Naturopathic Treatments for Mental Health
2019 Update

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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)

Objectives:
what you will learn today about naturopathic approaches and the role they play in holistic mental health
- Routine lab tests that screen for modifiable mental health risk factors
- Analysis of 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.
Stress and Mental Health: Where's the breaking point?

- Chaos physics
- Bifurcation point

Genetic Risk Factors
Xenobiotics
Toxic Metals
Nutritional deficiencies
Gut Dysbiosis
Pathogens
Drug addiction & side effects
Disordered Breathing
Loneliness
Dysfunctional family, homelife
Psychological Trauma
Raw, toxic thoughts and emotions

Stressful Life Event. Stuff Happens!

Resilience

- Genetic Risk Factors
Genetic risk factors

- Inherited, familial
- Psychiatric illness
  - Risk involves multiple genes with complex interactions
  - Genomic elements and regulatory pathways
  - Example: Schizophrenia and bipolar disorder
  - High impact of genetics demonstrated by twin studies
  - Biological individuality
  - Impaired metabolism?
- Genetic influences...
  - Russian Roulette?
  - Is it rigged?...Who stacks the cards?

Testing for genetic risks

- screening, Direct to Consumer vs professional geneticist
- DNA test companies
  - Direct-to-consumer tests typically considered accurate.
  - However, misinterpretation or lack of precise information can be problematic
- 3rd party vendors offer inexplicable interpretation of medical risks.
  - Effective results: downloading their DNA data
  - Performance on genetico-tissue panel average (50%)
- Clinical outcomes using DNA interpretation:
  - Complementary with medical advice and genetic counseling
  - Cause, effect, and potential outcomes

Eithical concerns using 3rd party interpretations:
- Companies: Promethease, Interpretome, LiveWello, Codegen.eu, and Enlis Personal.
- False positives? DTC reports may warrant genetic counseling for validation.

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)
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

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

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).
- Neuroepigenetics
  - Regulation of gene expression in the neuron,
  - Influenced by drugs and environment,
  - DNA methyltransferases (DNMTs)
  - Changes in chromatin

https://www.ncbi.nlm.nih.gov/pubmed/24452011

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

Example:
- Genetic Mutation: Polymorphism
  - Methylation defects
  - Increased homocysteine
- Elevated homocysteine
  - Increased risk for multiple metabolic disorders
  - CVD, Neurodegeneration, (AD, PD)
  - Depression, Increased risk neuropsychiatric illness

Elevated homocysteine
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- CVD, Neurodegeneration, (AD, PD)
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Homocysteine → neurotoxicity
- Elevated Homocysteine (Hcy)
  - A risk factor for Neurodegenerative diseases
  - Neurotoxicity: Hcy excess (plus B12, folate deficiency)
  - 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)

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, PSP) converts homocysteine into cysteine.
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 (Methylcobalamine)


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
- Methylation defects
  - Active form of folic acid
  - Methyl-cobalamine (B12)
  - Pyridoxyl-5-phosphate (B6)

CORRECTING HOMOCYSTEINE METABOLISM:
- Lower risk CVD
- Lower risk neurodegeneration
- Lower risk of depression

Normalizing homocysteine with nutritional supplements in depression and cognitive disorders

Karakułłą, Pol Merkur Lekarski. 2009 Feb

Common medical conditions that impact mental health:

- Hypothyroidism
- Subclinical thyroid disorders
- Adrenal stress, endogenous steroids
  - Transcranial hyperfunction
- Sex hormone effects
  - Hypogonadism, hypergonadism, PMS
- Pathogenic burden
- Oxidative (disturbed GI flora)
  - Persistent yeast, bacterial, viral burden
  - CHRONIC INFLAMMATION
- Toxic metals and xenobiotic burden
- Nutritional deficiencies
  - B12, folate, B6, Zn, Fe, Cu, Cu, etc.
- Anemia
- Other mineral-mineral deficiencies
- EPA imbalances
- Malabsorption syndromes
  - Celiac, gluten intolerance
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:
  - Should we screen depressed patients for hypothyroidism?

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
  - Low correlation of depression to clinical hypothyroid:
    - Vargas Navarro P, Rev Colomb Psiquiatr. 2017 Jul - Sep

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

Routine Thyroid panel:
- TSH
- T4 (Thyroxine)
- T3 uptake (or total T3)

Why routine thyroid lab tests fail to detect a problem?

Routine Thyroid panel:
- Wrong cut-off for normal TSH?
- 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

Why routine thyroid lab tests fail to detect a problem?

Routine Thyroid panel:
- TSH
  - Range varies by lab... ~ 0.3-4.5 MIU/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)
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 an elevated rT3, or rT3/T3 ratio... this can explain many thyroid disorders that go undetected
  - (Euthyroid sick syndrome)

Comprehensive thyroid testing

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

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)
    - thyroid peroxidases antibody (TPO-Ab)
  - Studies: 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 naïve patients with major depressive disorder.

Autoimmune thyroid often overlooked

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

- Hashimoto’s 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 with HT
  - 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?


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.

Barbero JD et al, 2019 Sep 16.

How do we know when to test thyroid?

Common symptoms of low thyroid

- Feeling Cold
- Easy Weight Gain/ Low Metabolism
- Aching Joints
- Poor Circulation
- Fatigue
- Dry, Brittle Hair/ Hair Loss
- Constipation
- Mental “Fogginess”
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)

Naturopathic approach to thyroid support

- Iodine is an essential nutrient
  - Deficiency of iodine
    - Supplementation in iodine deficiency
  - Dietary sources
    - Iodized salt
    - Seafood; Fish, seaweed
    - Dairy

- Zinc
  - Deficiencies seen in low-T3 syndrome
    - Zinc supplementation increases active fT3, lower rT3
  - Selenium:
    - Deficiencies seen in Low-T3 syndrome
      - Vitamin E selenium supplementation improves energy metabolism in postmenopausal women
      - Olivieri O, Biol Trace Elem Res. 1996 Jan
      - Use selenomethioine supplements (200 mcg)
      - Or eat Barzil nuts (source of dietary selenium), one per day
      - Talaei A, Nutr Hosp. 2015 Oct 1

To improve overall thyroid function

- 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
Herbal support for thyroid

- Adaptogenic and “energy tonic” herbs improve thyroid metabolism
- Improve peripheral thyroid metabolism
- Conversion of T4 → T3
- Liver metabolism

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

- 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
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
  - STUDIES suggest that Bacopa monnieri has the potential to improve cognition, particularly speed of attention
  - Kongkeaw C, J Ethnopharmacol. 2014

Potential herb-drug interactions

- **Ginseng:**
  - Traditional folk uses of ginseng include:
    - recovery from illness; increases a sense of well-being and stamina; improves both mental and physical performance; helps 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. (Affects metabolism of sedative drugs) i.e., Midazolam (used for sedation in surgery)
    - A 2012 open-label study concluded that patients taking Asian ginseng in combination with midazolam should be monitored for interactions
    - https://nccih.nih.gov/health/providers/digest/herb-drug

Nutritional approach to thyroid autoimmunity (Hashimoto’s Thyroiditis)

- **Selenium**
  - Selenium (selenomethionine) modifies autoimmune thyroid
    - Santos LR, Diagnostics (Basel). 2018 Dec
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6316875/
  - Selenomethionine supplement improves thyroid autoimmunity
    - Pirola I, Endocrinol Diabetes Nutr. 2019 Jun 10
  - Selenium and vitamin D interactions in thyroid autoimmunity
  - Selenium + low-dose T4 combination
    - Yu L, J Endocrinol Invest. 2017 Nov

- **Vit D**
  - Vit D deficiency in autoimmune thyroid
  - The Role of Vitamin D in Thyroid Diseases 2017 May 13
  - Immunomodulatory effect of vitamin D in thyroid autoimmunity
    - Gallo D, J Endocrinol Invest. 2019 Oct 4
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
  - Vitamin D (D3) + sunshine

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

Adrenal Stress response

THYROID impacts
- T3 levels
- Impaired conversion T4 → T3
- rT3 levels
- low T3 → 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

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
Evidence supports various stress management programs:

- Mindfulness Based Interventions

- meditation

- biofeedback
  Neurofeedback and Biofeedback for Mood and Anxiety Disorders
  Banerjee S, Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Nov.

- Smartphone Applications Utilizing Biofeedback Can Aid Stress Reduction

- progressive muscle relaxation
  decrease in the symptoms of depression, anxiety, stress (unemployed)

Normal circadian rhythms

<table>
<thead>
<tr>
<th>Cortisol (waking)</th>
<th>Melatonin (midnight)</th>
</tr>
</thead>
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Disturbed circadian rhythm

- Physical and mental health impacts
  Flattened diurnal cortisol slope and associated emotional and physical health outcomes
  Adam EK, Psychoneuroendocrinology. 2017 Sep;83:105-113.

- Low waking, flat Cortisol rhythm associated with fatigue

- Adrenal insufficiency in patients presenting with fatigue

- Atypical cortisol profile (in older adults) is associated with:
  depressive symptoms
  memory issues
Restoring circadian rhythm

- Stress management:
- EXERCISE: 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

- Sleep therapy
- Sleep hygiene
  - Melatonin:
    - Pavlova M, Continuum (Minneap Minn). 2017 Aug
    - Melatonin may be effective in depressed patients with substance abuse
    - Xie Z, Neurol Res. 2017 Jun

- 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

- Pregnenolone
  - Supplement effective in bipolar:
    - Brown ES, Neuropsychopharmacology. 2014 Nov
    - Pregnenolone may have beneficial effects on mood in depressed patients with substance abuse

- DHEA
  - Rx for depression
    - Peixoto C, CNS Neurol Disord Drug Targets. 2018;17(9):706-711
    - Libido, mood, and well-being in women
    - Panjari M, Hum Reprod Update. 2007 May-Jun

Neurosteroids

Steroid synthesis

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

- **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

- **Brain shrinkage:** in the association cortices and the hippocampus
  - Neuroprotective properties of estrogen
    - women who took HRT showed no significant shrinkage of the neocortex
      - Ros D, Neuroreport. 2004 Nov 15

- **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 recurrent GD
      - history of substance abuse/dependence
      - randomly assigned to receive pregnenolone (100mg/day) or placebo for 8 weeks.
      - Findings suggest that pregnenolone use may be associated with some improvement in manic and depressive symptoms.
    - Osuji IJ, Psychiatry Res. 2010 Jul 30

- **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 middle years may be beneficial, and should be considered.”
    - Sassarini DJ, Maturitas. 2016 Dec

  - Safety:
    - Bioidentical HRT (E2, E3, natural Progesterone) is safer than conventional synthetic versions
    - Holtorf K, Postgrad Med. 2009 Jan
    - Transdermal is safer than oral
      - Beck KL, Postgrad Med. 2017 Aug
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

Mahmoodi, Gynecol Endocrinol. 2010 Feb

Dr Dye’s protocol:
- advantages of BALANCED Bio-identical TRANSDERMAL HRT
  - Estradiol + Estriol + Progesterone + Pregnenolone + DHEA + Testosterone

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

HRT: precautions, interactions

- Intra-patient concerns:
  - Breast, ovarian cancer
  - Blood clots, CVD
- Estrogen to Progesterone
  - Interactions:
    - Estrogen:
      - https://www.drugs.com/drug-interactions/estradiol,estrogen-patches.html
    - Progesterone:
- Side effects:
  - Estrogen, Progesterrone:
    - https://www.drugs.com/sfx/progesterone-side-effects.html
  - Precautions:
    - Increased risk of:
      - Myocardial infarction
      - Stroke
      - Invasive breast cancer
      - Pulmonary emboli, deep vein thrombosis
      - An increased risk of development of venous thromboembolic disease in postmenopausal women of Asian or African ancestry
      - In women who are at risk of cardiovascular disease, the use of estrogen and progestin may be harmful
      - In women who are at risk of developing venous thrombosis
      - Engage in regular moderate-intensity aerobic activity to optimize protective effects and for cardiovascular health.

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


Neuroreceptors for testosterone

Testosterone

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


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

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.

19
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
- Possibility for affecting mood and behavior via gutbrain?
- And vice-versa?

Terminology

- Microbiota
  - Refers to different clusters of bacteria in the body
colonized by 100 trillion microbes, ten times more than human cells
Yu-Jie Zhang, Int J Mol Sci. 2015 Apr
- 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

What factors influence microbiota?

- C-sections vs vaginal birth
  - Skins, vaginal flora
  - risk of allergic disease later in life
- breast feeding, Breast milk
  - Gastrointestinal
  - Milk oligosaccharides, (prebiotics)
  - Benefits: protects gain diseases
  - immune defense, 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
Dietary polyphenols influence microbiota

- POLYPHENOLS in Bright colorful fruits and vegetables, teas
  - phenolic acids and flavonoids
- Polyphenol fermentation products support healthy flora
  - Repressed the growth of certain pathogenic bacteria
  - Is causing impact on normal flora
- Bifidobacterium spp. and probiotics such as Lactobacillus sp. were less severely affected.

Dietary polyphenols may play an important role in the maintenance of gastrointestinal health.

Lee HC, Bio Microbiol. 2018 Nov

Dietary polyphenols can affect human health because of their antioxidant and antimicrobial properties as well as free-radical scavenging activity.

的好处 of polyphenols on gut microbiota and implications in human health
Chapelon C, Infect Dis Rev. 2013 Aug

Diet affects microbiota

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

- 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 diabetes, malabsorption and systemic invasion by microbial pathogens.
  - Million M, Microb Pathog. 2017 Nov

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

- Exposure to toxins and chemicals
  - Drugs, Environmental pollutants, heavy metals,
    - Toxic metals:
    - Artificial sweeteners
      - Ruiz-Ojeda FJ, Adv Nutr. 2019 Jan 1
STRESS and microbiota

- 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

  Microbiota alteration is associated with the development of stress-induced despair behavior.
  
  So... modify microbiota to improve symptomatology.

- Social relationships
  - Close sustained relationships influence the gut microbiota.
  - Married individuals harbor microbial diversity.


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

  Mathis J, Leblanc E, Immn. 2019 Jan

- Psychological stress and microbiota (in IBS)
  - Study identified a microbial signature corresponding with psychological distress.

  Peter J, Psychosom Med. 2018

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".

  Lee HC, Res Microbiol. 2016 Nov

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

  Lederzsch, Curr Psychiatry. 2016 Nov
Unhealthy gut / unhealthy brain

- Intestinal microbiota regulate the CNS neuroimmune responses
- Bacterial dysbiosis → neuroinflammatory state
- \( \Rightarrow \) Increased risk of neurodegenerative diseases.
- Protocols for regulating and maintaining healthy intestinal microbiota are indicated
- \( \Rightarrow \) To lower risk and prevalence of neurodegenerative diseases.

Spielman LJ, Neurochem Int. 2018 Nov

Dysbiosis → Brain toxins

- Neurotoxins? \( \Rightarrow \) Production of toxic compounds
- Digestion of proteins results in the production of potentially toxic metabolites such as phenolic and sulphur-containing compounds.
- Stress, psychiatric illness, PTSD, and dysbiosis:

Windey K, Mol Nutr Food Res. 2012 Jan

Multiple illnesses associated with imbalanced microbiota: dysbiosis

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

Zhang YJ, Int J Mol Sci. 2015 Apr 2
https://www.mdpi.com/1422-0067/16/4/6769
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?
  - Recognizing Depression from the Microbiota Gut-Brain Axis.
  - Microbiota could be a direct cause for the disorder.
  - correcting these disturbance could alleviate depression
  - [Dinan, 2016](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4822287/)

- 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 MICROBIOTA in depression

- Diet, microbiota, and mental health
  - The microbiota-diet-inflammation trialogue in depression
  - 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
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


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 physical disorders)
  - Pathogenic bacteria
  - Yeast overgrowth
  - Markers for vitamin and mineral levels,
  - Oxidative stress,
  - Neurotransmitters

Microbial OAT
Improve Gut/Brain health with Diet and nutritional products

- Fermented foods: 
  - Sauerkraut
  - Yogurt
- Mediterranean diet: 
- Fish, greens, olive oil, nuts
- High dietary polyphenols:
  - Berries
  - Green tea
  - Chocolate
  - Coffee/tea
- Avoid pro-inflammatory, western diet high in sugar, processed grains, red foods, chemicals, etc.

OTC Supplements:
- Colostrum (LD, liposomal delivery)
- Probiotics
- Lactobacillus probiotics
- Saccharomyces boulardii (yeast)
- Resveratrol: 

Traditional Herbs for GIT immune health:
- Pau d'arco
- Berberine
- Oregano oil

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 of viable microorganisms to alter the host microflora for potential health benefits

- Synbiotic:
  - Supplement/food product containing prebiotics and probiotics (synergy)

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

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
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 (v.s placebo)

Inflammation in Depression and the Potential for Anti-Inflammatory Treatment

Connection between inflammation and vegetative sx pf depression
- independent of cognitive symptoms
Review article:
Majd M, Front Neuroendocrinol. 2019 Oct 22

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

- 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

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 Jan
Sources of chronic inflammation

- GIT, dysbiosis, Candida
- Antibiotics → disturbed flora
- Diarrhea, constipation
- Chronic infections
  - HIV, AIDS
  - EBV, CMV, Lyme’s (bouleriosis)
  - Periodontal, (bacteria)

Oral Health: The First Step to Well-Being.

Fiorillo L, Medicina (Kaunas). 2019 Oct


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

Other Factors: depression is an inflammatory disease, but where does the inflammation come from?

Berk M, BMC Med. 2013 Sep 12


Anti-inflammatory = antidepressant?

- Antidepressants are anti-inflammatory
  - Medical hypothesis... anti-inflammatory actions of antidepressants
    - Inflammation in Depression and the Potential for Anti-Inflammatory Treatment
      https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4973706/
  - 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

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 Ap metabolites are altered by curcumin
    - Animal studies report that curcumin may influence brain function and the development of dementia
      - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5052005/
  - Resveratrol and Other Polyphenols: preventive effects on common Brain Age-Related Diseases
    - Sarubbo F, Curr Med Chem. 2017
      - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5432007/
  - Modulation of Inflammation as a Way of Delaying Alzheimer's Disease Progression: The Diet's Role.
    - Busse R, Curr Alzheimer Res. 2016 Feb 22
      - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4766385/
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

- 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

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 plans
  - List anti-inflammatory foods
  - Focus on eating whole, plant-based foods that are rich in healthy fats and phytochemicals
  - Maintains stable glycemic response.
  - Avoid foods that are proinflammatory

Anti-inflammatory agents for depression

Systematic Review and meta-analysis

- 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).
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.


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

Compliance and acceptance in antidepressant treatment.

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. 2014 Aug 27

Nutritional support

to improve antidepressant efficacy

- Zinc supplements may improve outcomes of antidepressants
  The efficacy of zinc supplementation in depression
  Alt J, J Affect Disord. 2012 Jan

Zinc and intake of 34 antidepressant therapy evidence suggests the use of zinc supplements with antidepressants.
  Ranjbar E, Nutr Neurosci. 2014 Feb

- Multivitamin + Trace minerals:
  Increased mood and improved serotonin levels

- Vitamin D for PMS mood symptoms
  safe, effective — improving the quality of life in young women with PMS and severe hypovitaminosis

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


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:
- 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

Nutritional Supplements for depression
- SAMe
- 5-HTP
- Omega 3 oils
  - Fish oil, vs Krill oil
- Curcumin
- Vitamins: Folate, B6, B12
**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
- Promising but limited evidence.
  - Sharma A, J Clin Psychiatry. 2017 Jun

**Common interactions + precautions**

- SAMe
- 5-HTP
- St John's Wort
- Herb-Drug interactions checker:
  - [https://www.drugs.com/drug_interactions.html](https://www.drugs.com/drug_interactions.html)
- Common herbal interactions:

**SAMe interactions and precautions**

- Precaution:
  - Idiopathic hyperprolactinemia, OCD, Anxiety spectrum:
    - SAMe might increase anxiety and mania.
- Side-effects:
  - Side effects include nausea, headache, diarrhea, sleep problems.
  - Nausea, 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.
- Antidepressants.
- Amphetamines, risk of serotonin syndrome.
- St. John's wort.
- Narcotics, meperidine (Demerol) or tramadol (Ultram, ConZip) risk of serotonin syndrome.
- St. John's wort.

**Related links**:

- [https://www.drugs.com/mca/same](https://www.drugs.com/mca/same)
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 Placebo groups both 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 2 weeks of treatment and was apparent in all degrees of depression.

- 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 that of serotonin transporter (SERT) inhibitors.
- Every 5-HT exerts their influence via SHT.
- Authors recommend 5-HTP sustained-release for better pharmacodynamics.
- Adjunct 5-HTP SR could be an important new treatment for TRD.

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;
  - muscle pain or weakness.

- Drug Interactions
  - SSRIs/antidepressants that increase serotonin
  - Risk serotonin syndrome
    - SSRI/SSNRI
  - Interactions checker
    - https://www.drugs.com/drug-interactions/5-hydroxytryptophan,5-htp.html

St. John’s Wort precautions

Hypericum

- Likely safe when taken by mouth for up to 12 weeks. Some evidence suggests it can be used safely for up to one year.
- Side effects:
  - Insomnia;
  - Nausea;
  - Diarrhea;
  - Dizziness;
  - Headache;
  - Tiredness;
  - Dry mouth;
  - Headache;
  - Skin rash, tingling
- St. John’s Wort precautions
  - Do not combine St. John’s Wort with these medications: serotonin syndrome risk
    - Selective serotonin reuptake inhibitors (SSRIs)
    - Monamine oxidase (MAO) inhibitors
    - Serotonin antagonist (5-HT3) blockers
    - Warfarin
    - Birth control pills

Other like

Hypericum

Do not combine St. John’s Wort with these medications: serotonin syndrome risk

- Selective serotonin reuptake inhibitors (SSRIs)
- Monamine oxidase (MAO) inhibitors
- Nefazodone
- Tricyclic antidepressants (TCAs)
- Tricyclic antidepressants (TCAs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin antagonist (5-HT3) blockers
- Warfarin
- Birth control pills.
Favorite Herbal antidepressants

Saffron

- **SAFFRON**, (Crocus sativus), the spice.
- Traditional Persian spice used historically as mood elevating.
- Review of recent 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 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 alternative to standard treatments.

Shafiee M, J Affect Disord. 2018 Feb

**CONCLUSION:**
Saffron® increased mood, reduced anxiety and managed stress without side effects, offering a natural alternative to standard treatments.

Kell G, Complement Ther Med. 2017 Aug

**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

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/
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

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.

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
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 an mood stabilizer in clinical conditions of anxiety and depression in Ayurveda.

Bhattacharya SK, Phytomedicine. 2000 Dec

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

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.
  - 64 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.

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, neuroendocrine changes in cortisol, DHEA-S, and testosterone.
- OUTCOMES: statistically significant reduction in anxiety; and lowered depression scales, and cortisol reductions

Lopresti AL, Medicine (Baltimore). 2019 Sep

Pharmacologic overview of Ashwaganda (withania somnifera)

- 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

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
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)
  - Participants in the NC group received:
    - dietary counseling,
    - deep breathing relaxation techniques,
    - ashwagandha (Withania somnifera) (300 mg b.i.d. standardized to 1.5% with anolides, prepared from root).

- **Standardized psychotherapy intervention (PT)** (n = 40)
  - Participants in the PT group received:
    - psychotherapy,
    - and matched deep breathing relaxation techniques.

**OUTCOME**

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

Full-text: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729375/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2729375/)

**Assessments in anxiety spectrum**

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

**Favorite herbs for anxiety**

- Passiflora
- Ziziphus
- Kava Kava
- Valerian
Passion Flower
(Passiflora incarnata)
- Traditionally used as anxiolytic and hypnotic for sleep
- *Passiflora incarnata* L.: evaluation of clinical trials; preclinical experiments indicate multiple benefits, including:
  - anxiolytic, sedative, antitussive, antiallergic, and antidiabetic activities.
  - The plant has a good safety profile.
  - Requires more rigorous research methods
- Sedative properties w/ no record of toxicity

Rx passiflora
surgical stress and anxiety
- Used pre-elective surgery, compare *passiflora* vs melatonin
- 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

Zizyphus
for anxiety
- Traditional Chinese Medicine herbal
  - Commonly used in formula Suanzao-ren tang
  - Often used for anxiety and insomnia
- Appears to be safe used in combination with anxiolytic drugs, to improve outcomes
  - Modified Suanzao-ren tang 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 3-4 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 Suanzao-ren tang formula w/ paroxetine improved anxiety scores better than paroxetine alone, and as well as diazepam
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 < 0.01);
- FSZR caused fewer side effects than that of Diazepam.

In conclusion, Suanzaoching 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

Zizyphus health benefits

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

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;

- side effects or drug interactions have not been reported

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

- Most practitioners recommend Kava for acute only, or SHORT TERM use, < 8 weeks
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.

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.
  - Use NAKAMAL Kava process.. Traditional water extraction.

Other favorite remedies for anxiety

- Essential oils
  - Lavender
  - Bergamot
  - Lemon balm
- CBD
- Amino acids
  - Theanine
  - Glycine
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
  - Using therapeutic essential oils to support the management of anxiety
- May be combined with antidepressant medication

Favorite essential oils for anxiety

- Lavender, one of the most powerful anxiolytic essential oils,
  - STUDY: wisdom tooth removal:
    - reduces peri-operative anxiety
      - Karan NB, Physiol Behav. 2019 Nov 1
    - Used in capsules, oral
      - reduces anxiety-related symptoms and sleep disturbances in MDD patients
      - Fißler M, Complement Ther Med. 2014 Feb
  - Effective in oral capsules (80 mg);
  - effects on GAD similar to lorazepam
    - 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

- Bergamot, essential oil aromatherapy commonly used for psychological stress and anxiety
  - Bergamot essential oil inhalation improves from inhalation vapors of bergamot vs rest and water alone
    - Bergamot exerts psychological and physiological effects in a relatively short time.
  - 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
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
    - ORAL tablet dosing: shown to relieve stress effects
      - Cases J. Med Nutr Health. 2011 Dec

- **Essential oils and anxiolytic aromatherapy**
  - Setzer WN, Nat Prod Commun. 2009 Sep

Sleep disorders

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

Favorite Sleep remedies

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

5-HTP combinations

- 5-HTP combines well with other remedies
  - amino acid neurotransmitters:
    - Glycine, taurine, GABA, theanine, inositol
  - herbs
  - GABA + 5-HTP
    Combined γ-aminobutyric acid (GABA) and 5-hydroxytryptophan (5-HTP):
    - mixture modulates sleep quality
  - > individual amino acids .. Via both GABA and serotonin signaling
    - Hong KB, Life Sci. 2016 Apr

5-HTP precautions

- 5-HTP is generally regarded SAFE when taken by mouth appropriately.
- Potential side effects of 5-HTP include:
  - Digestive: heartburn, stomach pain, nausea, vomiting, diarrhea,
  - Sexual problems,
  - Muscle problems
- 5-HTP is POSSIBLY UNSAFE when taken by mouth in large doses.
  - Doses from a 10 grams daily have been linked to severe stomach problems and muscle spasms.
- Major Interaction
  - Drugs that increase serotonin: SSRIs, MAO-I
  - Risk Serotonin syndrome; Symptoms include high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea, head pressure, vomiting, and anxiety
- Moderate Interaction
  - Carbamezepine, diazepam (Valium) Demerol and other meds:
    check for drug interactions:
    https://www.drugs.com/drug-interactions/5-hydroxytryptophan-5-hydroxytryptophan.html
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
  - Hypersomnia
- Circadian rhythm sleep wake disorder and parasomnias
- Few side effects
  - Xie Z, Neurol Res. 2017 Jun

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.
- Melatonin as add-on therapy in psychiatric disorders with 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

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 produce anxiogenic effects
- PTSD enhances the extinction and blocking the reconsolidation of persistent fear memories
  - Blessing EM, Neurotherapeutics. 2015 Oct
Safety of medial cannabis?

- How effective and safe is medical cannabis as a treatment of mental disorders?
- A systematic review (1439 participants)
- THC- and CBD-based medicines,
  - given as adjunct to pharmaco- and psychotherapy
  - improvements of several symptoms of mental disorders,
  - minor side effects.
- Side effects:
  - Side effects occurred, but severe adverse effects were mentioned in single cases only.

Hoch E, Eur Arch Psychiatry Clin Neurosci. 2019 Feb

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

Review: Cannabis use and psychosis:
- psychotic illnesses arise more frequently in cannabis users compared to non-users,
- dose-dependent risk of developing psychotic illnesses,
- users have an earlier onset of psychotic illnesses compared to non-users,
- side-effects are associated with increased psychiatric rates, more hospitalizations and pronounced positive symptoms in psychotic patients.


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

Cannabidiol (CBD), the other important ingredient of traditional cannabis, ameliorates the psychotogenic effects of THC.
- anti-convulsant
- anti-oxidant
- anti-inflammatory

Hi CBD/ Low THC cannabis
- CBD does not have the hallucinogenic effects of THC even at high doses.
CBD side effects, precautions, interactions

Potential side effects:
- Agitation
- chills
- cough
- fever
- hoarseness
- irritability
- lower back or side pain
- pain or difficult urination
- unusual drowsiness, slurriness

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)
    - Benadryl
    - Cymbalta
    - Pregabalin
    - Zoloft
    - Amitriptyline

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.
  - Study: Hidese S, Nutrients. 2019 Oct 3

Glycine
Calming Amino Acid

- Glycine
  - Glycine 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.
  - Study: Razak MA, Oxid Med Cell Longev. 2017
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.

- 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

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
  cardiorespiratory coupling approach, HPV
- Reduced brain wave complexity (slow waves, delta)
- Steady 60 dB (A) pink noise improves sleep inductions

Listen:

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.
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

Sleep aid... Coordinate breath and light

HRV and relaxation breath
Dr Dye’s Patient with MDD, Post Traumatic stress

Breathing for relaxation response
Step 5 … mantra, peaceful phrase

1. Belly in
2. Inhale

4-5 seconds IN

“I … AM…”

“…here now”

“…at Peace”

“…relaxed”

“…content”

4-5 seconds OUT

Breakout…
Apply what you’ve learned

1. Find a partner
2. Together, propose a mock client, “treatment resistant”.
   - Warranting 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.