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Revisiting Depression — Dopamine-Serotonin Balance Gains Attention for Treatment-Resistant Depression

Analysis by Dr. Joseph Mercola | June 29, 2026

STORY AT-A-GLANCE

- A major clinical trial in The Lancet Psychiatry found that boosting dopamine with pramipexole improved symptoms in treatment-resistant depression. This challenges the long-dominant serotonin deficiency theory
- Supporting those findings, another study showed that agomelatine, a serotonin-blocking drug, consistently reduced anxiety and depression in multiple placebo-controlled trials
- Research shows polyunsaturated and monounsaturated fats (PUFs and MUFs) directly trigger platelet aggregation and serotonin release, while saturated fats do not, linking modern diets to serotonin excess
- Studies confirm that combinations of unsaturated fats amplify serotonin release even at sub-threshold levels, making everyday dietary choices especially relevant to serotonin-driven health risks and mood instability
- Increasing GABA helps your body break down serotonin, restoring calm, better sleep, and mood stability without SSRI side effects, making it a safer alternative for addressing depression and anxiety

Depression is one of the most common mental health challenges today, affecting 332 million people worldwide.[1] In the United States alone, over 21 million adults experience at least one major depressive episode each year.[2] For decades, the prevailing theory has

been that depression stems from a lack of serotonin, the brain's so-called "happiness chemical," and treatments have largely focused on raising serotonin levels through selective serotonin reuptake inhibitors (SSRIs).[3]

Yet many of those who turn to medication continue to struggle, leading to the recognition of what is now called treatment-resistant depression.[4] As the number of people in this group has grown, scientists have begun to probe deeper into the brain's chemistry, and what they are finding challenges long-held assumptions.

Emerging research points to an excess of serotonin, not a shortage, as a driving factor in depression. This perspective is gaining strength, supported by a major clinical trial in The Lancet Psychiatry,[5] where researchers tested an approach aimed not at boosting serotonin but at restoring balance between serotonin and dopamine — two opposing neurotransmitters that shape mood, motivation, and emotional stability.

Can Dopamine Agonists Help Treat 'Untreatable' Depression?

The featured study, conducted by the University of Oxford, focused on pramipexole, a drug originally licensed for Parkinson's disease, which works by boosting the brain chemical dopamine. Low dopamine function is strongly associated with loss of motivation, inability to feel pleasure, and poor stress resilience. Researchers set out to test whether pramipexole could help people living with treatment-resistant depression.[6,7]

- **The trial design tested dopamine augmentation alongside existing care —** The trial enrolled 150 patients across the U.K., with equal numbers assigned to receive either pramipexole or a placebo for 48 weeks. All participants continued their existing antidepressant medication during the trial period.

- **Pramipexole produced clear and sustained improvements —** By the 12th week, those receiving pramipexole showed clear improvements in depressive symptoms compared to the placebo group, and these benefits were maintained across the

nearly year-long trial. The results stood out because sustained improvements of this kind are rarely seen in patients already classified as resistant to conventional therapies.

- **Side effects limited tolerability for a subset of patients —** Around one in five individuals in the pramipexole group discontinued treatment due to adverse effects. Reported side effects included nausea, dizziness, and disturbances in sleep. While these issues limited the drug's tolerability for some, the majority of patients who continued saw meaningful gains in mood and function.

- **The trial built on earlier exploratory signals but provided the first long-term evidence —** Previous small-scale studies hinted at antidepressant benefits from pramipexole, but data on durability were lacking. This trial delivered the strongest evidence yet. According to Professor Michael Browning from the Department of Psychiatry at Oxford, who led the trial:

  > *"These findings on pramipexole are a significant breakthrough for patients for whom antidepressants and other treatments and therapies have not worked.*
  >
  > *Pramipexole is a medicine licensed for Parkinson's disease and works by boosting the brain chemical dopamine. This differs from the majority of other antidepressant medications which act on brain serotonin and may explain why pramipexole was so helpful in this study."*[8]

The key takeaway from this trial is that boosting dopamine activity — and lowering serotonin in the process — was effective where standard treatments had failed. It shows that so-called "untreatable" depression can, in fact, respond when approached from the opposite direction of conventional medicine.

Further Research Shows Blocking Serotonin Calms Stress and Lifts Mood

The evidence for serotonin excess is reinforced by clinical trials of drugs that block serotonin activity rather than raise it. Agomelatine, a selective antagonist of the 5-HT2C receptor, which is one of serotonin's key docking points, has demonstrated clear antidepressant and anxiolytic effects in multiple placebo-controlled studies. This shows that lowering serotonin signaling helps relieve symptoms of both depression and anxiety.[9,10]

- **Blocking serotonin activity directly addresses stress pathways —** The 5-HT2C receptor regulates adrenocorticotropic hormone (ACTH) release, which in turn drives the production of cortisol, the body's primary stress hormone. When serotonin overstimulates this receptor, stress pathways become overactive, worsening both anxiety and depression.

  By blocking serotonin at this site, agomelatine reduces excessive cortisol signaling and demonstrates that too much serotonin activity, not too little, contributes to these mood disorders.

- **Agomelatine shows consistent benefits across multiple trials —** In four large, randomized, placebo-controlled studies, the drug reliably reduced symptoms of depression and generalized anxiety disorder. This consistency is notable, as few psychiatric drugs achieve repeated success across so many trials. Patients treated with agomelatine experienced meaningful relief, while those on placebo did not.

- **It offers tolerability advantages over standard treatments —** Compared to SSRIs and benzodiazepines, agomelatine was linked to fewer side effects such as sexual dysfunction, weight gain, or abuse potential. These benefits make it attractive for long-term use.

  However, its widespread adoption has been limited by pharmacokinetic issues. More than 90% of the drug is lost during first-pass metabolism in the liver, requiring higher doses and regular monitoring of liver enzymes due to risks of hepatotoxicity.

Serotonin also drives aromatase, raising estrogen activity, which adds another layer of stress on your mood and metabolism. Learn more about this link in "**What You Need to Know About Estrogen and Serotonin**."

How PUFs and MUFs Drive Serotonin Release

Georgi Dinkov, a bioenergetic medicine researcher, explored how everyday dietary fats influence serotonin activity in the body. In his blog, he highlighted evidence showing that certain fats don't just provide energy but directly stimulate serotonin release, bypassing the usual metabolic pathways.[11]

- **Unsaturated fats act directly on platelets without conversion —** Dinkov highlighted a study[12] showing that polyunsaturated fats (PUFs) such as arachidonic acid, **linoleic acid**, and linolenic acid, along with **monounsaturated fats** (MUFs) like oleic acid, directly cause platelets to clump together and release serotonin.

  Normally, fatty acids need to be converted into downstream metabolites such as prostaglandins, leukotrienes, or thromboxanes to trigger these effects. In this case, no conversion is required — the unsaturated fats themselves directly stimulate platelets to dump their stored serotonin into circulation.

- **Arachidonic acid has a defined threshold response —** Experiments with washed platelet suspensions confirmed that concentrations of arachidonic acid above 30 micromolar caused platelets to clump and release serotonin that could not be inhibited by aspirin or by blocking common enzymatic pathways.

  At lower concentrations (below 20 micromolar), aspirin was effective in suppressing platelet responses. Once the threshold was crossed, however, neither aspirin nor other inhibitors prevented serotonin release, making the effect both direct and irreversible at higher levels.

- **Other unsaturated fats produce similar dose-dependent effects —** The same studies found that oleic, linoleic, and linolenic acids also produced dose-dependent serotonin release and platelet aggregation, whereas saturated fats did not induce these responses, even at concentrations as high as 100 micromolar. This highlights a unique property of unsaturated fats in driving serotonin activity that saturated fats do not share.

- **Combinations of unsaturated fats amplify serotonin release —** Another important observation was that combinations of unsaturated fats produced additive effects. When arachidonic acid and oleic acid were given together at levels too low to act on their own, they still triggered platelet aggregation and serotonin release.

  This demonstrates that different unsaturated fats reinforce one another, raising the likelihood of serotonin release when multiple types are present at the same time.

- **Modern diets make the additive effect highly relevant —** Since everyday diets typically contain mixtures of multiple PUFs and MUFs, the additive effect applies directly to real-world eating patterns. Even when individual fats are present at levels below the threshold for serotonin release, their combined presence may still trigger platelet activation and serotonin output.

Cutting back on these fats is essential for keeping serotonin in check, easing stress, and supporting a steady mood. To see practical steps for lowering your intake of LA, the most common PUFs in the modern diet, read "**Fed a Lie — The Truth About Seed Oils**."

Why GABA Is a Better Choice Than SSRIs

Even though the featured trial explored the use of a pharmaceutical drug, it is important to know that there are natural ways to suppress serotonin levels. One of the most effective strategies is to increase gamma-aminobutyric acid (GABA), available through supplementation and synergistic nutrients. GABA promotes the breakdown of serotonin, so when your GABA levels are higher, serotonin levels naturally fall.

- **GABA deficiencies are common in mood disorders —** Low GABA levels are frequently seen in people with depression and anxiety. Restoring GABA helps ease symptoms without raising serotonin further. As explained by Dr. Scott Sherr, director of integrative hyperbaric medicine and health optimization at Hyperbaric Medical Solutions and an expert on neurotransmitter balancers like GABA:

  > *"GABA deficiencies are associated with anxiety, with fear, with depression, with a short temper, phobias, impulsiveness, disorganization, addictions. It's even associated with schizophrenia and OCD [obsessive-compulsive disorder].*
  >
  > *You can also have things like IBS and diarrhea, hypertension, tinnitus, chronic pain, migraines, allergies, frequent urination, flushing, sweating, salt cravings, muscle tension. These are all things that could be signs of GABA deficiency. Many have been prescribed an SSRI for some of these symptoms, but … we know that depression is not related to serotonin deficiency."*

- **Supplementation shows measurable benefits —** Daily doses of 500 to 2,000 milligrams have reduced anxiety and improved sleep, even in people already taking SSRIs. Lower doses, around 100 milligrams, have also improved anxiety and depression scores in clinical settings. Combining GABA with L-theanine, an amino acid that acts as a natural GABA agonist, can further enhance these effects.

- **Caution with combined GABA-magnesium products —** While magnesium offers its own benefits, pairing it with high-dose GABA may lead to unwanted digestive effects. Still, the safety profile of GABA is strong. When taken in excess, some GABA is converted into succinic acid, a Krebs cycle intermediate that supports mitochondrial energy production, making supplementation both safe and metabolically useful.

- **Restoring GABA balances mood and stress without raising serotonin —** By correcting GABA deficiency, you support pathways tied to calmness, resilience, and restorative sleep. Unlike serotonin-targeting drugs, GABA supplementation avoids pushing serotonin to harmful levels, making it one of the most practical and low-risk strategies for managing depression, anxiety, and insomnia.

To learn why GABA offers a safer and more effective path than SSRIs, read "**SSRI Drugs Can Cause Chronic Fatigue Syndrome**." For more strategies to inhibit serotonin production, check out "**Media Twists Findings of Study Linking High Serotonin to Dementia**."

Frequently Asked Questions (FAQs) About Serotonin and Depression

Q: Why have I always been told that depression comes from low serotonin?

A: For decades, the serotonin deficiency theory shaped mainstream psychiatry and drove the rise of SSRIs. But newer research shows that your serotonin levels may actually be too high, and this excess suppresses dopamine, the neurotransmitter that drives motivation, pleasure, and resilience.

Q: What role does dopamine play in my mood?

A: When serotonin rises too high, dopamine activity drops, leaving you without drive or reward. Supporting your dopamine balance helps restore energy, optimism, and resilience in your daily life

Q: How does blocking serotonin improve mood and stress?

A: Serotonin overactivity at the 5-HT2C receptor drives the release of ACTH and cortisol, your body's primary stress hormone. Blocking that receptor calms the stress pathway and improves both depression and anxiety. This tells you that lowering serotonin signaling directly eases your stress response.

Q: If I have "treatment-resistant" depression, does this really mean I'm untreatable?

A: The Oxford study showed that what's called "treatment-resistant" depression may not be resistant at all — it may just need a different approach. By shifting your focus from raising serotonin to balancing it with dopamine and supporting GABA, you open the door to recovery that standard treatments overlook.

Q: Is there a safe way to lower my serotonin naturally?

A: Increasing GABA helps your body break down serotonin. If you're low in GABA, you may struggle with anxiety, poor sleep, muscle tension, or even digestive issues. Restoring your GABA levels helps bring calm, improve sleep, and lift your mood — all while lowering serotonin rather than raising it.

Sources and References

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