

# Use of Neurotransmitter Precursors for Treatment of Depression

by Stephen Meyers, MS

## Abstract

Insufficient activity of the neurotransmitters serotonin and norepinephrine is a central element of the model of depression most widely held by neurobiologists today. In the late 1970s and 1980s, numerous studies were performed in which depressed patients were treated with the serotonin precursors L-tryptophan and 5-hydroxytryptophan (5-HTP), and the dopamine and norepinephrine precursors tyrosine and L-phenylalanine. This article briefly reviews the published research on the efficacy of neurotransmitter precursors in treating depression, highlights the findings of studies, and discusses issues regarding the interpretation of those findings. The nature of the studies makes it difficult to draw firm conclusions regarding the efficacy of neurotransmitter precursors for treating depression. While there is evidence that precursor loading may be of therapeutic value, particularly for the serotonin precursors 5-HTP and tryptophan, more studies of suitable design and size might lead to more conclusive results. However, the evidence suggests neurotransmitter precursors can be helpful in patients with mild or moderate depression.

(*Altern Med Rev* 2000;5(1):64-71.)

## Introduction

Insufficient activity of the neurotransmitters serotonin and norepinephrine is a central element of the model of depression most widely held by neurobiologists today.<sup>1</sup> Nearly all of the drugs used to treat depression appear to enhance neurotransmission in one or both of these systems. In fact, understanding of the mechanism of action of antidepressant drugs in part gave rise to the model of depression.

The synthesis of most neurotransmitters is controlled within the brain. For some neurotransmitters, the amount of biochemical precursors present in the brain can influence their rate of synthesis. During the 1970s, researchers established a body of evidence indicating ingestion of dietary precursors of certain neurotransmitters could increase their levels in the brain.<sup>2</sup> This research suggested precursors of norepinephrine and serotonin might be useful in treating depression. In the late 1970s and 1980s, numerous researchers studied the use of the serotonin precursors L-tryptophan and 5-hydroxytryptophan (5-HTP), and the norepinephrine precursors tyrosine and phenylalanine in depressed patients.

Interest in neurotransmitter precursors was partly a function of the shortcomings of anti-depressant medications (particularly in terms of side-effects) available prior to Prozac and other selective serotonin re-uptake inhibitor drugs (SSRIs). It was hoped dietary precursors of key neurotransmitters might provide a more easily tolerated way of treating depression.

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## Why Neurotransmitter Precursors Might be Helpful in Treating Depression

The conceptual case for the effectiveness of neurotransmitter precursors builds upon the idea that depression is a result of an inadequate amount or insufficient activity of one or more neurotransmitters. Within limits, availability of the necessary precursors determines the amount of neurotransmitter synthesized. For example, serotonin production in the human brain can be increased two-fold by oral intake of L-tryptophan.<sup>3</sup>

Although administration of precursors appears to result in increased neurotransmitter synthesis, it is less clear whether it leads to augmentation of neurotransmitter release. An animal study found acute administration of L-tryptophan decreased the firing rate of serotonin neurons,<sup>4</sup> which might tend to counteract increased synthesis. However, results from other animal studies suggest L-tryptophan administration can enhance serotonin release under some circumstances, and the same may be true in humans.<sup>5</sup> Administration of 5-HTP has been associated with a significant increase in cerebrospinal fluid levels of 5-hydroxyindolacetic acid, the primary metabolite of serotonin, suggesting 5-HTP leads to an increased release of serotonin.<sup>3</sup>

The key question—which so far has not been answered—is whether increased neurotransmitter release leads to ongoing stimulation of neurotransmitter activity; i.e., the strength of signaling. The latter depends not only on the amount of neurotransmitter released by the presynaptic neuron, but also on how long neurotransmitters remain in the synaptic cleft, and on factors which influence firing of the postsynaptic neuron. Neurotransmitter systems are characterized by feedback mechanisms that help maintain equilibrium with respect to neurotransmitter activity. Thus, changed conditions in the short run, such as increased synthesis of a neurotransmitter, can

be balanced by adaptations within the system.

The time lag before appearance of a beneficial symptom-relieving effect of antidepressant drugs suggests late-developing factors may be more relevant to these drugs' clinical efficacy than their acute effect (inhibiting re-uptake of neurotransmitters). Imipramine (a tricyclic antidepressant) can block neurotransmitter re-uptake in a matter of hours, but it takes several weeks for patients to begin to feel less depressed. This time lag posed a challenge to the notion that the primary cause of depression was related to a reduced level of neurotransmitters in the synapse.

In recent years, many studies have investigated long-term adaptive changes produced by antidepressant drugs on norepinephrine and serotonin systems.<sup>6</sup> In addition, although most current antidepressant drugs are known to act on norepinephrine and serotonin systems, other factors appear to be involved in the mechanism of action of antidepressants. Dopamine, neuropeptides, neurohormones, intracellular second messengers, and modulation of gene expression may play a role in the mechanism of action of antidepressant drugs.<sup>7,8</sup>

## Research on the Efficacy of Neurotransmitter Precursors for Treating Depression

### Issues in Evaluating the Research Record

A number of issues make evaluating the scientific literature on antidepressant treatments difficult. One is the quality and duration of response to a given treatment. Response in terms of a reduction in the level of symptoms on a rating scale (“improvement”) is not the same as remission from illness. The latter requires a longer time frame to evaluate than the one-to-two-month treatment period most common in clinical studies, but is ultimately more important. Reduction in symptoms over the course of a study does not necessarily lead

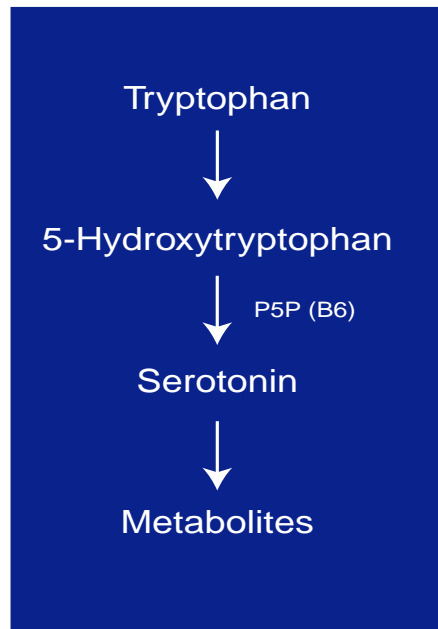
to long-term reduction, much less full remission. For example, one study of mildly depressed patients found a sizable improvement in the group given a placebo and the group given Prozac; however, the Prozac-treated group had many more patients who got substantially better and maintained their improvement.<sup>9</sup>

An additional challenge is the degree of similarity of patients in different groups in terms of the nature and severity of their depression. A given treatment may vary in its efficacy depending on the severity of the subject's depression.

Studies of antidepressants are of three general classes. In an open study, a treatment is given to a group of patients and their response is measured; a hypothetical contrast of the response to the treatment compared to that seen with a known drug is possible. The second class contrasts the experimental treatment with a drug of established efficacy. The third compares a treatment with placebo, sometimes using a standard drug as a third arm of the study.

For most psychiatric disorders, a given treatment is not considered effective without a placebo control. Placebo response rates vary widely across patient groups; it may be as high as 65 percent, even in a group with major depression.<sup>10</sup> Thus, if an open study finds that a particular treatment results in improvement of symptoms, it is difficult to judge how much of the effect was due to the treatment. Even if an experimental treatment appears comparable to a standard drug in terms of response, it may be that a placebo would have done as well as either treatment over the course of the study.

**Figure 1. Serotonin Biosynthesis**



### **Serotonin Precursors: 5-HTP and Tryptophan**

Serotonin synthesis is dependent upon the availability of L-tryptophan and its immediate metabolite 5-HTP within the central nervous system. The production and subsequent transport of L-tryptophan from the bloodstream into the central nervous system can be compromised by several factors, including vitamin B6 deficiency, cortisol excess, and increased levels of other L-tryptophan metabolites.<sup>11</sup>

Therapeutic use of 5-HTP bypasses the conversion of L-tryptophan into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin (see Figure 1). 5-HTP easily crosses the blood-brain barrier, and unlike L-tryptophan, does not require a transport molecule to enter the central nervous system. These factors might account for the inconsistent results in studies using L-tryptophan in the treatment of depression.

A research group in Europe conducted a number of studies with 5-HTP in the 1970s and early 1980s. Their first study found reduced depressive symptoms in 60 percent of patients given 5-HTP (200-3,000 mg/day), while a placebo group showed no improvement.<sup>12</sup> A double-blind study with four groups of 10 patients found 5-HTP (200 mg/day) was more effective than placebo and almost as effective as clomipramine (a tricyclic antidepressant).<sup>13</sup> In seven open studies with a total of 350 patients, 55 percent of the patients were considered to be responders to 5-HTP.<sup>14</sup> Overall, it was found to be effective in five and ineffective in two of those studies. In seven controlled studies with a total of 78 patients, a

positive response was noted in 60 percent of patients. In five of these studies, 5-HTP was found to be effective. The scientists concluded, "there are strong indications that 5-HTP is of therapeutic value."

Several studies of 5-HTP were also conducted in Japan in the 1970s. In a large open trial, 100 patients were given 50-300 mg/day.<sup>15</sup> Significant improvement was observed in 69 percent of the patients, and no significant side-effects were reported. The response rate in most of the patients was less than two weeks, which is interesting, as most antidepressant drugs take two weeks to a month to show benefit. In a 1975 open study, 24 patients hospitalized for depression were given 5-HTP. After two weeks of treatment, marked amelioration of depressive symptoms was observed in seven patients (29%).<sup>16</sup> In another Japanese study, 5-HTP (50-100 mg three times per day) was administered to 59 patients with mixed types of depression; unipolar, bipolar, and other subcategories, most with moderate-to-severe depression. Marked improvement was noted in 13 patients (22%) and moderate improvement in 27 patients (46%). Again, all responders to 5-HTP therapy noticed improvements within two weeks.<sup>17</sup> Yet another open study administered 5-HTP to 18 patients and found two (11%) very much improved and eight (44%) much improved.<sup>18</sup>

A German double-blind study reported in 1977 compared 5-HTP (in combination with benzerazide—a peripheral decarboxylase inhibitor—to supposedly inhibit conversion of 5-HTP outside the CNS) to imipramine in 30 patients. It found equal efficacy between the two treatments.<sup>19</sup> A 1985 British study assessed the efficacy of 5-HTP among patients suffering from major depression who were non-responders to several neurotransmitter reuptake inhibitors. 5-HTP or tranylcypromine was given during four weeks in a crossover design. Of 17 patients given 5-HTP, none responded, whereas of 26 patients treated with

tranylcypromine, 15 improved.<sup>20</sup> The authors felt 5-HTP was not an effective alternative in patients who had not previously responded to SSRIs.

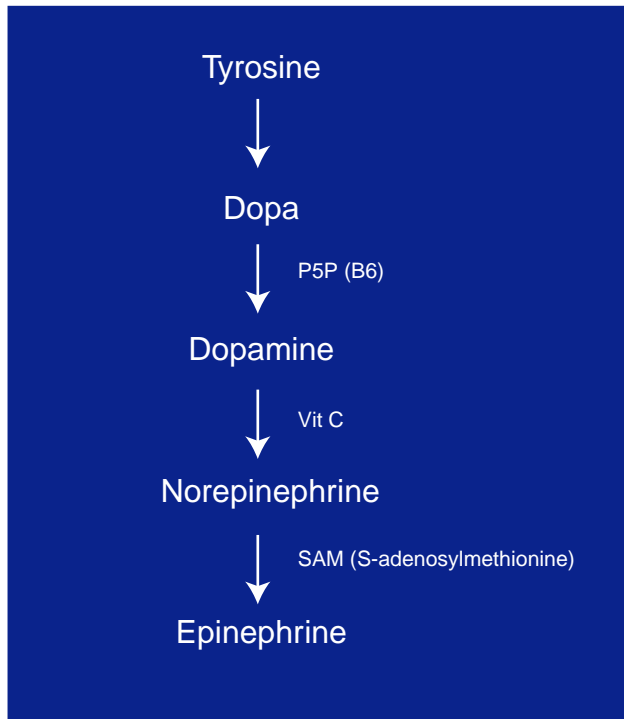
In a 1988 open study of 25 patients, the therapeutic efficacy of 5-HTP was found to be equal to traditional antidepressants.<sup>21</sup> Best results were obtained among patients with an anxious depressive syndrome and in patients with endogenous acute depression.

A 1991 Swiss study compared 5-HTP 100 mg three times per day with fluvoxamine (an SSRI used for depression and obsessive-compulsive disorder) 50 mg three times per day. In a double-blind, multicenter study, 36 subjects were evaluated over six weeks using four different diagnostic tools. Both treatment groups showed significant and nearly equal reductions in depression beginning at week two and continuing through week six. By week six, the two groups had about an equal number of patients showing 50 percent improvement in the Hamilton Rating Scale for Depression.<sup>22</sup>

In the studies cited above, it appears that most, if not all, of the subjects had been diagnosed with major depression. One double-blind study compared L-tryptophan with amitriptyline (a tricyclic antidepressant) over a three-month period among 115 outpatients diagnosed with mild or moderate depression. Based on scores on the Hamilton Depression Scale and a global rating of depression, L-tryptophan at a dose of 3 g per day was more effective than placebo, as effective as amitriptyline, and produced significantly fewer side-effects.<sup>23</sup>

While most of the studies described above indicate a therapeutic benefit from serotonin precursors, reviews by others have been more cautious. In a review published in 1978, the authors concluded the studies reviewed did not provide adequate evidence for an antidepressant effect of 5-HTP. They also felt L-tryptophan without concomitant

**Figure 2.** Biosynthesis of Catecholamines



antidepressant drug use did not appear to have a well-documented antidepressant effect.<sup>24</sup> Authors of a 1983 review were not convinced of L-tryptophan's antidepressant efficacy in marked-to-severe endogenous depression, but noted it might be more effective in moderate dysphoric states. They also noted that a serotonin-deficient subgroup of depressed patients might respond well to 5-HTP.<sup>25</sup> Another review was cautiously positive, stating, "results suggest that 5-HTP possesses antidepressant properties, but additional trials are indicated."<sup>26</sup>

The cautious interpretation by reviewers stems from the nature of most neurotransmitter precursor studies. Promising results have been obtained in open studies and in comparisons with tricyclic antidepressants. In the open studies, however, some or all of the improvement with precursor treatment might have been due to a placebo effect. Most of the comparison studies also lacked a placebo control group, and the number of patients per group was smaller than that which would normally be necessary to show a statistically

significant difference with a high degree of confidence between treatments.

### **Norepinephrine Precursors: Tyrosine and Phenylalanine**

Tyrosine is the precursor of norepinephrine, and L-phenylalanine is the direct precursor of tyrosine. Tyrosine and phenylalanine are also precursors of dopamine, another neurotransmitter which may play a role in depression (see Figure 2).

If animal studies are a reliable guide, there appears to be less scope for increasing norepinephrine synthesis with precursor loading than is the case for serotonin. Under normal conditions in the rat brain, tyrosine hydroxylase, the rate-limiting enzyme on the pathway from tyrosine to norepinephrine, is about 75-percent saturated with tyrosine.<sup>5</sup>

There has been much less research on the use of norepinephrine precursors for treating depression than the use of serotonin precursors. Two 1980 case studies suggested L-tyrosine may have potential as an antidepressant, but both had a very small sample size.<sup>27,28</sup> Later in the 1980s, a four-week clinical trial treated 65 outpatients with major depression in a double-blind comparison of L-tyrosine (100 mg/kg/day), imipramine, or placebo. It found no evidence that L-tyrosine had antidepressant activity.<sup>29</sup>

In a double-blind study reported in 1979, DL-phenylalanine (150-200 mg/day) or imipramine was administered to 40 depressed patients (20 in each group) for one month. No statistical difference was found between the two groups using the Hamilton Depression Scale and a self-rating questionnaire,<sup>30</sup> leading to a conclusion that DL-phenylalanine (DLPA) might have antidepressant properties.

In a 1980 open study, 11 patients with major depressive disorder were treated with D-phenylalanine (mean dose of 350 mg/day) for four weeks. The researchers found no evidence of antidepressant effect, but suggested

re-evaluation at higher doses.<sup>31</sup> In a later open study, 31 of 40 depressed patients responded to large doses of L-phenylalanine (up to 14 g/day).<sup>32</sup>

Given the reasonably positive results of the study comparing DLPA with imipramine, and the relatively low dose of DLPA which was used, it seems higher doses might be helpful in cases of depression in which low norepinephrine activity is involved.

## Conclusions

The preceding section illustrates the difficulty of drawing firm conclusions from the research on the use of neurotransmitter precursors for treating depression. While there is undoubtedly evidence that precursor loading may be of therapeutic value, particularly for the serotonin precursors 5-HTP and L-tryptophan, more studies of suitable design and size might lead to more conclusive results. In addition, the complex nature of neurotransmitter systems contributes to uncertainty whether the positive response seen in studies of relatively short duration would continue over the long run.

One might reasonably question how relevant the clinical research on neurotransmitter precursors is for the types of depression alternative practitioners are likely to see. Nearly all of the studies have involved patients with major depression, typically in a clinical setting. One reasonably large study of outpatients with mild or moderate depression found L-tryptophan was significantly better than placebo.<sup>22</sup> This study is also noteworthy because it followed the response of the subjects for a relatively long period (three months). Thus, in cases of mild or moderate depression, it does not seem unreasonable to use neurotransmitter precursors, especially given their relatively low degree of side-effects and low cost.

The clinical research provides somewhat limited guidance for choosing between

serotonergic or catecholaminergic precursors. Studies which have investigated the ratio of plasma tryptophan to the sum of the other large neutral amino acids (leucine, isoleucine, valine, tyrosine, phenylalanine) or erythrocyte membrane transport of these substances show a predictable response to serotonergic or catecholaminergic precursors or drugs.<sup>33-35</sup> This type of testing might be one way of choosing between serotonin or catecholamine stimulation in the depressed patient.

While use of neurotransmitter precursors may be a reasonable course of action for treating many cases of depression, practitioners should be aware that recent research on antidepressant drugs indicates they might have a more complex and far-reaching action than that associated with neurotransmitter precursors.<sup>6</sup> In addition, if the intensive research into development of faster acting antidepressant drugs with fewer side-effects bears fruit, the advantages of neurotransmitter precursors in terms of their better tolerability may be less relevant.

On the other hand, the decision with respect to neurotransmitter precursors and prescription antidepressant drugs is not necessarily a case of "one or the other." Growing numbers of individuals are combining various prescription drugs with alternative treatments, and the ranks of M.D.'s integrating alternative treatments into their practice is increasing. Given this evolution, combined use of neurotransmitter precursors with antidepressant drugs may be worth considering. Nearly all of the studies of such use have been conducted with tricyclic drugs. A small study conducted in 1986 found evidence of adverse effects from combined administration of tryptophan and Prozac.<sup>36</sup> Yet it seems possible that use of low dosages in combination might yield a positive synergy without adverse effects.

Another option that has received little research is combining serotonergic and catecholaminergic precursors. Two studies in the early 1980s investigated a mixture of 5-HTP

and tyrosine in depression. While these studies were too small for definite conclusions, the results indicate a tyrosine had a potentiating effect on the antidepressant capacity of 5-HTP.<sup>37</sup>

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