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Comparative study of efficacy of L-5-hydroxytryptophan and fluoxetine in patients presenting with first depressive episode

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ABSTRACT

Introduction: Role of L-5-hydroxytryptophan (L-5-HTP) in depression is relatively less studied but the literature has shown its robust role in depression. The present randomized double blind study was undertaken to assess the role of L-5-HTP as an antidepressant and to compare its antidepressant efficacy with fluoxetine in first depressive episode patients of Indian population.

Methods: A total of 70 patients of first depressive episode, all of whom were diagnosed with ICD-10 criteria, were recruited but only 60 patients completed the study and were randomly divided into two groups, receiving L-5-HTP and fluoxetine, respectively, for a period of 8 weeks. All patients were administered Hamilton Rating Scale for Depression (HAM-D) to assess severity of depression at baseline, 2 weeks, 4 weeks and 8 weeks. The efficacy of treatment was assessed by comparing HAM-D scores obtained at these examinations with the baseline examination; final evaluation of both efficacy and tolerance was assessed using the Clinical Global Impression (CGI) scale at the end of study.

Results: Both treatment groups showed significant and nearly equal reduction in HAM-D scores beginning at week two and continuing through week eight. Twenty-two patients (73.33%) in the L-5-HTP group and 24 patients (80%) in the fluoxetine group showed positive response at the end of the study.

Conclusion: L-5-HTP has definitely got antidepressant effect in patients of depression. Antidepressant effect was seen within 2 weeks of treatment and was apparent in all degrees of depression. The therapeutic efficacy of L-5-HTP was considered as equal to that of fluoxetine.

1. Introduction

Affective disorders are one of the most common psychiatric disorders and account for nearly 30–40% of the case load at various psychiatric facilities in India (Varma and Das, 1995). There is a marked variability in the prevalence rate of depression across the studies in India which range from 1.5 per 1000 (Sethi and Gupta, 1972) to 37.74 per 1000 (Nandi and Ajmany, 1975). The Epidemiological Catchment Area and National Co morbidity Survey studies suggested that the current rate of major depression is in the realm of 2 – *t*. It is believed that the true life time rate of major depression is probably in the realm of 10–20 per 100 (Joyce, 2009).

A response to a single antidepressant medication, classically measured as an attenuation of 50% or more in the intensity of depressive symptoms, is generally obtained in about 50–75% of patients with a first trial (Lonnqvist et al., 1994). Remission rates, in contrast are generally around 30% with a single agent (Blier et al., 2010). This is a disappointing result indicating that additional treatment measures must be taken in about two-third of patients after using an antidepressant medication at an adequate dose for a sufficient time.

Tryptophan depletion is widely used paradigm to study the role of the serotonergic system in the pathophysiology and treatment of depression (Neumeister, 2003). 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). 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).

Furthermore, administration of tryptophan has been used as an antidepressant but due to its side effects profile, it was no longer used (Shaw et al., 2002).

L-5-Hydroxytryptophan (L-5-HTP) is an aromatic amino acid naturally produced by the body from the essential amino acid L-tryptophan. Therapeutic use of L-5-HTP bypasses the conversion

Abbreviations: L-5-HTP, L-5-hydroxytryptophan; HAM-D, Hamilton Rating Scale for Depression; CGI, Clinical Global Impression.

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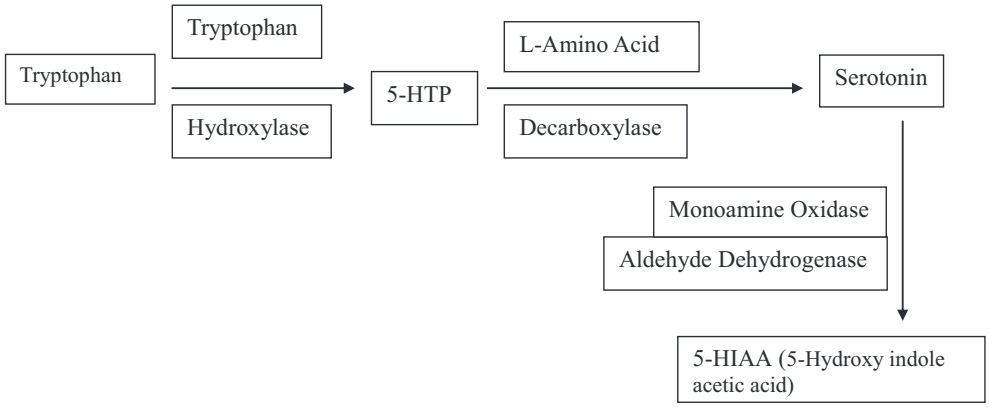

Scheme 1. Mechanism of action of 5-hydroxy indole acetic acid (5-HIAA).

of L-tryptophan into L-5-HTP by the enzyme tryptophan hydroxylase, which is the rate limiting step in the synthesis of serotonin as shown in Scheme 1 (O'Neil and Moore, 2003). L-5-HTP has been used clinically for over 30 years. In addition to depression, the therapeutic administration of L-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 (Birdsall, 1998).

The first large clinical open trial using L-5-HTP in the treatment of depression was done in 1972 with 107 patients having unipolar or bipolar depression using daily oral dosages of L-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 2 weeks) (Sano, 1972).

After this, many double blind, placebo controlled trials with L-5-HTP showed that L-5-HTP was superior to placebo. A double blind study compared L-tryptophan with amitriptyline over a 3 month period among 115 outpatients diagnosed with mild or moderate depression. Based on scores from the Hamilton Rating Scale for Depression (HAM-D) and a global rating of depression, L-tryptophan at a dose of 3 g per day was more effective than the placebo, as effective as amitriptyline, and produced significantly fewer side effects (Thomson et al., 1982).

Other double blind placebo controlled trials evaluated L-5-HTP in comparison with tryptophan in 15 patients with endogenous unipolar or bipolar depression at a daily oral dosage of 200 mg over 4 weeks. Marked improvement was observed in eight of the patients and L-5-HTP was found more effective than tryptophan or placebo (Van Praag, 1984).

It is amply clear that L-5-HTP has potential for being used as alternative to the traditional forms of therapy in depressive disorder; further work needs to be undertaken because no study has been done in the Indian population till date. This raises the question whether results of a western population could be generalized to the Indian population. Therefore, carrying out such studies in the Indian population is mandatory. The present study aims at comparing the efficacy of L-5-HTP and fluoxetine in patients presenting with first depressive episode.

2. Methods

2.1. Sample

This randomized, double-blind, parallel group study was started in May 2009 for 8 weeks in a tertiary center of northern India. The study group consisted of first depressive episode patients attending the Psychiatry Outpatient Department of Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India. Approval from the ethical board of this institute was granted and a sample of 70 outpatients with ICD-10 diagnosis of first depressive episode was recruited. After explaining the purpose and nature of the research, written informed consent to join the study was obtained from the patient, emphasizing that they could withdraw from the study whenever they wished to do so and that withdrawal from the study will no way affect the treatment, ensuring confidentially of the information.

Inclusion criteria included age from 20 to 50 years; patients fulfilling ICD-10 criteria for first episode depression. Exclusion criteria included patients with history of epilepsy, mental retardation, substance use disorder or any other organic brain disease or having taken any form of psychiatric treatment for current episode during the previous month, patients having active suicidal ideas, patients with psychotic symptoms, pregnant females or females planning pregnancy during the study period and refusal to give informed consent.

2.2. Measures

A semi-structured clinical interview: Designed by the author to tap into different socio-demographic variables, duration of illness and medications received.

HAM-D (Hamilton, 1960): This is a multiple choice questionnaire that clinicians may use to rate the severity of depression.

Clinical Global Impression (CGI) scale (Guy, 1976): This is a standardized assessment tool that allows clinician to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI scale consists of three global subscales formatted for use with the Global Scoring Sheet: severity of illness subscale, global improvement subscale and efficacy index subscale.

2.3. Study design

All patients were randomly allotted to two groups by a pharmacist using simple random sampling (34 patients in group A receiving L-5-HTP capsules and 36 patients in group B receiving fluoxetine capsules). To avoid bias, similar looking capsules of both drugs were given along with placebo, so that neither the investigator nor the patients knew which medicines were being used for the treatment. All patients in group A received L-5-HTP capsules 150 mg in three divided dosages during the first 2 weeks and then the dose was doubled (300 mg) after the second week. The dosages were increased to 400 mg in three divided dosages after the fourth week. Thereafter, the same dosages were continued. All patients in group B were given fluoxetine 20 mg capsules along with two placebo dosages during the first 2 weeks

and then increased to 30 mg along with placebo dosages after the second week. The dosages were increased to 40 mg along with placebo dosages after the fourth week. Thereafter, the same dosages were continued.

At the initial visit, the severity of depression was assessed on the HAM-D to establish baseline scores. After baseline assessment at first contact, the second, third and fourth assessments were carried out after 2, 4 and 8 weeks, respectively. During the treatment period, care was taken to rule out any environmental change or stressful event. Efficacy of treatment was assessed by comparing the HAM-D scores obtained at these examinations with the baseline score. The investigator recorded his assessment of the overall clinical picture for each patient at each visit; a final evaluation of both efficacy and tolerance was done at the end of the study using the CGI scale. Tolerance of treatment was assessed by recording any signs and symptoms of adverse events reported or observed during the study and any information pertaining to such. The observation period in both groups was of 8 weeks. Four patients from group A and six patients from group B dropped out of the study, the reason for which could not be ascertained as they never reported back and were thus excluded from study. There were 30 patients from both the groups who completed the study.

The initial baseline score of HAM-D was taken; subsequent reduction in HAM-D scores in relation to baseline score on days of observation were recorded and patients were rated according to reduction in baseline HAM-D scores as:

Recovery: Patients with reduction of 75–100% from baseline scores at the end of the study. *Moderate improvement*: A score reduction of 50–74% from baseline scores at the end of study. *Mild improvement*: A score reduction of less than 50% from baseline scores at the end of study. *Positive response*: Patients showing more than 50% reduction from baseline scores. *No response*: Patients with no reduction from baseline scores. *Deterioration*: Patients with more than baseline scores.

2.4. Statistical analysis

The data were subjected to statistical evaluation using Statistical Package for the Social Sciences (SPSS) 17 software. The data were assessed by mean, range and standard deviation. The discrete data was assessed in number and percentage. For categorical variables, 'Chi-square test' was used for comparison between two groups. For continuous variables Student's '*t*-test' was used (unpaired *t*-test for intra-group and paired *t*-test for inter-group comparison). The *P* values were two tailed and probability level for significant difference was set at <0.05 and $P < 0.01$ (highly significant).

3. Results

3.1. Socio-demographic profile

The mean age for patients in group A was 38.8 ± 7.04 years, which was comparable to mean age of 34.97 ± 8.59 of group B. No statistical difference was found between the two treatment groups as far as sex distribution was concerned. The majority of patients in both groups were illiterate or had primary education, i.e. 53.3% in the L-5-HTP group as compared to 36.7% in the fluoxetine group with no statistical significant. A majority of the patients belonged to rural background (73.3% in the L-5-HTP group and 70% in the fluoxetine group). No statistical significant difference was found between the two treatment groups on residential status and marital status as most of the patients in the two groups were married (83.3% in the L-5-HTP group and 63.3% in the fluoxetine group).

3.2. Degree of baseline depression based on HAM-D score

As shown in Table 1, baseline depression was very severe in 46.7% of patients in the L-5-HTP group and 53.3% of patients in the fluoxetine group. In the L-5-HTP group, 23.3% of patients had severe depression and 30% had moderate depression while in the fluoxetine group, 16.7% of patients had severe depression and 30% had moderate depression. Intergroup comparison did not show any statistically significant difference.

3.3. Response to medication

Table 2 shows the intra-group and inter-group comparison of change in HAM-D scores from baseline to 2 weeks, 4 weeks and 8 weeks of treatment. A mean reduction of 5.066 ± 3.720 SD in HAM-D scores was found at 2 weeks, 9.33 ± 6.519 SD at 4 weeks and 12.7 ± 8.53 SD at 8 weeks with L-5-HTP (group A) which was lesser than corresponding reduction with the fluoxetine (group B), i.e. 7.00 ± 2.791 SD at 2 weeks, 12.167 ± 4.418 SD at 4 weeks and 14.9 ± 5.37 SD at 8 weeks. Though the difference was highly significant statistically for both the groups individually, comparison between the two treatment groups did not reveal any significant difference at 2 weeks, 4 weeks and 8 weeks.

In Table 3, percentage of change in HAM-D scores were grouped into six classes, i.e. worsened HAM-D score, no change in HAM-D score, <35% decrease, 35–49% decrease, 50–74% decrease and ≥75% decrease. The percentage of decrease in HAMD scores of group A was 23.13%, 42%, 57.99% at 2 weeks, 4 weeks and 8 weeks, respectively, which were less as compared to group B, i.e. 31.34%, 54.45% and 63.54% at 2 weeks, 4 weeks and 8 weeks, respectively. After 4 weeks, positive response was observed in 19 patients of the L-5-HTP group as compared to 24 of patients receiving fluoxetine. After 8 weeks, positive response was observed in 22 patients of the L-5-HTP group as compared to 24 patients receiving fluoxetine with no statistical difference.

3.4. Safety and tolerability

A total of 14 patients (46.7%) in group A and 18 patients in group B (60%) reported adverse effects with no statistical significant difference (Table 4). The most common adverse effects in the L-5-HTP group were nausea, anorexia, headache; in the fluoxetine group nausea, anorexia, headache and insomnia predominated. In

Table 1
Baseline degree of depression on Hamilton Rating Scale for Depression (HAM-D).

HAM-D score	Degree of depression	Group A (L-5-HTP) ($n=30$)		Group B (fluoxetine) ($n=30$)		Comparison		
		N	%	*N*	%	χ^2	df	*P*
14–18	Moderate	9	30	9	30	0.467	2	0.792*
19–22	Severe	7	23.3	5	16.7			
More than or equal to 23	Very severe	14	46.7	16	53.3			

* Not significant.

Table 2
Intra-group and Inter-group comparison of change in HAM-D scores from baseline to 2 weeks, 4 weeks and 8 weeks with treatment.

	HAM-D		Mean ± SD	Intra-group comparison			Inter-group comparison		
	Baseline	2 weeks		*t*	df	*P*	*t*	df	*P*
Group A	21.90 ± 4.269	16.83 ± 6.529	−5.066 ± 3.720	7.455	29	<0.01**	0.992	58	0.326*
Group B	22.33 ± 4.412	15.33 ± 5.101	−7 ± 2.791	13.734	29	<0.01**			
	Baseline	4 weeks							
Group A	21.90 ± 4.269	12.57 ± 8.787	−9.33 ± 6.519	7.841	29	<0.01**	1.242	58	0.219*
Group B	22.33 ± 4.412	10.17 ± 5.902	−12.16 ± .418	15.082	29	<0.01**			
	Baseline	8 weeks							
Group A	21.90 ± 4.269	9.20 ± 10.61	−12.7 ± 8.53	8.151	29	<0.01**	0.785	58	0.436*
Group B	22.33 ± 4.412	7.43 ± 6.28	−14.90 ± 5.37	15.193	29	<0.01**			

* Not significant.
** Significant.

both groups most of the adverse events were first experienced during the first few days and were reported at week two.

3.5. Efficacy responders at 8 weeks

Response defined as CGI score less than four. At 8 weeks, 22 (73.33%) patients showed response with L-5-HTP, while 25 (80.33%) with fluoxetine treatment. Intergroup comparison did not reveal any statistical significant difference (Table 5).

4. Discussion

Though few studies in the past had examined the role of L-5-HTP in depression and compared it to various antidepressants, no Indian study had assessed its role in depression until now. Most antidepressant trials are scheduled for no longer than 4 weeks, a period not always sufficient to bring out a difference and to permit reliable evaluation (Quitkin and Rabkin, 1981). A difference in efficacy may take as long as 6 weeks of treatment to became apparent (Quitkin et al., 1984). For this reason, a period of 8 weeks was chosen for evaluation. Most of the socio-demographic variables showed no statistical difference between the two treatment groups. Similar results have been reported by previous double blind studies (Angst et al., 1977; Poldinger et al., 1991).

Best results with L-5-HTP were observed in patients of endogenous depression, involution or senile depression and anxious-agitated depression (Nakajima et al., 1978; Zmilacher et al., 1988). However, the present study did not look into different types of depression. Evaluating baseline depression is important to assess the efficacy of any anti-depressant drugs. As noted, most of the patients had a moderate to severe degree of baseline depression according to HAM-D scores in both treatment groups which were comparable to another study in past (Hechbech et al., 1977). Results revealed that both treatment groups showed significant and nearly equal reduction in HAM-D scores beginning at week two and continuing through week eight. This pattern is congruent with a double blind study which examined the role of L-5-HTP in depression and suggested that antidepressant action started within 2 weeks of treatment (Poldinger et al., 1991).

Most of the studies in the past had declared clear efficacy of L-5-HTP in depression (Fujiwara and Otsuki, 1974; Van Praag, 1984). Some double blind trials had found no significant difference in efficacy of L-5-HTP as compared to tri-cyclic antidepressants (Angst et al., 1977). A double blind placebo controlled trial evaluated L-5-HTP in comparison to clomipramine in 20 patients with endogenous unipolar or bipolar depression at daily oral

Table 3
Frequency related to the percent decrease in the HAM-D scale scores.

	% Decrease in HAM-D scores	Group A (L-5-HTP) (*n* = 30)		Fluoxetine Group B (*n* = 30)	
		%	*N*	%	*N*
After 2 weeks of treatment	Mean decrease	23.13		31.34	
	Worsened HAM-D score		1		0
	No change in HAM-D score		7		2
	<35% decrease		12		17
	35–49% decrease		8		5
	50–74% decrease		2		6
	75% or more decrease		0		0
After 4 weeks of treatment	Mean decrease	42.60		54.45	
	Worsened HAM-D score		2		1
	No change in HAM-D score		6		1
	<35% decrease		2		2
	35–49% decrease		1		2
	50–74% decrease		13		19
	75% or more decrease		6		5
After 8 weeks of treatment	Mean decrease	57.99		63.54	
	Worsened HAM-D score		2		1
	No change in HAM-D score		6		1
	<35% decrease		0		0
	35–49% decrease		0		4
	50–74% decrease		4		8
	75% or more decrease		18		16
Total number of patients evaluated		30		30	

Response rate at the end of study (drop of more >50% HAM-D)—group A: 22 patients; group B: 24 patients. Remission rate at the end of study (HAM-D score 7 or below)—group A: 18 patients; group B: 17 patients.

Table 4
Number of patients reporting side effects.

Side effects	Group A (L-5-HTP) (*n* = 30)	Group B (fluoxetine) (*n* = 30)	Comparison		
			χ^2	df	*P*
Present	14 (46.7%)	18 (60%)	1.07	1	0.301*
Absent	16 (53.3%)	12 (40%)			

* Not significant.

Table 5
Treatment response from final overall assessment of efficacy on Clinical Global Impression (CGI) scale.

Response	Group A (L-5-HTP) (*n* = 30)	Group B (fluoxetine) (*n* = 30)	Comparison		
			χ^2	df	*P*
Yes	22	25	0.884	1	0.347*
No	8	5			

* Not significant.

dosages of 200 mg over 3 weeks period. Marked improvement was observed in 11 of the patients and L-5-HTP and clomipramine were found equally effective (Van Praag, 1979).

Another double blind study compared L-5-HTP efficacy to a selective serotonin reuptake inhibitor (SSRI), fluvoxamine and revealed equal efficacy in the two treatment groups A total of 36 patients, all of whom were diagnosed with some form of depression, received either 100 mg of L-5-HTP thrice daily, or 150 mg of fluvoxamine (the SSRI) thrice daily. At the initial visit, severity of depression was assessed on the HAM-D and on a self-assessment scale (SAD) completed by the patients to establish baseline scores. Upon acceptance, the patients were examined every 2 weeks during the 6 week trial (i.e. three times after the initial examination). The efficacy of treatment was assessed by comparing the HAM-D and SAD scores obtained at these examinations with the baseline and with a final evaluation of both efficacy and tolerance by the CGI at the end of the study. Both treatment groups showed significant and nearly equal reduction in depression beginning at week two and continuing through week six. After 4 weeks, 15 of the 36 patients treated with L-5-HTP, and 18 of the 33 patients treated with fluvoxamine had improved by at least 50%, according to the HAM-D scores (Poldinger et al., 1991).

Antidepressants are ineffective in about 30% of patients with major depression. Some authors then advise treatment of non-responders with more selective reuptake inhibitors. In a double-blind, partial crossover study, 71 patients were selected for treatment during 4 weeks with oxaprotiline and/or fluvoxamine, two non-tricyclic antidepressants that are selective reuptake inhibitors or noradrenaline and serotonin, respectively. All patients had failed to respond to earlier treatment with cyclic antidepressants during the current episode. Only 13% of the patients responded, with 27% of them responding to oxaprotiline and none to fluvoxamine. Moreover, a low response of 27% was also obtained in the crossover phase, which included all non-responders to the first treatment, oxaprotiline being effective in 39% and fluvoxamine in 10% of the patients. The results indicate that selective reuptake inhibitors are not an effective alternative for non-responders to other cyclic antidepressants and that non-responders to "noradrenergic" antidepressants do not appear to have much chance of responding to "serotonergic" antidepressants and vice versa (Nolen et al., 1988).

One open trial using 99 therapy-resistant depressive out-patients were given daily oral dosages of L-5-HTP from 50 to 600 mg over 2 weeks period combined with the peripheral decarboxylase inhibitor. Astonishing recovery without side effects was observed in some 50% of the patients and significant improvement in a majority of the patients (Van Hiele, 1980). This was opposed by other previous studies which observed that L-5-HTP is not a therapeutically effective alternative in depressed patients who have not responded to reuptake inhibitors (Nolen et al., 1985, 1988).

The most common adverse effects of L-5-HTP are gastrointestinal and include nausea, vomiting, and diarrhea. Less commonly, headache, insomnia, and palpitation can occur. Intravenous administration of 200–300 mg of L-5-HTP can induce confusion, memory impairment, and symptoms of behavioral activation (primarily anxiety). These effects are generally much rarer with oral administrations, particularly at lower doses. A study comparing L-5-HTP to L-5-HTP plus a peripheral decarboxylase inhibitor found that gastrointestinal side effects were dose dependent and that they occurred more frequently in patients receiving L-5-HTP alone due to peripheral conversion of L-5-HTP to serotonin, which increases gut motility. In either case, gastrointestinal effects are usually moderate and often lessen or disappear once a steady dosage is achieved (Byerley et al., 1987).

Regarding adverse effects, the most common in the L-5-HTP group were nausea, anorexia and headache while in the fluoxetine group nausea, anorexia, headache and insomnia predominated. Two studies have found that the incidence of nausea due to L-5-HTP is decreased when smaller doses are used (Van Hiele, 1980; Magnussen and Nielsen-Kudsk, 1980) suggesting that the rate of adverse events may be dose proportional.

Studying the antidepressant role of L-5-HTP has many implications as it can be used as an alternative or augmenting therapy in depressive patients. Another issue which is of importance is changing dietary habits of the patients for, as we all know, L-5-HTP is an amino acid naturally produced by the body from L-tryptophan in the food. Food which contains high levels of L-tryptophan can help in alleviating depression. In this regard, educating clinicians as well as patients regarding dietary skills is imperative.

5. Conclusion

L-5-HTP definitely plays an antidepressant role in patients of depression. The antidepressant effect is apparent in all degrees of depression including severely depressed. The minimal effective dose of L-5-HTP to produce antidepressant effect is 150 mg/day; a significant number of patients improved with 300 mg of L-5-HTP. The antidepressant effect of L-5-HTP took 2 weeks to start which subsequently continued. L-5-HTP was well tolerated by patients. The antidepressant effect of L-5-HTP was equal to that of fluoxetine.

6. Limitations

Though the present study was conducted using sound methodology and strict inclusion criteria, there are certain limitations. Small sample size and a single sited study contained to a specific region limits the generalizability of the results to the rest of the Indian population. Lack of a placebo control group is also a limitation of the study. Besides, multicentral studies or metaanalysis studies in different geographical locations can increase accuracy of the results. Dietary intake was not taken into consideration as it may affect the level of L-5-HTP in individual patients. Further studies are required to explore the relationship between dietary changes and depression.

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