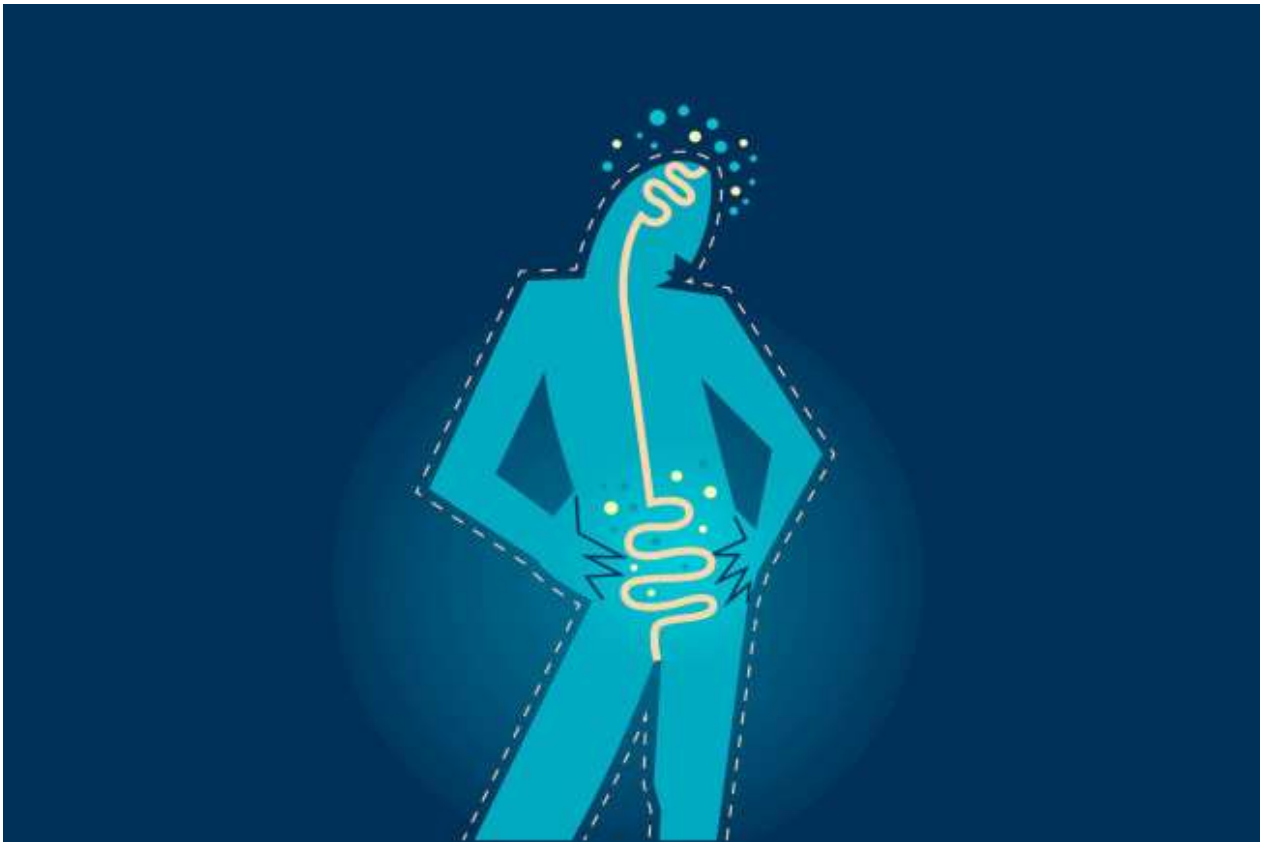
MIND

Gut Bacteria's Role in Anxiety and Depression: It's Not Just In Your Head

Mounting evidence shows bugs in your digestive system influence the brain. Experts are now testing psychobiotics as mental health remedies.

By Elizabeth Svoboda | October 4, 2020 6:00 PM



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Every muscle fiber in Tom Peters' body seemed to be conspiring to keep him in bed. His depression — an occasional visitor for more than a decade — had reemerged in the summer of 2019, and his legs and arms felt like concrete. The thought of spending another 12-hour day at his computer filled him with dread. As a technical day trader for stocks, he responded to demanding clients constantly. That felt impossible when his brain kept blaring his past failures at top volume.

Fielding the volley of work messages became a Sisyphean task. "There's always the overriding fear that I'm not going to come out of it, that I'm always going to feel this way," Peters says. "That probably is the scariest thing."

Peters, 50, had read about mood probiotics, gut bacterial strains marketed to help with depression and anxiety, but never felt like they were for him. "I was very skeptical," he says. When his wife, who was battling panic attacks, tried mood probiotics and saw her episodes diminish, he began to reconsider. After his depression symptoms returned last summer, and the Prozac he'd tried in the past had lost its potency, his wife went online and ordered him a bottle of the same oatmeal-colored capsules she was taking.

For decades, experts scoffed at the idea that gut bacteria affect our mental health. Many called it a fringe theory. Yet mounting evidence suggests that intestinal microbes profoundly shape our thinking and behavior. Human trials are now underway to investigate how these microbes boost our overall well-being. If the results hold up, new bacteria-based therapies could expand a mental health treatment landscape that has been mostly stagnant for decades.

"Current treatments [for mental health] are not great," says University of Calgary psychiatrist and microbe researcher Valerie Taylor. "When they do work, many of them are intolerable. People are desperate."

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More Than a Feeling

Anyone who's sprinted to the bathroom moments before a speech or felt a wave of nausea after public humiliation knows the gut and the brain are connected. Doctors have speculated about this linkage since ancient times. Hippocrates, who is credited with saying "all disease begins in the gut," speculated that black bile spilled from the spleen into the intestines and brought on dark moods.

Theories like these grew more sophisticated over the centuries as scientists learned more about the microorganisms in the human gut. (We now know there are literally trillions of them.) By the late 19th century, doctors argued that "melancholia," a then-common term for depression, arose from overgrowth of intestinal microbes. But physicians at the time understood little about what these microbes did in the body. So, early gut-based treatments — including major abdominal surgery for schizophrenia — were doomed to fail.

human cells in the body by a factor of at least 1.3 to 1. The human gut plays host to more than 100 trillion of these bacteria — a complex, interdependent microbial universe wedged between your ribcage and spine.

While the human genome consists of roughly 25,000 genes, the swarm of microbes in your gut expresses about 3 *million* distinct genes. Many of these bacterial genes help build molecules that let you digest food, keep harmful microbes at bay, and even feel emotions. For starters, the bacteria in your gut produce about 90 percent of the serotonin in your body — yep, the same happy hormone that regulates your moods and promotes well-being.

For Peters, the prospect of a new path looked tantalizing after enduring the marathon of traditional options. He had gone through multiple stints on Prozac — a selective serotonin reuptake inhibitor (SSRI) — and wondered if he'd maxed out the drug's potential. "I went off them for a while, then I went back on them, and I felt like I developed a resistance of sorts," he says. It's a familiar tale for almost anyone who takes SSRIs for long-term depression.

Years earlier, when Peters' old dose of Prozac wasn't working as well, his psychiatrist had prescribed him a new, higher dose, one that brought on annoying side effects. "On the higher dose, I felt like I was more sluggish," Peters says. "It drove me crazy." The memory of that unrelenting brain fog helped persuade him to give probiotics a try.

What Happens in the Vagus

In the mid- to late 2000s, John Cryan of Ireland's University College Cork was among the first to explore gut microbes' effects on the brain. A neurobiologist by training, Cryan had shown that rats stressed from birth later showed signs of both irritable bowel syndrome (IBS) and mood disturbance. "When they grew up," Cryan says, "they had a whole-body syndrome." This finding echoed doctors' observations that many patients with digestive symptoms also had mental health issues, and vice versa.

more relaxed counterparts. "It got us thinking — if you stress an animal, [maybe] there's a signature in the microbiome that's persisting," Cryan says.

In the past decade or so, more labs have started reporting that gut bacteria produce a smorgasbord of compounds that affect the mind in surprising ways, both good and bad for your emotional health. Some bacteria in the *Clostridium* genus generate propionic acid, which can reduce your body's production of mood-boosting dopamine and serotonin. Microbes like bifidobacteria enhance production of butyrate, an anti-inflammatory substance that keeps gut toxins out of the brain. Other species produce the amino acid tryptophan, a precursor to mood-balancing serotonin.

(Credit: SeanidStudio/Shutterstock)

Rather than passing from the gut to the brain via bloodstream, some of these chemicals affect the brain through intermediate channels, says University of Pittsburgh clinical research psychologist Lauren Bylsma. A major one, the vagus nerve, functions like a communication superhighway between the brain, gut and other organ systems in the human body. Recently discovered neuropod cells can activate or deactivate the vagus nerve, which interfaces with neurons in the brain. Research shows that certain gut bacteria help activate those neuropod cells.

While researchers continue to map the workings of what they've dubbed the "gut-brain axis" — the

evidence to support the notion. Earlier this year, Cryan and a team of international colleagues gave a group of stressed mice regular doses of a *Bifidobacterium* gut microbe for five weeks. By the end, the mice were more mobile and active than before. They were also more willing to interact and explore new areas.

The whole time, Cryan tracked changes in the mice's gut bacteria. During a treatment with *Bifidobacterium breve*, their gut bacteria started making more tryptophan. Treated mice also produced more of a protein called brain-derived neurotrophic factor (BDNF), which helps new neurons grow.

Even as scientists highlight these kinds of connections between gut microbe treatments and symptom improvement, the question of causality has lingered: Do gut bacterial changes actually drive mood and behavioral changes? A growing body of research suggests they do.

Several innovative studies since 2016 show that fecal transplants can shape behavior profoundly, according to Bylsma and Taylor. When mice in one Chinese study got transplants of feces from other healthy mice, their behavior remained unchanged. But when mice received fecal transplants from donors with signs of anxiety and depression, the mice started to show signs of mood disturbance. A separate study published in *Molecular Psychiatry* showed mice that received fecal transplants from depressed humans also developed depressive symptoms. On the other hand, stressed-out mice in a 2019 study received transplants from unstressed animals and began acting less depressed. By changing the intestinal microbiome, researchers "can actually change the rodents' behavior," says Bylsma, who was not involved with the studies. "That implies there is a causal effect."

From Petri Dish to Human Body

human-to-human poop exchange. Often, people ingest the feces in a pill. Sometimes, doctors offer poo-rich enemas to seed the digestive tract with new microbes. Taylor has started two small-scale fecal transplant trials — the first on people with bipolar disorder, and the second on those with depression — to find out whether feces from healthy human donors boosts recipients' moods and well-being. She is also taking samples of subjects' gut microbiomes before, during and after treatment to track any notable changes.

Human studies of oral probiotic therapy are a bit further along. A survey of small-scale controlled trials found that *Bifidobacterium* and *Lactobacillus* strains improved depressive symptoms overall, while other studies show similar effects on anxiety. One Australian study published in 2017 even suggests that a diet higher in beneficial bacteria can banish depression in more than a third of people. Microbes have also shown promise for less common mental health disorders: In a 2019 paper on a Japanese trial, 12 of 29 participants with schizophrenia who ingested a specific *Bifidobacterium* strain saw their depression and anxiety symptoms lift within four weeks.

Microbiologist Jeroen Raes thinks the cosmos of gut microbes that affect the human brain may be even larger than these initial trials suggest. Raes and his team at Belgium's VIB-KU Leuven Center for Microbiology have harvested poop samples from more than 1,000 people, scanning for gut microbe profiles that accompany their reported mood symptoms. So far, he's found that people with more butyrate-producing gut microbes — such as certain types of *Faecalibacterium* and *Coprococcus* — have a higher quality of life, while people with lower levels of *Coprococcus* are more likely to be depressed.

"psychobiotics." In that potential treatment universe, people with depression, anxiety or other mental health issues would routinely have their gut microbiomes sequenced. Those with high levels of bacteria tied to poor mental health, or low levels of bacteria that healthy people have in abundance, could receive a tailored probiotic or fecal transplant to fix the imbalance.

The probiotic strains Peters began taking — *Lactobacillus helveticus* and *Bifidobacterium longum* — hadn't been vetted in large-scale human clinical trials. But they have shown some mood-lifting promise in smaller human studies. Even so, before Peters popped one of the capsules for the first time, he felt his natural skepticism rearing up.

About a week into his new regimen, though, he began to notice a subtle mood shift that soon became more pronounced. "I felt sharper, more energetic — just a more positive outlook in general," he says. "I felt like I was more relaxed at night." Putting in a day at his desk no longer felt like rolling boulders up a hill. It wasn't that he was abnormally happy, or that he had endless reserves of enthusiasm. Instead, what he felt was an anchoring inner calm, as if the choppy waves he'd been riding had receded.

A Proving Ground

The next psychobiotics milestone, scientists say, will be full-scale clinical trials that show whether microbes or microbial cocktails boost well-being beyond placebo effects common in psychiatric treatment studies. "You need trials, and you need placebo control in those trials," Raes says. "If you have a trial that works, you need to replicate it in an index population."

We'll likely be waiting at least two years for those definitive results. One sticking point in the outcome could come from drug companies, and whether they can identify a substantial profit. Many gut-based remedies contain naturally occurring bacteria, which makes them difficult to patent.

"Who's making the money? It's not as obvious as in other areas," Cryan says. "If this was a pharmaceutical strategy, it would be very clear." (Strandwitz plans to get around this problem by patenting compositions of microbes and a particular way of delivering them to patients.)

Another issue is that, while certain types of bacteria have more profound effects on the brain than others, there probably won't be any magic-bullet strains that work for everyone. Some gut bacteria function best alongside a constellation of varieties, complicating the picture further — especially since gut bugs number in the trillions and represent more than 500 different species. "One bacterial profile might be good for one person and one for another person," says Bylsma. "The findings are not always consistent." And with fecal transplants, it can be difficult to control exactly which bacterial species a patient receives.

have already begun. In some circles, at-home fecal transplantation has exploded in popularity, fueled by testimonials that sing praises. But experts strongly discourage this, as stool samples that have not been tested could contain bacteria that cause life-threatening illness. "It is extremely dangerous," Raes says. "You do this at home, you have no control."

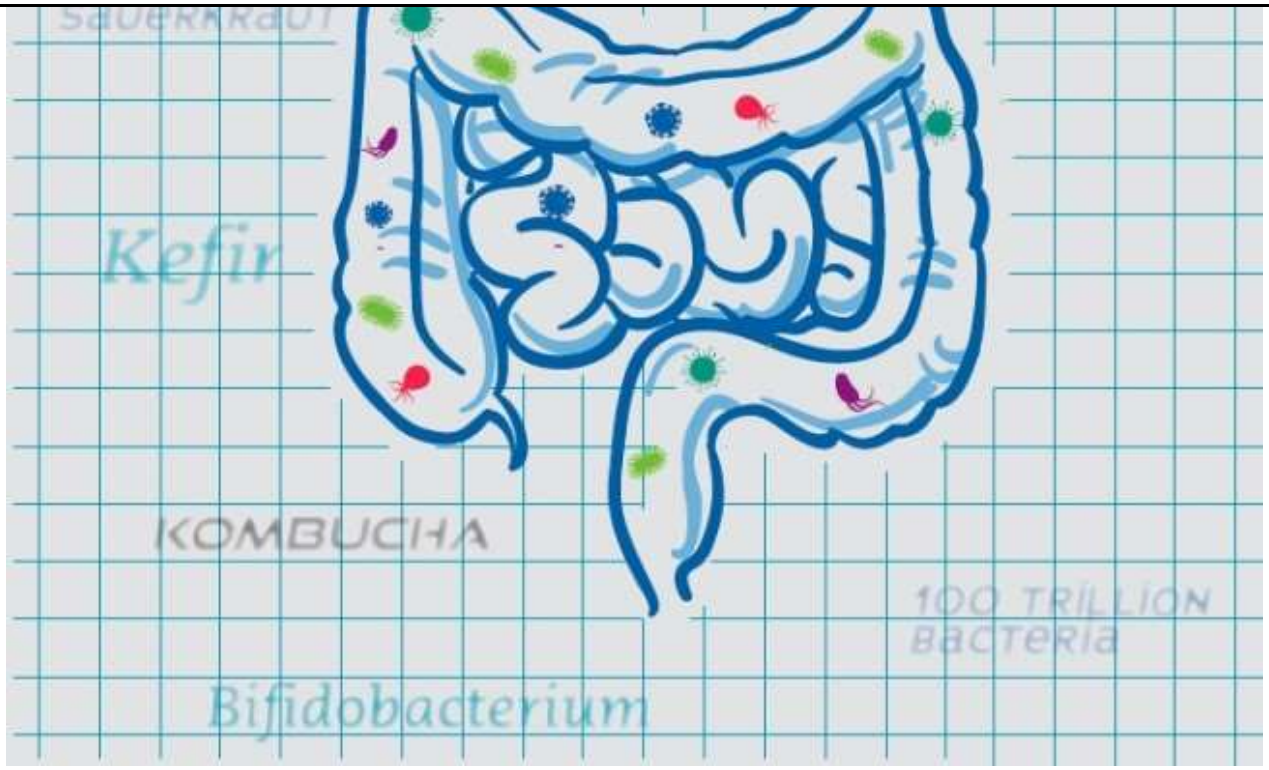
Over-the-counter probiotics offer a more mainstream DIY options. While doctors generally regard common strains like *B. breve* and *L. acidophilus* as safe for human consumption — they appear in foods like yogurt, kombucha and kefir — bacteria are bioactive substances, so ingesting them involves some level of risk.

And in the U.S., the supplement industry is largely unregulated. That means consumers have to take companies' word that probiotics contain the strains listed on the label.

Given the rapidly evolving state of gut-brain research, experts don't all agree on how to advise patients seeking treatment options. Raes won't recommend any gut-based therapy before it goes through full clinical trials. But Taylor contends that even if probiotic strains' effects on mood remain unproven, they don't appear harmful. When patients ask about probiotics, she doesn't discourage them from trying them out.

Peters avoids dissecting the sequence of internal events that banished his depression; he's just thrilled it's gone. Stress and time pressures remain constant in his work life, but he feels like he navigates these bumps more gracefully. "There are days I'm able to focus a thousand percent and there are days I'm not as productive, but there's more stability," he says. "It's not like a yo-yo, way up one day and way down another." Along with the probiotics, he takes a Prozac dose that's a fraction of what he took in the past. It has kept his old brain fog at bay. "To be able to get an extra hour or two out of my day so I can be present for my kids — to me, that's amazing."

What We Know About Probiotics



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It's becoming clearer that some probiotics help make your gut happy. A major review of recent studies shows they can treat irritable bowel syndrome (IBS) and various types of diarrhea. But navigating the options (and false claims) can be, well, a crapshoot. For example, a probiotic that treats influenza or common cold symptoms? There's little evidence to support this.

As for the impact on mental health, larger human trials will help determine their effectiveness. Meanwhile, a decade-plus of experimental study has helped researchers assemble a firststring lineup of promising bacterial strains. But those interested should proceed with caution. The probiotic supplement industry in the U.S. is "not FDA-regulated, so there could still be a risk," says Lauren Bylsma, a University of Pittsburgh clinical research psychologist.

Common treatments include:

Fermented foods: Foods like sauerkraut, yogurt and kefir — a type of fermented milk — naturally contain bacterial strains tied to anti-depressive effects, such as Lactobacillus helveticus or Lactobacillus acidophilus. That might explain the mood lift some people report from eating them.

L. helveticus and Bifidobacterium longum: This bacterial duo — a common combo in products

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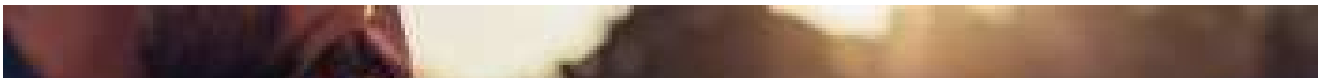

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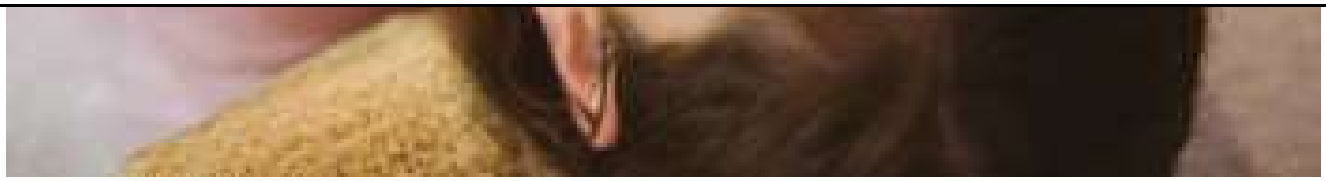

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