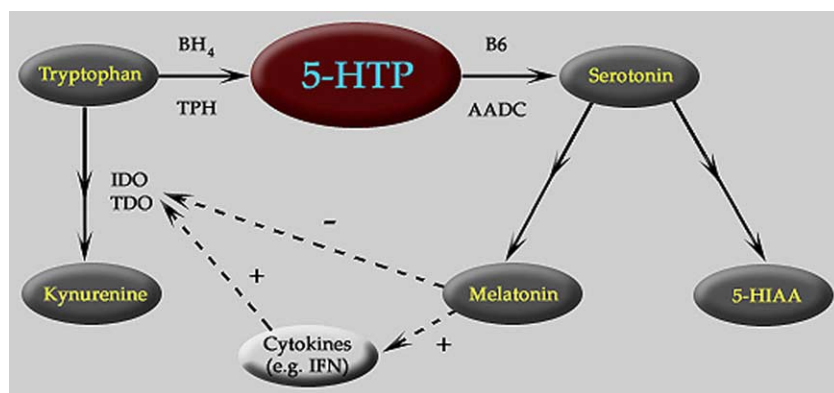
Fig. 2. Biochemical regulation of 5-HTP. The enzymes and cofactors involved in the reactions are listed next to the bold black arrows. Based on literature reviewed in the text, the dashed arrows and the plus and minus signs indicate increases or decreases in the metabolites shown. Abbreviations: AADC: aromatic L-amino acid decarboxylase; B6: pyridoxine; BH$_4$: L-*erythro*-tetrahydrobiopterin; 5-HIAA: 5-hydroxyindoleacetic acid; 5-HTP: L-5-hydroxytryptophan; IDO: indolamine 2,3-dioxygenase; IFN: interferon; TDO: tryptophan 2,3-dioxygenase; TPH: tryptophan hydroxylase.

2.1.1.2.2. Cytokines and indolamine 2,3-dioxygenase. There is evidence that the induction of cytokines, a family of proteins that mediate and regulate immunity, inflammation, and hemopoiesis, can modulate the availability of 5-HTP (Fig. 2). Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-2, and IFN-γ affect serotonin metabolism by stimulating or enhancing the stimulation of IDO, which leads to a peripheral depletion of tryptophan, which, in turn, leads to depletion of 5-HTP and serotonin (Carlin et al., 1989; Babcock & Carlin, 2000; Fig. 2). In particular, exogenous administration of IFN-α has been shown to cause depression in some patients (Musselman et al., 2001; Hauser et al., 2002; Loftis & Hauser, 2004). This IFN-induced depression has been attributed to the activation of the cytokine network (i.e., IFN-γ) and IDO, resulting in perturbations of the serotonergic system (Menkes & MacDonald, 2000; Bonaccorso et al., 2002; Capuron et al., 2003; Turner & Blackwell, 2005). In agreement with these findings, IFN-α treatment increases the kynurenine-to-tryptophan ratio, which estimates the activity of IDO, suggesting potentiated 5-HTP and serotonin catabolism (Bonaccorso et al., 2002). Thus, IFN-α may induce depression by a serotonergic-related mechanism (Schaefer et al., 2003; Wichers & Maes, 2004). To the extent that this is the mechanism for IFN-induced depression, it should be treatable with exogenous 5-HTP (Menkes & MacDonald, 2000; Turner & Blackwell, 2005).

2.1.1.2.3. Melatonin and tryptophan 2,3-dioxygenase. Melatonin, a hormone synthesized from serotonin in the pineal gland, can competitively inhibit TDO (Walsh et al., 1994; Walsh & Daya, 1997). Furthermore, the administration of melatonin to mice results in the up-regulation of the gene expression of TNF-α in peritoneal exudate cells and the up-regulation of gene expression of IL-1β, TNF-α, and IFN-γ in splenocytes (Liu et al., 2001), suggesting that melatonin contributes to the induction of proinflammatory cytokines, which may regulate the catabolism of tryptophan and ultimately the biosynthesis of 5-HTP and serotonin (Fig. 2).

2.1.1.3. Tryptophan hydroxylase. L-Tryptophan-5-monooxygenase, more commonly termed tryptophan hydroxylase, is the rate-limiting enzyme in neuronal serotonin synthesis (Kuhar et al., 1999). Tryptophan hydroxylase can be inhibited by numerous factors, including stress, insulin resistance, pyridoxine (vitamin B6) deficiency, insufficient magnesium, and high dosages of tryptophan (Green et al., 1980; Krieger, 1981; Maes et al., 1990). In addition, these same factors can increase the conversion of tryptophan to kynurenine, making tryptophan unavailable for 5-HTP and serotonin production (Birdsall, 1998).

Tryptophan hydroxylase requires the cofactor L-*erythro*-tetrahydrobiopterin (BH$_4$). Mice treated with 2,4-diamino-6-hydroxypyrimidine (DAHP), an inhibitor of BH$_4$ synthesis, have decreased serotonin levels in certain organs in the periphery, but not in the brain (Kobayashi et al., 1991).

Recently, there have been a number of reports regarding the association of genetic polymorphisms in the tryptophan hydroxylase genes (TPH1 and TPH2) with the serotonergic system (Arango et al., 2003; Harvey et al., 2004). TPH1 is mainly expressed in the periphery (Walther et al., 2003), while TPH2 is preferentially expressed in the brain (Zhang et al., 2004). Zhang et al. (2004) described a functional single-nucleotide polymorphism (SNP) in mouse TPH2 which leads to decreased serotonin levels in PC12 cells (a cell line commonly used as a neuronal cellular model). In a subsequent paper, these investigators reported the identification of a functional SNP in human TPH2 (hTPH2), which results in $\sim 80\%$ loss of function in serotonin production when hTPH2 is expressed in PC12 cells (Zhang et al., 2005).

The tryptophan hydroxylase genes, TPH1 and TPH2, have been tested in a series of association studies for their role in mood disorders and psychiatric symptoms. Zhang et al. (2005) found an increased frequency of the hTPH2 SNP among depressed patients compared with nondepressed controls. This is in agreement with Zill et al. (2004), who report a significant association with one of the SNPs in the TPH2 gene and major depression. A recent review indicates that alterations in these genes may be related to suicidal behavior (Preisig et al., 2005). Collectively, these findings support a critical role for tryptophan hydroxylase in the regulation of 5-HTP synthesis and mood.

2.1.1.4. L-Amino acid decarboxylase. 5-HTP is converted to serotonin by the enzyme aromatic L-amino acid decarboxylase (AADC), an enzyme that catalyzes the decarboxylation of a variety of aromatic L-amino acids; it converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine and 5-HTP to serotonin (Boadle-Biber, 1993). This enzyme acts both in the periphery and in the CNS, meaning that ingested 5-HTP can be converted into serotonin in the periphery of the body. Such peripheral serotonin cannot influence CNS serotonin levels because serotonin is unable to cross the blood–brain barrier. Additionally, it depletes substrate levels, resulting in little 5-HTP reaching the brain. Administration of decarboxylase inhibitors such as carbidopa blocks this peripheral conversion (see Section 4.2.2, "Coadministration of carbidopa").

Pyridoxine (vitamin B6) is a cofactor for AADC that has also been shown to regulate the levels of 5-HTP (Calderon-Guzman et al., 2004). In patients with AADC deficiency, 1 of the main goals for the management of the condition is to potentiate monoaminergic transmission. In a paper describing the treatment and outcomes of patients with AADC deficiency, all patients received pyridoxine supplementation; however, direct clinical benefit was not reported (Swoboda et al., 2003). Nevertheless, supplemental intake of pyridoxine has been suggested to improve mood (reviewed by Ellis & Pamplin, 1999, and McCarty, 2000). A recent study found that low plasma levels of pyridoxal phosphate (the phosphate derivative of pyridoxine) were

significantly associated with depression rating scale scores, suggesting that low pyridoxine levels may be related to symptoms of depression (Hvas et al., 2004).

3. Evidence for antidepressant efficacy of 5-hydroxytryptophan

3.1. Preclinical evidence for efficacy of 5-hydroxytryptophan

5-HTP is commonly given to rats or mice to test the SSRI potency of putative antidepressants (O'Neil & Moore, 2003). This simple in vivo test measures the potency of a compound in potentiating the serotonin syndrome induced by the administration of 5-HTP (Grahame-Smith, 1971). The behavioral and physiological features of this syndrome include hypolocomotion, head twitch, forepaw treading, tremors, hindlimb abduction, flat body posture or hunched back, cyanosis, and hyperthermia. In rodents, 5-HTP induces a serotonin syndrome at dosages of 100–200 mg/kg (Casal et al., 2000; Nisijima et al., 2000, 2001; see Section 4.4.3 for more on serotonin syndrome). This 5-HTP-induced syndrome is potentiated by SSRIs. Consequently, putative antidepressants can be tested for their degree of potentiation of the 5-HTP-induced syndrome. This test has been shown to have predictive validity for antidepressant action. In particular, it predicts the ability of the compound to inhibit serotonin re-uptake and the compound's efficacy as an antidepressant.

Although 5-HTP has not been directly investigated as an "antidepressant" compound in rodents, 5-HTP has been used to manipulate serotonin levels in rats. Behavioral studies show that 5-HTP administration reverses the increases in avoidance responding induced by sleep deprivation and serotonin depletion in rats (Tenen, 1967; Tanaka et al., 1972; Smith & Kennedy, 2003). Taken together, these findings indicate that 5-HTP attenuates the hyperalgesia induced by sleep deprivation, thus suggesting that the administration of 5-HTP restores serotonin levels in rats.

3.2. Clinical evidence for antidepressant efficacy of 5-hydroxytryptophan

3.2.1. Study designs used

Definitive, large-scale studies of efficacy and safety have not been conducted for 5-HTP. In conducting our own review of the literature, we were able to identify 27 studies that evaluated the efficacy of 5-HTP for depression (total $N = 990$). Because these studies were heterogeneous in terms of design, duration, and dose, meta-analysis is not feasible. We therefore employed a descriptive approach, broadly categorizing these studies according to design.

Eleven of these studies were double-blind, placebo-controlled (DB-PC) studies (Table 1). Among the 11 DB-PC studies, the authors reported that 5-HTP was superior to placebo in 7 of them. However, the sample sizes in all these studies were quite small, and only 5 of these studies were able to show statistical significance. Of these, 1 was a monotherapy relapse prevention study (van Praag & de Haan, 1981), 3 were augmentation studies (Alino et al., 1976; Nardini et al., 1983; Quadbeck et al., 1984), and 1 tested a 5-HTP/dopamine agonist combination against placebo, rather than 5-HTP alone (Rousseau, 1987).

A number of open-label studies have also been done, although given the study design, these results are largely uninterpretable (Table 2). Investigators have also done at least 5 active comparator studies (Table 3). Two of these studies failed to show any difference between 5-HTP and the comparator, imipramine (Angst et al., 1977), or fluvoxamine (Poldinger et al., 1991), while 2 determined that 5-HTP was less effective than tranylcypromine for treatment-resistant depression (Nolen et al., 1985, 1988). One compared 5-HTP alone versus 5-HTP and a peripheral decarboxylase inhibitor (PDI), with neither group showing much improvement (Brodie et al., 1973).

3.2.2. Strength of efficacy data

Overall, it is difficult to draw any definitive conclusions regarding the efficacy of 5-HTP for depression, given the limitations described earlier (Section 3.2.1, "Study designs used"). Only a few studies, most of them augmentation studies, were of sufficient quality to show statistical superiority to placebo. Alino et al. (1976) conducted a small double-blind, placebo-controlled trial comparing nialamide and 5-HTP with nialamide and placebo. This study involved 30 psychiatric inpatients diagnosed with "endogenous" depression. After 15 days, the group exposed to the combination with 5-HTP had a mean Hamilton Depression Rating scale (HAM-D) reduction of 58% versus 39% for the nialamide and placebo group. Twelve of 14 were rated as definitely improved or in complete remission, compared with only 6 of 15 in the placebo group. Both results were significant. A similar augmentation study was conducted by Nardini et al. (1983). The combination of clomipramine and 5-HTP was compared against clomipramine and placebo in a 28-day trial. Of the 24 patients who completed the trial, 13 were given 5-HTP and 11 placebo. The 5-HTP group showed a 56% decrease in HAM-D, while the placebo group mean HAM-D decreased by 41%. Quadbeck et al. (1984) compared 3 groups of 8 patients, 1 receiving tryptophan, another trypophan and 5-HTP, and the last group, low-dose nomifensine. In this study, the group given 5-HTP and tryptophan showed the greatest improvement, with a mean HAM-D decrease of 61% versus 38% for tryptophan alone and 27% for low-dose nomifensine.

Three monotherapy studies showed statistical superiority of 5-HTP over placebo. van Praag et al. (1972) treated 10 patients in a double-blind comparison; 5 patients in the 5-HTP group showed a mean decrease in HAM-D of 35% versus a 6% increase for the placebo group. The difference

Table 1
Double-blind, placebo-controlled trials of 5-HTP for depression

Author/year	N	Patients	Design	Dose (mg/day)	Dose schedule	Duration (days)	Results by drug group		5-HTP better than placebo?	Statistically significant?
							5-HTP	Placebo		
Alino et al., 1976 (a.k.a. Lopez-Ibor)	30	Unipolar	5-HTP vs. placebo Augmentation of nialamide (MAOI)	50–300	BID	15–20	12/14 Markedly improved 58% Reduction in HAM-D after 15 days	6/15 Markedly improved 39% Reduction in HAM-D	Yes	Yes
Barlet & Pailard, 1973	25 in 5-HTP group	Unipolar	5-HTP vs. placebo	200–800	?	10–240	19 of 25 improved	Placebo rate not known	?	?
Mendlewicz & Youdim, 1980	58	34: Bipolar 24: Unipolar	5-HTP and MAOI vs. 5-HTP vs. Placebo	300	?	32	5-HTP and MAOI better than placebo, 5-HTP alone not better	Same as 5-HTP	No	?
Nardini et al., 1983	26	Unipolar	5-HTP vs. placebo Augmentation of clomipramine	300	?	28	56% Reduction in HAM-D 7/13 Marked improvement (CGI) 0/13 Worsened	Clomipramine 41% Reduction HAM-D 4/11 Marked improvement (CGI) 2/11 Worsened	Yes	Yes
Rousseau, 1987	50	Elderly depressed	Dihydroergocristine (DA) and 5-HTP vs. placebo	200–300	BID-TID depending on dose	60	12% Reduction in HAM-D	1% Increase in HAM-D	Yes	Yes
van Praag et al., 1972	10	Severely depressed	5-HTP vs. placebo	200–3000	?	21	34% Reduction in HAM-D 3/5 Improved on 5-HTP	6% Increase in HAM-D 0/5 Improved on Placebo 2/5 Worse placebo	Yes	Trend (Fisher .08)
van Praag, 1979	20 in 5-HTP group	Unipolar and bipolar	5-HTP vs. clomipramine vs. placebo	200	?	21	11/20, 5-HTP group	Clomipramine equally effective Placebo rate not known	?	?
van Praag & de Haan, 1981	20	14: Unipolar 6: Bipolar	Crossover, relapse, prevention	200	?	2 years (1 year on 5-HTP)	6/20 had relapses Relapse rate 0.35/patient Significantly less depressed over year	17/20 had relapses Relapse rate 1.2/patient	Yes	Yes
van Praag, 1984	15 in 5-HTP group	Unipolar and Bipolar	5-HTP vs. tryptophan vs. placebo	200	?	28	67% Reduction in HAM-D	30% Reduction in HAM-D placebo, 48% tryptophan	Yes	Yes
Quadbeck et al., 1984	24	Depressed	5-HTP and tryptophan vs. tryptophan vs. low-dose nomifensine	75–150	TID	21	5-HTP and tryptophan combination 61% Reduction in HAM-D	Tryptophan 38% reduction Low-dose nomifensine 27% Reduction	Yes	Yes
Zarcone et al., 1977	6	Treatment-resistant depression	5-HTP vs. placebo, non-random, crossover	500–3250	?	11–15 (5 days on 5-HTP)	2/6 Decrease in depressive ratings on 5-HTP	Unclear due to crossover design	Unclear	No

Abbreviations: DB: double-blind; PC: placebo-controlled; ?: not reported/not available; DA: dopamine agonist.

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Table 2
Open-label trials of 5-HTP for depression

	N	Patients	Notes	Dose (mg/day)	Dose schedule	Length (days)	Result
Fujiwara & Otsuki, 1973	20	Endogenous depression		50–200	?	7–28	10/20 Markedly improved
Kaneko et al., 1979	18	12: Unipolar; 3: bipolar; 3: first episode		150–300	?	10–28	10/18 Improved
Kline & Sacks, 1963	50	20: Classical depression; 30: schizoaffective	17 also taking MAOI	10–50 mg/ dose i.v.	Single dose	1	18/20 Typical depression marked improvement, 1 partial 7/30 Schizoaffective, marked 15/30 Partial
Kline et al., 1964	59	"Depressive element"	DB, 5-HTP vs. 5-HTP	100–200 i.v.	QID	1	11/31 marked; 6/31 partial;14/31 no change
Kline & Sacks, 1980	25	Depression resistant to MAOIs		100–300	?	"A few hours– A few days"	11/25 Marked 8/25 Partial
Matussek et al., 1974	23	21: Unipolar; 1: bipolar; 1: schizoaffective		300	TID	14	7/23 Good improvement or symptom-free
Nakajima et al., 1978	59	21: Bipolar; 17: unipolar; 9: presenile or senile; 4: neurotic; 7: other		150–300	?	21+	40 (67.8%) had favorable response (13 markedly)
Sano, 1972	107	Endogenous depression		50–300	?	7–35	74/107 Markedly improved
Takahashi et al., 1975	24	Unipolar depression		300	?	14	7/24 Markedly improved
van Hiele, 1980	99	44: Endogenous; 24: w/ endogenous features; 31: personal depression		50–600	Several small doses	Weeks–months	43 Complete recovery 8 Improved
Zmilacher et al., 1988	25	Depressed	5-HTP alone or with benserazide PDI	300	?	14	13/25 Very good or good improvement No difference between groups

Abbreviations: DB: double-blind; OL: open-label; PC: placebo-controlled; R: randomized; ?: not reported/not available; PDI: peripheral decarboxylase inhibitor.

was significant by independent *t* test ($t=2.37$, $P=0.05$). In a subsequent study, van Praag and de Haan (1981) studied relapse rates in a double-blind crossover trial and found that the 5-HTP-treated group had significantly fewer relapses. Table 4 summarizes the studies reviewed in which the efficacy of 5-HTP was at or near statistical significance.

Mendlewicz and Youdim (1980) reported the only study in which 5-HTP appears to have been clearly nonefficacious. They treated a combination of unipolar and bipolar patients with either 5-HTP alone, 5-HTP and a MAOI, or placebo. 5-HTP alone failed to show superiority to placebo, but the 5-HTP/MAOI combination was superior to placebo.

Together, these results suggest that 5-HTP may have at least limited efficacy in the treatment of depression because

there is replication of positive findings. However, there is always the possibility of Type I error. Additionally, only 2 of these studies examined 5-HTP as monotherapy, and it is entirely possible that 5-HTP may behave differently as an augmenting agent. Obviously, larger, better-controlled studies should be conducted to conclusively establish the effectiveness of 5-HTP.

One might question whether these positive studies should be "cancelled out" by the negative studies listed. However, it is common for antidepressant studies not to demonstrate superiority to placebo, even trials with large sample sizes (Stang et al., 2005). In 51 adequate and well-controlled trials submitted by pharmaceutical companies for U.S. regulatory approval, drugs eventually approved as antidepressants fail

Table 3
Active comparator studies

	N	Patients	Design	Dose (mg/day)	Dose schedule	Length (days)	5-HTP result	Active comparator	5-HTP beats comparator?	Statistically significant?
Angst et al., 1977	30	Endogenous depression	5-HTP vs. imipramine, R, DB	200–1200	?	20+	Performed equally, number improved not reported	Imipramine equally effective	Equal	No
Brodie et al., 1973	7	6: Psychotic depression; 1: schizoaffective	5-HTP vs. 5-HTP and PDI, Non-random	250–3250	?	1–15	1 Improved, none worsened	None improved	N/A	No
Nolen et al., 1985	44	Treatment-resistant depression	OL, 5-HTP vs. tranylcypromine, crossover	20–200	BID	28	0/17 Improved in 5-HTP group	Tranylcypromine: 15/26 improved	No	Yes
Nolen et al., 1988	47	Treatment-resistant depression	DB and OL, crossover between MAOI, tricyclic, and 5-HTP	20–200	BID	21	No improvement on 5-HTP	Tranylcypromine: 5/11 improved Nomifensine: no improvement	No	No/Yes
Poldinger et al., 1991	69	Unipolar Depression	R,DB, 5-HTP vs. fluvoxamine	300	TID	42	27/34 improved (CGI) 61% reduction in HAM-D	Fluvoxamine 23/29 Improved (CGI) 56% Reduction in HAM-D	Equal	No

Abbreviations: DB: double-blind; OL: open-label; PC: placebo-controlled; R: randomized; ?: not reported; N/A: not reported/not available; PDI: peripheral decarboxylase inhibitor.

to demonstrate statistical superiority to placebo roughly half of the time (Khan et al., 2003). Antidepressant drug trials are said to suffer from a lack of assay sensitivity (Temple & Ellenberg, 2000).

Among the active-controlled studies shown in Table 3, there are 2 studies (Angst et al., 1977; Poldinger et al., 1991) in which 5-HTP appeared to perform equally to the active comparator. However, because these studies lacked placebo arms, their interpretation is problematic. Although 1 interpretation is that the active treatments were equally effective, it is also possible that these treatments were equally ineffective (Stang et al., 2005). This is especially true in studies of depression (Khan et al., 2003).

4. Practical considerations for using 5-hydroxytryptophan

4.1. Brain imaging

In the early 1990s, 5-HTP labeled with [^{11}C] became available for studies using positron emission tomography (PET) to assess serotonin-related metabolic activity in the brain (Hartvig et al., 1992; Reibring et al., 1992). In addition to studying serotonin synthesis, [^{11}C]5-HTP has also been used to identify and detect neuroendocrine tumors. A recent review found that [^{11}C]5-HTP PET was better than computed tomography and somatostatin receptor scintigraphy for tumor visualization, and [^{11}C]5-HTP PET was also suggested as a possible tool for tumor therapy monitoring (Sundin et al., 2004). Another potential use for 5-HTP in brain imaging research is fluorine tagged 5-HTP for use with magnetic resonance studies. Dingman et al. (2004a) created this new compound as a probe for investigating neural development in chicks. Importantly, the authors found that administration of the fluorine tagged 5-HTP during development did not impair performance on a T-maze behavioral task (Dingman et al., 2004b).

More commonly, 5-HTP is used as a treatment or augmentation strategy to improve affective functioning. The practical considerations regarding this clinical use are discussed in the following Sections (4.2–4.4).

4.2. Dosage in previous human studies

While serotonin stores cannot be directly influenced, 5-HTP can be. It can be taken as a dietary supplement and is well absorbed from an oral dose, with about 70% ending up in the bloodstream (Magnussen & Nielsen-Kudsk, 1980; Magnussen et al., 1981). However, review of the literature reveals a lack of data on dosage and usage considerations. The doses used in the studies listed in Tables 1 Tables 2 Tables 3 Tables 4 ranged from 20 to 3250 mg/day, with the majority administering 5-HTP at doses between 200 and 300 mg/day, regardless of whether carbidopa or another medication was coadministered. Among the published studies of

Table 4
Subset of studies with 5-HTP superior to placebo at or near 0.05 level of significance

Author/year	Drug being augmented	HAM-D % decrease			Number improved		
		5-HTP (%)	PBO (%)	*P* value	5-HTP	PBO	*P* value (Fisher exact)
Alino et al., 1976	Nialamide (MAOI)	58	39	<.05 (*t* test)	12/14	6/15	.013
Nardini et al., 1983	Clomipramine (nSRI)	56	41	.05 (Mann–Whitney)	7/13	4/11	.23 (ns)
Quadbeck et al., 1984	Tryptophan	61	38	<.05 (ANCOVA)	Not reported	Not reported	Not reported
van Praag, 1984	None (monotherpay)	67	30	Significant (*P* value not reported)	Not reported	Not reported	Not reported
van Praag et al., 1972	None (monotherapy)	34	6 (increase)	.095 (trend; Mann–Whitney) .05 (independent samples *t* test)	3/5	0/5	.08 (trend)

	Design	Relapse rates					
		Number of relapses per patient			Number of relapsed patients		
		5-HTP	PBO	*P*	5-HTP	PBO	*P*
van Praag & de Haan, 1981	Relapse prevention; crossover, 1 year per tx	0.35	1.2	<.01 (McNemar) <.001 (sign test)	6/20	17/20	.0005

Abbreviations: HAM-D: Hamilton Depression Rating Scale; PBO: placebo; MAOI: monoamine oxidase inhibitor; nSRI: nonselective serotonin re-uptake inhibitor; DA: dopamine; tx: treatment; ?: not reported.

5-HTP for depression, many did not report the dosing schedule. Of the studies that did report a dosing schedule, 3 used a twice-per-day (BID) schedule (Alino et al., 1976; Nolen et al., 1985, 1988), 4 used a 3-times-per-day (TID) schedule (1 began with a BID schedule, then went to a TID schedule as dose was increased; Matussek et al., 1974; Quadbeck et al., 1984; Rousseau, 1987; Poldinger et al., 1991), and 1 used a 4-times-per-day (QID) schedule (Kline et al., 1964). Perhaps coincidentally, those that used TID dosing appeared to have better efficacy results. The recommended dosing frequency was TID in a recent review article (Birdsall, 1998).

4.2.1. Pharmacokinetic considerations

The half-life of 5-HTP is relatively short (4.3 ± 2.8 hr; Westenberg et al., 1982), and its time to maximal concentration is $1–2$ hr (Magnussen & Van Woert, 1982). With less frequent dosing, plasma levels tend to have higher peaks and lower troughs. Two studies have found that the incidence of nausea due to 5-HTP is decreased when smaller doses are used (van Hiele, 1980; Magnussen & Van Woert, 1982), suggesting that the rate of adverse events may be dose proportional. Compared with BID dosing, for any given total daily dose, TID dosing should tend to reduce the risk of adverse events. It is especially important to minimize the risk of serotonin syndrome if 5-HTP is to be coadministered with SSRIs or other serotonergic antidepressants (see Section 4.4.3, "Serotonin syndrome").

4.2.2. Coadministration of carbidopa

The conversion of 5-HTP to serotonin is regulated by the enzyme aromatic L-amino acid decarboxylase (Boadle-Biber, 1993), the same enzyme that regulates the conversion of L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine. Patients with Parkinson's disease often receive treatment with carbidopa–levodopa, a combination of the decarboxylase inhibitor carbidopa and L-DOPA. By blocking peripheral conversion of L-DOPA to dopamine in the periphery, more L-DOPA penetrates the blood–brain barrier. The same rationale exists for administering carbidopa along with 5-HTP. In a recent study of healthy volunteers, the addition of carbidopa resulted in a 14-fold increase in 5-HTP plasma levels (Gijsman et al., 2002). Efficacy studies have been conducted both with and without the addition of a peripheral decarboxylase inhibitor (PDI). However, there seems to be no consensus as to whether the addition increases the effect of 5-HTP (Zmilacher et al., 1988).

4.3. Commercial availability of 5-hydroxytryptophan

5-HTP is extracted from the *G. simplicifolia* plant of West Africa. It is typically available as the L-enantiomer, where most of the biological activity resides (Penn et al., 1977). It is usually sold as a crude extract of the plant or in 25, 50, or 100 mg pills. 5-HTP is available in Europe under the brand names oxitriptan and Ro-0783/B. In the United States, it is commercially available under the Dietary Supplement Health and Education Act of 1994. As a result, it is exempted from prior Food and Drug Administration (FDA) approval (in contrast to prescription pharmaceuticals) and is sold directly to the public, in health food stores, and other outlets, without prescription.

4.4. Safety issues regarding 5-hydroxytryptophan

4.4.1. Common adverse effects

The most common adverse effects of 5-HTP are gastrointestinal (GI) and include nausea, vomiting, and diarrhea. Less commonly, headache, insomnia, and palpi-

tations can occur. A study comparing 5-HTP to 5-HTP plus a peripheral decarboxylase inhibitor (PDI) found that GI side effects were dose dependent and that they occurred more frequently in patients receiving 5-HTP alone. This may be due to peripheral conversion of 5-HTP to serotonin, which increases gut motility. Such conversion is blocked by PDIs. In either case, GI effects are usually moderate and often lessen or disappear once a steady dosage is achieved. Intravenous administration of 200 to 300 mg of 5-HTP can induce confusion, memory impairment, and symptoms of behavioral activation (primarily anxiety). These effects are generally much more rare with oral doses, particularly at lower doses (reviewed by Byerley et al., 1987).

4.4.2. Eosinophilia myalgia syndrome

In 1989 and 1990, ingestion of contaminated L-tryptophan caused an epidemic of eosinophilia myalgia syndrome (EMS) that affected over 1500 people and caused at least 38 deaths (FDA, 1998). The FDA subsequently banned the sale of over-the-counter tryptophan. These cases sparked fears that 5-HTP might also cause EMS. However, as of August 1998, the FDA reported that only 10 cases of EMS possibly associated with 5-HTP had been documented worldwide, none resulting in death (FDA, 1998). No new cases of EMS have since been reported, and subsequent authors have noted that none of these cases has been definitively linked to 5-HTP, despite 20 years of use (Das et al., 2004).

In 1 of the reported cases, a high-performance liquid chromatography (HPLC) peak was detected and referred to as Peak X; the chemical structure of this contaminant was found to be similar to 2 case-implicated contaminants from L-tryptophan shown to cause EMS (Michelson et al., 1994) and was further identified as tryptophan-4,5-dione, a putative neurotoxin (Klarskov et al., 1999). In a 1998 study, 6 commercial preparations of 5-HTP were found to contain this impurity, but at levels between 1/7 and 1/34 of that observed in a case-implicated batch (Williamson et al., 1998). However, a recent review of the safety of 5-HTP criticized the methods of these studies, as well as the possibility of tryptophan-4,5-dione existing as a stable impurity in over-the-counter formulations of 5-HTP (Das et al., 2004).

4.4.3. Serotonin syndrome

4.4.3.1. Animal data.
At dosages of less than 50 mg/kg/day, there appear to be no toxicities associated with 5-HTP administration (Chaouloff, 1993; Gainetdinov et al., 1999; Semont et al., 2000). However, as discussed in Section 3.1 ("Preclinical evidence for efficacy of 5-hydroxytryptophan"), the administration of 5-HTP to rodents at dosages of 100–200 mg/kg induces serotonin syndrome.

In rodents, this syndrome is characterized by hypolocomotion, head twitch, forepaw treading, tremors, hindlimb abduction, flat body posture or hunched back, cyanosis, and hyperthermia. Specifically, in rats, 100 mg/kg of 5-HTP increases rectal temperatures to more than 40 °C. At this dose, rats begin to show abnormal behavior and fever as early as 15 min after the drug injection, and all of the rats die between 75 and 90 min after drug administration (Nisijima et al., 2000, 2001). Hirai et al. treated Sprague–Dawley and Wistar rats (reportedly a rat strain that is most sensitive to 5-HTP) and observed lethal damage in the kidneys. The authors note that the difference of LD_{50} in rats depended on differences in the rates of serotonin formation and 5-HTP degradation in the kidneys (Hirai and Nakajima, 1979).

One paper describes 5-HTP toxicosis in dogs (Gwaltney-Brant et al., 2000). Neurological and GI signs included seizures, depression, tremors, hyperesthesia, ataxia, vomiting or diarrhea, signs of abdominal pain, and hypersalivation. The doses of 5-HTP ingested ranged from 2.5 to 573 mg/kg—the minimum toxic dose reported was 23.6 mg/kg.

4.4.3.2. Human data.
In humans, serotonin syndrome is characterized by hypertension, hyperthermia, flushing, hyperreflexia, dizziness, disorientation, and myoclonus (Sternbach, 1991). It is a theoretical possibility with any drug that affects the serotonin system, including SSRIs and tricyclic antidepressants (Lane & Baldwin, 1997). Cases of serotonin syndrome have been reported in patients taking L-tryptophan and fluoxetine together (Lane & Baldwin, 1997) and in patients switching from 1 SSRI to another (Mills, 1995).

To our knowledge, however, serotonin syndrome has not been reported in humans in association with 5-HTP, either as monotherapy or in combination with other medications. Regarding the combination of 5-HTP with SSRIs, we know of only 1 relevant study (Meltzer et al., 1997). Single doses of 5-HTP were administered to 16 patients taking (multiple doses of) fluoxetine, none of whom manifested signs or symptoms of serotonin syndrome. In the same study, single doses of 5-HTP were administered to 14 patients taking tricyclic antidepressants (which inhibit serotonin re-uptake to varying degrees). Again, none of these patients showed evidence of serotonin syndrome.

In a multiple-dose study of 26 patients, 5-HTP was used to augment clomipramine, a potent inhibitor of serotonin re-uptake. There were no signs of serotonin syndrome or other serious adverse events (Nardini et al., 1983). In addition, trials with patients taking 5-HTP together with MAOIs, a class of antidepressants notorious for its many drug interactions, did not indicate any side effects attributable to serotonin syndrome (Alino et al., 1976; Kline & Sacks, 1980; Nicolodi & Sicuteri, 1996). Finally, 5-HTP has been given in combination with tryptophan, with no signs of serotonin syndrome (Quadbeck et al., 1984). Taken together, these safety findings are encouraging; however, in view of the small numbers of patients exposed in these studies, these findings must be regarded as preliminary. According to the

Rule of Three (Hanley & Lippman-Hand, 1983), the observation of zero cases of serotonin syndrome among the ∼ 870 patients exposed to 5-HTP means that the upper end of the 95% confidence interval for the true rate of serotonin syndrome with 5-HTP could still be as high as $3/n = 3/870 = 0.34\%$.

When serotonin syndrome does develop, symptoms often appear within 2 hr of increasing the dose of a serotonergic drug (Mills, 1995). Serious complications can rarely occur and, in extreme cases, deaths have been attributed to serotonin syndrome (Mills, 1995). However, symptoms of serotonin syndrome, even at mild levels, can now be sensitively monitored using the Serotonin Syndrome Scale (SSS; Hegerl et al., 1998), and serotonin syndrome is often a self-limited condition: 70% of cases show complete resolution within 24 hr after discontinuation of serotonergic drugs (Mills, 1995).

5. Future directions

Unfortunately, because 5-HTP is a dietary supplement and not a prescription pharmaceutical, there is comparatively little financial incentive for extensive clinical research as to its efficacy and safety for depression. However, in view of (1) the clear role of serotonin in depression, (2) 5-HTP's obvious role in serotonin synthesis, and (3) the number of factors biochemically "upstream" from 5-HTP that are subject to dysregulation, we believe that 5-HTP supplementation deserves to be reconsidered as a possible significant addition to the antidepressant armamentarium. However, at the present time, we believe that it is premature to recommend its widespread clinical use. Instead, we recommend further clinical trials to address outstanding questions regarding its efficacy and safety. In the meantime, because it is clear that patients will take 5-HTP either with or without medical supervision, we would urge that patients, to the extent possible, do so under supervision. And we would urge physicians to be attentive to the safety issues described in this paper. Finally, with regard to 5-HTP's efficacy, we would recommend that physicians adopt an attitude balancing open-mindedness with healthy skepticism.

Acknowledgment

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