

Obesity medicine expert discusses the connection between metabolism and mental health

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Recent data from the Centers for Disease Control and Prevention reveals that more than 40% of American adults are classified as obese and 36%

report symptoms of anxiety, depression or both. According to Shebani Sethi, MD, a clinical assistant professor in psychiatry and behavioral sciences, the two epidemics are closely linked.

Board-certified in both psychiatry and obesity medicine, Sethi is the founder of Stanford Medicine's Metabolic Psychiatry Clinic, the first academic clinic focused on treating patients with both mental [illness](#) and [metabolic disorders](#)—conditions like [insulin resistance](#) or pre-diabetes, high cholesterol, hypertension, and overweight or obesity.

Sethi coined the term "metabolic psychiatry" in 2015 after seeing a high prevalence of metabolic disorders among her treatment-resistant psychiatric patients and realizing that to provide proper psychiatric care, she needed to address the two problems simultaneously.

She spoke with us about how metabolic disorders affect the brain and how treating mental illness with nutrition can offer new hope for patients.

How do you define metabolic psychiatry?

Metabolic psychiatry is a new subspecialty focused on targeting and treating metabolic dysfunction to improve mental health outcomes. Growing evidence points to a connection between mental illness and altered metabolism in the brain; thus, treatment addressing this dysfunction may improve patient outcomes.

The rates of metabolic conditions are already very high in the general population. [One study](#) found that up to 88% of American adults have poor metabolic health, and in people with psychiatric diseases, the rates are higher. In fact, [research](#) from Stanford Medicine colleagues suggests that developing a metabolic disorder such as insulin resistance can double your risk for depression, even if you have no prior history of

mental illness.

The good news is that in our clinic, we've seen encouraging improvements in mental health after treating metabolic conditions through non-pharmacological methods (including [diet](#) and [lifestyle changes](#)) in combination with medications. [Research](#) shows that those with treatment-resistant [bipolar disorder](#) fared better when insulin resistance was addressed.

For a long time, doctors have thought of nutrition as mostly a secondary therapy, an add-on to medications that might lower blood pressure or improve diabetes. But we have realized that nutritional metabolic therapy can serve as a significant medical intervention for mental illness, one that can change the structure and function of the brain. We take lessons from our neurology colleagues who recognized over a century ago the links between metabolism in the brain and body, which led to successfully treating pediatric epilepsy with ketogenic diets before the advent of the first anti-seizure drug.

It's easy to see how mental illness could lead to conditions such as obesity or diabetes because someone who's struggling mentally might be unable to eat well or exercise. But you're saying the reverse is also true. How does that work?

We don't know all the mechanisms, but we do know that patients who are diagnosed with a first episode of schizophrenia—before they've even been treated with medications—already have disrupted insulin and glucose metabolism in the brain.

As insulin resistance develops, the brain becomes "leakier," meaning more substances can pass through the blood-brain barrier and get into

brain tissue. This results in a buildup of toxic substances and increased inflammation. We see significantly more inflammation in the brains of people with mental illness, especially in treatment-resistant patients, than in healthy people.

There has also been a lot of [research](#) over the last century regarding metabolism and mitochondrial dysfunction, and how that affects brain activity in mental illness. Mitochondria are the site for energy production and consumption in the cell. If they aren't working properly, the communication and connections between brain cells—also known as neural networks—are less stable, which impairs cognition and worsens mental health.

We're studying whether a change in diet, in particular a ketogenic diet, can improve this instability in the brain. Working alongside a neuroscientist colleague from UC San Francisco, Judith Ford, we are recruiting patients who have been diagnosed with either bipolar disorder or schizophrenia in a [randomized control trial](#) that explores the effects of a ketogenic diet on insulin resistance and neural network stability, as measured through functional MRI.

Can you tell us more about the ketogenic diet and why it might be beneficial for some patients with severe mental illness?

I want to stress that a ketogenic diet is not for everyone. It should really be called a therapy rather than a diet, because it's a metabolic intervention meant to be undertaken with medical supervision.

That said, a ketogenic diet is a very low-carbohydrate, [high-fat diet](#) with moderate protein intake. Patients on this diet avoid bread, rice, pasta and cereals, while consuming whole foods like eggs, avocado, nuts, fish and

chicken. Vegetarians can also go on a ketogenic diet, but food options may be limited.

Restricting carbohydrates forces the body to burn fat for energy and causes the liver to make compounds called ketones, which can be used to fuel brain cells instead of glucose. In our clinic, we try to sustain patients in what we call "nutritional ketosis," which means their bodies get all the necessary nutrition while maintaining blood levels of ketones between 0.5 and 5 millimolar. (This is quite different from ketoacidosis, a dangerous state of 50 millimolar ketones or higher.)

Although ketogenic diets sometimes get a bad rap, lumped together with fad diets that can be dangerous or hard to maintain, ketogenic diets have been used for decades to treat pediatric epilepsy and other neurodegenerative conditions. There's a lot of research showing that ketogenic diets increase the growth of mitochondria and reduce inflammation and oxidative stress in the brain, but until now, no one has studied the effect of a ketogenic diet specifically on mental illness.

You recently completed a pilot study of patients with severe mental illness who tried the ketogenic diet for four months. Can you describe some of your preliminary results?

In this [pilot study](#), we taught 22 patients with severe bipolar disorder or schizophrenia how to maintain a ketogenic diet. It was all real-world, meaning we didn't control food intake in a temporary inpatient setting and we didn't deliver meals, but instead taught patients how to buy and prepare their own food. Despite the severity of their mental illness, our patients were able to successfully adopt the ketogenic diet as a lifestyle change. However, there is a selection bias, as those who entered the study may have been a more motivated population.

After four months, our preliminary results were very encouraging: They included a 30% reduction in central abdominal fat, an 11% drop in BMI and a 17% drop in cardiac inflammation, as measured by a marker called high-sensitivity C-reactive protein. Perhaps most importantly, we saw a 30% improvement in our patients' clinical global impression inventory, which is the gold-standard psychiatric assessment we use to evaluate symptoms of mental illness. Additionally, we saw improvements in sleep.

We are analyzing the rest of the data and will present our results at the International Society for Bipolar Disorders conference next June. Also, we are enrolling patients for randomized control trials to compare a [ketogenic diet](#) with diets based on the standard USDA [Dietary Guidelines](#). It's one step at a time, but if we're able to change the structure and function of the brain through non-pharmacological methods like diet, that's a very positive step forward for chronic [mental illness](#).

Can you give an example of a patient who might be treated in your clinic? How is your approach different from treating only their mental illness or only their metabolic disorder?

I treat patients who have either a psychiatric condition alone or a psychiatric condition as well as a metabolic issue, including patients with eating disorders. After I do a physical exam, take a full medical and psychiatric history, and review metabolic biomarkers, I evaluate the patient's eating pattern and medications to see what metabolic interventions might be appropriate.

I rely heavily on non-pharmacological interventions and do a lot of nutrition counseling, which I find very satisfying. Often, my patients

have misconceptions about what's healthy and what's not, so I start from scratch and teach them "Nutrition 101," taking a science-based approach. I also evaluate whether certain types of therapy or medications might be helpful: Are they an emotional eater or not?

Although medications can be life saving, some psychiatric drugs can contribute to metabolic dysfunction, so I collaborate with my patients' other doctors to adjust their medications when possible—avoiding medicines that cause weight gain or insulin resistance. After all, in our Hippocratic oath, we vow to use all measures available to benefit our [patients](#), including dietary regimens.

Provided by Stanford University Medical Center

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