Rethinking Depression: Moving Beyond the "Chemical Imbalance Theory" Towards Gut-Centric Alternatives

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Abstract

The treatment landscape for depression has long been dominated by the notion of a chemical imbalance in the brain, a model perpetuated by the widespread prescription of Selective Serotonin Reuptake Inhibitors (SSRIs). However, recent critiques challenge the validity of this theory, highlighting the lack of substantial evidence and questioning the mechanisms of SSRIs. Despite their efficacy for some, SSRIs fail to provide relief for many individuals, underscoring the urgent need for alternative treatments. This paper traces the historical evolution of depression theories from ancient beliefs to modern psychiatry, focusing on the rise and fall of the chemical imbalance theory. While hailed as miracle drugs, the true efficacy of SSRIs remains elusive, clouded by uncertainties regarding their mechanisms of action.

Amidst this uncertainty, emerging research in nutritional psychiatry offers promising alternatives to traditional pharmacological approaches. Studies suggest a link between the microbiome and mental health, with evidence supporting the benefits of dietary interventions and probiotics in mitigating depressive symptoms. Embracing a functional medicine approach that combines conventional and natural interventions could revolutionize depression treatment. By acknowledging the individuality of depression and tailoring treatment plans accordingly, psychiatrists can better address the diverse needs of patients. Integrating non-traditional approaches into mainstream psychiatry, however, poses several challenges.

Through critical analyses of professional discourse, media, and recent research, this paper advocates for a paradigm shift in depression treatment, moving away from the simplistic notion of a chemical imbalance towards a more holistic and personalized approach. By exploring alternative treatments and fostering collaboration between conventional and natural medicine, we can better serve the diverse needs of individuals struggling with depression.

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Introduction

Depression has affected people for as long as humans have roamed the earth, although it wasn't recognized as a "disorder" until around the 19th century. Today, it affects more than 350 million people worldwide and 8.3% of the US adult population. Despite its longevity and the numerous professionals who specialize in treating it, many individuals will never gain relief from their depression. At their outset, pharmaceuticals for depression were boasted as miracle drugs. Although they have fallen short of delivering this promise, they remain the predominant treatment for depression and other mental health issues today.

Up until only a few years ago, psychiatrists and pharmaceutical companies perpetuated the false narrative that depression is caused by a chemical imbalance in the brain. The advent of this theory was followed soon after by the development of novel drugs known as SSRIs, which were said to cure depression by restoring depleted serotonin in the brain. To this day, there lacks significant evidence to support both this theory and the proposed function of SSRIs. Nonetheless, SSRIs were taken by storm and have become one of the most prescribed drugs in America–and not for no reason. SSRIs provide some relief in about 46 to 60 percent of users, and for many people, have been a lifesaving drug. For some, however, the relief they experience from depression is obscured by a plethora of distressing side effects. Additionally, no one knows exactly *how* SSRIs treat depression, not even the most distinguished researchers or psychiatrists. In fact, the exact causes of depression are still up for debate. What we do know is that the other 40 to 54 percent of people that SSRIs don't work for are in dire need of an alternative.

The idea of mental disorders being solely contained within the head has experienced a paradigm shift in the past decade. The denunciation of this theory in just a few journal articles spread quickly in the media, leaving many patients on SSRIs perplexed. The media portrayed

SSRIs as a farce and psychiatrists as fraudsters, leading some patients to lose trust in their providers. Yet, even before this dispute had reached the media, psychiatric research was underway in search of improved treatment options. Nutritional psychiatry, for instance, is an emerging field of research that regards food, supplements, and lifestyle changes as potential alternatives to SSRIs. Though in its early stages, the research is proving to have immense promise. Significant improvements in depressive symptoms have been observed from treatments including specific nutrients, probiotic bacteria, and even strict dietary regimens. But unlike SSRIs that had huge pharmaceutical companies rooting for their success, natural remedies for depression lack the support and necessary funding to gain traction. As a result, some patients have taken matters into their own hands by executing their own alternative regimens.

Despite the response rate to SSRIs not getting any better, the approach to this illness has stagnated over the past several decades with there being little initiative to make change. This report seeks to bring awareness to emerging treatment options, as well as some of the obstacles to their implementation, in hopes of sparking urgency to establish more effective remedies. In a country where depression kills more people per year than motor vehicle accidents, patients deserve more than a band-aid drug.

The Evolution of Depression and the Chemical Imbalance Theory

Centuries before Depression was established as a diagnosis in the DSM-III, religious figures, philosophers, and doctors theorized several different causes or origins of mental anguish. The earliest known cases of depression were in the second millennium B.C.E. in Mesopotamia. At this time, mental ills were believed to be caused by demonic possession and were dealt with by a priest. This belief was shared across several cultures, including Ancient Greeks, Romans,

Chinese, and Egyptians, who often utilized unfortunate practices like beating and starving to cure patients of their evils (Schimelpfening, 2023). While Greek and Roman philosophers and physicians had theorized more physiological explanations–such as Hypocrates' idea of the four imbalanced body fluids called humors–spiritual explanations held by well-respected Romans prevailed well into the common era, as well as the harsh and barbaric treatments it warranted.

Depression gained its association with the brain from a Persian doctor named Rhazes in 925 BC, who was the first to propose behavioral therapies with positive rewards as opposed to the torture that had preceded (Schimelpfening, 2023). Doctors like Rhazes, however, were in the minority through the Middle Ages and well into the Renaissance, as religion dominated European thought and the perception of mental illness. Many mentally ill people during the 17th century were placed in "lunatic asylums" in which they were locked in small cages or kept within city walls (Schimelpfening, 2023). Towards the end of the Renaissance period, the voice of physicians began to regain some influence. Many resonated with Robert Burton's 1621 publication, *Anatomy of Melancholy,* which detailed the supposed social and psychological causes of Melancholia–today's major depressive disorder (MDD)–including fear, loneliness, and toxins in the body amongst others. In his book, he recommended remedies like diet, exercise, herbs, and music, which mirror what are considered holistic or functional approaches today. This framework was overcome, however, by the influence of the Enlightenment, during which depression was purported as an inherent weakness of temperament or aggression, resulting in many being locked away or shunned by society.

The term psychiatry was first used in 1808 to describe the new and evolving discipline, which became a medical specialty in the late 18th and 19th centuries (though practitioners were referred to as "alienists" until the 20th century) (Bhugra & Gupta, 2011). The field took off in the

19th and 20th centuries with the emergence of several influential theories. Namely, the psychodynamic theory was founded by Austrian neurologist Sigmund Freud, who was renowned for his unique take on behavior and depression. Freud believed individuals possessed an internal, unconscious mental force that drove them to emotions and actions (Schimelpfening, 2023). While this is no longer the dominant model, Freud's emphasis on inner work and providing individuals with the tools to handle their internal conflicts can largely be considered the seed from which modern-day therapy grew.

The 20th century marked a shift away from the "inner conflict" perspective to the idea of depression as a conscious behavioral issue. The behaviorist movement, emerging in the early 1900s, suggested that depression and other mental illnesses were learned behaviors. Adherents of the movement believed such behaviors could be unlearned using practices like reinforcement to establish healthier behaviors (Schimelpfening, 2023). Cognitive theories emerged near the end of the behaviorist movement in the 1960s and 70s, causing some overlap between the two theories. Cognitive theorist Aaron Becks and psychologist Martin Seligman viewed depression as an error in the way individuals process information and interpret events; automatic interpretation of events as negative or the feeling of helplessness over situations, they believed, is what causes depressive symptoms. These early perceptions of depression played a large role in the development of cognitive behavioral therapy (CBT), a method of 'training' to prevent errors of cognition (citation). CBT has persisted as a prevalent framework in mental health care today.

Treating Depression

The 19th and 20th centuries saw a dramatic shift away from theories focused solely on experiences or personal traits towards a hybrid model in which biological, psychological, and social factors each play a role in the development of depression. Additionally, the 20th century

was the first time in which physicians began treating depression as a physiological condition–something that patients cannot control or "reverse" on their own. Depression was subjected to the same 'one organ-one target' paradigm that many other physical ailments had fallen under, thus warranting similar treatments: medical procedures and pharmaceuticals. While researchers toggled with factors such as genetics, hormones, and brain anatomy in search of an etiological explanation, treatments for depression failed to produce significant improvements. Lobotomies–a surgery that breaks the connection between the frontal lobe and the thalamus–were popularized by Dr. Walter Freeman in the 1940s (Mcleod, 2023). Patients who underwent this procedure reported feeling calmer, but often experienced a change in personality or complications that were fatal, leading to its ill repute by the late 50s. Electroconvulsive Therapy (ECT), which induces seizures in patients, flourished in the late 1940s and 50s (Mcleod, 2023). What was originally used in severe cases of schizophrenia and major depression eventually became a mainstay biological treatment for several psychiatric disorders. While ECT was effective in reducing depressive symptoms, ethical ramifications–such as its use as a threat in mental hospitals–led to the gradual descent of its popularity. Everything changed with the discovery of isoniazid, a medication for tuberculosis that was found to effectively reduce depressive symptoms in the late 50s (Schimelpfening, 2023). In the coming decades, this discovery would not only dramatically change how depression was treated, but also how it was discussed and depicted to the public. For example, pharmaceutical publications such as the 1967 article in **Figure 1.,** often presented depression as inevitable for women and mothers, and pharmaceuticals as the easy fix.

You can't set her free.
But you can help her feel less anxious.

You know this woman.

She's anxious, tense, irritable. She's felt this way for months.

Beset by the seemingly insurmountable problems of raising a young family, and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance may have helped some, but not enough.

SERAX (oxazepam) cannot change her environment, of course. But it can help relieve anxiety, tension, agitation and irritability, thus strengthening her ability to cope with day-to-day problems. Eventually—as she regains confidence and composure—your counsel may be all the support she needs.

Indicated in anxiety, tension, agitation, irritability, and anxiety associated with depression.

May be used in a broad range of patients, generally with considerable dosage flexibility.

Contraindications: History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychoses.

Precautions: Hypotensive reactions are rare, but use with caution where complications could ensue from a fall in blood pressure, especially in the elderly. One patient exhibiting drug dependency by taking a chronic overdose developed upon cessation questionable withdrawal symptoms. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive prolonged use in susceptible patients (alcoholics, ex-addicts, etc.) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Caution patients against driving or operating machinery until absence of drowsiness or dizziness is ascertained. Warn patients of possible reduction in alcohol tolerance. Safety for use in pregnancy has not been established.

Not indicated in children under 6 years; absolute dosage for 6 to 12 year-olds not established.

Side Effects: Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever, euphoria and dysmetria.

Availability: Capsules of 10, 15 and 30 mg. oxazepam.

To help you relieve anxiety and tension

Serax® (oxazepam)

Wyeth Laboratories
Philadelphia, Pa.

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Figure 1. Article on Serax (oxazepam) published in the Journal of the American Medical Association in 1967 by Wyeth Laboratories.

The first antidepressant to hit the market was Tofranil (imipramine) in 1959, followed by several other medications categorized as tricyclic antidepressants (TCA). Tofranil was originally developed to treat schizophrenia but failed as an antipsychotic. Instead, Tofranil and other TCAs were found to alleviate depression symptoms in schizophrenia patients with comorbid depression and later were proposed to block the reuptake of 5-HT (also known as serotonin) and norepinephrine (Ang et al., 2022). While these early medications were effective, they came with many concerning side effects including disorientation, confusion, and the potential for overdose.

By the early 1960s, psychiatrists were beginning to recognize the need for a greater understanding of *what* they were treating before an effective drug could be established. Etiological research for depression blossomed during this time, but because a direct investigation of the brain's neurochemistry wasn't yet possible, theories of depression were derived mainly from the observed actions of antidepressants. With each new antidepressant development, a pattern became increasingly evident: the drugs were multiplying the level of

monoamines–neurotransmitters involved in mood and emotional regulation–in users' brains. Further research involving drugs that lowered monoamine levels even seemed to cause depression in some individuals (Ang et al., 2022). An accumulation of several observations like these led to the prominent theory of the 1960s– "the monoamine hypothesis". This theory, which attributed depression to monoamine deficiency, was widely accepted among practitioners and swiftly influenced the development of serotonin reuptake inhibitors (SSRIs).

Much of the initial public interest and excitement around antidepressants–such as Effexor, Ritalin, and Serax–was attributed to the advertisements. Magazines, newspapers, and journals like the *American Journal of Psychiatr*y depicted women smiling and in relief; their ability to complete everyday tasks like cleaning dishes or taking care of their kids had been restored; and they could finally be themselves again with the simple fix of a drug. One of the first psychiatric drugs to be marketed in this way was Miltown (meprobamate) (*CBC Radio*, 2017). Miltown was the first widely prescribed mental health pharmaceutical as well as the first "blockbuster drug." Although today it is classified as a sedative, Miltown was widely marketed towards women as an anti-anxiety, anti-tension drug, using some eye-opening headlines like "Take the misery out of menopause," and "Pregnancy can be made a happier experience." Carter Products, the producers of Miltown, were one of the first pharmaceutical companies to realize the immense market they had in housewives, presenting depression and anxiety as something "normal" women are afflicted with. The stereotypical depressed housewife became the premise for the majority of antidepressant advertisements in the coming decades.

While these advertisements appear as nothing more than a marketing scheme to today's viewers, such language and imagery may have been somewhat beneficial for the community of depressed individuals, beyond influencing them to take a particular drug. Open discussion of

depression in the media normalized the concept of everyday people having mental struggles and inspired more to seek help for their condition unashamedly. What was once taboo and misunderstood was now a condition many could accept and talk about openly, especially now that relief was obtainable in the comfort of one's home. Unfortunately, how depression was depicted in these advertisements was far from accurate, likely laying the foundation for existing stigmas around mental illness today. While 2.5 times as many women take antidepressants as men, and statistically, women are two times as likely to be diagnosed with depression, the reality is that men are likely equally affected by depression but less inclined to seek the help they need. This unfortunate reality may be partly due to these early illustrations that suggested mothers and housewives were the only people in society who could become depressed. Despite its inaccuracy, this was the picture that continued to be painted well into the 20th century, as demonstrated by the advertisement in **Figure 2**.

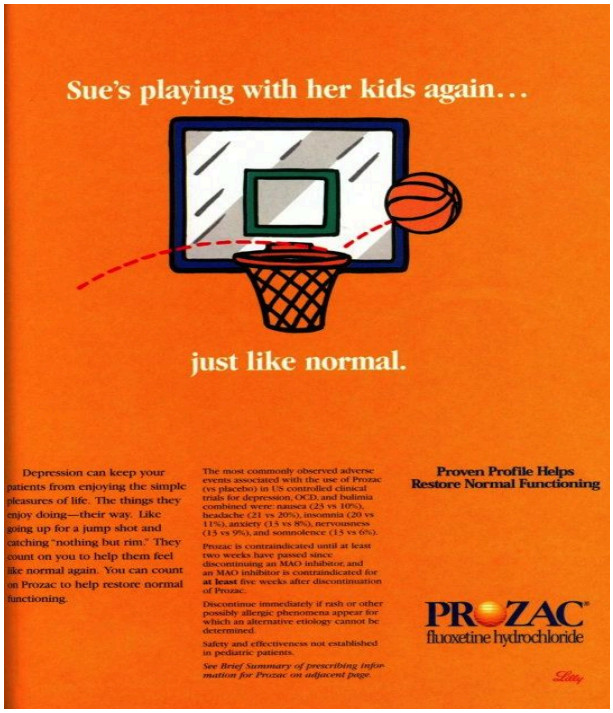

Figure 2. 1886 advertisement for Prozac (fluoxetine hydrochloride) published by Eli Lilly Pharmaceutical Company

Selective Serotonin Reuptake Inhibitors

The first SSRI to be approved by the FDA was Prozac (fluoxetine) in 1980, around the same time that Major Depressive Disorder was established in the DSM-III (Schimelpfening, 2023). Unlike the pharmaceuticals that preceded it, Prozac was designed to target what was believed to be the exact cause of depression, without the unwanted side effects. Consequently, its

development sparked a monumental change in the antidepressant market; SSRIs began to rapidly hit the shelves and quickly became the dominant treatment for depression and mood-related disorders. In addition to their marketing, the language used in many psychiatric publications and by large pharmaceutical companies around SSRIs created the perception of an idealized scientific relationship between the drugs and depression, which further legitimated the serotonin theory and the idea of SSRIs as a "breakthrough" drug. SSRIs were said to work by inhibiting serotonin transporters from pulling serotonin back into the neurons they originated from (presynaptic neurons). Consequently, the serotonin remains in the gap between two neurons called the synapse, where it can interact readily with receptors to send signals to other cells (Mcleod, 2018). A common representation of this mechanism is depicted in **Figure 3**. The enhancement of serotonin activity that SSRIs supposedly allow is what many were made to believe had cured their depressive state. While pharmaceutical companies described depression as a serotonin deficiency that only SSRIs could cure, and professional organizations echoed such rhetoric, the experienced effectiveness of SSRIs was what truly perpetuated the notion that depression is the result of a chemical imbalance in the brain.

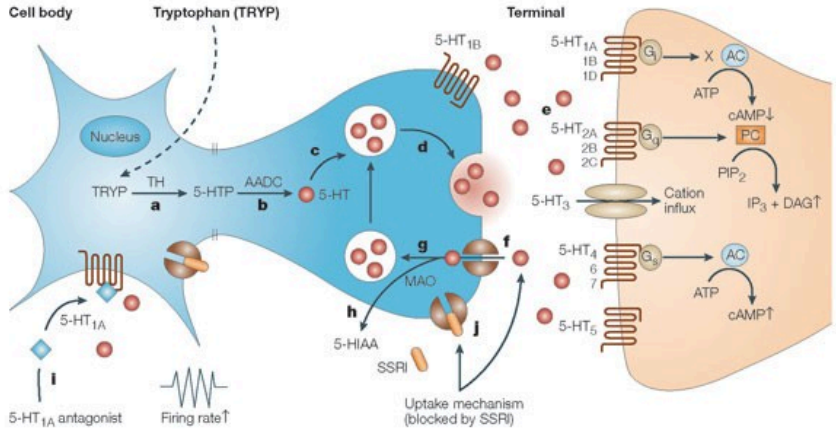

Figure 3. Graphical depiction of SSRI mechanism of action.
SSRI compounds and serotonin neurotransmitters are represented by orange ovals and red circles, respectively.

When Controversy Sparked

Almost immediately after the inception of SSRIs, which led to widespread acceptance of the chemical imbalance theory, several well-known psychiatrists issued publications criticizing the theory. In 1997, psychologist David Healy in *The Antidepressant Era* argued that no abnormalities in serotonin had been substantiated in a way that warranted widespread acceptance of the theory (Ang et al., 2022). Then in 2005, Jeffrey Lacasse and Johnathan Leo published an article in PLOS Medicine challenging pharmaceutical companies' incorrect representation of the serotonin theory in advertising. Lacasse and Leo argued that the medical marketplace was being shaped in a way that benefited pharmaceutical companies rather than consumers. The seductive nature of antidepressant advertisements, they suggested, had influenced patients to present with self-diagnosed chemical imbalances, despite not having a clue what this meant. A sentiment included at the end of the article from Elliot Valenstein, a professor of neuroscience, stated "What physicians and the public are reading about mental illness is by no means a neutral reflection of all the information that is available." Valenstein's input summarizes the distinct incongruency Lacasse and Leo argued had existed between scientific literature and the claims made in SSRI advertisements at the time (Leo & Lacasse, 2005). Finally, Ronald Pies, one of the most prestigious American psychiatrists, in his 2014 article Nuances, Narratives, and the Chemical Imbalance Debate in Psychiatry referred to the chemical imbalance theory as an urban legend, claiming that responsible psychiatrists had never believed or endorsed it. These early attempts to dismantle the chemical imbalance theory received immense backlash from within the psychiatric sphere, as the market for SSRIs was gaining momentum and many practitioners still firmly believed in the science. Having largely taken place behind the scenes, however, this early discourse failed to reach the public until much later.

Healy and Pies, while both rejecting the chemical imbalance theory, were partially responsible for keeping its surrounding controversy at bay and away from the public. In 2011, Pies denounced opponents of psychiatry as having “mendaciously” attributed the phrase “chemical imbalance” to psychiatrists and blamed pharmaceutical companies for perpetuating the theory beyond merely an idea. Yet in an interview at a later date, Pies admitted that the chemical imbalance explanation was often used in practice to save time and comfort patients about their condition, though he denied using it in his own practice. Similarly, in 2015 Healy regarded chemical imbalance as merely “neurobabble” whose influence is attributed to marketing and the public domain, yet in a later statement seemingly condoned doctors using the theory to justify their prescriptions (Ang et al., 2022). At the time, it was predicted that around 85 percent of the American population was convinced that this theory was based on the grounds of intricate psychological research, as SSRI pamphlets and articles from the American Psychiatric Association had made it seem. Consequently, the number of US citizens taking antidepressants daily multiplied fourfold (Ang et al., 2022).

By the mid-2000s, antidepressants had come to be known as “smiles in a jar” or a miracle drug to many. Despite a sprinkling of publications throughout the years denouncing the theory, few psychiatrists commented publicly on the rise of this drug. The controversy around the chemical imbalance theory and SSRIs had been a conversation confined to academics, doctors, and drug makers until the late 21st century when it was brought to light by a large “umbrella” study conducted by Joanna Moncrieff and her colleagues. This review, published in Nature’s Molecular Psychiatry journal in 2022, involved 361 publications in six major areas of research, spanning 56 years.

Beginning in 2020, Moncrieff and colleagues surveyed data from the past decade in search of substantial evidence linking serotonin and depression and ended their study in 2022 with their hands empty. In the report, Moncrieff denounces the serotonin theory of depression, stating that the main areas of serotonin research provide no support for the hypothesis that depression is caused by lowered serotonin activity or concentration. The study paints SSRIs as a type of scientific mystery, speculating on their function as amplified placebos or emotional blunters. Moncrieff details evidence that SSRIs actually reduce serotonin levels, suggesting that they have never done what they were said to do (Moncrieff et al., 2022). This was a hard pill to swallow for the approximately one in five American adults with depression relying on SSRIs every day; however, what was even more shocking to the public was the response from psychiatrists (Brueck, 2022).

Some psychiatrists argued to uphold the theory, stating it was too early to come to such conclusions; others believed Moncrieff's conclusions were drawn from substantial bias and flawed methodology. Since its publication, Moncrieff's umbrella study has been highly criticized. Notably, Jauhar and colleagues, who published “A leaky umbrella has little value” the following year, critiqued Moncrieff's study for overstating conclusions, selectively reporting or oversimplifying data, and errors in their interpretation of research. Jaguar and colleagues specifically cite inconsistencies in the applied metrics for classifying evidence, shedding light on primary studies that were acknowledged but omitted from consideration at the expense of others with less significant results (Jauhar et al., 2023). Contrary to this heated response, the majority of psychiatrists were unphased by Moncrieff’s conclusions, denoting them as “old wine in new bottles” (Kirkey, 2022). Echoing the sentiments voiced by Healy and Pies the decade prior, most psychiatrists responded with something along the lines of “I was not surprised,” or “it was about

time.” According to the large majority of responses, Healy and Pies were right in saying that psychiatrists had never believed depression was due to an imbalance of brain chemicals. Many believed it was a gross oversimplification from the get-go. Yet, what was puzzling to many people was why they hadn't been told sooner. According to some psychiatrists, it was out of concern for their patients.

Individuals often gain comfort from being able to explain their ailments and how they are managed or cured. To many patients with depression, the chemical imbalance theory served as an ounce of hope that they are as normal as ill people can be; that they aren't imagining their pain, and there is a solution to their problem. Depression had diverged far from its earlier views as insanity or animalistic. While there were certainly stigmas around people with mental illness, they were not nearly as pervasive as the “facts” and science. With such a widespread theory suddenly debunked, and skepticism of SSRIs surfacing, many patients were overcome with fear and uncertainty. One moment their pain was understood and treatable and the next they were back to square one–a medical mystery. Some patients were left questioning everything they thought they knew about psychiatry and mental health. Some individuals, like Kelley Manley, were itching to come off of antidepressants in fear of their future health.

Manley, a 43-year-old mom of two children under five, had witnessed her own mother become swallowed by depression until she was ultimately taken by suicide, and found herself battling similar struggles after the birth of her children. After coming off antidepressants in 2010 and trying every natural remedy she could find–breathwork, sound healing, daily exercise, therapy, integrative psychiatry consultations–Manley landed right back where she was 10 years ago, taking Lexapro, just in the wake of Moncrieff's publication. Manley and others were left unsure where to turn next and weary of who to trust. While Manley continued on Lexapro

despite the circulating concerns, many others have not experienced such a happy conclusion to their story (Manley, 2023). Some have experienced crippling withdrawal symptoms as a result of SSRI discontinuation, while others have remained on SSRIs with zero signs of relief and so many questions unanswered: How could one trust a field that had silently deceived them for years upon decades? What was the rationale? Where do they go from here? These questions were posed by even some professionals and are yet to be answered; however, there are many opinions on the matter.

A "War" on Drugs

In an interview with *The National Post*, Marnie Wedlake, a psychotherapist and assistant professor at the School of Health Studies at Western University, exclaimed, "They had a professional duty to tell people…if they knew this was a false narrative…they should have been out there saying, 'No, no, no. Correction.' But they did not. They just let it go." She states later that blaming psychiatry and the drug industry entirely is "too tidy," suggesting that society has pathologized the human condition by using language that medicalizes thoughts and feelings (Kirkey, 2022). With a failing mental health system in a society that has seemingly lost its ability to deal with despair, a simple explanation (chemical imbalance theory) and a quick fix (like SSRIs) might be necessary to keep things under control, especially as psychotherapeutic resources reach peak inaccessibility. Along similar lines, Mark Horowitz, coauthor of the 2022 umbrella study states, "I'm not sure that putting faith in some chemical to make up for social ills that tend to make us depressed is ever going to be a successful way forward" (Brueck, 2022).

Alternatively, some psychiatrists argue that if the drugs work and the people are satisfied, what harm has the silence done? Dr. Allen Frances, a professor emeritus of psychiatry at Duke

University who helped create the fourth edition of the DSM in 1994, made the point that "Continued attacks on the 'chemical imbalance theory' [could] have the harmful unintended consequence of discouraging people with severe depression from taking the meds they desperately need and won't get well without." Frances stresses that "Severe depressions do require meds and rarely respond to anything else" (Kirkey, 2022). In contrast, Moncrieff argues that "whether they work or not depends on how we understand what they are doing," and unfortunately researchers are still yet to understand what causes depression, never mind how antidepressants work (Kirkey, 2022). With the reversal effect of SSRIs losing traction, psychiatrists have begun searching for other explanations for its large success rate. Some believe they have an emotional blunting effect, while others like Harvard professor Irving Kirsch, chalk them up to be nothing more than an amplified placebo effect.

In *Placebo Effect in the Treatment of Depression and Anxiety*, Kirsch evaluated published and unpublished clinical trial data on the placebo response of antidepressants in the treatment of depression and anxiety. Kirsch had previously published three highly controversial meta-analyses on the placebo effect in the treatment of depression, in which he utilized data submitted to the Food and Drug Administration (FDA) between 1979 and 2016. In each of his analyses, Kirsch found that participants given either antidepressants or a placebo both experienced significant improvements according to the criterion for clinical significance by the National Institute for Health Care Excellence (NICE). The difference in outcome between participants on antidepressants versus placebo, however, was below the significance level (Kirsh, 2019). Kirsch concluded that these results can be explained by the placebo effect. With the difference in outcome between the drug and placebo groups being statistically, but not clinically significant, it raises the question: Do SSRIs function as both a placebo and a genuine drug?

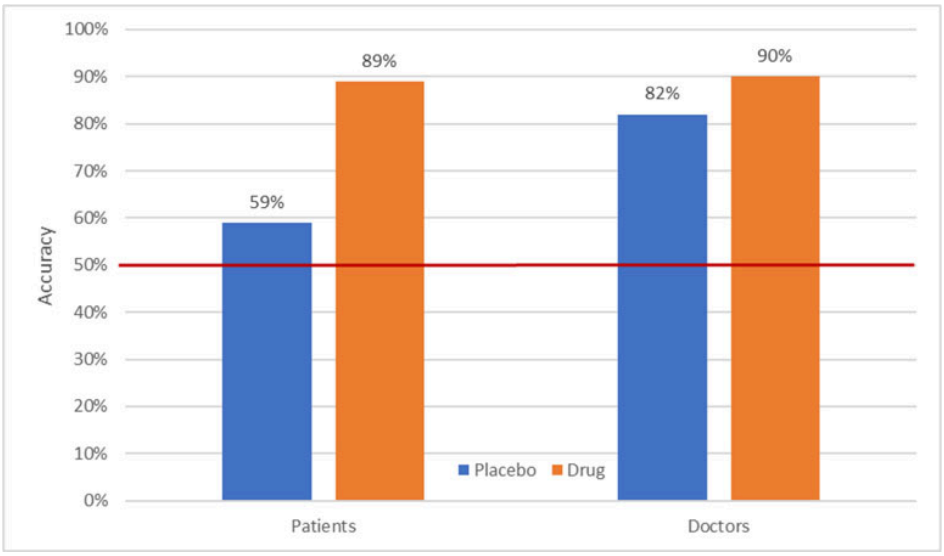

Figure 4. Breaking double-blind. Percentage of doctors and patients that correctly guessed their "group" in randomized drug trials.

In clinical trials where patients were randomized to antidepressants or a placebo, patients and doctors who were asked to guess the group they had been assigned overwhelmingly guessed correctly, indicating that the trials were not truly double-blind (Figure 4). Kirsch believes the drug-placebo difference in outcome was statistically significant because of what patients knew about the trials. Based on their suspected group placements, patients reacted accordingly: increasing their response to the drugs or decreasing their response to the placebo. This was observed in a 1986 study by Rabkin et al, in which 78% of patients and 87% of doctors broke blind in a study where patients were randomized to imipramine, phenelzine, and a placebo. Interestingly, the majority of nonresponders who were assigned an active drug and almost half of the responders on placebo guessed their assigned group correctly, indicating that patients' response to treatment did not dictate the accuracy of judgment for treatment assignment in most cases (Kirsch, 2019). In 2013, Baethge et al. conducted a meta-analysis to determine if this phenomenon applied to clinical trials. An analysis of blinding in 47 clinical trials found a positive correlation between the likelihood of breaking blind and drug-placebo difference.

Kirsch notes that the breaking of blind could be from the presence of side effects, as the effects of placebos known as “nacebo” are normally experienced to a lesser extent, which could allow participants to determine the group to which they've been randomized (Kirsch, 2019). Conversely, Moncreiff suggests that participants can learn to recognize subtle changes in their body produced by the medication, independent of the disclosed side effects (Moncrieff et al., 2022). Aimee Hunter and colleagues performed two studies, one in 2010 and one in 2015, that provided indirect support for this idea. Patients who had never taken antidepressants experienced no difference between the placebo and the active drug, while those who had taken antidepressants experienced a significant drug-placebo difference (Kirsch, 2019). Ultimately, Kirsch and colleagues concluded that the improvement observed in depressed patients following SSRI treatment is largely due to the placebo response; however, they recognize that this fact would not counteract the effectiveness of the drug. This raises questions about how psychiatrists are to proceed with prescribing SSRIs with what we know–and don't know–about their mechanism of action.

Kirsch proposes three solutions to this problem; the first is to continue prescribing antidepressants, but as “active placebos.” He states that while patients would continue to reap the benefits of the drugs’ placebo effect, continued use of SSRIs has greater associated risks, specifically concerning side effects and relapse. Open-label placebos (OLP), on the other hand, have fewer associated risks and have been found effective in studies in which it was explained to patients that placebos have been found effective in treating their condition (Kirsch, 2019). Unfortunately, there currently lacks sufficient research to support the efficacy of OLPs in the treatment of depression, which brings Kirsch to his final solution: psychotherapy. Studies have shown that long-term outcomes are significantly better for patients who receive psychotherapy as

opposed to medication. Similarly, the relapse rate for individuals receiving cognitive behavioral therapy and interpersonal therapy was reported by the National Institute of Mental Health to be 36 and 33 percent, respectively, compared to the 50 percent relapse rate for patients on antidepressants (Brueck, 2022). While pursuing psychotherapy may appear to be a clear-as-day solution to depression, it is widely inaccessible in the United States, as it is rarely covered by insurance and ranges from 100 to 200 dollars per session. According to a 2023 survey conducted by Mental Health America, 42 percent of adult Americans reported being unable to receive necessary care because they could not afford it (*Mental Health America,* 2023).

Is Psychiatry to blame?

It is apparent that mental health care in the United States is long overdue for reform. While the true cause of depression might never be determined, there are clear deficits in how it's treated and seemingly little urgency to address them. With thousands of patients struggling to find relief from "normal" treatment options, psychiatrists continue grabbing at straws to uphold SSRIs. It is important that researchers determine the mechanism of SSRIs so that patients can make informed decisions about what they're putting in their bodies, but there must be equal if not more urgency to explore alternative options for those lacking effective treatment altogether. Why is convenience, rather than efficacy, evidently the standard of care for depression? Why are people with inadequate responses to antidepressants deemed "treatment resistant?"According to Joal Paris, a professor of psychiatry at McGill University, "[It] has something to do with the toxic relationship between industry and academia…drug companies encourage doctors to prescribe often, and heavily," he said, and have "paid many academic psychiatrists to promote their products" (Kirkey, 2022). Patients who consider themselves victims of this relationship–having spent a fortune on pharmaceuticals only to become reliant or turned away as

untreatable–have grown immense resentment towards the field of psychiatry. In their eyes, the antidepressant industry is nothing more than a corporate scheme puppeteered by psychiatrists and large pharmaceutical companies. Some are even convinced their prescriptions were designed to stagnate or worsen their condition to earn psychiatrists an extra buck. This narrative of psychiatrists as schemers and master manipulators has contributed to a growing distrust and resentment towards the industry, especially as such opinions are published by large newspapers and media groups.

One article published in *The Guardia*n in 2013 stands out in particular for the author's use of extreme language and wordplay to directly attack the field of psychiatry. The article is riddled with emotion and anger from the author, Will Self, whose trusted psychiatrist apparently fueled the development of Self's late drug addiction. Drug pushers, disease mongers, and state-licensed drug dealers are among a few of the names Self assigns psychiatrists throughout the article, which he uses not only to question the validity of drug prescriptions but to paint the intentions of psychiatrists as inherently malicious. Self credits developers and followers of the DSM as the foremost individuals responsible for the advancement of medical pseudoscience over the past two decades (Self, 2013). Dr. James Davies, a professor at the University of Roehampton, presents a similar position in his 2019 lecture "Psychiatry & Big Pharma: Exposed." Since the addition of Major Depression to the DSM-III in 1980 and the pervasion of antidepressant drugs that followed, new mental disorders have appeared in every new edition with a plethora of psychopharmaceuticals to follow. Dr. Davies shared that between the years 1950 and 2014, the number of psychiatric conditions in the DSM more than tripled. He argues that developers of the DSM and ICD have wrongly medicalized the human experience by inflating the number of

mental disorders that exist. The consequence, Dr. Davies suggests, is not only a vast population of stigmatized individuals but many instances of unnecessary prescribing of drugs.

Despite the great deal of scrutiny the DSM and ICD have been put under in the past few decades, drug development for the over 300 mental illnesses they contain has not stagnated. In a normal supply and demand chain, it would make sense as to why more diagnoses would demand more drugs; however, drugs require extensive research and testing before they hit the market. Some drugs have taken up to 15 years to complete all three phases of clinical trials before approval, yet Spravato (Esketamine), one of the newest antidepressant drugs designed for "treatment resistant" depression, only underwent a little under two years of testing before receiving FDA approval in 2019. So how have those involved in the development and approval of these psychiatric drugs managed to keep up with the demand? Self suggests it's because those who fund drug trials, university research, and learned journals are the same ones who profit from the drugs reaching the market. How could such a blatant conflict of interest be overlooked? One reason could be that nearly a quarter of the population has been led to believe that antidepressants are their lifeline. Are these many people truly mentally ill, or is there something else at play? Self believes this to be a textbook example of iatrogenesis.

Iatrogenesis is the harm or illness brought upon patients by their caregivers as a result of healthcare interventions such as medications or procedures. It seems contradictory that a psychiatrist would cause intentional harm when the profession is fundamentally built upon "do[ing] no harm." But to Self the reason is clear as day: psychiatrists have become so wrapped up in pharmaceuticals that their patients are no longer at the center of their work. Certainly, not all practitioners in psychiatry are ill-intentioned or "avaricious" as Self suggests, but it's possible that the excitement around these proclaimed miracle drugs has caused psychiatrists to develop

tunnel vision, whereby patients in need of less conventional care are overlooked, not out of greed but out of habit. Not to mention, teachings such as the serotonin theory have been ingrained in academics for decades, meaning modern psychiatrists may not know any better but to practice under these frameworks. These psychiatrists are not withholding patients from quality care, per se, but are simply limited in the "tools" they were given in their "toolbox".

Societally, we are taught to trust that doctors have our best interest. It's not often that someone questions a doctor's authority and when they do it's followed with sharp criticism. As individuals without medical degrees, we have an inherent lack of entitlement or ability to go up against medical opinions–who are we to question something we likely know nothing about? This sentiment, however, is not universal across all professions. We have picked and chosen which professionals are authoritative and which warrant our criticism based on arbitrary criteria. Self explained, for example, that we often dismiss the opinions of therapists or counselors because of their lack of ability to assign well-defined diagnoses, prescribe medications, or hospitalize patients, which somehow subtracts from their credibility and authority as a professional (Self, 2013). For psychiatry, the sentiment has been ambivalent. Up until around the 1980s, psychiatry was seen as a compilation of theories and ideas with no real direction or backing. Once they began producing pharmaceuticals that were supported with biological explanations, and people began to experience their efficacy, the questionability of psychiatry was somewhat obscured. Psychiatrists receive a medical degree, prescribe medications, and hospitalized patients which suggests their likeness to medical doctors. A thorough look into the diagnostics of psychiatry, however, highlights their dissimilarity to medicine and where much of the ambivalence around psychiatry arises.

How Are Psychiatric Diseases Diagnosed?

While there are hundreds of different psychiatric disorders, each with its own set of diagnostic criteria, and psychiatrists with varying diagnostic 'preferences,' there is one consistent feature among nearly all psychiatric conditions that makes their diagnosis similar and equally challenging: the symptoms are rarely visible and not easily quantifiable. Consequently, a psychiatrist's primary diagnostic tool is their judgment. In the case of depression, psychiatrists generally couple a physical exam with a series of questionnaires and conversations before diagnosing a patient. Most diagnostic questionnaires are Likert scale survey questions based on the criteria in the DSM or International Classification of Diseases (ICD). Based on these evaluations, psychiatrists decide whether their patients meet the criteria for a diagnosis. Another major difference between diagnoses for psychiatric disorders and those for physical ailments is how they are established. When we go to the doctor's office presenting with physical symptoms, we are met with a series of tests whose results most often point definitively to a diagnosis. To a layperson, a diagnosis based on visual and quantifiable measures seems completely reasonable, but the diagnostic criteria for psychiatric diagnoses are much less definitive. According to child psychiatrist and Professor at the University of Lincoln, Sami Timimi, most psychiatric diagnoses were reached by consensus or voted into existence by those involved in the development of the DSM or ICD. The criterion in these manuals, Timimi adds, represents the opinions of powerful people within the psychiatric systems, but nothing that has been traced back to naturally occurring systems (*Council for Evidence-Based Psychiatry*, 2014). Dr. Davies adds that some developers of the DSM, whom he had the opportunity to interview, admitted that science played a very minor role in putting together the DSM. He stated that due to the great deal of voting involved in its development, the DSM represents a work of culture (*Council for Evidence-Based*

Psychiatry, 2014). In other words, unlike the objective science offered by radiographs in the diagnosis of a broken bone, the DSM and ICD both offer criteria for psychiatric diagnoses that are based almost entirely on opinions and medical pseudo-science.

Researchers have identified a number of limitations associated with categorical diagnostic systems like the DSM that they believe impact the validity of diagnoses. Fried and Nesse in their article "Depression is not a Consistent Syndrome," discuss the issues with treating depression as a heterogeneous disorder. They demonstrate through their analysis of 3,703 outpatient cases of depression, how expecting every patient to present the same could result in those whose symptoms deviate from "textbook" depression going mis- or undiagnosed (Fried & Nesse, 2015). Similarly, as Haslam and colleagues point out in their article, "Dimensions Over Categories," an individual who exhibits symptoms of two or more different disorders has an increased risk of being misdiagnosed due to symptom overlap. Haslam et al also point out that because diagnostic manuals are static, they don't account for changes in individuals' symptoms, which could result in patients being over- or under-treated for their disorder. Diagnoses for psychiatric disorders are also based on arbitrary thresholds, Haslam argues. For example, 70 milligrams per deciliter has diagnostic significance for individuals with hypoglycemia, as it marks the point at which other physiological systems may be affected. Sadness, disinterest in activities, and other textbook symptoms of depression that are not easily measured, however, are arbitrary indications of the condition, Haslam suggests, and therefore unhelpful in characterizing the severity of each case (Haslam et al., 2020).

Some psychiatrists acknowledge the limitations of these manuals by incorporating alternative diagnostic models into their practice. One such model is known as the medical model of mental health or the biological approach. Under this model, psychiatric disorders are treated

much like a broken bone would be–as if there is a physical root cause. Psychiatrists who use this model understand physical symptoms such as insomnia or loss of appetite as outward signs of an inner physical disorder and aim to discover the root cause of these disorders by grouping together and classifying related symptoms into syndromes. Each mental illness is believed to have a physical root cause associated with either genetics, neurotransmitters, neurophysiology, or neuroanatomy (Adan et al., 2019). While practitioners of this model aim to rely heavily on physical determinants for diagnosis, there unfortunately lacks sufficient evidence to support physical or biological causes for psychiatric disorders. Consequently, diagnoses under this model still partially rely on the discrete categories in the DSM or ICM, in addition to the physical symptoms exhibited by the patient. As for treatment, despite attempts to unearth new explanations for psychiatric disorders, there have been minimal advancements in treatment approaches under this model. In fact, practitioners of the medical model are some of the only ones who continue to practice and endorse electroconvulsive therapy and lobotomy, some of the earliest treatments for schizophrenia, depression, and anxiety disorders (Mcleod, 2018). Even so, these treatments were largely abandoned after the discovery of antipsychotics–a convenient and apparently safer alternative–leaving drugs to remain the dominant approach even by less traditional practitioners.

Psychiatrists are not con artists; they don't prescribe medications with malicious intent, and most care deeply about providing an effective treatment for their patients. The problem, however, is that as knowledge of mental disorders grows and diagnostic manuals are critiqued, the profession and its frameworks evolve minimally to address the shortcomings that surface. Drug therapy has assumed an instrumental role in psychiatry for reasons beyond its lucrativeness and apparent efficacy. For depressed individuals with busy lifestyles, medications might feel

more manageable than carving out time for psychotherapy; some might find medication far less intimidating than opening up to a therapist; and to those who perceive medication as inherently more “medical”, it may seem like the most reliable approach. Some of these patients, however, take medications daily, despite not seeing improvements, because they were given no other option. Psychiatrists don't have all the answers for these patients yet, but certainly, there is more they can do, collectively, to find them. Despite the field’s apparent stagnation over the past few decades, subsets of psychiatrists have made efforts to grow their knowledge of psychiatric diseases and how to better approach them. One emerging field–nutritional psychiatry–has made some promising gains.

Eat Better, Feel Better

Everybody has heard the phrase “Eat better, feel better.” We've been taught in school that a balanced diet, consisting of fruits, vegetables, lean meats, dairy, and whole grains, is the recipe for health; and we've all seen picture-perfect families enjoying wholesome meals on TV. Most of us know that it's not a facade: eating better truly can make you feel better, not only physically but mentally. Yet in a persistently inflated economy where nearly 8.4 million Americans work multiple jobs just to make ends meet, convenience has become the ultimate selling point when it comes to food. The Western diet–one composed of primarily fast and processed foods that are high in sugar and trans fats–describes the majority of Americans’ diets today (Zinöcker & Lindseth, 2018). While often this is due to accessibility or affordability of certain foods, many Americans simply don't know how to eat “right.”

Everywhere we go–social media, TV, the grocery store–we are surrounded by conflicting nutritional advice. Some say to restrict food groups like carbohydrates or fat while others

encourage their consumption. And to make matters worse, our own doctors are shaky on the topic of nutrition. Most often the topic of nutrition is associated with physical health. After all, poor diet is one of the leading reasons 40% of America is considered obese and that thousands die from coronary artery disease each year. Growing evidence also suggests that nutrition plays an equally important role in our cognitive and emotional well-being. If nutrition is known to play such a vital role in our overall health, why hasn't it become a more prominent component of health care? Why are so many Americans being left to suffer the consequences of their unbeknownst food choices? One reason could be the tendency of doctors to place a bandage over nutritional deficits with pharmaceuticals. Unless they are obese, most physicians are relatively unconcerned with what their patients are consuming; however, once they become ill due to a poor diet they are viewed as beyond what nutrition can cure. This perception, in addition to physicians' lack of nutritional knowledge, has led to a major divide between medicine and nutrition.

The Nutrition Gap

In 2015, Dr. Shushrut Jangi interviewed a woman battling multiple myeloma, a rare form of cancer that typically afflicts older individuals. At just 38 years of age, she was faced with an ultimatum: whether she would succumb to the effects of this deadly illness or undergo a rigorous treatment consisting of drugs she felt were equally toxic. Ultimately, the women decided to go against all odds to pursue a controversial nutritional therapy known as the Gerson Diet. Although many physicians thought she was crazy and told her she would reduce her odds of survival, she wasn't the first of its kind. Many patients afflicted with a range of illnesses have come to believe the Western diet is to blame and have pursued dietary regimens in place of traditional medicine. In fact, nutrition and medicine have a long history together: from the Greek physician,

Hippocrates, who famously stated “Let food be thy medicine” in 400 BC, to the discovery of vitamins in 1912, and the first studies linking diets heavy in fruits and vegetables to reduced cancer risk in 1997 (Witkamp & Van Norren, 2018). Nonetheless, when Dr. Jangi visited his interviewee for the first time, expecting to see someone riddled with the effects of their illness, he was astonished by her appearance. After battling myeloma for nearly the length of her prognosis, the interviewee was glowing. Granted, her outward appearance did not reflect the state of her internal health.

In five years, the woman had been to countless clinics and rehabilitation centers, met with numerous practitioners, and tried different diets and regimens only to receive blood work results that made her question her decision to pursue nutrition against medical advice. But ultimately, the interviewee did not regret her journey. If it didn't heal her from cancer, she hoped that it at least lit a fire under practitioners to study nutrition more closely so that patients like her aren't left to self-experiment in the future. Over time, her journey became not just about curing her cancer, but changing the narrative that says conventional medicine is the only way to achieve wellness. She told Dr. Jangi that she “think[s] this whole nutrition thing isn’t going to work until conventional doctors start to recognize it might have an impact…but we aren’t even there yet” because “Most doctors don’t consider that diet has a place beside drugs.” Although Dr. Jangi wishes she had undergone chemotherapy alongside her diet change, he agrees that with the cost of pharmaceuticals at an all-time high, it is time that physicians broaden their horizons and consider the potential of dietary changes as a preventative or even therapeutic approach (Jangi, 2015).

What has led modern-day medicine to stray so far away from its nutritional roots? Many blame the nutritional gap on the lack of education. Most medical schools only spend a couple of

weeks studying nutrition. This has left doctors uncomfortable discussing the topic with their patients, and patients to research and experiment with nutrition on their own. Others blame pharmaceutical companies who have partnered with physicians to phase out practitioners of non-pharmacological medicine, like Max Gerson. Gerson practiced medicine in New York in the 1930s and was known for his diet–the Gerson diet–that was devoid of processed foods and could apparently cure migraines, arthritis, forms of tuberculosis, and even cancer. Several patients were freed from their ailments as a result of this dietary regimen, including over 20 cancer patients; however, Gerson lacked the numbers and sufficient evidence to be considered reputable by any means. This being the case, his regimen was blacklisted from several medical associations and eventually disappeared from most American hospitals. Even still, patients with cancer and other ailments resonate with Gerson's philosophies to this day. His claims that "poisons" in processed foods are making people sick inspire self-experimentation with diet by more than 75% of patients diagnosed with cancer and several others with ailments like Crohn's disease, muscular dystrophy, and depression–often without the knowledge of their physicians (Jangi, 2015). These individuals have created online communities to support one another, report their successes, and offer solace to those just entering their journey, in some ways as a substitute for the support they feel they are lacking from their providers.

There is no doubt that the medications work and there is much evidence to support their efficacy. But often, such medications only mask the pain or prolong survival and come with an array of side effects that can be even more menacing than what they are treating. For many patients, a life relying on a concoction of pills isn't one they're willing to accept, not to mention one they're able to afford. The average American spends over 1,400 dollars on prescription pharmaceuticals each year, which has contributed to the more than 100 million Americans left in

debt from obtaining healthcare (Rakshit et al., 2022). History has proven the healing properties of nutrition and its centrality to our health; however, in much the same way as behavioral therapies were seen in the wake of SSRIs hitting the shelves, nutrition has merely lost its relevance in the world of medicine.

Nutritional therapies have the potential to bring a more affordable, long-term approach to disease treatment and prevention, which could be used alone or in concert with conventional methods; however, these methods are largely under-researched. Why must patients be the ones to explore alternative options, sometimes to the detriment of their own health? For physicians trained in modern medicine, it's because nutrition is not a level they're willing to stoop down to. Many physicians view nutrition as fringe medicine, likely due to pop-culture practitioners using their platform to promote quack nutritional claims with little to no evidence behind them. Other physicians think the solution is too simple. In an interview, Dr. Eliot Berson, an ophthalmologist at Massachusetts General, shared that when he told his audience at a national conference that his work had been inspired by what he learned from his patients, he was returned with laughter. Audience members wanted more animal studies and randomized clinical trials, and when Dr. Berson gave it to them, it still wasn't enough. “We doctors are too stubborn and too slow to accept that kind of simplicity,” Dr. Berson said (Jangi, 2015). Doctors aren't willing to take nutrition seriously without the black-and-white science under their nose; and because pharmaceuticals work and they're easy to prescribe, most doctors aren't willing to give nutrition the time of day.

Nutritional Psychiatry

Fortunately, some physicians are beginning to recognize the impact nutrition could have and are taking leaps to close the nutritional gap. Proponents of the emerging field of nutritional

psychiatry, for example, are working towards designing scientifically rigorous experiments to define the role of nutrition in mental health. Research under this initiative is beginning to suggest that mood disorders like depression and anxiety are exacerbated or even caused by poor eating habits such as the Western diet. In 2013, a meta-analysis conducted by Psaltopoulou and colleagues consisting of eight cohort studies and one case-control found a strong link between adherence to a Mediterranean diet and reduced risk of depression (Naidoo, 2019). A systematic review in 2018, which combined 20 longitudinal and 21 cross-sectional studies, also found evidence for the protective effects of the Mediterranean diet against depression (Naidoo, 2019). Two notable randomized controlled trials conducted in 2019 observed mental health improvements in adults on Mediterranean-style diets. The HELFIMED trial, in which 152 self-reported adults with depression adopted a Mediterranean diet supplemented with fish oil supplements, observed a direct correlation between reduced depression and greater adherence to the diet after only 6 months (Parletta et al., 2017). Likewise, PREDI-DEP, an ongoing trial testing the effectiveness of an extra-virgin olive oil-enriched Mediterranean diet in reducing the recurrence and symptoms of depression is seeing similarly intriguing results (Sánchez-Villegas et al., 2019).

While it's clear from these studies that more than our physical health is affected by what we eat, far more evidence–especially that of randomized control trials–is needed to gain the attention of modern medicine practitioners. Currently, there is a lack of understanding of specific cellular or metabolic mechanisms underpinning these associations, as well as a fundamental understanding of how specific nutrients affect signaling processes like the immune system, metabolism, and neurotransmission. Additionally, the majority of existing knowledge in this area is attributed to animal studies. Despite these drawbacks, many researchers see immense promise

in this field and continue taking active steps toward a brighter future for mental health care. In fact, recent attempts to identify specific dietary components associated with mental health decline have made headway toward uncovering the root cause of depression and related disorders. One study, for example, observed the cognitive and neurochemical effects of stressed adolescent rats normalize after being fed a diet enriched in omega-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid and vitamin A; a 2016 study found a link between consumption of high dietary fiber and reduced depression risk; and recent preclinical studies have indicated the benefits of fermented foods in alleviating depressive symptoms in various animal models (Hills et al., 2019). While each of these studies appears to have vastly different findings, one common factor makes them even more significant than they appear. Each of those components–omegas 3s, fiber, fermented foods, etc.–interacted with the gut in ways that altered its microbial composition. Similarly, recent findings suggest that ultra-processed foods–a large component of the Western diet–cause both structural and behavioral changes to the microbiome that result in various inflammatory disorders, including depression (Zinöcker & Lindseth, 2018). Based on these discoveries, it is becoming apparent that the missing piece of the puzzle may not be a drug or a specific nutrient, but actually the unique target(s) living inside of every individual–their microbiome.

How Does the Gut Microbiome Influence Our Health?

In recent years, “gut health” and “the gut microbiome” have become buzzwords in the health and wellness industry. Whether they are found plastered across food and supplement aisles or on the cover page of popular magazines, it is unlikely that one hasn't come across the terms at some point or even purchased a probiotic to “benefit” their health in some way. The gut microbiome industry was valued at $84.27 million in 2021 and is expected to grow by 31.24

percent between now and 2030 (Berger, 2022). But how has it gained so much attention? While there might be a handful of people reading journal articles in their spare time, much of these health “fads” arise due to lay press and social media influencers spreading undersupported or even false information. “Nutraceutical,” a term coined in the 1980s by Stephen Defelice, refers to a variety of non-pharmaceutical compounds that are believed to have an impact on health and disease. Similarly, the phrase ‘functional foods’ was designed to refer to a category of food products believed to provide health benefits beyond that of regular foods (Witkamp & Van Norren, 2018). New nutraceuticals, or supplements, and functional foods usually find their way into the regimens of the self-experimenters described prior, followers of alternative medicines like herbalists or naturopaths, or people who reject conventional medicine altogether. To those who use them, they are viewed as “the remedy your doctor doesn't want you to know about”–sometimes even advertised as such–but to those who haven't fallen for the TikTok or celebrity endorsement, they are bogus. Supplement and pharmaceutical companies have similar goals: to find the magical remedy that overshadows the rest; however, unlike pharmaceutical companies, most supplements aren't regulated by the FDA. Meaning, that apart from parameters around the types of health claims they can make on the packaging, supplements don't have to be checked for safety or effectiveness before making it onto the shelf.

This is the case for probiotics. This supplement, claiming to improve digestive health, provide immune support, and sometimes even cure the flu by balancing the gut, is found in nearly every shape and form: capsules, powders, juices, and even yogurt. Despite the limited clinical evidence that exists to support the health benefits they are claimed to have, most customers choosing between probiotic and regular yogurt will pick the former without even knowing why. Many consumers' knowledge of probiotics and the gut microbiome extend as far

as the label of their probiotic; and as far as they know, maintaining a "balanced gut" is necessary for their health. But when doctors were asked if individuals should be taking a daily probiotic, many responded no (Simon, 2016). Doctors typically caution against commercial health products such as probiotics, not because they will damage the individual's health–although some could–but because it's hard to know what exactly is in the products. A 2015 analysis of 16 different probiotic products, for instance, found that only one contained the exact bacterial species disclosed on the label (Simon, 2016). Additionally, because most of the health claims on these products aren't proven, most doctors suggest using products or treatment protocols that have clinical evidence to support them. Despite the reputation probiotics amassed over the past decade from their commercialization, not all claims about probiotics are completely bogus. In fact, some health benefits of probiotics have been scientifically backed long before the term reached the mainstream. During the time in which probiotics rose to fame over false claims and spotty science, research behind the scenes has alluded to new and exciting implications for the potential role of probiotics in health and disease.

The word probiotic, originating from the Latin meaning "for life," is a broad term for a substance that contributes to the diverse community of microbes in the body and confers beneficial properties to one's health (Simon, 2016). Probiotics contain a wide array of bacterial and fungal species based on those native to the human microbiome. Most commonly, they contain bacteria belonging to the groups *Lactobacillus* and *Bifidobacterium*, and sometimes yeasts like *Saccharomyces boulardii* (*National Center for Complementary and Integrative Health*, 2019). Fermented foods, which are produced using live bacterial cultures, naturally contain probiotics; however, for supplemental purposes, probiotic bacteria are bulk cultured and fermented in a laboratory before reaching the shelf in capsule form. Research suggests that

probiotic supplements interact with our existing community of microbes to produce substances involved in digestion or immune modulation. Research has also pointed to their role in producing anti-inflammatory substances, which is why they are implicated as potential remedies for IBS, ulcerative colitis, and other inflammatory disorders (Johnson et al., 2021). Probiotics might also help restore microbial diversity after it's been depleted by things like antibiotics. The trouble with probiotics, however, is what we know–and don't know–about their target.

The Science of the Gut

The gut microbiota refers to the extremely diverse community of microorganisms inhabiting our gastrointestinal (GI) tract. Interestingly, while the gut microbiota is not a new phenomenon, only recently were technologies innovated to begin mapping its diverse community. And despite these capabilities, its composition has not nearly been fully comprehended. This has created significant challenges in the development of probiotics, or at least ones that doctors can stand behind. Probiotics trials suffer a variety of shortcomings: small sample size, lack of appropriate randomization, lack of product characterization, etc. But, one of the greatest obstacles to developing clinically significant probiotics is the lack of uniformity across human subjects. Some researchers compare the gut microbiome to the human fingerprint, as each one harbors a community of microbes that is distinct from another. Every piece of food, a milligram of a drug, or a singular bacteria that enters the human gut is encountered by potentially thousands of microbial species that communicate with each other to decide on an appropriate response. If each microbiome is compositionally distinct, a probiotic could produce a vastly different response from one individual to the next. While past research trials have never produced results quite this dramatic, it is important to consider how these characteristics have

affected our knowledge of probiotics' capacity to influence our health. Researchers are still unsure of which probiotic strains are the most helpful, how much is too much, and who is most likely to benefit from their use. It's not even known if probiotics are safe for daily consumption, which is a major flag to many doctors (Tamayo, 2008).

With little knowledge of their potential side effects, not only is daily probiotic use risky, but some doctors like Dr. Alessio Fasano, chief of pediatric gastroenterology and nutrition at MassGeneral Hospital for Children, worry they could have a similar destiny as penicillin, the once-believed "cure-all" whose overuse led to the development of antibiotic-resistant superbugs (Simon, 2016). Some research suggests that daily use of probiotics by healthy individuals may cause permanent, potentially negative, alterations to their microbiome composition. Fasano and others worry that promiscuous probiotic use might not only damage individual health but impact their curative potential in the future, as despite the many gaps in our existing knowledge, ongoing research continuously points to the microbiome as a promising target in future disease treatment. Curating drugs or probiotics for this purpose, however, requires an understanding of gut microbes at a depth that researchers have struggled to reach. Determining the functional role of microbes in the human body poses several challenges. Firstly, it's still not entirely known just how diverse the microbiome is. While its genetic content has been mostly characterized, the parts of its content that remain a mystery–mainly the non-bacterial components–could hold functional significance. Secondly, while studying the microbiome composition has led to some useful elucidations, the significance of such findings could have few implications for the greater population due to the large microbial diversity across individuals. Consequently, researchers have only a narrow understanding of what a "healthy" microbiome looks like.

Studies of the gut-brain axis have helped a great deal to close this knowledge gap. The gut-brain axis is responsible for modulating cell-to-cell communication between the gut and the brain, branching pathways of the immune, nervous, and neuroendocrine systems (Foster et al., 2021). Research on the gut-brain axis has taken place for over a century, with its first major breakthrough in 1904 being the discovery of cephalic digestion, the phase in which the stomach prepares the GI tract for food processing via autonomic (involuntary) signaling pathways (Foster et al., 2017). Today, studies of the gut-brain axis primarily revolve around human disease due to its pertinent role in maintaining homeostasis. Gut-brain studies are primarily conducted in small mammals that harbor many of the same structures and processes as the human body. Germ-free mice (lacking a microbiome) for example, have lent support for several associations between gut-brain interactions and diseases, such as irritable bowel syndrome, diabetes, obesity, and behavioral and neuropsychiatric disorders. Consequently, much of this knowledge is attributed to animal models, signifying a lack of clinical evidence to support human counterparts. Nonetheless, researchers' and physicians' growing understanding of the gut-brain axis has contributed to an evolution of medical approaches and how the broader topic of human health is understood and discussed amongst professionals and the public.

Inherent in the study of the gut-brain axis is the concept of interconnectedness–a view of the human body as a system of connected pathways that communicate with one another and the environment to maintain its normal functions–or homeostasis. Health, in this way, can be defined broadly as when a group of systems in the body work together to maintain order, whilst a diseased state is the accumulation of disorder throughout the body that arises from one or more malfunctioning systems. The body's natural ability to detect and stop this cycle in its tracks is why common colds don't always become pneumonia or why cellular mutations don't always lead

to cancer. These safeguards known as communication pathways serve to maintain the body's steady state and play a critical role in the prevention of disease. Increasingly, research has suggested the role of the gut-brain axis as a moderator of these pathways. For example, metabolic byproducts of gut microbes have been evidenced to play a crucial role in pathways throughout the entire body (Foster et al., 2017). Accordingly, gut dysbiosis–a change in the normal composition of microbes in the gut–has been linked to consequences beyond those of the gut, interfering with nearly every process in its periphery and ultimately, causing disease.

The composition of the gut has been found critical to the function of its resident microbiota. Gut microbes are stored within the intestinal mucosa, an immune-related barrier that closely manages the diffusion of material into and out of the gut. The microbial contents of the intestinal mucosa influence its permeability, which dictates the ease at which certain materials can cross it. This barrier, which is normally tightly packed with epithelial cells, discourages the diffusion of microbes or their byproducts known as metabolites. Stress and diet, however, are two factors that can damage the structural integrity of this barrier, allowing microbes and their metabolites to traverse the barrier and interact with immune or neuronal cells outside of the gut (Foster, 2017). These interactions can induce an array of immune responses, one of which is the inflammatory response. Inflammation is one of the body’s defenses against harmful stimuli, such as pathogens or toxins, and is vital to human health. During inflammation, the body temporarily disrupts homeostasis in what is called a positive feedback loop. Through this process, immune cells and other mediators of healing are attracted to the disrupted site, exacerbating inflammation until normal conditions are restored. Inflammation can also be chronic, however, in which case homeostasis is never fully restored, and disease results.

In a 2013 study, germ-free mice were found to have an exaggerated stress response. Colonizing the mice's guts with a bifidobacteria, a prevalent bacterial species in the human gut, restored the mice's stress responses to a normal level, indicating the pertinent role the microbiome plays in activating the immune system in response to environmental stressors (Foster at al., 2017). Major stress is widely known as a factor of behavioral changes and neuropsychiatric disease; however, very few individuals are aware of the distinct link between neuropsychiatric health and inflammation outside of the psychiatric sphere. While it had not yet been given the name "gut-brain axis," the influence of bacteria on emotions and behavior was observed centuries ago. 18th-century vitalists were some of the first people to consider the possibility of the gut-brain axis playing a systemic role (Lewandowska-Pietruszka, 2022). Yet only in the 21st century did researchers begin to understand the complex, bidirectional relationship that the gut and the brain share. Today, mood disorders like depression are rarely addressed as an immune response, nor as something to do with inflammation, but as something fixed within the brain. This narrow understanding of depression and other mental illnesses that many psychiatrists share demonstrates the pertinence of continued research in this area.

The Gut-Brain Axis as a Target for Depression

As early as 1910, the microbiome has been implicated in the etiology of depression. That year, Dr. George Porter Philips reported improved depressive symptoms in adults with melancholia, to whom he had administered a course of supplements containing lactic acid-producing bacteria (Foster, 2016). Up until the early 2000s, however, scientists lacked substantial equipment and technologies to realize the mechanisms at play. The development of sequencing technologies in the 20th century truly opened up a world of possibilities for this area of research. Researchers could now classify microbial species in the gut from just a small amount

of bacterial DNA, and with this information could begin deducing their functional roles and the consequences of their absence. Thus far, researchers have characterized specific bacterial genera that are more or less prevalent in depressed patients; identified metabolites and immune factors that may be implicated in its etiology; and pinpointed microbes that may directly influence specific neural and immune mechanisms in the body. The HPA axis, a neuroendocrine component responsible for mediating the effects of stress on the body, is one such mechanism evidenced as having a close relationship with the gut (Foster, 2016).

Under stress, the HPA axis promotes the production of a steroid hormone called glucocorticoids, which is fed into a "negative feedback loop" to inhibit the effects of stress signals on the body, thereby restoring homeostasis. The inflammatory factors that are released in response to stress-induced gut dysbiosis further activate the HPA axis, however, which prolongs the presence of stimulus and results in chronic stress (Foster, 2022). Under these conditions, the immune system is rendered insensitive to the inhibitory functions of glucocorticoids, disrupting the body's natural ability to alleviate stress. Chronic stress and inflammation disrupt other parts of the body as well, including the brain's regulatory and signaling mechanisms. This series of events is what some researchers believe causes depressive symptoms in MDD and various other conditions. Recent research has discovered ways to modify the HPA axis by targeting the gut microbiome with specific probiotics. In one study, for example, the administration of *L. rhamnosus* was found to mitigate depressive behaviors in mice by reducing stress-related glucocorticoid production (Hills et al., 2019).

The gut microbiota is also directly involved in the modulation of neurotransmitters. For this reason, the gut is sometimes referred to as the second brain, as many of the prominent neurotransmitters in the brain are also produced and secreted by microbes in the gut (Foster et

al., 2022). Neurotransmitters are the “language” the gut and brain use to communicate; when something in the body has gone amiss, they notify one another via neurotransmission. Communication, however, isn't always flawless: there are a lot of factors that influence the flow of information along the gut-brain axis, one of them being dysbiosis. Gut bacteria synthesize neurotransmitter precursors as well as catalyze the synthesis of neurotransmitters through dietary metabolism. Tryptophan, for example, is a precursor for serotonin that is metabolically regulated by the microbiota. Cytokines–proteins produced as a result of stress-induced dysbiosis–are also reported to affect the synthesis, release, and reuptake of neurotransmitters (Foster et al., 2022). Depletion of specific microbes in the gut can therefore confer both direct and indirect effects on communication to the brain.

Administration of probiotics, namely ones of the *Lactobacillus* and *Bifidobacterium* species, has been shown to restore depleted levels of neurotransmitters that are implicated in the occurrence of depression. In a randomized, placebo-controlled trial, for example, administration of *L. plantarum* was found to significantly reduce plasma kynurenine (a tryptophan metabolite involved in immune suppression), which when elevated, has been positively correlated with the severity of depressive symptoms in MDD patients (Johnson et al., 2021). The probiotic *L. reuteri* has also been found to reduce inflammation and cognitive deficits associated with depression by inducing the secretion of microbial histamine, an immune neurotransmitter that suppresses the production of inflammatory factors (Johnson et al., 2021).

One largely unexplored but potentially significant phenomenon having to do with the gut is epigenetics. Early research is beginning to support the ability of microbes to alter the expression of the human genome in the gut-brain axis. Epigenetic modifications are long-lasting and heritable, and therefore often manifest as diseases or disorders; however, because only the

expression rather than the DNA sequence itself is modified, epigenetic changes are reversible (Johnson et al., 2021). There are several factors believed to influence the occurrence of epigenetic changes, including lifestyle factors, environmental pollutants, and psychological stress. Gut dysbiosis is believed to be the main source of altered genome expression in the gut-brain axis. Thus, repopulating the microbiome with probiotic bacteria could potentially reverse epigenetic changes associated with their depletion. Several strands of research have indicated butyrate-producing bacterial strains as suitable probiotics for the treatment of epigenetic-related depression. Butyrate is a short-chain fatty acid that is believed to confer a protective role on gut permeability, as well as exert anti-inflammatory effects. These immune supportive properties conferred by butyrate-producing probiotics like *F. prausnitzii*, *L. planarum*, *B. infantis*, and *closridium butyricum* have been shown to ameliorate depressive behaviors in mice (Johnson et al., 2021).

While epigenetic research in this area is in its early stages, researchers believe modulating the gut microbiota with probiotics to reverse epigenetic changes holds immense potential as a preventative and therapeutic approach to depression. Another noteworthy area of research is the use of fecal microbiota transplants (FMT) in the treatment of depression. FMT is already an established and effective treatment against recurrent *Clostridium difficile* infection, a bacteria that can lead to life-threatening diarrhea and inflammation in the colon (Guinane & Cotter, 2013). Emerging research, however, has lent promise to FMT as an effective treatment against other GI or microbiota-related conditions, such as depression. In plain terms, FMT is the transfer of healthy stool from one individual to another via colonoscopy, enema, a nasogastric tube, or in capsule form. While it may sound unprecedented, the composition of microbes in our stool nearly mirrors that in our gastrointestinal tract, and thus the composition of a “poop pill”–as

they are commonly called–is essentially equivalent to a probiotic capsule, except one comes from the lab and the other is derived from a natural source. Similarly to how *C. diff* is treated, MDD patients would receive a fecal transplant from a healthy donor in hopes that it would ameliorate their depressive symptoms. A systematic search of five databases using the key terms FMT and psychiatric disease found 21 studies–including 8 clinical and 20 preclinical trials–in which decreased depressive and anxiety-like symptoms were reported following the transplantation of healthy microbiota into the subjects. In some of these studies, the inverse was observed, in which transplantation of fecal microbiota from depressed donors resulted in the transmission of depressive symptoms to healthy donors (Chinna et al., 2020).

There are undeniably several potential alternatives to SSRIs in the treatment of depression. Each has undergone at least a few clinical trials and several preclinical trials, having almost nothing but successful outcomes. But this amount of research only scratches the surface as far as what's required for such methods to gain FDA approval, and most psychiatrists won't bat an eye unless it's been obtained. This leaves some outstanding questions: (1) why haven't these potential alternatives to SSRIs received more attention from professionals and (2) what are the necessary steps to get them on their radar?

Conclusion

To this day, there is nothing but speculation as to what causes depression; some believe it is nutrition, some think it is genetic, and others still stand firmly behind the chemical imbalance theory. But with extensive research over several decades producing nothing but inconsistent outcomes, researchers are beginning to think there isn't a single explanation for depression. In the words of Dr. James Murrough, director of the Depression and Anxiety Center for Discovery

and Treatment at the Icahn School of Medicine, “Depression may in fact be many different illnesses, each requiring a different type of treatment…[and] we have seen this play out time and again.” Historically, personalization has been the missing piece to seeing significant breakthroughs, like recovery from cancer. This would explain why some patients respond well to SSRIs while others experience merely the opposite effect. Preclinical studies have repeatedly supported probiotics, dietary changes, FMT, and various other emerging treatments as effective stand-alone interventions or as adjuncts to antidepressants. While there is clearly a need for more evidence behind such treatments before they are implemented–especially from clinical trials–it is apparent that the missing piece is not a lack of research nor willingness from patients, but a sense of urgency from professionals. These preclinical studies have laid a strong foundation for translation to humans, yet minimal action has been taken to put these methods into practice. Only those with the resources and ability to self-treat have been able to reap the potential benefits of these treatments–but patients should not have this obligation.

There is an urgent need to explore the etiology of depression further and identify new targets that not only improve treatment for those who don't respond to frontline therapy but aid in predicting and even preventing the development of depression altogether. Integrating new and what could be considered non-traditional approaches into modern medical practice will undoubtedly face challenges. Many practicing psychiatrists have never known a time when anything else but SSRIs were prescribed for depression. In medicine, however, there have been numerous instances in which unconventional practices transformed health care for the better. Functional medicine, for example, takes a whole health approach to disease treatment and prevention. It seeks to treat the root causes of disease by combining natural and conventional interventions, thereby creating a personalized treatment plan that addresses patients’ overall

health. Functional medicine has proved, in practice, that conventional and natural approaches are not mutually exclusive. In fact, oftentimes pairing diet changes, exercise, or supplements with drugs and procedures will trump the use of one intervention over the other. Taking a functional medicine approach to psychiatry would minimize the amount of gambling that takes place in the treatment of depression. Psychiatrists would have a plethora of interventions to choose from, allowing them to treat depression case by case–after all, depression has never been black and white, so why should it be treated as such? While "natural" remedies like probiotics, diets, and FMT are under-researched, and potentially tainted by commercialization, adopting a functional approach to psychiatry might help bring these options into fruition. While such a transition will undoubtedly be challenging, it is not impossible. It all comes down to whether psychiatrists are willing to think outside the pillbox.

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