Understanding Nutritional Psychiatry

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Scientists Find a Possible Link Between Gut Bacteria and Depression
A new study identifies bacteria in the microbiome that could produce neurotransmitters and potentially influence activity in the brain.
Nutritional Biochemistry and Neuropsychiatric Health

- Amino Acids are essential precursors for neurotransmitter production
- Vitamins and minerals are required cofactors for neurotransmitter production
- Microbiome affects bidirectional gut/brain communication
- Diet/nutritional support can modulate epigenetic triggers
- Chronic inflammation is implicated in mood disorders
- Mitochondrial function impacts ROS, O&NS
Standard American Diet (SAD)

- Significant decline in fruit and vegetable intake
  - Reduced intake of vitamin and mineral cofactors
- Sugar: 2#/year in 1940s-152# year in 2016
  - Increased TCA cycle requirements for B vitamins, Mg
  - Increased inflammation
  - Reduced BDNF
- Decline in fish intake
  - Omega 3 deficit
- Inadequate fiber
  - Impaired gut microbiota
- Increased consumption of refined and processed foods
  - High sugar/low nutrient density/low fiber
Impact of Dietary Patterns

- **Western Diet**

- **Mediterranean diet**

- **Fast food**

The dietary support group demonstrated significantly greater improvement between baseline and 12 weeks on the MADRS

Number needed to treat (NNT) based on remission scores was 4.1
Nutritional medicine as mainstream in psychiatry

Jerome Sarris, et al. on behalf of The International Society for Nutritional Psychiatry Research

....the emerging and compelling evidence for nutrition as a crucial factor in the high prevalence and incidence of mental disorders suggests that diet is as important to psychiatry as it is to cardiology, endocrinology, and gastroenterology. Evidence is steadily growing for the relation between dietary quality (and potential nutritional deficiencies) and mental health, and for the select use of nutrient-based supplements to address deficiencies, or as monotherapies or augmentation therapies.

....We advocate recognition of diet and nutrition as central determinants of both physical and mental health.

Mood and Sugar

- Decreases BDNF
- Wastes minerals e.g. Mg, Ca
- Increases pro-inflammatory cytokines
- Increases utilization of B vitamins
Mood and Sugar

- Westover AN, Marangell LB. A cross-national relationship between sugar consumption and major depression? Depression and Anxiety. 2002;16:118–120.

Stress and Digestive Function

- “Stress inhibits and interferes with every aspect of digestive functioning and with the efficient use of nutrients. Stressed-out people can’t make very good biological use of even the most healthy diets.”—James S. Gordon, founder of the Center for Mind-Body Medicine and a former researcher at the National Institute of Mental Health
Methylation /Transsulfuration/Folate BH4

- Methylation:
  - Require B vitamins, multiple minerals
  - Increased Hcy linked to inflammation and mood disorders

- Transsulfuration
  - Requires B vitamins, minerals
  - Impact GSH production

- Folate cycle
  - B vitamin dependent
  - MTHFR mutations

- BH4
  - Serotonin and Dopamine production
B vitamins

- Essential for methylation/transsulfuration/folate cycle
- Required for neurotransmitter processing
- Depleted by stress, increased sugar intake, OCP
- Requires activation by gastric acid-PPIs interfere
- B12 deficiency reduces NMDA receptor activity
B vitamins


Folate

  - NNT =4
  - mean folate levels were low but within the normal range at baseline in the study and, as such, response was not linked to overt folate deficiency.
Table 1.

Randomized trial results of adjunctive folate treatment in major depressive disorder: A 10-week trial measuring the effect of folate when combined with fluoxetine.

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>MEAN HDRS AT END OF STUDY</th>
<th>RESPONSE RATE, ‰</th>
<th>REMISSION RATE, ‰</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEN (N = 40)</td>
<td>WOMEN (N = 69)</td>
<td>MEN (N = 40)</td>
</tr>
<tr>
<td>Folate</td>
<td>12.3</td>
<td>6.8</td>
<td>61.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.5</td>
<td>11.7</td>
<td>63.6</td>
</tr>
<tr>
<td>Difference</td>
<td>+1.8</td>
<td>−4.9</td>
<td>−2.5</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>&lt; .001</td>
<td>NS</td>
</tr>
</tbody>
</table>

Coppen et al. 2000

MTHF

Neurometabolic Disorders: Potentially Treatable Abnormalities in Patients With Treatment-Refractory Depression and Suicidal Behavior  Pan et al. 2016

- CSF metabolite abnormalities were identified in 21 of the 33 participants with treatment-refractory depression. Cerebral folate deficiency (N=12) was most common, with normal serum folate levels and low CSF 5-methyltetrahydrofolate (5-MTHF) levels. All patients with cerebral folate deficiency, including one with low CSF levels of 5-MTHF and tetrahydrobiopterin intermediates, showed improvement in depression symptom inventories after treatment with folic acid; the patient with low tetrahydrobiopterin also received sapropterin. None of the healthy comparison subjects had a metabolite abnormality.

Magnesium

**Zinc**

- Zahra Solati, et al. *Zinc monotherapy increases serum brain-derived neurotrophic factor (BDNF) levels and decreases depressive symptoms in overweight or obese subjects: A double-blind, randomized, placebo-controlled trial*, Nutri Neurosci 2014 18:4, 162-168,

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*A meta-analysis of all studies without flaws demonstrated a statistically significant improvement in depression with Vitamin D supplements (±0.78 CI ±0.24, ±1.27).*
Inflammation


- Depression is often present in acute, inflammatory illnesses.
- Higher levels of inflammation increase the risk of developing depression.
- Administering endotoxins that provoke inflammation to healthy people triggers classic depressive symptoms.
- One-quarter of patients who take interferon, a medication used to treat hepatitis C that causes significant inflammation, develop major depression.
- Remission of clinical depression is often associated with a normalization of inflammatory markers.

Kopschina Feltes P 2017
Omega 3

Gut-Brain Axis and the Microbiome

- High rates of comorbidity between gastrointestinal and psychiatric illnesses
- Bi-directional communicative and regulatory system involving (but not limited to) the brain and central nervous system and the enteric environment of the gut
- Messages sent/received by gut and brain via the enteric nervous system (ENS) through neural pathways such as the efferent sympathetic system and the afferent vagal nerve, as well as through the bloodstream

Gut-Brain Axis and the Microbiome

- Gut and its microbiota affect immunity, endocrine function, neural development, cognition and behavior, as well as regulation of behavior
- Stress and the accompanying arousal affect the gastrointestinal function in top-down and bottom-up signals via the ENS
- Mood disorders affect more than half of all patients with irritable bowel syndrome/antidepressants one of the most common pharmaceutical interventions for irritable bowel syndrome
- Changes in behavior alter gut microbiota composition, while modifications of the microbiome can induce depressive-like behaviors.
Antibiotic Exposure and the Risk for Depression, Anxiety, or Psychosis: A Nested Case-Control Study

Lurie I et al, 2015

- Treatment with a single antibiotic course was associated with higher risk for depression with all antibiotic groups, with an adjusted OR (AOR) of 1.23 for penicillins (95% CI, 1.18–1.29) and 1.25 (95% CI, 1.15–1.35) for quinolones. The risk increased with recurrent antibiotic exposures to 1.40 (95% CI, 1.35–1.46) and 1.56 (95% CI, 1.46–1.65) for 2–5 and >5 courses of penicillin, respectively. Similar association was observed for anxiety and was most prominent with exposures to penicillins and sulfonamides, with an AOR of 1.17 (95% CI, 1.01–1.36) for a single course of penicillin and 1.44 (95% CI, 1.18–1.75) for >5 courses. There was no change in risk for psychosis with any antibiotic group.

Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers

Messaoudi et al. 2011
Results: Compared to participants who received the placebo intervention, participants who received the 4-week multispecies probiotics intervention showed a significantly reduced overall cognitive reactivity to sad mood, which was largely accounted for by reduced rumination and aggressive thoughts.

Gluten

- PubMed literature search (dates 1953–2011) - 162 original articles associating psychiatric and neurologic complications to celiac disease or gluten sensitivity.
- 36 seizure disorders
- 20 ataxia and cerebellar degeneration
- 26 neuropathy
- 20 schizophrenia
- 14 depression
- 12 migraine
- up to 10 articles each for anxiety disorders, attention deficit and hyperactivity disorder, autism, multiple sclerosis, myasthenia gravis, myopathy, and white matter lesions.
Gluten

- Patients with neurological disease of unknown etiology were found to have a much higher prevalence of circulating antigliadin antibodies (57%) than either healthy control subjects (12%) or those with neurological disorders of known etiology (5%).

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**Fig. 1.** Presynaptic impairment of cerebellar Purkinje cells by an antibody to glutamic acid decarboxylase (GAD).

Vojdani, A et al. 2008
Mitochondrial function


Mitochondrial Function

- Mitochondrial dysfunction and inflammation implicated in the pathogenesis of depression and other affective spectrum disorders
- Monoamines, energy metabolism and inflammatory pathways inter-related in many complex manners
- Many drugs used to treat depression exert effects on mitochondria and inflammation, as well as on monoamines
- Mitochondrial-targeted treatments also exert effects on inflammation, and demonstrate efficacy in affective spectrum disorders

- Many studies support a crucial role for oxidative & nitrosative stress (O&NS) in the pathophysiology of unipolar and bipolar depression. These disorders are characterized inter alia by lowered antioxidant defenses, including: lower levels of zinc, coenzyme Q10, vitamin E and glutathione; increased lipid peroxidation; damage to proteins, DNA and mitochondria; secondary autoimmune responses directed against redox modified nitrosylated proteins and oxidative specific epitopes.

Scapagnini, G et al. Antioxidants as Antidepressants Fact or Fiction? CNS Drugs (2012) 26: 477

- Reactive oxygen and nitrogen species have been shown to modulate levels and activity of noradrenaline, serotonin, dopamine and glutamate,
- MDD associated with lowered concentrations of endogenous antioxidant compounds, such as vitamin E, zinc and coenzyme Q10, or enzymes, such as glutathione peroxidase, and with an impairment of the total antioxidant status.
In this trial, the estimated mean baseline Bipolar Depression Rating Scale (BDRS) score was 19.7 (SE= 0.8), and the mean BDRS score at the end of the 8 week open label treatment phase was 11.1 (SE= 0.8). This reduction was statistically significant (p<0.001). Improvements in functioning and quality of life were similarly evident.

Seventeen participants were available for this report. Very large effect sizes in favor of NAC were found for depressive symptoms and functional outcomes at endpoint. Eight of the ten participants on NAC had a treatment response at endpoint; the same was true for only one of the seven participants allocated to placebo.
Use of proton-pump inhibitors is associated with depression: a population-based study

Volume 30, Issue 1 January 2018, pp. 153-159

Use of PPIs was associated with a higher GDS score in linear regression analysis (p = 0.014) after adjusting; also, use of PPIs was associated with increased adjusted probability of depression in logistic regression (p = 0.045). Higher PPIs dosages were associated with increased probability of depression (p for trend = 0.014).

Rabeprazole and Psychiatric Symptoms

Annals of Pharmacotherapy Vol 41, Issue 7-8, pp. 1315 - 1317

An otherwise healthy 55-year-old woman was prescribed rabeprazole 20 mg/day administered in the morning for persistent symptoms of dyspepsia. Ten days later, she presented with a 7 day history of marked anxiety associated with panic attacks, night terror (pavor nocturnus), episodic mental confusion, and attention deficit. Within 2 days of discontinuing rabeprazole, the patient recovered completely from the neuropsychiatric manifestations.

Not a Usual Suspect; Rabeprazole Therapy Presenting as a Severe Neuropsychiatric Illness: Case Report

The International Journal of Psychiatry in Medicine Vol 33, Issue 3, pp. 311 – 315

We report the case of a patient who, as a result of exposure to the proton pump inhibitor rabeprazole, developed a severe and disabling admixture of neuropsychiatric symptoms. Because of its widely appreciated placebo-like side effect profile, rabeprazole was never suspected as being the cause of his symptoms.
CONCLUSIONS AND RELEVANCE Use of hormonal contraception, especially among adolescents, was associated with subsequent use of antidepressants and a first diagnosis of depression, suggesting depression as a potential adverse effect of hormonal contraceptive use.

Botanicals

Curcumin

St. John’s Wort

Ashwagandha
Developmental exposure to glyphosate-based herbicide and depressive-like behavior in adult offspring: Implication of glutamate excitotoxicity and oxidative stress

Daiane Cattani a, b, Patrícia Acordi Cesconetto a, b, Mauren Kruger Tavares b, Eduardo Benedetti Parisotto a, b, Paulo Alexandre De Oliveira c, Carla Elise Heinz Rieg a, b, Marina Concli Leite b, Rui Daniel Schröder Prediger c, Nestor Cubas Wendt a, Guilherme Razzera a, Danilo Wilhelm Filho b, Ariane Zamoner a, c, d, e, f
Optimizing Outcomes

- **Dig deep:**
  - Chemical imbalance causes symptoms - What is root cause of chemical imbalance?

- **Address core underlying problems**
  - Inflammation
  - Nutrient deficits
  - Gut dysfunction
  - Mitochondria
  - Genetics

- **Expand the toolkit**
  - Drug therapy + talk therapy = improved outcomes
  - **Drug therapy + talk therapy + nutrition therapy + lifestyle change** can further optimize outcomes
Which leg is holding up the chair?

Would you sit down if one leg was missing?

Vicki Kobliner MS RDN

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