

Nutritional Supplements for Depression

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Objectives

- Identify supplements being studied for use in depression (St. John's Wort, Omega 3, Folate family, Vitamin D)
- Determine which supplements have evidence of benefit
- Determine which supplements have been shown NOT to be beneficial
- Consider practice changes to include the use of supplements in depression

Research Challenges

- Large topic: presenting highlights, not exhaustive research
- Hard to standardize
 - Many small RCTs, few meta-analyses
 - Meta analysis often limited by low quality studies or heterogeneity
 - Unable to routinely distinguish between mono- and adjuvant therapy
 - Absence of evidence of is not evidence of absence

Note about statistics

Standard Mean Difference: “A summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways (for example, all studies measure depression but they use different psychometric scales).”

- $+/- 0.2$ = small
- $+/- 0.5$ = medium
- $+/- 0.8$ = big

Hamilton Depression Rating Scale

- 21-item questionnaire; scores are based on first 17 questions
- 52 point maximum
- Scale
 - 0-7 normal
 - 8-13 mild depression
 - 14-18 moderate depression
 - 19-22 severe depression
 - ≥ 23 = severe depression

- Clinically significant change: 3 points

SSRIs and TCAs

Cochrane Database of Systematic Reviews

Antidepressants versus placebo for depression in primary care

Cochrane Systematic Review - Intervention | Version published: 08 July 2009 [see what's new](#)

[BMC Psychiatry](#). 2017; 17: 58.

Published online 2017 Feb 8. doi: [10.1186/s12888-016-1173-2](https://doi.org/10.1186/s12888-016-1173-2)

PMCID: PMC5299662

PMID: [28178949](https://pubmed.ncbi.nlm.nih.gov/28178949/)

Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis

2009 Cochrane: TCA vs placebo (12 trials)

- SMD -0.49
- NNH (withdrawal due to side effects): 4-30

2017 Systematic Review: SSRI vs placebo (131 trials)

- HDRS = ↓ -1.94 points HDRS

Better Than What? Difficulty of assessing efficacy of pharmacology

- 74 FDA-registered studies of 12 antidepressants
- Of 37 with positive results...
 - 36 were published
- Of 36 studies with negative or questionable results...
 - 22 not published
 - 11 published in a way that conveyed a positive outcome
 - 3 published
- Published: 94% positive
- FDA analysis: 51% positive

St. John's Wort (botanical name *Hypericum perforatum* L.)

- How? Mechanism unclear
- Why?
 - 2008 Cochrane Review (29 studies in 5489 patients)
 - 2016 systematic review (35 trials, 7,000 people)
- What?
 - 2008: superior to placebo, similarly effective as standard antidepressants
 - 2016: compared to placebo, **SMD = 0.49 = 3 points on HDRS**; comparable effect to antidepressant
- AE:
 - Induces cytochrome P450. Caution with oral contraceptives, some antibiotics, protease inhibitors, certain immunosuppressants
 - Fewer AE compared to antidepressants
- Dose: Common recommended dose is 300mg TID



St. John's Wort

Complementary/Integrative Therapies That Work: A Review of the Evidence

PDF PRINT COMMENTS

SHARE + f t

BENJAMIN KLIGLER, MD, MPH, and RAYMOND TEETS, MD, Icahn School of Medicine at Mount Sinai, New York, New York

MELISSA QUICK, DO, Group Health Cooperative, Seattle, Washington

Am Fam Physician. 2016 Sep 1;94(5):369-374.



AAFP:

- Level A evidence rating for benefit in mild to moderate depression
- Do not use in combination with SSRIs

Omega 3 / N-3PUFA



- How? Anti-inflammatory; supports neurotransmission
- Why?
 - 2015 Cochrane Review (mono- and adjuvant therapy)
 - 2017 meta-analysis (adjuvant therapy)
- What?



Omega-3 fatty acids for depression in adults (Review)

DHA-EPA vs Placebo (20 trials)

- SMD = - 0.3
- 2.1 points on HDRS (*recall difference for SSRI 1.94)

Omega 3 : similar benefit to SSRI
on HDRS, neither significant?



Omega-3 fatty acids for depression in adults (Review)

DHA-EPA vs Antidepressant (1 trial; 40 participants)

- MD on HDRS = - 0.7 in both groups

Similar to SSRI; not significant

Omega-3 fatty acids for depression in adults (Review)

- Subgroup analysis: EPA (8 studies)
 - SMD = - 0.37 (EPA only) and -0.40 (EPA predominant)

EPA > DHA?

N-3PUFA as adjuvant

- 2017 meta-analysis by Schefft et. al. (10 studies; 402 patients)
 - SMD – 0.48 in favor of n-3 PUFA supplementation
 - Subgroup: larger effect in patients with out comorbidities (SMD -0.7); no benefit in patients with comorbidities
- Cochrane Review: Subgroup analysis of adjuvant therapy (12 studies)
 - SMD = -0.16
 - Comparison: SMD -0.32 in individuals NOT receiving adjuvant therapy (6 studies)

N-3PUFA as adjuvant

Conclusion: Do Omega-3s enhance the benefit of SSRIs?

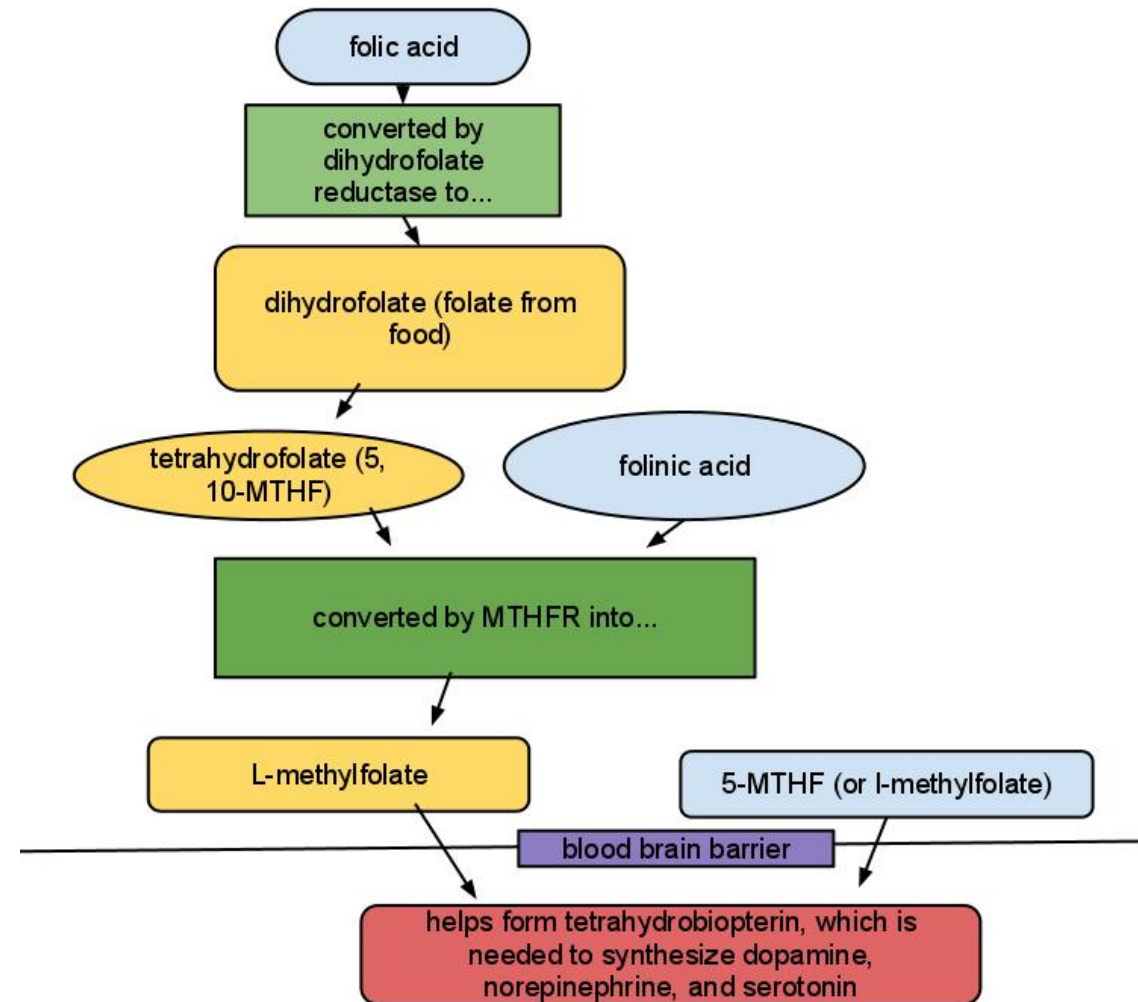
- Yes per Schefft (2017); No per Cochrane (2015)
- Unclear why the different conclusions
- No added risk by augmenting SSRI with n-3PUFA
- Dose: 1-2 g/d

N-3PUFA: Conclusions

- Cochrane: “At present, we do not have sufficient high quality evidence to determine the effects of n-3PUFAs as a treatment for MDD. Our primary analyses suggest a small-to-modest, non-clinically beneficial effect of n-3PUFAs on depressive symptomology compared to placebo; however the estimate is imprecise, and we judged the quality of the evidence on which this result is based to be low/very low.”
- Me:
 - Small, insignificant benefit compared to placebo (and similar to SSRIs?)
 - Significant benefit as adjuvant in healthy people in 1 meta-analysis
 - Favor EPA over DHA
 - No AEs
 - DHA/EPA also associated with (per Cochrane)...
 - Lower triglycerides (although without decrease in CV mortality)
 - Associated with lower risk of preterm birth when taken during pregnancy

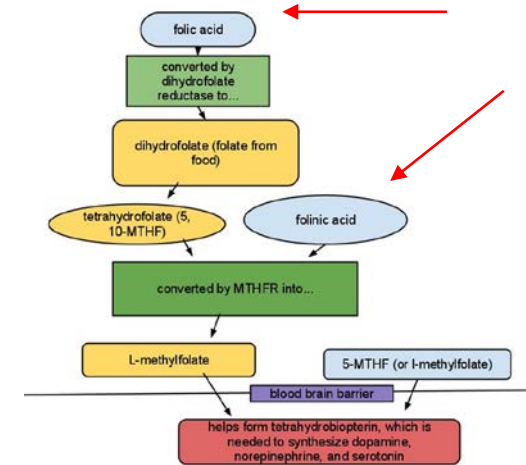
Folate family (Folate, L-Methylfolate, and S-Adenosyl –L-methionine)

- How?



Folate/Folic acid

Why/what?

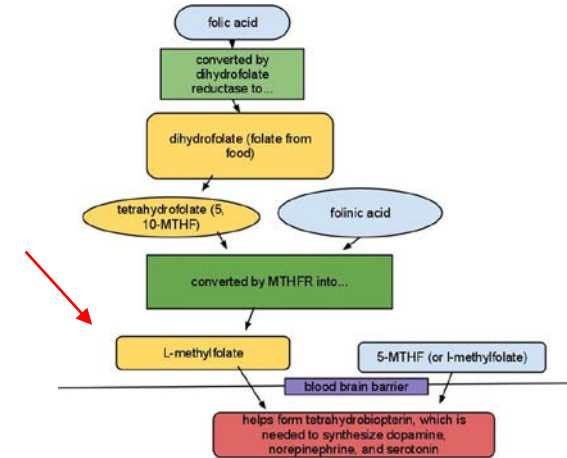


- Scheffert meta-analysis (3 RCTs; 600 participants; 1 overlap with Cochrane)
 - Adjuvant: **SMD = -0.26**
 - Conclusion: no benefit

“Small” difference

L-Methylfolate

Why/what?



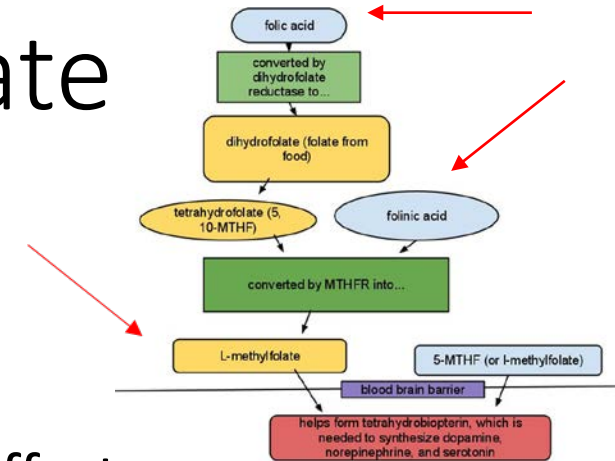
- 2017 meta-analysis by Schefft et. al. (2 RCT; ~250 participants)
 - Adjuvant: **SMD = -0.54 for 15mg/d in arm of 61 people**; no difference at 7.5 mg/d
 - Conclusion: unable to complete meta-analysis

Small trial, “medium” difference

Folate/Folic acid/L methylfolate

Why/what?

- 2003 Cochrane Review (3 RCTs; 247 participants)
 - Methyltetrahydrofolate vs trazodone: Similar effect
 - Adjuvant (2 studies):
 - Adding folate → ↓HDRS (2.65 points)
 - “Limited evidence that adding folate to other antidepressant may be helpful, but larger trials are needed before patients and clinicians can be confident that it will be helpful.”
 - AE: none



Heterogeneous, but
outcome seems positive?

S-Adenosyl –L-methionine (SAMe)

Why/what?

- 2016 Cochrane Review (8 studies; 934 participants)
 - Monotherapy vs placebo: **SMD -0.54**
 - Monotherapy vs TCA or SSRI: SAMe = pharmacotherapy
 - Adjuvant:
 - HAM–D response rate: 36% with SAMe vs. 17% with placebo
 - Remission rate: 25% with SAMe vs 11% with placebo
 - NNT for remission was 1 in 7.
 - Very low quality evidence

S-Adenosyl –L-methionine (SAMe)

- AE
 - Cases of mania in patients with bipolar
 - Theoretical possibility of hyperhomocysteinaemia
 - Mild GI and headache
- Dose: 200 mg to 1600 mg/d taken in divided doses

Effective as mono- and
adjuvant therapy, but
has AEs

Folate family - Conclusions

Folate/Folinic acid:

- Safe
- Non-significant benefit as adjuvant?
- L-Methylfolate:
 - Adjuvant: WEAK evidence for benefit at 15mg/d
 - Consider in MTRF mutation? Probably many RCTs out there...
- SAMe:
 - Weak evidence that it is better than placebo, comparable to imipramine and escitalopram, and beneficial as adjuvant
 - More side effects, including hypomania

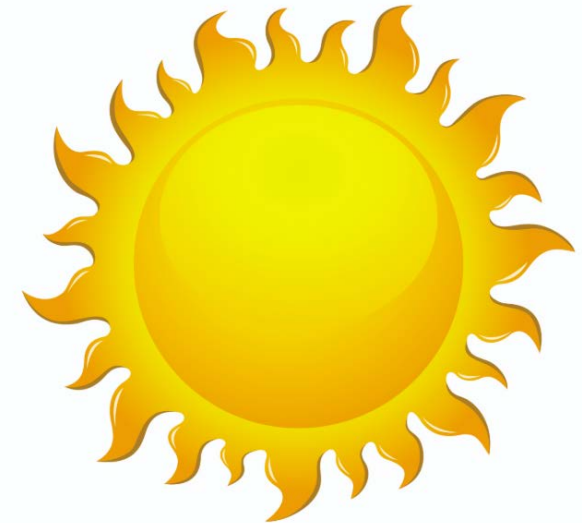
Vitamin D

- How?

- Well established association between depressive disorders and Vitamin D deficiency from a lack of sun exposure
- First noted two thousand years ago

- Why?

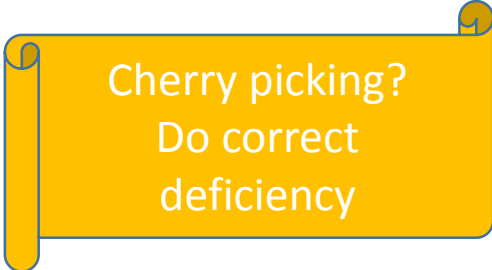
- 2014 meta-analysis of 15 RCTs
- Excluded “flawed” studies, i.e.
 - Interventions that did not \uparrow 25OHD
 - Inappropriate Vit D dosing
 - Baseline 25OHD not measured
 - Baseline 25OHD was sufficient*
 - *definition of deficiency was not specified in the review



Vitamin D

What? (7 RCTs “without flaws”)

- **SMD + 0.78** (> 0 indicating improvement in symptoms)

A yellow callout box with a dark blue border and rounded corners, containing text. The box is positioned in the lower right area of the slide.

Cherry picking?
Do correct
deficiency

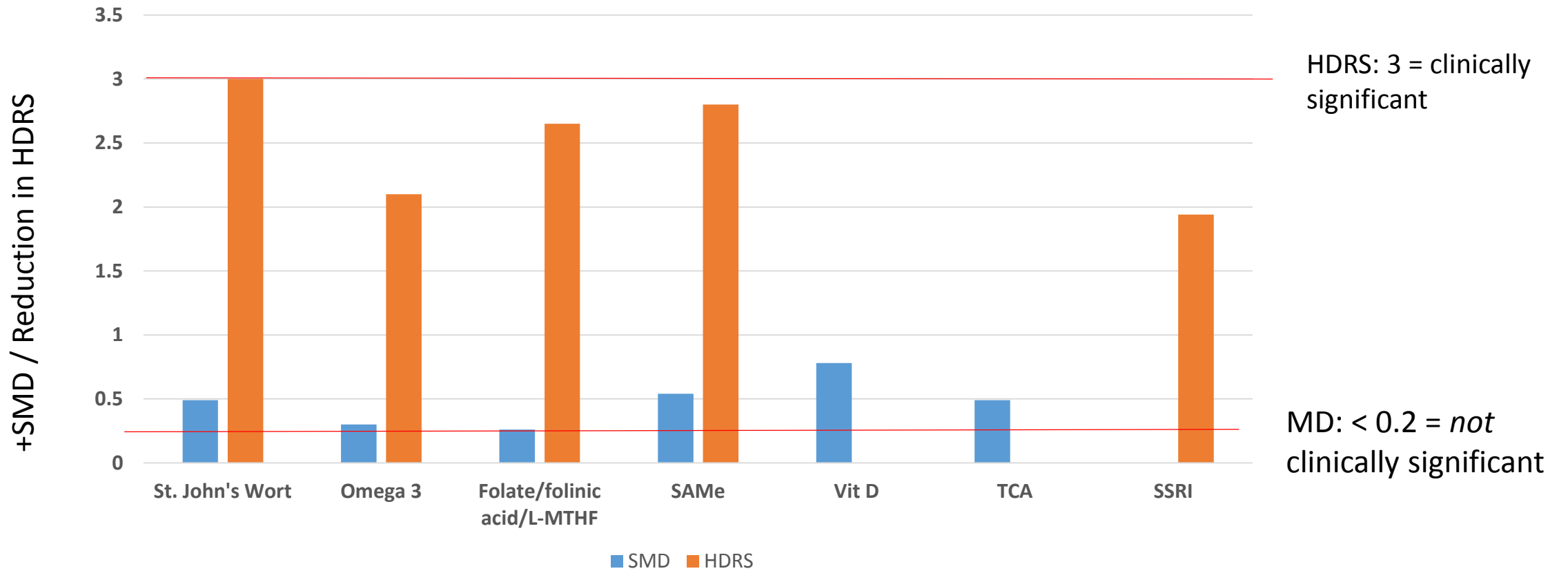
What else doesn't work?

- Inositol
- Vitamin Bs Cochrane regarding postnatal depression: “There is insufficient evidence to conclude that selenium, DHA or EPA prevent postnatal depression. There is currently no evidence to recommend any other dietary supplement for prevention of postnatal depression.”

What else does work?

- Probiotics?
 - RCT (40 participants) show improved mood in MDD
 - Improved mood in healthy people
- A nutritious diet!

Comparative efficacy



2017 meta-analysis: 35 studies; poor quality evidence	20 trials; low/very low quality evidence	3 RCTs; heterogeneous	8 studies; very low quality evidence	Correcting deficiency <i>only</i>	2009 Cochrane: 12 studies	2017 meta-analysis: 131 trials
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How this will change my practice

- Yes try St. John's Wort (if not on hormonal contraception, etc.)
- Yes offer EPA-predominant Omega 3
- Yes offer L-methylfolate
- Might offer SAME if no concern for bipolar

Please no meds!

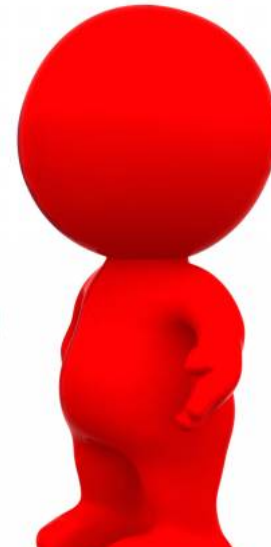


Give vitamin D
600-800 IUs/d

My D is in
the drain!



Please help
my SSRI!



- Yes recommend Omega 3 and folate or L-methylfolate
- SAME?

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