

Non-pharmacological Interventions in the Treatment of Depression

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Learning Objectives

1. Understand how inflammation can cause depression
2. Understand potential mechanisms for the efficacy of non-pharmacological agents in treating depression, especially reduced inflammation and increased monoamine production
3. Understand how to assess a psychiatric patient in an integrated manner, including responding to a patient who does not want, or has failed, traditional anti-depressant therapy, especially in the young and the elderly

Overview

- Many patients are using non-pharmacological treatments including herbal medicine or Complementary and Alternative Medicine (CAM) to manage affective disorders
 - A survey of outpatients indicated that 54% of those suffering from severe depression used CAM or herbal treatments over a 12 month period
 - An survey of psychiatric inpatients revealed that 44% had used herbal medicine to treat their psychiatric condition over the past 12 months

A way to think about non-traditional therapies

- Unlike single active mechanisms associated with regular drug development (SSRI), other formulations, such as herbs, often incorporate multiple effects.
- Epigenetic studies have shown that one herbal formula can have a unique gene expression profile more extensive than that seen in its individual constituents.
- These multi-modal effects are best conceptualized as:
 - **Synergy**- a single pharmacological effect generated by “a combination of substances” working together “that is greater than would have been expected from a consideration of individual contributions”
 - **Polyvalence**-a range of biological activities that a compound might exhibit, possibly due to the multiple different activities of one chemical or the effect of multiple compounds on different physiological processes.

Hypericum Perforatum (St. John's Wort)

- Analysis of the well-known herbal anti-depressant, Hypericum Perforatum (HP) ("perforated leaf") more popularly known as St. John's Wort ("wort" means "plant"), using "omic" genetic technologies (pharmacogenomics, proteomics (epigenetics) and metabolomics) in a comparison with Clomipramine (C) TCA (SNRI) and a popular Chinese medicine formulation for depression (Xiao-yao-san or "XYS") showed that all 3 compounds expressed proteins in rat hippocampal cells (HP 64, XYS 40, C 90) with 43 overlapping in the areas of energy metabolism.
- HP and C both increased expression of DRP-2 (Dihydropyrimidinase-Related Protein), involved in axonal outgrowth and regeneration, and Heat Shock protein 70, known to protect against neural degeneration by assisting in the correct folding of newly synthesized proteins.
- Hypericum Perforatum is as effective as Clomipramine in treating MDD, because it has a similar function as a TCA by acting as an SNRI, but with much reduced side effects, including no sedation, weight gain, cardiac or sexual side effects, the latter property most likely due to its reduced protein expression (64 vs 90).

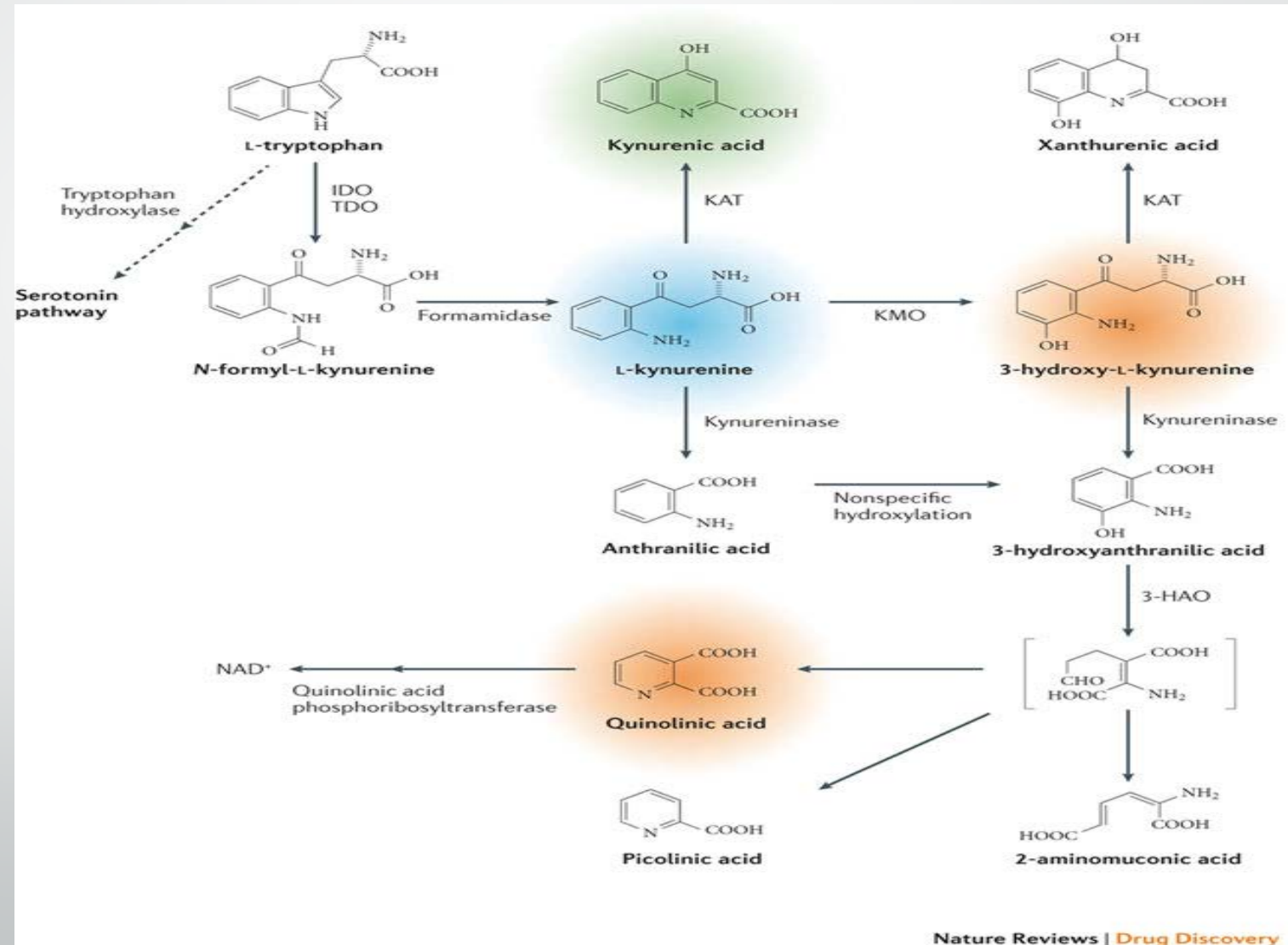


Inflammation and Depression

- Research has demonstrated that inflammation associated with medical conditions, especially pain, can cause depressive type symptoms, and that inflammatory cytokines are elevated in patients with major depressive disorder, in particular Interleukin (IL)-1, IL-6, Tumor Necrosis Factor (TNF)-alpha and C-reactive protein (CRP).
- Studies have shown increased brain activity in regions of the brain associated with depression, especially the subgenual cingulate cortex, resulting in decreased connectivity to the amygdala, medial prefrontal cortex and the nucleus accumbens following peripheral administration of a Typhoid vaccination and associated release of IL-1, IL-6 and TNF-alpha. A similar response was seen to infections originating in the brain.
- During inflammation, tryptophan, the biochemical precursor and rate-limiting substrate for serotonin synthesis, is metabolized in a manner that produces a neurotoxic metabolite, quinolinic acid, an NMDA agonist, mediated by the enzyme Indoleamine 2, 3-Dioxygenase (IDO), which is up-regulated by IFN-gamma and TNF-alpha. Reduced production of kynurenic acid results in increased glutamate and free radical production, both of which are implicated in depression.

Kynurenine/Tryptophan Pathway

IDO expression is readily inducible by various inflammatory stimuli within the central nervous system (CNS), whereas TDO is preferentially expressed in the liver and is the normal metabolic pathway.



Other sources of inflammation/inflammatory cytokines

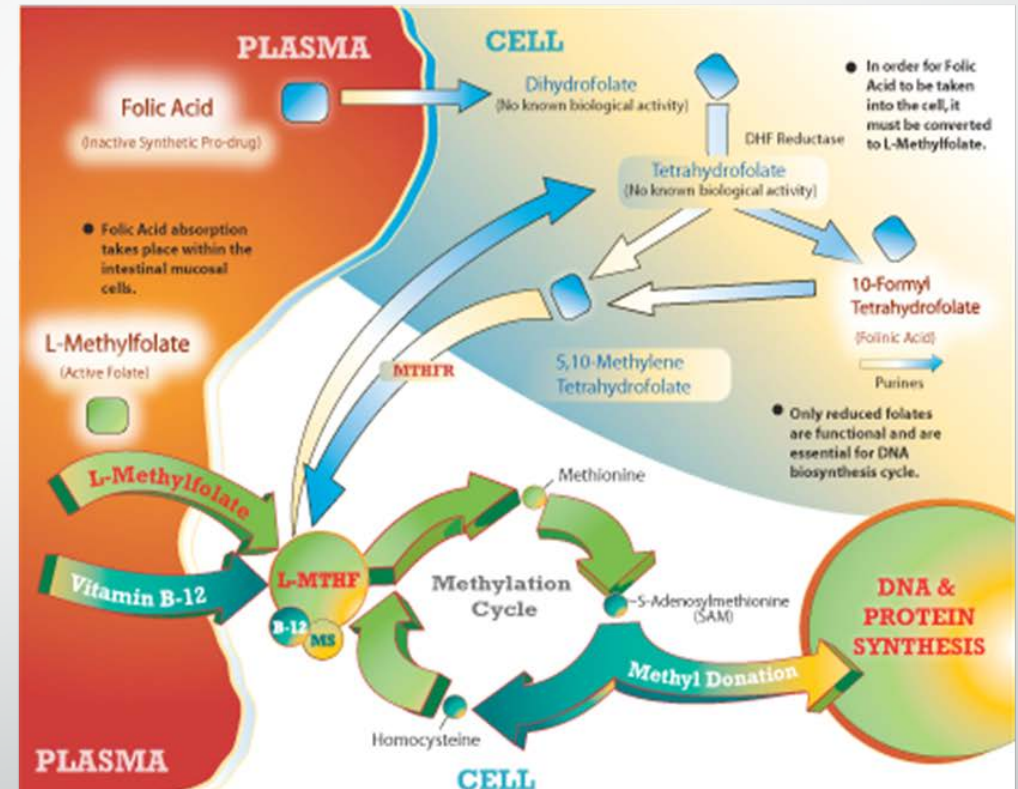
- Inflammatory states cause increased risk of depression, heart disease and type 2 diabetes
- Chronic stress activates peripheral and central nervous system immune cells to release inflammatory cytokines, while also causing increased cortisol which stimulates fat storage by way of higher blood sugar
- Obesity increases the production of inflammatory cytokines in adipose tissue
- Intestinal problems, caused by food allergies or exposure to toxins, reduce the protective balance of microflora in the gut and intestinal lining, causing inflammation and related cytokine release

The importance of the Folate & Methylation cycles

- Folate and B12 deficiency have been shown to cause depression along with other CNS disorders.
- The conversion of homocysteine (Hcy) to methionine, mediated by methionine synthase, requires a reduced form of folate, 5-methyltetrahydrofolate (5-MTHF) along with Vitamin B12.
- Methionine, the by-product of this reaction, is the substrate for the synthesis of SAMe, the sole methyl donor group in more than 100 methylation reactions in the body, including the production of DNA, proteins, phospholipids and neurotransmitters.
- Hence deficiencies in folate and/or B12 are associated with increased rates of depression, especially in the elderly. However, supplementation with Vitamin B12 alone has not been shown to improve depression.
- Some individuals cannot produce normal amounts of 5-MTHF because they have mutations in the gene that creates the enzyme that produces 5-MTHF, namely methyl tetra hydro Folate reductase (MTHFR). The two most common mutations are known as 677 and 1298, and their presence reduces the body's ability to synthesize MTHFR, thereby resulting in less production of Serotonin and related depression
- Additionally, patients with this mutation accumulate excess homocysteine in the blood, due to reduced production of Methionine, which is a marker for Cardiovascular disease risk

Methylenetetrahydrofolate reductase (MTHFR)

- Enzyme encoded by MTHFR gene
- Part of larger testing strategy called SNPs
- 2 main mutation types: 677 and 1298
- Both alter enzyme function
- So what?



MTHFR C677T mutation

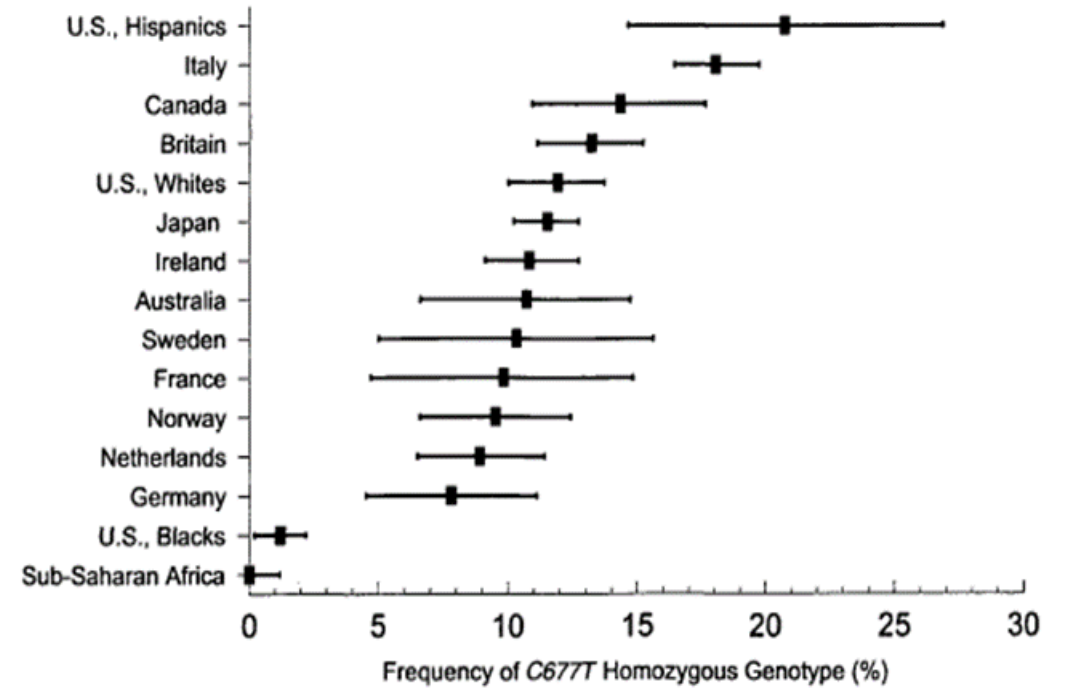
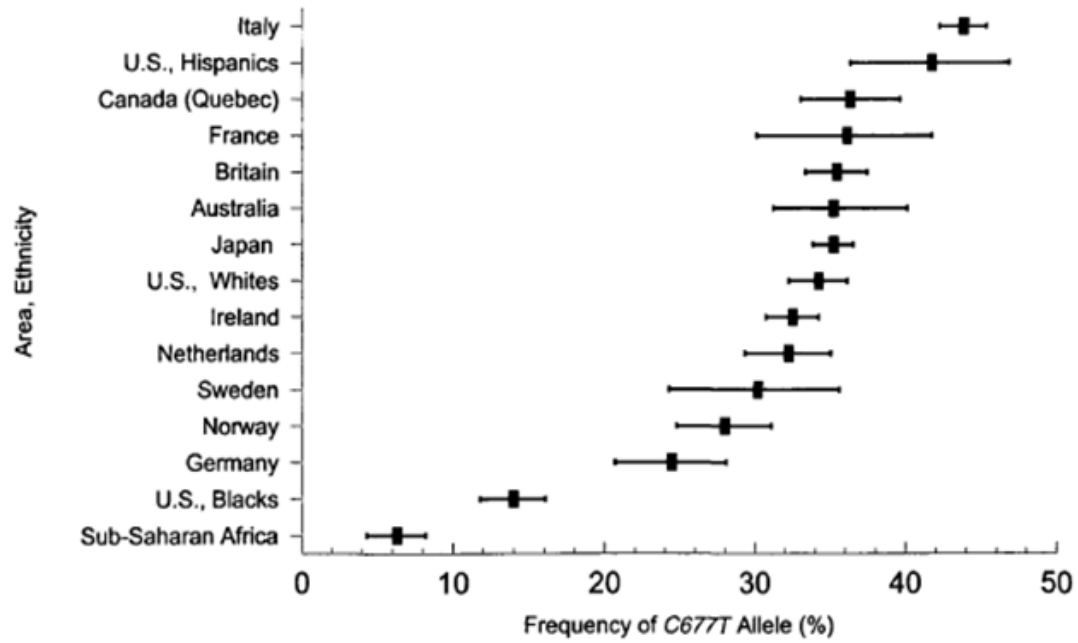


FIGURE 2. Population frequency of the C677T allele of 5,10-methylenetetrahydrofolate reductase (MTHFR), by geographic area and ethnicity, 1995–1999. Data were obtained from table 1.

Remediation of Deficiency

- If a blood test reveals low levels of folate, supplement with 15 mg of 5-MTHF per day, thereby avoiding any complications should the patient be deficient in MTHFR
- If a blood test shows low levels of B12 or higher levels of methylmalonic acid (MMA), consider supplementing with Vitamin B12 as adjunct treatment to protect cognition and increase responsiveness to antidepressant therapy

S-Adenosylmethione (SAM-e)

- In multiple controlled clinical trials involving 791 patients, with a daily dose rate of 800 mg BID, SAM-e was shown to have anti-depressant activity comparable to TCAs with markedly less side effects, was effective as an adjunct medication with SSRI non-responders, and significantly improved depression and reduced aggression in schizophrenic patients (800 mg/d)
- In HIV+ patients with MDD, SAM-e significantly reduced depressive symptoms
- SAM-e may offer protection against Alzheimer's disease by ensuring appropriate methylation of, and reduced levels of, Beta amyloid and Tau proteins implicated in the disease
- SAM-e was as effective as NSAIDs in treating osteoarthritis with fewer GI side effects, and reduced elevated bilirubin levels associated with cholestasis of pregnancy, making it especially helpful in patients with Depression and comorbid osteoarthritis and/or liver problems
- SAM-e was effective in treating Levodopa-induced depression (via indigenous SAM-e depletion) associated with Parkinson's disease; doses between 800 mg and 3600 mg/d showed no serious side effects

S-Adenosylmethione (SAM-e)

- **Mechanism of action:** increases concentrations of monoamine neurotransmitters serotonin and norepinephrine via improved methylation
- **Use:** administer 20 minutes before breakfast and lunch, and not after 4 p.m. due to activating effects and possible sleep disturbance
- **Dosing:** 400 mg/d starting, increasing every 5-7 days up to 800 mg/BID; elderly 200 mg/d start; effects seen within 10 days generally, but can take longer
- **Benefits** compared to regular anti-depressants: does not cause weight gain, sedation, sexual dysfunction nor cognitive interference
- **Side effects:** GI related-nausea, loose bowels, diarrhea, abdominal discomfort and vomiting (rare)
- **Caution:** avoid in bipolar disorder due to chance of precipitating mania; relatively untested in children

Rhodiola Rosea

- Popular plant widely distributed at high altitudes in the mountainous regions of Europe and Asia
- Used for centuries in traditional medicine to stimulate the nervous system, enhance physical and mental performance, prevent high altitude sickness, and alleviate fatigue, psychological distress, depression and impotence
- Extensively studied in Scandinavia and Russia, where it is considered to be an adaptogen—a substance that nonspecifically increases the resistance of an organism to a variety of chemical, biological and physical stressors
- Provided statistically significant reduction in symptoms of mild to moderate depression, measured by the Hamilton Rating scale for Depression (HAM-D) with no side effects at standardized doses of 340 and 680 mg/day
- Co-administration with TCAs caused a marked reduction in TCA side effects



Rhodiola Rosea

- **Mechanism of action:** increases monoamine activity (serotonin, dopamine and norepinephrine) via inhibition of degradation enzymes (monoamine oxidase A & B) along with increased hippocampal neurogenesis (rat study) and moderation of opioid peptide release during stress
- **Use:** take early in the day, ideally 30 min before breakfast to maximize absorption and avoid insomnia related to activation amid late administration
- **Dosing:** 340 mg/d for depression (100-170 mg/d for reduced fatigue and improve mental performance under stress, tested among physicians working at night and medical students in Russia)
- **Benefits:** reduced depression and anxiety, improved stress response and cognition, reduced fatigue; does not cause weight gain, sedation, sexual dysfunction nor cognitive interference
- **Side effects:** none with other medications; not tested in pregnancy; rarely causes insomnia and irritability, especially at high doses
- **Caution:** avoid in bipolar disorder due to chance of precipitating mania; untested in pregnant women

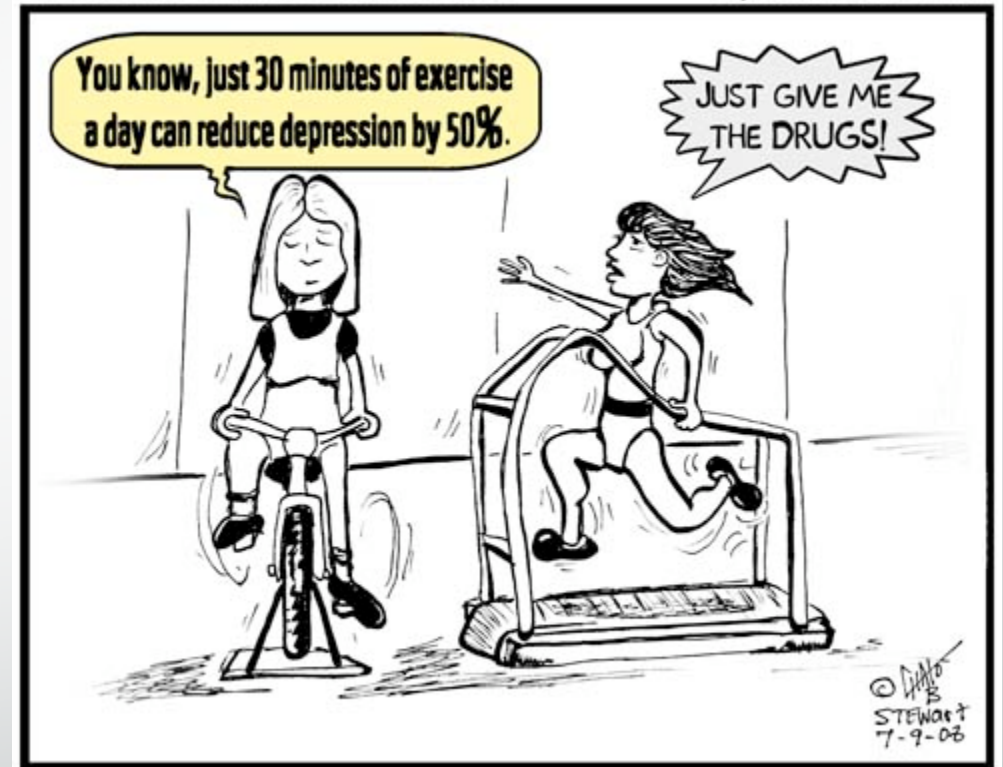
Psychobiotics



- Certain bacteria can produce neuro-active substances in the gut which then travel to the brain and exert their effects
- Bifidobacterium infantis increases tryptophan levels, a precursor to Serotonin; Escherichia, Bacillus and Saccharomyces produce norepinephrine; Candida, Streptococcus, Escherichia and Enterococcus produce serotonin, while Bacillus and Serratia can produce dopamine
- The human gut (can be referred to as the microbiome) contains more than 1000 species of bacteria, is colonized at birth, and can change suddenly (1 day) in response to stress, to include Caesarian birth (prevents normal colonization), early life stress, and a high fat high sugar diet
- Evidence from rodent studies shows that stress alters the gut barrier function, allowing molecules to enter the bloodstream, stimulating toll receptors (TLRs) and inflammatory cytokines
- Ingestion of Lactobacillus GG has been shown to up-regulate production of IL-10, an anti-inflammatory cytokine hypothesized to be produced by anti-depressants

Exercise

- Long been shown to protect against depression, especially in the elderly
- Recently shown to be a treatment for depression, with similar efficacy as antidepressants
- Both anaerobic and aerobic exercise confers benefits, with aerobic exercise in one study found to be particularly effective in treating somatic symptoms related to MDD in older adults
- Supervised exercise, including weight-training and cardiovascular exercise, was significantly more effective at reducing depressive symptoms than unsupervised exercise, possibly due to guaranteed adherence and social support, with more intense efforts linked to a greater reduction in depressive symptoms, indicating a dose-response effect
- In one study, a prescription of 3 x 30 minute sessions per week at 60-80% maximum heart rate for 8 weeks was effective
- Larger studies are needed to clarify these findings, to include efficacy in severe depression



Vitamin D₃

- Low Vitamin D levels are present in a study of people who attempted suicide, who also had higher blood levels of inflammatory cytokines IL-1 and IL-6
- Low levels of Vitamin D were found in people suffering from MDD, though supplementation with Vitamin D has not, to date, been found to improve depression
- Lower levels of Vitamin D in the elderly was associated with increased all cause mortality
- Vitamin D deficiency (< 50 nmol/L) was associated with increased all cause dementia and Alzheimer's
- Optimum levels of Vitamin D for good health have not been established, with the Institute of Medicine recommending 50 nmol/L and the Endocrine Society recommending 75 nmol/L
- Vitamin D regulates neurotrophin expression, affecting the development, survival and function of neural cells; Vitamin D receptors are expressed throughout the brain, including the hippocampus and Dentate Nucleus; Vitamin D reduced amyloid-induced cytotoxicity and apoptosis in primary cortical neurons

Talk Therapy

- Short term psychodynamic therapy (40 hours) yielded an effect size of 0.97, which increased to 1.51 when reassessed at 9 months
- The mean effect size of antidepressant medications approved by the FDA between 1987 and 2004 was 0.31, with TCAs having an effect size of 0.17



Conclusions

1. Inflammation contributes to depression, so assessing patients for their inflammatory status by measuring CRP and advocating measures to reduce inflammation (reduce weight, switch to a low fat low sugar diet) can help with the management of depression
2. Consuming probiotics, especially psychobiotics, might help to decrease inflammation (Lactobacillus GG) and to increase monoamine production (Streptococcus, Escherichia and Enterococcus for serotonin)
3. Consider Rhodiola in a pharmaceutical grade formulation for a patient with mild to moderate depression, one experiencing stress or fatigue, and someone experiencing side effects from their anti-depressant medications (especially TCAs)
4. Consider use of SAM-e in a pharmaceutical grade formulation as a first line anti-depressant, especially in those with Parkinson's disease, liver disease or osteoporosis

Conclusions

5. Consider St. John's Wort in a pharmaceutical grade formulation to treat all categories of depression-mild, moderate and severe-particularly in patients (likely younger) who are not taking additional medications (such as women using oral contraceptives or medications metabolized via the CYP-450), and who are experiencing depressed mood, lethargy, anhedonia, suicidal tendencies and/or somatic symptoms.
6. Check Vitamin D levels, Folate and B12 levels, and supplement to optimal levels; in the case of 5-MTHF, at 15 mg/d to avoid the problems associated with MTHFR mutations, and with Vitamin D₃ 1000-2000 iu/day to achieve neuro-protective serum Vitamin D blood levels in the range of 50-75 nmol/L.
7. Become educated about the full panoply of anti-depressant treatments, to include non-pharmacological alternatives, in order to offer patients the best care and avoid being seen as representatives of "big Pharma."
8. Use supplements and herbal formulations manufactured to the highest pharmaceutical standards, best to use distributors who independently test products, ideally each batch. (Gold Partners – Emerson Ecologics)

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