

Complimentary and Alternative Therapy in Psychiatry

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No conflicts

In compliance with the ACCME Standards for Commercial Support of CME, as the speaker I do not have any relevant financial relationships to disclose in relation to this presentation.

Randomized Placebo-Controlled Adjunctive Study of an Extract of *Withania somnifera* for Cognitive Dysfunction in Bipolar Disorder



Method: Sixty euthymic subjects with *DSM-IV* bipolar disorder were enrolled in an 8-week, double-blind, placebo-controlled, randomized study of WSE (500 mg/d) as a procognitive agent added adjunctively to the medications being used as maintenance treatment for bipolar disorder. Study enrollment and data analyses were completed between December 2008 and September 2012. Cognitive testing at baseline and 8 weeks assessed primary efficacy outcomes. Psychopathology and adverse events were monitored at scheduled visits.

Results: Fifty-three patients completed the study (WSE, $n = 24$; placebo, $n = 29$), and the 2 groups were matched in terms of demographic, illness, and treatment characteristics. Compared to placebo, WSE provided significant benefits for 3 cognitive tasks: digit span backward ($P = .035$), Flanker neutral response time ($P = .033$), and the social cognition response rating of the Penn Emotional Acuity Test ($P = .045$). The size of the WSE treatment effect for digit span backward was in the medium range (Cohen $d = 0.51$; 95% CI, 0.25–0.77). None of the other cognitive tasks showed significant between-group differences. Mood and anxiety scale scores remained stable, and adverse events were minor.

High impact journal
Respected authors
Unmet need

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✓ Placebo control

✓ Double blind

✗ Size (60)

✗ Drop outs unaccounted (12%)

✗ Primary outcome not positive

Bonferroni: divide p cut-off by tests: $0.05/6 = 0.0083$

✓ Effect size = medium

✓ Replicated (in healthy subjects)

✓ Backed by basic science



Light Therapy



Probiotics



Folate



Omega-3



Saffron



Lavender



Light Therapy



400 BCE: Hippocrates

Employs *heliotherapy* on island of Kos



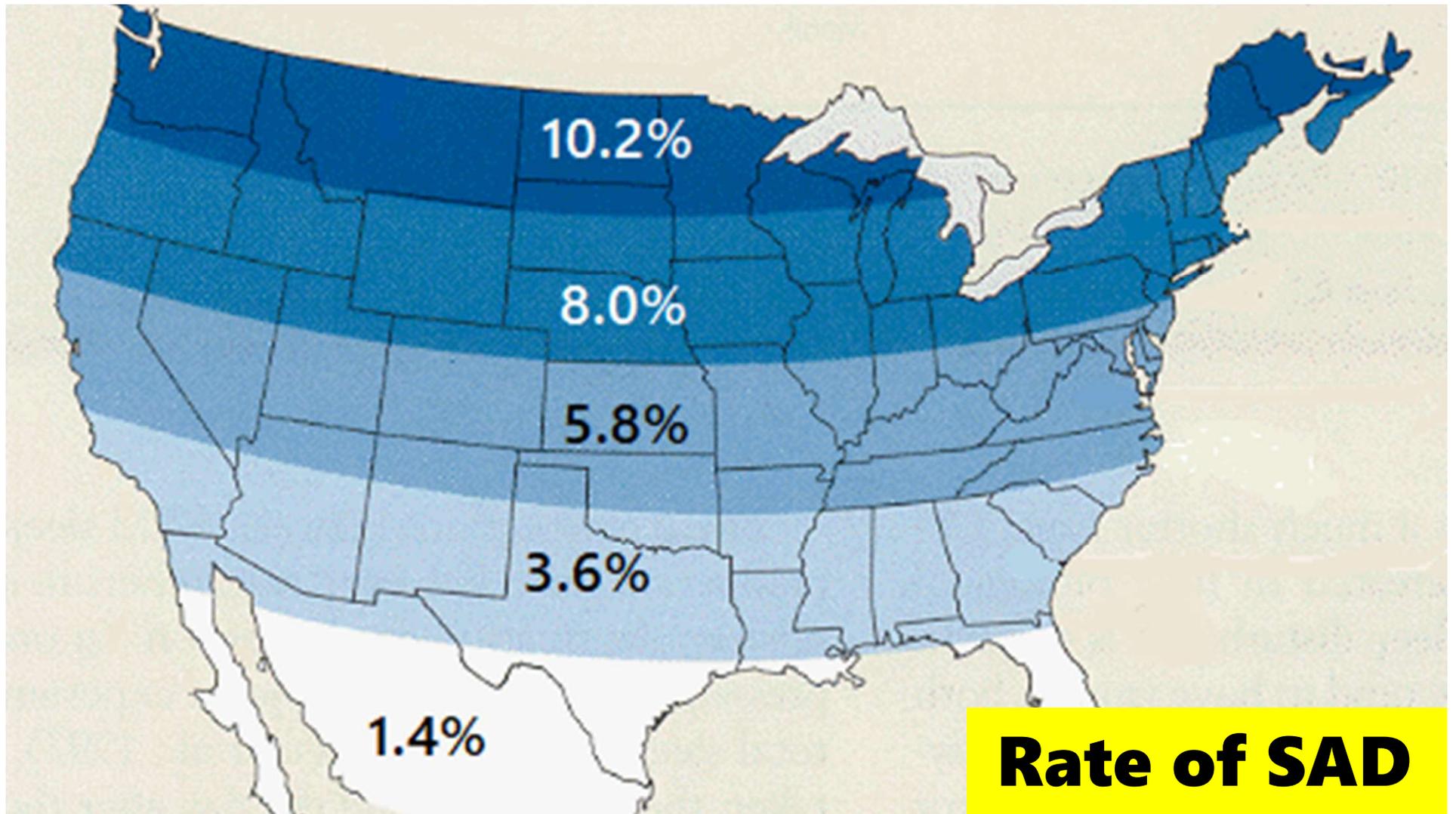
1859: Florence Nightingale

Sunlight fosters recovery from illness

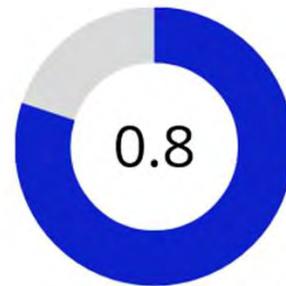
A portrait of Norman Rosenthal, a middle-aged man with glasses, wearing a blue blazer over a grey turtleneck sweater. He is smiling slightly and looking directly at the camera against a dark background.

1984: Norman Rosenthal

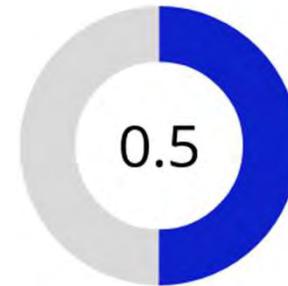
Discovers light therapy at NIMH



Light Therapy Effect Size



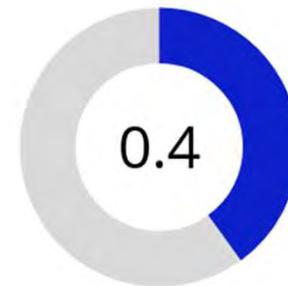
Seasonal



Non-seasonal



Augmentation



Bipolar

Mårtensson B et al, J Affect Disord 2015;182:1–7
Tao L et al, Psychiatry Res 2020;291:113247
Lam RW et al, Can J Psychiatry 2020;65(5):290–300
Geoffroy PA et al, Sleep Med Rev 2019;48:101213

Light Therapy in Other Disorders

| | |
|--------------------------------|--|
| Depression | Youth, elderly, anorexia, perinatal, bipolar |
| PTSD | Core symptoms |
| Bulimia | Winter |
| Male sexual dysfunction | Winter (testosterone lower in winter) |
| Insomnia | Any season (start 5am) |
| Dementia | Sleep, mood, cognition |
| Traumatic brain injury | Sleep, mood, energy |
| Parkinson's | Sleep, mood, motor symptoms |
| Pain syndromes | Fibromyalgia and back pain |

Light Therapy



Brouwer A et al, Acta Psychiatr Scand 2017;136:534-548
Rosenthal NE, Winter Blues, Guilford Press, 2012

Optimize start time with AutoMEQ test at cet.org (usually 5-8 am)

Do not use after 2:00 pm

Duration 30-60 minutes, taper slowly in bipolar (raise by 15 min/week)

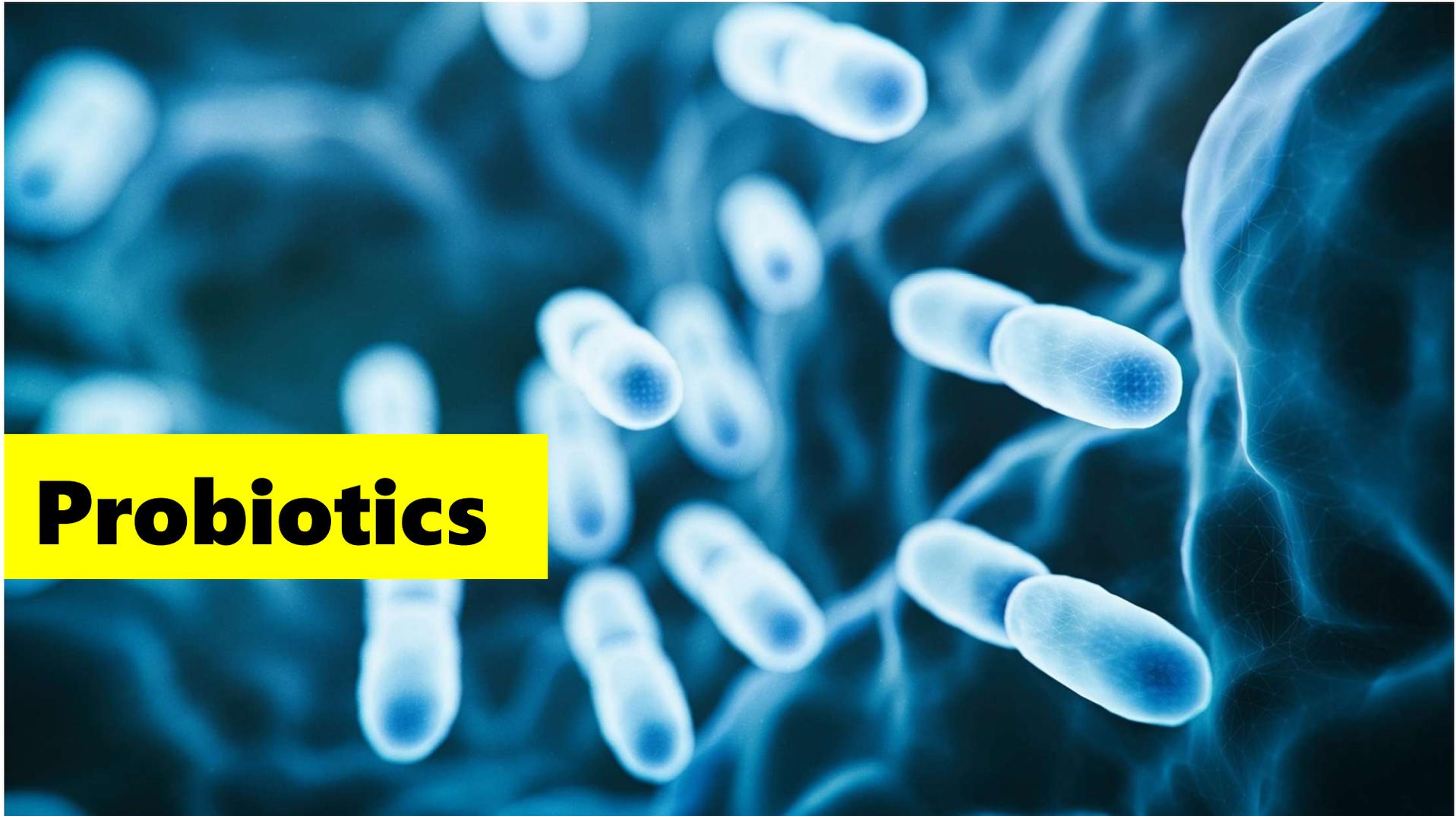
10,000 Lux

UV filter

Carex Daylight Sky or Elite at cet.org or chrisaikenmd.com/lighttherapy

Start 2 weeks before winter depression

Risks: Photosensitivity, aggravate eye disease, headache, eye strain, mania



Probiotics



1907: Élie Metchnikoff

Discovered health benefits of probiotics in yogurt (after Nobel for immunology)



1928: Alexander Fleming

Discovery of penicillin heralds antibiotic era

A photograph of Peter Turnbaugh, a man with dark hair and a light beard, wearing a grey sweater and blue jeans. He is sitting on a red chair against a wooden wall. A yellow banner is overlaid on the left side of the image.

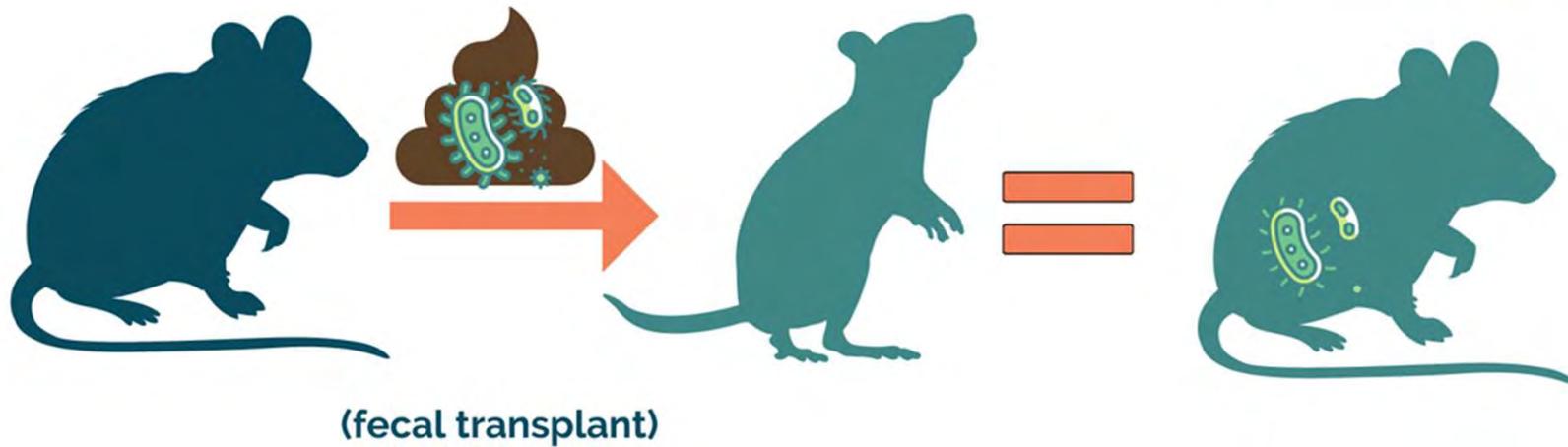
2006: Peter Turnbaugh

Fecal transplant renews probiotic interest

Obese Mouse

Lean Mouse

Becomes
Obese Mouse



Disease transplanted through microbiome

2022: Vowst and Rebyota approved for *C Diff*



Probiotics Trials of DSM Depression/Anxiety

18 Depression

9 Anxiety

- Small to medium effect size
- Effective in TRD
- Less effective in non-clinical samples
- No large trials
- Cognitive benefits
- Multiple strains best

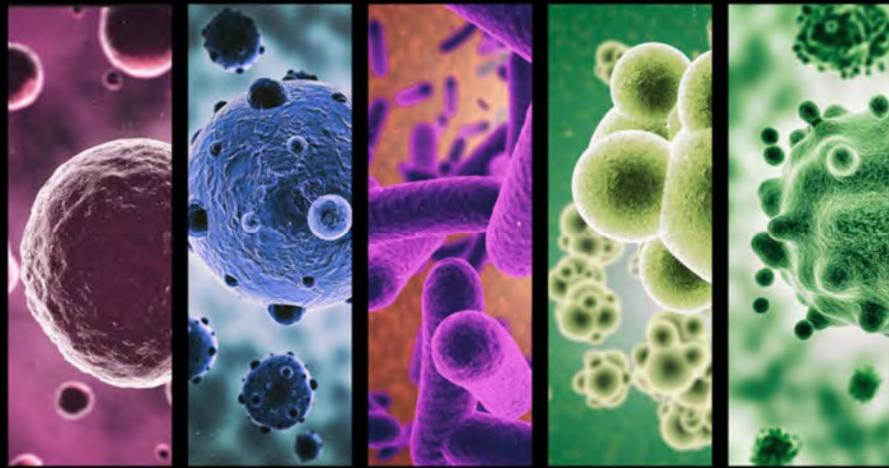
Asad A et al, Nutr Rev 2025;83(7):e1504-e1520

Miyaoka T et al, Clin Neuropharmacol 2018;41(5):151-155

Ferrari S et al, J Tradit Complement Med 2024;14(3):237-255

Zandifar A et al, Brain Behav 2025;15(3):e70401

Probiotics



2-10 billion CFUs

Lactobacillus & Bifidobacterium families;
Streptococcus thermophiles

Major depression, bipolar disorder,
anxiety, autism, cognition, dementia,
negative symptoms of schizophrenia

Constipation, irritable bowel syndrome,
inflammatory bowel disease,
dyslipidemia, weight loss, antibiotic-
associated diarrhea, *C. difficile* infection

Lifted Naturals Mood Boosting
Trunature Advanced Digestive
chrisaikenmd.com/supplements

Risks: Gas. Avoid in immunocompromised.

Methylfolate





1931: Lucy Wills

Discovery of folate (anemia)

1960s: Folate Labs Enter Practice



Which Folate?

Folic Acid

Synthetic precursor of methylfolate

Worked in small but failed in large trial of depression

Folinic Acid (Leucovorin)

Natural precursor of methylfolate

Uncontrolled trials in depression

2 small RCTs in autism (2 mg/kg/day, maximum of 50 mg/day)

Which Folate?

Methylfolate

Brain active form, precursor in synthesis of monamines

Positive in large RCTs of depression

S-adenosylmethionine (SAMe)

Part of folate cycle, precursor in synthesis of monamines

Equaled antidepressants in RCTs, but failed against placebo

Product is fragile and has poor bioavailability

Methylfolate in Depression

Randomized trials

- 3 placebo (n=483): 15 mg effective (d=0.4); 7.5 mg not
- 2 antidep comparator (n=127): Equaled trazodone, amitriptyline
- 1 Enlyte trial (n=330): Large effect as monotherapy (MTHFR C677T or A1298C)

Enlyte Ingredients

l-Methylfolate (7 mg)

Folic acid

Folinic acid

B1, B2, B3, B6, and B12

Iron

Magnesium

Zinc

Coenzyme Q10

Omega-3 fatty acids

(EnBrace HR is identical but marketed for peripartum)

Methylfolate

Predictors of Response

MTHFR homozygous at C677T or A1298C

Obesity (BMI \geq 30 kg/m²)

Inflammation (hs-CRP \geq 3 mg/L)

Peripartum

Eating disorders

Renal failure and GI disease

Poor nutrition

Alcohol use disorders

Smoking

Medications

Lamotrigine, valproate, carbamazepine, phenytoin, fluoxetine, oral contraceptives, methotrexate, metformin, sulfasalazine, warfarin, and triamterene

Methylfolate

15 mg qd

FDA Cleared medical food for depression

May treat: Bipolar depression, autism,
negative symptoms of schizophrenia

Prescription or OTC (MethylPro, Opti-
Folate) chrisaikenmd.com/supplements

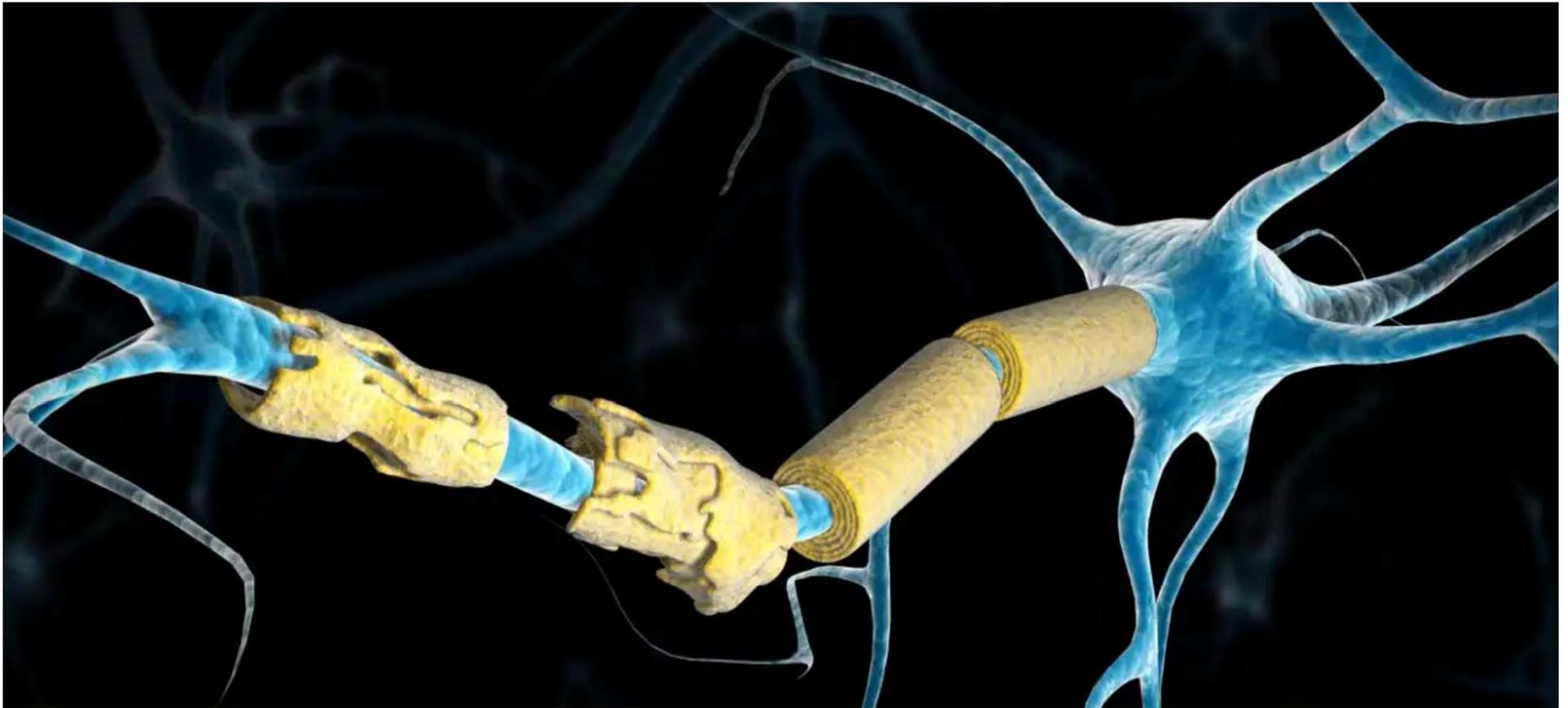
Risks: Masks B12 deficiency



Omega-3



**800 BCE:
Angel in book
of Tobias
uses fish liver
used to cure
blindness**



1978: Omega-3 deficit in animals causes eye damage and nerve demyelination; depression in humans



1975: Omega-3s explain Inuit heart health

Omega-3 in Depression

Randomized trials

- Over 40 trials of 10,000 subjects as antidepressant augmentation
- Positive when 1) Clinical depression 2) EPA:DHA \geq 2:1
- Effect size medium (0.5-0.6)

Omega-3



**1,000-4,000 mg qd of EPA + DHA
EPA:DHA \geq 2:1**

**Major depression, bipolar depression,
borderline personality disorder, ADHD,
autism, negative symptoms of
schizophrenia, irritability**

**Elevated triglycerides (FDA cleared),
psoriasis, acne, fatty liver**

**Prescription (Vascepa) or OTC
chrisaikenmd.com/supplements**

**Risks: Possible anticoagulant effects (stop
1 week prior to surgery, restart after
surgery). Avoid in CHF and atrial
fibrillation. Reflux, fishy taste, diarrhea.**

Saffron



800 BCE: Persia

Saffron used for melancholy

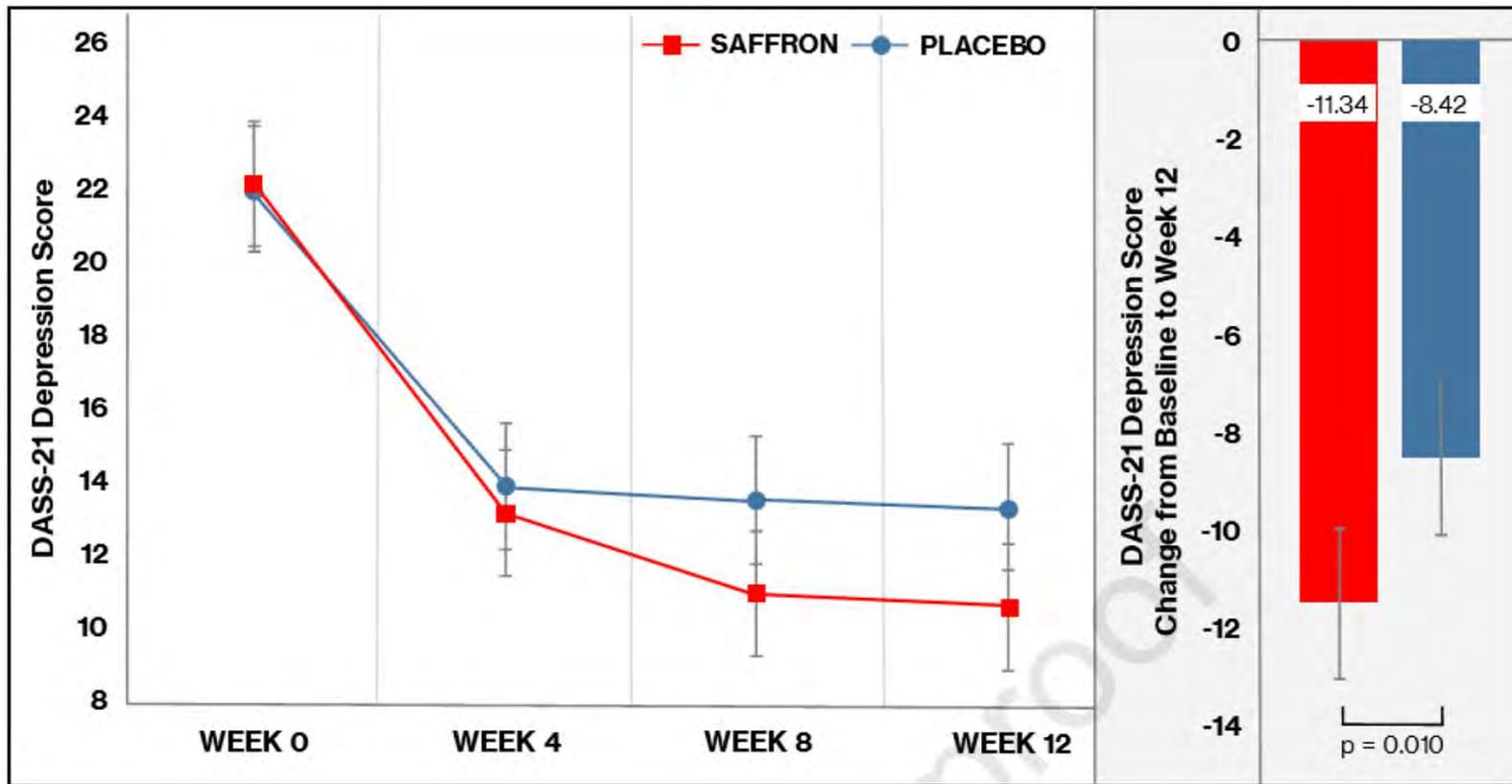


Saffron

Randomized trials in psychiatry

- Depression (mild): 22 RCTs involving 1,620 subjects
- Including adolescents (12-18) and elderly
- OCD: 2 small trials compared to SSRIs
- ADHD: 2 small trials compared to methylphenidate
- Deepens sleep quality in large placebo RCTs
- Improves sexual function in men and women in small trials

Saffron in Subclinical Depression



Saffron



30 mg qd (can divide bid)

Depression, sleep quality

Possibly: ADHD, OCD, sexual dysfunction, opioid use disorder (aug to MAT)

Medical benefits: Diabetes, weight loss, acute stroke, fatty liver disease, macular degeneration, premenstrual syndrome

Affron (proprietary extract)

chrisaikenmd.com/supplements

Risks: fatigue, nausea, anticoagulant



Lavender

**77 AD:
Greek
physician
Dioscorides
recommends
lavender for
indigestion,
headaches, and
sore throat**



Lavender (Silexan)

Randomized trials in depression and anxiety

- 8 randomized trials, 1,938 subjects
- GAD: Superior to paroxetine 20 mg, equal to lorazepam 0.5 mg, superior to placebo (large effect size 0.9)
- MDD (mild-moderate): Equal to sertraline 50 mg
- Mixed anxiety/depression: Superior to placebo

Lavender



80-160 mg qhs (or divide bid)

Generalized Anxiety Disorder

Major Depression

Insomnia associated with anxiety

Premenstrual syndrome

CalmAid (Silexan) OTC

chrisaikenmd.com/supplements

Risks: Lavender burping, nausea.

Theoretical risk of gynecomastia in

adolescent boys (estrogen-like structure)

but recent studies suggest no risk of this.

Hareng L et al, Arch Toxicol 2024;98(1):347-361

Hawkins J et al, Int J Pediatr Adolesc Med. 2022;9(2):117-124

Questions?

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