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The Treatment of Depression with L-5-Hydroxytryptophan versus Imipramine

Results of Two Open and One Double-Blind Study

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Summary. In the last few years several open studies supported the hypothesis that L-5-HTP may be an effective antidepressant. Because of the lack of a controlled double-blind trial we started our own investigations to confirm this hypothesis in L-5-HTP. In 1972 we performed two open dose finding trials with L-5-HTP in combination with Benzerazide. These open studies were followed by a double-blind trial comparing L-5-HTP in combination with Benzerazide to Imipramine in 30 patients. Assessments were carried out on day 0, 5, 10, 15 and 20.

For data collection we used the Hamilton Rating Scale for Depression, the AMP-system, a Global Rating Scale of Severity of Depression and a Brief Rating Scale for the Behaviour on the ward. In this article we report only a part of the results, mainly on the findings with the AMP-system and the Hamilton Rating Scale for Depression.

During our double-blind trial we could not find any significant difference in efficacy of L-5-HTP and Imipramine. The same was found in an open trial. Furthermore the L-5-HTP results showed no difference compared with the results of an Imipramine treatment in 40 patients in earlier double-blind studies.

L-5-HTP and Imipramine caused different patterns of side effects. L-5-HTP caused mainly gastrointestinal side effects and Imipramine caused mainly dryness of the mouth and tremor. The gastrointestinal side effects caused by L-5-HTP seemed to be dose dependent.

Key words: L-5-Hydroxytryptophan – Imipramine – Double-blind trial – Open study – Depression – Switch to hypomania.

Zusammenfassung. In den letzten Jahren ergaben verschiedene offene Prüfungen Hinweise für die Hypothesen, daß L-5-HTP ein wirksames Antidepressivum sei. Weil kontrollierte doppelblinde Prüfungen fehlten, begannen wir

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eigene Untersuchungen, um diese Hypothese zu überprüfen. Im Jahre 1972 führten wir 2 offene Studien mit L-5-HTP, in Kombination mit Benzerazid durch. Diesen beiden offenen Prüfungen folgte eine Doppelblindstudie in der wir L-5-HTP in Kombination mit Benzerazid gegen Imipramin an 30 Patienten prüften. Die Untersuchungen der Patienten wurden an den Tagen 0, 5, 10, 15 und 20 durchgeführt.

Für die Datensammlung benützten wir die Hamilton-Skala für Depressionen, das AMP-System, eine globale Rating-Skala des Schweregrades der Depression und eine Rating-Skala des Verhaltens auf den Abteilungen. In diesem Artikel führen wir nur einen Teil der Resultate auf, vor allem solche, die mit dem AMP-System und der Hamilton-Skala für Depressionen gewonnen wurden.

Die Doppelblindprüfung ergibt keine signifikanten Wirkungsunterschiede zwischen L-5-HTP und Imipramin; das gleiche gilt für eine offene Prüfung. Die L-5-HTP Resultate zeigten ferner keinen Unterschied zu den Ergebnissen von Imipraminbehandlungen an 40 Patienten aus früheren doppelblinden Prüfungen.

L-5-HTP und Imipramin verursachten verschiedene Arten von Nebenwirkungen, L-5-HTP vor allem gastrointestinale Nebenwirkungen und Imipramin vor allem Mundtrockenheit und Tremor. Die gastrointestinalen Nebenwirkungen bei L-5-HTP scheinen dosisabhängig zu sein.

Schlüsselwörter: L-5-Hydroxytryptophan – Imipramin – Doppelblindprüfung – Offene Prüfung – Depression – Wechsel zu Hypomanie.

Introduction

Pare and Sandler tried in 1959 to treat depressive patients with L-5-HTP, but without success: they gave doses of 15.5 to 150 mg during 48 h with and without the MAO-inhibitor Iproniazide. Kline et al. reported in 1964 dramatic antidepressive effects of L-5-HTP in combination with a MAO-inhibitor, but were unable to replicate these findings in an double-blind trial in 1964. In the face of these early experiences a casuistic report of Persson and Roos (1967) could not change the conclusion that L-5-HTP has no antidepressant effect. A new impetus was created by Sano in Japan (1971, 1972) who enthusiastically reported successful treatments in 74 of 107 endogenous depressive patients treated by L-5-HTP in daily doses of 200 mg orally and maximum doses up to 800 mg in combination with Trihexiphenidyl (6 mg per day) or Metoclobromid (15 mg per day). Reported side-effects were nausea and gastrointestinal disturbances. Fujiwara (1973) treated another 20 patients with daily doses of 50—200 mg L-5-HTP for 1—4 weeks and observed an improvement in 50% of these cases.

Barlet and Pailard (1974) and Aussilloux and co-workers (1975) mentioned an antidepressant action of L-5-HTP in involutional melancholia. Other reports about an antidepressive action were given by Soulairac (1973). Another report of Matussek et al. (1974), including some of our own results, did not suggest a strong antidepressive action of L-5-HTP. L-5-HTP was also administered intraveneously

(Gaillard et al., 1973) and the uptake by the brain was found to be the same as in the periphery and seemingly higher in depressive syndromes than in other disorders. Pretreatment with a decarboxylase inhibitor (Benzerazide) did not modify either the arterial plasma levels or the quantities of the L-5-HTP uptake. In recent studies (for instance van Praag et al., 1974), L-5-HTP was also given together with a decarboxylase inhibitor to inhibit the synthesis of 5-HT (Serotonin) in the periphery, to avoid gastrointestinal side effects, and to increase the concentration of 5-HTP in the CNS.

Several studies with L-5-HTP as an antidepressant were carried out in combination with other drugs, for instance in a double-blind trial, with Nialamide versus Nialamide alone (Ayuso Gutierrez et al., 1974; Lopez-Ibor et al., 1976) and a combination of L-5-HTP with Clomipramine (van Praag et al., 1974) in therapy resistant depressions. The authors assumed an additive effect of the two compounds, suggesting an increase of Serotonin at the central Serotonin receptors.

Many biochemical investigators have advanced the hypothesis of the existence of two different types of depressive syndromes, type A with a disorder of Norepinephrin metabolism or disposition, and type B with disorder of the Serotonin metabolism or disposition (Maas, 1975; Schildkraut, 1974; van Praag, 1974). Based on this hypothesis the clinical effects of L-5-HTP were correlated with biochemical variables. Van Praag (1974), Fujiwara and Otsuki (1974) determined the content of 5-HIAA, the metabolite of Serotonin, in the CSF and found a lower concentration in the assumed indolamine type of depression: these patients responded to L-5-HTP. Takahashi et al. (1975) treated 20 depressed patients with L-5-HTP in daily doses of 300 mg orally for two weeks and found a response in 5 patients. The L-5-HTP administration was associated with a slightly significant increase in the levels of 5-HIAA in the CSF in the responders and non-responders to the treatment. During the treatment they could not find an increase of 5-HIAA in correlation to the response to this treatment, but they found an increase of HVA. Therefore the authors could not support the hypothesis that L-5-HTP does serve as a replacement therapy for deficiency of Serotonin; instead they found that the dopaminergic system may be influenced by the treatment.

Some doubts about the validity of CSF levels of 5-HIAA determinations have been raised by the most recent paper of Burns and co-workers (1976), because lumbar 5-HIAA levels may not accurately reflect brain 5-HIAA content.

Bridges et al. (1976) confirmed lower 5-HIAA concentrations in the ventricular CSF of psychiatric patients suffering from depression.

Another attempt was made to correlate the response to L-5-HTP with endocrine changes. Takahashi et al. (1973) found a therapy-resistance to L-5-HTP in patients who were categorized as non-responders to HGH (plasma human growth hormone).

In a most recent study with healthy subjects Puehringer et al. (1976) showed that the intraveneous application of L-5-HTP stimulated the growth hormone and prolactin release. This release correlated with the peak of the mood elevation. Takahashi (1976) determined blood platelet Serotonin levels before, during, and after administration of L-5-HTP with a maintenance dose of 300 mg daily in 9

depressed patients. During the treatment with L-5-HTP, Serotonin levels increased to normal levels, while the depressive symptomatology was not improved. In another trial Takahashi and co-workers (1976) found that non-responders, to L-5-HTP had significantly lower excretion levels of 5-HT and 5-HIAA in urine, and lower plasma levels of 5-HT than responders.

From the literature we can conclude that there is strong evidence for the hypothesis that L-5-HTP may be an effective antidepressant, but there is a lack of controlled double-blind trials to confirm this hypothesis. With the aim to confirm it, we started our own study in 1972 with two open trials to investigate the action of L-5-HTP in combination with the decarboxylase inhibitor Benzerazide, followed by a double-blind study versus Imipramine. Initially we felt somewhat pessimistic about this study, because the results of our early open trials with L-Tryptophane, the precursor of L-5-HTP, had been negative (Angst, 1972).

Method

Experimental Design

Three different studies with L-5-HTP were conducted between 1972 and 1976. Study I and study II were open studies with 10 and 11 patients respectively on L-5-HTP; study III was a double-blind trial (15 patients on L-5-HTP versus 15 on Imipramine). Study I consisted of 10 severely depressive hospitalized patients who had already been treated without any success by tricyclic antidepressants; study II consisted of newly admitted non-pretreated hospitalized depressive patients; in study III the patients were selected in the same way as in study II and randomly assigned to the two groups. Assessments were carried out on day 0, 5, 10, 15, and 20 of the treatment; in the studies II and III additional assessments were carried out on days 1 and 3. The data were collected by using the Hamilton Rating Scale for Depression, the AMP-system, a

Table 1. Sex, age and mean dosage of treatment

		Groups				
		Open trials		Double-blind-trial		Earlier three double-blind trials
		I	II	III A	III B	IV
		L-5-HTP + Benzerazide	L-5-HTP + Benzerazide	L-5-HTP + Benzerazide	Imipramine	Imipramine
N		10	11	15	15	40
Mean dosage in mg	L-5-HTP	190	1200	800	—	—
	Benzerazide	375	375	375	—	—
	Imipramine	—	—	—	150	150
Sex	m	3	4	8	5	13
	f	7	7	7	10	27
Age (years)	$\bar{x}$	54.8	48.5	45.1	52.5	53.2
	s	8.7	18.0	8.9	9.4	12.1
Minimal duration of treatment in days		20	20	20	20	20

Global Rating of Severity of Depression and a Brief Rating Scale for the Behaviour on the Ward. Finally the results were compared to those of earlier double-blind studies with Imipramine (group IV, 40 patients). The following statistical tests were used: analyses of variance of Friedman, Wilcoxon Tests, *t*-tests, *u*-tests and two-way-analyses of covariance for repeated measurements.

Patient Samples

Table 1 shows size, sex, diagnosis, and age distribution of the 5 different groups. There is a difference in age between groups III A and IV B ($P \leq 0.05$).

Treatment

Table 1 gives some information about the mean dosage and planned duration of treatment, i.e., at least 20 days. L-5-HTP was always given together with Benzerazide that was administered 30 min before the L-5-HTP. In the double-blind study all patients received two types of capsules. One yellow capsule contained either 125 mg Benzerazide (decarboxylase-inhibitor) or 50 mg Imipramine, one red capsule contained 100 mg L-5-Hydroxytryptophan or placebo. Benzerazide was administered in order to block the decarboxylase in the periphery to provide a better supply of L-5-HTP in the CNS and to avoid gastrointestinal side-effects as much as possible.

The reference group IV (40 patients on Imipramine) consisted of 3 earlier conducted double-blind trials with 150 mg Imipramine daily.

Results

From all the results we present only those obtained by the Hamilton Rating Scale for Depression (items 1—17) and by the AMP-system (scale 5 = somatic-depressive syndrome; scale 8 = retarded-depressive syndrome).

One-Group-Analyses

Each group was analyzed separately by the Friedman test with the three different scales (Table 2). A highly significant improvement ($P \leq 0.001$) was obtained in all

Table 2. One-group analyses: Analysis of variance (Friedman) results of 20-day treatment (*P*-values)

	Open trials		Double-blind trial		Earlier double-blind trials
	I	II	III A	III B	V
			L-5-HTP	Imipramine	
Hamilton scale	n.s.	0.001	0.001	0.001	0.001
AMP-scales					
5. Somatic-depressive syndrome	0.05	0.001	0.001	0.001	0.001
8. Retarded-depressive syndrome	n.s.	0.05	0.001	0.001	0.001
11. Autonomic syndrome	n.s.	n.s.	n.s.	0.10	0.05
12. Neurological syndrome	n.s.	n.s.	n.s.	n.s.	n.s.

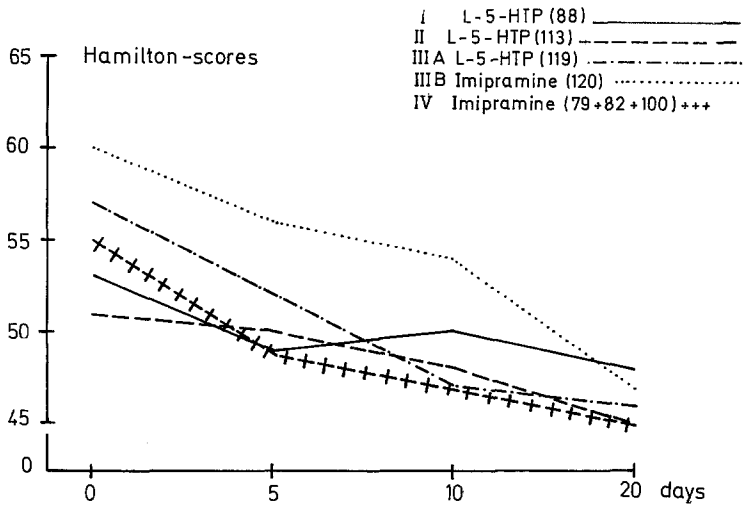

Fig. 1. Hamilton-scale item 1—17 (unadjusted means)

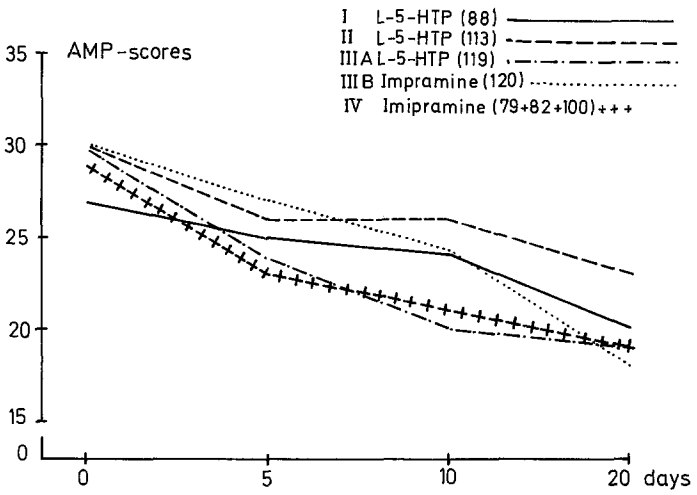

Fig. 2. AMP-scale: Course of the *somatic-depressive* syndrome (*t*-values)

groups but one by the Hamilton Rating Scale for Depression (Fig. 1). The only group that did not show any significant improvement was the open trial I with very low doses of L-5-HTP. This group consisted of 10 severely depressive hospitalized patients who had been resistant to tricyclic antidepressant, and it was therefore a poor responder group.

A similar result was obtained by the two scales of the AMP-system. The AMP-system scale 5 (somatic-depressive syndrome) consists mainly of items reflecting sleep disturbances and loss of appetite. The patients of all groups showed a significant improvement on this scale and this was also true for group 1 ($P \leq 0.05$) (Fig. 2). The improvement was mainly due to better sleep. On AMP-

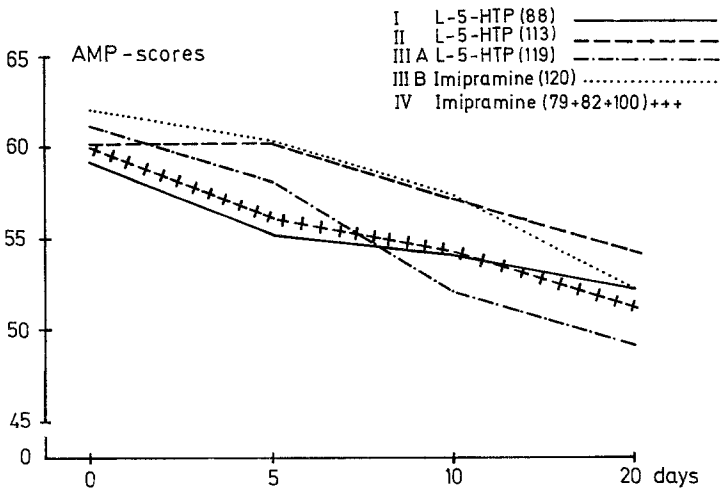

Fig. 3. AMP-scale: Course of the *retarded-depressive* syndrome (*t*-values)

Table 3. Mean scores of Hamilton scale (item 1—17) and AMP scale 5 and 8

		N	Day			
			0	5	10	20
Hamilton						
I	L-5-HTP	10	23	19	20	18
II	L-5-HTP	11	21	20	18	15
III A	L-5-HTP	15	27	23	17	16
III B	Imipramine	15	30	26	24	17
IV	Imipramine	40	25	19	17	15
AMP scale 5 somatic-depressive syndrome (*T*-values)						
I	L-5-HTP	10	57	55	54	50
II	L-5-HTP	11	60	56	56	53
III A	L-5-HTP	15	60	54	50	49
III B	Imipramine	15	60	57	54	48
IV	Imipramine	40	59	53	51	49
AMP scale 8 retarded-depressive syndrome (*T*-values)						
I	L-5-HTP	10	59	55	54	52
II	L-5-HTP	11	60	60	57	54
III A	L-5-HTP	15	61	58	52	49
III B	Imipramine	15	62	60	57	52
IV	Imipramine	40	60	56	54	51

scale 8 (retarded-depressive syndrome) all groups showed some improvement but in group one this improvement was statistically not significant (Fig. 3).

The Raw-scores (means) obtained by the three different scales are reproduced in Table 3.

The conclusion is that all three scales reflect a significant improvement of all groups except group I that consisted of mainly therapy-resistant depressions.

Two-Group-Analyses

All patients had been examined on days 0, 5, 10, and 20 of the treatment. The different groups were statistically compared by a two-way analysis of covariance for repeated measurements. In this way we compared the results of the two open trials (I and II), the results of the two groups in the double-blind trial (III A versus III B); furthermore we compared results obtained by the open trials I and II with L-5-HTP to those obtained by the double-blind trial with L-5-HTP (III A). Finally, we compared the results of the double-blind trials with the results of three groups (IV) treated in earlier double-blind trials by Imipramine, to test whether the groups selected for the double-blind trials were more or less similar to earlier studies conducted in our department. The following results were obtained (Table 4):

— Open trial I versus open trial II with L-5-HTP: None of the instruments reflected significant differences between the two treatment-groups; only the Hamilton Rating Scale showed an interaction ($P \leq 0.01$) between group I and

Table 4. Two-group analysis (two-way analysis of covariance of repeated measurement)

		Hamilton (1—17)		AMP-syndrome 5		AMP-syndrome 8	
		G	I	G	I	G	I
Open trial I	(5-HTP)						
vs.		n.s.	0.01	n.s.	n.s.	n.s.	n.s.
Open trial II	(5-HTP)						
Open trial I	(5-HTP)						
vs.		n.s.	0.10	n.s.	n.s.	n.s.	0.001
Double-blind trial III A	(5-HTP)						
Open trial II	(5-HTP)						
vs.		n.s.	n.s.	0.10	n.s.	0.05	n.s.
Double-blind trial III A	(5-HTP)						
Double-blind trial III A	(5-HTP)						
vs.		n.s.	0.10	n.s.	n.s.	n.s.	n.s.
Double-blind trial III B	(5-HTP)						
Double-blind trial III A	(5-HTP)						
vs.		n.s.	n.s.	n.s.	n.s.	n.s.	0.10
Double-blind trial IV	(Imipramine)						
Double-blind trial III B	(Imipramine)						
vs.		n.s.	0.05	n.s.	0.05	n.s.	0.10
Double-blind trial IV	(Imipramine)						

G = Variance between groups; I = Interaction

group II. As can be seen from Table 3, group I does not show a steady improvement in contrast to group II, in which the patients had a more favourable response.

— Results of the double-blind trial (L-5-HTP versus Imipramine): The analysis does not show any significant differences beween the two groups III A versus III B. The Hamilton Rating Scale for Depression shows a trend of an interaction ($P \leq 0.10$), which is due to a more rapid decrease of the score in the L-5-HTP group within the first five days of treatment.

— Open trial I with L-5-HTP versus double-blind trial III A with L-5-HTP: There is a highly significant interaction between the two groups measured by the AMP-syndrome 8 (retarded-depressive syndrome) and a trend toward an interaction measured by the Hamilton Rating Scale for Depression ($P \leq 0.10$). There is no difference in the variance between groups. Group I showed in the AMP-syndrome 8 initially a more marked improvement during the first 5 days than the other group. The latter showed steady improvement during the twenty days of treatment.

— Open trial II with 5-HTP versus double-blind trials with 5-HTP III A: The Hamilton rating Scale does not show any significant differences between the two groups. The retarded-depressive syndrome gives a significant difference between the two groups ($P \leq 0.05$) in favour of the group that was treated blindly (mean-scores-see Table 3). Furthermore we find a trend ($P \leq 0.10$) towards a difference between the two groups measured by the scale for the somatic-depressive syndrome. The blindly treated group shows a greater improvement than the open treated one does. We think that this result has also to be interpreted as significant because we compared only 10 to 15 patients in each group.

— Comparison between the reference group III B on Imipramine and earlier trials with Imipramine (IV): All three instruments reflect a significant interaction between group III B on Imipramine and IV on Imipramine. The Hamilton Rating Scale shows that the initial value of the referrence group III B was higher than the value obtained in earlier trials (IV) and that in the latter there was a fast improvement within the first 5 days of the treatment. The initial values measured by the AMP-scales 5 and 8 was not significantly different between the two groups, but there was also a more rapid improvement in group IV compared to group III B. Therefore we can conclude that group III B was a high morbid group with a lower chance of response to Imipramine than earlier groups on Imipramine (IV). This conclusion has some implications for the interpretation of the interaction ($P \leq 0.10$) found by the Hamilton Rating Scale for Depression within groups III A and III B of the double-blind study. The conclusion is that we found no difference in response to the two types of treatment.

Side Effects

The side effects of L-5-HTP and Imipramine show different patterns (Table 5). L-5-HTP caused mainly gastrointestinal side effects and Imipramine caused mainly dryness of the mouth and tremor. The gastrointestinal side effects caused by L-5-HTP seemed to be dose dependent. During our first open trial (I) with low doses of

Table 5. Side effects of L-5-HTP and Imipramine

Group	Coefficient of severity Day				McNemar-test
	0	5	10	20	
Dryness of the mouth					
I	27	13	17	20	n.s.
II	21	15	12	06	n.s.
III A	11	13	16	09	n.s.
III B	13	47	40	18	1%/day 5
Tremor					
I	10	10	07	07	n.s.
II	06	09	03	03	n.s.
III A	02	02	07	04	n.s.
III B	00	13	11	11	5%/day 5
Nausea					
I	00	00	00	00	n.s.
II	00	18	24	30	10%/day 5
III A	04	16	16	09	n.s.
III B	13	16	13	09	n.s.
Diarrhoea					
I	00	07	03	03	n.s.
II	00	03	18	18	n.s.
III A	02	07	07	00	n.s.
III B	00	00	00	00	n.s.

L-5-HTP only one out of ten patients developed nausea and vomiting. With higher doses five out of eleven (II) and 3 out of 15 (III A) patients showed signs of nausea, vomiting, and diarrhoea, while 2 showed abdominal spasms.

The gastrointestinal side effects were not very severe in any group of patients as shown in Table 5.

In looking at the severity of the autonomic and neurological syndrome of the AMP-system, we noticed different time courses of these syndromes under the treatment with L-5-HTP (I, II, II A) and Imipramine (III B). The initial increase of autonomic and neurological side effects caused by Imipramine (III B) did not appear in the L-5-HTP groups. The comparison of the two groups of the double-blind trials (III A/III B) by means of the analyses of covariance showed a statistical tendency ($P \leq 0.10$) towards a different effect of both substances on the autonomic syndrome. Only Imipramine caused an increase of the autonomic syndrome until day 10, followed by a slight decrease. A similar difference was apparent with the neurological syndrome, reaching statistical significance $P \leq 0.05$) on day 5.

In consideration of the different patterns of side effects of L-5-HTP and Imipramine it is very difficult to judge which of these side effects cause the patients more discomfort.

Hypomania and Acute Brain Syndrome

Looking for hypomanic symptoms we noticed an increase of euphoria in one patient in each L-5-HTP-group (N = 3). Twice this euphoria was only very slight, once moderate. During the treatment with Imipramine (III B) we found the same slight change of mood in 1 patient.

In addition to these studies we treated 3 patients with L-5-HTP + Benzerazide. A hospitalized chronic severely depressed patient was treated several times with high dosages (up to 1500 mg L-5-HTP). During 3 different periods of treatment she became clearly manic for 1 to several days (she never had any manic syndromes in her previous history). Twice she developed an acute brain syndrome with disorientation in time and space and delirious overactivity.

Another patient, who had never been hypomanic before, developed after a slight dosage of 100 mg L-5-HTP an acute anxiety state for about 3 h and switched then to hypomania with euphoria, logorrhoea and overactivity. One day later she had completely recovered from both the hypomania and depression. This effect could not be reproduced in a subsequent depressive episode.

In another outpatient the treatment with L-5-HTP had to be interrupted after one week because of pains in the stomach.

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