COALITION FOR METABOLIC HEALTH

Exploring Ketogenic Metabolic Therapy in Serious Mental Illness

An estimated **14.6 million** American adults live with schizophrenia spectrum, bipolar, or major depressive disorders[1], many of whom experience symptoms despite available psychiatric medications.[2,3]

Although these serious mental illnesses (SMI) have long been viewed primarily as disorders of brain chemistry, growing evidence suggests they are often accompanied by poor metabolic health such as elevated blood sugar, impaired cellular energy production, and chronic inflammation. Left unaddressed, metabolic dysfunction may contribute to disease severity, treatment resistance, and broader health complications.[2,3,4,5]

This evolved understanding has catalyzed rigorous scientific inquiry into ketogenic therapy, a high-fat, moderate protein, and very low carbohydrate dietary intervention (typically defined as less than 50 grams of total carbohydrates per day), as an adjunctive approach to target the metabolic disruptions underlying SMI.

The Hidden Burden of Serious Mental Illness

Recent economic analyses estimate that mental illness costs the U.S. economy approximately $282 billion annually through healthcare spending, reduced productivity, diminished workforce participation, and other downstream impacts.[6] In 2024, nearly 30% of adults with SMI, representing approximately 4.3 million people, did not receive mental health treatment.[7] The health burden extends beyond psychiatric care alone.

The Hidden Burden of Serious Mental Illness

Individuals with SMI experience disproportionately high rates of obesity, type 2 diabetes, cardiovascular disease, and other chronic conditions that increase treatment complexity.[2,8,9] These overlapping health challenges are reflected in markedly poorer long-term outcomes. Compared with the general population, individuals with SMI lose an estimated 10 to 20 years of life expectancy.[3,9]

Where Metabolic Health Meets Brain Health

Many of the biological processes that govern metabolic health, including blood sugar regulation, inflammation, and the body's ability to use insulin effectively, also play important roles in brain function. In people with SMI, researchers have identified disruptions in how the brain uses glucose for energy, as well as neurotransmitter activity and neuroplasticity – processes that help the brain generate and use energy efficiently.[3,4,5,10] Because the brain consumes approximately 20% of the body's energy despite representing only about 2% of body weight, even modest impairments in cellular energy production may affect cognition, mood regulation, and psychiatric symptom expression.[3] Complicating this picture, medications used to treat SMI can contribute to metabolic dysfunction. Some antipsychotics and mood-stabilizers are associated with weight gain, insulin resistance (a metabolic state in which the body's cells become less responsive to insulin, requiring the body to produce more of the hormone to regulate blood glucose), and other cardiometabolic conditions that may increase long-term health risks.[3,11,12] Despite the importance of these medications in symptom management, many individuals continue to experience functional impairment, suggesting that key biological drivers of SMI remain unaddressed.[3,8]

Ketogenic Metabolic Therapy: A New Approach to Brain Energy

Interventions that aim to restore metabolic function by providing the brain with an efficient alternative fuel source may address biological pathways that conventional psychiatric treatments largely bypass, bridging the gap between symptom management and long-term health outcomes.[3] Ketogenic therapy works by reducing dietary carbohydrates to shift the body away from relying primarily on glucose for energy, causing the liver to produce ketones, an alternative fuel derived from fat that the brain can use independently of glucose. This shift may help the brain access an alternative source of energy when glucose-related pathways are impaired, supporting cellular energy production and reducing inflammation, two processes increasingly implicated in SMI.[2,3,4,5]

Ketogenic Metabolic Therapy: A New Approach to Brain Energy

Across primarily case series and uncontrolled pilots, ketogenic therapy has been associated with improvements in metabolic health for patients with SMI, including reductions in weight, body mass index (BMI), waist circumference, blood pressure, fasting glucose, and insulin resistance, often alongside improvements in symptoms of depression and psychosis, cognitive performance, and quality of life.[2,8,13,14,15,16]

Two recent randomized clinical trials (RCT) provide the first controlled evidence in psychiatric populations:

- **Depression: In an RCT of 88 adults with treatment-resistant depression,** participants assigned to a ketogenic diet experienced greater improvements in depressive symptoms and higher remission rates (25% vs. 9%) at six weeks compared with a plant-based diet. Both groups received regular dietary support, although the ketogenic group also received prepared meals. Between-group differences were not significant at 12 weeks, but improvements were maintained even though most participants had discontinued the diet. Exploratory analyses suggest the largest effects were in those with more severe depression at baseline.[17]
- **Schizophrenia and Bipolar Disorder: In a one-month RCT, adults with** schizophrenia-spectrum and bipolar-1 disorder assigned to a ketogenic diet showed significant improvements relative to diet-as-usual in BMI, insulin resistance, and HbA1c, a measure of blood glucose over time. Among 25 participants who continued the ketogenic diet for four months, depressive symptoms, psychiatric symptoms, and cognition all improved from baseline, with greater ketone production – not weight loss – associated with greater improvements in depression and glycemic control.[18]

Researchers have also reported preliminary biological evidence supporting other proposed mechanisms of action. In one study, ketogenic therapy was associated with significant reductions in levels of brain glutamate, an excitatory neurotransmitter that may play a role in manic episodes [13], while another reported a 32% increase in brain-derived neurotrophic factor (BDNF), a protein involved in learning, memory, and neuronal resilience.[14]

Looking Ahead: Treating Metabolic Health as Part of Mental Health

While findings to date are encouraging, larger randomized controlled trials and longer-term studies are needed to better define efficacy, identify which patients are most likely to benefit, and clarify the role of ketogenic therapy within psychiatric care.

As understanding of the links between metabolic health and brain function continues to evolve, ketogenic therapy represents a promising new frontier in the treatment of serious mental illness.

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