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Naturopathic Treatments for Mental Health
2019 Update

John M Dye, ND
Professor Emeritus
Southwest College of Naturopathic Medicine

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What do Naturopaths know about mental health?

- Mind-Body Connection
- Biochemical, nutritional, metabolic interactions
- Genetic, nutrigenomic influences on mental health
- Gut-brain interactions
- Herbal-nutritional influences on mental health
- Detoxification
- Hormone and neuro-steroid restoration
- Biofeedback, neurofeedback
- Transcranial magnetic stimulation (TMS)

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Objectives:
what you will learn today about naturopathic approaches and the role stay play in holistic mental health

- Routine lab tests that screen for modifiable mental health risk factors
- common genetic SNPs that influence mental health
  - Ways to access and make use of one's genetic profile.
  - Nutrigenomic interventions to improve genetic expression, and prevent illness
- common over-the-counter herbal and nutritional supplements with documented evidence to improve mood
- Recognize a mechanism to explain the connection between gut bacteria (dysbiosis) and mental health
  - Including strategies to improve regulation of gut/brain axis
- Resources for locating qualified naturopathic doctors for collaboration.

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Stress and Mental Health: Where's the breaking point?

- Chaos physics:

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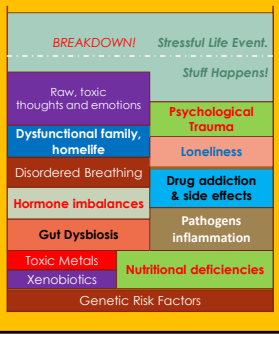
Stress and Mental Health: Where's the breaking point?

- Chaos physics:
  - Bifurcation point



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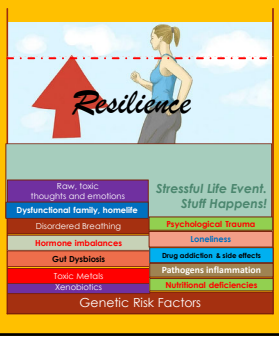
Stress and Mental Health: Where's the breaking point?

- Chaos physics:
  - Bifurcation point



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Genetic risk factors

- Inherited, familial
- Psychiatric illness
  - Risk involves multiple genes with complex interactions
    - genomic elements and regulatory pathways
    - Example: Schizophrenia and bipolar disorder
      Chen C, Sci Transl Med. 2018 Dec 19
      https://www.ncbi.nlm.nih.gov/pubmed/30545964
    - high impact of genetics demonstrated by twin studies:
      Polderman TJ, Nat Genet. 2015 Jul;
      https://www.ncbi.nlm.nih.gov/pubmed/25985137
  - Biological individuality…
    - impaired metabolism?
- Genetic influences….
  - Russian Roulette?
  - Is it rigged? … Who stacks the cards?

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Testing for genetic risks

- screening, Direct to Consumer vs professional geneticist
  - DNA test companies
    - DNA tests are typically considered **accurate.**
    - However, misinterpration or lack of precise information can be problematic
      - requiring advanced analysis guidance and interpretation
    - **3rd party vendors offer inexpensive interpretation of medical risks.**
      - 89%users reported downloading their raw data.
      - 94% used at least one tool, most commonly Promethease (63%)
        Nelson SC, Am J Hum Genet. 2019 Jul 3
        https://www.ncbi.nlm.nih.gov/pubmed/31240612
      - **Ethical concerns using 3rd party interpretations:**
        Companies: Promethease, Interpretome, LiveWello, Codegen.eu, and Enlis Personal.
        Badalato L, Eur J Hum Genet. 2017 Nov;
        https://www.ncbi.nlm.nih.gov/pubmed/29565420
      - **False positives? DTC reports may warranet genetic counseling for validation:**
        Tandy-Connor S, Genet Med. 2018 Dec
        https://www.ncbi.nlm.nih.gov/pubmed/29565420
- Helps make more informed choices that may relate to healthy living.
  - DNA effects metabolism: caffeine consumption, lactose digestion, gluten tolerance,
  - Understanding Predisposition to medical conditions allows for preventive care,

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Genetic impact on health…
What can be done?

- Can genes be modified, edited?
  - Maybe? In the future…
- RESEARCH →
  - CRISPR (clustered regulatory interspaced short palindromic repeats)
  - ZFNs (Zinc-Finger Nucleases)
  - TALENs (Transcription Activator-Like Effector Nucleases)

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Genetic impact on health…
What can be done?

- THE BIG QUESTION:
  Can we change Genetic **EXPRESSION**?
  - *Epigenetics:*
    - the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself.
  - **Epigenetic** changes alter the physical structure of DNA.
  - One **example** of an **epigenetic** change is DNA methylation — the addition of a methyl group, or a "chemical cap," to part of the DNA molecule, which prevents certain genes from being expressed. ..
    → Altering genetic expression
  - the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself.

    https://www.livescience.com/37703-epigenetics.html

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Relationship between:
Genetics, Stress, and Mental Illness

- DNA, (genes) instruct cells in specific metabolic pathways
- Epigenetics, modifications in genetic expression
  - Environment → DNA can be temporarily modified to alter how genes are read and expressed.
- DNA modifications have been seen in the brains of clinically depressed people who committed suicide.
  - Suicides had 8-fold greater number of ***methylated C-phosphate G*** (CpG) sites:
    This increased **DNA methylation** may be a significant contributor to the neuropathology and psychopathology underlying the risk of suicide in depression.

Haghighi F, Dialogues Clin Neurosci. 2014 Sep
https://www.ncbi.nlm.nih.gov/pubmed/25364291

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Epigenetics and psychiatry

Research indicates changes in genetic expression due to chronic stress:

- Genes regulating Methylation are modified in chronic stress
  - Long-lasting DNA methylation changes occur in stress-related disorders, such as
    - major depressive disorder
    - posttraumatic stress disorder (PTSD).

    Klengel T, Neuropharmacology. 2014 May;
    https://www.ncbi.nlm.nih.gov/pubmed/24452011
- Neuroepigenetics
  - Regulation of gene expression in the neuron,
    - influenced by drugs and environment.
    - DNA methyltransferases (DNMTs)
    - Changes in chromatin

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Epigenetics: *Can a change in the environment change genetic expression?*

Example:

- **Genetic Mutation: Polymorphism**
  - **methylation defects**
  - **Impaired MTHFR**
    - **→ increased homocysteine**

Kevere L. Nord J Psychiatry. 2014 Feb
https://www.ncbi.nlm.nih.gov/pubmed/23586533

- **Elevated homocysteine**
  - ***Impaired genetic expression of MTHFR →***
  - Increased risks for multiple metabolic disorders:
    - **CVD,**
    - **Neurodegeneration, (AD, PD)**
    - **Depression.**

Increased risk neuropsychiatric illness:

Kang HJ. Oncotarget. 2016 Oct 18
https://www.ncbi.nlm.nih.gov/pubmed/27626182

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Homocysteine → neurotoxicity

- ***Elevated Homocysteine*** (Hcy)
  - = risk factor for ***Neurodegenerative diseases***
  - ***Neurotoxicity:*** Hcy excess (plus B12, folate deficiency)

Obeid R. FEBS Lett. 2006 May 29;
https://www.ncbi.nlm.nih.gov/pubmed/16677571

  - homocysteine (Hcy) plays a role in brain damage, cognitive and memory decline.
    - amyloid and tau protein accumulation,
    - apoptosis, and neuronal death.
  - genetic alteration in metabolic enzymes → **neurotoxic effects**
    - (methionine synthase, methyltetrahydrofolate reductase (MTHFR),
    - cystathionine β-synthase (CβS),
    - cystathionine-γ-lyase (CγL)

Bhatia P. Fundam Clin Pharmacol. 2015 Dec
https://www.ncbi.nlm.nih.gov/pubmed/26374956

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Modifiable genetic expression:
MTHFR *Variant* → Homocysteine elevation

MTHFR genetic mutations

MTHFR variants, mutations occur (inherited)
Errors in metabolism due to certain genetic variants
→ Inefficient capacity to metabolize homocysteine.

→ ***increased homocysteine***

- ***Normal Homocysteine metabolism***
  - Re-methylation pathway
    - **B12 and folate** regenerates methionine,
  - trans-sulphuration pathway
    - **B6** (pyridoxal 5' phosphate, P5P) converts homocysteine into cysteine.

Zaric BL. Curr Med Chem. 2019
https://www.ncbi.nlm.nih.gov/pubmed/29532755

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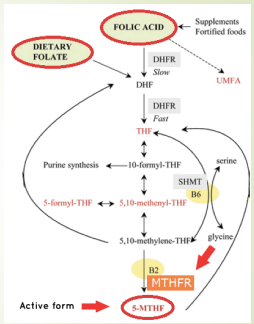
5-MTHF (methyl-tetra-hydro-folate) is active form of folate

- Methylation defects can impair ability to make active methyl-folate (5-MTHF)
- 5-MTHF is required to metabolize homocysteine.
- Active B vitamins are essential to methylation pathways
  - Dietary folate, folic acid
  - Vit B6 (Pyridoxyl-5-Phosphate)
  - Vit B12 (Methycobalamine)

Clarke R, Semin Thromb Hemost, 2000
https://www.ncbi.nlm.nih.gov/pubmed/11011852

Garibalia SF, Int J Vitam Nutr Res, 2012 Aug
https://www.ncbi.nlm.nih.gov/pubmed/23591643



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Improving genetic expression

MTHFR mutations

- ✓ **impaired ability to metabolize folate to 5-MTHF**
- ✓ **Impaired ability to metabolize Homocysteine**
- ✓ → **ELEVATED HOMOCYSTEINE**

Rx nutritional supplements to improve homocysteine metabolism

- **Rx *Methyl-Folate* (MTHF)**
  - **ACTIVE form of folic acid**
- **Methyl-cobalamine (B12)**
  - **ACTIVE form of B12**
- **Pyridoxyl-5-phosphate (B6)**
  - **ACTIVE B6**

- **CORRECTING HOMOCYSTEINE METABOLISM:**
  - **Lower risk CVD**
  - **Lower risk neurodegeranation**
  - **Lower risk of depression**

Normalizing homocysteine with nutritional supplements in depression and cognitive disorders

Karakula H, Pol Merkur Lekarski, 2009 Feb
https://www.ncbi.nlm.nih.gov/pubmed/19388520

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Common medical conditions that impact mental health:

- Hypothyroidism,
  - subclinical thyroid disorders
- Adrenal stress, endogenous steroids
  - hypo and hyper function
- Sex hormone effects
  - Menopause, hypogonadism, PMS
- Pathogenic burden
  - Dysbiosis (Disturbed GI flora)
  - Persistent yeast, bacterial, viral burden
  - CHRONIC ***INFLAMMATION***
- Toxic metals and xenobiotic burden
- Nutritional deficiencies
  - B12, folate, B6, Zinc, iron deficiencies
    - Anemia
- Other Vitamin-mineral deficiencies
- EFA imbalances
- Malabsorption syndromes
  - Celiac, gluten intolerance

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Thyroid function and mental health

- Common symptoms of hypothyroidism may overlap with depression
  - Fatigue, weakness, sluggishness
  - Achy muscles
  - Weight gain
  - Feeling cold
  - Feeling down or depressed
- Hypothyroidism is associated with a high prevalence of depression
  - Recommendation: screen hypothyroid patients for depression:
    - Mohammad MYH. J Family Med Prim Care. 2019 Aug 28 https://www.ncbi.nlm.nih.gov/pubmed/31548961
  - Shouldn't we screen depressed patients for hypothyroidism?

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Thyroid and mental health

- **Is routine testing necessary? (maybe not)**
  - **STUDY:**
    insignificant numbers of psychiatric admissions tested positive in screening for hypothyroidism:
    - ***Thyroid function testing in an inpatient mental health unit. Low yield suggests routine screening is not justified***

      Garnier KA, Australas Psychiatry. 2016 Jun https://www.ncbi.nlm.nih.gov/pubmed/26435373

    Low correlation of depression to clinical hypothyroid:

    Vargas Navarro P, Rev Colomb Psiquiatr. 2017 Jul -Sep https://www.ncbi.nlm.nih.gov/pubmed/28728797

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Thyroid and mental health

- **Is routine testing necessary? (maybe not)**

QUESTION:
How reliable are routine thyroid screening lab tests for detecting sub-clinical thyroid disorders?

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Why routine thyroid lab tests may fail to detect thyroid problems?

Routine Thyroid panel:

- TSH
- T4 (Thyroxine)
- T3 uptake (or total T3)

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Why routine thyroid lab tests fail to detect a problem?

Routine Thyroid panel:

- **Wrong cut-off for normal TSH?**
  - hypothyroidism and depression share some clinical features
  - **Range varies by lab… ~ 0.3-4.5**
    - **Upper end of this range may indicate sluggish thyroid function**
  - **a new TSH cut-off value** in hypothyroidism based on depression symptoms., using Beck depression scores
    - less than 10 was considered healthy and more than 10 were considered depressed.
  - TSH scores in depression, including those treated with levothyroxine
    - the optimal cut- off value for **depression** of TSH in depression was **2.5 MIU/L** with 89.66% sensitivity.
    - based on **severe depression** The optimal TSH cut- off was **4 MIU/L**.TSH
  - ***NEW cut-off based on symptoms, not simply lab reference range***

Talaei A, BMC Psychiatry. 2017 Sep 7
https://www.ncbi.nlm.nih.gov/pubmed/28882111

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Why routine thyroid lab tests fail to detect a problem?

Routine Thyroid panel:

- TSH
  - Range varies by lab… ~ 0.3-4.5 MUI/L
    - Upper end of this range may indicate sluggish thyroid function
- **T4 (Thyroxine)**
  - **T4 is largely inactive (must be converted to free-T3)**
  - **Free T4 is more reliable to assess thyroid function**
- T3 uptake (or total T3)

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What's missing in routine thyroid lab tests?

Routine Thyroid panel:

- TSH
- T4 (Thyroxine)
- **T3 uptake (or total T3)**
  - **T3-uptake is an unreliable way to measure *active T3**
  - ***LOW T3 syndrome (poor conversion T4 → T3)***
- ***Free T3 is active,***
  - **however Total Free T3 testing fails to distinguish T3 from the inactive rT3**
- ***rT3 is inactive.*** **Some patients have normal (euthyroid) lab tests yet have have an elevated rT3, or rT3/T3 ratio… this can explain many thyroid disorders that go undetected**
  - (Euthyroid sick syndrome)

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Comprehensive thyroid testing

- **Comprehensive thyroid panel:**
  - TSH
  - Free T4
  - Free T3
  - Reverse-T3 (rT3)
  - anti-thyroid antibodies
    - Anti-TPO
    - Anti-TGb

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Thyroid function and suicidality

- **Thyroid function in suicide attempters**
  - **suicide attempters (vs non-attempters) had significantly higher serum levels in:**
    - **thyroid stimulating hormone (TSH),**
    - **anti-thyroglobulin (Tg-Ab) and**
    - **thyroid peroxidases antibody (TPO-Ab)**
      - (all $p < 0.001$).
    - **"biomarkers of suicide risk in MDD"**
      - *…"suggesting the importance of regular assessment of thyroid function parameters for suicide prevention, and possible treatment for impaired thyroid function for intervention of suicide in MDD patients."*

STUDY: Association of thyroid dysfunction with suicide attempts in first-episode and drug naive patients with major depressive disorder.

https://www.ncbi.nlm.nih.gov/pubmed/31446378

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Autoimmune thyroid often overlooked

Is thyroid autoimmunity itself associated with psychological well-being in euthyroid Hashimoto's thyroiditis?

- **Hashimotots thyroiditis (autoimmune thyroid)**
- **May be euthyroid (normal TSH, T4, T3 lab tests)**
- Mental health was negatively correlated with anti-TPO (r=-0.287, p<0.01).
  - Health-related quality of life (**HRQoL**) is impaired
  - depression and anxiety scores are high in euthyroid patients w HT
    - independent of levothyroxine replacement.
- Thyroid autoimmunity itself may have an impact on psychological well-being in euthyroid patients with HT.
- **STUDY: Is thyroid autoimmunity itself associated with psychological well-being in euthyroid Hashimoto's thyroiditis?**
  - https://www.ncbi.nlm.nih.gov/pubmed/28260699

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Early psychosis and thyroid antibodies

- STUDY:
  - 70 outpatients with early psychosis
  - **Those w positive thyroid antibodies (TPO-Abs) correlated with**
    - **Greater negative and depressive symptoms**
    - **poorer function (P < .05).**
- study suggests that anti-thyroid antibodies are associated with a more severe phenotype with increased negative symptoms and poorer functioning in early psychotic patients.
  - ***Association between anti-thyroid antibodies and negative symptoms in early psychosis.*** https://www.ncbi.nlm.nih.gov/pubmed/28260699 Barbero JD et al, 2019 Sep 16.

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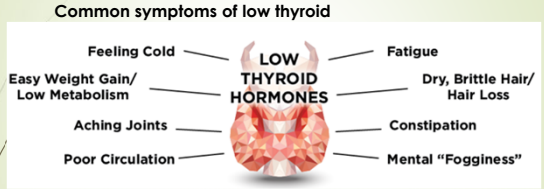
How do we know when to test thyroid?

Common symptoms of low thyroid



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Naturopathic approach to screening for thyroid disorders

- **Who needs testing?**
  - **Even if they test euthyroid or take thyroid medication:**
- Thyroid Symptoms
- Signs, physical exam
  - Low body temperatures
    - BBT, average Waking. . (< 97° F)
    - ***Low average daytime temperate*** [<97.8° F]
  - Delayed Achilles tendon reflexes
  - Hypercarotenodermia (yellowish skin, w/out jaundice)

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Naturopathic approach to thyroid support

To improve overall thyroid function

- **Iodine** is an essential nutrient
  - deficiency of iodine
    Delange F. Eur J Nucl Med Mol Imaging. 2002 Aug
    https://www.ncbi.nlm.nih.gov/pubmed/12192542
  - Supplementation in iodine deficiency
    Ali NI. Diabetes Metab Syndr. 2019 Jan - Feb
    https://www.ncbi.nlm.nih.gov/pubmed/30641788

    Niwattisaiwong S. Cleve Clin J Med. 2017 Mar
    https://www.ncbi.nlm.nih.gov/pubmed/28322679
  - Dietary sources
    - Iodized salt
    - Seafood; Fish, seaweed
    - Dairy
- **Zinc**
  - Deficiencies seen in low-T3 syndrome
    - Zinc supplements: increase active fT3, lower rT3

      Nishiyama S. J Am Coll Nutr. 1994 Feb
      https://www.ncbi.nlm.nih.gov/pubmed/8157857
- **Selenium:**
  - Deficiencies seen in Low-T3 syndrome
    - Study concluded that reduced peripheral T4 conversion is related to impaired Se status in the elderly.

      Olivieri O. Biol Trace Elem Res. 1996 Jan
      https://www.ncbi.nlm.nih.gov/pubmed/8816573
  - Use selenomethioine supplements (200 mcg)
  - Or eat Barzil nuts (source if dietary SELENIUM), one per day

    Talaei A. Nutr Hosp. 2015 Oct 1
    https://www.ncbi.nlm.nih.gov/pubmed/28882111

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Selenium from Brazil nuts helps thyroid

- It is known that Brazil nuts (from the Brazil nut tree—*Bertholletia excelsa*) are the richest food source of selenium.
  - Eating brazil nuts has improved thyroid function and reduced autoimmunity in studies

EFFECT OF SELENIUM SUPPLEMENTATION VIA BRAZIL NUT (BERTHOLLETIA EXCELSA, HBK) ON THYROID HORMONES

Barcza Stockler-Pinto M. Nutr Hosp. 2015 Oct 1
https://www.ncbi.nlm.nih.gov/pubmed/26545554

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Herbal support for thyroid

- Adaptogenic and "energy tonic" herbs improve thyroid metabolism
  - improve peripheral thyroid metabolism
  - conversion of T4 → T3
    - Liver metabolism

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Herbal Tonics

- **Ashwaganda** (withania)
  - STUDY: subject w elevated TSH:
    - treatment with ashwaganda improved serum TSH, T3, and T4 levels significantly compared to placebo.

Sharma AK. J Altern Complement Med. 2018 Mar
https://www.ncbi.nlm.nih.gov/pubmed/28829155

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Herbal Tonics

- **Ginseng**
  - Benefits thyroid metabolism
    - thyroid function improved: → Increased T3, T4, Decreased rT3
    - Benefits seen in heart patients, (CHF)

Dai X. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1999 Apr
https://www.ncbi.nlm.nih.gov/pubmed/11783267

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Herbal Tonics

- **Bacopa**
  - THYROID STUDY: Bacopa monnieri could increase T4 concentration by 41%
    - suggesting that it can be used as a thyroid-stimulating drug.
    - Kar A, J Ethnopharmacol, 2002 Jul https://www.ncbi.nlm.nih.gov/pubmed/12065164
  - STUDIES suggest that Bacopa monnieri has the potential to improve cognition, particularly speed of attention

Kongkeaw C, J Ethnopharmacol, 2014 https://www.ncbi.nlm.nih.gov/pubmed/24252493

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Potential herb-drug interactions

- **Ginseng:**
  - Traditional and folk uses of ginseng include:
    - recovery from illness; increases a sense of well-being and stamina; improves both mental and physical performance; treats erectile dysfunction, hepatitis C, and symptoms related to menopause; and lowering blood glucose and controlling blood pressure.
- **Potential for Ginseng Herb-Drug Interaction**
  - Current evidence suggests that ginseng induces activity of the drug-metabolizing enzyme CYP3A in the liver and possibly the gastrointestinal tract. (effects metabolism of sedative drugs) Ie, Midazolam (used for sedation in surgery)
    - A 2012 open-label study concluded that patients taking Asian ginseng in combination with sedatives should be monitored for interactions

https://nccih.nih.gov/health/providers/digest/herb-drug

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Nutritional approach to thyroid autoimmunity (Hashimoto's Thyroiditis)

- **Selenium**
  - Selenium (selenomethioine) modifies autoimmune thyroid
    - Santos LR, Diagnostics (Basel), 2018 Dec https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6241875/
  - Selenomethionine supplement Improves thyroid autoimmunity
    - Pirola I, Endocrinol Diabetes Nutr, 2019 Jun 10 https://www.ncbi.nlm.nih.gov/pubmed/31198738
  - **Selenium and vitamin D interactions in thyroid autoimmunity**
    - Krysiak R, Pharmacol Rep, 2019 Apr https://www.ncbi.nlm.nih.gov/pubmed/30844687
  - Selenium + low-dose T4 combination
    - Yu L, J Endocrinol Invest, 2017 Nov https://www.ncbi.nlm.nih.gov/pubmed/28534148
- **Vit D**
  - Vit D deficiency in autoimmune thyroid
    - **The Role of Vitamin D in Thyroid Diseases** Kim D, Int J Mol Sci, 2017 Sep 12 https://www.ncbi.nlm.nih.gov/pubmed/28895880
  - **Immunomodulatory effect of vitamin D in thyroid autoimmunity**
    - Gallo D, J Endocrinol Invest, 2019 Oct 4. https://www.ncbi.nlm.nih.gov/pubmed/31584143

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Naturopathic approach to thyroid support

- To improve overall thyroid function
  - Nutritional supplements:
    - Iodine
    - Selenium
    - Zinc
  - Thyroid herbs: (to improve conversion of T4 → T3)
    - Ashwaganda
    - Ginseng
    - Bacopa)
- To reduce thyroid auto-antibodies
  - Selenium + low dose T4
  - Vit D (D3) …***sunshine***

Rx thyroid medications
thyroid hormone replacement
- Natural desiccated thyroid
- Levothyroxine (T4)
- Liothyronine (T3)
- Compounded T3/T4 (combination)

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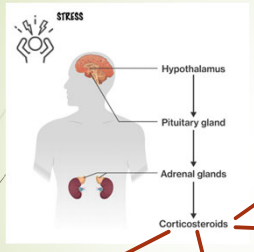
Adrenal Stress response



THYROID impacts
- T3 levels
  - impaired conversion T4→ T3
- rT3 levels
  - Inert → fatigue, depression

BLOOD SUGAR impacts
- Insulin function
- Hyper- and hypo-glycemia
- Weight regulation

MOODS, ENERGY
- Depression
- Fatigue
- Anxiety
- insomnia

STRESS regulation
- stress tolerance
- Cardiovascular, BP
- Circadian rhythms, Sleep

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Stress reduction

- Integrative health approach that combines relaxation, nutrition, herbal tonics. and exercise

Naturopathic approaches:
Nutritional and botanical interventions to assist with the adaptation to stress

Kelly GS. Altern Med Rev. 1999 Aug
https://www.ncbi.nlm.nih.gov/pubmed/10468649

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Evidence supports various stress management programs:

- **Mindfulness Based Interventions.**
  Hofmann SG, Psychiatr Clin North Am. 2017 Dec.
  https://www.ncbi.nlm.nih.gov/pubmed/29080597
- **meditation,**
  Goyal M, JAMA Intern Med. 2014 Mar
  https://www.ncbi.nlm.nih.gov/pubmed/24395196
- **biofeedback,**
  - **Neurofeedback and Biofeedback for Mood and Anxiety Disorders**
    Ranerjee S. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Nov
    https://www.ncbi.nlm.nih.gov/pubmed/30299634
  - **Smartphone Applications Utilizing Biofeedback Can Aid Stress Reduction**
    - ***skin conductance***
      Dillon A, Front Psychol. 2016 Jun 17
      https://www.ncbi.nlm.nih.gov/pubmed/27378963
- **progressive muscle relaxation**
  decrease in the symptoms of depression, anxiety, stress (unemployed)
  Merakou K, Explore (NY). 2019 Jan – Feb
  https://www.ncbi.nlm.nih.gov/pubmed/30228090

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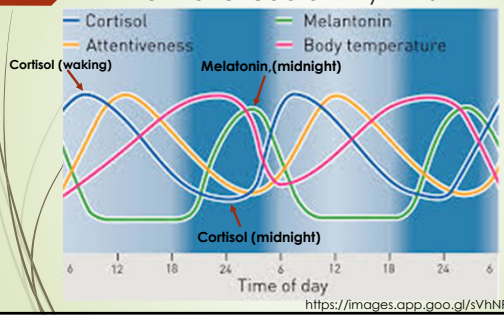
Normal circadian rhythms



https://images.app.goo.gl/sVhNRPWSjRxmqRJd8

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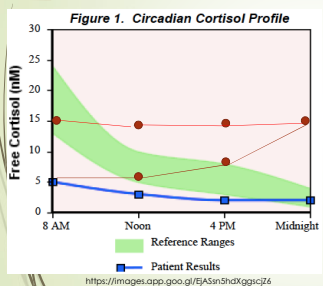
Disturbed circadian rhythm



https://images.app.goo.gl/EjASsn5hdXggscjZ6

- Physical and mental health impacts
  STUDIES indicated ***flatter diurnal cortisol slopes*** and poorer health in 10/12 ***emotional and physical health outcomes*** examined.
  Adam EK, Psychoneuroendocrinology. 2017 Sep
  https://www.ncbi.nlm.nih.gov/pubmed/28578301
- Low waking flat Cortisol rhythm is associated w fatigue
  Cortisol secretion and fatigue
  Kumari M, Psychoneuroendocrinology. 2009 Nov
  https://www.ncbi.nlm.nih.gov/pubmed/19497676
- Adrenal insufficiency in Patients presenting w fatigue presenting to psychosomatic clinic:
  Matsubayashi S, Endocr J. 2019 Oct 8
  https://www.ncbi.nlm.nih.gov/pubmed/31597820
- atypical cortisol profile (in older adults) is associated with:
  - Depressive symptoms
  - Memory issues
  Fiocco AJ, Stress. 2006 Sep;9(3):143-52
  https://www.ncbi.nlm.nih.gov/pubmed/17060048

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Restoring circadian rhythm

- Stress management:
- EXECERISE:
  coordinate exercise w circadian rhythm; > daytime
  muscle mitochondrial adapt to their own circadian rhythm …exercise same time of day

  Gabriel BM, Nat Rev Endocrinol. 2019 Apr
  https://www.ncbi.nlm.nih.gov/pubmed/30655625
- Sleep therapy
  - Sleep hygiene
    Pavlova M, Continuum (Minneap Minn). 2017 Aug
    https://www.ncbi.nlm.nih.gov/pubmed/28777176
  - Melatonin:
    Xie Z, Neurol Res. 2017 Jun
    https://www.ncbi.nlm.nih.gov/pubmed/28460563
- HORMONE REPLACEMENT in deficient states
  - Adrenal cortical extract (raw adrenal gland supplement)
  - Cortisol, (hydrocortisone) …for low/flat cortisol
  - Pregnenolone, DHEA

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Rx Adrenal hormones? → *Neurosteroids*

- **Cortisol (hydrocortisone)**
  mimic circadian rhythm… AM dosing of hydrocortisone:
  Venneri MA, J Clin Endocrinol Metab. 2018 Aug 1
  https://www.ncbi.nlm.nih.gov/pubmed/29846607
- **Pregnenolone**
  - **Supplement effective in bipolar:**
    Brown ES, Neuropsychopharmacology. 2014 Nov
    https://www.ncbi.nlm.nih.gov/pubmed/24917198

  Pregnenolone may have beneficial effects on mood ***In depressed patients with substance abuse***
  Osuji IJ, Psychiatry Res. 2010 Jul 30
  https://www.ncbi.nlm.nih.gov/pubmed/20493557
- **DHEA**
  - **Rx for depression**
    Peixoto C, CNS Neurol Disord Drug Targets. 2018;17(9):706-711
    https://www.ncbi.nlm.nih.gov/pubmed/30124161
  - **Libido, mood, and well-being in women**
    Panjari M, Hum Reprod Update. 2007 May-Jun
    https://www.ncbi.nlm.nih.gov/pubmed/17208951

    Pluchino N, J Steroid Biochem Mol Biol. 2015 Jan
    https://www.ncbi.nlm.nih.gov/pubmed/24892797

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Neurosteroids

Steroid synthesis

- Cholesterol
  - **Adrenal** Precursors
    - ➢ **Corticosteroid *(cortisol)***
    - ➢ ***Pregnenolone***
      - ➢ ***DHEA***
      - Gonads
        - ➢ ***Testosterone***
          - ➢ ***Estrogen***
  - ***→Brain-derived Neurosteroids***
    - ***Neurotransmitters, neurotrophic factors, active peptides***

48

The brain has neuro-receptors for sex hormones

- **Estrogen:**
  - ***premature or early menopause***
    - → adverse effects on cognition, mood, cardiovascular, bone, and sexual health, as well as an increased risk of early mortality.
    - psychological impact of early menopause
    - Study Recommendations: > hormone therapy and counseling.
      Faubion SS, Climacteric. 2015
      https://www.ncbi.nlm.nih.gov/pubmed/26445383
  - ***Brain aging***
    - estrogen has brain neuroprotective, neurotrophic and antioxidant modes of action
    - postmenopause → vulnerability of elderly women to brain degeneration
      Lejri I, Front Aging Neurosci. 2018 Apr 27
      https://www.ncbi.nlm.nih.gov/pubmed/29755342
    - **Brain shrinkage:** in the association cortices and the hippocampus
      - Neuroprotective properties of estrogen
      - women who took HRT showed no significant shrinkage of the neocortex.
        Raz N, Neuroreport. 2004 Nov 15
        https://www.ncbi.nlm.nih.gov/pubmed/15538189

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Pregnenolone
for bipolar and schizophrenia

- **Pregnenolone for cognition and mood in dual diagnosis patients**
  - Pregnenolone may have beneficial effects on mood and cognition
  - **STUDY:**
    - 70 participants with bipolar disorder or recurrMDD
    - + history of substance abuse/dependence
    - randomly assigned to receive pregnenolone (100mg/day) or placebo for 8weeks.
    - Findings suggest that pregnenolone use may be **associated with some improvement in manic and depressive symptoms,**

Osuji IJ., Psychiatry Res. 2010 Jul 30
https://www.ncbi.nlm.nih.gov/pubmed/20493557

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Rx Estrogen, HRT

- ***Mood***
  - No clear evidence that E therapy alone is effective for depression
  - "What appears to be universally accepted is that treatment, with estrogen, for **low mood in women during midlife years** may be beneficial, and should be considered."
    Sassarini DJ, Maturitas. 2016 Dec
    https://www.ncbi.nlm.nih.gov/pubmed/27823736
- ***Safety:***
  - Bioidentical HRT (E2, E3, natural Progesterone) is safer than conventional synthetic versions
    Holtorf K, Postgrad Med. 2009 Jan
    https://www.ncbi.nlm.nih.gov/pubmed/19179815
  - Transdermal is safer than oral
    Beck KL, Postgrad Med. 2017 Aug;
    https://www.ncbi.nlm.nih.gov/pubmed/28540770

51

HRT: Hormone balancing bio-identical

STUDY:
bioidentical Estrogen + Progesterone (w/ or w/out DHEA, testosterone)

- 97% experienced symptom control,
- **Mental symptoms improved in 90% of the patients**

Mahmud K, Gynecol Endocrinol. 2010 Feb
https://www.ncbi.nlm.nih.gov/pubmed/19995152

Dr Dye's protocol:
advantages of BALANCED *Bio-identical* *TRANSDERMAL* HRT

- **Estradiol + Estriol + Progesterone + Pregnenolone + DHEA + Testosterone**

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Safety of HRT?

- **POSITION STATEMENT ON MENOPAUSE-2017 UPDATE**
  - AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
  - AMERICAN COLLEGE OF ENDOCRINOLOGY

Although these conventional organizations have not endorsed use of compounded bio-identical hormones, they do agree in principle:

RECOMMENDATIONS:

- **transdermal** (vs oral) estrogen preparations may be considered less likely to produce thrombotic risk and perhaps the risk of stroke and coronary artery disease.
- when the use of progesterone is necessary, **micronized** (natural) **progesterone** is considered the safer alternative.
- in symptomatic menopausal women who are at significant risk from the use of hormone replacement therapy, the use of **selective serotonin re-uptake inhibitors** and possibly **other nonhormonal agents** may offer significant symptom relief.

Cobin RH, Endocr Pract. 2017 Jul
https://www.ncbi.nlm.nih.gov/pubmed/28703650

53

HRT: precautions, interactions

- Primary concerns:
  - Breast, ovarian cancer
  - Blood clots, CVD
  - Check for interactions:
    Estrogen:
    https://www.drugs.com/drug-interactions/estradiol-estrogen-patches.html

    progesterone
    https://www.drugs.com/drug-interactions/progesterone-topical.html
  - Side effects
    - Estrogen, Progesterone:
      https://www.drugs.com/sfx/progesterone-side-effects.html

- Precautions:
- Increased risks of:
  - myocardial infarction,
  - stroke,
  - invasive **breast cancer**,
  - pulmonary emboli, and **deep vein thrombosis**
  - An increased risk of developing probable dementia in postmenopausal women 65 years of age or older has also been reported.
  - Risks should be assumed to be similar for other doses, combinations, and dosage forms of **estrogens** and **progestins**.
  - **Progestins** with estrogens should be prescribed at the lowest effective doses and for the shortest duration possible.

    https://www.drugs.com/sfx/progesterone-side-effects.html

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Neuroreceptors for testosterone

Testosterone

- ***low levels*** of testosterone, in both sexes. are associated with:
  - **mental disorders,**
  - **sexual dysfunction**
  - **cognitive impairment**
  - **STUDY: recommendation:**
    physicians should "***carefully assess testosterone levels, not only in the management of sexual dysfunctions but also when seeking to help patients with severe mental or organic diseases***"

Ciocca G, Sex Med Rev. 2016 Jan
https://www.ncbi.nlm.nih.gov/pubmed/27872000.

55

Neuroreceptors for testosterone

Testosterone

- Chronic ***elevated levels*** of testosterone are associated with
  - ***Impulsivity***
  - ***Psychiatric, mood disorders***
  - ***Suicidality***

Agrawal J, Mol Neurobiol. 2019 Jun
https://www.ncbi.nlm.nih.gov/pubmed/30264294

- ***Drug interactions and precautions:***
  https://www.drugs.com/drug-interactions/testosterone-topical.html

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GUT-BRAIN:
intestinal flora impacts mental health

Gut/brain

- biochemical signaling between
  - **gastrointestinal tract**
    - including the enteric nervous system
  - **central nervous system**
    - hypothalamic–pituitary–adrenal axis (HPA axis),
- "**microbiome–gut–brain axis**".
  - role of the gut flora in signaling between GI tract and CNS

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Gut flora and neuro-psychiatric disorders

- GIT, CNS Interactions are vulnerable
  - variations of microbiome, microbiota-derived products
    - can be modified by Antibiotics, diet, prebiotics, probiotics, etc
    - → neuro-immune and neuro-psychiatric effects
  - Compromised microbiota: predisposes susceptibility to
    - CNS autoimmune diseases, such as multiple sclerosis.
    - Neuropsychiatric disorders, such as autism, depression, anxiety, stress.

Wang Y., Brain Behav Immun. 2014 May
https://www.ncbi.nlm.nih.gov/pubmed/24370461

- Possibility for affecting mood and behavior via gut/brain?
  - And visa-versa?

58

Terminology

- **Microbiota**
  - Refers to different clusters of bacteria in the body

colonized by 100 trillion microbes, ten times more than human cells

- Impacts of Gut Bacteria on Human Health and Disease

Yu-Jie Zhang, Int J Mol Sci. 2015 Apr
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4425030/

- **Microbiome**
  - Genetic characteristics of bacteria various parts of the body
    - modifiable:
      Today, vs the one we were born with
      - The first months, plus 1st year, impact health later in life

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What factors influence microbiota?

- **C-sections vs vaginal birth**
  - Skins, vaginal flora
  - risk of allergic disease later in life
- **breast feeding, Breast milk**
  - Colostrum
  - Milk oligosaccharides, (prebiotics)
  - Benefits: protections gains diseases
    - > immune defenses, anti-infection
    - Immune disorders,
      - autoimmunity
- **Early Exposure to antibiotics**
- **Exposure to outdoors, nature**
- **Exercise activities**.
  - Athletes have different microbiota
- **Dietary influences**
  - Western diet
  - Mediterranean diet

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Dietary polyphenols influence microbiota

- **POLYPHENOLS in Bright colorful fruits and vegetables, teas**
  - phenolic acids and flavonoids
- **polyphenol fermentation products support heathy flora**
  - Repressed the growth of certain pathogenic bacteria
    - *Clostridium perfringens*, *Clostridium difficile*, and *Bacteroides* spp.,
  - Sparing impact on normal flora
    - Bifidobacterium spp. and probiotics such as Lactobacillus sp. were less severely affected.
  - **Dietary phenolics may play an important role in the maintenance of gastrointestinal health.**

    Lee HC, Res Microbiol. 2006 Nov
    https://www.ncbi.nlm.nih.gov/pubmed/16962743

    can affect human health because of their antioxidant and antimicrobial properties as well as free-radical scavenging activity.
  - **Benefits of polyphenols on gut microbiota and implications in human health**

    Cardona F, J Nutr Biochem. 2013 Aug
    https://www.ncbi.nlm.nih.gov/pubmed/23849454

61

Diet affects microbiota

- Influence of Mediterranean, carbohydrate, and protein DIETS
  - Relation to microbiota, obesity and inflammatory state

    Lopez-Legarrea P, Asia Pac J Clin Nutr. 2014
    https://www.ncbi.nlm.nih.gov/pubmed/25164445
- Effects of malnutrition

  gut microbiota alteration is associated with severe acute malnutrition
  - ***Disturbances in microbiota:***
    - leads to deficiencies in energy metabolism, vitamin biosynthesis, Immune protection,
    - is associated with diarrhea, malabsorption and systemic invasion by microbial pathogens.

    Million M., Microb Pathog. 2017 May
    https://www.ncbi.nlm.nih.gov/pubmed/28853763

62

Xenobiotics damage microbiota

- Effects of **antibiotics, and food additives** on microbiota,
  - increase the risk of diseases due to microbial alterations.

    Dudek-Wicher RK, Prz Gastroenterol. 2018
    https://www.ncbi.nlm.nih.gov/pubmed/30002765
- Exposure to toxins and chemicals
  - Drugs, Environmental pollutants, heavy metals,
    - **Toxic metals:**

      Richardson JB, Sci Rep. 2018 Apr 26
      https://www.ncbi.nlm.nih.gov/pubmed/29700420
    - **Artificial sweeteners**

      Ruiz-Ojeda FJ, Adv Nutr. 2019 Jan 1
      https://www.ncbi.nlm.nih.gov/pubmed/30721958

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STRESS and microbiota

Stress is a major factor known to alter the gut microbiota and the gut barrier function.

- **Early life is a vulnerable period** :
  - gut microbiome shapes the host immune homeostasis and the nervous system.
  - increase the risk of developing stress-related disorders later in life.

    Dawson SL, JMIR Res Protoc. 2019 Oct 21
    https://www.ncbi.nlm.nih.gov/pubmed/31638593

Microbiota alteration is associated with the development of stress-induced despair behavior.

Marin IA, Sci Rep. 2017 Mar 7
https://www.ncbi.nlm.nih.gov/pubmed/28266612

- Rx… **modify microbiota to improve symptomatology.**

Mohajeri MH, Eur J Nutr. 2018 May
https://www.ncbi.nlm.nih.gov/pubmed/29748817

64

STRESS and microbiota

- Social relationships
  - close sustained relationships, influence the gut microbiota.
  - married individuals harbor microbial diversity

    Dill-McFarland KA, Sci Rep. 2019 Jan 24
    https://www.ncbi.nlm.nih.gov/pubmed/30679677

- History of Child abuse (ACEs)
  - → adverse changes in gut microbiota composition during pregnancy
    - Impacts stress response in PG, inflammatory state,

      Hantsoo L, Brain Behav Immun. 2019 Jan
      https://www.ncbi.nlm.nih.gov/pubmed/30399404

- Psychological stress and microbiota (in IBS)
  - Study identified a microbial signature corresponding with psychological distress
    - Bacteria associated w distress, anxiety, depression, and stress perception

      Peter J, Psychosom Med. 2018
      https://www.ncbi.nlm.nih.gov/pubmed/30095672

65

Gut/brain and psychiatric disorders

- mental health and microbiome
  - **"Abnormalities in this microbiota-gut-brain axis have emerged as a key component in the pathophysiology of depression"**
  - Mechanisms
    - direct stimulation of central receptors,
    - peripheral stimulation of neural, endocrine, and immune mediators
    - epigenetic regulation of histone acetylation and DNA methylation.

      Lee HC, Res Microbiol. 2006 Nov;
      https://www.ncbi.nlm.nih.gov/pubmed/31646148

- PTSD and microbiome
  - Susceptibility to PTSD due to lingering effects of imbalanced gut microbiota in early life may

    Leclercq S, Can J Psychiatry. 2016 Apr
    https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4794957/

66

Unhealthy gut /unheathy brain

- **intestinal microbiota regulate the CNS neuroimmune responses**
- **bacterial dysbiosis → *neuroinflammatory state***
  - *→increased risk of neurodegenerative diseases.*
- ***protocols for regulating and maintaining healthy intestinal microbiota*** are indicated
  - to lower risk and prevalence of neurodegenerative diseases.

Spielman LJ, Neurochem Int. 2018 Nov
https://www.ncbi.nlm.nih.gov/pubmed/30114473

67

Dysbiosis → Brain toxins

- Neurotoxins? …*Production of toxic compounds*
  - digestion of proteins results in the production of potentially toxic metabolites such as phenolic and sulphur-containing compounds.

Windey K, Mol Nutr Food Res. 2012 Jan
https://www.ncbi.nlm.nih.gov/pubmed/22121108

  - Stress, psychiatric illness, PTSD, and dysbiosis:

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Multiple illnesses associated w Imbalanced microbiota: dysbiosis

- Diabetes
- Obesity
- Cancers: , stomach, colon
- Gastrointestinal disease
  - IBD, IBS, Colic,
  - Necrotizing enterocolitis (< preterm infants)
  - Intestinal permeability
- asthma
- Autism
- Depression, mood disorders
- Neurodegeneration
  - Parkinson's
  - Cognitive decline

Zhang YJ, Int J Mol Sci. 2015 Apr 2
https://www.ncbi.nlm.nih.gov/pubmed/25849657

69

Depression… (a gut feeling?)

- Acute depression
  - Associated with higher levels of dysbiotic bacteria
    - Bacteroidetes, Proteobacteria and Actinobacteria, whereas levels of Firmicutes were significantly reduced
  - Levels of Faecalibacterium were inversely related to severity of depressive symptoms.
  - bacteria → Mood?

Timothy G. Dinan, Genome Med. 2016
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4822287/

- **Recognizing Depression from the Microbiota Gut-Brain Axis.**
  - *microbiota could be a direct cause for the disorder.*
  - *correcting these disturbance could alleviate depression*

Liang S, Int J Mol Sci. 2018 May 29
https://www.ncbi.nlm.nih.gov/pubmed/29843470

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Intestinal flora and Chronic inflammation

- Chronic inflammation has been associated with
  - Changes in gut flora
    - → Changes in neurotransmitter concentrations
  - adult stress, depression
  - childhood trauma.
- Gut microbiota is, ***modulated by diet***
  - plays a role in depression.
- **Research suggests we explore Interventions that TARGET MICROBIATA in depression**

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Diet, microbiota, and mental health

- **The *microbiota-diet-inflammation trialogue* in depression**

Koopman M, Curr Opin Psychiatry. 2017 Sep
www.ncbi.nlm.nih.gov/pubmed/28654462

- **Fruits and vegetables help support health microbiota**
  - **Bad diet → depression?**
    Low fruit and vegetable intake
    →*incr rates of depression, anxiety*
  - **The association between fruit and vegetable consumption and mental health disorders**

McMartin SE, Prev Med. 2013 Ma
https://www.ncbi.nlm.nih.gov/pubmed/23295173

72

Bacteria causing depression?

- **Microbiome colonies of MDD differs from healthy controls**
- STUDY: Germ-free Mice:
  - Transplantation of fecal flora to mice:
    - 'depression microbiota' derived from MDD patients
    - 'vs healthy microbiota' derived from healthy control individuals.
  - ***depression*** (vs healthy) ***microbiota*** Induced depression-like behaviors

Zheng P, Mol Psychiatry. 2016 Jun
https://www.ncbi.nlm.nih.gov/pubmed/27067014

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Lab tests for dysbiosis

- **Comprehensive Stool culture, parasitology**
  - Identifies:
    - Gut pathogens
    - Normal flora, imbalanced flora
    - Mycology (fungal, yeast)
- SIBO screen (breath test)
  - Small intestinal bacterial overgrowth
- **Urinary organic acids (OAT) (or Microbial OAT)**
  Identifies metabolites (associated with behavioral, psychiatric and and physical disorders)
  - Pathogenic bacteria
  - Yeast overgrowth
  - markers for vitamin and mineral levels,
  - oxidative stress,
  - neurotransmitters

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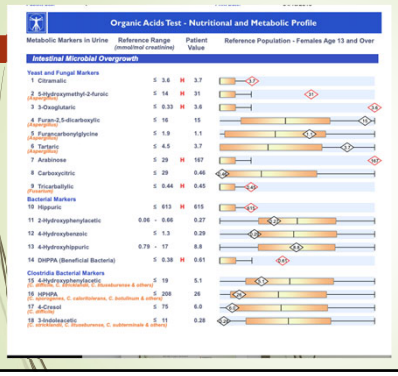

Microbial OAT

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Improve Gut/Brain health with Diet and nutritional products

- Fermented foods. pubmed
  - Sauerkraut
  - yogurt
- Mediterranean diet pubmed
  - Fish, greens, olives/olive oil, grapes
- Hi dietary polyphenols Pubmed
  - Blueberries
  - Green tea
  - Chocolate
  - Coffee/tea
- Avoid pro-inflammatory western diet high in sugar, processed grains, fried foods, chemicals. Etc. Pubmed
- OTC Supplements
  - Colostrum (LD, liposomal delivery)
  - Probiotics: Pubmed
    - Lactobacilis probiotics
    - Sacromyces boulardi (yeast)
  - Resveratrol: Pubmed
- Traditional Herbals for GIT immune health
  - Pau d'arco Pubmed
  - Berberine Pubmed
  - Oregano oil Pubmed

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Medical interventions for microbiome

- **Anti-pathogenic, Immune support**
  - **Colostrum, transfer factors,**
  - **berberine**
  - **Oregano oil capsules**
- **Prebiotic**
  - **Non-digestible substance, typically oligosaccharides, that selectively stimulate growth of naturally occurring bacteria on the colon**
    - **Examples: FOS, GOS, inulin, colostrum, polyphenols**
- **Probiotic**
  - **Supplement/food product containing a sufficient number if viable microorganizations to alter the host microflora for potential health benefits**
- **Synbiotic**
  - **Supplement/food product containing prebiotics and probiotics (synergy)**

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Probiotics target mood and anxiety

- STUDY: Two novel strains demonstrated ability to reduce depression and anxiety (placebo controlled)
  - Combination probiotic therapy:
    - ***Lactobacillus helveticus*** **R0052**
    - ***Bifidobacterium longum*** **R0175**

after 30 days:
Improved scores for depression, anxiety, global severity, anger-hostility, lower cortisol

Messaoudi M, Br J Nutr, 2011 Ma
https://www.ncbi.nlm.nih.gov/pubmed/20974015

RESEARCH:
Review and ***meta-analysis*** on probiotics for depression:
"We found that probiotics were associated with a significant reduction in depression"

Huang R, Nutrients. 2016 Aug 6
https://www.ncbi.nlm.nih.gov/pubmed/27509516

78

Inflammation and mental health

- Inflammation and depression
  - Accumulating evidence supports a bidirectional association between depression and inflammatory processes,
  - anti-inflammatory treatments are effective in depression (vs placebo) .**Inflammation in Depression and the Potential for Anti-Inflammatory Treatment**
    Kohler O, Curr Neuropharmacol, 2016
    https://www.ncbi.nlm.nih.gov/pubmed/27640518
  - Connection between **Inflammation and vegetative sx pf depression**
    - independent of cognitive symptoms
      review article:

      Majd M, Front Neuroendocrinol, 2019 Oct 22
      https://www.ncbi.nlm.nih.gov/pubmed/31654681

79

Inflammation and microbiota

- Vicious cycle:
  - Psychological stress → gut microbiota → immune activation (inflammation) → neurodevelopmental disorders and behavior changes → impaired neurophysiology and impaired stress response "**Role of gut microbiota in the interaction between immunity and psychiatry: a literature review.**"

    Dubois T, Psychiatr Danub, 2019 Sep
    https://www.ncbi.nlm.nih.gov/pubmed/31488756
- Treatments work both ways:
  - effective depression treatments could have a far-reaching impact on inflammation and health.

    Kiecolt-Glaser JK, Am J Psychiatry, 2015 Nov 1
    https://www.ncbi.nlm.nih.gov/pubmed/26357876

80

Inflammation and brain health

- Inflammation and neurodegenerative diseases
  - Common factor:
    Inflammation, and chronic immune activation

Inflammation in CNS neurodegenerative diseases.
interactions between the peripheral immune system and the brain

Stephenson J, Immunology, 2018 Jun
https://www.ncbi.nlm.nih.gov/pubmed/29513402

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Sources of chronic inflammation

- GIT, dysbiosis,
  - Candida
  - Antibiotics → disturbed flora
    - Diarrhea, constipation
- Chronic infections
  - Slow virus
    - EBV, CMV, Lyme's (buoleriosis)
  - Periodontal. (bacteria)

Oral Health: The First Step to Well-Being.

Fiorillo L, Medicina (Kaunas). 2019 Oct
https://www.ncbi.nlm.nih.gov/pubmed/31591341

- Other Factors:
  - psychosocial stressors,
  - poor diet, (western diet, sugar)
  - physical inactivity,
  - obesity,
  - smoking,
  - Insomnia, OSA
- vitamin D deficiency.

… depression is an inflammatory disease, but where does the inflammation come from?

Berk M, BMC Med. 2013 Sep 12
https://www.ncbi.nlm.nih.gov/pubmed/24228900

82

Anti-inflammatory = antidepressant?

- **Antidepressants are anti-inflammatory**
  - Medical hypothesis…***anti-inflammatory actions of antidepressants***
    Inflammation in Depression and the Potential for Anti-Inflammatory Treatment

    Kohler O, Curr Neuropharmacol. 2016
    https://www.ncbi.nlm.nih.gov/pubmed/27640518
- Curcumin… a plant polyphenol with potent anti-inflammatory, antioxidant, and neuroprotective properties, as a novel antidepressant.
  - "**Curcumin appears to be safe, well-tolerated, and efficacious among depressed patients**"

    Ng QX, J Am Med Dir Assoc. 2017 Jun 1
    https://www.ncbi.nlm.nih.gov/pubmed/28236605

83

Anti-inflammatory treatments

- **Anti-inflammatory therapy? PROMISING**
  - **Curcumin? Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease.**
    - studies have shown that Aβ metabolism is altered by curcumin
    - animal studies report that curcumin may influence brain function and the development of dementia,

    Goozee KG, Br J Nutr. 2016 Feb 14
    https://www.ncbi.nlm.nih.gov/pubmed/26652155
  - **Resveratrol and Other Polyphenols → preventive effects on common Brain Age-Related Diseases**

    Sarubbo F, Curr Med Chem. 2017
    https://www.ncbi.nlm.nih.gov/pubmed/28738770
  - **Modulation of Inflammation as a Way of Delaying Alzheimer's Disease Progression: The Diet's Role.**

    Businaro R, Curr Alzheimer Res. 2018 Feb 22
    https://www.ncbi.nlm.nih.gov/pubmed/28847284

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Anti-inflammatory = antidepressant?

- Anti-inflammatory diet
  - Fish oils. Omega 3 and depression
    "…thought to induce an antidepressant effect, including anti-inflammatory action and direct effects on membrane properties".
    Burhani MD, J Integr Neurosci. 2017
    https://www.ncbi.nlm.nih.gov/pubmed/29254106
  - Dietary Polyphenols and antioxidants
    - Colorful berries, fruits:
    - Studies show protective effect in different neurological and mental disorders.
      - modulate monoaminergic neurotransmission in the brain … potential antidepressant-like activity

      Pathak L, Expert Opin Investig Drugs. 2013 Jul;
      https://www.ncbi.nlm.nih.gov/pubmed/23642183

85

Diet and inflammation

- Diet:
  - **Western diet is pro-inflammatory**
    - Processed grains, sugar, fried foods, red meat
  - **Anti-Inflammatory Diet in Clinical Practice: A Review**
    - Specific foods effect inflammatory pathways within the body.
    - anti-inflammatory diet plan:
      - Eat anti-inflammatory food
        - focus on eating whole, plant-based foods that are rich in healthy fats and phytonutrients
      - Maintains stable glycemic response.
    - avoid foods that are proinflammatory

  Ricker MA, Nutr Clin Pract. 2017 Jun
  https://www.ncbi.nlm.nih.gov/pubmed/28350517

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Anti-inflammatory agents **for depression**

Systematic Review and meta-analysis

- Randomized controlled trials
- **Efficacy and safety of anti-inflammatory agents for the treatment of major depressive disorder: a systematic review and meta-analysis of randomized controlled trials.**
- OUTCOMES:
  - anti-inflammatory agents reduced depressive symptoms in MDD compared with placebo.
  - NSAIDs, omega-3 fatty acids, statins and minocyclines, → significant antidepressant effects for major depressive disorder (MDD).

  Bai S, et al. J Neurol Neurosurg Psychiatry. 2019 Oct 28.
  https://www.ncbi.nlm.nih.gov/pubmed/31658959

87

anti-inflammatory adjuvant therapy **for schizophrenia**

- Significant overall effects were found for anti-inflammatory agents for reducing total, positive and negative symptom scores in the Positive and Negative Syndrome Scale.
- General functioning was significantly enhanced by overall anti-inflammatory agents.
- There were no significant differences in side effects compared with placebo.
- Baseline total Positive and Negative Syndrome Scale score and illness duration were identified as moderating factors in the effects of anti-inflammatory augmentation on psychiatric symptom improvements.
  - Cho M, Aust N Z J Psychiatry. 2019 Aug
    https://www.ncbi.nlm.nih.gov/pubmed/30864461

88

Antidepressants
questionable efficacy and compliance

Antidepressants do perform better than placebo, generally

- ***Poor tolerability and compliance*** is widespread in both primary care and psychiatric practice,
  - ***Comparative efficacy and acceptability of 21 antidepressant drugs***
    Cipriani A, Lancet. 2018 Apr 7
    https://www.ncbi.nlm.nih.gov/pubmed/29477251
  - ***Compliance and acceptance in antidepressant treatment.***
    Demyttenaere K, Int J Psychiatry Clin Pract. 2001
    https://www.ncbi.nlm.nih.gov/pubmed/24936994
  - ***Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents***
    no clear advantage for antidepressants in this group
    Cipriani A, Lancet. 2016 Aug 27
    https://www.ncbi.nlm.nih.gov/pubmed/27289172

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Nutritional support
to improve antidepressant efficacy

- **Zinc supplements** may improve outcomes of antidepressants
  The efficacy of zinc supplementation in depression
  Lai J, J Affect Disord. 2012 Jan
  https://www.ncbi.nlm.nih.gov/pubmed/21798601
  Effects of zinc supplementation on efficacy of antidepressant therapy evidence supports the use of zinc supplements with antidepressants
  Ranjbar E., Nutr Neurosci. 2014 Feb
  https://www.ncbi.nlm.nih.gov/pubmed/23602205
- **Multivitamin + Trace minerals:**
  - Increased mood and improved serotonin levels
    Muss C, Neuro Endocrinol Lett. 2016
    https://www.ncbi.nlm.nih.gov/pubmed/26994381
- **Vitamin D** for PMS mood symptoms
  - safe, effective, ---improving the quality of life in young women with PMS and severe hypovitaminosis
    Tartagni M, J Pediatr Adolesc Gynecol. 2016 Aug
    https://www.ncbi.nlm.nih.gov/pubmed/26724745

NOTE: consider targeted supplementation based on individual nutritional assessment, including laboratory (such as Functional micronutrient assessment profiles)

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Natural add-on therapies to antidepressants

REVIEW ARTICLE: (2019)
Natural health products, dietary minerals and over-the-counter medications as add-on therapies to antidepressants in the treatment of major depressive disorder: a review

Evidence supports use of safe adjunct therapeutics and nutraceuticals

- S-Adenosyl-L-Methionine; *(SAMe)*
- folate; *(methyl-folate, 5-MTHF)*
- omega-3 fatty acids;
- curcumin;
- N-acetylcysteine; *(NAC)*
- saffron;
- 5-hydroxytryptophan; *(5-HTP)*

Dome P. Brain Res Bull. 2019 Mar
https://www.ncbi.nlm.nih.gov/pubmed/30599219

91

Ethical use of natural products and supplements

- clinical concerns:
  - the lack of scientific support for their efficacy
  - Questions regarding patient safety,
    - Side effects?
    - Known and unknown drug interactions
  - Questions about product purity,
    - quality assurance?
- Comments:
  Natural Products in Neurodegenerative Diseases: A Great Promise but an Ethical Challenge
  Di Paolo M, Int J Mol Sci. 2019 Oct 18
  https://www.ncbi.nlm.nih.gov/pubmed/31635296

- Argument FOR use
  - Preliminary research including some meta-analyses and research reviews, support safe use of natural products natural Questions regarding patient safety,
  - Potential risks appear to be relatively small compared to conventional meds,
    - Potential benefits outweigh small risks,
  - Most side-effects and nutrient- and herb-/drug interactions are known by integrative physicians and can be avoided or monitored
  - Preference for high-quality products, independent ingredient assays, quality assurance, including physician-only (and physician-preferred) brands

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Nutritional Supplements for depression

- SAMe
- 5-HTP
- Omega 3 oils
  - Fish oil, vs Krill oil
- Curcumin
- Vitamins:
  - Folate,
  - B6,
  - B12

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SAMe for depression?

- **S-adenosyl methionine (SAMe) for depression in adults.**
- systematic review included eight trials comparing SAMe with either placebo, imipramine, desipramine or escitalopram.
  - **Lacks quality evidence of efficacy** in this review article:
  - Galizia I, Cochrane Database Syst Rev. 2016 Oct 10 https://www.ncbi.nlm.nih.gov/pubmed/27727432
  - **Promising but limited evidence** Sharma A. J Clin Psychiatry. 2017 Jun https://www.ncbi.nlm.nih.gov/pubmed/28682528

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Common interactions + precautions

- SAMe
- 5-HTP
- St John's Wart
- Herb-Drug interactions checker:
  - https://www.drugs.com/drug_interactions.html
  - Common herbal interactions https://nccih.nih.gov/health/providers/digest/herb-drug

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SAMe interactions and precautions

Precaution:

- **bipolar disorder, OCD, Anxiety spectrum:**
  - SAMe might increase anxiety and mania.
- Side-effects:
- **Side effects** from SAMe are ***rare*** and if they occur, usually ***mild***
  - Nauseam upset stomach
  - Mild insomnia
  - Dizziness
  - Irritability
  - Anxiety
  - Sweating
  - Constipation
  - Diarrhea

Possible drug interactions include:

- ***Antidepressants* and other drugs and supplements that increase levels of serotonin.** (serotonin syndrome).
- **Antipsychotics.** Risk serotonin syndrome.
- **Amphetamines.** risk of serotonin syndrome.
- **Dextromethorphan.** risk of serotonin syndrome.
- **Narcotics.** meperidine (Demerol) or tramadol (Ultram, ConZip) risk of serotonin syndrome.
- **St. John's wort.** Risk serotonin syndrome.

https://www.drugs.com/mcp/same

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5-HTP and depression

- As a serotonin precursor, 5-hydroxytryptophan has long been used as a nonpharmacological treatment for depression.
- **Comparative study of efficacy of 5-HTP and fluoxetine in patients presenting with first depressive episode**
  - 5-HTP and Prozac groups bth showed significant and nearly equal reduction in HAM-D scores beginning at week 2 and continuing through week 8
  - 5-HTP has definitely got antidepressant effect in patients of depression. Antidepressant effect was seen within 2weeks of treatment and was apparent in all degrees of depression.

    Jangid P. Asian J Psychiatr. 2013 Feb
    https://www.ncbi.nlm.nih.gov/pubmed/23380314
- **Adjunctive 5-Hydroxytryptophan for Treatment-Resistant Depression:**
  - Treatment-resistant depression (TRD) is a major unmet need.
  - Interestingly, elevating 5-hydroxytryptamine appears to treat TRD.
  - Adjunctive administration of **5-hydroxytryptophan (5-HTP)** safely elevated 5-hydroxytryptamine beyond effect of Serotonin transporter (SERT) inhibitors
    - Many SSRI's exert their influence via SERT
    - Authors recommend 5-HTP sustained-release for better pharmacodynamics
  - **adjunct 5-HTP SR could be an important new treatment for TRD.**

    Jacobsen JPR, Trends Pharmacol Sci. 2016 Nov
    https://www.ncbi.nlm.nih.gov/pubmed/27692695

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5-HRT precautions and interactions

- Evidence supports its safety when taken for a short period of time.
- Potential side-effects: (unlikely)
  - drowsiness;
  - nausea, vomiting, stomach pain, heartburn;
  - diarrhea;
  - loss of interest in sex.
  - severe tingling or numbness;
  - skin rash, bruising, fever; or
  - muscle pain or weakness.
- **Drug interactions**
  - SSRIs/antidepressants that increase serotonin
  - Risk serotonin syndrome
- Interactions checker
  https://www.drugs.com/drug-interactions/5-hydroxytryptophan,5-http.html

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St John's Wart precautions

hypericum

LIKELY SAFE when taken by mouth for up to 12 weeks. Some evidence suggests it can be used safely for over one year.

- Side effects:
  - trouble sleeping,
  - vivid dreams,
  - difficulty sitting still, nervousness,
  - irritability,
  - stomach upset,
  - tiredness,
  - dry mouth,
  - dizziness,
  - headache,
  - skin rash, tingling
  - Diarrhea

St. John's wort in the morning or take a lower the dose if it seems to be causing sleep problems.

- Other risks: https://www.webmd.com/vitamins/ai/ingredientmono-329/st-johns-wort

Do not combine St. John's Wort with these medications:
(interactions; serotonin syndrome risk)

- selective serotonin reuptake inhibitors (SSRIs)
- tricyclic antidepressants (TCAs)
- monoamine oxidase (MAO) Inhibitors.
- nefazodone.
- triptans for migraine.
- dextromethorphan.
- warfarin.
- birth control pills.

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Favorite Herbal antidepressants
Saffron

- SAFFRON, (Crocus sativus), the spice,
  - Traditional Persian spice used historically as mood elevator
  - Review of Research data (2018) supports antidepressant and anti-anxiety properties of saffron, clinical trials demonstrated that saffron and its active constituents possess antidepressant properties:
    - Actions similar to those of current antidepressant medications such
      - Such as fluoxetine (Prozac), imipramine (Tofranil) and citalopram (celexa)
        - ,with fewer reported side effects.
- **CONCLUSION:**

  Saffron may exert antidepressant effects and represents an efficacious and safe treatment

  Shafiee M, J Affect Disord. 2018 Feb
  https://www.ncbi.nlm.nih.gov/pubmed/29136602
- **CONCLUSION:**
  - affron® increased mood, reduced anxiety and managed stress without side effects, offering a natural alternative to standard treatments.
    - Kell G, Complement Ther Med. 2017 Aug
      https://www.ncbi.nlm.nih.gov/pubmed/28735826

100

Saffron vs fluoxetine

Prozac (fluoxetine)

- Double-blind randomized trial
  - 40 adult outpatients w **major depression**
  - Rx 15 mg saffron 2x/day
  - vs Prozac 10 mg 2x/day
  - x 8 weeks

Performed as well as fluoxetine

Noorbala AA, J Ethnopharmacol. 2005 Feb 28
https://www.ncbi.nlm.nih.gov/pubmed/15707766

101

Saffron (Crocus sativus)
vs placebo and **Fluoxetine**

- **Systematic review and meta-analysis, (2019)**
  - **Crocus sativus vs placebo and Fluoxetine** in treating depression
  - Antidepressant effects are better than placebo and comparable to fluoxetine
    - Khaksarian M, Psychol Res Behav Manag. 2019
      https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6503633/

102

Saffron vs **Celexa** (citalopram)

Crocus sativus L. vs Citalopram in the Tx of MDD with Anxiety

- 66 patients with major depression + anxiety
- Rx saffron (30 mg/day) or citalopram (40 mg/day)
- x 6 weeks.
- Outcomes: saffron effect in depression, comparable to citalopram

Ghajar A, Pharmacopsychiatry. 2017 Jul; https://www.ncbi.nlm.nih.gov/pubmed/27701683

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Saffron vs imipramine

Comparison of Crocus sativus L. and imipramine in the treatment of depression: double-blind randomized trial

- **30 pts w MDD** double-blind,
- Rx: saffron 30 mg/day
- Vs imipramine 100 mg/day
- x 6-week
- **Outcomes: antidepressant effects similar to imipramine, fewer side effects**
  - imipramine's side effects anticholinergic effects such as dry mouth and also sedation were observed more often that was predictable.

Akhondzadeh S, BMC Complement Altern Med. 2004 Sep 2 https://www.ncbi.nlm.nih.gov/pubmed/15341662

104

Meta-analysis: (2018)
Saffron effective in MDD

Seven studies were included in this meta-analysis

- confirmed efficacy comparable to synthetic antidepressants.
- Saffron was safe without serious adverse events reported

Yang X, Neuropsychiatr Dis Treat. 2018 May 21 https://www.ncbi.nlm.nih.gov/pubmed/29849461

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Other favorite herbs for mood:

Ashwaganda

(withania somnifera)

anti-depressant and anxiolytic effects

- **Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides:**
  - **Traditional Ayurvedic herb Used to stabilize mood and behavior**
  - **Rat study:**
    - **Withania** induced an ***anxiolytic effect***, comparable to that produced by lorazepam,.
    - also exhibited an ***antidepressant effect***, comparable with that induced by imipramine,
    - The investigations support the use of WS as a mood stabilizer in clinical conditions of anxiety and depression in Ayurveda.

Bhattacharya SK, Phytomedicine. 2000 Dec
https://www.ncbi.nlm.nih.gov/pubmed/11194174

106

Ashwaganda

helps relieve anxiety

- **An alternative treatment for anxiety:**
  a systematic review of human trial results reported for the Ayurvedic herb ashwagandha (Withania somnifera).
  - Systematic review of the literature,
    - related to anxiety and stress
  - five human trials met inclusion criteria.
  - OUTCOMES demonstrated improvements (> placebo) in anxiety or stress scales
    - Significantly better than placebo in most cases

Pratte MA, J Altern Complement Med. 2014 Dec
https://www.ncbi.nlm.nih.gov/pubmed/25405876

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Ashwaganda

helps relieve depression & anxiety in schizophrenics

- **Effects of a standardized extract of Withania somnifera (Ashwagandha) on depression and anxiety symptoms in persons with schizophrenia**
  - 12-week, randomized, placebo-controlled, double-blind study.
  - 66 patients w anxiety and depression, Active treatment was with 1,000 mg of standardized withania extract (WSE)
  - Effects favored WSE over placebo … for depression and anxiety-depression scores. Adverse events were mild and transient.

Gannon JM, Ann Clin Psychiatry. 2019 May
https://www.ncbi.nlm.nih.gov/pubmed/31046033

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Ashwaganda
helps relieve stress

- **STUDY:**
  An investigation into the stress-relieving and pharmacological actions of an ashwagandha (Withania somnifera) extract: A randomized, double-blind, placebo-controlled study.
  - placebo vs 240mg of a standardized ashwagandha extract
  - Outcomes were: depression and anxiety scales, PLUShormonal changes in cortisol, DHEA-S, and testosterone.
- **OUTCOMES:** statistically significant reduction in anxiety; and lowered depression scotes, and cortisol reductions

Lopresti AL, Medicine (Baltimore). 2019 Sep
https://www.ncbi.nlm.nih.gov/pubmed/31517876

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Pharmacologic overview of Ashwaganda (withania somnifera)

Studies indicate multiple health benefits:

- anti-microbial,
- anti-inflammatory,
- anti-tumor,
- anti-stress,
- neuroprotective, neuroregenerative
- cardioprotective,
- anti-diabetic
- Anti-oxidative
- Mitochondrial protective

Dar NJ, Cell Mol Life Sci. 2015 Dec
https://www.ncbi.nlm.nih.gov/pubmed/26306935

110

Resistance Training Exercise
helps depression

Effects of a 9-month resistance training intervention on quality of life, sense of coherence, and depressive symptoms in older adults

CONCLUSION:

- Resistance training is beneficial for environmental quality of life and sense of coherence. Attending resistance training twice a week seems to be the most advantageous for these aspects of psychological functioning.

Kekäläinen T, Qual Life Res. 2018 Feb
https://www.ncbi.nlm.nih.gov/pubmed/29124498

111

Naturopathic care for anxiety:

STUDY: a randomized controlled trial

Employees with moderate to severe anxiety of longer than 6 weeks randomized to receive care over a period of 12 weeks.

- ***naturopathic care* (NC)** (n = 41)
- or ***standardized psychotherapy intervention* (PT)** (n = 40)

- **Participants in the NC group** received:
  - **dietary counseling,**
  - ***deep breathing relaxation*** techniques,
  - a standard **multi-vitamin,**
  - ***ashwagandha*** *(Withania somnifera)*
    - (300 mg b.i.d. standardized to 1.5% with anolides, prepared from root).
- ***Participants in PT group*** received:
  - psychotherapy,
  - and matched deep breathing relaxation techniques,
  - placebo. Supplements

- **OUTCOME**
  - Anxiety scores were lower in both groups,
  - Significantly greater reductions in anxiety in NC group vs PT group
    - 56.5% reduction in anxiety in the NC group,
      - 30.5% in PT group
  - Significant improvements ***quality of life measures*** in the NC group as compared to PT

Cooley K. PLoS One. 2009 Aug 31

Full-text: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729375/

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Assessments in anxiety spectrum

Consider medical factors

- Hyperthyroid
- Hyperactive-adrenal
- Hyperventilation syndrome
  - Respiratory alkalosis vs seizure
- Use of Drugs, stimulants
- Dysbiosis, Candida infections

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Favorite herbs for anxiety

- Passiflora
- Ziziphus
- Kava Kava
- Valerian

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Passion Flower
(Passiflora incarnata)

- Traditionally used as anxiolytic, and hypnotic for sleep
  - **Passiflora incarnata L.: evaluation of clinical trials:** preclinical experiments indictate multiple benfits, including:
    - anxiolytic, sedative, antitussive, antiasthmatic, and antidiabetic activities.
    - The plant has a good safety profile.

    requires more rigorous research methods
    https://www.ncbi.nlm.nih.gov/pubmed/24140586
  - Sedative properties w no record of toxicity: https://www.ncbi.nlm.nih.gov/pubmed/31643352

115

Rx passiflora
surgical stress and anxiety

- Used pre- elective surgery,
  - for pre- and post- surgical anxiety, pain, compare ***passiflora vs melatonin***

    Rokhtabnak F. Anesth Pain Med. 2016 Oct 2 https://www.ncbi.nlm.nih.gov/pubmed/28920038
- Used pre-dental extraction:
  - Passiflora incarnata showed anxiolytic effect similar to midazolam, and was safe and effective for conscious sedation in adult patients who underwent molar extraction
    - Passiflora showed little or no interference with memory function

    Dantas LP. Med Oral Patol Oral Cir Bucal. 2017 Jan 1; https://www.ncbi.nlm.nih.gov/pubmed/27918731

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zizyphus
for anxiety

- Traditional Chinese Medicine herbal
  - Commonly used in formula Suanzaoren tang
  - Often used for anxiety and insomnia
- Appears to be safely used in combination with anxiolytic drugs, to improve outcomes
- **Modified Suanzaorentang Had the Treatment Effect for Generalized Anxiety Disorder for the First 4 Weeks of Paroxetine Medication: A Pragmatic Randomized Controlled Study**
  - Paroxetine does not show satisfactory therapeutic for the first 2-4 weeks of medication.
    - Diazepam is always concurrently used although it has some shortcomings such as physical dependence and withdrawal reactions
  - **NOTE: in this study, in the first 4 weeks, combining modified Suanzaorentang formula w paroxetine improved anxiety scores better than paroxetine alone, and as well as diazepam,**

Song MF, Evid Based Complement Alternat Med. 2017; https://www.ncbi.nlm.nih.gov/pubmed/28553362

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Zizyphus: for sleep

- Jujube fruit or seed
- **Treatment for Insomnia**
  - **Traditional Chinese herbal zizyphus formula SUANZAOREN TANG (FSZR)**
- Meta-analysis of high-quality RCTs showed:
  - FSZR was superior to placebo ($P < 0.01$);
  - FSZR plus Diazepam was superior to Diazepam alone ($P < 0.05$);
  - FSZR caused fewer side effects than that of Diazepam.
- In conclusion, Suanzaorentang could be an alternative treatment for insomnia in clinic. FSZR exerted sedative and hypnotic actions mainly through the GABAergic and serotonergic system.
  - Zhou QH, Front Pharmacol. 2018 Feb 9 https://www.ncbi.nlm.nih.gov/pubmed/29479317

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Zizyphus health benefits

- **Therapeutic effects of Ziziphus jujuba Mill. fruit in traditional and modern medicine: a review.**
  - **Other health benefits:** antibacterial, antioxidant, sedative, hepato-protective, anti-hyperglycemic, and anti-hyperlipidemic activities

    Sobhani Z, Med Chem. 2019 Oct 31 https://www.ncbi.nlm.nih.gov/pubmed/31670624
- Note: **Anticancer activity of Ziziphus mauritiana roots against human breast cancer cell line.**
  - Extract of the roots of plant exhibited significant anticancer activity (70%) against the breast cancer cell line

    Batool M, Pak J Pharm Sci. 2019 Jul: https://www.ncbi.nlm.nih.gov/pubmed/31608895
- **side effects or drug interactions have not been reported**

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Kava Kava for Anxiety

- **Kava Kava for anxiety symptoms:**
  - **A systematic review and analysis of randomized clinical trials**
    - Kava Kava was shown to be more effective than placebo in 3 of the 7 trials.
    - Adverse events were shown to be the same as placebo (P = 0.574),
    - laboratory values analyzing hepatotoxicity were no different when compared to baseline except in two studies.

    Smith K. Complement Ther Clin Pract. 2018 https://www.ncbi.nlm.nih.gov/pubmed/30396607
  - Most practitioners recommend Kava for acute only, or SHORT TERM use, < 8 weeks

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Kava Kava interactions?

- Kava, ***Piper methysticum***
- Potential INTERACTIONS:
  - Few studies are mixed regarding interaction potential of kava.
  - potential for use of kava + CNS depressants can increase risk of drowsiness and motor reflex depression.
  - However, a 2012 review concluded that kava supplements, when consumed per product label recommendations, are not likely to affect the efficacy or toxicity of medications.
- Precautions, RISKS:
  Kava has been reported to have hepatotoxic effects.
  Long-term and/or heavy use of kava may result in jaundice
  Kava has been associated with several cases of dystonia.

  https://nccih.nih.gov/health/providers/digest/herb-drug

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Kava lactones and the kava-kava controversy.

- Kava-kava is a traditional beverage of the South Pacific islanders and has had centuries of use without major side effects
- Standardized extracts of kava-kava produced in Europe have led to many serious side-effects
  - Traditional use was oral extraction shewing on the root
  - The extraction process (aqueous vs. acetone in the two types of preparations) is responsible for the difference in toxicity
  - Acetone extractions loose glutathione content, which is hepatoprotective

  Whitton PA, Phytochemistry. 2003
  https://www.ncbi.nlm.nih.gov/pubmed/13679089
- Use NAKAMAL Kava process .. Traditional water-extraction

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Other favorite remedies for anxiety

- Essential oils
  - Lavender
  - Bergamot
  - Lemon balm
- CBD
- Amino acids
  - Theanine
  - Glycine

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Essential oils
for stress and anxiety

- Consider using an aerosol diffuser, or spray mist, aromatherapy
- Widely used as a complementary therapy for anxiety, insomnia, convulsion, pain, and cognitive deficit symptoms
  - promising source for modulation of the GABAergic system and sodium ion channels.
    - Wang Z, Molecules. 2018 May 2 https://www.ncbi.nlm.nih.gov/pubmed/29724056
  - **Using therapeutic essential oils to support the management of anxiety**

Lowring LM, J Am Assoc Nurse Pract. 2019 Oct; https://www.ncbi.nlm.nih.gov/pubmed/31169787

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Favorite essential oils for anxiety

- **Lavender**, is one of the most powerful anxiolytic essential oils,
  - STUDY: wisdom tooth removal:
    - **reduces peri-operative anxiety**
      Karan NB, Physiol Behav. 2019 Nov 1 https://www.ncbi.nlm.nih.gov/pubmed/31505191
  - Used in capsules, oral
    reduces anxiety related symptoms and sleep disturbances in MDD patients

    May be combined a antidepressant medication
    Fillier M, Complement Ther Med. 2014 Feb;22 https://www.ncbi.nlm.nih.gov/pubmed/24559818
  - **Effective in oral capsules (80 mg):** *effects on GAD similar to lorazepam*
    Kasper S, Int J Psychiatry Clin Pract. 2013 Nov https://www.ncbi.nlm.nih.gov/pubmed/23808618
  - Efficacy of orally administered Silexan in patients with **anxiety-related restlessness and disturbed sleep**--A randomized, placebo-controlled trial.
    The study confirms the calming and anxiolytic efficacy of Silexan.
    Kasper S, Eur Neuropsychopharmacol. 2015 Nov https://www.ncbi.nlm.nih.gov/pubmed/26293583

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Favorite essential oils for anxiety

- **Bergamot**
  - Bergamot essential oil: aromatherapy commonly used **for psychological stress and anxiety**
    - Scores for indicators of stress (salivary cortisol, HRV) improved from inhalation vapors of bergamot vs rest and water alone
      - Bergamot exerts psychological and physiological effects in a relatively short time.
        - Watanabe E, Forsch Komplementmed. 2015 https://www.ncbi.nlm.nih.gov/pubmed/25824404
  - **Bergamot (Citrus bergamia) Essential Oil Inhalation Improves Positive Feelings in the Waiting Room of a Mental Health Treatment Center:**
    - Fifteen minutes of bergamot essential oil exposure improved participants' positive feelings compared with the control group (17% higher).
      - **Han X,** Phytother Res. 2017 May https://www.ncbi.nlm.nih.gov/pubmed/28337799

126

Favorite essential oils for anxiety

- **Lemon balm**
  - Melissa officinalis L. has been shown as an anti-stress and anxiolytic agent.: inhibits GABA metabolism
    Combination EO may improve insomnia and its comorbid depression and anxiety.
    - Ranjbar M, Integr Med Res. 2018 Dec https://www.ncbi.nlm.nih.gov/pubmed/30591886
  - ORAL tablet dosing: shown to relieve stress effects
    - Cases J, Med J Nutrition Metab. 2011 Dec https://www.ncbi.nlm.nih.gov/pubmed/22207903
- **Essential oils and anxiolytic aromatherapy**
  - Setzer WN, Nat Prod Commun. 2009 Sep https://www.ncbi.nlm.nih.gov/pubmed/19831048

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Sleep disorders

- Consider medical conditions
- Sleep apnea
- Caffeine or stimulant intake…
- Sleep hygiene
  - Night-lights
  - Laptops
  - EMFs

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Favorite Sleep remedies

- Zizifus (Suanzaoren tang)
- 5 HTP
- Melatonin
- CBD
- Glycine
- Magnesium

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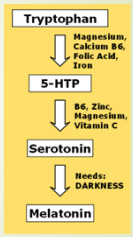
5-Hydroxytryptophan (5-HTP) sleep, depression,

- **5-Hydroxytryptophan (5-HTP**) is the intermediate metabolite of the essential amino acid L-tryptophan (LT) in the biosynthesis of serotonin
  - therefore it may be taken with meals without reducing its effectiveness.
  - 5-HTP is well absorbed (70%) from an oral dose,
  - It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin.
- **5-HTP** has been shown to be effective in treating a wide variety of conditions:
  - **depression, fibromyalgia, binge eating associated with obesity, chronic headaches, and insomnia**.

Birdsall TC, Altern Med Rev. 1998 Aug
https://www.ncbi.nlm.nih.gov/pubmed/9727088



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5-HTP combinations

- **5-HTP combines well w other remedies**
  - **amino acid neurotransmitters:**
    - **Glycine, taurine, GABA, theanine, inositol**
  - **Melatonin**
  - **herbs**
- **GABA + 5-HTP**
  combined γ-aminobutyric acid (GABA) and 5-hydroxytryptophan (5-HTTP:
  - mixture modulates sleep quality
  - > individual amino acids .. Via both GABA and serotonin signaling
    - Hong KB, Life Sci. 2016 Apr 1
      https://www.ncbi.nlm.nih.gov/pubmed/26921634

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5-HTP precautions

- 5-HTP is **generally regarded SAFE** when taking by mouth appropriately.
  - 5-HTP has been used safely in doses up to 400 mg daily for up to one year.
- Potential side effects of 5-HTP include:
  - Digestive: heartburn, stomach pain, nausea, vomiting, diarrhea,
  - drowsiness,
  - sexual problems,
  - muscle problems
- 5-HTP is **POSSIBLY UNSAFE** when taken by mouth in large doses.
  - Doses from 6-10 grams daily have been linked to severe stomach problems and muscle spasms.
- **Major Interaction**
  - **Drugs that increase serotonin: SSRIs, MAO-Is**
    - **Risk Serotonin syndrome;** Symptoms include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea. heart problems, shivering, and anxiety
- **Moderate interaction**
  - **Carbidopa, dextromorphan (Robitussin DM), Demerol and other meds: check for drug interactions:**
    https://www.drugs.com/drug-interactions/5-hydroxytryptophan,5-htp.html

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Melatonin
for sleep and mood

- pineal gland releases melatonin at night
- Melatonin is considered safe, well-tolerated in short and long-term use
- → synchronizes the circadian rhythms,
- → improves the onset, duration and quality of sleep.
- Effective for
  - insomnia,
  - sleep-related breathing disorders,
  - hypersomnolence,
  - circadian rhythm sleep-wake disorders and parasomnias.
- Few side effects.
  - Xie Z, Neurol Res. 2017 Jun
    https://www.ncbi.nlm.nih.gov/pubmed/28460563

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Melatonin
antioxidant, neuroprotective
psychiatric disorders

- melatonin has **neuroprotective effects:**
  may be useful in prevention of Alzheimer's and neurodegenerative diseases
  - affects neuroplasticity, potential antidepressant properties.
    Lee JG, Brain Sci. 2019 Oct 21
    https://www.ncbi.nlm.nih.gov/pubmed/31640239
- Melatonin as add-on therapying **psychiatric disorders w insomnia**
  - in mood disorders
    - bipolar disorder, major depressive disorder, seasonal affective disorder),, ADHD, peri-surgical anxiety, schizophrenia.
    - somatoform disorders, fibromyalgia, pain
      - Geoffroy PA, Encephale. 2019 Nov
        https://www.ncbi.nlm.nih.gov/pubmed/31248601

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Cannabidiol (CBD)
for stress and anxiety disorders

- existing preclinical evidence strongly supports CBD, administered acutely, as a treatment for:
  - ***generalized anxiety disorder, panic disorder, social anxiety disorder,***
  - ***obsessive-compulsive disorder,***
  - ***post-traumatic stress disorder***
- evidence from human studies supports CBD treatment for multiple anxiety disorders
- Tolerated at higher dose: Does NOT product anxiogenic effects
- PTSD: enhances the extinction and blocking the reconsolidation of persistent fear memories.
  - Blessing EM, Neurotherapeutics. 2015 Oct
    https://www.ncbi.nlm.nih.gov/pubmed/26341731

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Safety of medial cannabis?

- **How effective and safe is medical cannabis as a treatment of mental disorders?**
  - **A systematic review. (1629 participants)**
- THC- and CBD-based medicines,
  - given as adjunct to pharmaco- and psychotherapy
  - → improvements of several symptoms of mental disorders,
    - but not with remission.
- Side effects:
  - Side effects occurred, but severe adverse effects were mentioned in single cases only.

Hoch E, Eur Arch Psychiatry Clin Neurosci. 2019 Feb
https://www.ncbi.nlm.nih.gov/pubmed/30706168

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Cannabis and risk of psychosis

- **Cannabis Use and the Risk of Psychosis and Affective Disorders**
- High THC is risky:
  (THC, the main psychoactive ingredient of cannabis)
  - interacts with genetic predisposition and perhaps other environmental risk factors.
  - **heavy use of high-THC/low-CBD types of cannabis increases the risk of psychosis**
    - merits public health education.

Sideli L, J Dual Diagn. 2019 Oct 24
https://www.ncbi.nlm.nih.gov/pubmed/31647377

- Review: **Cannabis use and psychosis:**
  - psychotic illness arises more frequently in cannabis users compared to non-users,
  - dose-dependent risk of developing psychotic illness,
  - users have an earlier onset of psychotic illness compared to non-users.
  - use was also associated with increased relapse rates, more hospitalizations and pronounced positive symptoms in psychotic patients.

Hasan A, Eur Arch Psychiatry Clin Neurosci. 2019 Sep 28
https://www.ncbi.nlm.nih.gov/pubmed/31563981

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CBD may have neuro-modulating benefits

- **CBD as an anti-psychotic drug?**
  - Reduces many of the anxiety and psychotic-like effects of THC
  - **".. this cannabinoid can be a safe and well-tolerated alternative treatment for schizophrenia"**

Zuardi AW, Braz J Med Biol Res. 2006 Apr
https://www.ncbi.nlm.nih.gov/pubmed/16612464

- Cannabidiol (CBD), the other important ingredient of traditional cannabis, ameliorates the psychotogenic effects of THC
  - anti-psychotic,
  - anti-epileptic,
  - anxiolytic
  - anti-depressant
  - anti-oxidant,
  - anti-inflammatory

Elsaid S, Prog Mol Biol Transl Sci. 2019
https://www.ncbi.nlm.nih.gov/pubmed/31601406

- **Hi CBD/ Low THC cannabis**
  CBD does not have the hallucinogenic effects of THC even at high doses

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CBD side effects, precautions, interactions

Potential side effects:

- Agitation
- chills
- cough
- fever
- hoarseness
- irritability
- lower back or side pain
- painful or difficult urination
- unusual drowsiness, sluggishness

- https://www.drugs.com/sfx/cannabidiol-side-effects.html

Multiple possible interactions:

- See drug interaction checker:
  - https://www.drugs.com/sfx/cannabidiol-side-effects.html
- **AVOID combining w drugs that cause CNS depression**
  - **opioids**
- Some potential drug interactions:
  - Alcohol, and other intoxicants
  - Naproxen (Aleve) , acetaminophen (Tylenol)
  - Benedryl
  - Cymbalta
  - Pregabalin
  - Zoleft
  - Zertec

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Theanine
Calming Amino acids

- **Theanine**
  - **Effects of L-Theanine on Stress-Related Symptoms and Cognitive Functions, RCT**
    - 200 mg dose
    - Scores improved for sleep latency, sleep disturbance, and use of sleep medication
      - after L-theanine administration, compared to the placebo administration
    - promotes mental health w stress-related ailments and cognitive impairments.
      - Hidese S, Nutrients. 2019 Oct 3 https://www.ncbi.nlm.nih.gov/pubmed/31623400
  - STUDY:
    - Conclusions: (l-theanine administration 8-week) is safe and has multiple beneficial effects on **depressive symptoms, anxiety, sleep disturbance and cognitive impairments in patients with MDD.**
    - **Hidese S,** Acta Neuropsychiatr. 2017 Apr https://www.ncbi.nlm.nih.gov/pubmed/27396868

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Glycine
Calming Amino Acid

- **Glycine**
  - **G**lycine has the property to enhance the ***quality of sleep and neurological functions***
  - Other Health Benefits:
    - effectual in treating metabolic disorders in patients with **cardiovascular diseases, several inflammatory diseases, obesity, cancers, and diabetes.**

Razak MA, Oxid Med Cell Longev. 2017 https://www.ncbi.nlm.nih.gov/pubmed/28337245

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Magnesium, sleep, and cognitive function

- **Magnesium supplements**
  - improve subjective measures of insomnia in elderly
    - score, sleep efficiency,
    - Sleep time
    - sleep onset latency,
    - early morning awakening,
    - Abbasi B, J Res Med Sci. 2012 Dec; https://www.ncbi.nlm.nih.gov/pubmed/23853635
  - ***Magnesium – L- Threonate (Neuro-Mag)***
  - is the most appropriate Mg salt and dose for oral treatment that strengthens cholinergic system and improves brain related functions

    Sadir S, Pak J Pharm Sci. 2019 Jan, https://www.ncbi.nlm.nih.gov/pubmed/30829204

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Steady Pink noise another sleep remedy

- Pink noise exposure group showed significant enhancement in the percentage of stable sleep time compared to the control group
  - based on the analysis of electrocardiography (ECG) signal with cardiopulmonary coupling approach. HRV
    - reduced brain wave complexity (slow waves, delta)
      - Zhou J, J Theor Biol. 2012 Aug 7 https://www.ncbi.nlm.nih.gov/pubmed/22726808
- **steady 60 dB (A) pink noise improves sleep inductions**
  - Kawada T, Ind Health. 1993 https://www.ncbi.nlm.nih.gov/pubmed/8340228
- Listen:

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Slow Breathing… for sleep

- Breathing patterns
  - Heart and Respiratory rate (HRR) during relaxation
    - respiratory sinus arrhythmia,, HRV, concept of "coherence"
    - STUDY: HRR in 87 healthy subjects
      - day-resting periods vs deep sleep relaxation…
    - **when HRR, during "day-resting" was near to deep sleep relaxation, the subjects felt healthier, indicated better mental well-being and less depressive moods.**
      - Compared the ability to relax…correlated to assessments of…
        - somatic complaints,
        - General health-related quality of life,
        - anxiety and depression.
    - **von Bonin D**, Psychiatry Res. 2014 Nov 30 https://www.ncbi.nlm.nih.gov/pubmed/25011731

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Breath therapy?

- Slow to 6 breaths per minute
- Pair w soft blue light q 10 seconds.
  - **Uses rhythmically pulsing soft blue light to guide and slow your breathing rate**
- **HRV… slow respirations**
  - **Influence of a 30-Day Slow-Paced Breathing Intervention Compared to Social Media Use on Subjective Sleep Quality and Cardiac Vagal Activity**
  - **Laborde S,** J Clin Med. 2019 Feb 6 https://www.ncbi.nlm.nih.gov/pubmed/30736268

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Sleep aid.. Coordinate breath and light

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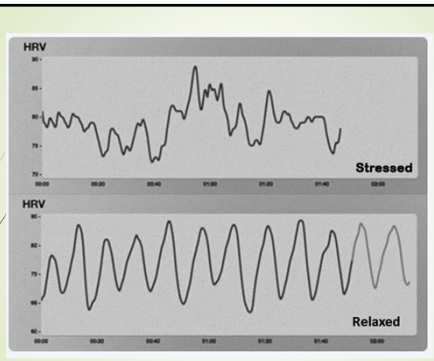

HRV and relaxation breath

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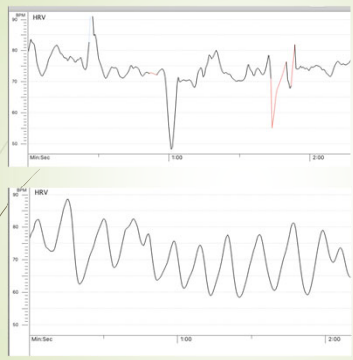

Dr Dye's Patient with MDD,
Post Traumatic stress

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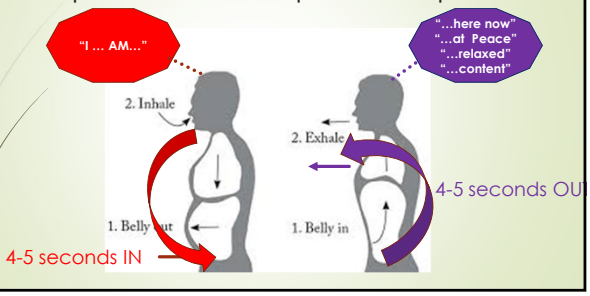
Breathing for relaxation response

Step 5 … mantra, peaceful phrase



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Breakout…
Apply what you've learned

1. Find a partner
2. Together, propose a mock client, "treatment resistant"..
   - Warranting a referral for complementary naturopathic care
3. Describe at least two lab tests that might be indicated
   - How might lab results help guide treatment options
4. Name at least two herbs that might be indicated in this case
   - what are the indications for these herbs?
5. Name at least two other supplements or products worthy of consideration in this case.

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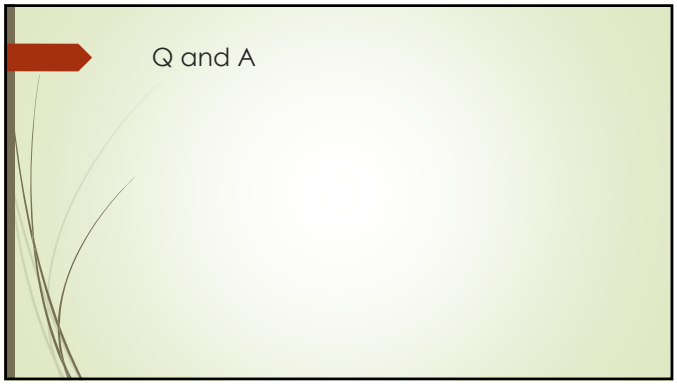

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