

## No evidence that depression is caused by low serotonin levels, finds comprehensive review

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**Source:** University College London **Joanna Moncrieff**

**Summary:** After decades of study, there remains no clear evidence that serotonin levels or serotonin activity are responsible for depression, according to a major review of prior research.

### FULL STORY

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After decades of study, there remains no clear evidence that serotonin levels or serotonin activity are responsible for depression, according to a major review of prior research led by UCL scientists.

The new umbrella review -- an overview of existing meta-analyses and systematic reviews -- published in *Molecular Psychiatry*, suggests that depression is not likely caused by a chemical imbalance, and calls into question what antidepressants do. Most antidepressants are selective serotonin reuptake inhibitors (SSRIs), which were originally said to work by correcting abnormally low serotonin levels. There is no other accepted pharmacological mechanism by which antidepressants affect the symptoms of depression.

Lead author Professor Joanna Moncrieff, a Professor of Psychiatry at UCL and a consultant psychiatrist at North East London NHS Foundation Trust (NELFT), said: "It is always difficult to prove a negative, but I think we can safely say that after a vast amount of research conducted over several decades, there is no convincing evidence that depression is caused by serotonin abnormalities, particularly by lower levels or reduced activity of serotonin.

"The popularity of the 'chemical imbalance' theory of depression has coincided with a huge increase in the use of antidepressants. Prescriptions for antidepressants have risen dramatically since the 1990s, with one in six adults in England and 2% of teenagers now being prescribed an antidepressant in a given year.

"Many people take antidepressants because they have been led to believe their depression has a biochemical cause, but this new research suggests this belief is not grounded in evidence."

The umbrella review aimed to capture all relevant studies that have been published in the most important fields of research on serotonin and depression. The studies included in the review involved tens of thousands of participants.

Research that compared levels of serotonin and its breakdown products in the blood or brain fluids did not find a difference between people diagnosed with depression and healthy control (comparison) participants.

Research on serotonin receptors and the serotonin transporter, the protein targeted by most antidepressants, found weak and inconsistent evidence suggestive of higher levels of serotonin activity in people with depression. However, the researchers say the findings are likely explained by the use of antidepressants among people diagnosed with depression, since such effects were not reliably ruled out.

The authors also looked at studies where serotonin levels were artificially lowered in hundreds of people by depriving their diets of the amino acid required to make serotonin. These studies have been cited as demonstrating that a serotonin deficiency is linked to depression. A meta-analysis conducted in 2007 and a

sample of recent studies found that lowering serotonin in this way did not produce depression in hundreds of healthy volunteers, however. There was very weak evidence in a small subgroup of people with a family history of depression, but this only involved 75 participants, and more recent evidence was inconclusive.

Very large studies involving tens of thousands of patients looked at gene variation, including the gene for the serotonin transporter. They found no difference in these genes between people with depression and healthy controls. These studies also looked at the effects of stressful life events and found that these exerted a strong effect on people's risk of becoming depressed -- the more stressful life events a person had experienced, the more likely they were to be depressed. A famous early study found a relationship between stressful events, the type of serotonin transporter gene a person had and the chance of depression. But larger, more comprehensive studies suggest this was a false finding.

These findings together led the authors to conclude that there is "no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations."

The researchers say their findings are important as studies show that as many as 85-90% of the public believes that depression is caused by low serotonin or a chemical imbalance. A growing number of scientists and professional bodies are recognising the chemical imbalance framing as an over-simplification. There is also evidence that believing that low mood is caused by a chemical imbalance leads people to have a pessimistic outlook on the likelihood of recovery, and the possibility of managing moods without medical help. This is important because most people will meet criteria for anxiety or depression at some point in their lives.

The authors also found evidence from a large meta-analysis that people who used antidepressants had lower levels of serotonin in their blood. They concluded that some evidence was consistent with the possibility that long-term antidepressant use reduces serotonin concentrations. The researchers say this may imply that the increase in serotonin that some antidepressants produce in the short term could lead to compensatory changes in the brain that produce the opposite effect in the long term.

While the study did not review the efficacy of antidepressants, the authors encourage further research and advice into treatments that might focus instead on managing stressful or traumatic events in people's lives, such as with psychotherapy, alongside other practices such as exercise or mindfulness, or addressing underlying contributors such as poverty, stress and loneliness.

Professor Moncrieff said: "Our view is that patients should not be told that depression is caused by low serotonin or by a chemical imbalance, and they should not be led to believe that antidepressants work by targeting these unproven abnormalities. We do not understand what antidepressants are doing to the brain exactly, and giving people this sort of misinformation prevents them from making an informed decision about whether to take antidepressants or not."

Co-author Dr Mark Horowitz, a training psychiatrist and Clinical Research Fellow in Psychiatry at UCL and NELFT, said: "I had been taught that depression was caused by low serotonin in my psychiatry training and had even taught this to students in my own lectures. Being involved in this research was eye-opening and feels like everything I thought I knew has been flipped upside down.

"One interesting aspect in the studies we examined was how strong an effect adverse life events played in depression, suggesting low mood is a response to people's lives and cannot be boiled down to a simple chemical equation."

Professor Moncrieff added: "Thousands of people suffer from side effects of antidepressants, including the severe withdrawal effects that can occur when people try to stop them, yet prescription rates continue to rise. We believe this situation has been driven partly by the false belief that depression is due to a chemical imbalance. It is high time to inform the public that this belief is not grounded in science."

The researchers caution that anyone considering withdrawing from antidepressants should seek the advice of a health professional, given the risk of adverse effects following withdrawal. Professor Moncrieff and Dr Horowitz are conducting ongoing research into how best to gradually stop taking antidepressants.

Story Source:

Materials provided by **University College London**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Joanna Moncrieff, Ruth E. Cooper, Tom Stockmann, Simone Amendola, Michael P. Hengartner, Mark A. Horowitz. **The serotonin theory of depression: a systematic umbrella review of the evidence.** *Molecular Psychiatry*, 2022; DOI: 10.1038/s41380-022-01661-0

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