

Depression Is Not a Serotonin Deficiency: Toward a Multisystem Account of Distress

Abstract

A single-molecule account of depression is appealing because it converts severe human suffering into a tidy biochemical deficiency. But major depressive syndromes are clinically heterogeneous, and a compelling explanatory metaphor is not equivalent to an established cause. This paper argues for a layered formulation: sleep and circadian disruption, immune signaling, endocrine status, medication effects, nutrition, gut-brain interactions, trauma, social circumstances and personal meaning may each contribute to a particular presentation. The aim is not to deny psychiatric disease or claim that one dietary intervention cures it. It is to refuse the inference that a diagnostic label explains its own cause.

The category is not the mechanism

Major depressive disorder is defined largely by a constellation of reported symptoms and functional changes over time. Two patients may satisfy the same criteria yet differ dramatically: one has an inflammatory condition and profound fatigue; another has a delayed sleep schedule, severe anxiety and bereavement; a third has bipolar depression, medication-associated changes or untreated sleep apnea. These people may require very different investigations and treatments. The diagnosis helps communicate risk and organize care; it does not establish an identical biochemical defect in every patient.

The popular claim that depression is simply caused by too little serotonin is inadequately supported. An umbrella review published by Moncrieff and colleagues found no consistent evidence for such a generalized deficiency. That finding does not demonstrate that serotonin signaling is irrelevant, that antidepressants never help, or that patients should stop prescribed medication. A medicine can alter a pathway and produce benefit without proving that a lack of that pathway caused the original illness. Aspirin relieving pain does not mean pain was caused by an aspirin deficiency.

The terrain hypothesis without the mystique

The books behind this essay propose that depression can emerge from physiological conditions which render emotional regulation more difficult. That idea is strongest when translated into specific, measurable relationships. Repeated sleep restriction can undermine attention and affective regulation; thyroid abnormalities can resemble psychiatric disorders; certain nutritional deficiencies can produce neuropsychiatric symptoms; inflammatory signaling changes the experience of fatigue, reward and motivation. Bile-acid profiles and microbial metabolites are additional emerging research subjects, not established universal causes.

These pathways are reciprocal. Depression may alter food intake, movement, sleep and medication use, and those changes may then alter metabolic and inflammatory signals. A finding that a biomarker differs between depressed and nondepressed people cannot alone reveal which direction causation runs. Rather than searching for one hidden toxin behind every case, a more promising question is whether identifiable physiological subgroups have distinct risk factors, symptom profiles and treatment responses.

Meaning is a clinical variable, not a laboratory analyte

Human beings do not suffer as isolated nervous systems. Loss, humiliation, isolation, moral conflict, economic insecurity, chronic pain and relationship rupture can deepen depression even when standard blood tests are normal. The Covenant Psychiatry manuscripts call attention to the patient's commitments and lived environment. As a conceptual position, this is valuable: the outcome of care should include agency, relationships and everyday functioning, not merely improvement on one symptom scale.

Yet meaning must not become blame. Moral disobedience is not a validated psychiatric biomarker; spiritual interpretations belong to the person and must never be imposed as diagnoses. Faith-concordant practices may be valuable when freely chosen, but they cannot substitute for urgent care where suicide risk, psychosis, mania, severe self-neglect or medical illness is present. A humane multisystem model protects patients from both biological reductionism and moral coercion.

A better clinical question

Instead of asking only, “Which drug treats this label?”, ask, “What maintains this person's particular symptoms today?” That question can include sleep timing, medical comorbidity, substances, nutrition, trauma, interpersonal danger and previous treatment response. It also recognizes that psychotherapy and medication have established roles, and their effects should be considered alongside—not automatically displaced by—environmental or dietary interventions.

The frontier proposition is that depression may be more intelligible when viewed as a family of convergent syndromes with diverse causal pathways. Its value will depend on specificity: named mechanisms, observable distinctions and openness to findings that undermine preferred explanations. The strongest challenge to simplistic psychiatry is not another simplicity. It is greater diagnostic precision.

Diagnostic heterogeneity is the starting point, not an inconvenience

Two people may satisfy identical symptom criteria for major depression while sharing few causes. One develops low mood after insomnia and prolonged caregiving; another describes new anhedonia with weight loss, thyroid dysfunction and an inflammatory illness; a third experiences episodic depression within a bipolar course. A questionnaire may assign similar severity to all three, yet the clinical decisions differ. This does not render diagnostic categories meaningless. A syndrome is useful for identifying distress, estimating risk and organizing care. The error begins when the syndrome is mistaken for one molecular defect. Even the description of antidepressants as selective serotonin reuptake inhibitors specifies an immediate pharmacological action rather than proving that the original illness consisted of a serotonin deficiency. Treatment response likewise does not retrospectively reveal a unique cause: pain relief after an anti-inflammatory does not establish that every pain syndrome begins as an inflammatory disorder.

A layered causal map for depressive symptoms

A usable multisystem account should separate predisposition, precipitant, mediator, maintaining process and consequence. Sleep disruption may precede low mood, follow it, or create a feedback loop. Persistent inflammation could influence fatigue and reward processing through immune-to-brain signaling, but an elevated inflammatory marker is neither specific to depression nor diagnostic of an inflammatory depressive subtype. Thyroid disorders, anemia, medication effects, sleep apnea, substance exposure and nutritional deficiencies may imitate or amplify depressive symptoms. Interpersonal loss, social isolation, occupational stress and traumatic experience can affect cognition, sleep and behavior without requiring their meaning to be reduced to a blood test. Conversely, treating every depressive episode as a purely psychological response risks missing a systemic disease. This architecture explains why the right question is not whether depression is biological or existential, but which interacting processes matter most for this particular episode.

What a discriminating clinical investigation would measure

A prospective cohort could measure sleep timing, mood trajectories, functional capacity, medications, stressors and relevant clinical laboratory findings before and after treatment. Investigators should preregister hypotheses about individual pathways rather than searching a vast dataset for appealing correlations. An intervention aimed at sleep should first demonstrate sleep improvement and then examine whether mood improves more in participants with objectively disordered sleep than in those without it. A thyroid correction should be judged in biochemically confirmed disease rather than given as a universal antidepressant strategy. Multiple possible responders should be identified before randomization, with outcomes extending beyond symptom-score shifts to return of ordinary functioning. This design would also test whether combining individually justified interventions improves durability more than indiscriminate bundles of supplements or investigations.

The therapeutic implication is sequencing, not therapeutic maximalism

A whole-person assessment must not become a demand for every patient to purchase extensive panels, adopt elimination diets or discontinue evidence-based care. Immediate suicide risk, psychosis, mania, severe functional deterioration and medication harms still require conventional assessment. Once urgent needs are addressed, clinicians can ask which modifiable factor is likely to yield the greatest benefit with the lowest burden. A sleep intervention may change the patient's ability to participate in psychotherapy; improved social safety may make medication adherence possible; correction of a documented deficiency may reduce fatigue without resolving grief. This is a pragmatic, testable proposal for more precise care. It rejects serotonin reductionism without replacing it with an equally simplistic assertion that inflammation, diet or the microbiome explains every depressed mind.

Evidence boundary

This is a conceptual essay, not evidence that depression has a single nutritional, infectious or hepatobiliary cause. It does not establish a cure. Sudden discontinuation of psychiatric medication can cause withdrawal or relapse; changes require individualized clinical oversight.