

# Integrative therapeutics: Anxiety & Depression

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# Objectives

- Anxiety
  - Background
  - Clinical Evaluation
  - Management Strategies
    - Psychotherapy
    - Pharmaceuticals
    - Natural treatment
  - Case
  - Wrap-up
- Depression
  - Background
  - Clinical Evaluation
  - Management Strategies
    - Psychotherapy
    - Pharmaceuticals
    - Natural treatment
  - Case
  - Wrap-up

## Case Presentation

- C.V 41 y.o male. Diagnosis: Schizoaffective Disorder, Social Phobia, and a subclinical Generalized Anxiety Disorder.
- Treatment: Lamotrigine 100mg bid, Lorazepam 0.5mg tid, Paliperidone 6mg od. CBT group



- Supplements:
  - 5000 IU Vitamin D drops,
  - High potency B-complex with the following dosages (B1 50mg, B2, 25mg, Niacinamide 80mg, Vitamin B6 250mg, B5 50mg, B12 100mcg, Folic acid 0.2mg, Biotin 80 mcg, Choline citrate 40mg)
  - 15mL bid 3:1 ratio EPA:DHA Fish oil (6900mg total fish oil with 4500mg EPA and 1500mg DHA),
  - Magnesium Citrate 300mg od



- 1 week follow up:
  - C.V tapered off of Lorazepam 0.5mg
  - 5mg Glycine powder tid, dissolved under his tongue.
- 1 month follow up:
  - remained off the Lorazepam
  - tapered off Paliperidone
- 3 month follow up:
  - lowered Lamotrigine to 75mg bid



- Current Symptoms:
  - Self-reported improvement in mood
  - no delusions of grandeur
  - He discussed increased socialization and even prospective dating.
  - Not experienced pain or tension in his back.

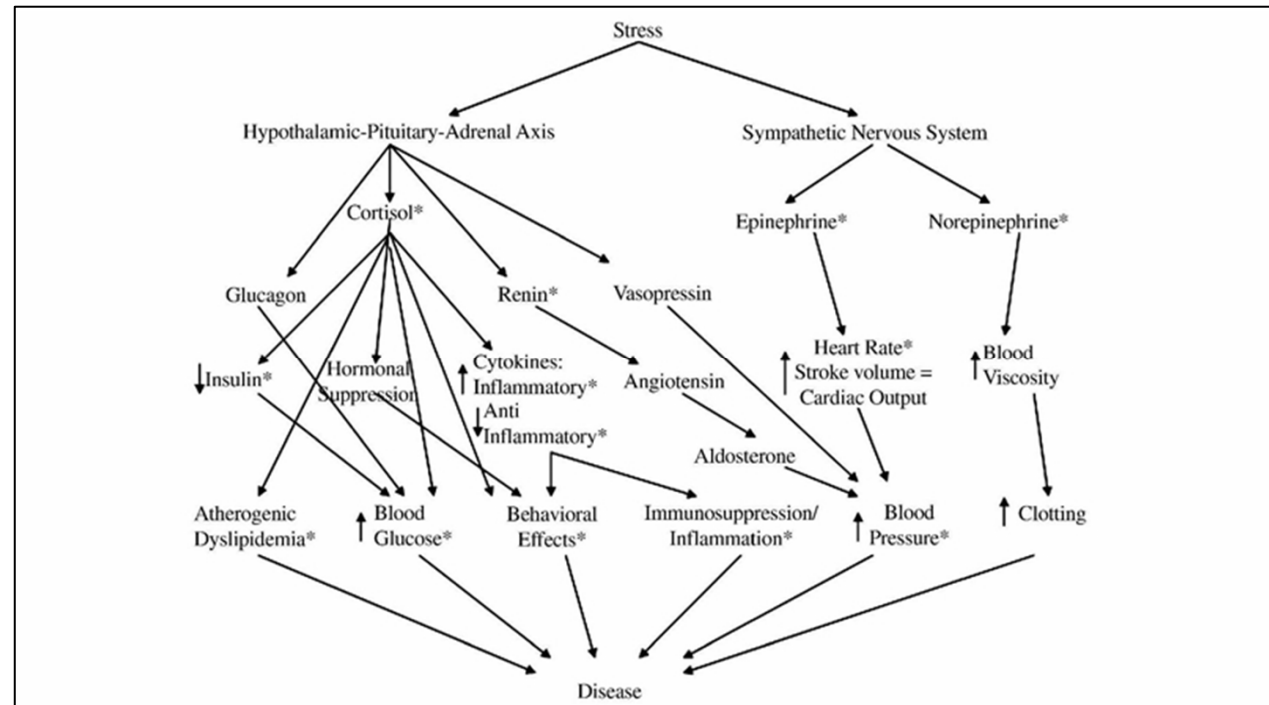


## Continued care

- Continues to see the psychiatrist and the psychologist within the practice to gradually taper off medications, as well he follows up with me approximately once a month.
- Future supplement change:
  - Gradually lower Glycine to as needed
  - Decrease EFA to 1500mg/day



# Metabolic effects of HPA Axis





# Integrative Approaches to Mental Health

## Lifestyle

Stress management

Exercise

## Diet/nutrition

## Psychotherapy

## Pharmacotherapy

## Natural Treatment



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# The results of food preparation technology

Foods that compliment a busy lifestyle

Energy dense but nutrient poor diets

Lack of physical exercise

Increase in chronic, noncommunicable diseases



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## Food = Mood

- Inadequate eating habits can aggravate mental illness
- Brain is one of the most metabolically active organs in the body

Neurotransmitters:  
The Emotional  
Regulators

Serotonin

GABA

Dopamine

Norepinephrine

Acetylcholine

What do  
these items  
have in  
common?





  
**New Roots**  
HERBAL










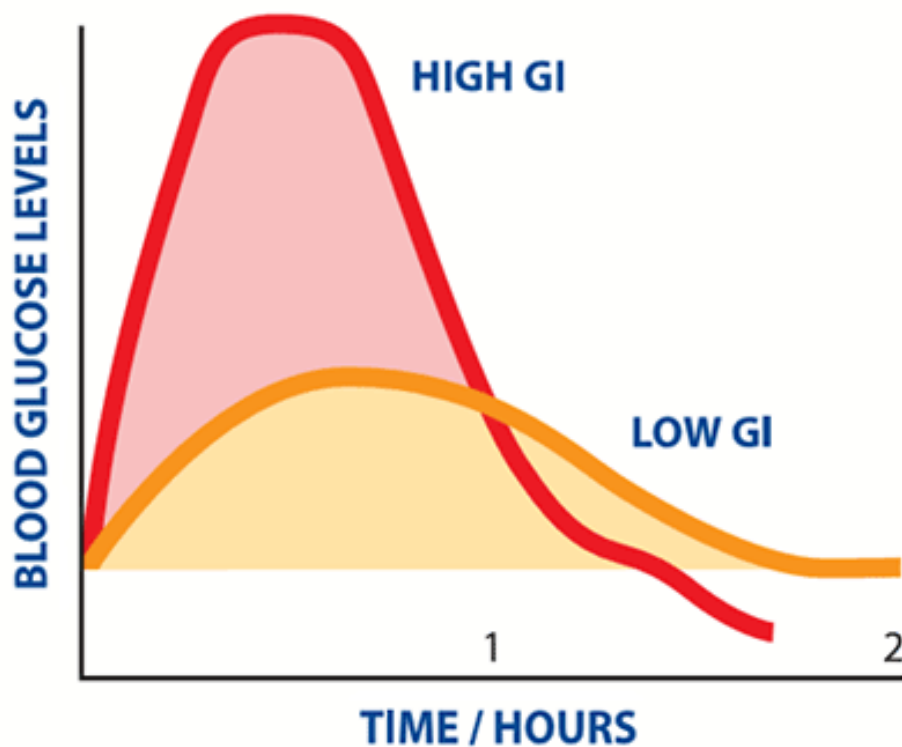


  
**New Roots**  
HERBAL

A photograph of a person's bare torso, showing a large belly. A measuring tape is wrapped around the waist, with the number 50 visible. The person is wearing a silver watch on their left wrist. A teal rectangular box is overlaid on the left side of the image, containing white text. The background is a blurred indoor setting.

Help! My  
brain is  
starving!!!!

# Blood Sugar Blues



# Symptoms of Hypoglycemia

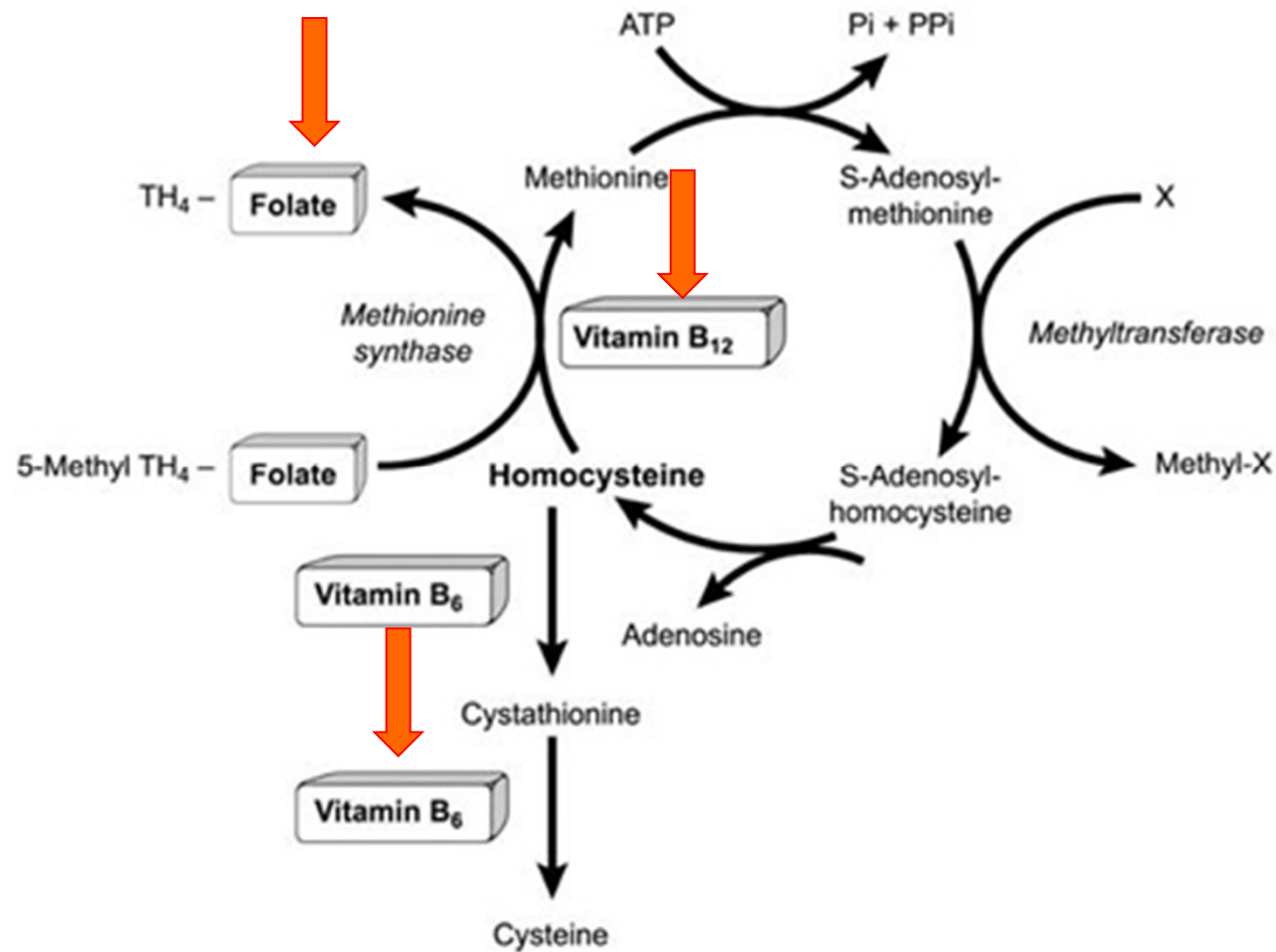
- Headache
- **Depression, anxiety**, irritability, and other psychological disturbances
- Blurred vision
- Excessive sweating
- Mental confusion
- Incoherent speech
- Nocturnal hypoglycemic episodes
- Bizarre behavior
- Convulsions

Pizzorno: A Textbook on Natural Medicine, 3<sup>rd</sup> Edition

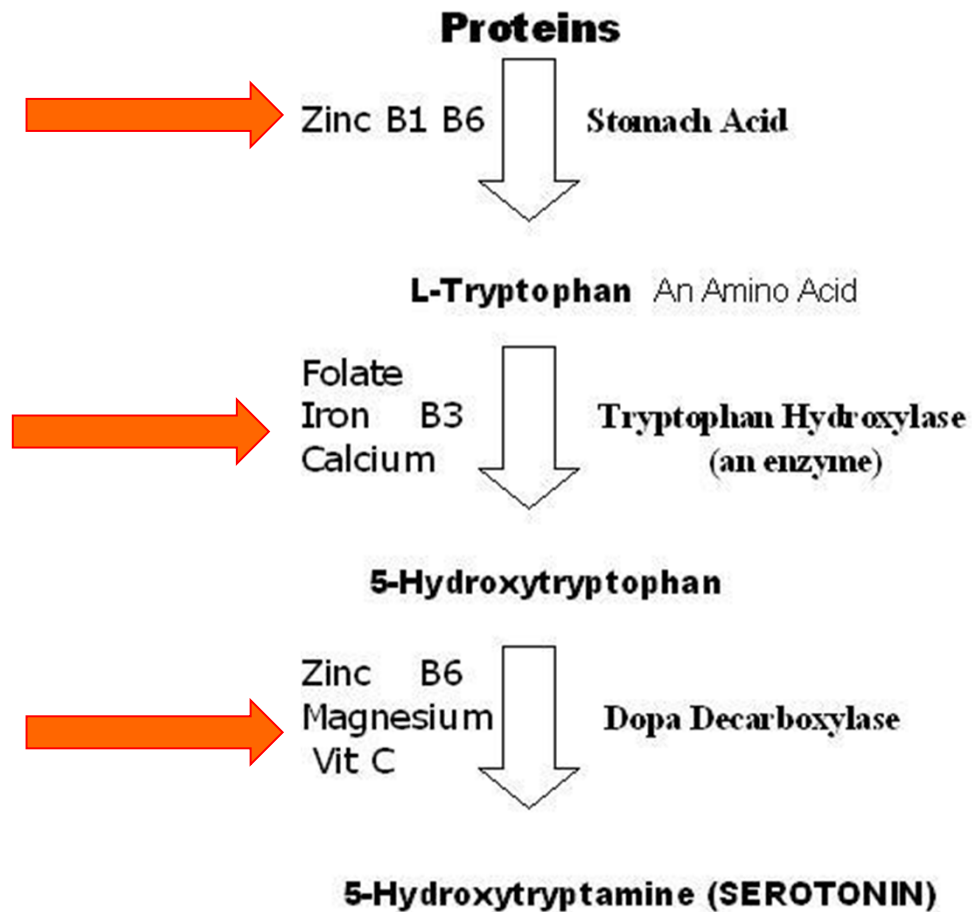
# Nutrient Deficiency and Mood

Deficient Vitamins	Behavioural Effect
Thiamin (B1)	Depression, apathy, anxiety, irritability
Riboflavin (B2)	Depression, irritability
Niacin (B3)	Apathy, anxiety, depression, hyperirritability, mania, memory deficits, delirium, dementia, emotional lability
Pantothenic acid (B5)	Restlessness, irritability, depression, fatigue
Pyroxidine (B6)	Depression, irritability, sensitivity to sound
Folic Acid (B9)	Forgetfulness, insomnia, apathy, irritability, depression, psychosis, delirium, dementia
Cobalamin (B12)	Psychotic states, depression, irritability, confusion, memory loss, hallucinations, delusions, paranoia
Biotin	Depression, lassitude, somnolence
Vitamin C	Lassitude, hypochondriasis, depression, hysteria

# Methylation Cycle



# Serotonin Metabolism







RESEARCH

Open Access

# Nutritional and herbal supplements for anxiety and anxiety-related disorders: systematic review

Shaheen E Lakhan\*, Karen F Vieira

## Abstract

**Background:** Over the past several decades, complementary and alternative medications have increasingly become a part of everyday treatment. With the rising cost of prescription medications and their production of unwanted side effects, patients are exploring herbal and other natural remedies for the management and treatment of psychological conditions. Psychological disorders are one of the most frequent conditions seen by clinicians, and often require a long-term regimen of prescription medications. Approximately 6.8 million Americans suffer from generalized anxiety disorder. Many also suffer from the spectrum of behavioural and physical side effects that often accompany its treatment. It is not surprising that there is universal interest in finding effective natural anxiolytic (anti-anxiety) treatments with a lower risk of adverse effects or withdrawal.

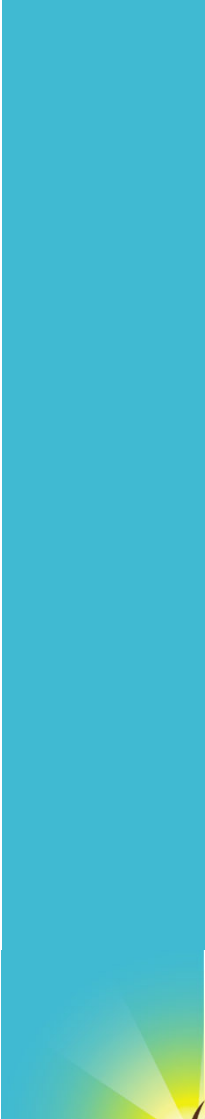
**Methods:** An electronic and manual search was performed through MEDLINE/PubMed and EBSCO. Articles were not dated by date of publication. Available clinical studies published in English that used human subjects and examined the anxiolytic potential of dietary and herbal supplements were included. Data were

**Table 5 Trials testing lysine**

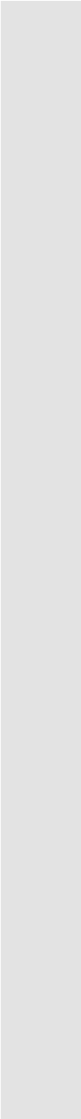
Reference	Study Design	Sample Population	Intervention	Control	Length of Treatment	Outcomes	Direction of Evidence	Reported Adverse Events
Jezova (2005) [67]	Randomized; Double-blind; Parallel Group	29 healthy male subjects at the upper limit of the normal range of a trait anxiety scale <sup>1</sup>	Mixture of L-lysine and L-arginine (3 g each/day)	Placebo	10 days	Amino acid treatment enhanced adrenocorticotropic hormone, cortisol, adrenaline and noradrenaline levels and galvanic skin responses during stress; no effect on heart rate and blood pressure.	+	None
Smriga (2007) [68]	Randomized; Double-blind; Parallel Group	108 healthy Japanese adults	Oral L-lysine (2.64 g/day) and L-arginine (2.64 g/day)	Placebo	1 week	L-lysine/L-arginine treatment significantly reduced trait and state anxiety; also decreased basal levels of salivary cortisol and chromogranin-A in male subjects	+	None

STAI: State Trait Anxiety Inventory.

# Lysine

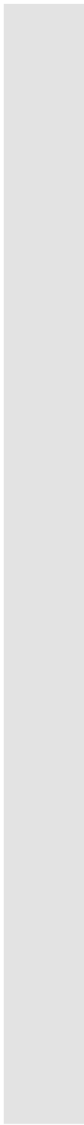


## Pyridoxine (B6)

- Important for the biosynthesis of GABA, dopamine and serotonin
  - Increases carbohydrate metabolism
  - Metabolizes amino acids, like tryptophan
- 



# Magnesium

- Produces calming effect
  - Decreases nervousness
  - Decreases insomnia
- 

**Table 6 Trials testing magnesium**

Reference	Study Design	Sample Population	Intervention	Control	Length of Treatment	Outcomes	Direction of Evidence	Reported Adverse Events
Carroll (2000) [75]	Randomized; Double-blind; Parallel Group	80 healthy males	Berocca: oral multivitamin <sup>1</sup>	Placebo	28 days	Multivitamin treatment significantly reduced anxiety as measured by GHQ-28, HADS and PSS.	+	Not reported
De Souza (2000) [76]	Randomized; Double-blind; Crossover (4)	44 women with adverse premenstrual symptoms but otherwise in good health	(1) 200 mg Mg, (2) 50 mg vitamin B <sub>6</sub> , (3) 200 mg Mg + 50 mg vitamin B <sub>6</sub> per day	Placebo	One menstrual cycle	200 mg/day Mg + 50 mg/day vitamin B <sub>6</sub> significantly reduced anxiety-related premenstrual symptoms	+	Participants were not specifically asked, but none were reported spontaneously
Hanus (2004) [77]	Randomized; Double-blind; Parallel Group	264 patients with generalized anxiety (DSM-III-R) of mild-to-moderate intensity <sup>2</sup>	Sympathy: extracts of <i>crataegus oxyacantha</i> and <i>eschscholtzia californica</i> plus magnesium	Placebo	3 months	Significant clinical improvement in anxiety <sup>3</sup> in favour of the combination treatment	+	No serious AEs related to treatment <sup>4</sup>

GHQ-28: General Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; PSS: Perceived Stress Scale; DMS-IIR: Diagnostic and Statistical Manual of Mental Disorders, third edition revised; HAMA: Hamilton Anxiety Scale; HAMA-SOM: Hamilton Anxiety Scale, subscore somatic anxiety; HAMA-T: Hamilton Anxiety Scale, total score (HAMA-T)

1. Multivitamin containing vitamin B1 (15 mg), B2 (15 mg), niacin (50 mg), pantothenic acid (23 mg), B6 (10 mg), biotin (150 mcg), folic acid (400 mcg), B12 (10 mcg), C (500 mg), calcium (100 mg), magnesium (100 mg), zinc (10 mg).

2. Total HAMA score between 16 and 28.

3. Measured by HAMA-T and HAMA-SOM and subjective patient-rated anxiety.

4. Headache, muscular stiffness, insomnia, drowsiness, indifference, anxiety, palpitations, nausea (4), gastralgia, diarrhea, gastric heaviness, dysuria, colic renal pain, morning sluggishness (3), asthenia.

# Magnesium & B6



# Dietary Fiber

## Depression and Glycemic Intake in the Homebound Elderly

D. Mkaya Mwamburi<sup>1</sup>, Elizabeth Liebson<sup>2</sup>, Marshal Folstein<sup>3</sup>, Kathleen Bungay<sup>5</sup>, Katherine L. Tucker<sup>4,6</sup>, and Wei Qiao Qiu<sup>7,\*</sup>

<sup>1</sup>Department of Public Health and Family Medicine, Tufts University

<sup>2</sup>McLean Hospital, Harvard University Medical School

<sup>3</sup>Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy at Tufts University

<sup>4</sup>Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA)

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<sup>6</sup>Department of Health Sciences, Northeastern University

<sup>7</sup>Departments of Psychiatry and Pharmacology & Experimental Therapeutics, Boston University School of Medicine

### Abstract

**Background**—Depression is associated with an increase in the incidence of type 2 diabetes, but the mechanism is unclear. We aimed to study the relationship between depression and glycemic intake in the elderly, and examine whether antidepressant use modified this relationship.

**Design, Setting and Participants**—We evaluated 976 homebound elders in a cross-sectional study. Depressed was defined by having a Center for Epidemiological Studies Depression (CES-D) score  $\geq 16$ . Antidepressant use was documented. Glycemic index (GI), Glycemic load (GL), and fasting blood insulin levels were measured.

**Results**—Depressed elders had slightly higher GI (Mean  $\pm$  SD:  $55.8 \pm 3.8$  vs.  $55.1 \pm 3.7$ ,  $P = 0.003$ ) and higher insulin levels (Median: 84.0 vs. 74.4 pmole/ml,  $P = 0.05$ ) than non-depressed elders. Depressed elders receiving antidepressants, primarily selective serotonin reuptake inhibitors (SSRI), had lower GI (Mean  $\pm$  SD:  $55.1 \pm 4.7$  vs.  $56.2 \pm 3.4$ ,  $P = 0.002$ ) and GL (Median: 170.3 vs. 6826.3,  $P = 0.03$ ) than those not taking antidepressants. After adjusting for potential confounding variables, GI remained positively associated with depression ( $\beta = +0.65$ , SE = 0.28,  $P = 0.02$ ); logarithm of GL was positively associated with depression ( $\beta = +0.33$ , SE = 0.17,  $P = 0.05$ ) and negatively associated with antidepressant use ( $\beta = -0.54$ , SE = 0.18,  $P = 0.003$ ).

**Conclusions**—Prospective studies are needed to examine whether high glycemic intake is a mediating factor between late life depression and the risk of type 2 diabetes.

## Carbohydrate Reward and Psychosis: An Explanation For Neuroleptic Induced Weight Gain and Path to Improved Mental Health?

Simon Thornley<sup>1,\*</sup>, Bruce Russell<sup>2</sup> and Rob Kydd<sup>3</sup>

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<sup>2</sup>*School of Pharmacy, Faculty of Medical & Health Sciences The University of Auckland, Private Bag 92019, Auckland, New Zealand;* <sup>3</sup>*Clinical Psychological Medicine Faculty of Medical & Health Sciences The University of Auckland, Private Bag 92019, Auckland, New Zealand*

**Abstract:** Evidence links dopamine release in the mid-brain to the pathophysiology of psychosis, addiction and reward. Repeated ingestion of refined carbohydrate may stimulate the same mesolimbic dopaminergic pathway, rewarding such eating behaviour and resulting in excessive food intake along with obesity. In this paper, we explore the role of dopamine in reward and psychosis, and discuss how reward pathways may contribute to the weight gain that commonly follows antipsychotic drug use, in people with psychotic illness. Our theory also explains the frequent co-occurrence of substance abuse and psychosis. From our hypothesis, we discuss the use of carbohydrate modified diets as an adjunctive treatment for people with psychosis.

**Keywords:** Antipsychotic agents, addictive behaviours, glycemic index, carbohydrates.







# Omega-3 Fatty Acids

**Lev Gertsik, MD<sup>1</sup>, Russell E. Poland, PhD<sup>2,3</sup>, Catherine Bresee, MS<sup>3</sup>, and Mark Hyman Rapaport, MD<sup>3,4</sup>**

<sup>1</sup>California Clinical Trials Medical Group

<sup>2</sup>Department of Psychiatry and Behavioral Sciences, Meharry Medical College

<sup>3</sup>Department of Psychiatry and Behavioral Neurosciences, Cedars-Sinai Medical Center

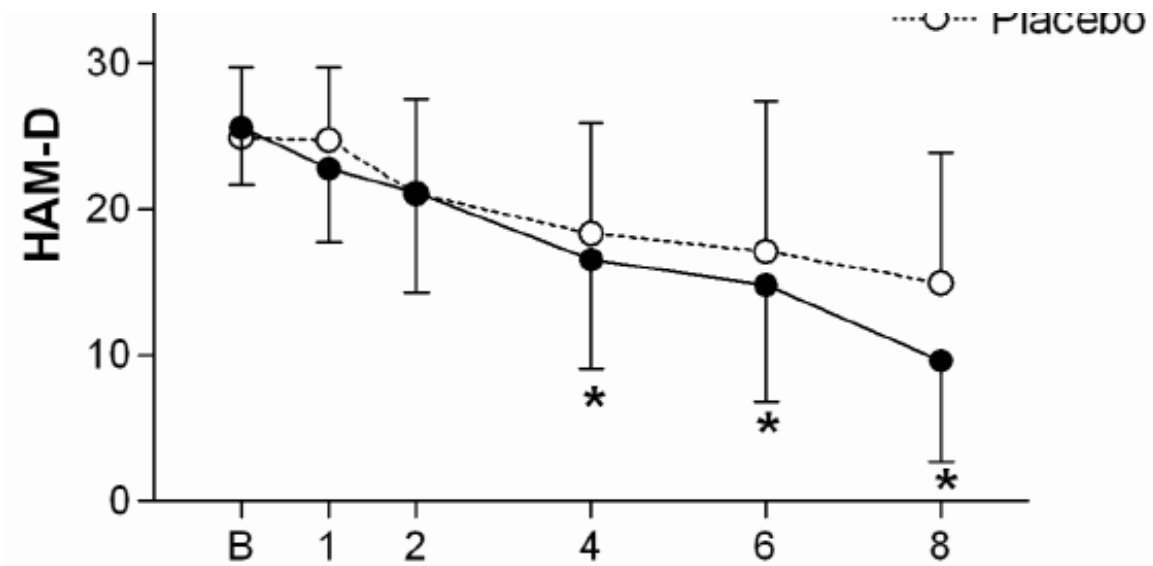
<sup>4</sup>Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA

## **Abstract**

The objective of this study was to explore the efficacy of combination therapy with citalopram plus omega-3 fatty acids versus citalopram plus placebo (olive oil) in the initial treatment of individuals with Major Depressive Disorder (MDD). We hypothesized that combination therapy would not only lead to greater efficacy, but a more rapid onset of therapeutic response.

Forty-two subjects participated in this nine week randomized, masked, placebo-controlled study of





**Figure 1.** HAM-D measures of depressive symptoms for subjects treated with citalopram + placebo or

## Meta-analysis: Effects of Eicosapentaenoic Acid in Clinical Trials in Depression

M. Elizabeth Sublette, M.D., Ph.D.<sup>a,b</sup>, Steven P. Ellis, Ph.D.<sup>a,b</sup>, Amy L. Geant, B.A.<sup>a</sup>, and J. John Mann, M.D.<sup>a,b,c</sup>

<sup>a</sup>Division of Molecular Imaging and Neuropathology, New York State Psychiatric Institute, NY, NY

<sup>b</sup>Department of Psychiatry, Columbia University, NY, NY

<sup>c</sup>Department of Radiology, Columbia University, NY, NY

### Abstract

**Objective**—Randomized trials of omega-3 polyunsaturated fatty acid (PUFA) treatment for depression have differed in outcome. Recent meta-analyses ascribe discrepancies to differential effects of eicosapentaenoic acid (EPA) vs. docosahexaenoic acid (DHA) and to diagnostic heterogeneity. This meta-analysis tests the hypothesis that EPA is the effective component in PUFA treatment of major depressive episodes.

**Data Sources**—PubMed was searched (1960 through June 2010) using terms “Fish Oils”[Mesh] AND (“Depressive Disorder”[Mesh] OR “Bipolar Depression”) AND “Randomized Controlled Trial”[Publication Type], for placebo-controlled trials of PUFA supplementation, a depressive episode as primary disorder, published in English, supplemented by manual bibliography review.

**Study Selection**—The search yielded 15 trials involving 916 participants.

**Data Extraction**—Sample sizes; PUFA doses; mean ages, baseline and endpoint depression ratings and standard deviations; and *p* values were extracted.

**Data Synthesis**—In a mixed-effect model, percentage of EPA in the supplements was the fixed-effect predictor, dichotomized into two groups: EPA < 60% or EPA ≥ 60% of EPA + DHA. Secondary analyses explored relevance of treatment duration, age, and EPA dose.

**Results**—Supplements with EPA ≥ 60% showed benefit on standardized mean depression scores (SMD, for EPA ≥ 60% = 0.558, 95% CI = (0.277, 0.838), *z* = 4.195, *p* = 0.001; for EPA < 60% = -0.026, 95% CI = (0.200, 0.148), *z* = -0.316, *p* = 0.756), with negligible contribution of random effects or heteroscedasticity, and no effects of treatment duration or age. Supplements with EPA < 60% were ineffective. Exploratory analyses supported a non-linear model, with improvement determined by the dose of EPA in excess of DHA, within the range 200 to 2200 mg EPA.

**Conclusions**—Supplements containing EPA ≥ 60%, in dose range 200 to 2200 mg EPA in excess of DHA, were effective against primary depression. Translational studies are needed to determine mechanisms of EPA’s therapeutic benefit.



# Tryptophan



Tryptophan involved in the production of serotonin



Synthesis of serotonin is heavily dependent upon availability of L-Tryptophan within the CNS

L-  
Tryptophan

*Isr J Psychiatry Relat Sci.* 2010 ; 47(1): 56–63.

## **Tryptophan–Kynurenine Metabolism as a Common Mediator of Genetic and Environmental Impacts in Major Depressive Disorder: The Serotonin Hypothesis Revisited 40 Years Later**

**Gregory F. Oxenkrug, MD, PhD**

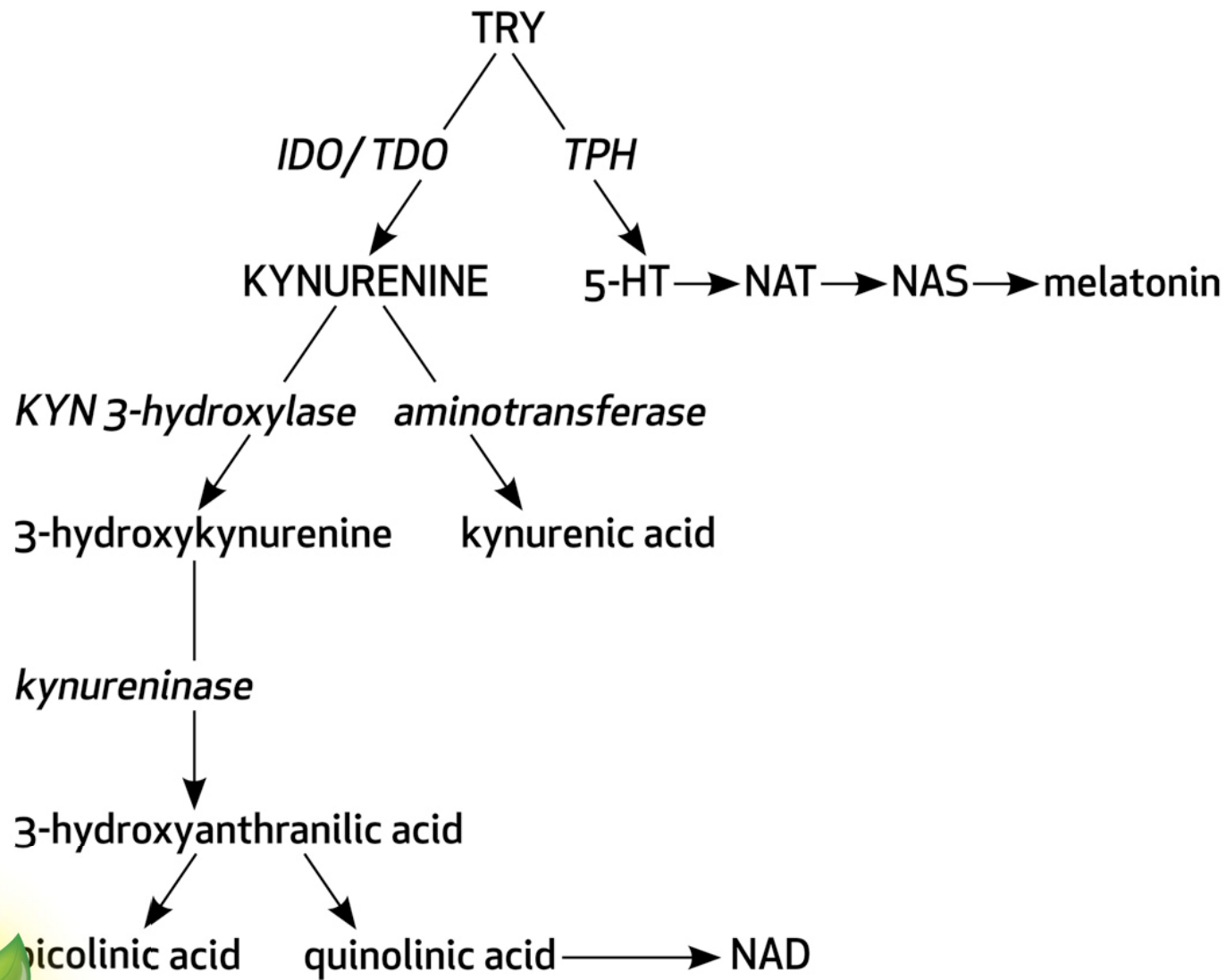
Department of Psychiatry, Tufts University School of Medicine and Tufts Medical Center, Boston, Massachusetts, U.S.A.

### **Abstract**

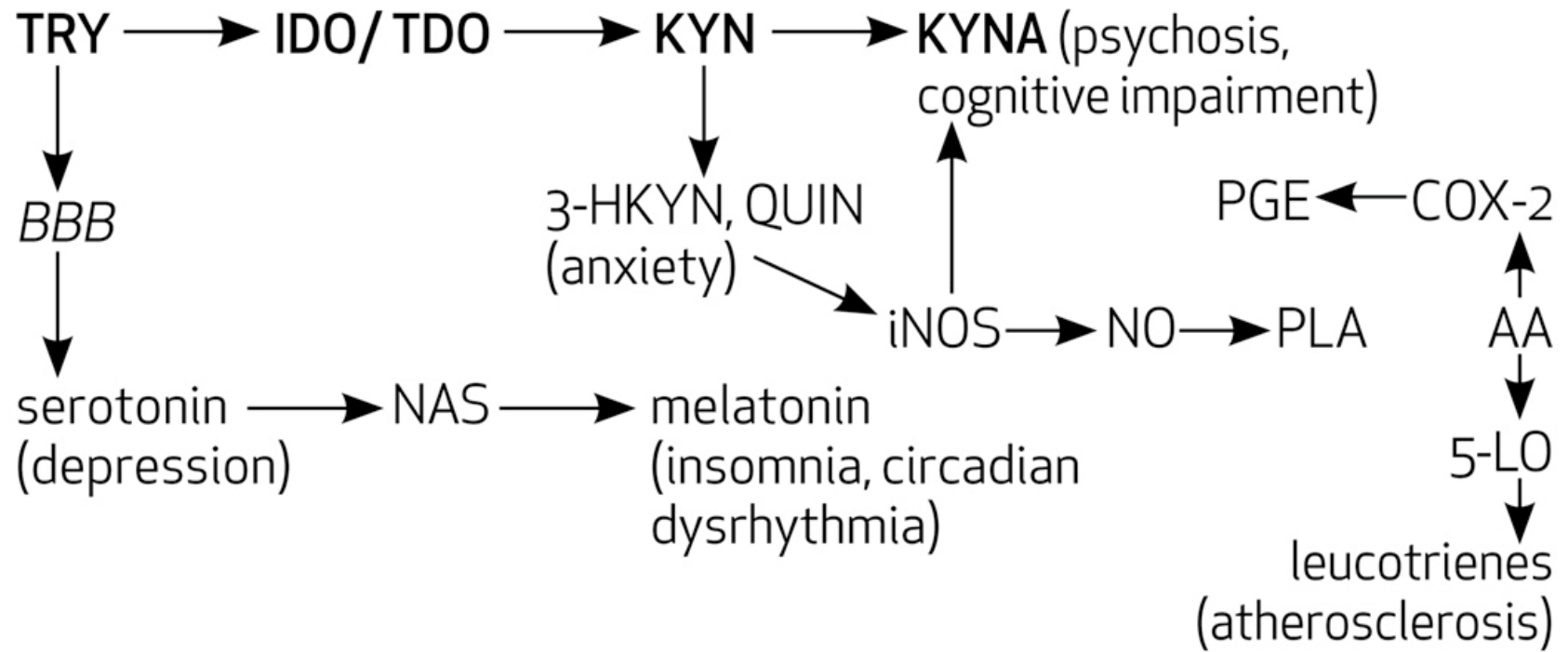
The original 1969 Lancet paper proposed, “in depression the activity of liver tryptophan-pyrrolase is stimulated by raised blood corticosteroids levels, and metabolism of tryptophan is shunted away from serotonin production, and towards kynurenine production.” Discovery of neurotropic activity of kynurenines suggested that up-regulation of the tryptophan-kynurenine pathway not only augmented serotonin deficiency but also underlined depression-associated anxiety, psychosis and cognitive decline.

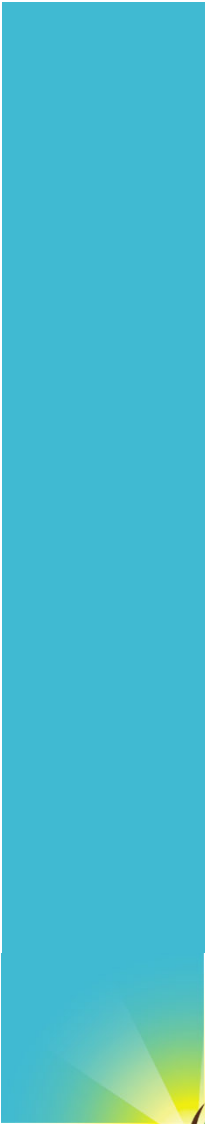
The present review of genetic and hormonal factors regulating kynurenine pathway of tryptophan metabolism suggests that this pathway mediates both genetic and environmental mechanisms of depression. Rate-limiting enzymes of kynurenine formation, tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) are activated by stress hormones (TDO) and/or by pro-inflammatory cytokines (IDO). Simultaneous presence of high producers alleles of proinflammatory cytokines genes (e.g., interferon-gamma and tumor necrosis factor-alpha) determines the genetic predisposition to depression via up-regulation of IDO while impact of environmental stresses is mediated via hormonal activation of TDO. Tryptophan-kynurenine pathway represents a major meeting point of gene-environment interaction in depression and a new target for pharmacological intervention.

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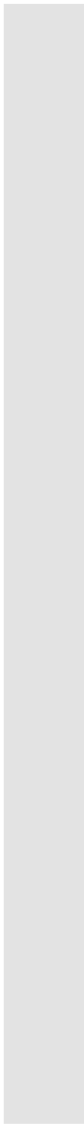




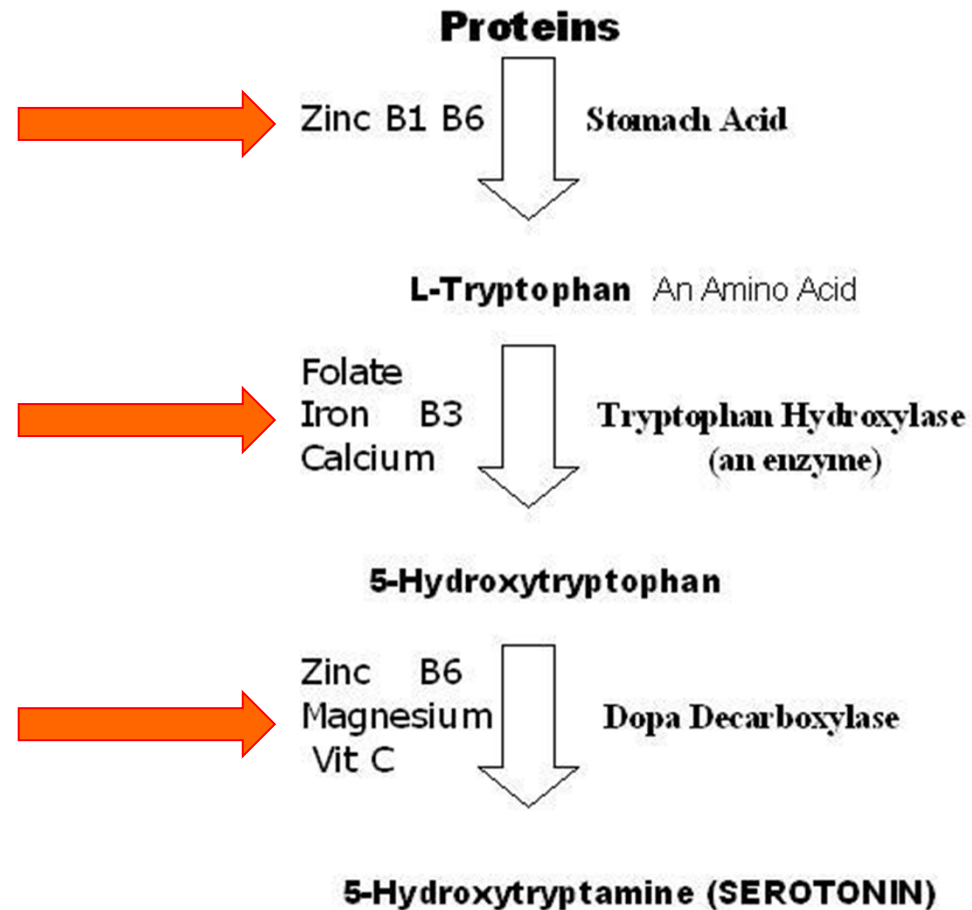




## Factors that compromise L-Tryptophan production

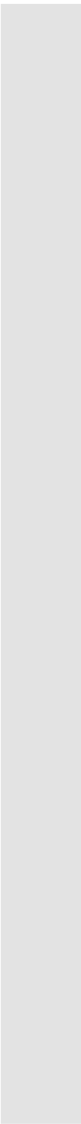
- Stress, elevated cortisol, Vitamin B deficiency
  - Elevated serum kynurenine
  - Binding transport protein that is shared by 5 other amino acids
  - L-Tryptophan is also used for synthesis of protein and production of niacin
  - Requires transport molecule to gain access to CNS
- 

# Tryptophan Metabolism





## Benefits of 5-HTP

- Well absorbed from an oral dose
  - Absorption not affected by presence of other amino acids
  - Cannot be shunted into niacin or other protein synthesis
  - Easily crosses blood brain barrier
- 

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Volume 65, Issue 1, Pages 138-144, 2005

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## 5-Hydroxytryptophan plus SSRIs for interferon-induced depression: Synergistic mechanisms for normalizing synaptic serotonin

[Erick H. Turner](#)  [Aaron D. Blackwell](#)

Received 2 January 2005; accepted 5 January 2005; published online 09 March 2005.

[Abstract](#) [Full Text](#) [PDF](#) [Images](#) [References](#)

### Summary

Interferon- $\alpha$  (IFN) is widely used in the treatment of certain cancers and viral infections, including hepatitis C (HCV). Unfortunately, depression is a common side effect of IFN therapy, affecting approximately a third of HCV patients receiving IFN therapy. Studies have shown that selective serotonin reuptake inhibitors (SSRIs) can effectively treat IFN-induced depression in only 63–75% of cases. For the remaining percentage, depression often necessitates dose reduction of or discontinuation from IFN therapy. Emerging evidence indicates that IFN may cause depression by affecting brain serotonin. IFN has been shown to increase serotonin reuptake and to decrease serotonin synthesis. We hypothesize that SSRIs are not fully effective because they affect only serotonin reuptake, not serotonin synthesis, and that effective treatment must address *both* uptake *and* synthesis. 5-Hydroxytryptophan (5-HTP) effectively increases central nervous system synthesis of serotonin. It is the immediate precursor of serotonin and is widely available as a dietary supplement, which is well absorbed after an oral dose. Several double-blind studies have shown 5-HTP to be effective in the treatment of nondrug-induced depression. We hypothesize that patients who become depressed on IFN will respond to the synergistic combination of SSRIs plus 5-HTP.







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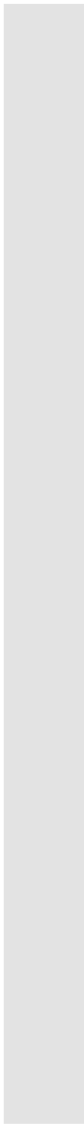
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[http://www.medical-hypotheses.com/article/S0306-9877\(05\)00088-X/abstract](http://www.medical-hypotheses.com/article/S0306-9877(05)00088-X/abstract)



## Drug- Nutrient Interaction

- Serotonin Sickness Syndrome
  - In theory if 5-HTP taken with SSRI have a higher risk of interaction.
  - Interactions have been reported with L-Tryptophan but not with 5-HTP
- 

*Afr J Psychiatry (Johannesbg)*. 2012 Jan;15(1):25-9. doi: <http://dx.doi.org/10.4314/ajpsy.v15i1.3>.

### **Elevated plasma homocysteine in association with decreased vitamin B(12), folate, serotonin, lipids and lipoproteins in depressed patients.**

Ebesunun MO, Eruvulobi HU, Olagunju T, Owoeye OA.

Chemical Pathology, Olabisi Onabanjo University, Sagamu, Nigeria. [onoebe@yahoo.com](mailto:onoebe@yahoo.com)

#### **Abstract**

**OBJECTIVE:** Increased plasma homocysteine, decreased vitamin B(12) and folic acid levels have been implicated in depressive mood. Plasma homocysteine, vitamin B(12), folic acid tryptophan, lipids and lipoproteins were determined in depressed patients and controls.

**METHOD:** Sixty subjects consisting of 30 depressed patients and 30 apparently healthy volunteers, who served as controls, were selected for this study. Anthropometric indices and biochemical parameters were determined using standard procedures.

**RESULTS:** The results showed a significantly higher plasma homocysteine level amongst depressed patients when compared with the corresponding controls ( $p < 0.001$ ), the percentage increase was 116%, while the plasma vitamin B(12) ( $p < 0.01$ ), total cholesterol, high density lipoprotein cholesterol and low density lipoprotein cholesterol levels ( $p < 0.001$ ) were markedly lower when amongst depressed patients when compared with the corresponding controls; the percentage differences were 21%, 42% and 42% respectively. Plasma triglyceride, folic acid and tryptophan levels amongst depressed patients were not significantly different from the controls. The male subjects had significantly higher plasma tHcy levels than the female counterparts ( $p < 0.001$ ).

**CONCLUSION:** This study showed a significant increase in plasma tHcy coexisting with a decrease in plasma vitamin B(12) TC, LDLC and HDLC, in depressed patients. Increased plasma homocysteine could be a sensitive indicator of plasma B vitamin deficiency.





Link between B12  
deficiency and brain  
dysfunction



Critical methyl donor  
groups

Cobalamin  
(B12)



## Folate (B9)



- Closely linked to brain functioning
- Folic acid deficiency is common among people with anxiety



## S-adenosyl- methionine

- Study: Open-label trial SAME as an adjunctive treatment for depression
  - SAME 800mg bid (titrated from 400mg)
  - Study length: 6 weeks
  - Outcome measurements:
    - Psychological questionnaires
    - Pre- & post-treatment serum homocysteine levels
  - Results: significant decrease in pre-treatment to post-treatment homocysteine levels

Alpert JE, Papakostas G, Mischoulon D, et al. S-adenosyl-L-Methionine (SAME) as an adjunct for resistant major depressive disorder. *J Clin Psychopharmacol.* 2004; 24 (6)661-664

## Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment parenteral and oral S-adenosylmethionine

T Bottiglieri, P Godfrey, T Flynn, M W P Carney, B K Toone, E H Reynolds

### **Abstract**

**Cerebrospinal fluid (CSF) S-adenosylmethionine (SAM) levels were significantly lower in severely depressed patients than in a neurological control group. The administration of SAM either intravenously or orally is associated with a significant rise of CSF SAM, indicating that it crosses the blood-brain barrier in humans. These observations provide a rational basis for the antidepressant effect of SAM, which has been confirmed in several countries. CSF SAM levels were low in a group of patients with Alzheimer's dementia suggesting a possible disturbance of methylation in such patients and the need for trials of SAM treatment.**

studies SAM was administered intravenous route daily for 14 days examining CSF SAM in a control group of patients with neurological disorders that the lowest values were seen in patients with dementia.<sup>12</sup> Recently an oral form of SAM has become available,<sup>13</sup> which enabled us to examine CSF SAM levels in a group of demented patients before and after oral SAM treatment for several months.

### **Patients and methods**

CSF SAM was examined in a) a) normal control groups comprising 16 patients with clinically definite multiple sclerosis, seven with motor neuron disease, seven with explained peripheral neuropathy, seven with benign intracranial hypertension, seven with dementia and one with cerebral

# Acute Administration of Zn, Mg, and Thiamine Improves Postpartum Depression Conditions in Mice

Sara Nikseresht MSc<sup>1</sup>, Sahابه Etebary MSc<sup>2</sup>, Morteza Karimian PhD<sup>1</sup>, Fatemeh Nabavizadeh PhD<sup>1</sup>, Mohammad Reza Zarrindast PhD<sup>3</sup>, Hamid Reza Sadeghipour PhD<sup>1</sup>

## Abstract

**Background:** Postpartum depression (PPD) affects approximately half of new mothers. Chronic exposure to progesterone during pregnancy and its withdrawal following delivery increases depression and anxiety. In addition, there are complex interactions between hormones, neurotransmitters, and trace elements. Zinc (Zn) and magnesium (Mg) influence the nervous system by impacting synaptic neurotransmission in the brain. Thiamine (Vit B<sub>1</sub>) deficiency results in a high percentage of depressive behaviors. Elevated levels of reactive oxygen species in pregnancy are implicated in the pathogenesis of major depression.

**Methods:** We examined the effects of different combinations of Zn, Mg, and Vit B<sub>1</sub> in an animal model of PPD. ZnCl<sub>2</sub>, MgCl<sub>2</sub>, and thiamine-HCl were administered to PPD-induced mice. Depression, anxiety-related behavior, and total antioxidant capacity (TAC) were assessed. Depression and anxiety-like behavior were evaluated by the forced swimming test (FST) and elevated plus-maze, respectively.

**Results:** The acute combined administration of Zn, Mg, and Vit B<sub>1</sub> significantly decreased immobility time in FST, increased the percentage of both time spent in- and entries to open arms in the elevated plus-maze, and augmented TAC.

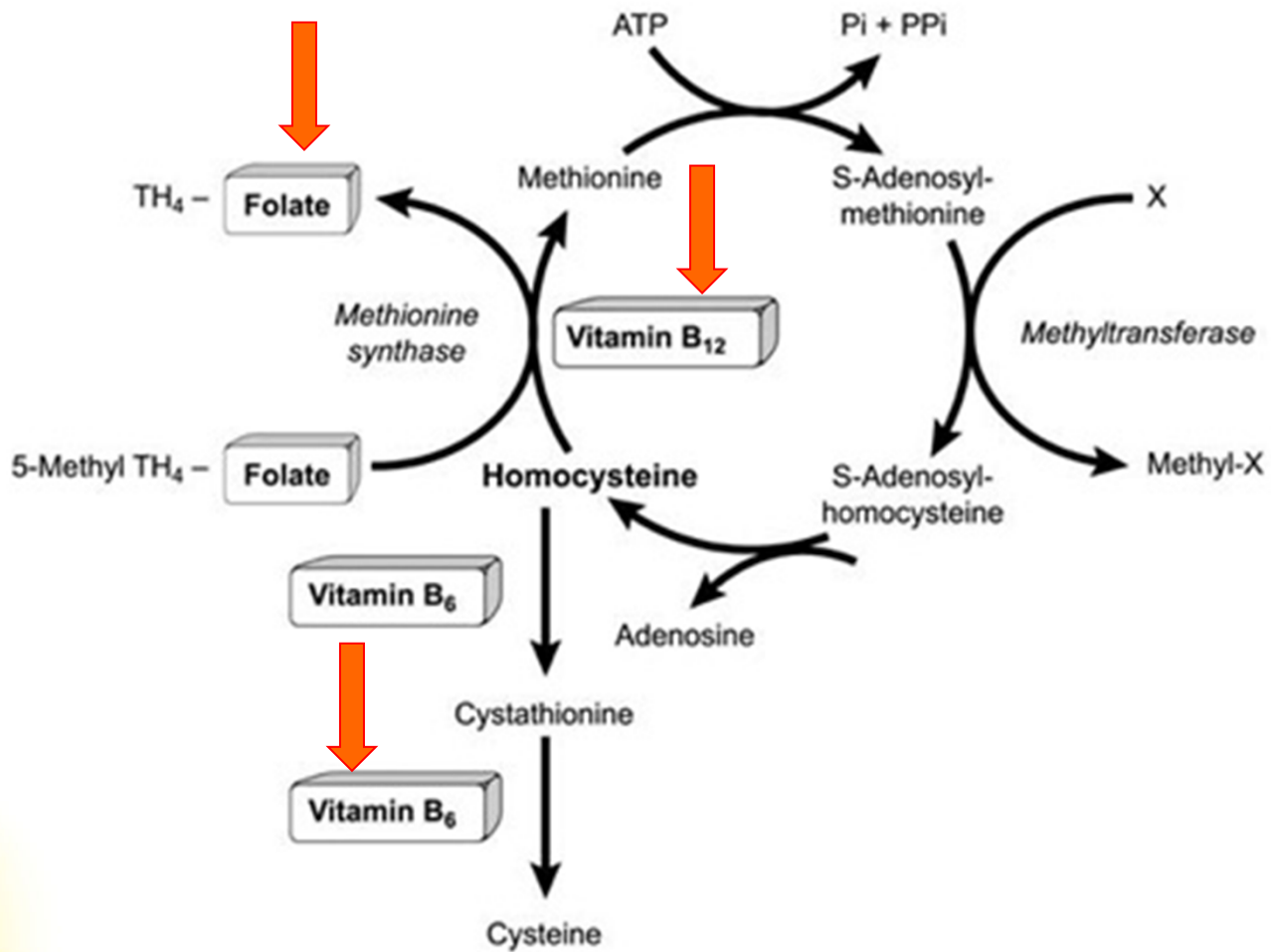
**Conclusion:** Our data suggest that acute administration of combined treatment with Zn, Mg, and Vit B<sub>1</sub> on postpartum day 3 improves depressive symptoms and anxiety-like behaviors. Our evaluation of TAC is in accordance with behavioral results.

**Keywords:** Anxiety, depression, magnesium, thiamine, Zinc

Cite this article as: Nikseresht S, Etebary S, Karimian M, Nabavizadeh F, Zarrindast MR, Sadeghipour HR. Acute Administration of Zn, Mg, and Thiamine Improves Postpartum Depression Conditions in Mice. *Arch Iran Med.* 2012; 15(5): 306 – 311.



# Methyl Cycle



ORIGINAL ARTICLE

## Association Between Low Serum 25-Hydroxyvitamin D and Depression in a Large Sample of Healthy Adults: The Cooper Center Longitudinal Study

MINHTU T. HOANG, BS; LAURA F. DEFINA, MD; BENJAMIN L. WILLIS, MD, MPH; DAVID S. LEONARD, PhD; MYRON F. WEINER, MD; AND E. SHERWOOD BROWN, MD, PhD

**OBJECTIVE:** To investigate the association between serum vitamin D levels and depression in a large database of patients from the Cooper Clinic.

**PATIENTS AND METHODS:** We conducted a cross-sectional study of 12,594 participants seen at the Cooper Clinic from November 27, 2006, to October 4, 2010. Serum 25-hydroxyvitamin D [25(OH)D] was analyzed, and depression was defined as a Center for Epidemiologic Studies Depression Scale (CES-D) score of 10 or more. Those with and those without a history of depression represented 2 distinct populations with respect to CES-D scores; accordingly, they were analyzed separately.

**RESULTS:** In the total sample, higher vitamin D levels were associated with a significantly decreased risk [odds ratio, 0.92 (95% confidence interval, 0.87-0.97)] of current depression based on CES-D scores. The finding was stronger in those with a prior history of depression [odds ratio, 0.90 (95% confidence interval, 0.82-0.98)] and not significant in those without a history of depression [odds ratio, 0.95 (95% confidence interval, 0.89-1.02)].

**CONCLUSION:** We found that low vitamin D levels are associated with depressive symptoms, especially in persons with a history of depression. These findings suggest that primary care patients with a history of depression may be an important target for assessment of vitamin D levels.

*Mayo Clin Proc.* 2011;86(11):1050-1055

brain is associated with depression, at least in the elderly.<sup>9</sup> In addition, vitamin D may have an effect on neurotransmitters, inflammatory markers, calcium homeostasis in the brain, and nerve growth factor synthesis.<sup>5,10-15</sup> Vitamin D receptor knockout mice exhibit depression-like behaviors such as poorer performance on swim tests, less activity, and more anxiety than wild-type controls.<sup>16</sup> Thus, these data on animals and humans suggest that vitamin D may have a role in depression.

Prior studies in humans have shown conflicting associations between vitamin D levels and depression. Several small clinical studies have found an association between low 25-hydroxyvitamin D [25(OH)D] levels and depression.<sup>17-19</sup> To date, 5 population-based studies have explored the association between 25(OH)D and depression, with conflicting results.<sup>20-24</sup> Hoogendijk et al<sup>20</sup> examined 1282 people aged 65 to 95 years in Amsterdam and found 14% lower 25(OH)D levels in those with major and minor depression, defined by a Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or more, when compared with controls. Stewart and Hirani<sup>21</sup> studied 2070

# Vitamin D





# Botanicals

# Bacopa (Bacopa monnieri)

- Brahmi – Ayurveda
- Increasing cognitive activity
- Reduces anxiety symptoms (nervousness, palpitation, insomnia, headache, lack of concentration, fatigue/exhaustion, anorexia, tremors, dyspepsia/flatulence, and irritability).
- Modulates acetylcholine, dopamine, serotonin and noradrenalin pathways
- 30 mL of bacopa syrup daily (12g of dry crude extract) has been used for 1 month in patients with anxiety
- 300mg for 12 weeks to reduce anxiety



## An Acute, Double-Blind, Placebo-Controlled Cross-over Study of 320 mg and 640 mg Doses of *Bacopa monnieri* (CDRI 08) on Multitasking Stress Reactivity and Mood

Sarah Benson,<sup>1</sup> Luke A. Downey,<sup>1,2</sup> Con Stough,<sup>1\*</sup> Mark Wetherell,<sup>3</sup> Andrea Zangara<sup>1,4</sup> and Andrew Scholey<sup>1</sup>

<sup>1</sup>Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne, Australia

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Little research exists in humans concerning the anxiolytic, antidepressant, sedative, and adaptogenic actions the traditional Ayurvedic medicine *Bacopa monnieri* (BM) possesses in addition to its documented cognitive-enhancing effects. Preclinical work has identified a number of acute anxiolytic, nootropic, and adaptogenic effects of BM that may also co-occur in humans. The current double-blind, placebo-controlled cross-over study assessed the acute effects of a specific extract of BM (KeenMind<sup>®</sup> - CDRI 08) in normal healthy participants during completion of a multitasking framework (MTF). Seventeen healthy volunteers completed the MTF, at baseline, then 1 h and 2 h after consuming a placebo, 320 mg BM and 640 mg of BM. Treatments were separated by a 7-day washout with order determined by Latin Square. Outcome measures included cognitive outcomes from the MTF, with mood and salivary cortisol measured before and after each completion of the MTF. Change from baseline scores indicated positive cognitive effects, notably at both 1 h post and 2 h post BM consumption on the Letter Search and Stroop tasks, suggesting an earlier nootropic effect of BM than previously investigated. There were also some positive mood effects and reduction in cortisol levels, pointing to a physiological mechanism for stress reduction associated with BM consumption. It was concluded that acute BM supplementation produced some adaptogenic and nootropic effects that need to be replicated in a larger sample and in isolation from stressful cognitive tests in order to quantify the magnitude of these effects. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12612000834853). Copyright © 2013 John Wiley & Sons, Ltd.



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# Borage (*Borago officinalis*)

- Native to Syria
- Seeds are often pressed to produce oil very high in gamma linolenic acid (GLA)
- Decreases cardiovascular reactivity to acute stress



# Chamomile (*Matricaria recutita*)

- Sedative/mild relaxant
- Most widely found herbal tea preparation in the US
- Effects considered to be mediated via modulation of the GABA system
- Flavone apigenin – benzodiazepine receptor ligand with anxiolytic activity
- For sedation: 3 cups of tea/day or 1-4mL tincture 3x/day

# Gotu Kola

- Produces CNS depression
- In Ayurveda it is believed to develop the crown chakra
- 12 g in grape juice or 120 mg/day
- 500mg twice daily

## A Double-Blind, Placebo-Controlled Study on the Effects of Gotu Kola (*Centella asiatica*) on Acoustic Startle Response in Healthy Subjects

Bradwejn, Jacques MD, FRCPC<sup>\*</sup>; Zhou, Yueping MD, PhD<sup>‡</sup>; Koszycki, Diana PhD<sup>\*</sup>; Shlik, Jakov MD, PhD<sup>†</sup>

Journal of Clinical Psychopharmacology: December 2000 - Volume 20 - Issue 6 - p 680-684  
Articles

BUY

Abstract

Author Information

Investigations of the pharmacologic profile of medicinal plants have revealed that a number of plants with purported anxiolytic activity bind to cholecystokinin (CCK) receptors. This finding is intriguing in view of the proposed involvement of CCK in the pathophysiology of fear and anxiety. This double-blind, placebo-controlled study was undertaken to evaluate the anxiolytic activity of Gotu Kola (*Centella asiatica*) in healthy subjects. Gotu Kola has been used for centuries in Ayurvedic and traditional Chinese medicine to alleviate symptoms of depression and anxiety. Recent studies in the rat have shown that long-term pretreatment with Gotu Kola decreases locomotor activity, enhances elevated-plus maze performance, and attenuates the acoustic startle response (ASR). In this study, the authors evaluated the effects of Gotu Kola on the ASR in humans. Subjects were randomly assigned to receive either a single 12-g orally administered dose of Gotu Kola (N = 20) or placebo (N = 20). The results revealed that compared with placebo, Gotu Kola significantly attenuated the peak ASR amplitude 30 and 60 minutes after treatment. Gotu Kola had no significant effect on self-rated mood, heart rate, or blood pressure. These preliminary findings suggest that Gotu Kola has anxiolytic activity in humans as revealed by the ASR. It remains to be seen whether this herb has therapeutic efficacy in the treatment of anxiety syndromes.



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# Hop (*Humulus lupulus*)

- Sedative, hypnotic, anticonvulsant properties
- Usually combined with valerian for sleep
- 2 tablets of standardized extracts of valerian (187 mg) and hop (41.9mg) combination for 28 days to improve sleep

# Kava (Piper methysticum)

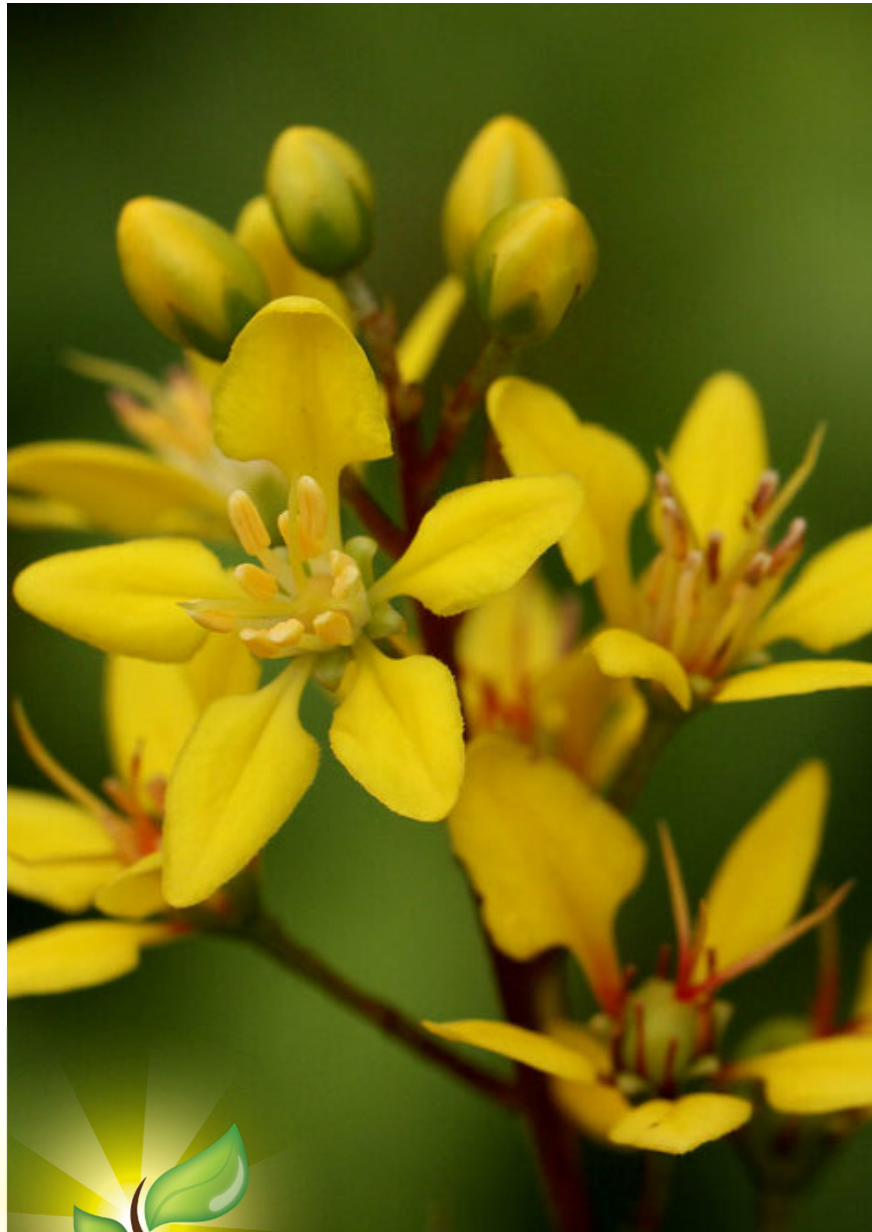
- Shrub from the South Pacific islands
- Calming effect/anxiolytic – concerns over liver toxicity
- Kavalactones interact with GABA voltage-gated sodium ion channels, enhancing ligand binding across GABA-a receptor subtypes, and reduce excitatory neurotransmitter release via blockade of calcium ion channels
- 60-280mg of kavalactones for short term anxiety

**Table 3 Trials testing kava**

Reference	Study Design	Sample Population	Intervention	Control	Length of Treatment	Outcomes	Direction of Evidence	Reported Adverse Events
Volz (1997) [42]	Randomized; Double-blind; Parallel Group	101 outpatients with anxiety of non-psychotic origin <sup>1</sup>	Kava-kava extract WS 1490 (90- 110 mg dry extract = 70 mg kl per capsule)	Placebo	24 weeks	Significant reduction in anxiety (HAMA, CGI, SCL-90-R, AMS) in favour of kava-kava treatment.	+	Excellent tolerability, similar to placebo; no clinically relevant changes in laboratory results. Stomach upset.
Scherer (1998)* [48]	Open-label; Uncontrolled Observational study	52 outpatients with nonpsychotic anxiety	Kava preparation (no dose reported in abstract)	N/A	Not reported in abstract	42 patients (80.8%) rated kava treatment as "very good" or "good".	+	Rare
Malsch (2001) [45]	Randomized; Double-blind; Parallel group	40 adult outpatients with non-psychotic nervous anxiety, tension and restlessness, impairing work performance, normal social activities and relationships <sup>2</sup>	Pre-treatment with benodiazepines (tapered off over two weeks) followed by capsules of 50 mg/day of dry extract standardized to 35 mg kava lactone for three weeks	Pre-treatment with benodiazepines (tapered off over two weeks) followed by placebo for three weeks	5 weeks	Significant reduction in anxiety (HAMA, BF-S, EAAS, CGI) in kava-treated group.	+	No serious adverse events

# KAVA





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# Galphimia (*Galphimia glauca*)

- Traditional Mexican and Central American cultures
- Leaves used for nervous disorders
- Serotonergic galphimine B is the active constituent
- 310 mg bid

# Lemon Balm (*Melissa officinalis*)

- Mild sedative and spasmolytic
- Elevation of GABA levels from inhibition of GABA-transaminase
- Usually in combination with valerian



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## Passion flower (*Passiflora incarnata*)

- Chrysin, flavonoid component of passion flower → antianxiety effects and altered benzodiazepine receptor binding
- passionflower as effective with less side effects as oxazepam
- 260 mg administered orally 30 min before dental surgery reduced subjective anxiety

**Table 2 Trials testing passionflower**

Reference	Study Design	Sample Population	Intervention	Control	Length of Treatment	Outcomes	Direction of Evidence	Reported Adverse Events
Bourin (1997) [34]	Randomized; Double-blind; Parallel Group	182 outpatients with adjustment disorder with anxious mood	Euphytose <sup>1</sup> ; 2 tablets, 3 times a day	Placebo tablets	28 days	Significant reduction in HAMA scores (from D7 to D28) in favour of Euphytose treatment	+	No serious AEs. Dry mouth Headache Constipation Drowsiness
Akhondzadeh (2001) [32]	Randomized; Double-blind; Parallel group	36 outpatients with DSM-IV for GAD for at least 6 months	45 drops/day of Passiflora extract plus placebo tablet	Oxazepam 30 mg/day plus placebo drops	4 weeks	Decrease in HAMA for both treatments <sup>2</sup> ; overall no significant difference in efficacy between treatments	+	Higher impairment of job performance in oxazepam group; overall no significant difference in total side effects <sup>3</sup>
Movafegh (2008) [33]	Randomized; Double-blind; Parallel Group	60 patients undergoing inguinal herniorrhaphy	Oral Passiflora incarnata (500 mg, Passipy™ IranDarouk)	Placebo	Given as pre-medication 90 minutes before surgery	NRS anxiety scores were significantly lower in the passiflora group	+	Not reported

AEs: Adverse events; HAMA: Hamilton Anxiety Scale; DMS-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; GAD: generalized anxiety disorder; NRS: numerical rating scale.

1. Combination of *Crataegus oxyacantha* (10 mg), *Ballota foetida* (10 mg), *Passiflora incarnata* (40 mg), *Valeriana officinalis* (50 mg), *Cola nitida* (15 mg) and *Paullinia cupana* (15 mg).

2. D4 oxazepam; D7 passiflora.

3. Passiflora, mild/moderate: Dizziness, Drowsiness, Confusion, Ataxia, Allergic reaction, Impairment of job performance.

# PASSIONFLOWER



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# Scullcap (*Scutellaria lateriflora*)

- sedative
- Single dose of skullcap may be effective in reducing anxiety (for approximately 2 hrs)
- Baicalin and baicalein compounds contribute to its anxiolytic activity via binding to the benzodiazepine site of GABA-a

# Gingko (Gingko biloba)

- Beneficial for patients who have adjustment disorder with anxious mood
- May be beneficial in elderly patients with anxiety related to cognitive decline



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## Roseroot (*Rhodiola rosea*)

- Commonly used for its anti-fatigue and mood-elevating effects
- May be helpful in mild anxiety

# Ashwagandha (*Withania somnifera*)

- Rasayana in Ayurveda
- Enhances physical and mental performance
- Useful in endocrine and nervous system disorders
- Doses range from 125-1200mg/day





# Lavender (*Lavandula angustifolia*)

- Active constituent, Linalool, causes potentiation of GABA
- Small positive effect of using lavender through aromatherapy
- 1-4 drops/tablespoon of base oil for massage
- 2-4 drops in 2-3 cups of boiling water, followed by inhalation of vapours for aromatherapy

**Table 4 Trials testing St. John's wort**

Reference	Study Design	Sample Population	Intervention	Control	Length of Treatment	Outcomes	Direction of Evidence	Reported Adverse Events
Taylor (2000) [63]	Open-label; Uncontrolled; Observational	13 subjects with a primary DSM-IV diagnosis of OCD of at least 12 month duration	Fixed dose of 900 mg/day of 0.3% hypericin (a psychoactive compound in Hypericum)	N/A	12 weeks	Significant improvement in Y-BOCS scores in SJW group (comparable to those seen in clinical trials with SSRIs).	+	Diarrhea Restless sleep
Volz (2002) [61]	Randomized; Double-blind; Parallel Group	149 outpatients diagnosed with somatization Disorder <sup>2</sup> , undifferentiated somatoform Disorder <sup>3</sup> , or somatoform autonomic Dysfunctions <sup>4</sup>	Hypericum extract LI 160 (600 mg/day)	Placebo	6 weeks	Significant reduction in anxiety (HAMA-SOM, CGI, HAMA-T, HAMA-PSY, HDS, SCL-90-R, SCL-90-R-ANX) in favour of SJW treatment.	+	Verywell tolerated. Mild/moderate: Abdominal pain Arthritis Arrythmia Bronchitis Cystitis Headache Neuralgia
Muller (2003) [62]	Open-label; uncontrolled observational	500 patients diagnosed with depression comorbid with anxiety	(1) 500 mg valerian extract <sup>5</sup> and 600 mg/day St John's Wort <sup>6</sup> (2) 1,000 mg valerian extract <sup>7</sup> and 600 mg/day St John's wort <sup>6</sup>	N/A	6 weeks	Significant reduction in anxiety disorder symptoms (HAMA) in both treatment groups. Higher dosage results in greater improvements.	+	Allergy Bad dreams Sleep disorders Dysphoria

# ST. JOHN'S WORT



## St. John's wort (*Hypericum perforatum*)

- Comparable to paroxetine for the treatment of mild to moderate depression
- Antidepressant action involves nonselective inhibition of neuronal reuptake serotonin, dopamine, norepinephrine, GABA, and L-glutamate, decreased degradation of neurochemicals and a sensitization of and increased binding to various receptors
- Possible drug interactions

# Efficacy of *Hypericum* extract WS<sup>®</sup> 5570 compared with paroxetine in patients with a moderate major depressive episode – a subgroup analysis

Erich Seifritz<sup>a</sup>, Martin Hatzinger<sup>b</sup> and Edith Holsboer-Trachsler<sup>c</sup>

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## ABSTRACT

**Objectives:** efficacy and tolerability of WS<sup>®</sup> 5570 for the treatment of acute mild-to-moderate depression, has been demonstrated in various studies. Here, we present a subgroup analysis of a double blind, randomised trial to compare the therapeutic efficacy of WS<sup>®</sup> 5570 with paroxetine in patients suffering from a major depressive episode with moderate symptom intensity.

**Methods:** moderate depression was defined by a baseline Hamilton Depression Rating Scale (HAM-D) total score between 22 and 25. Patients received, after a single blind placebo run-in phase of 3–7 d, either 3 × 300 mg/d WS<sup>®</sup> 5570 or 20 mg/d paroxetine for six weeks. The change of the HAM-D total score was used to describe the efficacy of WS<sup>®</sup> 5570 compared with paroxetine in the subgroup of patients with moderate depression.

**Results:** the reductions of the HAM-D total score were significantly more pronounced in patients treated with 3 × 300 mg/d WS<sup>®</sup> 5570 compared to 20 mg/d paroxetine.

**Conclusions:** patients treated with WS<sup>®</sup> 5570 not only showed a reduction in depression severity score but also yielded greater response and remission rates compared with patients treated with paroxetine.

## KEYPOINTS

- Various studies showed the efficacy and tolerability of WS<sup>®</sup> 5570 for the treatment of acute mild-to-moderate depression.
- Beneficial effects of WS<sup>®</sup> 5570 have been also shown in patients with moderate-to-severe depression.
- In this study reductions of the HAM-D total score were significantly more pronounced in patients with moderate depression treated with WS<sup>®</sup> 5570 compared with paroxetine.
- Patients treated with WS<sup>®</sup> 5570 not only showed a reduction in depression severity score but also yielded greater response and remission rates compared with patients treated with paroxetine.

## ARTICLE HISTORY

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## KEYWORDS

Hypericum extract;  
moderate major depressive  
episode; paroxetine; St.  
John's wort; WS<sup>®</sup> 5570



## Saffron (*C. sativus*)

- Used to improve mood in traditional Persian medicine
- Contains 40-50 active therapeutic constituents → antidepressant, anxiolytic and hypnotic effects
- Crocin → Acts via reuptake inhibition of dopamine and norepinephrine
- Safranal → serotonin reuptake inhibition
- 50mg/day for improving mood and reducing anxiety

Georg Thieme Verlag KG Stuttgart · New York

## The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis

Barbara Tóth, Péter Hegyi, Tamás Lantos, Zsolt Szakács, Beáta Kerémi, Gábor Varga, Judit Tenk, Erika Pétervári, Márta Balaskó, Zoltán Rumbus, Zoltán Rakonczay, Emese Réka Bálint, Tivadar Kiss, Dezső Csupor

[> Author Affiliations](#)

[> Further Information](#)

Abstract

Full Text

References

Figures

Supplementary Material

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### Abstract

Herbal products, especially *Hypericum perforatum* extracts, have been widely used as first-line treatments for mild to moderate depression. Recently, several randomized, controlled clinical trials have been conducted to evaluate the efficacy of another plant, saffron (*Crocus sativus*), in mild to moderate depression. We have carried out a literature review of currently available published randomized, controlled clinical trials to give an up-to-date evaluation of the efficacy of saffron in mild to moderate depression, compared to placebo or routinely used antidepressants. The meta-analysis is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines using the PICO (patients, intervention, comparison, outcome) format and was conducted using the statistical programs Comprehensive Meta-analysis and RevMan. PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science databases were searched for relevant studies. Only placebo or active controlled, randomized clinical studies involving patients suffering from mild to moderate depression and using pharmacological doses of saffron *per os* were included. Hedges' *g* was used to calculate effect sizes. Risk of bias was assessed using the Cochrane Collaboration tool, and heterogeneity was tested by both performing the Cochran's *Q* test and calculating Higgins' *I*<sup>2</sup> indicator. Eleven randomized trials were included in the qualitative analysis, and nine were pooled for statistical analysis. According to the present meta-analysis, saffron has a significant effect on the severity of depression. Available data from randomized, controlled clinical trials support that saffron is significantly more effective than placebo ( $g = 0.891$ ; 95% CI: 0.369–1.412,  $p = 0.001$ ), and non-inferior to tested antidepressant drugs ( $g = -0.246$ ; 95% CI:  $-0.495$ – $0.004$ ,  $p = 0.053$ ).





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# Turmeric (*Curcuma longa*)



- Used in Ayurveda and TCM
- Curcumin → anti-inflammatory, antioxidant, neuroprotective and monoaminergic modulatory
- Inflammation viewed as causative agent in depression → turmeric strong anti-inflammatory
- 500-1000mg curcumin/day
- Consider combining with saffron

41 y.o male

Diagnosis:

- Social Anxiety Disorder (subclinical)
- PTSD (subclinical)
- GAD

Symptoms:

- Fatigue
- Insomnia
- Anxiety

Case



## Medication:

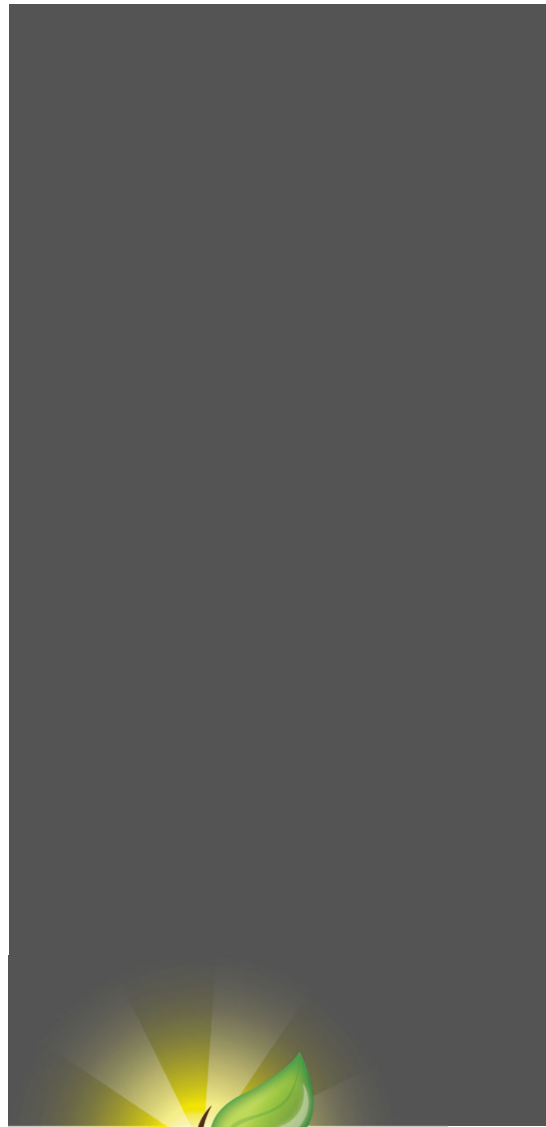
- Clonazepam 1.5mg during the day and 0.5mg at night
- Cipralext 10mg od

## Supplements

- 1500mg High Potency 3:1 EPA: DHA Fish oil
- Magnesium Citrate 300mg at bed-time

## CBT Group Therapy

- Diet:
  - 35mg Soluble/Insoluble Fiber
  - Whole foods based diet
  - Incorporate snacking between meals
  - Protein based diet for breakfast



### 1 month follow-up:

- improved sleep quality
- 30 min before falling asleep
- Supplement: 1mg Melatonin 30 min before clonazepam

### 2 month follow-up:

- Sleep quality continues to improve
- Reports lowered anxiety

### 6 month follow-up:

- Tapered off clonazepam
- Supplement: 2mg Melatonin, 5000IU Vitamin D for 5 months



## 1 year follow-up:

- Continues to report good quality sleep
- Resolution of anxiety symptoms
- Increased energy

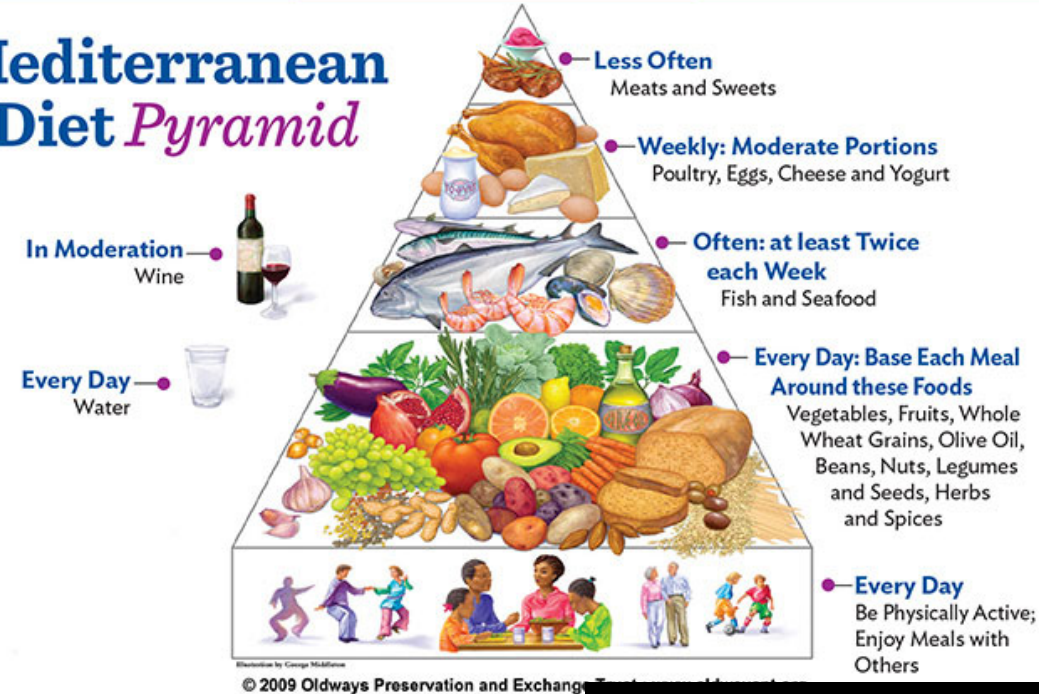
## Next steps

- Taper off cipralex with 5-HTP



Putting it all  
together: Guide

## Mediterranean Diet Pyramid

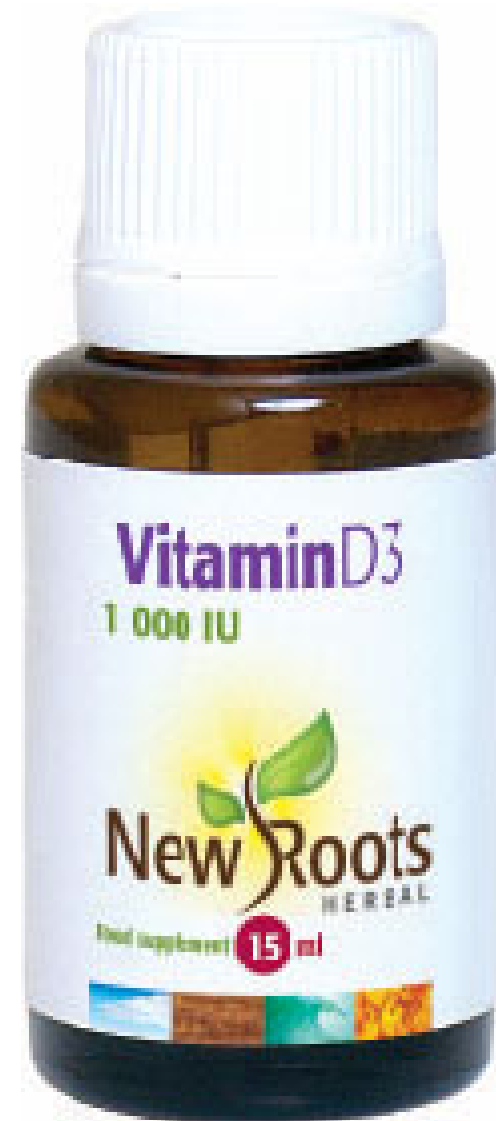


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# Macro Nutrients

# Vitamin D

Check vitamin D levels  
2000 IU – 5000 IU/day



Nutritional information	1 capsule (554 mg)
Thiamin (vit. B1) (from 50 mg thiamin HCl)	44,6 mg (4 055%*)
Riboflavin (vit. B2)(from 50 mg riboflavin + 5 mg riboflavin 5'-phosphate sodium)	53,8 mg (3 843%*)
Niacin (vit. B3) (from 50 mg inositol hexanicotinate, flush-free)	45,45 mg NE (284%*)
Pantothenic acid (vit. B5)(from 50 mg D-pantothenate calcium)	45,8 mg (763%*)
Vitamin B6 (from 20 mg pyridoxine HCl + 5 mg pyridoxal 5'-phosphate)	19,9 mg (1 421%*)
Vitamin B12 (methylcobalamin)	150 µg (6 000%*)
Folate (calcium-L-methylfolate)	500 µg (250%*)
Biotin	75 µg (150%*)
Choline	50 mg
Inositol	50 mg
PABA (para-aminobenzoic acid)	50 mg

\*NRV: Nutrient Reference Value in %.



# B-Complex

1 capsule/day with food (breakfast or lunch)





Nutritional information	1/2 scoop (2,344 g)
Betaine (trimethylglycine)	1 g
Inositol	0,375 g
Choline (bitartrate)	0,25 g
Zinc (from zinc bisglycinate)	7,5 mg (75%*)
Vitamin B6 (pyridoxine) (from 2,5 mg pyridoxal 5'-phosphate)	1,7 mg (121%*)
Vitamin B12 (methylcobalamin)	375 µg (15 000%*)
Folate (from calcium-L-methylfolate)	250 µg (125%*)

\*NRV: Nutrient Reference Value in %.

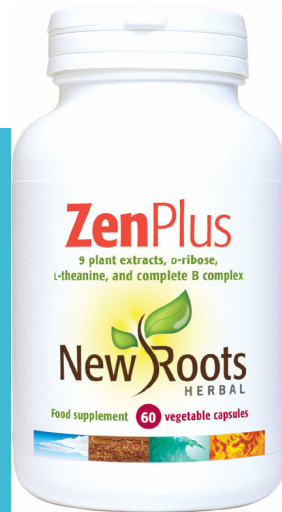


# Homocysteine Balance

1/2 scoop/day with breakfast/lunch



# Zen Plus



Synergistic botanical  
and Nutrient support

Addresses adaptogenic  
stress response

1 capsule 2x/day with  
meal



## Nutritional information:

	<b>1 capsule (807 mg)</b>
L-Theanine	100 mg
Ashwagandha (2,5% withanolides)	75 mg
Rhodiola (5% rosavins)	50 mg
Holy basil (10% ursolic acids)	50 mg
Passionflower (4% flavonoids)	50 mg
Oat 10:1	50 mg
Astragalus (3% astragalosides)	25 mg
D-Ribose	25 mg
Phellodendron (0,1% berberine)	15 mg
Red jujube	12,5 mg
Magnolia (80% magnolol+honokiol 50:1)	7,5 mg
Thiamin (vitamin B <sub>1</sub> (from 25 mg thiamin hcl)	22,3 mg (2 027%*)
Riboflavin (vit. B <sub>2</sub> ) (from 25 mg riboflavin + 2,5 mg riboflavin-5'-phosphate sodium)	26,9 mg (1 921%*)
Niacin (vit. B <sub>3</sub> ) (from 7,5 mg nicotinamide + 17,5 mg inositol hexanicotinate)	23,4 mg NE (146%*)
D-Pantothenic acid (vit. B <sub>5</sub> ) (from 25 mg D-pantothenate calcium)	22,9 mg (382%*)
Vitamin B <sub>6</sub> (from 25 mg pyridoxine hcl + 2,5 mg pyridoxal-5'-phosphate)	22,3 mg (1 593%*)
Inositol	25 mg
Biotin	37,5 µg (75%*)
Folate (calcium-L-methylfolate)	500 µg (250%*)
Vitamin B <sub>12</sub> (methylcobalamin)	75 µg (3 000%*)
Choline (bitartrate)	25 mg
PABA ( <i>para</i> -Aminobenzoic acid)	25 mg

Nutritional information		2 softgels (3 260 mg)
Concentrated marine lipids (wild anchovie)		2 640 mg
Providing essential fatty acids omega-3:		
EPA (eicosapentaenoic acid)	1 320 mg	
DHA (docosahexaenoic acid)	660 mg	
Vitamin E (D- <i>alpha</i> tocopherol, 20 IU)		13,4 mg $\alpha$ -TE (112%*)
Reference Value in %		
Oils of pharmaceutical grade, molecular distillation.		



Wild Omega 3  
EPA 660mg/DHA  
330mg

2 capsules 2x/day with a meal (active depression/anxiety) for at least 1 year

2 capsules/day with a meal (maintenance)



**Nutritional information**

**1 softgel  
(363 mg)**

Lavender essential oil

80 mg

Vitamin E (D-alpha-tocopherol)

6,7 mg  $\alpha$ -TE (56%\*)

\*NRV: Nutrient Reference Value in %



# Lavender Oil

Sleep support

1 capsule/day at bed-time

Or can be used for anxiety, use 1 capsule/day away just after a meal



**Nutritional information:**

**3 capsules  
(1 566 mg)**

Reishi ( <i>Ganoderma lucidum</i> ) (8:1)*	238,5 mg
Maitake ( <i>Grifola frondosa</i> ) (8:1)*	238,5 mg
Shiitake ( <i>Lentinula edodes</i> ) (8:1)*	238,5 mg
Chaga ( <i>Inonotus obliquus</i> ) (8:1)*	238,5 mg
Cordyceps ( <i>Paecilomyces hepiali</i> ) (8:1)*	123 mg
Lion's mane ( <i>Hericum erinaceus</i> ) (8:1)*	123 mg

\*Standardized extract, 40% polysaccharides.

Hot-water extraction.



# Resilience Mushroom Blend

Adaptogen

Helps with stress response

1 capsule 3x/day - good for long-term use



# Ginkgo Formula

Key brain health ingredients like Ginkgo, Bacopa, Lion's Mane, Gotu Kola

Great to increase memory, focus and cognition



#### Nutritional information:

	1 capsule
Lion's mane ( <i>Hericium erinaceus</i> ) (40% polysaccharides, providing 35% beta-glucans)	170 mg
L-Glutamine	150 mg
Siberian ginseng ( <i>Eleutherococcus senticosus</i> ) (0,8% eleutherosides)*	100 mg
<i>Ginkgo biloba</i> * (24% ginkgo flavonoid glycoside, 6% terpene lactones)	80 mg
L-Theanine	50mg
<i>Ginkgo biloba</i> (leaves)	40 mg
Gotu kola ( <i>Centella asiatica</i> )	40 mg
<i>Bacopa monnieri</i> * (25:1) (45% bacosides)	30 mg
Huperzine A (from <i>Huperzia serrata</i> )*	200 mcg

\*standardised extracts



# Wrap Up

- Clinical Evaluation:
  - Anxiety
    - BAI
    - GAD-7
    - STAI
  - Depression
    - BDI
- Management
  - Lifestyle – Exercise, Meditation, Yoga
  - Diet
  - Psychological Counselling (CBT, Mindful)
  - Supplements
    - Methylation Cycle
    - Tryptophan Metabolism
    - Lipid support



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Opinions expressed in this article are not necessarily those of the editors, the CAND nor its board of directors.*

## Stress Effects of Childhood Allergies/Illness on Children and Their Family Members

**Dr. Sarah Hardy Walsh, ND, Dr. Baljit Khamba, ND, MPH, and Dr. Deborah Kennedy, ND, PhD**

Allergic disorders have become common in both children and adults, with asthma occurring in 12% of children and 8% of adults, food allergies in 2-4% of children and 1-2% of adults, and 20-25% of the population reporting symptoms of allergic rhinitis.<sup>1,2,3</sup> Chronic allergic illnesses can become a pressing burden to the patient, their caregiver and taxing to the healthcare system overall. The objectives of this article are to explore the effects of allergic illnesses on the stress experience of the atopic children and their families.

chronic stress can trigger the release of pro-inflammatory cytokines (interleukins 1 and 6, tumour necrosis factor alpha and interferon alpha), which contribute towards further glucocorticoid release.<sup>8</sup>

The chronic activation of the HPA axis and the resulting cortisol concentrations from a young age in children with atopy plays a role in the overall activation and chronicity of atopic conditions. One study examined healthy children (aged 8-14) and children with ongoing atopic dermatitis, but currently in remission. The subjects were age and sex matched and divided into two groups (healthy vs. atopic dermatitis). The subjects were exposed to stressful psychosocial stimuli, while having intervals of pre and post salivary cortisol, heart rate and perceived stress measured. Compared to healthy children, this study found that the children with atopic dermatitis had a blunted adrenocortical response to the stress, suggesting that atopic children have a hyporeactive or blunted stress response, which contributes to their physical symptoms and an increased potential for a mental health comorbidity.<sup>9,10</sup>



UPDATE

EDITORIAL

CASE



## Effectiveness of Vitamin D in the Treatment of Mood Disorders: A Literature Review

Baljit K. Khamba ND, MPH;<sup>1</sup> Monique Aucoin, BMSc, ND (cand.);<sup>5</sup> Dina Tsirgielis, BSc;<sup>1</sup> Alex Copeland, BSc;<sup>1</sup> Monica Vermani, PsyD;<sup>1,3</sup> Catherine Cameron, MD;<sup>1</sup> Isaac Szpindel, MD;<sup>1</sup> Bob Laidlaw, BSc;<sup>1</sup> Irvin Epstein, MD;<sup>1,2</sup> Martin Katzman, MD<sup>1,2,3,4</sup>

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**Abstract** Depression is a mood disorder that has a significant negative impact on the lives of many individuals. Since vitamin D deficiency is prevalent in the North American population, recent scientific research is investigating the connection between insufficient vitamin D and the pathogenesis of mood disorders, as well as the nutrient's potential as a therapeutic agent. Several epidemiological studies have shown a relationship between low levels of vitamin D and the presence of depression. A small number of intervention trials have found a potential trend toward the reduction of depressive symptoms from vitamin D supplementation; however, many of the studies had limitations which restrict the conclusions that can be drawn. Further research in the field is warranted.

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# Thank you!

Register with the link below to receive access to:

- The presentation slides
- A practitioner guide to Mental Health

<https://www.newrootsherbal.eu/en/mental-health>

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Thank you!

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