

Keeping the Blues at Bay

A Holistic Approach to Maintaining a
Positive Mood in Dark Times

What is Depression?



Depression - A Spectrum of Disorders

- Unipolar major depression
- Persistent depressive disorder (dysthymia)
- Disruptive mood dysregulation disorder
- Premenstrual dysphoric disorder
- Substance/medication induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorder (eg, minor depression)
- Unspecified depressive disorder
- Adjustment disorder with depressed mood



Which is it?

-Who cares?

- o “As with other psychiatric disorders defined by syndromes, each depressive disorder likely represents an etiologically heterogeneous group of conditions, with similar clinical manifestations, that are not currently distinguishable and that do not yet have differentially targeted treatments.”

UpToDate

I will come back to this point



Symptoms

- Dysphoria (sad or irritable mood) or Loss of interest in activities that were once enjoyable,
- and at least four additional symptoms:
 - appetite disturbance
 - sleep disturbance
 - fatigue
 - psychomotor agitation or retardation
 - feelings of worthlessness, sinfulness or guilt
 - trouble with concentration
 - thoughts of death or suicidal ideation



Depression Without Sadness

- o Many patients present to doctors with primarily physical complaints, not complaints about their mood (70% in one international study)
- o For some people, anxiety or irritability predominate
- o Anhedonia (loss of pleasure in usual activities) has been the most useful clue for me



Epidemiology

- **Projected lifetime risk of Major Depressive Disorder at age 75 was 23.2%**
 - Archives of General Psychiatry 2005;62(6):593-602.
- **Mean age at onset 30 years**
 - Arch Gen Psychiatry 2005;62(10):1097-106. Jama 2003;289(23):3095-105.
- ***“By 2020, major depression is expected to be second only to ischemic heart disease as a cause of disability.”***
 - American Journal of Managed Care 2007;13(2):65-72.



Burden of Illness

- Approximately 15% of patients hospitalized for major depression eventually commit suicide.
- Persons with major depression have a 4.8 times greater risk for work disability than asymptomatic individuals and report significantly poorer intimate relationships and less satisfying social interactions.



Suicidal Thoughts

- o Extremely common – about 70% of my general medical intakes have had thoughts of suicide at some time
 - o A recent study in Colorado showed 30% of high school students commonly think of suicide and feel hopeless
 - o Suicide is one of the top 10 causes of death in all age groups and one of the top three causes in young adults and teenagers.
 - o Generally transient – if survived
 - o Beware impulsivity
- Crisis Line (888) 849-5728 (707) 445-7715



Comorbidities

- o Depression is both a major contributor to, and a common result of, many other chronic health conditions.

Arch. of Gen. Psychiatry 1994;51(1):8-19.

- o Asthma
- o Allergy
- o Autoimmune Diseases (arthritis, SLE, MS etc.)
- o Endocrine disorders
- o Cancer
- o Osteoporosis
- o Obesity
- o CV Disease
- o Chronic Pain



Comorbidities

- o DM2:
 - o Patients with DM2 have 2x risk of Depression
 - o Having both confers ↑mortality vs. just one
 - Diabetes care 2005;28(6):1339-45. Diabetes care 2001;24(6):1069
- o CV Disease:
 - o As an independent risk factor for coronary disease, depression confers a risk greater than that related to smoking.” Psychosomatic Medicine 2003;65(2):201-10.
 - o Depression most often precedes the cardiovascular event, rather than the reverse. JAMA 2007;297(4):411-2.
 - o Mechanism may be behavioral (↓activity, etc.) JAMA. 2008 Nov 26;300(20):2379-88.



Efficacy & Limitations of Current Mainstream Treatment Approach

“Although 90% of depressed patients respond to medication. . . up to 60% of these will never achieve [full] remission of symptoms.”

Stahl SM 1999: J. Clin. Psychiatry 60:213-214.



Bias in Publication

- **74 FDA-registered studies; 31% were not published.**
- **Studies viewed by the FDA as having positive results:**
 - **37 were published;**
 - **1 not published.**
- **Studies viewed by the FDA as having negative or questionable results:**
 - **3 published**
 - **22 not published**
 - **11 published in a way that conveyed a positive outcome**
 - findings with respect to the protocol-specified primary outcome were nonsignificant;
 - publication highlighted a positive result as if it were the primary outcome
- **Studies viewed as positive “were approx. 12x as likely to be published.”**

N Engl J Med 2008;358:252-60



Drugs and Placebos

- Systematic review of antidepressant trials submitted to the FDA for approval of 6 widely prescribed antidepressants (many of which were not published):
 - 80% of the response to medication was duplicated in placebo control groups.
 - The mean difference between drug and placebo on the Hamilton Depression Scale was less than 2 points (on a 64-point scale).

○ **Kirsch I, Moore TJ, Scoboria A, Nicholls SS.** The emperor's new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. *Prevention & Treatment* 2002;5(Article 23).



“Active” Placebos

- There is less difference in effectiveness when antidepressants are compared with placebos with side effects that mimic the effects of the antidepressants
- *The Cochrane Database of Systematic Reviews* 2006 Issue 1
Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. **Active placebos versus antidepressants for depression** Moncrieff J, Wessely S, Hardy R



Placebo Response

- Placebo response rates vary widely across patient groups
- May be as high as 65 percent, even in groups with major depression
- Placebos aren't all bad, but it is best if they are cheap and safe. . . .



SSRI Risks/Side effects

- **Persistent pulmonary hypertension of the newborn (PPHN)**
- **Increase suicide risk (acutely) in children and adolescents**
- **Weight gain**
- **Sexual dysfunction**
- **Emotional detachment**
- **Twice the annual rate of bone loss (vs TCA's)**
- **Discontinuation difficulties**
- **Induction of Mania, agitation, aggression, paranoia**

Koren, G., Canadian J Pharmacology, 2009. Winter, (1):e66-7

J Psychopharmacol. 2008 Sept;22(7):792-80

Rosen CJ: Serotonin Risin-The Bone, Brain Bowel Connection. NEJM, 360:10957-959



Adverse Endocrine Effects

- o Metabolic syndrome
 - o Weight gain associated with atypical antipsychotics occurs in first few months after initiation and may not stabilize for more than a year

Highest Wt Gain Risk	Moderate Wt Gain Risk	Minimal Wt Gain Risk
Clozapine	Risperidone *0	Ziprasidone (Geodon)
Olanzapine *2.31	Quetiapine *0	Aripiprazole

o *Incident Diabetes Risk HR

- o J Clin Psych 2006; 67(Suppl 9):25-30; metaanalysis in Am J Manag Care. 2007 Nov;13(7 Suppl):S170-7



Complex Polypharmacy

- o If you are bipolar and..
 - o Have ever taken an atypical antipsychotic
 - o Have more than 6 episodes of depression
 - o Attempted suicide
 - o Earn over \$75,000
-
- oyou have >64% chance of being treated with 4 or more medications



J. Clin Psychiatry 2009;70(2):155-162.

Antidepressant use tripled in last decade

- Success = 50% improvement in 50% of patients
 - In STAR-D, >90% of “remitters” had at least 1 residual symptom (sleep disturbance, weight gain most common)
Psychol Med. 2010 Jan;40(1):41-50.
- 86% have one or more side effects
 - Docs record only 1/20 of these compared to patients completing questionnaire; we only record 1/3 of the frequently occurring or bothersome ones J Clin Psychiatry. 2010 Apr;71(4):484-90
- Only 50% still taking them after 4 months
 - One study found only 44% continued x 6 months
 - 63% who discontinued did not discuss with their doc
 - BMC Psychiatry. 2009 Jun 16;9:38



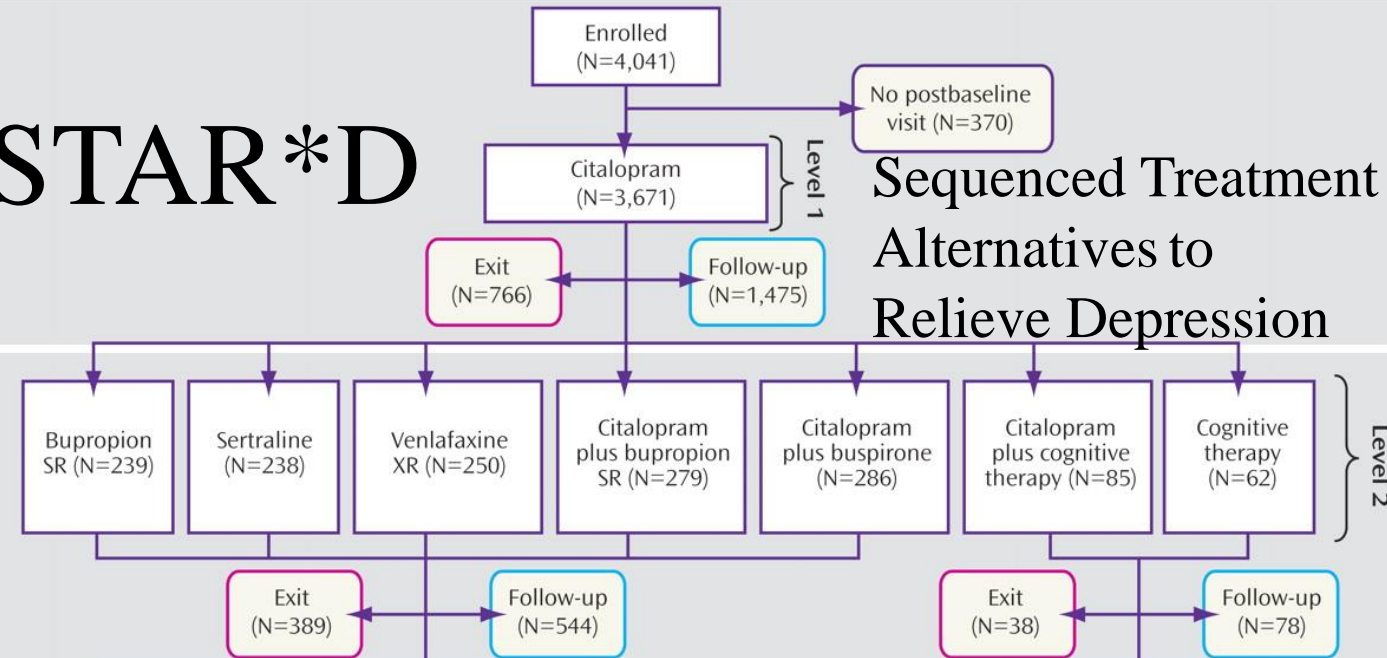
Step
1

STAR*D

Sequenced Treatment Alternatives to Relieve Depression

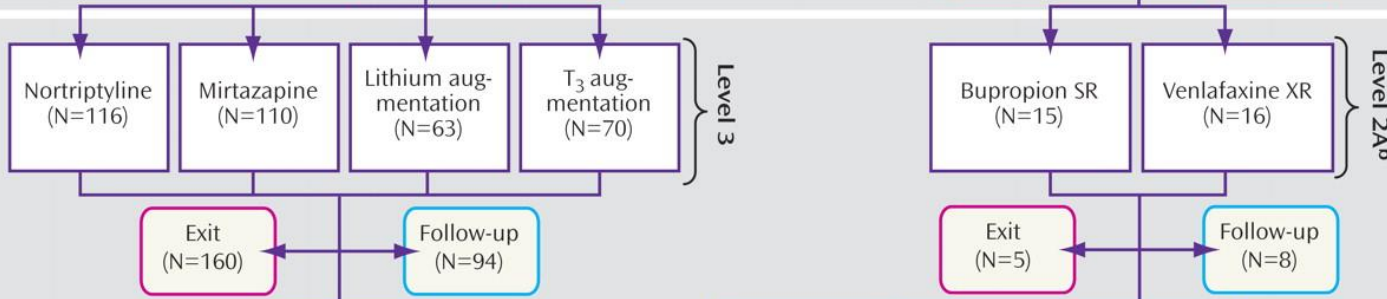
Remission
Rates
36.8%

Step
2^a



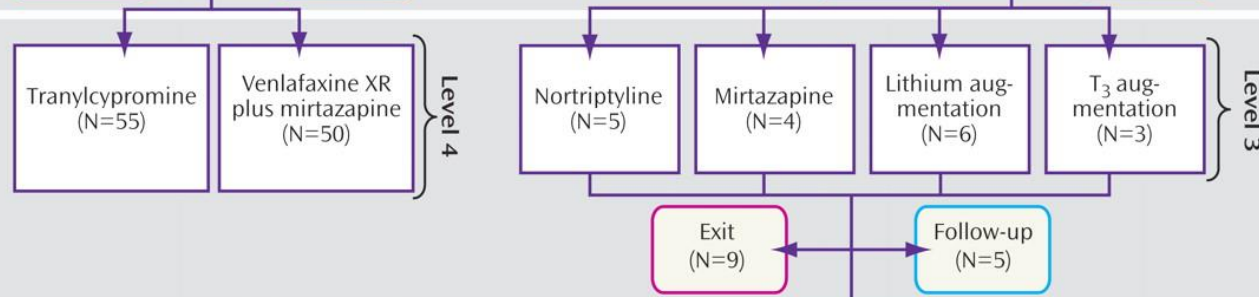
30.6%

Step
3



13.7%

Step
4



Overall
13% 67%

Step
5^b

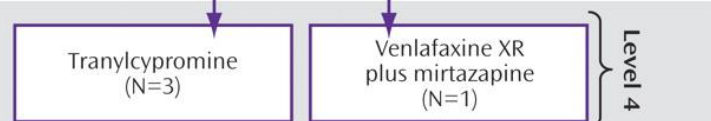


TABLE 3. Acute Treatment Outcomes by Treatment Step

Feature	Treatment Step ^a							
	Step 1 (N=3,671)		Step 2 (N=1,439)		Step 3 (N=390)		Step 4 (N=123)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
QIDS-SR ₁₆ score at entry to step	15.4	4.3	12.3	4.9	13.4	4.6	14.0	4.6
QIDS-SR ₁₆ score at exit from step	8.6	5.8	9.4	5.8	11.5	5.5	12.0	5.7
Change in QIDS-SR ₁₆ during step (%)	-43.4	36.1	-20.3	51.9	-12.3	34.4	-11.6	37.1
Weeks to remission ^b (for those remitting)	6.3	3.8	5.4	4.5	5.6	4.4	7.4	4.8
Weeks to response ^c (for those responding)	5.5	3.5	6.5	4.0	6.4	4.1	8.3	4.4
Weeks in treatment	10.1	4.1	9.3	5.0	8.6	5.2	9.2	5.3
Cumulative weeks in treatment	10.1	4.1	19.1	6.9	28.1	8.6	37.9	8.9
	N	%	N	%	N	%	N	%
Remission at each step exit	1,346	36.8	439	30.6	53	13.7	16	13.0
Response in each step	1,776	48.6	408	28.5	65	16.8	20	16.3
Intolerable side effects ^d	599	16.3	281	19.5	100	25.6	37	30.1

^a Sums do not always equal N due to missing values. Percentages are based on available data.

^b Exit QIDS-SR₁₆ ≤ 5.

^c 50% or more reduction in QIDS-SR₁₆ score from entry score at each step.

^d Proportion of participants who left the level prior to 4 weeks for any reason and those who left thereafter whose exit form indicated intolerance.

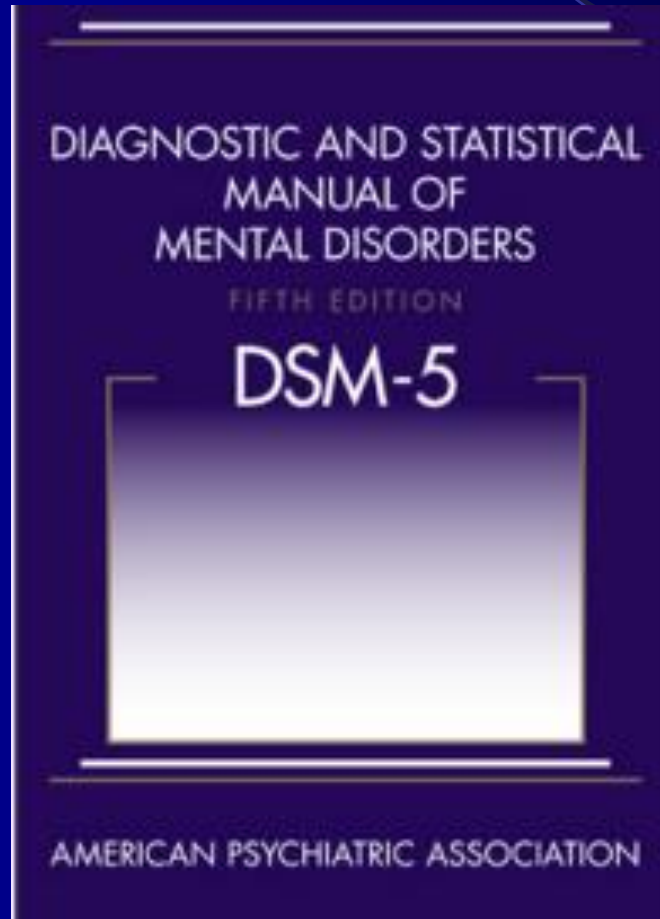
The overall cumulative remission rate was 67%, but with dropouts 51%.

Weeks to remission 6.3 +/- 3.8 weeks. (Longer than we thought)
If you have tried two AD's, it's time to augment (T3, Li)



Name it, Blame it, Tame it

DSM-V:
100% Accuracy,
0% Validity



Is depression a
Prozac®
deficiency?



Problems with Reductionism:

- Depression is a syndrome, not a diagnosis, and is often a symptom of another condition
 - Nutritional deficiencies – methylation. Vit. D, Zn, Mg, ω -3
 - Brain inflammation – allergies, infections. Toxins, mold
 - Hormonal imbalance – thyroid, adrenal, gonadal, insulin
 - Digestive dysfunction – via #1, #2, neuroactive peptides
 - Toxins – heavy metals, solvents, mold
 - Chronic/acute stress – PTSD, loss, etc.



For effectiveness, treatment must match the cause

Models of Depression

- Learned Helplessness (Behavioral Therapy)
- Social Defeat (Hierarchical social theory)
- Response Contingent Positive Reinforcement (operant conditioning)
- Attachment Early Relational Trauma/Loss (psychodynamic/depth psychological)
- Role disruption (IPT-social)
- Neurochemical/Genetic/epigenetic (biological)
- Each model implies a different, albeit limited, treatment approach



The Map is not the Territory

- o Each of these models is like one blind man describing his part of the elephant
- o The art is to keep all of these models in mind and to move back and forth between them while working with the patient.



What is Depression?

(Connie's more existential take on it)

- o A final common pathway for expression of dis-ease in the Mind/Body/Spirit
- o A survival mechanism for animals when sick, or in the winter?
- o A cry of distress or a call to action when some circumstance needs to be altered



What Causes Depression?

- Multifactorial:
 - Body: Biological Factors
 - Mind: Patterns of Thought
 - Spirit: Loss of Connection and Purpose
 - Environment: Toxic or nurturing
 - Social support: Loneliness, disconnection
 - Life Events
 - Sudden Stressful Events
 - Longterm Intolerable Conditions
 - Early Environmental Stress Predisposes



Treatment should be focused on the level(s)
most out of balance

Tacks Rule #1



- If you are sitting on a tack, it takes a lot of aspirin to make the pain go away.
 - You can substitute psychotherapy, meditation, organic foods, etc for the aspirin and the rule still holds
- The proper treatment for tack-sitting is tack removal





Tacks Rule #2

- If you are sitting on two tacks, removing just one does not result in a 50% improvement.





Tacks Rule #2

- If you are sitting on two tacks, removing just one does not result in a 50% improvement.



A Corollary to the Tacks Rules

- If you are sitting on a tack and you use morphine to make it feel good, this may prevent you from removing the tack
- (See Peter Kramer in Listening to Prozac)



Causes of Depression

- o Body: Biological Factors
- o Mind: Patterns of Thought
- o Spirit: Loss of Connection and Purpose
- o Environment: Toxic or nurturing
- o Social support: Loneliness, disconnection



Body Causes

- Deferred to the end of this section
- Often overemphasized in current biological model of depression



Causes of Depression

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Mind

- o General level of challenge and stimulation
- o Patterns of thought: negative, pessimistic, self-defeating, external focus of control
- o Learned helplessness
 - o Dogs taught to be helpless are noted to have alterations in neurotransmitter levels, which normalize on being re-educated in control



Causes of Depression

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Spirit

- o Lack of purpose, value and meaning in life
- o Absence of centering, praying or meditating regularly



Causes of Depression

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- o Mind: Patterns of Thought
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Environment

- Is workplace or school healthy, supportive, nurturing
- Toxins, allergens, pollutants
- Lack of connection with earth, plants, beauty
- Overcrowding
- Lack of Sunlight



Causes of Depression

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Social

- o Loss of parent
- o Number and quality of connections
- o Low level of perceived support



Culture of Depression

- **VALUES:**
 - Money and accumulation privileged over relationships
- **MEDIA:**
 - Corporate values (consumerism and materialism) promoted via heavy media
- **RESOURCES:**
 - Per capita income declining since mid -70's, while material expectations rising
- **SOCIAL BONDS BROKEN:**
 - Chronic loneliness-extended family disconnection and fragmentation, few multigenerational families, and larger stable communities
- **SPIRITUAL-NATURE:**
 - Disconnection from nature



Body Causes

- o Genetic - 10% concordance in siblings
- o Nutrition
- o Lack of Exercise
- o Inflammation
- o Hormonal
 - o Thyroid
 - o Sex hormones
 - o Adrenal
- o Substances
- o Other Illnesses



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Nutrition

- o Nutritional tacks
 - o MSG, aspartame
 - o Allergens
 - o Etc.
- o Nutritional lacks
 - o Omega-3's
 - o Methylation
 - o Amino acids
 - o Etc.



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Inflammation and the Brain

- Proinflammatory cytokines (IL-1, IL-6, TNF- α) and bacterial toxins produce symptoms of depression and anxiety (think about treating MS, hep C)
- Depression is more common in inflammatory diseases like heart disease and autoimmune disease
- • Treatment-resistant depression is characterized by elevated IL-6



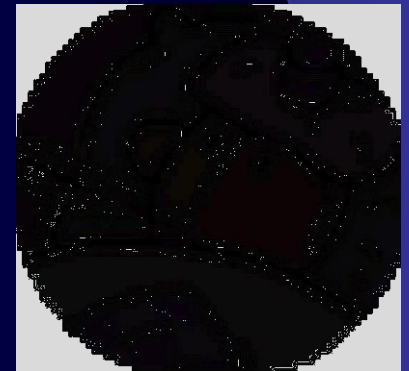
Cytokine Hypothesis

- Depression is a behavioral response to physical illness
 - Low mood is the product of malaise
 - Humans interpret lack of energy, motivation as a moral failure leading to cognitive symptoms as feelings of guilt, unworthiness and irritability



Sickness Behavior Resembles the
Vegetative Symptoms of Depression

The International Journal of Neuropsychopharmacology, 2002, 5 , pp 375-388

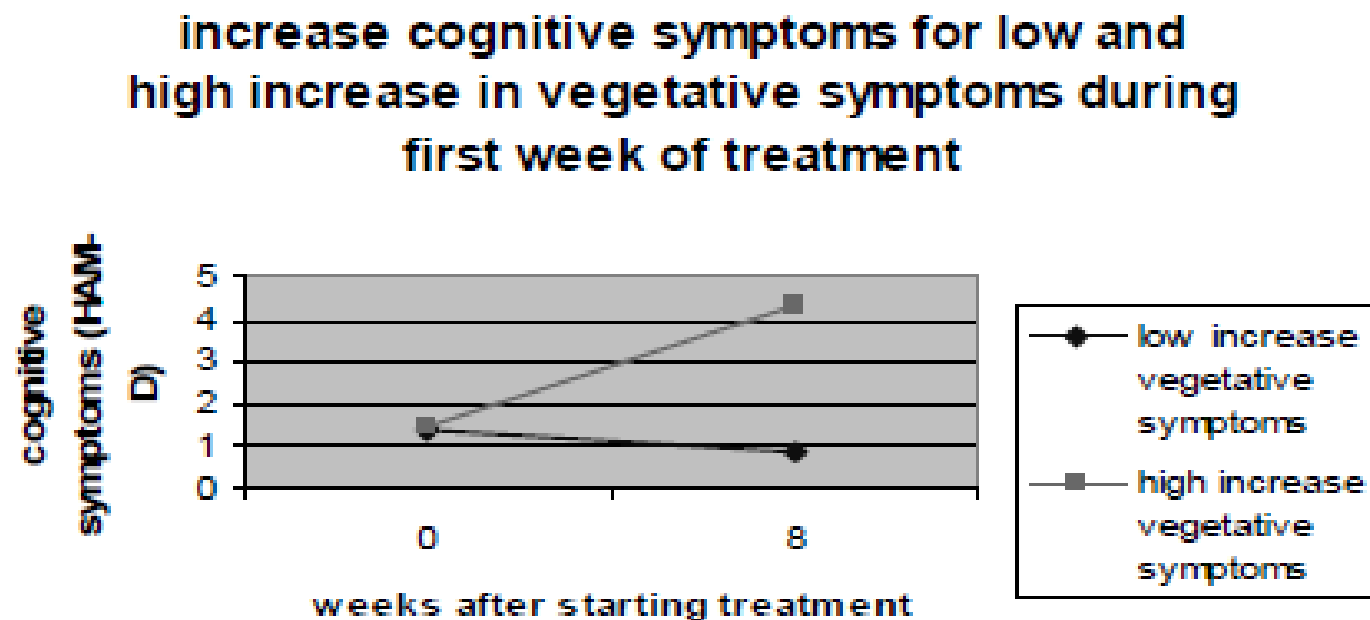


IFN- α for Hep C

- HAM-D and MADRS scores increased during IFN- α tx
- Vegetative symptoms increased immediately
- Cognitive symptoms increased 8 weeks after starting treatment



Increase in vegetative symptoms in first week differentiates subjects with cognitive complaints after 8 weeks, $\beta=3.34$, $p=0.003$



Mechanisms

- Serotonin

- Inflammation \uparrow fxn of IDO (indoleamine 2,3-dioxygenase)
 - breaks down tryptophan
 - creates glutamate agonists (Neurotoxic TRYCATs)

- Norepinephrine, Dopamine

- IL-1, IL-2 and TNF- α

- HPA axis

- IL-1, IL-6 and TNF- α



5-HT System

Immune activation

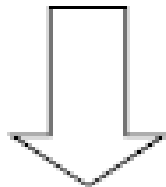
TRP \Rightarrow 5-HT

BBB

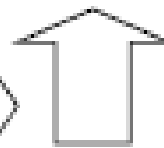
IFN α



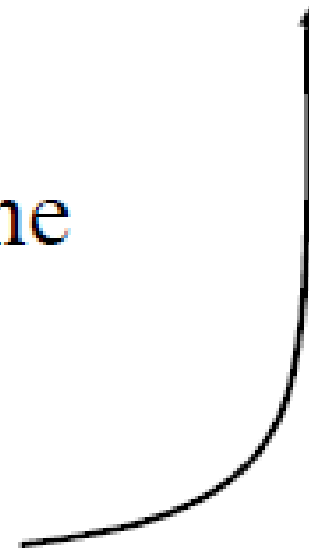
IFN γ



kynurenine



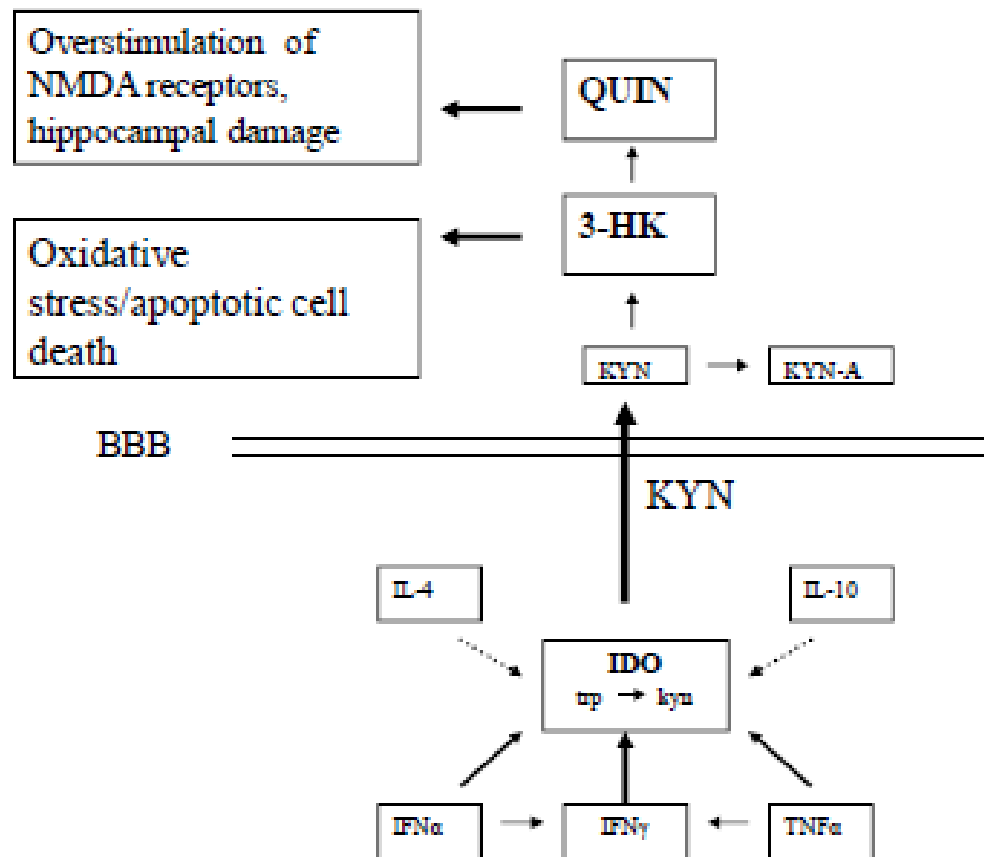
TRP



Indoleamine-2,3-dioxygenase



TRYCAT Pathway (Tryptophan Catabolites)



Body Causes

- o Inflammation
 - o IFN - iatrogenic
 - o Food Allergy – elevates circulating cytokines
 - o Chronic Infection
 - Lyme Disease
 - HIV disease
 - Hepatitis C
 - o Autoimmune disease
 - Lupus
 - Rheumatoid arthritis
 - Inflammatory bowel disease

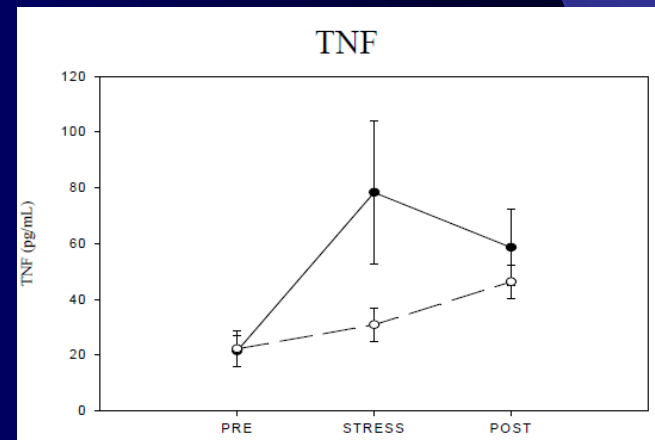
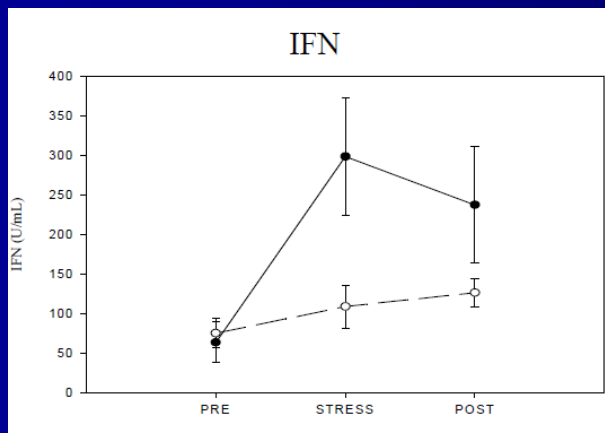


Psychological Stress Increases Immune Mediators

Animals - Plasma IL-6 increases following:

- Restraint stress and aversive stimuli (Zhou et al, 1993)
- Immobilization stress (Takaki et al., 1994)
- Open-field stress (LeMay et al., 1990)

Humans – University students pre, post and at time of exam



Body Causes

- o Genetic
- o Nutrition
- o Lack of Exercise
- o Inflammation
- o Hormonal
 - o Thyroid
 - o Sex hormones
 - o Adrenal
- o Substances
- o Other Illnesses



Hormonal Causes: Thyroid

- o Thyroid: high or low

Blood tests \pm reliable; consider am temperature testing.

Transthyretin needed to transport thyroxine into CNS

- o T3!

- o Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with thyroxine plus liothyronine

- o 15 visual-analogue scales for mood and physical status

- 10 were significantly better after treatment with thyroxine plus triiodothyronine than thyroxine alone

1999 NEJM Volume 340:424-429



Hormonal Causes

- Sex hormones, and changes therein
 - Postpartum
 - PMS
 - Menopause - action of estrogen on 5HT 2A receptor and serotonin transporter in brain
 - Andropause – low testosterone in men
 - Decreased libido Decreased muscle mass, strength
 - Sexual dysfunction Fatigue
- Other – diabetes, adrenal



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Body Causes - Substances

- Substance Abuse
- Toxins – solvent exposure, etc.
- Medications That Can Cause Depression
 - Hormones
 - Blood pressure medicines - Antihypertensives
 - Anticonvulsants
 - Steroids
 - Digitalis
 - Antiparkinsonian agents
 - Antineoplastic agents
 - Antibiotics
 - Pain medications, benzodiazepines
 - Acid blockers: cimetidine, ranitidine



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Body Causes

- o Other Illnesses
 - o Heart Disease
 - o Lung Disease
 - o Neurological disease
 - o Pain Disorders



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
 - o Bibliotherapy
 - o Talk therapy – Cognitive Behavioral Therapy, Positive Psychology
- o Diet – omega 3
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Removal of Tacks

- o This can be huge – depression can be a catalyst for major life change
 - o Toxic Relationships
 - o Unresponsive Career Path
 - o Toxic Environment
 - o Etc.
- o Caveat: Judgment can be clouded while depressed, people or other factors may be scapegoated – don't act impulsively!
- o Smaller tacks warrant removal as well



Nutritional Tacks in Depression

Caffeine and Simple Sugars

- A small controlled trial found that eliminating refined sucrose and caffeine from the diets of people experiencing unexplained depression resulted in improvements by 1 week, and symptoms worsened when patients were challenged with these substances but not with placebo challenge.

- Kreitsch K, et al: Prevalance, presenting symptoms, and psychological characteristics of individuals experiencing a diet-related mood disturbance. Behav Ther 19:593–604, 1988



Food Additives

- MSG and Aspartame – Excitatory Amino Acids should probably be limited
- Antagonists of glutamate can decrease symptoms of depression
- **Glutamate and Depression, Clinical and Preclinical Studies** *IAN A. PAUL^a, and PHIL SKOLNICK^b* **Annals of the New York Academy of Sciences** Volume 1003 Page 250 - November 2003



Food Allergens

- Cytokine levels rise after meals with foods to which an individual is sensitive
- Gluten-free diet may alleviate depressive and behavioural symptoms in adolescents with coeliac disease: a prospective follow-up case-series study BMC Psychiatry. 2005 Mar 17;5:14



Alcohol

- Although consumption of alcohol transiently increases the turnover of serotonin, the long-term result is diminished levels of serotonin and catecholamines.



Medical/Body Tacks

- o Correct other medical problems:
 - o Inflammatory Conditions
 - o Pain management
 - o Hormonal Imbalances
 - o Sleep disturbances
 - o Etc.



Mind/Emotional Tacks

- o Address Trauma/Take out Emotional Trash – EMDR, other techniques
- o Address Negative Automatic Thoughts
- o Address verbally and otherwise abusive relationships (work and intimate relationships)

o See Therapy section later



Other Tacks

- o Environmental Exposures and Lack of Exposure to Natural Environment
- o Social Isolation
- o Etc.



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
- o Diet – omega 3
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Exercise

- More than 1000 trials have examined the relationship between exercise and depression.
- As effective as psychotherapy
- As effective as zoloft, imipramine
- Long-term effective:
 - One study supervised x 10 weeks, then independent: as effective at 26 months as initially.

Cochrane Database Syst Rev. 2008;(4):CD004366.

BMJ. 2001;322(7289):763–767.

Clin Psychol Sci Pract. 2006;13(2):179–193

J Clin Psychol Med Settings. 2008;15(2):140–147.



How Exercise Works

- o Exercise may increase levels of serotonin and endorphins
 - o benefits have been reported even when naloxone is administered to block endorphins.
- o Exercise requires that patients take an active role in their recovery — locus of control!
- o Leads to improved self-esteem and self-confidence as body strength and self-image improve.
- o Provides a “time out” period—an opportunity to leave troubles behind temporarily.



Types of Exercise

- o High-energy exercise more effective than low energy
- o Resistance or Aerobic effective
- o Yoga also effective
 - o Indian J Clin Psychol 1993; 20: 82-87.
 - o As effective as imipramine, slightly less than ECT. J Affect Disord 2000; 57: 255-257



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
- o Diet – omega 3
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Phototherapy

- Seasonal affective disorder (SAD)
- May be useful as an adjunctive modality added to pharmacotherapy in both unipolar and bipolar depression
- *The Cochrane Database of Systematic Reviews* 2006 Issue 1
Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. **Light therapy for non-seasonal depression**
Tuunainen A, Kripke DF, Endo T.
- 30 minutes of bright (10,000 lux), white (full-spectrum) light daily
- Loaners in our office – usually benefits are seen within 1-2 weeks



Negative Ions

- Two randomised controlled trials have compared high-density air ionisation (1×10^4 ions/cm³) with low-density air ionisation (2.7×10^6 ions/cm³) for winter depression. Patients were exposed to an air ioniser at home for 30 minutes each morning over 2 to 3 weeks. High-density air ionisation was more effective than low-density ionisation.
- Terman M, Terman JS. Treatment of seasonal affective disorder with high-output negative ionizer. J Altern Complement Med 1995; 1: 87-92
- Terman M, Terman JS, Ross DC. A controlled trial of . timed bright light and negative air ionization for treatment of winter depression. Arch Gen Psychiatry 1998; 55: 875-882



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
- o Diet – omega 3
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Psychotherapy

- When studied head-to-head with medication, generally equivalent response rates, but therapy has lower relapse rate after discontinuation
- Patients in IPT reported greater satisfaction with treatment, and patients in both IPT and CBT reported significantly greater effects of treatment on their capacity to establish and maintain interpersonal relationships and to recognize and understand sources of their depression than did patients in IMI-CM or placebo.
- **Short- and long-term effects of medication and psychotherapy in the brief treatment of depression: further analyses of data from the NIMH TDCRP**
Psychotherapy Research Issue: Volume 10, Number 2 / February 01, 2000
pages: 215 - 234



Psychotherapy –In Combination

- 55% Response rate nefazodone
- 52% Response rate psychotherapy
- 85% Response rate combined-treatment group ($P < 0.001$).

N Engl J Med. 2000 May 18;342(20):1462-70.



Psychotherapy: Evidence-based Approaches

- Psychoeducation
- Motivational Interviewing
- Cognitive-Behavioral Therapy
- Relaxation Strategies
- Skills Training
- Interpersonal Therapy
- +/-Positive psychology
- Mindfulness — Meta-analysis, Journal of Consulting and Clinical Psychology.

Vol 78(2), Apr 2010, 169-183.



Mindfulness-based Therapy

- In patients with anxiety and mood disorders, this intervention was associated with effect sizes (Hedges's g) of 0.97 and 0.95 for improving anxiety and mood symptoms, respectively. These effect sizes were robust, were unrelated to publication year or number of treatment sessions, and were maintained over follow-up.

Journal of Consulting and Clinical Psychology. Vol 78(2), Apr 2010, 169-183.



Bibliotherapy

o Feeling Good by Dr. David Burns has been studied:

J Consult Clin Psychol. 1989 Jun;57(3):403-7.

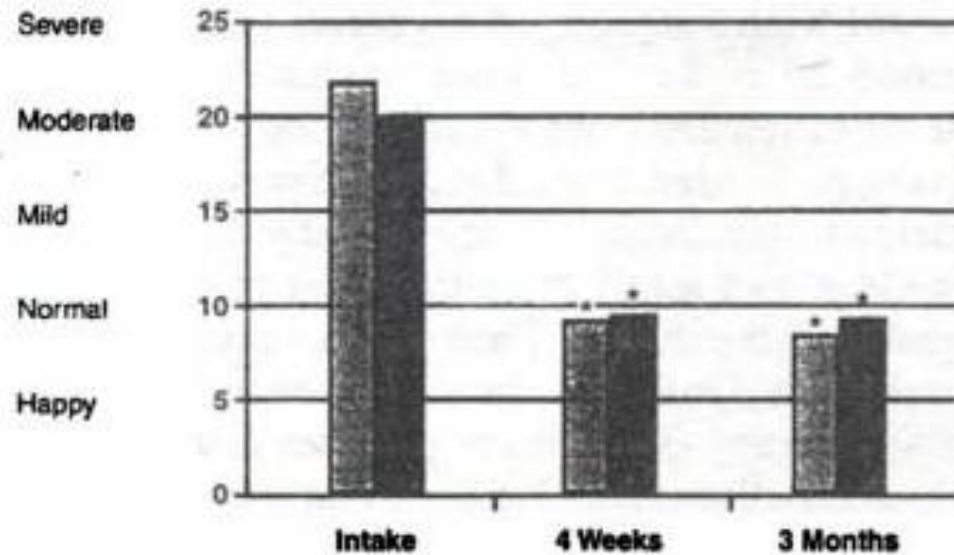
J Consult Clin Psychol. 1990 Oct;58(5):665-7.

J Consult Clin Psychol. 1995 Aug;63(4):644-50.

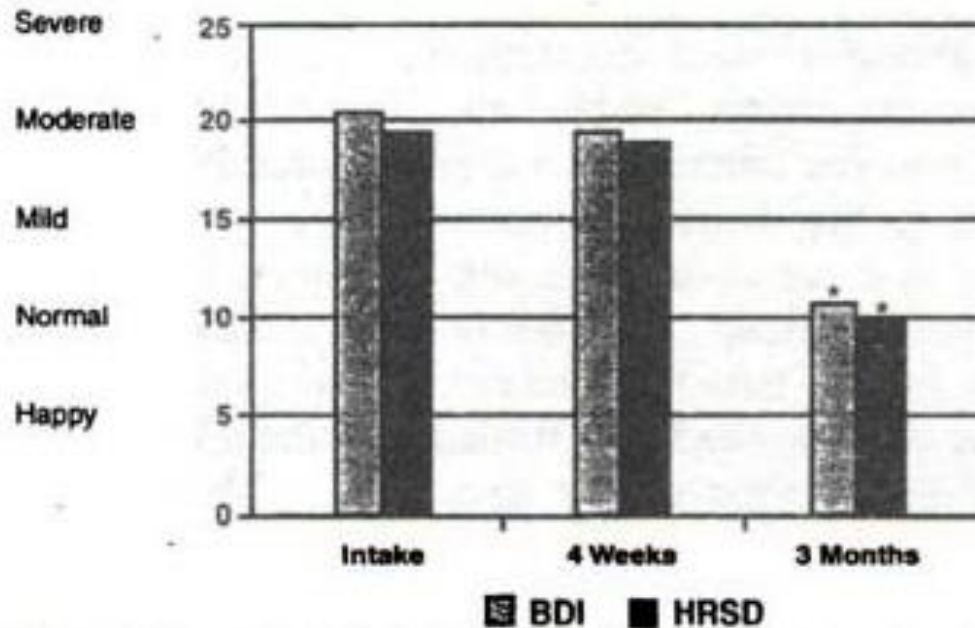
J Consult Clin Psychol. 1997 Apr;65(2):324-7.



Immediate Bibliotherapy Group



Delayed Bibliotherapy Group



Bibliotherapy

- ↓ HAM-D 11.6 points – CBT from therapist x 12 weeks
- ↓ HAM-D 10.6 points - bibliotherapy after four weeks



Bibliotherapy - Three-year follow-up

- 58% - moods continued to improve following the completion of the initial study.
- 72% - still free of clinical depression (failed the criteria for a major depressive episode)
- 70% had not sought or received any further treatment with drug therapy or psychotherapy during the follow-up period



Some Other Suggestions:

- Journal Writing: Has been studied for physical illness, such as asthma and general medical complaints (# of visits to student health center)
- Internet-based CBT: MoodGym <http://moodgym.anu.edu.au/welcome>
- Internet support groups: Heavy users of the Internet groups were more likely to have resolution of depression (CES-D Scale score 22) during follow-up than less frequent users Am J Psychiatry 159:2062-2068, December 2002
- Volunteering: Health benefits seen for altruism, also decreases isolation. Beneficial effect of formal volunteering on depression demonstrated in Americans' Changing Lives study Li, Yunqing; Ferraro, Kenneth F. [Journal of Health and Social Behavior](#), Volume 46, Number 1, March 2005, pp. 68-84(17)



Music

o Music Therapy

- o J Gerontol. 1994 Nov;49(6):P265-9. Effects of a music therapy strategy on depressed older adults. Hanser SB, Thompson LW
- o J Music Ther. 2000 Fall;37(3):170-82. The effect of reminiscence music therapy sessions on changes in depressive symptoms in elderly persons with dementia. Ashida S.
- o Using Music Techniques To Treat Adolescent Depression Journal of Humanistic Counseling, Education and Development v38 n1 p39-46 Sep 1999

o GIM (guided imagery and music) sessions - positively affect mood and reduce cortisol levels

- o Health Psychol. 1997 Jul;16(4):390-400. Effects of guided imagery and music (GIM) therapy on mood and cortisol in healthy adults. McKinney CH, Antoni MH, Kumar M, Tims FC, McCabe PM

o Music for Depressed Inpatients

- o better depressive scores

- o improved weekly, indicating a cumulative dose effect

Arch Psychiatr Nurs. 2004 Oct;18(5):193-9. Effects of music on major depression in psychiatric inpatients. Hsu WC, Lai HL.



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
- o Diet
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Diet for Depression

- o Generally healthful diet is recommended, with:
 - o 5-9 servings fruits and veggies,
 - o limited sugar and caffeine, trans fats, etc.
 - o augmented fish or fish oil



Nutrition and Depression

Associations between dietary pattern scores at phase 5 and CES-D depression at phase 7 ($n = 3486$)

	<i>Lowest tertile OR</i>	<i>Highest tertile OR (95% CI)</i>	<i>P^a</i>
Whole food dietary pattern - rich in fruit, vegetables and fish			
Model 1 ^b	1	0.64 (0.49-0.83)	0.001
Model 3 ^d	1	0.74 (0.56-0.99)	0.04
Processed food dietary pattern - rich in processed meat, chocolates, sweet desserts, fried food, refined cereals and high-fat dairy products			
Model 1	1	1.75 (1.25-2.45)	0.001
Model 3	1	1.58 (1.11-2.23)	0.01

Model 1: adjusted for gender, age and energy intake.

Model 3: model 1 plus adjustment for marital status, employment grade, education, physical activity, smoking habit, hypertension, diabetes, cardiovascular disease, self-reported stroke, use of antidepressive drugs and cognitive functioning.

Some trend observed when removed individuals depressed at time point 5. *** - diet preceded the depression

The British Journal of Psychiatry (2009) 195: 408-413



Omega-3 Fats

- Epidemiology suggests deficiency of omega-3 fatty acids or an imbalance in the ratio of omega-6 and omega-3 fatty acids correlates positively with increased rates of **depression**

Bruinsma KA, Taren DL: Dieting, essential fatty acid intake, and depression. Nutrition Reviews 58(4):98–108, 2000

- Fish oil is an effective mood stabilizer in bipolar disorder (5 caps twice a day)

- **Omega 3 Fatty Acids in Bipolar Disorder** Arch Gen Psychiatry. 1999;56:407-412 A Preliminary Double-blind, Placebo-Controlled Trial



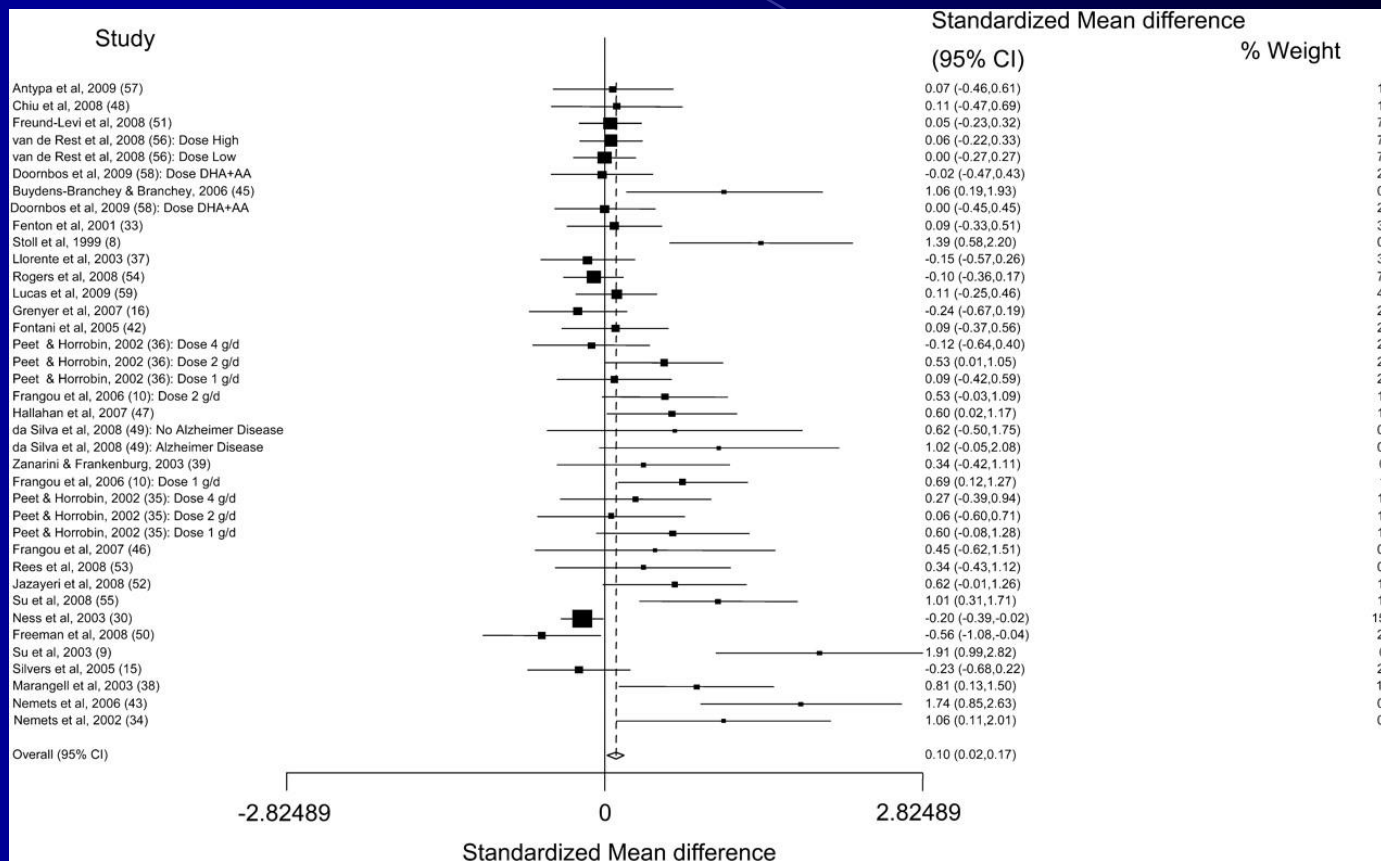
Omega-3 Fatty Acids

Potential Mechanisms of Anti-Depressive Effects

- Down regulate proinflammatory mediators associated with depression including IL-1 and IL-6
- Down regulate hypothalamic CRF and plasma NE
- Increase dopamine and serotonin receptor binding capacity
- Enhance transthyretin-mediated thyroid transfer to brain



FIGURE 3. Forest plot showing individual and combined effect size estimates and 95% CIs for all trials in the analysis, in order of standardized baseline depression scores



Appleton, K. M et al. Am J Clin Nutr 2010;91:757-770

Greater treatment effects were found in trials enrolling individuals with more severe depressive symptoms at baseline



Dose, duration not analyzed in meta-analysis

HRSD scores	Omega 3	Placebo
Pretreatment (week 0)	22.5 \pm 3.9	22.1 \pm 3.9
Posttreatment (week 8)	8.9 \pm 3.7	15.7 \pm 3.2 P < 0.001

6.6 grams per day x 8 weeks

European Neuropsychopharmacology 13 (2003) 267–271

In my review, studies with adequate dose and long enough (>42 days) saw benefit



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
- o Diet – omega 3
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Methylation and Depression

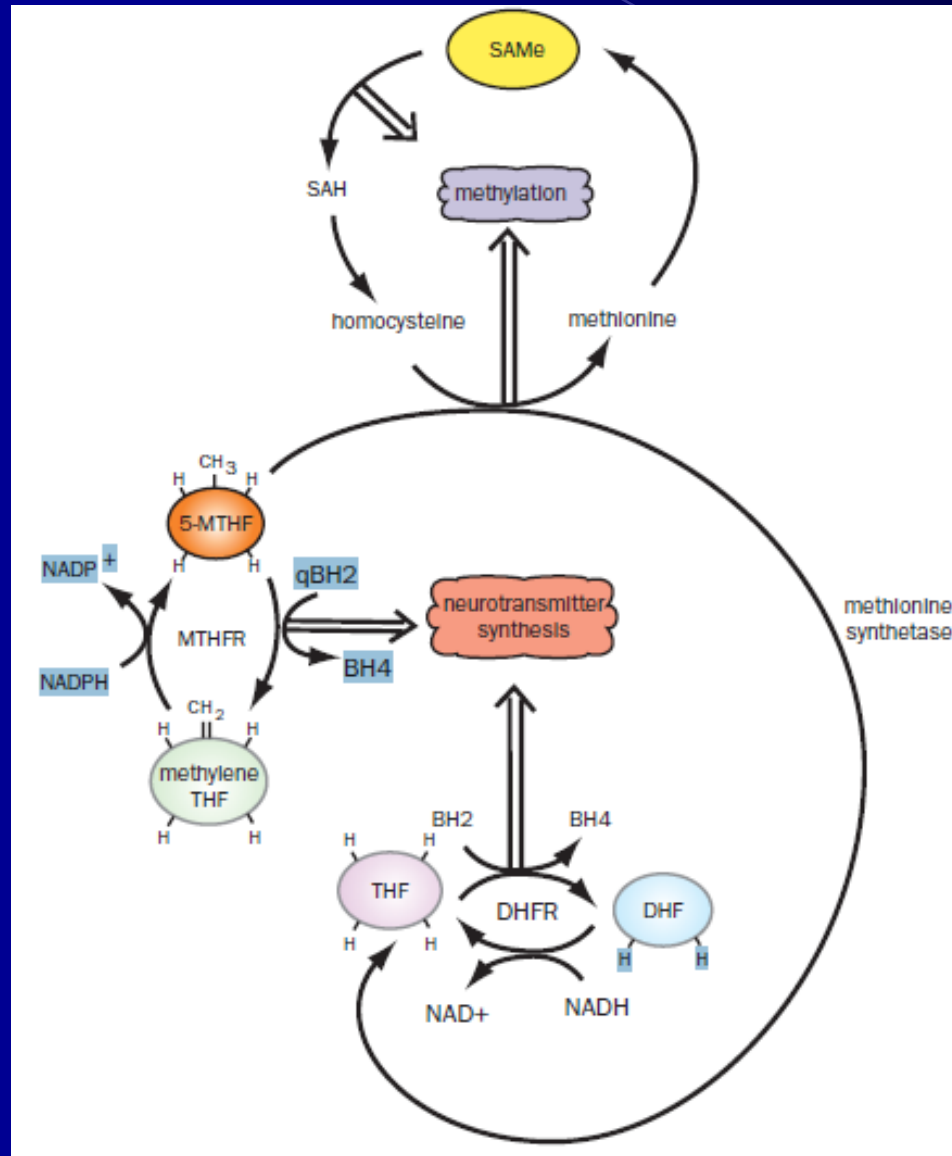
Cofactors:

Folate

B12

B6

Betaine



Also:

- Production of phosphatidylcholine
- Regulation of DNA
- Recycles homocysteine
- Recycles glutathione



SAMe

- Methyl donor in at least 35 important biochemical pathways in the body
- Antioxidant – precursor to glutathione
- S-Adenosyl Methionine production is impaired in people who are depressed.¹
- Supplementation with SAM-e increases levels of serotonin, dopamine and phosphatides, and improves serotonin and dopamine receptor site binding.



SAMe

- Treatment with antidepressant drugs that results in improved mood also results in increased levels of SAM-e, regardless of the drug used.
- Other beneficial effects
 - Osteoarthritis
 - Fatty liver and cholestasis of pregnancy
- Potential worry is increase in homocysteine, which should be preventable with B-complex supplementation



SAMe

- **45 published RCTs - at least 8 used an active comparator.**

- **Superiority to placebo in 6 of 8 placebo-controlled studies**

- **Equivalency to placebo in the other 2**

- **Equivalent to TCAs in 6 of 8 comparison trials**

- **More effective than imipramine in one study**

- **Obstet Gynecol Clin North Am. 2009 Dec;36(4):789-807**



SAMe as Adjunct

- o Speed response to antidepressants
- o Increase response to imipramine in treatment-resistant depression
- o Cautions:
 - o May provoke Mania
 - o May elevate homocysteine



The downsides

- o Most effective parenteral – poor absorption
 - o I use 400 mg bid with bromelain to boost absorption
- o Significant quality issues
 - o Overall, nearly half (6 out of 13) of products tested did not pass testing by consumerlab.com
- o \$\$\$



SAMe Quality

- o Approved Brands included:
 - o GNC SAMe 100 mg (Actimet®)
 - o Natrol SAMe 200mg (disulfate ditosylate)
 - o Nature Made® Joint Action™ 200 mg (1,4-butanedisulfonate)*
 - o Nature Made SAM-e 200mg (1,4-butanedisulfonate)
 - o NutraLife SAMe 200 mg (tosylate disulphate)*
 - o Puritan's Pride Inspired by Nature SAM-e 200mg (form not indicated)
 - o Source Naturals SAMe, 200 mg (disulfate tosylate)
 - o The Vitamin Shoppe SAMe, 200 mg (1,4-butanedisulfonate, disulphate [sic] tosylate)
 - o Twinlab SAM-e, 200 mg (tosylate)



SAMe Expense

- o 400 mg SAMe 30 pills ~\$18-20 wholesale
- o \$0.30 – 0.45 per 200 mg
(1600 mg/d costs \$2.40 – 3.60 per day)
- o An alternate approach is to supplement B vitamins, betaine(trimethylglycine), methionine – no studies, but I have found this to be very helpful empirically
- o (From Fatigued to Fantastic Daily Energy Enfusion, Methylguard, etc.))



B Vitamins

- o Depression is the most common symptom of folate deficiency
- o Involved in biosynthesis of serotonin and dopamine and norepinephrine
- o Borderline or low folate levels are found in 31% to 35% of depressed adults (up to 90% in the elderly)
- o 60% of population has MTHFR polymorphism
- o C→T genotypes: up to 4X the general
- o population risk for depression. Arch. Gen. Psychiatry 2003, 618– 626 Journal of Psychopharmacology 18(4) (2004) 567–571

o Other studies say no difference. Pharmacogenomics. 2008 Dec;9(12):1809-23



Enhancement of the antidepressant action of fluoxetine by folic acid

	Change in Hamilton rating scale score at week 6 or 10		
	Responder	Poor responder ≤50%	
<i>All patients</i>			
Fluoxetine+folic acid	42 (82.4%)	9 (17.6%)	Chi-Square=4.535 <i>P</i> <0.05
Fluoxetine+placebo	36 (62.1%)	22 (37.9%)	
<i>Women</i>			
Fluoxetine+folic acid	31 (93.9%)	2 (6.1%)	Chi-Square=8.656 <i>P</i> <0.005
Fluoxetine+placebo	22 (61.1%)	14 (38.9%)	



Journal of Affective Disorders Volume 60, Issue 2,
November 2000, Pages 121-130

Folate

- Subjects with low folate levels
 - more likely to have melancholic depression
 - significantly less likely to respond to fluoxetine
Am J Psychiatry 1997; 154: 426–8
- Folic acid enhances lithium prophylaxis
 - 40% reduction in affective morbidity in patients who had their plasma folate increased to 13 ng/ml or above
J Affect Disord 1986; 10: 9–13
- A placebo controlled trial in depression utilising 15 mg daily of folic acid for 4 months showed improvement in mood and neuropsychological function

Botez MI, Botez T, Leveille J, *et al.* Neuropsychological correlates of folic acid deficiency: facts and hypotheses. In: Botez MI, Reynolds EH, eds. *Folic acid in neurology, psychiatry, and internal medicine*. New York: Raven Press, 1979:435–61



Overcoming a stressful childhood?

Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: Altering epigenetic marking

Nat Neurosci. 2004 Aug;7(8):847-54

Stress responses are programmed early in life by maternal care and associated with epigenomic marking of the hippocampal glucocorticoid receptor. To examine whether such epigenetic programming is reversible in adult life, we centrally infused the adult offspring with the essential amino acid L-methionine, a precursor to S-adenosyl-methionine that serves as the donor of methyl groups for DNA methylation. Methionine infusion reverses the effect of maternal behavior on DNA methylation, GR expression, and hypothalamic-pituitary-adrenal and behavioral responses to stress, suggesting a causal relationship among epigenomic state, GR expression, and stress responses in the adult offspring.



Folic acid caution

- Supplementation of folic acid linked to malignancy risk
 - Folic acid > 3 years increased colon CA risk
OR=1.35, Fife J et al, Colorectal Dis. 2009 Oct 27. [Epub ahead of print]
 - No increased risk and actually decreased risk of recurrent adenoma in those who were deficient

Am J Clin Nutr. 2009 Dec;90(6):1623-31. Epub 2009 Oct 28.

Connie's editorial: Eat the Food!!



Food Sources Folic Acid

- o Beans
- o Greens
- o Whole Grains

Food	Micrograms (μg)	% D V ^
*Breakfast cereals fortified with 100% of the DV, ¾ cup	400	100
Cowpeas (blackeyes), immature, cooked, boiled, ½ cup	105	25
Spinach, frozen, cooked, boiled, ½ cup	100	25
Great Northern beans, boiled, ½ cup	90	20
Asparagus, boiled, 4 spears	85	20
Vegetarian baked beans, canned, 1 cup	60	15
Spinach, raw, 1 cup	60	15
Green peas, frozen, boiled, ½ cup	50	15
Broccoli, chopped, frozen, cooked, ½ cup	50	15



B Vitamin Recommendations

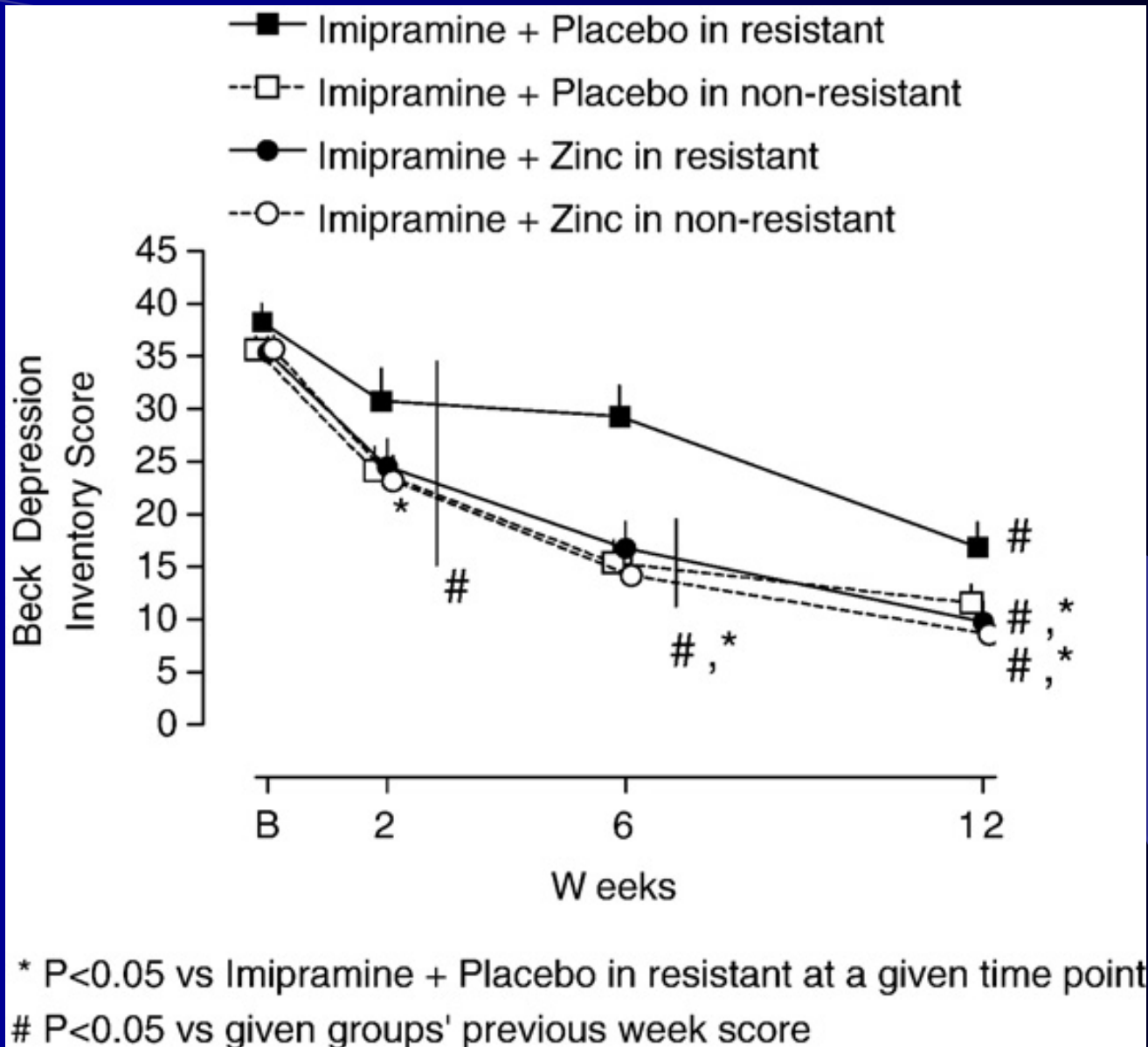
- Consider testing B-12 and homocysteine
- Recommend B-100 B complex daily
- Consider 100 mg per day of B6, 5-15 mg folic acid if not using drugs



Zinc and Depression

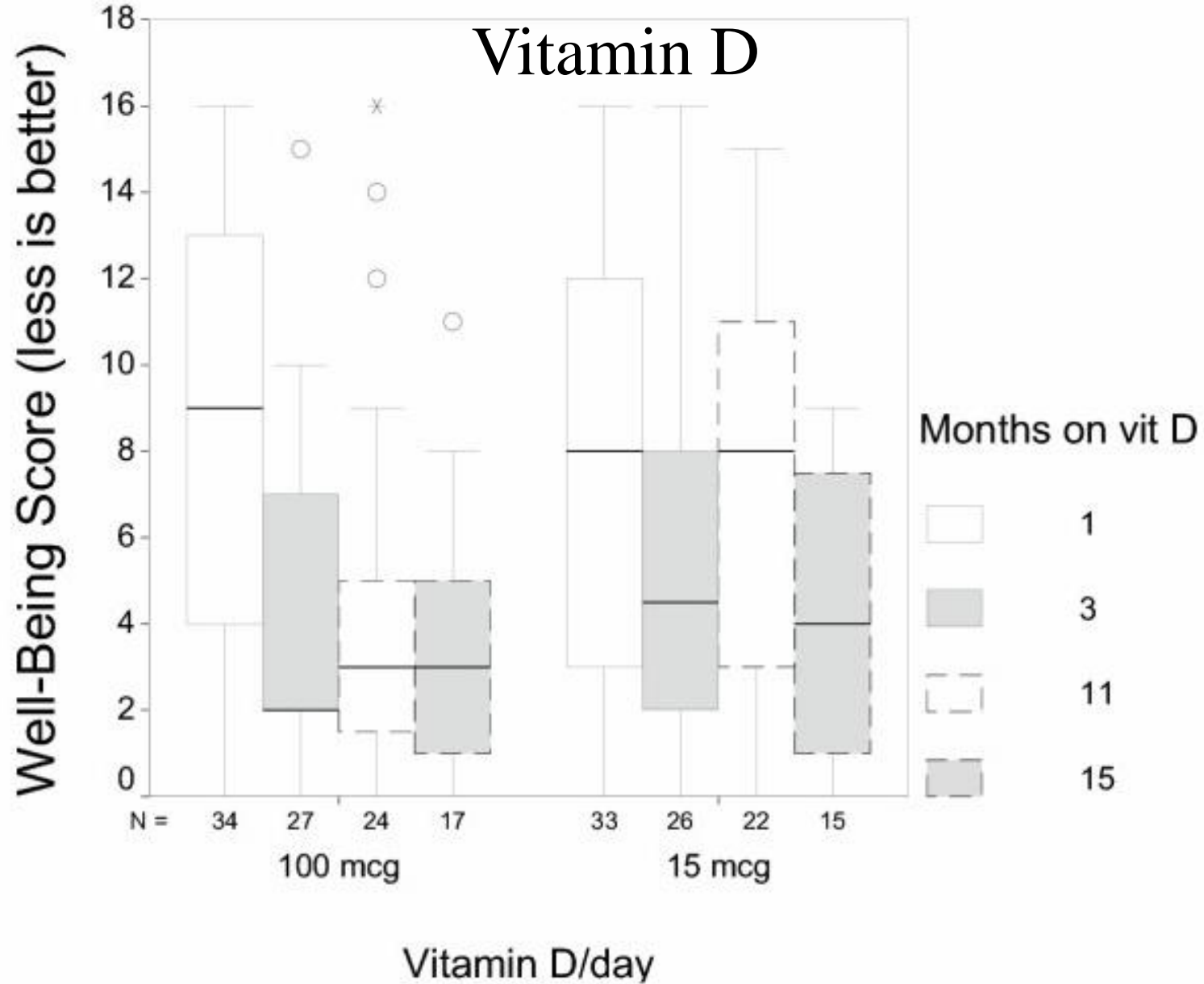
- Non-competitive NMDA receptor antagonist
- Loads of preclinical support
- Just starting to be studied in humans





J Affect Disord. 2009 Nov;118(1-3):187-95. Epub 2009 Mar 10.





Winter well-being

$p=0.002$
4000IU

$p=0.108$
600 IU

Vieth *et al. Nutrition Journal* 2004 3:8

Vitamin D

- o Vitamin D.

- o SAD

- Depression was alleviated in patients receiving vitamin D but not in those receiving light therapy. Gloth FM, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. J Nut Health Aging 1999; 3: 5-7



Magnesium

- o Also an NMDA receptor antagonist
- o MgCl_2 is as effective in the treatment of depressed elderly type 2 diabetics with hypomagnesemia (<1.8) as imipramine 50 mg daily *Magnes Res* **21** (2008), pp. 218–223
- o Intracellular Mg correlates with depression (serum does not)
- o Review: *Medical Hypotheses* 74(4) April 2010, Pages 649-660

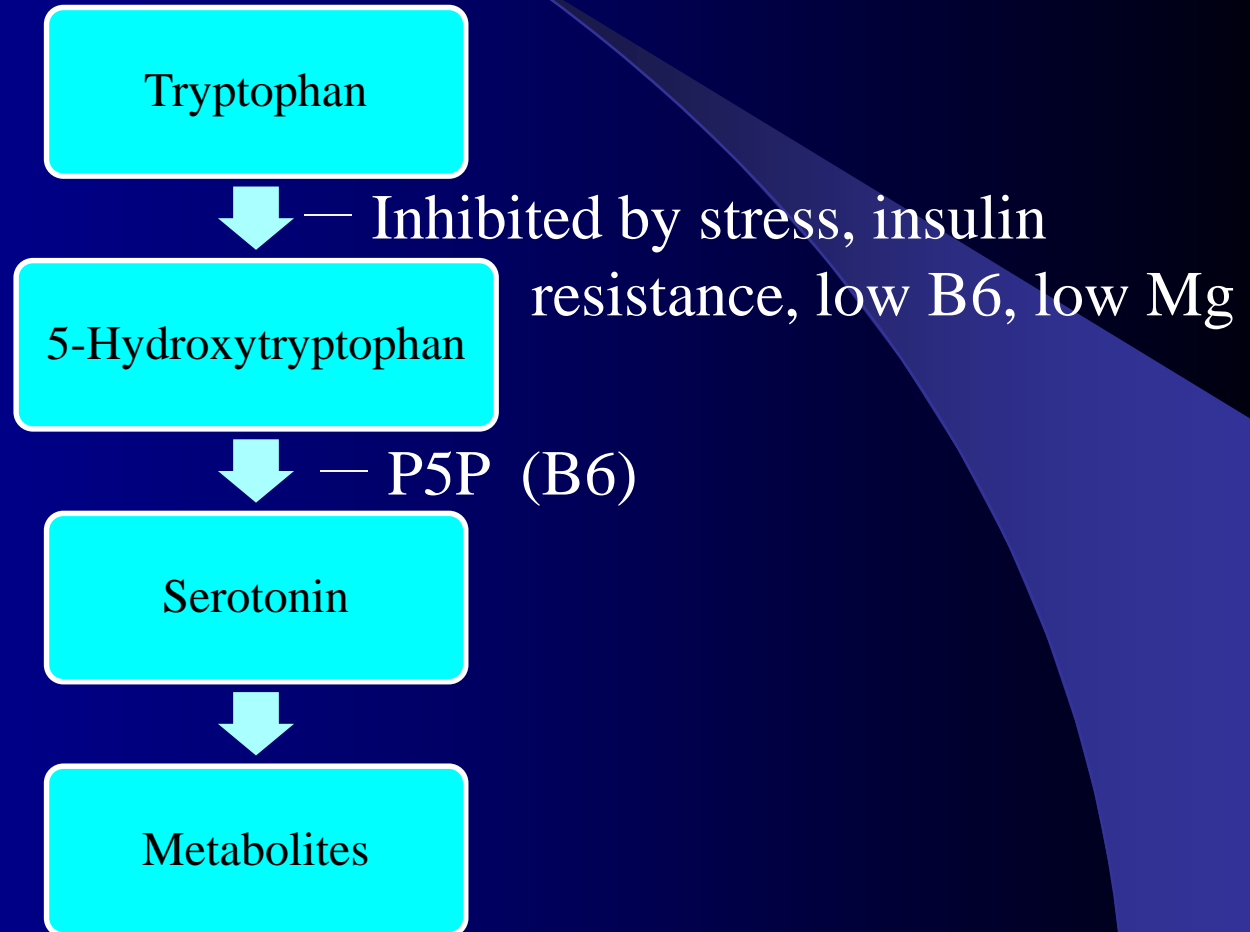


Vitamin E.

- One small, uncontrolled trial, nine subjects with prolonged treatment-resistant major depressive disorder, stable x 6 months
 - 6 of the 9 patients had $> 80\%$ improvement in their depression scores.
- Moriches S, Sonohara M, Murakami H, et al. Vitamin E treatment of prolonged depression: a report of nine cases. Int Med J 2000; 7: 33-36



5HTP – 5-Hydroxytryptophan



5HTP

- 5-HTP (50 - 300 mg/day) is more effective than placebo and almost as effective as pharmaceutical antidepressants
- Multiple studies show a response rate about 60%, response within two weeks



5HTP – Safety concerns

- o Do not combine with pharmaceutical antidepressants – possibility of serotonin syndrome (agitation, insomnia, aggression, headaches, palpitations, nausea, cramping, and diarrhea) (Though my patients have done this without problems)
- o Possible contamination issues: 1998 Mayo Clinic paper, confirmed by FDA

I use Thorne Research 5HTP – confirmed by chromatography to be pure



Other Amino Acids

- DLPA 200 mg per day as effective as imipramine in a 1979 study Beckmann H, Athen D, Olteanu M, Zimmer R. dl-Phenylalanine versus imipramine: a double-blind study. Arch Psychiatr Nervenkr 1979; 227: 49-58
- DLPA was more effective than placebo in women with premenstrual depressed mood Giannini AJ, Sternberg DE, Martin DM, Tipton KF. Prevention of late luteal phase dysphoric disorder symptoms with dl-phenylalanine in women with abrupt β -endorphin decline: a pilot study. Ann Clin Psychiatry 1989; 1: 259-263
- Tyrosine has not been shown to be effective



NAC

- N-acetyl-cysteine is helpful for depression in bipolar disorder
- 1 gram bid showed benefit by 8 weeks
 - Biol Psychiatry. 2008 Sep 15;64(6):468-75.



Botanicals

- o Herbs
- o Aromatherapy
- o I will not address homeopathics, flower essences, etc.



St. John's Wort (*Hypericum perforatum*)

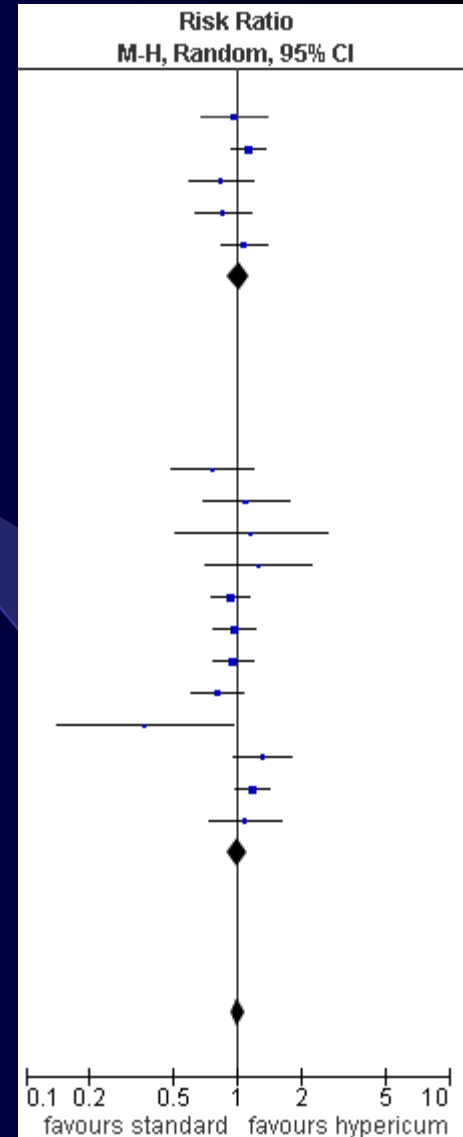
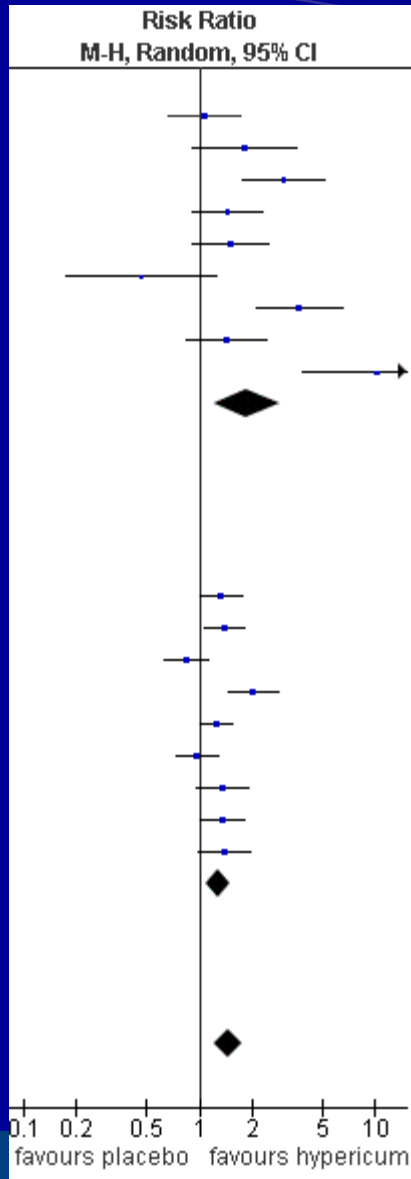
Multiple mechanisms of action:

- affects serotonin, dopamine, norepinephrine, and GABA reuptake inhibition
- in vitro monoamine oxidase inhibition
- L-glutamate
- inhibit interleukin-6 and increase cortisol production



St. John's Wort

- Mild to moderate depression
- Dose: 900 mg per day of extract (standardized to at least 0.3% hypericin or 2-5% hyperforin)
- Methanolic extract vs. others



vs. Placebo

vs. Antidepressants

Cochrane Database Syst Rev. 2008 Oct 8;(4):CD000448.



St John's Wort: Side Effects

- o Fewer than pharmaceutical antidepressants, but can include: gastrointestinal upset, allergic reaction, fatigue, dry mouth, restlessness, constipation, photosensitivity, and I have had 3 patients with neuropathy (tingling, numbness in fingers or toes)

o



SJW – Drug Interactions

- Avoid combination with pharmaceutical antidepressants
- Multiple drug interactions because it increases some of the detox enzymes: induction of cytochrome P450 3A4 and others
 - Lowers levels of HIV medications
 - Affects some blood pressure medications, blood thinners, possibly birth control pills



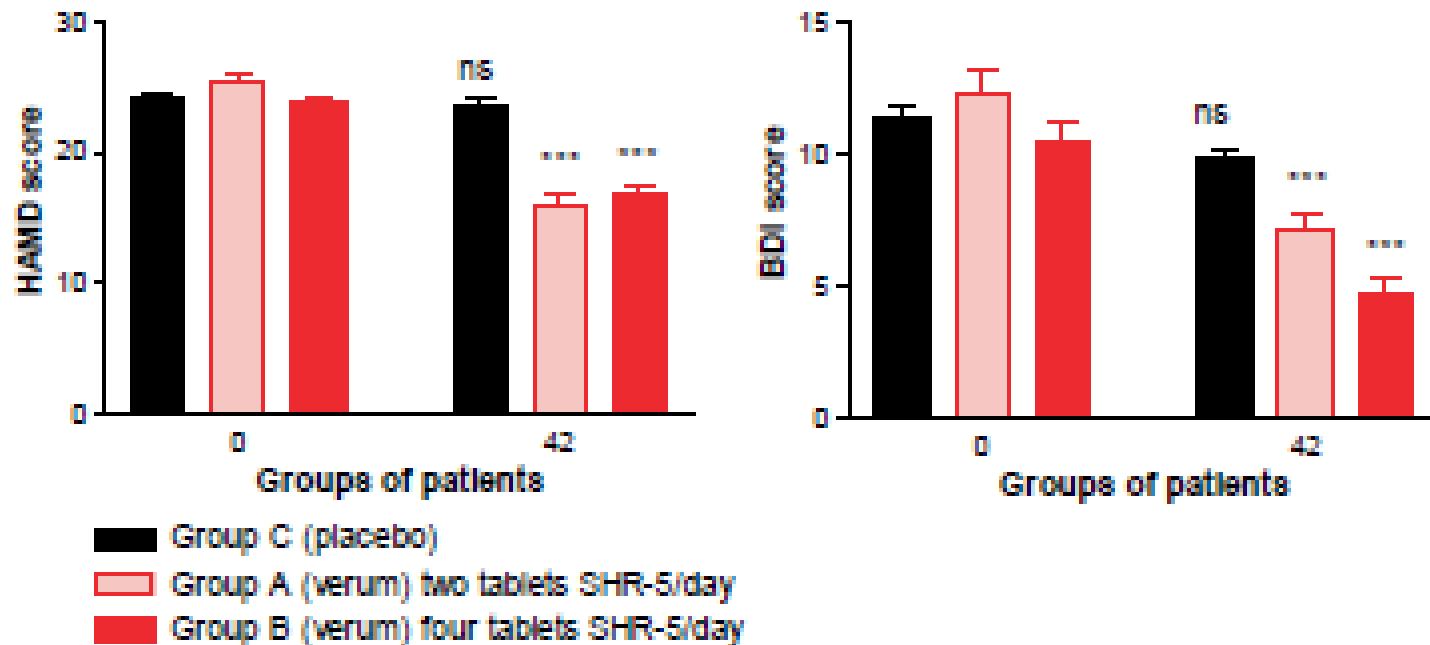
Rhodiola rosea

Placebo-controlled trial in male medical students during an exam period: improvements in physical fitness, psychomotor function, mental performance, and general wellbeing, as well as reductions in mental fatigue, improved sleep patterns, a reduced need for sleep, greater mood stability, and a greater motivation to study

Spasov AA, Wikman GK, Mandrikov VB, et al. A double-blind, placebocontrolled pilot study of the stimulating and adaptogenic effect of Rhodiola rosea SHR-5 extract on the fatigue of students caused by stress during an examination period with repeated low-dose regimen. Phytomedicine 2000;7:85-89.



Rhodiola Rosea for Depression



Nordic Journal of Psychiatry
2007, Vol. 61, No. 5 : Pages 343-348

Rhodiola rosea

- o Mechanism:
 - o HPA Axis
 - o protein kinases p-JNK
 - o nitric oxide
 - o defense mechanism proteins (e.g. heat shock proteins Hsp 70 and FoxO/DAF-16)
- o Dose: 100 – 300 mg in most studies
- o Drug interactions: none known



Aromatherapy Clinical Trials

- In chronic hemodialysis patients hiba oil is an effective, non-invasive means for the treatment of depression and anxiety, lavender alleviates anxiety.

Psychological effects of aromatherapy on chronic hemodialysis patients Authors: Itai Tet al. Psychiatry and Clinical Neurosciences, Volume 54, Number 4, August 2000, pp. 393-397(6)

- lavender, marjoram, eucalyptus, rosemary, and peppermint blended in proportions of 2:1:2:1:1 in arthritis patients
 - Significantly decreased both the pain score and the depression score of the experimental group compared with the control group

Taehan Kanho Hakhoe Chi. 2005 Feb;35(1):186-94. [The effects of aromatherapy on pain, depression, and life satisfaction of arthritis patients] Kim MJ, Nam ES, Paik SI.

- Lavender improved depression and insomnia in female college students Taehan Kanho Hakhoe Chi. 2006 Feb;36(1):136-43.



Ginkgo biloba

- In a double-blinded placebo-controlled trial, elderly patients (51 to 78 years of age) with depression were maintained on standard drug treatment to which they were unresponsive, treatment group was additionally given 240 mg of ginkgo daily
- After 1 month, Hamilton Depression Scale scores of the treatment group dropped by 50%, whereas those of the control group dropped only 7%

○ Schubert H, Halama P: Depressive episode primarily unresponsive to therapy in elderly patients: Efficacy of *Ginkgo biloba* extract Egb 761 in combination with antidepressants. Geriatrics Forsch 3:45–53

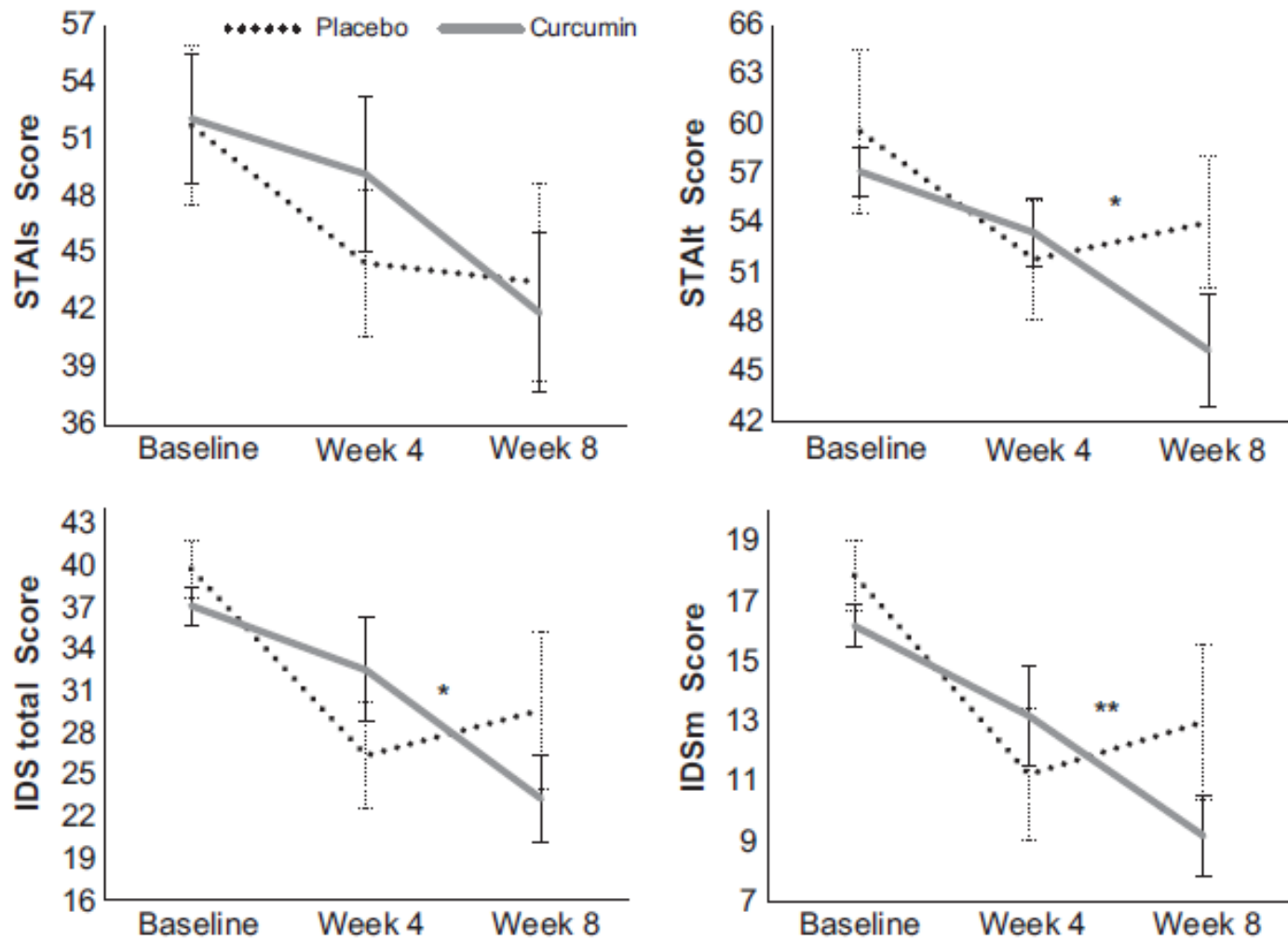


Turmeric

- Curcumin 1000 mg vs fluoxetine 20 mg vs combo
- Responders (on HAM-D17 scale)
 - combination group (77.8%)
 - fluoxetine (64.7%)
 - curcumin (62.5%)
- Differences were not statistically significant ($P = 0.58$). Mean change in HAM-D17 score at the end of six weeks was comparable in all three groups ($P = 0.77$). [Phytother Res.](#) 2014 Apr;28(4):579-85



o Possibly more helpful in atypical depression



101



Probiotics

- Not quite ready for prime time
- Placebo-controlled trials:
 - Normal (nondepressed) individuals - less reactivity to sad mood [Brain, Behavior, and Immunity](#) April 2015
 - Normal volunteers: decreased anxiety, depression [British Journal of Nutrition](#) / Volume 105 / Issue 05 / March 2011, pp 755-764
 - Decreased anxiety in CFS [Gut Pathog.](#) 2009; 1: 6.
- IBS patients – Prebiotic decreased anxiety [Aliment Pharmacol Ther](#) 2009, 29:508–518



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
- o Diet – omega 3
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Antidepressants

- o You hear plenty about this elsewhere



How long?

- Patients unimproved at week 6 had a remission rate at week 12 of 31%–41% in a study of fluoxetine
- Recommend at least an 8 week trial before switching



Augmentation/Boosting

In case of inadequate response to antidepressants, or to get a faster response:

- o Lithium – up to 300 mg tid
- o Thyroid, especially T3 (cytomel)
- o Folic acid

o SAMe



Weight Gain

- Worst with tricyclics, mirtazapine
- Worse with paxil than other SSRI's
- Least with Bupropion (Wellbutrin, or “Well but thin”)



Antidepressant-related Sexual Dysfunction

- Change antidepressants: remeron, wellbutrin do not interfere
- Antidotes:
 - Granisetron or Ondansetron – effective in case reports, no more than placebo in randomized trial
 - Amantadine 100 – 200 mg per day
 - Cyproheptadine 2 to 8 mg. q.d. or 4 to 12mg. p.r.n. 1-2 hours before sexual activity
 - Ginkgo – effective in 86% in one case series; no more than placebo in controlled trial
 - Ropinirole – 54% responders, mean dose of 2.1 mg/day
 - Bupropion above 30 mg per day
 - Ritalin – small case series
 - Bethanechol – studied in men



Other Side Effects/Worries

- Withdrawal syndromes – particularly challenging with effexor and paxil
- Idiosyncratic neuropathy, muscle weakness, etc.
- Possible Sensitizing Effects
 - Increased suicidality in some people, especially early in treatment
 - Observation of tolerance or emergent treatment resistance after long-term therapy
 - Onset of resistance upon rechallenge with the same antidepressant drug in some patients

More long-term studies are needed



Treatment Options

- o Remove Tacks
- o Exercise
- o Light
- o Psychotherapy
- o Diet – omega 3
- o Supplements
- o Drugs
- o Magnets, Electricity, etc.



Acupuncture

Wait list control

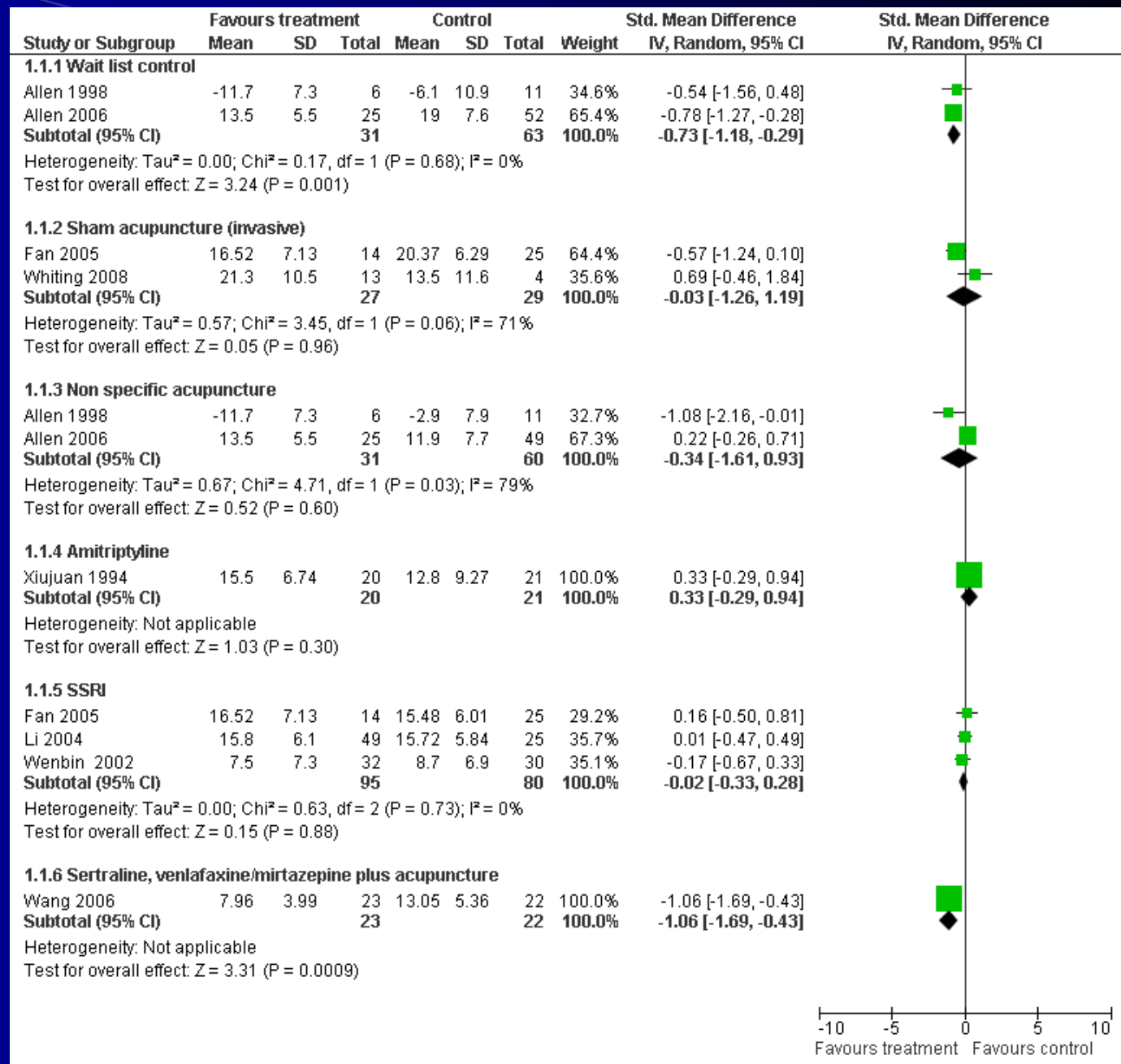
Sham acupuncture

Nonspecific
acupuncture

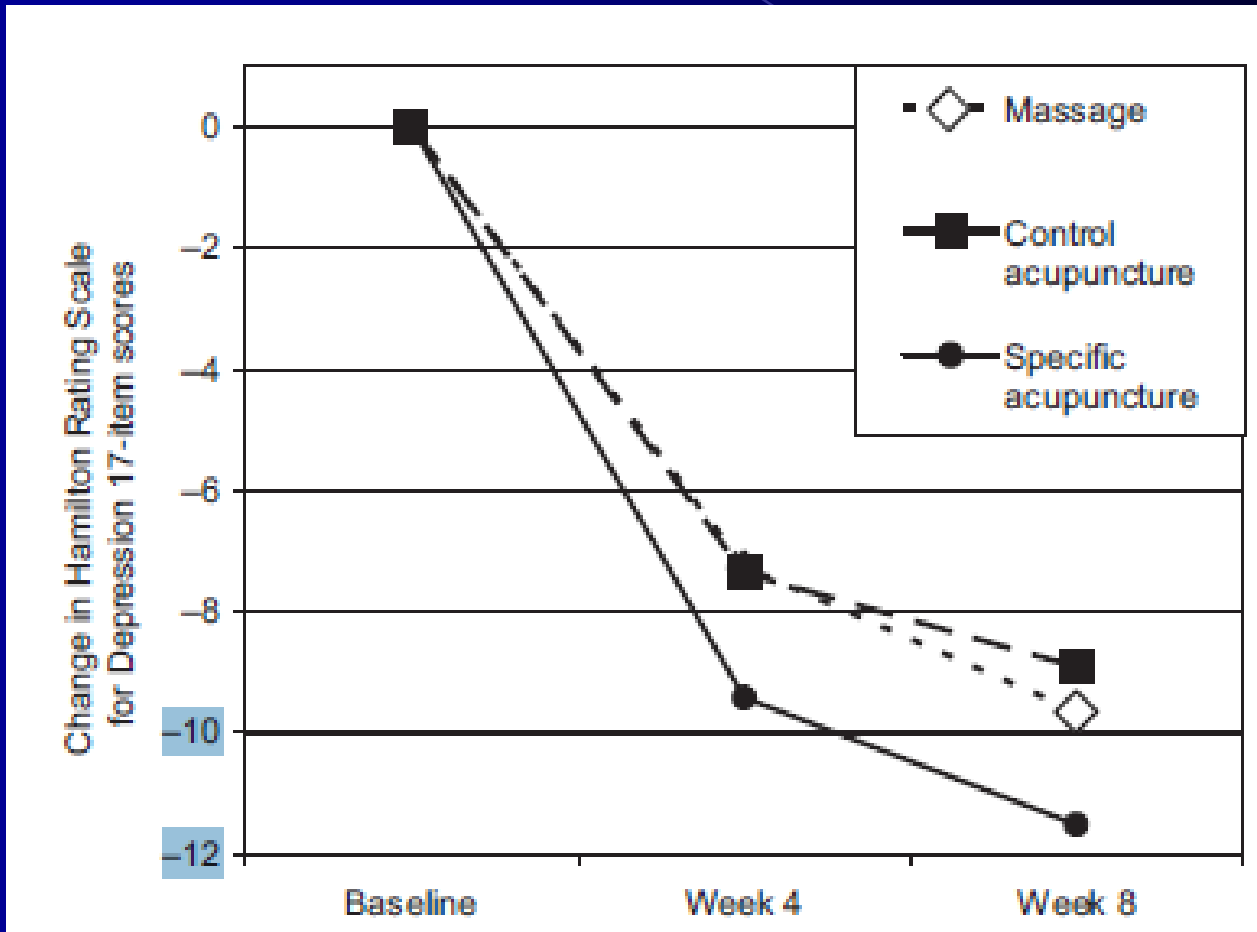
Amitriptyline

SSRI

Multidrug +/- Acu



Acupuncture for Depression in Pregnancy



o Obstet Gynecol. 2010 Mar;115(3):511-20.



Electroconvulsive Therapy

- Effective in achieving remission in 90% of patients
- Reserved for suicidal, psychotic, or catatonic patients
- Side effects:
 - Cardiac events
 - Postictal confusion
 - Memory loss



- o “I couldn’t remember if my daughter was married or not. . . .”

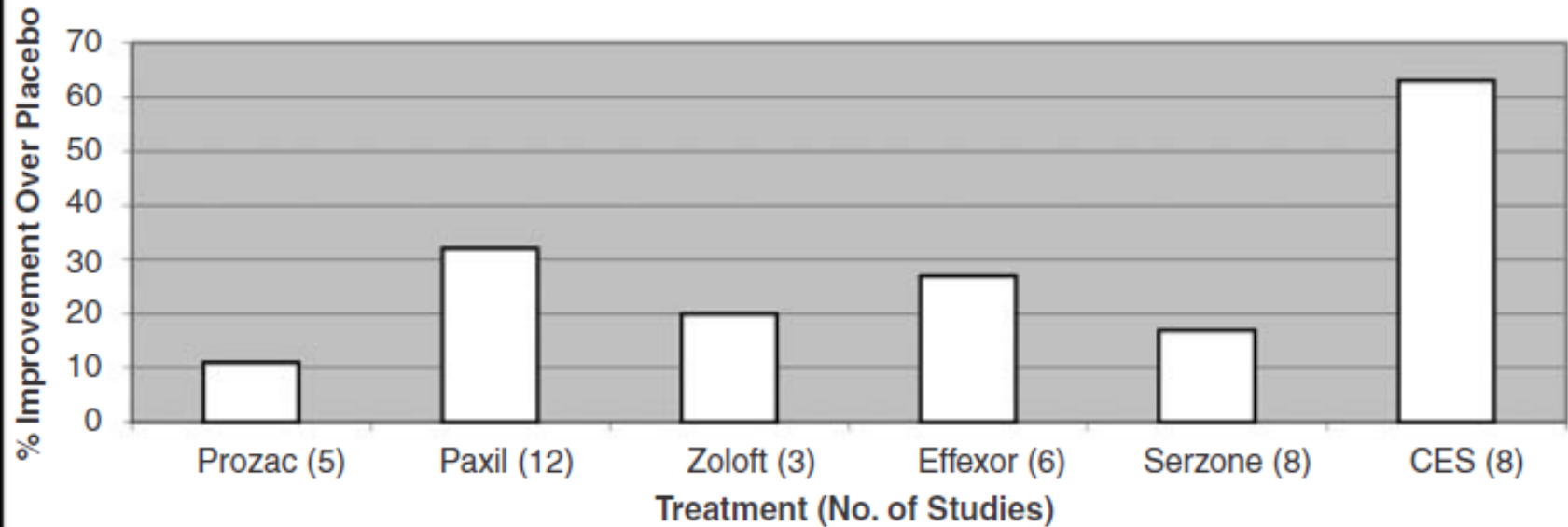


Cranial Electrical Stimulation

- Microcurrent levels of electrical stimulation applied across the head via transcutaneous electrodes
- 1 milliampere x 20 – 60 minutes qam
- 26 published studies; 81% report benefit
- 57-63% improvement vs. placebo (better than most medication trials)



Efficacy of Medication of CES Over the Placebo Response



Journal of Neurotherapy, Vol.
9(2):7-26 2005

Transcranial Magnetic Stimulation

- Uses a time-varying magnetic field, and localized pulsed magnetic field over the surface of the head induces electrical currents in the brain, depolarizing the axonal membranes of these cells, causing them to fire
- Topographically selective mild electrical stimulation to left dorsolateral prefrontal cortex seems to treat depression



Mechanisms of Action

Action	Medications	ECT	rTMS
Can Induce Mania	Yes	Yes	Yes
Alters Blood Flow/Glucose Metabolism in Mood Circuits	Yes	Yes	Yes
Serotonin Level Changes	Simulated by some types of SSRI's	Yes	Yes
Dopamine Level Changes	Some Types	Yes	Yes
Gene Expression	Some Types	Yes	Yes
Modulates Cortical Neuron Excitability	Some Types	Yes	Yes
Effects are Cumulative (with time)	Yes	Yes	Yes



rTMS

- Five meta-analyses of existing rTMS trials have each shown that out of all rTMS trials conducted and available in the literature (16 open, 24 controlled comparisons and 5 comparisons against ECT), rTMS has a statistically significant antidepressant effect greater than sham
- Cochrane Review in 2001 concluded no difference from ECT.



rTMS Side Effects

- o No seizures have been reported since 1997 with the exception of one “pseudo-seizure” as reported by Conca et al (2000)
- o No negative cognitive, cardiovascular, or direct brain sequelae reported as a result of rTMS
- o Still experimental in the USA



Vagal Nerve Stimulator

- o 40% response rate
- o 17% remission rate



Putting it all together



How Can I Do All This When I Can't Get Out of Bed in the Morning?

Sometimes, depression causes so much inertia, that any treatment requiring more commitment than swallowing a pill once a day may be difficult:

- o Consider a stepped treatment plan, with biological approaches or drugs initially to allow enough improvement to then implement exercise, psychotherapy, etc.



Start Somewhere - patient

- o Make a list of personal “tacks”
 - o Look at which may be modifiable, or rank them
- o Find allies
 - o Personal
 - o Professional
 - o Peer support – opportunity for altruism benefit
- o Pick a positive intervention
 - o Exercise
 - o Gratitude Journal
 - o Supplement plan



Start Somewhere - provider

- Hold hope and positive intention in the relationship
- Facilitate:
 - Making a list of personal “tacks” – use MI to see what they can modify
 - Finding allies –
 - Frame yourself as one (not an MDeity handing down salvation from on high)
- Pick a positive intervention
 - Assess and address underlying illness
 - Go for the gut – source of inflammation
 - Consider thyroid (not the fix, but can be a bridge)
 - Offer tools



Tools

- o Handout with all your recommendations – “pseudodementia” in depressed patients
- o Identify therapists in your area
- o Identify support groups – 211info.org
- o Self help options to reinforce counseling:
 - o Books
 - Feeling Good, David Burns
 - Forgive for Good, Fred Luskin
 - Full Catastrophe Living, Jon Kabat Zinn
 - o Websites
 - <http://www.authentic happiness.sas.upenn.edu/Default.aspx>
 - www.Moodgym.org
- o CBT handouts, positive psychology handouts (gratitude journal is my favorite)
- o Remind them of their own tools – “What has worked in the past?”



Basics for Healing the Body-Mind

- The Mood-balancing Lifestyle:

Diet – not SAD

Exercise: BDNF

Sleep – social rhythm therapy

Relax

Positive Thoughts – seek out positive
people, consider a news fast

Green (avoid toxins)



Eating Right for Your Brain

- Address allergies/sensitivities up front (gluten and dairy)
- Eat whole, real, fresh, organic, unprocessed food (or more like this than you are)
- Eat a lot of fruit and vegetables (phytonutrients)
- Eat foods with plenty of fiber
- Eat high-quality protein with each meal
- Eat food containing omega-3 fats



Tuning Up Brain Chemistry with Supplements

- A multivitamin and mineral
- Methylation (folate or 5-MF 800–2000 mcg, B6 25–50 mg, B12 1000 mcg/d)
- Vitamin D3 2000 U–5000 U/day
- Omega-3 fatty acids (EPA/DHA) 2–4 g/day

Consider Calcium/magnesium 600/400 mg

Zinc 30 – 60 mg per day (caution re: Cu depletion)



And then you can get fancy. . .



Serotonin: Natural Agonists

- 5-methyl-tetrahydrofolate
- Vitamin D
- St John's Wort
- DHA (fish oil)
- 5-HTP



Glutamate in Depression

- Excessive glutamate is associated with depression (this may be why anticonvulsants can be useful adjuvants)

Glutamate



GAD (glutamic acid decarboxylase)

↑ by B6, taurine

↓ by methionine, cortisol

GABA



Glutamate Reuptake

GLT-1 (primary reuptake of glutamate)

– GLT-1 inhibitors:

- o Mercury
- o Homocysteine
- o Arachidonic acid
- o Cortisol



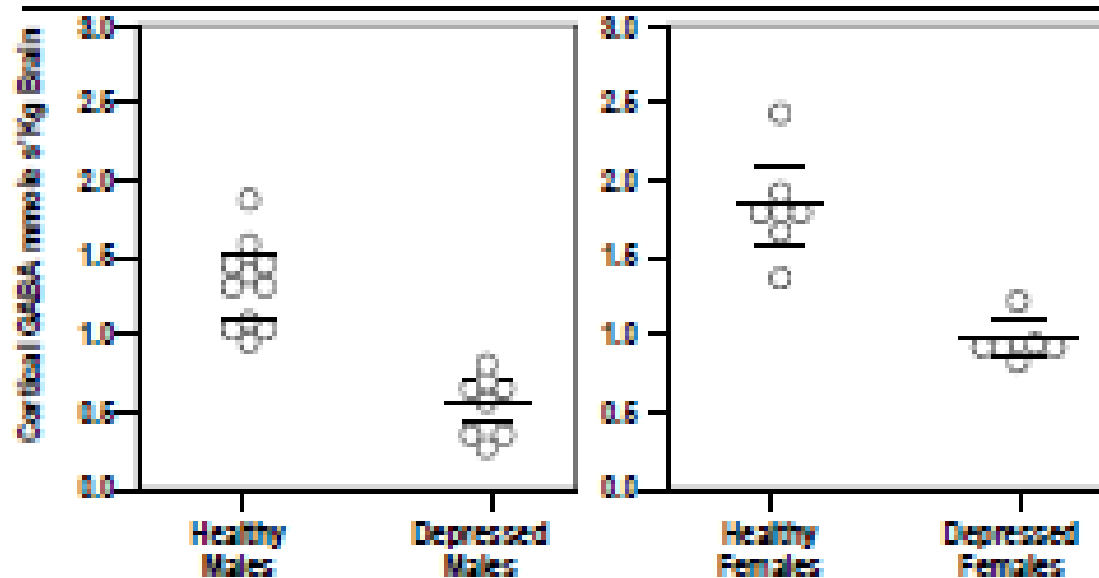
Glutamate: Natural Antagonists

- Lithium
- Vitamin D
- Magnesium
- Glutathione (NAC) – there is a glutamate-NAC exchange transport protein



GABA

Cortical GABA Concentrations in Healthy and Depressed Subjects



Sanzara et al. Arch Gen Psychiatry. 1989;66:1043-47.



GABA Metabolism

- See GAD under glutamine above



GABA: Natural Agonists

- Progesterone- allopregnenolone
- Taurine, vitamin B6
- Valerian, passionflower, hops



BDNF

- Factors that increase:
 - DHA
 - Caloric restriction
 - Physical exercise
 - Mental exercise



- Vitamins, minerals, and mood Psychol Bull.
- 2007;133(5):
- 747-60.

