In 1965, in a paper published in the American Journal of Psychiatry, the NIMH’s Joseph Schildkraut put forward a chemical imbalance theory of affective disorders. It was he said, ‘at best a reductionistic oversimplification of a very complex biological state’. He also stated that at the time of writing there was no evidence to support or disprove the theory.

Schildkraut’s theory inspired a generation of researchers to test it. Although Schildkraut thought that norepinephrine was the neurotransmitter most likely to be deficient in those diagnosed with depression, researchers quickly turned their attention to serotonin. In 1969, Malcolm Bowers, of Yale University, was one of the first to investigate whether depressed patients had low levels of serotonin metabolites in their cerebrospinal fluid. He studied eight depressed patients who had all been exposed to antidepressants and announced their 5-HIAA levels were lower than normal but not ‘significantly’ so.

In 1971 researchers at McGill University said they too failed to find a ‘statistically significant’ difference in the 5-HIAA levels of depressed patients. They also failed to find any correlation between 5-HIAA levels and the severity of depressive symptoms.

In a follow up study in 1974 Bowers concluded: ‘Depressed patients who had not been exposed to antidepressants had perfectly normal 5-HIAA levels’. In the same year, Joseph Mendels and Alan Frazer, researchers at the University of Pennsylvania, looked at the evidence that had lead to Schildkraut to put forward his theory and concluded: ‘The literature reviewed here strongly suggests that the depletion of brain norepinephrine, dopamine or serotonin is in itself not sufficient to account for the development of the clinical syndrome of depression’.

Later, in 1984, NIMH investigators again studied the low-serotonin theory and lead investigator James Maas and others discovered 5-HIAA levels varied widely in depressed patients. They drew the conclusion: ‘Elevations or decrements in the functioning of serotonergic systems per se are not likely to be associated with depression’.

This last point is in agreement with a recent and definitive review of all basic antidepressant research published in the New England Journal of Medicine. As it stated: ‘Numerous studies of norepinephrine and serotonin metabolites in plasma, urine and cerebrospinal fluid, as well as post-mortem studies of the brains of patients with depression, have yet to identify the purported deficiency reliably’. In other words, and to quote the leading journal The Pharmacological Basis of Therapeutics, the data for the neurotransmitter hypothesis of mood disorder ‘are inconclusive and have not been consistently useful either diagnostically or therapeutically’.

The absence of supporting evidence has led to a professional ‘crisis of faith’ in the chemical imbalance theory, as some of the following comments testify:

- ‘Many neuroscientists no longer consider a chemical imbalance theory of depression and anxiety to be valid.’ (Dr David D. Burns, Professor of Psychiatry, Stanford University)

- ‘Chemical imbalance is sort of last-century thinking. It’s much more complicated than that.’ (Dr. Joseph Coyle, Professor of Neuroscience at Harvard Medical School)
• ‘After decades of trying to prove [the chemical-imbalance theory], researchers have still come up empty-handed.’ (Marcia Angell, former editor of The New England Journal of Medicine).

• ‘Despite pseudoscientific terms like “chemical imbalance” nobody really knows what causes mental illness. There’s no blood test or brain scan for major depression.’ (Dr Darshak Sanghavi, clinical fellow at Harvard Medical School)

• ‘We do not know the aetiology of really any of the mental disorders at the present time.’ (previous Director of Research at the American Psychiatric Association)

• ‘Research has yet to identify specific biological causes of any of these [mental] disorders.’ (U.S. Congressional Report, entitled: The Biology of Mental Disorders; New Developments in Neuroscience)

• ‘The results of decades of neurotransmitter-depletion studies point to one inescapable conclusion, low levels or serotonin, norepinephrine or dopamine do not cause depression.’ (Professor Irving Kirsch, Harvard Medical School)

• ‘We still don’t know the relationship between biology and the mental disorders.’ (Carol Bernstein previous president of the American Psychiatric Association)

• ‘Patients have been diagnosed with chemical imbalances, despite that no test exists to support such a claim, and that there is no real conception of what a correct chemical balance would look like.’ (Dr David Kaiser Psychiatric Times)

• ‘As a scientific venture, the theory that low serotonin causes depression appears to be on the verge of collapse. This is as it should be; the nature of science is ultimately to be self-correcting. Ideas must yield before evidence.’ (Dr Jonathan Rottenberg, Psychology Today)

• ‘A simplistic biological reductionism has increasingly ruled the psychiatric roost… [we have] learned to attribute mental illness to faulty brain biochemistry, defects of dopamine, or a shortage of serotonin. It is biobabble as deeply misleading and unscientific as the psychobabble it replaced.’ (Andrew Skull, Professor of History of Psychiatry, Princeton University, Lancet)

Although scientists have been testing the chemical imbalance theory’s validity for over 40 years – and despite literally thousands of studies – there is still not one piece of direct evidence proving the theory correct. The chemical imbalance theory, in relation to any mental health disorder is thus unsubstantiated, yet a societal belief in chemical imbalances, largely owing to effective pharmaceutical marketing, remains prevalent today.

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(Last revised: 15 March 2014)


4 Bowers M., 1974, Lumbar CSF 5-hydroxyindoleacetic acid and homovanillic acid in affective syndromes, *Journal of Nervous and Mental Disease*, 158: 325-30


8 Quoted in Davies J., *Cracked: why psychiatry is doing more harm than good* (London: Icon (2013))