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Diets and Disorders:
Can Foods or Fasting Be Considered Psychopharmacologic Therapies?

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Most people agree that eating a "healthy diet" confers health benefits,[1] but defining "healthy" foods and specific benefits is increasingly confusing and controversial. The $37 billion vitamin and supplement industry[2] and the $14 billion functional and integrative medicine industry[3] are both reflections of our patients' desire to use dietary interventions to treat or prevent health conditions, whether or not there are data to support them. This article addresses dietary interventions that are purported to have psychopharmacologic properties for use in psychiatry.

When thinking about dietary interventions, there are several models to consider:

1. Adding something to the diet (eg, vitamins)
2. Removing something from the diet (eg, toxins/allergens)
3. A combination of adding and removing foods—"healthy diets"
4. The gut microbiome
5. Fasting and the ketogenic diet

Adding Something to the Diet

Additions of vitamins and essential fatty acids to the diet are the best studied dietary interventions in psychiatry.[4]

Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential fatty acids that are incorporated into neuronal cell membranes and affect neurotransmitter modulation and signal transduction pathways and have an anti-inflammatory effect.[5] Supplementation with EPA and DHA has been best studied in mood disorders,[5] with one meta-analysis showing a significant effect over placebo and EPA being more effective than DHA in depressive disorders.[6] In psychotic disorders, there have also been small, controlled, positive trials, but further research is needed.[5]

Folic acid is a B vitamin required for nucleotide synthesis, DNA methylation, and neuronal function.[7] Polymorphisms in the methylenetetrahydrofolate reductase (*MTHFR*) gene can reduce folate activity.[8] Folate deficiency has been found in depressive disorders and schizophrenia.[5] Trials of supplementation in the treatment of major depression have been mixed, with a recent meta-analysis revealing no significant difference from placebo.[3] In schizophrenia, only a few, small trials have been published, with mixed results.[9]

Vitamin E is an antioxidant that binds free radicals, which are often found to be elevated in mood disorders, schizophrenia, and Alzheimer's disease (AD).[10–12] Despite much interest in its use to prevent and treat AD, a 2017 Cochrane Review found no evidence that it improves cognitive function or prevents the progression of mild cognitive impairment to AD.[13] Antioxidants have also been studied as a treatment for schizophrenia, but a 2016 Cochrane Review showed no differences between antioxidants and placebo.[12] Vitamin E has also been studied as a treatment for tardive dyskinesia, but, again, a 2018 Cochrane Review found no evidence that it improves symptoms.[11]

Vitamin D is known to have a role in human physiology beyond bone health. Most cells and tissues in the human body, including the brain, have vitamin D receptors.[14] Many studies have found low levels of vitamin D in patients with a variety of psychiatric disorders, including depressive disorders, bipolar disorder, and schizophrenia.[15] Randomized controlled trials (RCTs) of vitamin D supplementation have been relatively small and primarily for depressive disorders. Two separate meta-analyses of vitamin D supplementation for the treatment of major depression have shown conflicting results, one showing no significant effect[16] and the other, which included only studies in which patients were identified to be deficient in vitamin D, showing a significant effect.[17,18]

Removing Something From the Diet

Elimination diets systematically remove nutrients or substances from the diet, assuming that something in the diet is causing symptoms. In psychiatry, these diets are sometimes used in children diagnosed with attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD).[14–16] For ADHD, artificial food colors are often eliminated, and for ASD, gluten and/or casein are often eliminated, but other substances can be part of elimination diets.[19] A 2013 meta-analysis of dietary interventions for ADHD found a significant effect for elimination of artificial food colors, but often in individuals selected for food sensitivities.[20] For ASD, however, a 2017 systematic review found little evidence to support the use of elimination diets.[21]

Both Adding and Removing Foods: "Healthy Diets"

Some clinicians and researchers believe that adding "healthy" foods and eliminating "unhealthy" foods may address some psychiatric disorders. The best evidence for this comes from the SMILES trial, an RCT of patients with moderate to severe depression assigned to either a diet intervention of 7 counseling sessions to adopt the Mediterranean diet or 7 social support sessions.[17] At the end of 12 weeks, there was significantly greater improvement in the diet group relative to the control group, with remission rates of 32% vs 8%.[22]

The Gut Microbiome

There is increasing evidence that the microorganisms inhabiting the gut have significant effects on metabolism and the brain.

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Microbes produce hormones, neurotransmitters, and inflammatory molecules found in the human bloodstream that may play a role in obesity, diabetes, and inflammation[23,24] and also depression and anxiety.[25] What we eat likely affects the microbiome.[26] However, most of this research remains in animal models at the preclinical stages. Nonetheless, probiotics are increasingly used[27] for purported health benefits with almost no clinical data to support their effectiveness.

Fasting and the Ketogenic Diet

Fasting and the ketogenic diet have been used in treatment-refractory epilepsy, with response rates of over 50% in children.[28] The mechanisms of action include increasing mitochondrial function, increasing GABA-ergic neurotransmission, decreasing glutamatergic neurotransmission, decreasing inflammation, and changing the gut microbiome.[29,30] Research in psychiatric disorders is just beginning; an animal model[31] and case studies[32] suggest this intervention may reduce psychotic symptoms, but controlled trials are needed.

Conclusion

Dietary interventions are an area of interest for many patients and clinicians, but the evidence base is limited, with conflicting results. Foods and fasting can sometimes have psychopharmacologic properties, but many claims are unfounded or have been disproved. Despite this, many of our patients are trying these interventions. Clinicians may want to ask patients if they are trying these interventions in order to offer accurate and reliable information.

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