TRYPTOPHAN and 5-HTP IN SEROTONIN DEFICENCY SYNDROME

NEW ASPECTS OF THE MECHANISMS OF ACTION AND MODE OF ADMINISTRATION

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Biosynthesis of

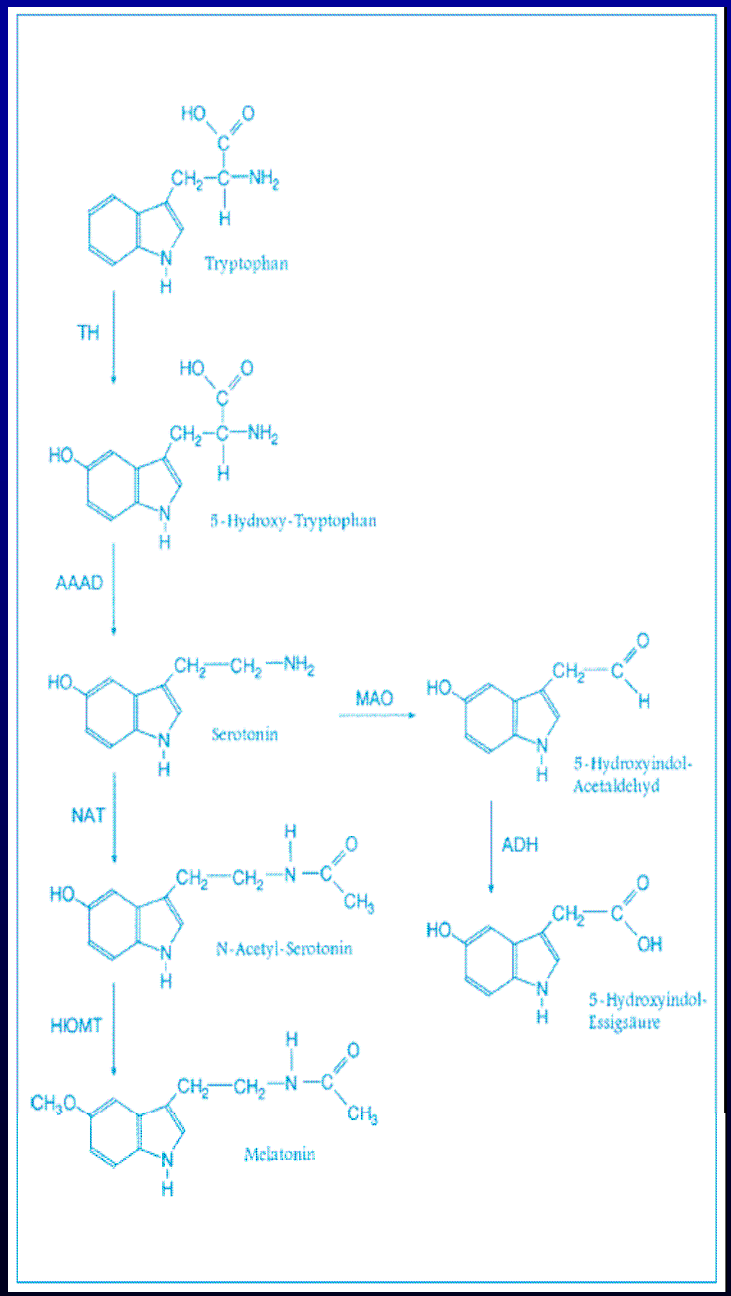
5-HYDROXYTRYPTOFAN

and

MELATONIN

in relation to

TRYPTOPHAN



TRYPTOPHAN AND 5-HYDROXYTRYPTOFAN DEFICENCY IN DEPRESSION

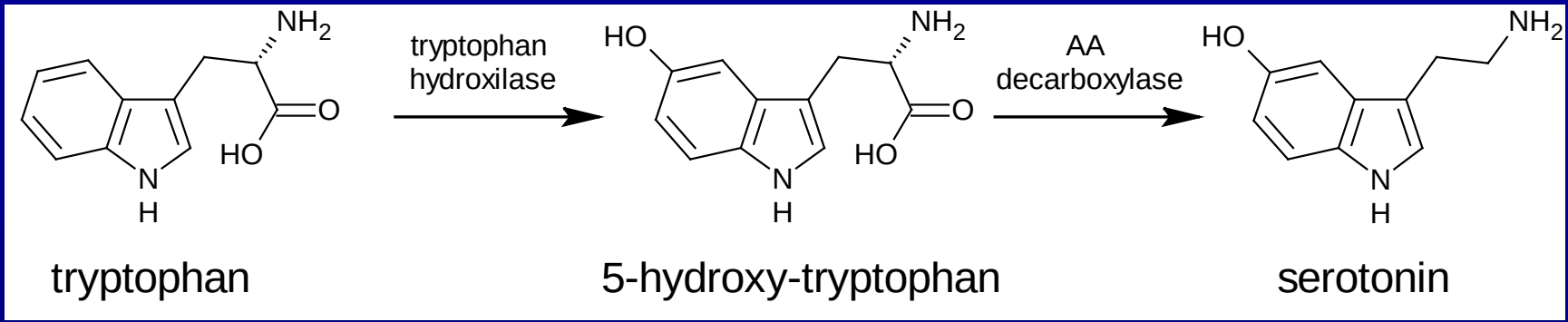
STATE OF ART

Tryptophan (LT) and 5-hydroxy-tryptophan (5HTP) have been used in the treatment of various pathologies related to serotonin deficiency in the CNS:

- mild depression
- fibromyalgia syndrome
- vasomotor headache
- anxiety / depression syndrome

In a number of cases of the 108 clinical trials the results have been controversial.

THE SEROTONIN PATHWAY



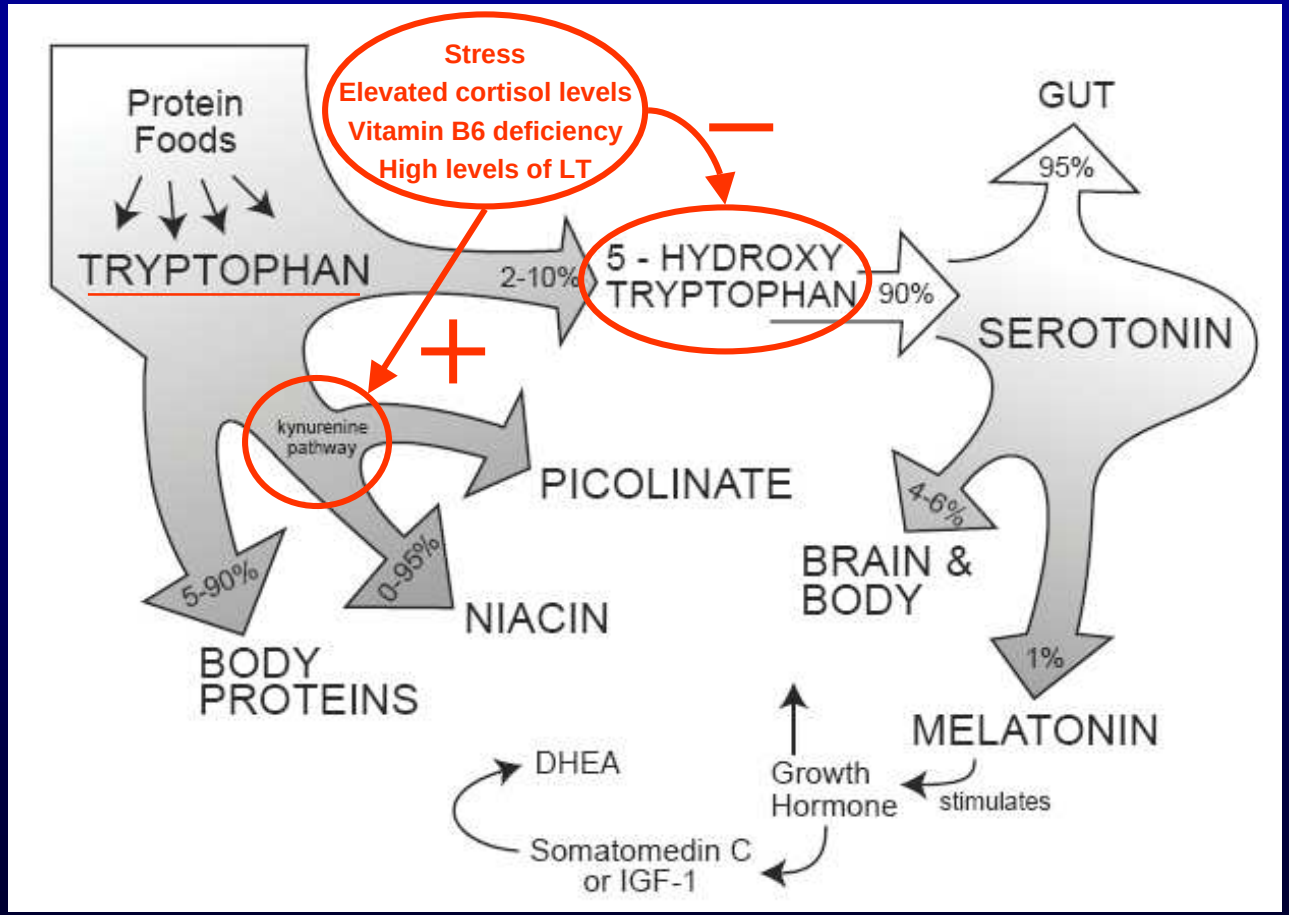
All serotonin used in the CNS is synthesized from LT (an essential AA poorly present in the dietary proteins) to 5HTP though a hydroxilase which is the rate limiting step in the serotonin synthesis.

Tryptophan hydroxylase can be inhibited by numerous factors, including stress, insulin resistance, vitamin B6 deficiency and insufficient magnesium.

5HTP easily crosses the blood-brain barrier, not requiring the presence of a transport molecules as is the case of LT, which shares a “shuttle” protein with several others AA.

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

THE GREATER PART OF LT IS USED IN SYNTHESIS OF PROTEINS OR IN THE PRODUCTION OF OTHER METABOLITES THROUGH THE KYNURENINE PATHWAY



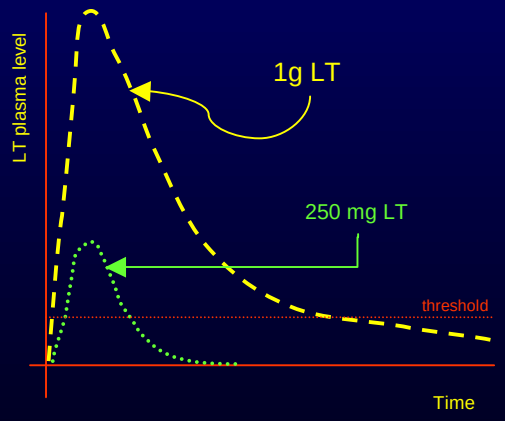
High dosages of LT will stimulate the conversion of LT to kynurenine, lowering serum LT levels

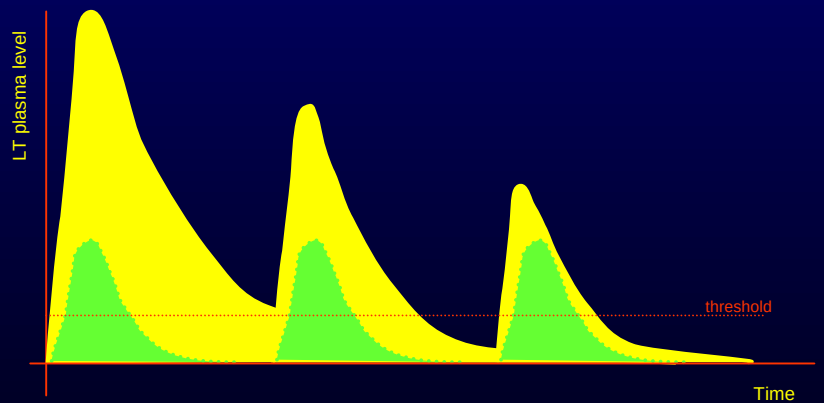
John H. Juhl, D.O.

Altern Med Rev 1998;3(5):367-375

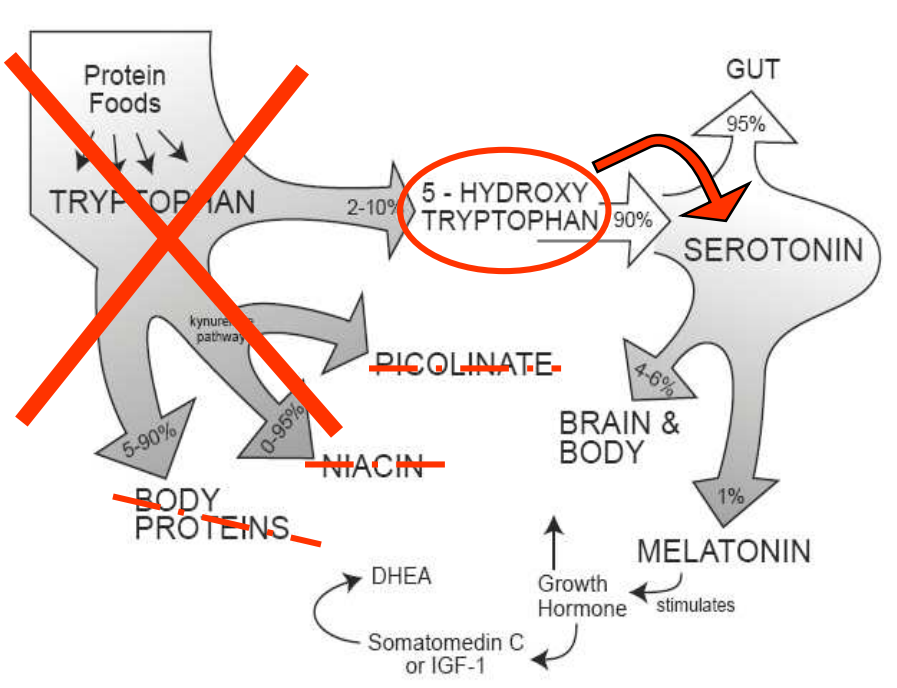
"There are four not-insurmountable problems in using tryptophan to increase flux through the serotonin pathway:

1. **availability**,
2. **concern about purity,**
3. **the large dose required**, **and**
4. **up-regulation of tryptophan pyrrolase, the degradation enzyme induced by higher concentrations of tryptophan".**





ADMINISTRATION OF 5HTP ALONE WILL EXCLUDE THE KYNURENINE PATHWAY



PROBLEMS RELATED TO ADMINISTRATION OF NORMAL-RELEASE ("BOLUS") 5HTP:

- **Local saturation of AAAD.**
- **5HTP crossing BBB with difficulties in long-term depressive states.**
- **Possibility of side-effects (nausea) in high 5HTP dosage (100mg 3 die).**

Administration of "bolus" 5-HTP requires multiple daily administration that might contrary to the chronobiological requirements of the organism, on one hand, and decrease patient compliance, on the other.

A NEW STRATEGY IN THE TREATMENT OF DEPRESSION

WITH 5HTP / LT

A rapid administration of low doses of 5-HTP

- Supply an “hit” dosage for a rapid conversion in serotonin to assure an initial therapeutic effect
- The absorption of 5HTP is rapid and it may be taken with meals without reducing its effectiveness
- Low dosages prevent the local saturation of AAAD
- Doses ≤ 50 mg are indicated to prevent collateral effects (nausea)

A protracted administration of low quantities of LT

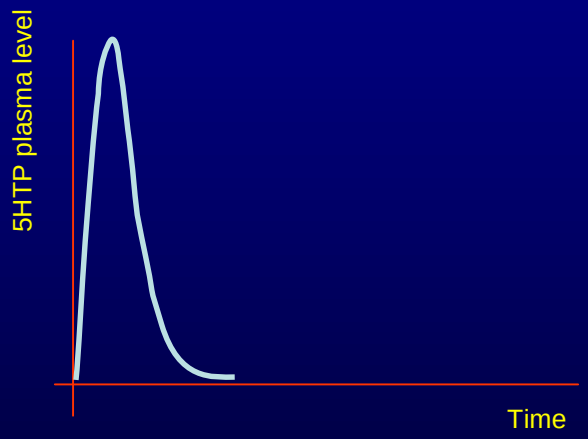
- The protracted availability of low levels of LT maintain the effects initially obtained with 5HTP
- The large doses normally required are unnecessary since “hit” effects are obtained with the low-dose 5HTP
- Low plasma LT levels prevent the up-regulation of the kynurenine pathway and / or the local saturation of AAAD.
- The alternate administration of 5HTP and LT assure the possibility to supply serotonin precursors for both metabolic pathways

In the therapy of the depression 5HTP has been normally used in dosage comprised between 50 up to 2000 mg in three daily administrations. A significantly better compliance in a correct chronobiological manner will be obtained with two administration (in morning and at midday)

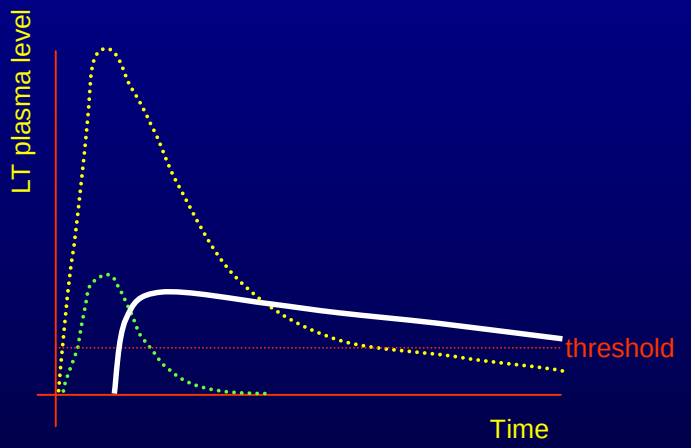
A NEW TWO-LAYER TABLET:

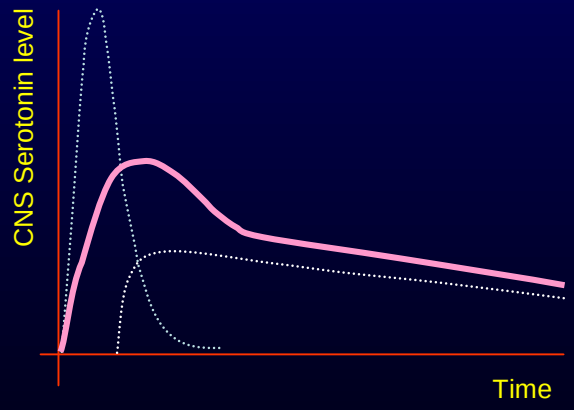
CONTROLLED RELEASE - FAST AND PROTRACTED

LAYER
5-HTP "FAST"



LAYER
LT "PROTRACTED"





CLINICAL TRIALS OF LT and/or 5-HTP USE IN DEPRESSION

Since the early 1970s, at least 15 studies have evaluated the clinical effects of LT and/or 5-HTP in depression.

From the results obtained in double blind studies:

94/161 patients improved

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

THE COCHRANE COLLABORATION®

Tryptophan and 5-Hydroxytryptophan for depression (Review)

Shaw K, Turner J, Mar C

Main results

108 trials were located using the specied search strategy. Of these, only two trials, involving a total of 64 patients, were of sufficient quality to meet inclusion criteria. The available evidence suggests these substances were better than placebo at alleviating depression (Peto Odds Ratio 4.10; 95% confidence interval 1.28-13.15; RD 0.36; NNT 2.78). However, the evidence was of insufficient quality to be conclusive.

Fig. 00 L-Tryptophan and 5-HTP versus placebo for the treatment of depression

01.01 Numbers of responders

Review: Tryptophan and 5-Hydroxytryptophan for depression
Comparison: 01 L-Tryptophan and 5-HTP versus placebo for the treatment of depression
Outcome: 01 Numbers of responders

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Thomson 1982	13/21	5/15		79.4	3.04 [0.82, 11.22]
Van Praag 1972	3/5	0/5		20.6	13.08 [1.01, 170.31]
Total	26	20		100.0	4.10 [1.28, 13.15]

Total events: 16 (Treatment), 5 (Control)
Test for heterogeneity chi-square=0.99 df=1 p=0.32 I² =0.0%
Test for overall effect z=2.38 p=0.02

0.1 0.2 0.5 1 2 5 10
Favours control Favours treatment

Fig. 01 Side-effects of L-Tryptophan and 5-HTP versus placebo

02.01 Numbers with side-effects

Review: Tryptophan and 5-Hydroxytryptophan for depression
Comparison: 02 Side-effects of L-Tryptophan and 5-HTP versus placebo
Outcome: 01 Numbers with side-effects

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Thomson 1982	3/28	0/26		74.2	7.42 [0.74, 74.66]
Van Praag 1972	1/5	0/5		25.8	7.39 [0.15, 372.38]
Total	33	31		100.0	7.41 [1.01, 54.19]

Total events: 4 (Treatment), 0 (Control)
Test for heterogeneity chi-square=0.00 df=1 p=1.00 I² =0.0%
Test for overall effect z=1.97 p=0.05

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

THE COCHRANE COLLABORATION®

Tryptophan and 5-Hydroxytryptophan for depression (Review)

Shaw K, Turner J, Mar C

Implications for research

Large, well designed, placebo-controlled, randomized controlled trials are needed to assess clinical utility of 5-HTP and tryptophan in the treatment of depression. Future studies should focus on the following issues:

- **evaluation of efficacy in well-defined subgroups of patients with unipolar depression of varying severity**
- **evaluation of side-effects, particularly potentially life-threatening side-effects.**
- **comparisons of different dosage, frequency of administration, and preparations of 5-HTP and tryptophan**

Clinical study with patients suffering by serotonin deficits syndromes

A NEW CLINICAL TRIAL PROTOCOL

Double blind, randomized, placebo controlled grouped efficacy study to evaluate the efficiency of Tryptochron® to improve mood in men and women suffering by mild depression (Stankov et al. 2005)

50 subjects (50% women, 50% men) divided in 5 groups, 10 subjects per group aged 35 to 75 years suffering by mild depression

Mood will be recorded by standardized questionnaires (21 points Hamilton depression score)

For each subject, the status of mood will be recorded two times during study visits: at the study start and at the end of the study after 30 days

Any adverse event and serious adverse event reported by the subject or observed by the investigator will be recorded

Double blind, controlled study with patients suffering by mild depression (N=100)

Group A	50 mg 5HTP fast		250 mg Tryptophan protracted
Group B	Placebo fast		Placebo protracted
Group C	50 mg 5HTP fast		Placebo protracted
Group D	Placebo fast		250 mg Tryptophan protracted
Group E	50 mg 5HTP fast		100 mg 5HTP fast

Two timed per day (morning and midday)

Pre-post evaluation of HAMD score

Treatment time 4 weeks

Project No. 04_5-HTP/TP_AP

Date day month year

Patient/Subject No.

Initials of Patient/Subject

Investigational Center No.

Day of examination

Code of drug

Dosage

Signature of Investigator

Project No. 04_5-HTP/TP_AP

HAMD

GB

Notes:

1. Depressed mood (Sadness, hopeless, helpless, worthless)

- Absent. 0
- These feeling states indicated only on questioning. 1
- These feeling states spontaneously reported verbally. 2
- Communicates feeling states non-verbally - i.e. through facial expression, posture, voice, and tendency to weep. 3
- Patients reports virtually only these feeling states in his spontaneous verbal and non-verbal communication. 4

2. Feelings of guilt

- Absent. 0
- Self reproach, feels he has let people down. 1
- Ideas of guilt or rumination over past errors or sinful deeds. 2
- Present illness is a punishment. Delusion of guilt. 3
- Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations. 4

3. Suicide

- Absent. 0
- Feels life is not worth living. 1
- Wishes he were dead or any thoughts of possible death to self. 2
- Suicide ideas or gestures. 3
- Attempts at suicide (any serious attempts rate 4). 4

4. Insomnia early

- No difficulty falling asleep. 0
- Complains of occasional difficulty falling asleep - i.e., more than half an hour. 1
- Complains of nightly difficulty falling asleep. 2

5. Insomnia middle

- No difficulty. 0
- Patient complains of being restless and disturbed during the night. 1
- Waking during the night - any getting out of bed rates 2 (except for purposes of voiding). 2

6. Insomnia late

- No difficulty. 0
- Waking in early hours of the morning but goes back to sleep. 1
- Unable to fall asleep again if he gets out of bed. 2

7. Work and activities

- No difficulty. 0
- Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies. 1
- Loss of interest in activity; hobbies or work - either directly reported by the patient, or indirect in listlessness, indecision and vacillation (he feels he has to push self to work or activities). 2
- Decrease in actual time spent in activities or decrease in productivity. In hospital rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores. 3
- Stopped working because of present illness. In hospital rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted. 4

8. Retardation (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

- Normal speech and thought. 0
- Slight retardation at interview. 1
- Obvious retardation at interview. 2
- Interview difficult. 3
- Complete stupor. 4

9. Agitation

- None. 0
- Fidgetiness. 1
- Playing with hands, hair, etc. 2
- Moving about, can't sit still. 3
- Hand wringing, nail biting, hair-pulling, biting of lips. 4

10. Anxiety psychic

- No difficulty. 0
- Subjective tension and irritability. 1
- Worrying about minor matters. 2
- Apprehensive attitude apparent in face or speech. 3
- Fears expressed without questioning. 4

Notes (Use a seprate page if necessary)

HAMD

11. Anxiety somatic (Physiological concomitants of anxiety, such as: Gastro-intestinal: dry mouth, wind, indigestion, diarrhea, cramps, belching; Cardio-vascular: palpitations, headaches; Respiratory: hyperventilation, sighing; Urinary frequency; Sweating

- Absent 0
- Mild 1
- Moderate 2
- Severe 3
- Incapacitating 4

12. Somatic symptoms gastrointestinal

- None 0
- Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen. 1
- Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms. 2

13. Somatic symptoms general

- None 0
- Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability. 1
- Any clear-cut symptom rates 2. 2

14. Genital symptoms (Symptoms such as: Loss of libido, Menstrual disturbances)

- Absent 0
- Mild 1
- Severe 2

15. Hypochondriasis

- Not present 0
- Self-absorption (bodily) 1
- Preoccupation with health 2
- Frequent complaints, requests for help, etc. 3
- Hypochondriacal delusions 4

16. Loss of weight. Rate either A or B

A. When rating by history

- No weight loss 0
- Probable weight loss associated with present illness 1
- Definite (according to patient) weight loss 2
- Not assessed 3

B. On weekly ratings by ward psychiatrist, when actual weight changes are measured

- Less than 1 lb. weight loss in week 0
- Greater than 1 lb. weight loss in week 1
- Greater than 2 lb. weight loss in week 2
- Not assessed 3

17. Insight

- Acknowledges being depressed and ill. 0
- Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc. 1
- Denies being ill at all. 2

18. Diurnal variation

A. Note whether symptoms are worse in morning or evening. If no diurnal variation, mark 0.

- No variation 0
- Worse in A.M. 1
- Worse in P.M. 2

B. When present, mark the severity of the variation. Mark "None" if no variation.

- None 0
- Mild 1
- Severe 2

19. Depersonalization and derealization (such as: Feelings of unreality, nihilistic ideas)

- Absent 0
- Mild 1
- Moderate 2
- Severe 3
- Incapacitating 4

20. Paranoid symptoms

- None 0
- Suspicious 1
- Ideas of reference 2
- Delusions of reference and persecution 3

21. Obsessional and compulsive symptoms

- Absent 0
- Mild 1
- Severe 2

Adverse / Serious Adverse Effects

AE yes no Date: _____

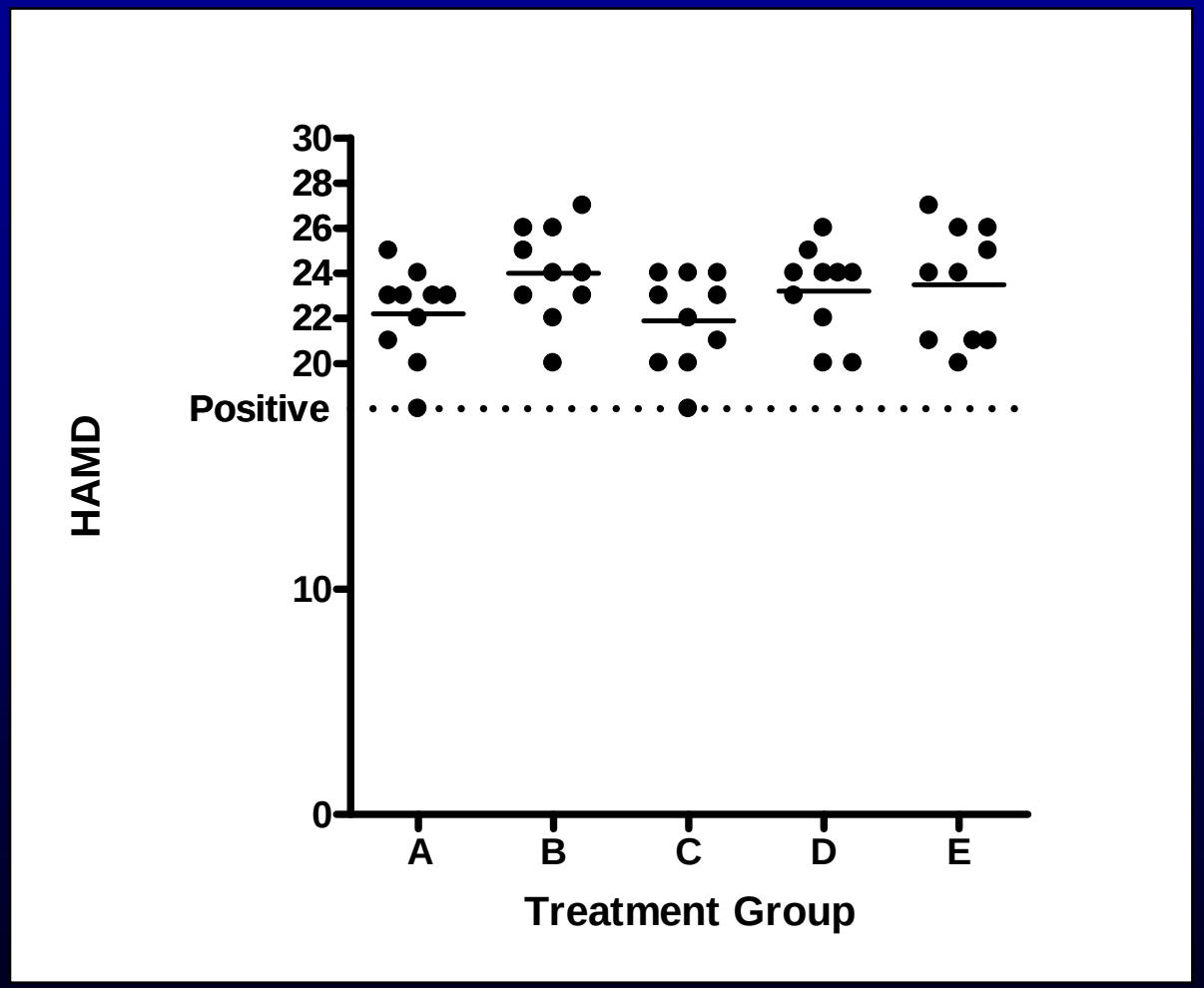
Relationship (Score) 1 2 3 4 5 6

Use additional page(s) for description

SAE yes no Date: _____

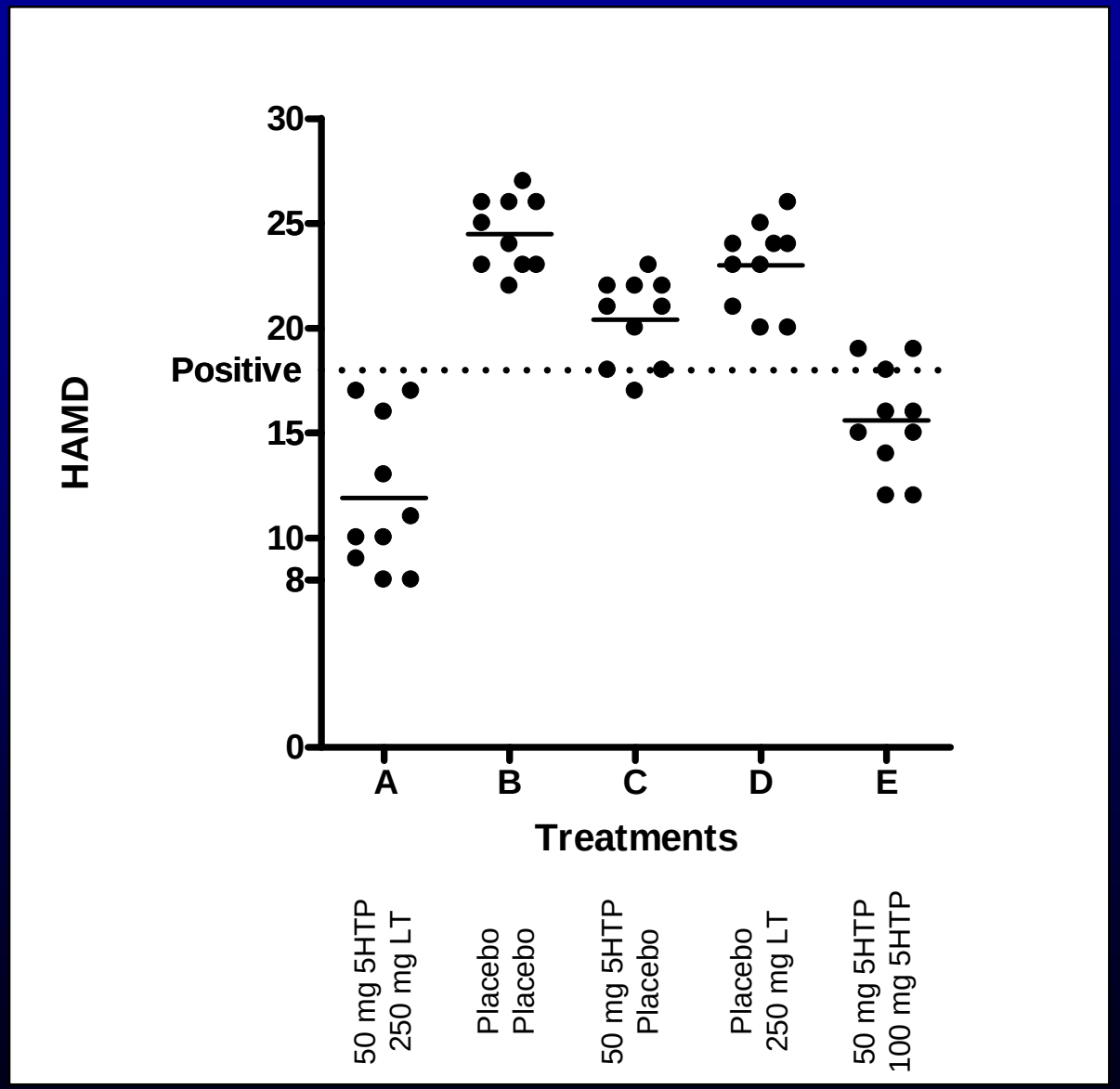
Use additional page(s) for description

RESULTS
(Stankov et al. 2005)



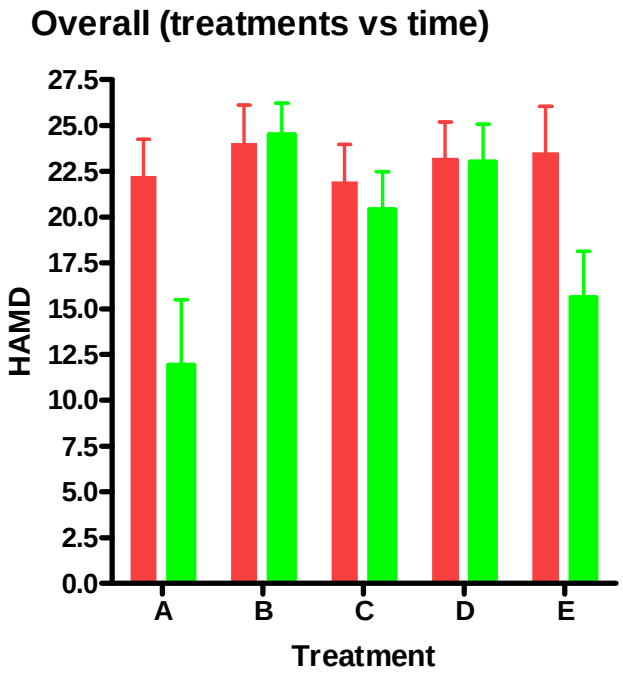
RESULTS

(Stankov et al. 2005)



RESULTS
(Stankov et al. 2005)

TWO WAY ANOVA



Source of Variation	P value summary	Significant?
Interaction	***	Yes
Treament	***	Yes
Time	***	Yes
Subjects (matching)	***	Yes

Time 0 vs Time 30

Treament	Difference	t	P value	Summary
A	-10.30	13.36	P<0.001	***
B	0.5000	0.6484	P > 0.05	ns
C	-1.500	1.945	P > 0.05	ns
D	-0.2000	0.2594	P > 0.05	ns
E	-7.900	10.24	P<0.001	***

RESULTS
(Stankov et al. 2005)

NUMBER OF ADVERSE EFFECTS

Group A	50 mg 5HTP fast	250 mg Tryptophan protracted	**ns**
Group B	Placebo fast	Placebo protracted	**ns**
Group C	Placebo fast	250 mg Tryptophan protracted	**ns**
Group D	50 mg 5HTP fast	Placebo protracted	**ns**
Group E	50 mg 5HTP fast	100 mg 5HTP fast	**p>0.05***

*** Slight self limited nausea**

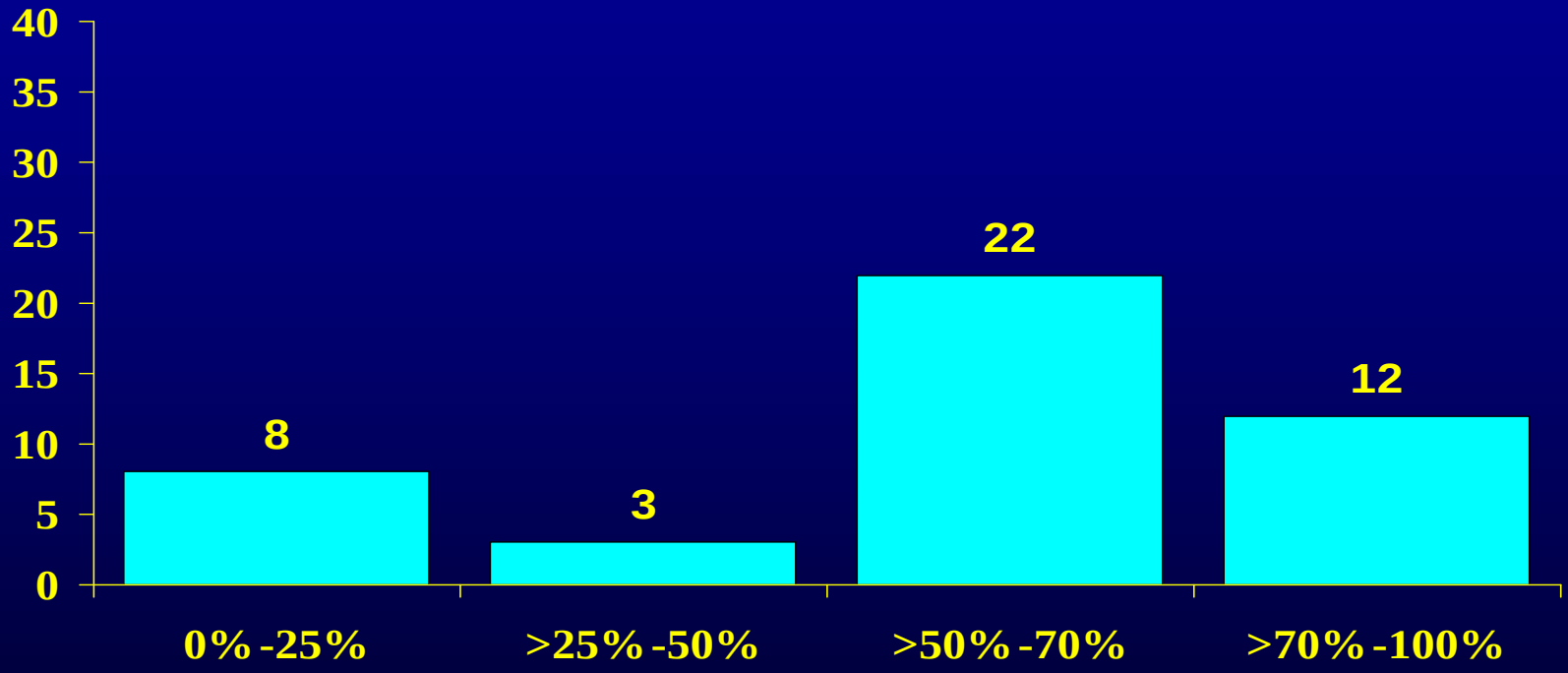
Open labeled study in patients suffering by constant cephalic attacks (del Bene et al., 2009)

50 mg 5HTP
fast

250 mg Tryptophan
protracted

One times per day (morning)
Patients with more than 15 pain attacks / month
Pre-post evaluation of frequency of attacks
Treatment time 8 weeks

Number of patients with attack frequency reduction (N= 45)



Note: mean reduction was 66,6% over all patients
Only one drop out due to mild gastro-intestinal side effects

Two double blind, placebo controlled studies in patients suffering by fibromyaglia

Group A	50 mg 5HTP fast	250 mg Tryptophan protracted	**N=30**
Group B	Placebo fast	Placebo protracted	**N=28**

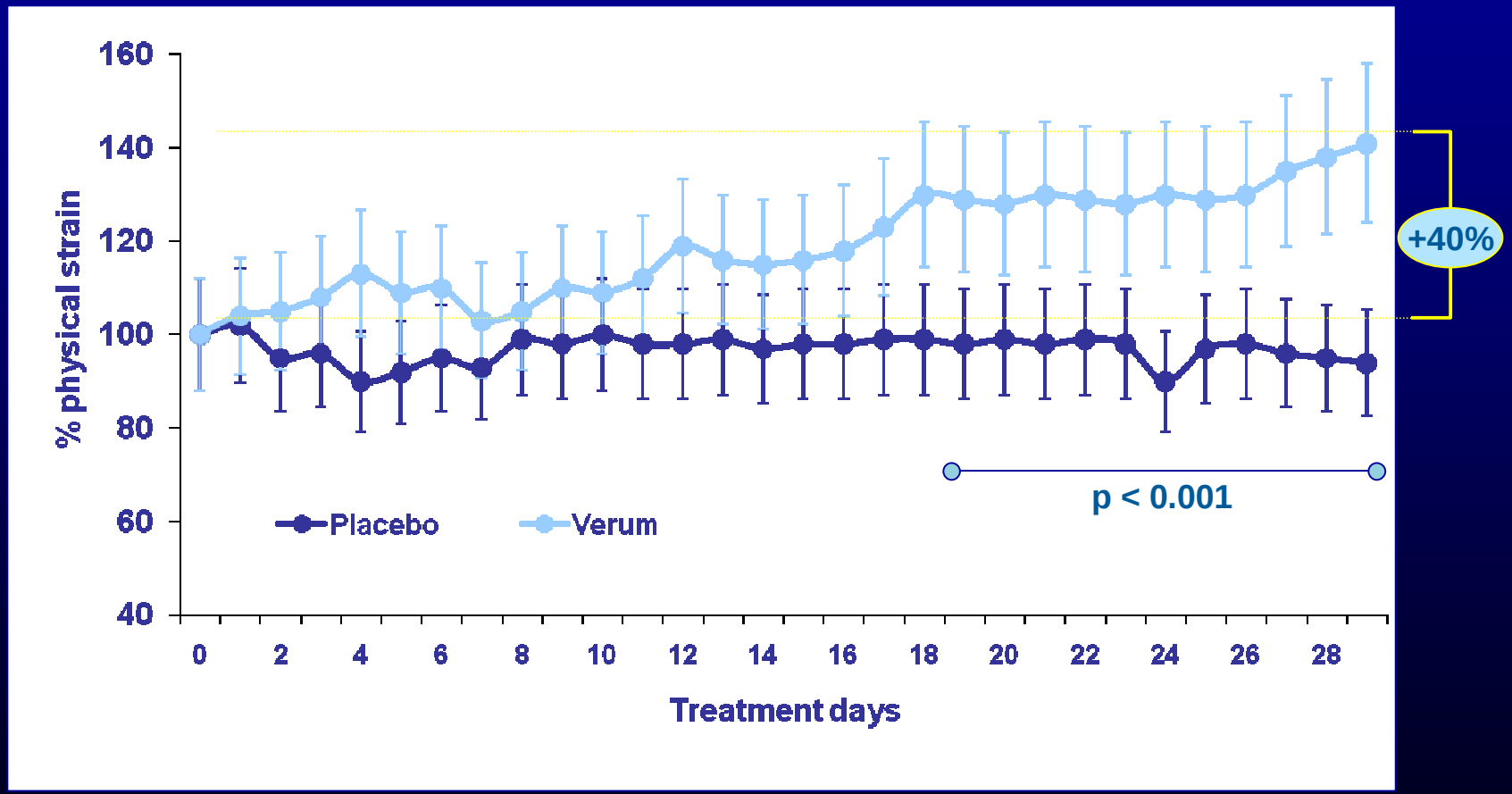
Four tablets per day (2 x morning; 2 x midday)

Pre-post evaluation of pain

Treatment time 4 weeks

Tryptophan in chronic pain - Study by Prof. Zastrow[1] – (I)

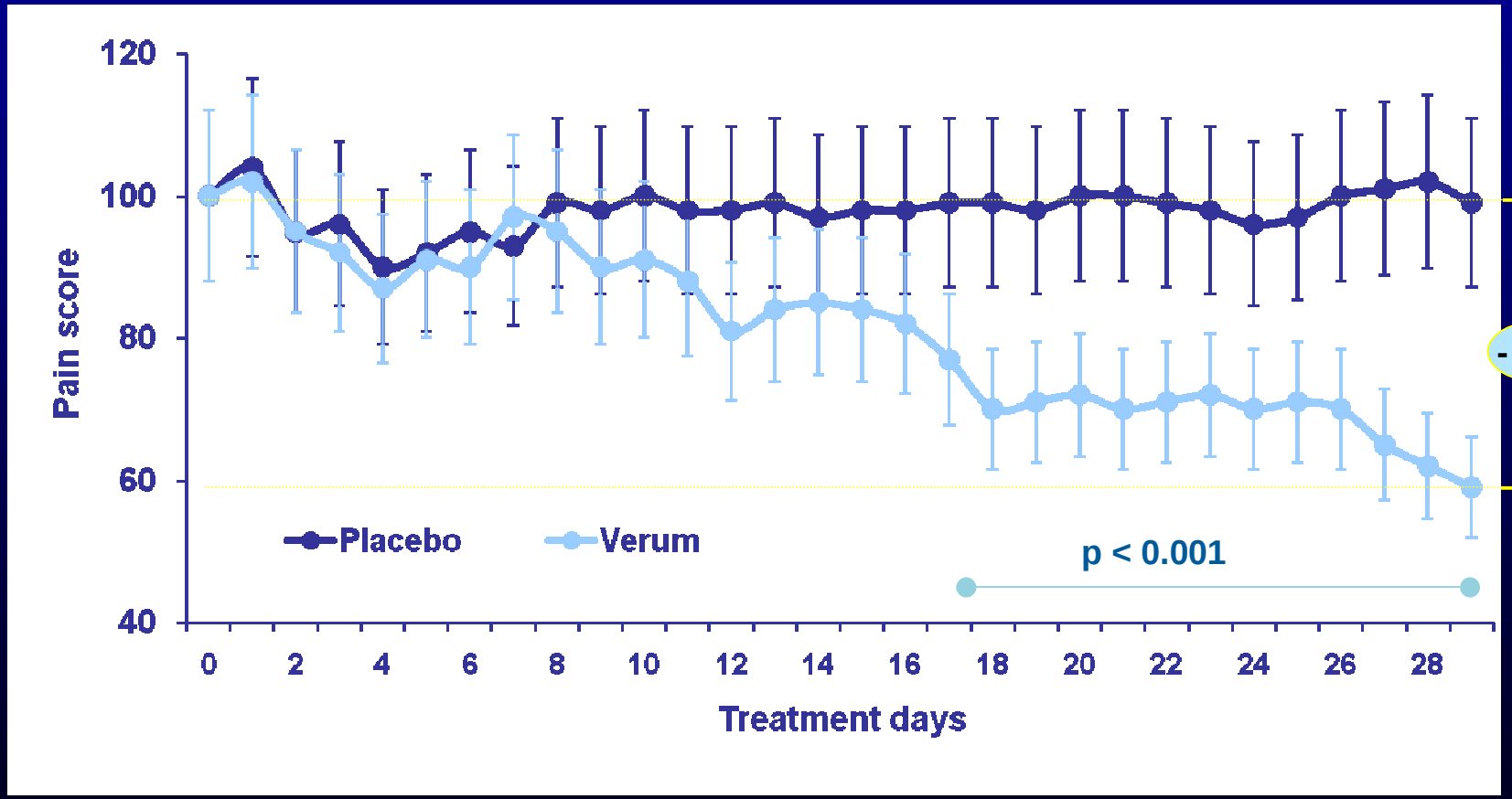
Physical endurance significantly increased by 40% (Active over Placebo)
after 4 weeks of treatment (N = 36)



[1] unpublished data

Tryptophan in chronic pain – Study by Prof. Zastrow[1] – (II)

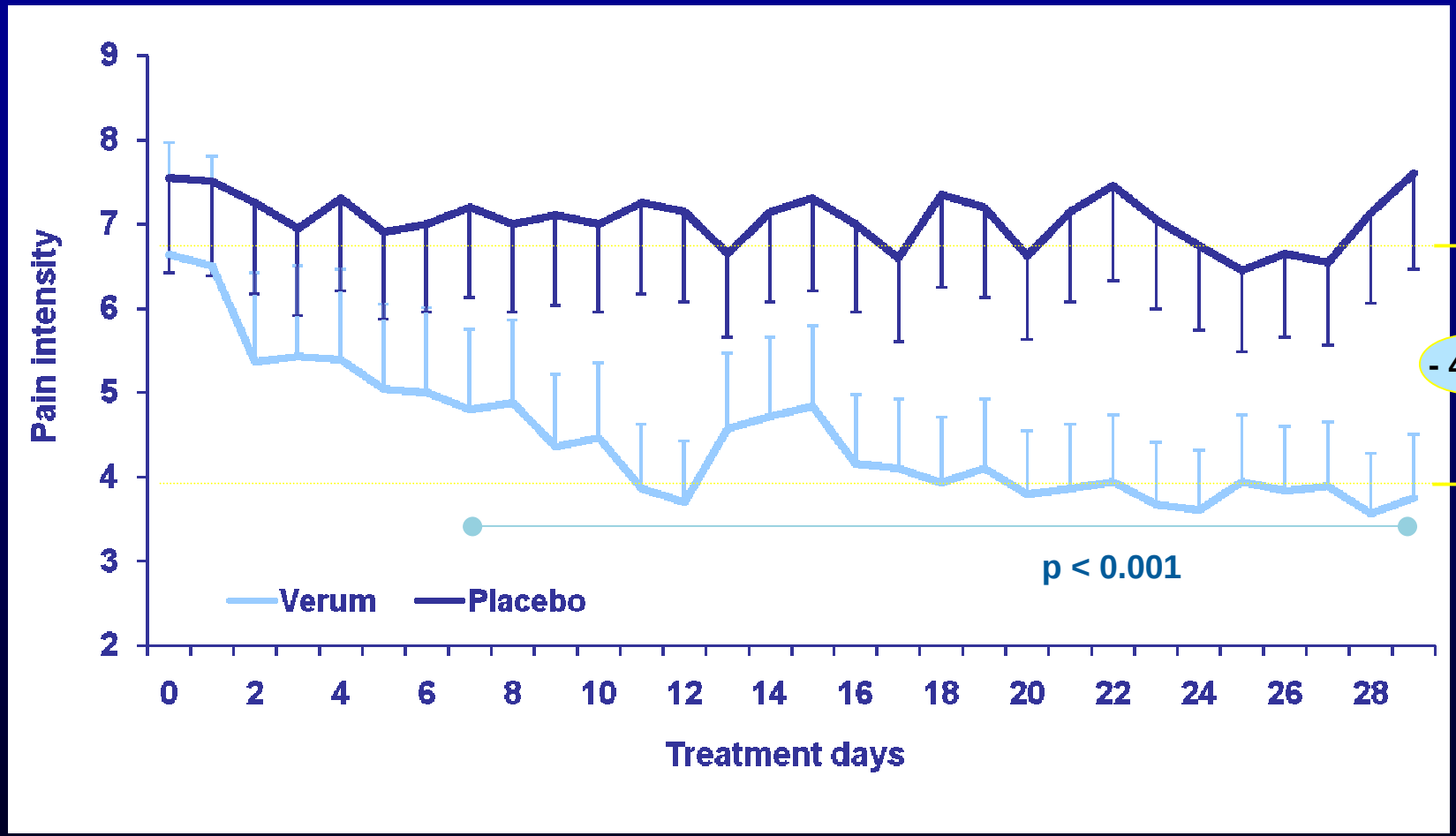
Reduction of pain-score by 40% **in the morning** during
a 4-weeks treatment period (Active over Placebo; N = 36)



[1] unpublished data

Tryptophan – in fibromyalgia - Study Prof. Fricke[1] – (I)

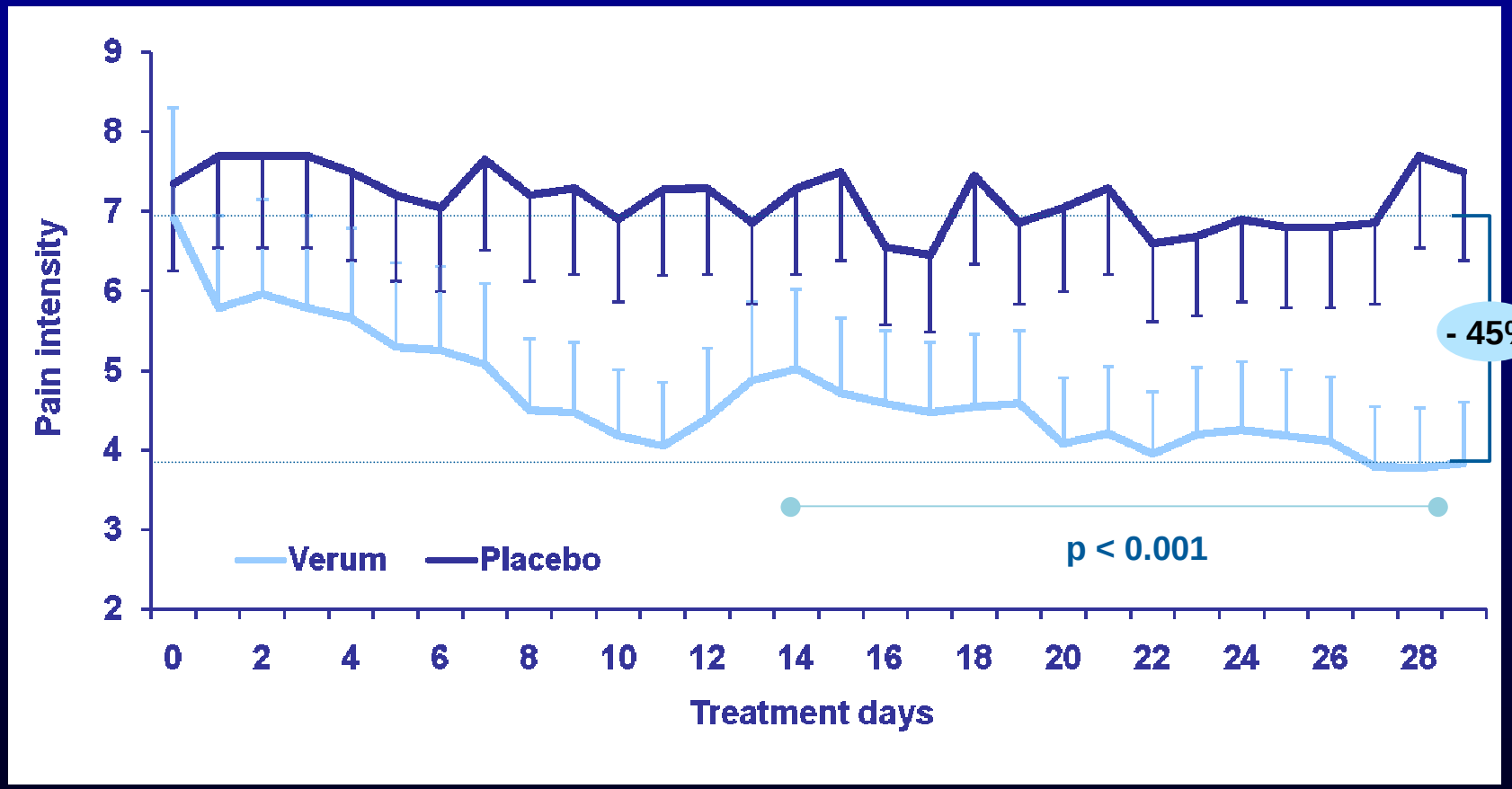
Reduction of pain intensity by 43% **in the morning** during a 4-weeks treatment period (Active over Placebo; N = 22)



[1] unpublished data

Tryptophan in fibromyalgia – Study by Prof. Fricke[1] – (II)

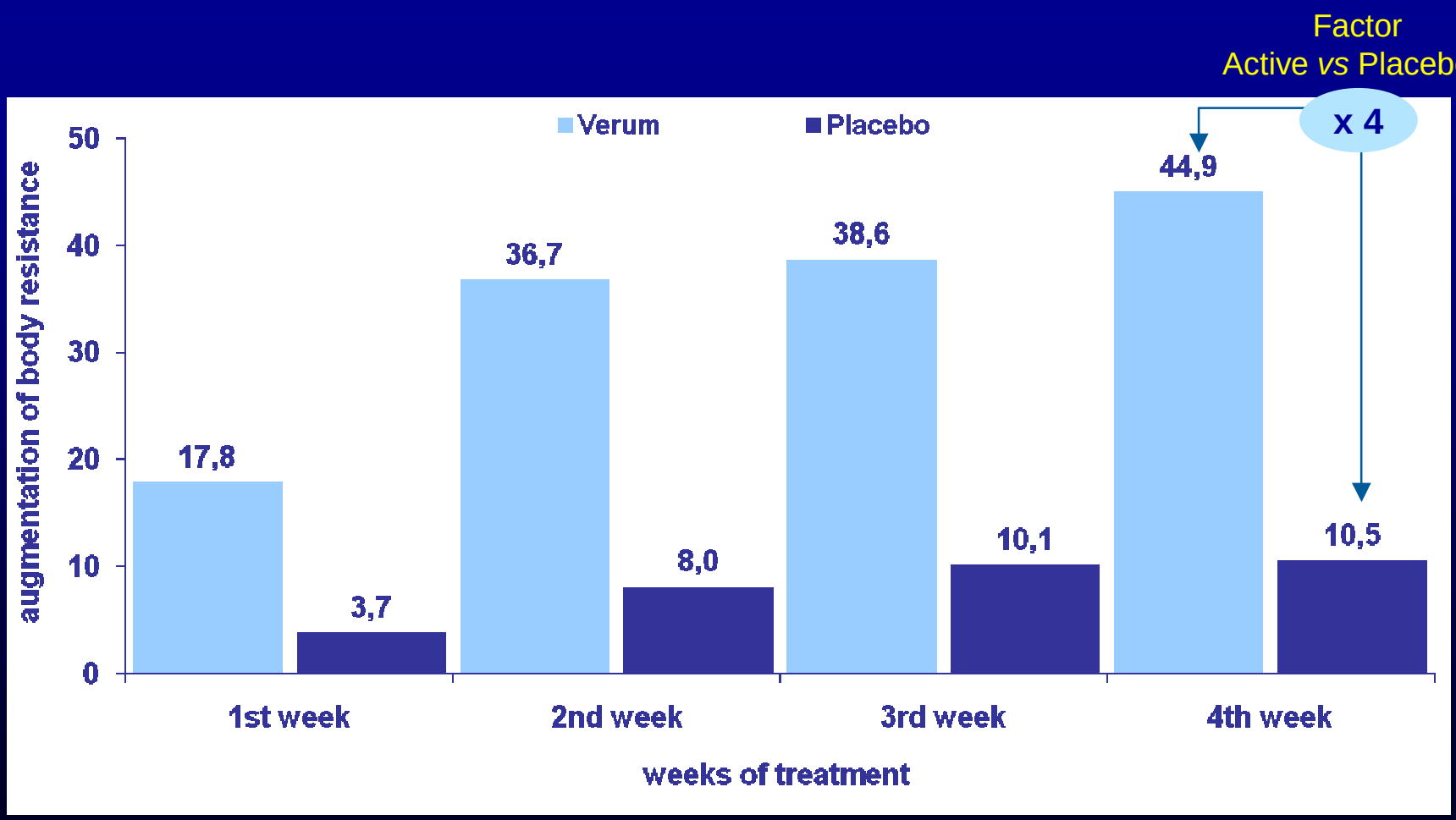
Reduction of pain intensity by 45% **in the evening** during a 4-weeks treatment period (Active over Placebo; N = 22)



[1] unpublished data

Tryptophan in fibromyalgia – Study by Prof. Fricke[1] – (III)

Weekly increase of physical endurance Active over Placebo (N = 22)



[2] Common Factor of effectiveness Verum *vs* Placebo at pain therapy: x 2

[1] unpublished data

Tryptophan – only minor side-effects in both studies (N = 58)

Side effects	***Active***	***Placebo***	***p < 0.05***
Sweating	0	1	No
Anxiety	1	0	No
Dizziness	0	1	No
Concentration problems	0	1	No
Sleep disturbancies	3	5	No
Initial day-time tiredness	8	0	Yes, as expected
Nausea	1	2	No
Total	***13***	***10***	***No***

CONCLUSIONS:

1. High doses of LT alone induce the kynurenine pathway and produce no consistent effects in the substitution of low serotonin levels (data from literature)
2. High levels of 5HTP might induce side effects (nausea, epigastric burning) and are not efficient in all cases of mild depression
3. Low doses of 5HTP and/or LT alone are insufficient in the treatment of mild depression
4. The therapeutically-correct formulation of lower dosages of 5HTP (50 mg) and LT (250 mg) given together in a predetermined pattern of fast and protracted release give excellent results in the treatment of patients suffering of serotonin deficit syndrome, e.g. pain, depression, headache
5. This patented formulation avoids the activation of the kynurenine pathway and provides sufficient amount of serotonin precursors in time

Biosynthesis of

MELATONIN

in correlation to

SEROTONIN