Understanding Depression

Beyond the Chemical Imbalance: What the Evidence Shows and What It Means in Practice

Introduction

Most patients have a clear idea about what depression is. Usually it is some version of a chemical imbalance, a problem with serotonin, something inherited, or a brain condition they will have for life. Historically these ideas or similar ones have formed the basis on which clinicians explain depression to patients. The idea is simple, it removes blame, and it points directly towards a treatment. It is also, in its usual form, not what the evidence supports.

This document sets out to do three things. First, to clearly examine the dominant narratives looking at the evidence base as a whole. Second, to describe what depression looks like when read more accurately: less a fixed biological fault and more a process the mind and body move into under particular conditions. Third, to look at what this changes in practice, including how we explain depression to patients and how the words we choose affect the people who hear them.

It is not a guideline or a treatment protocol, and it does not replace NICE or professional guidance. It is a synthesis aimed at clinicians who already work biopsychosocially and who have noticed the gap between the simplified models used in teaching and public messaging and the reality we actually see day to day. The companion document on antidepressants covers prescribing and medication evidence in more detail; the focus here is on what depression is and how we talk about it.

Throughout, depression refers to populations defined by current diagnostic criteria. None of what follows questions the seriousness of depression or the value of treatment. Depression is common, often disabling and sometimes life-threatening, and guideline-based care remains essential. The argument is only that we can be more accurate about what we are treating, and that accuracy helps patients.

The common story, and what the evidence supports

The common story	What the evidence supports
Depression is caused by a chemical imbalance, usually too little serotonin.	No consistent evidence of a serotonin deficiency or specific chemical imbalance. Neurotransmitters take part in wider regulatory systems; drug effects do not prove an underlying deficiency.
Depression is a genetic condition.	Genes contribute to vulnerability, not destiny. Risk is spread across thousands of tiny effects, there is no “depression gene”,

The common story	What the evidence supports
	and measured genetic variation explains only a small fraction of risk.
Depression is a fixed biological brain disease, like diabetes.	Brain differences are small, non-specific, overlap heavily with healthy people, and largely track the state rather than a fixed lesion. Most change as the person recovers.
Depression is a thing you have.	Depression is better understood as a state you enter: a process arising from interacting stressors, physiology and context, which tends to maintain itself once established.

The Current Dominant Narrative

The biomedical account of depression became dominant for understandable reasons. It fitted the rest of medicine, it supported a clear treatment, and it offered patients relief from the idea that depression was a weakness or a failure of will. That reassurance was sound — depression is neither — but the biological-defect model is not the only, or the best way, to reach that conclusion. It has done real good while resting on three claims that do not hold up: chemical imbalance, inherited disease, fixed brain disorder. It is worth clearly examining the evidence behind each.[1]

The chemical imbalance

The idea that depression is caused by too little serotonin began as a reasonable inference from how early antidepressants worked. If a drug that raises serotonin lifts mood, perhaps low serotonin causes low mood. Decades of research have not borne this out. Recent systematic reviews drawing together serotonin metabolites, receptor and transporter imaging, depletion experiments and genetic studies find no consistent evidence that depression is caused by reduced serotonin activity or by a chemical imbalance of any simple kind.[2]

The logical error is worth naming, because patients make it too. That a treatment relieves a symptom tells us nothing about an underlying deficiency. Alcohol relieves social anxiety without anxiety being a shortage of alcohol; paracetamol helps a headache that is not caused by a lack of paracetamol. Antidepressants act on neurotransmitter systems, but those systems are involved in learning, stress adaptation, emotional processing and neuroplasticity, not in topping up a missing chemical. The honest description is that medication can shift how these systems behave, not that it corrects a known fault.

The picture is not entirely settled, and it is fair to say so. The most prominent umbrella review has been contested, with critics arguing that its method can obscure genuine serotonergic signals and that few researchers ever held the crude deficiency model in the

first place.[3] However I think its reasonable to say that the evidence does not support a simple serotonin-deficiency account in the way it is commonly presented.

The genetic condition

Depression runs in families, and twin studies put its heritability at around thirty to forty per cent.[4] This is often heard as evidence that depression is, at root, an inherited disease. The genetics says something more limited and more interesting.

Heritability is a population statistic, not a personal one. It does not mean a given person's depression is forty per cent genetic; it describes how much of the variation across a population, under particular conditions, tracks genetic differences. It rises and falls with circumstance, growing where adversity and inequality are greater. More tellingly, when very large studies look for the actual genes, they find risk scattered across many thousands of variants, each of vanishingly small effect, most sitting in broad developmental and regulatory pathways rather than anything mood-specific.[5] There is no single depression gene and no small set of them. Measured genetic variation accounts for only around five to ten per cent of the variation in risk, a long way short of the heritability estimates, and polygenic risk scores overlap so heavily between affected and unaffected people that they predict nothing useful for an individual.

What genes appear to shape is sensitivity, not outcome: tendencies in stress reactivity, emotional response, sleep and temperament that influence how a person meets their circumstances. The candidate-gene studies that once suggested specific genes interacting with adversity have mostly failed to replicate.[6]

This is also where the old nature-versus-nurture split breaks down. Genes are not simply switched on at birth and left to run; their expression is regulated continuously by experience, through what is loosely called epigenetics. Prolonged stress can turn up the sensitivity of stress-response systems, while safety, supportive relationships and activity can turn it down again, and these adjustments are dynamic rather than fixed.[7] It gives a concrete mechanism for something clinicians see all the time: that biology and life experiences are not two separate stories but one, and that a system shaped by hard experience can be reshaped by better experience. It is part of why recovery remains possible even after long difficulty.

The fixed biological brain disease

The third claim is that depression is a fixed brain disease, often by analogy with diabetes: a chronic biological condition requiring lifelong correction. Brain research is usually offered in support. Read carefully, it does not provide it.

The differences seen on imaging are real but small, highly variable, and heavily overlapping with healthy people, so that no scan can tell a depressed brain from a non-depressed one.[8] They are not specific, appearing across anxiety, trauma and chronic stress alike. And they relate more to illness duration, repeated episodes, early adversity, poor sleep and chronic

stress than to the diagnosis itself. Most importantly, they tend to shift as the person recovers, whether through therapy, medication, changed circumstances or restored sleep. A fixed disease does not come and go with the state it is supposed to explain. The diabetes analogy does not really hold up when you examine it: there is no established clearly defined mechanism, no objective scientific marker to test or confirm, and no stable lesion or deficit that persists between episodes.

This matters because the analogy carries a hidden message. Telling someone they have a deficiency or implying a brain or chemical balance problem implies permanence and limited agency. Neither the neurotransmitter research nor brain imaging research supports that message, and as the later section on explanation shows, the message itself has costs.

What Depression Actually Is: A Process, Not a Defect

If depression is not a chemical imbalance, not an inherited disease and not a fixed lesion, the obvious question is what it is. The most defensible reading of the evidence is that depression is better understood as a process than as a thing a person has: a state the mind and body move into under particular conditions, and which tends to sustain itself once established.

The starting clue is heterogeneity. People who meet criteria for depression differ enormously in their symptoms, histories, triggers, physiology and course;[9] two patients can share the same diagnosis with barely a symptom in common.[10,11] This is partly because the criteria themselves were arrived at by expert committee, through negotiation and revision across successive editions of the manuals, rather than discovered in nature; the thresholds for how many symptoms, and for how long, are conventions agreed for consistency, and they have shifted over time.[12] No single mechanism has been found, some have been proposed but not held up when examined by research. Many different pathways, biological and social, converge on a broadly similar state of low mood, reduced drive and impaired function.[13,14] The diagnosis names the convergence, not a shared cause.

Read as a process, depression usually arises in relation to something: loss, defeat, threat, entrapment, prolonged strain, exhaustion, or physiological disruption such as illness or sustained poor sleep. Often there is no single event, because the relevant factor is cumulative load rather than a discrete incident, which is why patients so often cannot name a cause. Sometimes the trigger is mainly bodily and sometimes mainly circumstantial; both are clinically valid, and the same end state can be reached by either route.

One of these triggers in particular has a useful body of work behind it. The social-rank account of depression notes that low mood often follows defeat, and that what tends to turn a passing low state into a depressive one is entrapment: defeat combined with no apparent way out. In social animals, losing a contest prompts an involuntary down-regulation, a retreat from challenge that is protective when a fight cannot be won; the suggestion is that depression recruits something similar in people who feel beaten and

stuck.[15] The empirical support is good, with perceived defeat and entrapment predicting depression at least as strongly as loss itself.[16] The framing is likely to be recognised by many clinicians because trapped is so often the word patients use to describe their situation. It helpfully points to a precise task: restoring a sense of movement or progress, however gradual, rather than simply lifting mood.

Seen this way, many of the symptoms look less like random malfunction than like a coordinated, if unwelcome, shift: withdrawal, reduced energy, heightened threat sensitivity, loss of interest and a turning-inward of attention. All in service of a period of withdrawal from life to aid recovery.

The state, however, is also self-maintaining, which is why it can continue long beyond whatever set it off. Withdrawal removes sources of reward, inactivity worsens sleep and energy, rumination amplifies threat, and disrupted sleep degrades emotional regulation, each feeding the others until the pattern holds itself in place. This is the most useful single idea for formulation: not what is broken, but what is keeping the loop going. The network theory of psychopathology gives this a formal shape, treating the disorder not as a hidden cause sitting beneath the symptoms but as the symptoms themselves locking into a self-sustaining web.[17] It also explains why interventions as different as activity, sleep repair, talking therapy, medication and a change in circumstances can all help: each interrupts the loop at a different point. Behavioural activation makes the logic clear, working precisely by restoring the rewarding activity whose loss helps drive the cycle, and it performs about as well as more elaborate therapies with far less complexity.[18]

A newer line of thinking, still developing but worth knowing about, comes from computational accounts of mood. These treat mood as something like the brain's running estimate of how rewarding and controllable the world is likely to be, updated by experience. Depression can then be understood as a negative estimate that has become locked in: a model of the world as low in reward and beyond one's control, which tends to confirm itself, because once someone expects little and acts accordingly they stop encountering the evidence that might revise it.[19] The account is more theoretical than the others here and should be held lightly, but it captures the self-maintaining quality well and gives a clean rationale for why getting someone moving and acting, against the grain of the expectation, can begin to shift the state: action generates the surprises that update the model. The same logic throws light on something the antidepressant evidence makes hard to ignore: that a large part of the response to treatment with antidepressants in trials comes from placebo. If mood is partly an estimate of how much reward and control lie ahead, then the things that surround any treatment, a credible explanation, a clinician who expects improvement, the ritual of being prescribed something, are not artefacts around the active ingredient; they are themselves inputs the system uses to revise its estimate. That is one reason an inert tablet can produce measurable change in the same mood circuits as an active drug. A response shaped by expectation is not a false one: the circuits move, and the person genuinely feels better. It is a real effect with an intelligible mechanism, woven through

every treatment we offer. The companion guide on antidepressants takes the evidence on this further.

Finally, the state is reversible. The biological changes that accompany depression largely track the state and move with it rather than persisting as damage. None of this implies the state is mild. A process can be profound: severe psychomotor retardation, in which movement, speech and thought slow dramatically, makes plain that these are deep bodily changes, not simply an intense version of low mood, and the same is true of the cognitive impairment, disrupted appetite and physical collapse seen at the severe end. The point of the framework is not that such changes are minor but that, however severe, they are states the system has entered and can leave, rather than fixed damage. That a person can be mute and immobile in deep depression and then, weeks later, be fully restored is itself evidence of reversibility. This does not make depression a matter of will; a process can be severe, disabling and dangerous. But it reframes the clinical task. The question shifts from what is wrong inside this person to what state they are in, how they came to enter it, and what is holding them there. That question has possible answers a clinician and patient can better work with.

What the Science Actually Shows

The process account is not an alternative to looking at the biology. Quite the opposite, it is what the biology, read without the disease assumption, actually describes. Across every system studied, the findings point the same way: real changes, mostly small and non-specific, strongly shaped by context, and consistent with a stressed and dysregulated state rather than a discrete illness. One concept ties much of this together. Allostasis is the body's capacity to stay stable through change, constantly adjusting its stress, hormonal, autonomic and immune systems to meet demand; allostatic load is the cumulative cost when that adjustment runs too long without recovery, and the regulating systems themselves begin to drift out of balance.[20] Read this way, the scattered biological findings below are less a list of separate abnormalities than facets of a single overloaded regulatory state. The social evidence, often treated as soft, is in fact among the most robust of all.

The brain

The most consistent structural findings are small average differences in regions such as the hippocampus and prefrontal cortex, with distributions that overlap heavily with healthy people and no diagnostic value in any individual.[8] They track illness duration, recurrence, early adversity and chronic stress more than the diagnosis, and are best read as neuroplastic adaptation to prolonged stress rather than a primary fault. Functional imaging tells a similar story: increased default-mode activity often linked to rumination, reduced engagement of control networks,[21] and blunted reward responses that fit the clinical picture of anhedonia.[22] One often-studied region, the subgenual anterior cingulate, tends to be overactive in more severe depression and to settle as people recover, whether recovery

comes through therapy, medication or a change in circumstances.[23] The detail matters less than the pattern: the activity tracks the state and moves with it, which is hard to square with a fixed lesion and easy to square with a state the brain can enter and leave. These are correlations that vary with mood, sleep, medication and method, appear across other stress-related conditions, and shift as people recover. No imaging measure is reliable enough to diagnose depression or guide treatment, and machine-learning models that perform well in one dataset rarely generalise.

Stress physiology and the autonomic nervous system

Altered stress regulation is commonly reported, most often involving the hypothalamic-pituitary-adrenal axis, though the findings are inconsistent and many patients show no measurable abnormality.[24] Where changes appear they track cumulative adversity and current strain more than diagnosis, and in chronic or trauma-related presentations cortisol activity may be reduced rather than raised. Autonomic measures point the same way: reduced heart rate variability is often seen, suggesting less physiological flexibility and slower recovery from stress, but it is shaped by sleep, fitness, cardiometabolic health and medication and is not specific to depression.[25] Both are better read as altered stress adaptation than as a primary endocrine or autonomic disorder.

Inflammation

Many studies report modest elevations in inflammatory markers such as C-reactive protein and interleukin-6 in depressed groups,[26] and experimentally induced inflammation can produce fatigue, low motivation and withdrawal, the cluster sometimes called sickness behaviour.[27] This offers a plausible link between immune signalling and mood. But the average differences are small and strongly influenced by factors common in depressed populations, including obesity, smoking, inactivity, poor sleep, chronic illness and socioeconomic stress. The evidence does not support depression as primarily an inflammatory disease; inflammation looks like one strand of a broader stress-physiology response, prominent in some patients and absent in others.[28]

Sleep and circadian rhythm

Sleep disturbance is one of the most reliable features of depression, and one of the most clinically useful, because the relationship runs both ways. Depression disrupts sleep, and disrupted sleep deepens and maintains depression.[29] Sleep studies show reduced deep sleep, earlier and denser REM and fragmented continuity, though these vary and overlap with anxiety and chronic stress. Circadian disruption, from irregular routines and reduced daylight, alters hormonal rhythms and energy regulation. Experimentally, sleep loss and circadian misalignment impair emotional regulation, threat sensitivity and reward processing even in healthy people, while restoring regular sleep is associated with improved mood.[30] Sleep is therefore both a driver and a consequence, which is why it takes a central place in formulation and management.

The social evidence

The associations between depression and social conditions are among the most consistent in the entire field, far more robust than most biological findings. The link with adversity is strong, repeatedly demonstrated, and often dose-related: greater cumulative childhood adversity is associated with higher rates of later depression, earlier onset and more complex, recurrent courses.[31] Adult stressors show the same pattern, with relationship loss, financial insecurity, unemployment, poor housing, caregiving strain, discrimination, chronic illness and isolation all raising risk, particularly where demands outstrip recovery, support or control.[32]

Prevalence is not evenly spread. It is consistently higher in populations facing deprivation, insecurity and marginalisation, patterns that individual vulnerability cannot explain, since chronic social stress affects sleep, stress physiology, physical health and the chance to recover.[33] Depression is also diagnosed about twice as often in women as in men, a gap shaped substantially by social role, exposure to adversity and differences in how distress is expressed and recorded rather than by biology alone. Loneliness deserves particular mention: it predicts depressive symptoms and poorer outcomes, while supportive relationships buffer stress and help stabilise regulation.[34] Far from being the soft end of the evidence, the social findings are some of the hardest, and they integrate directly with the biology, since adversity becomes depression through exactly the sleep, stress, immune and reward pathways described above.

Practical Implications

If depression is a self-maintaining state rather than a fixed fault, several things follow for practice, and most of them concern how we understand a patient and what we say to them.

Diagnosis describes, formulation explains

The diagnosis remains useful. It supports communication, access to care and a shared language. But it describes a pattern; it does not explain why this person became unwell now. Treated as an explanation, it lets the real contributors, such as sleep loss, chronic stress, physical illness, loss or adversity, slip from view, and invites the patient to hear the label as a verdict on something fixed inside them. Formulation supplies what diagnosis cannot: an account of the predisposing, precipitating, perpetuating and protective factors particular to this person, and especially of what is keeping the loop going. That is also where the leverage for change usually lies.

How we explain it: the effect of our words

The explanation we offer is not neutral information. It is part of the intervention, and the evidence on this is sobering. Biological and genetic explanations are usually given in good faith, to relieve the self-blame patients so often carry. They can ease it, but they carry a cost. People who understand their own depression mainly in biochemical or genetic terms

tend to expect less improvement and to feel less able to influence it, and emphasising the fixedness of brain chemistry weakens their sense that change is possible.[35] The effect reaches clinicians too: in one well-known study, clinicians shown a biological account of a patient's symptoms reported less empathy than those given a psychosocial account, despite the usual assumption that biological framing should increase it.[36]

The same research points to the remedy. Framing that stresses the malleability of these systems, rather than their permanence, offsets the pessimism and protects a sense of agency.[37] The lesson from this is not to avoid biology but to present it honestly and as changeable: real biological changes, of a kind the brain and body can move out of, shaped by sleep, stress, circumstance and treatment. An explanation built around a process the patient can influence does more good than one built around a defect they cannot. This also means expectation is an active ingredient in every treatment, not a contaminant of the evidence: the way a clinician frames a prescription, or a plan, is part of what determines whether it helps, which I view as a real opportunity. For example, if I am prescribing an antidepressant I often ask something like 'if this medication were to begin to work for you in just the right way, what might you begin to notice?'. This often leads to real and concrete life changes such as 'spending more time with the kids', or 'I'd actually be going out more', or 'I'd want to get up in the mornings'. People often say things like this, and exploring a little further with one or two details, and the difference this might make to them might only take less than a minute but can make a real difference, and further help to interrupt the loops that maintain depression.

Putting it into words

What follows are three ways of explaining depression that I have found useful in the consulting room. Different patients resonate with different ones; the point is to have more than a single causal story to offer, and to choose the framing that fits the person in front of you. There are many framings suppprted by the available evidence, and all three share a common thread, which is to present depression as a changeable state rather than a fixed fault.

A state, not a fault. The broadest framing, and a reasonable default, is to describe depression as a state the system has moved into rather than a defect, imbalance or fault in the person. I often use an everyday image. A car left overnight with its lights on will not start in the morning: the battery is flat, nothing is broken, and once it is charged the car runs as before. Depression can be a little like this, the system run down under sustained load so that function suffers, while the machinery itself remains sound and can recover. The body does something similar when ill or injured, pulling back and dialling down energy, appetite and interest while it recovers, and depression can resemble that protective retreat, set off this time by stress, loss or exhaustion rather than infection, and become stuck because the usual way out has not opened. Something like: "This is a state your system has moved into, not something broken in who you are, and states can change."

The cycle that keeps it going. Low mood leads to withdrawal and inactivity, which remove the small rewards that lift mood and worsen sleep, which deepens exhaustion and leaves more time to dwell, which lowers mood further. Drawing this loop out, even on paper, shows that there is no single cause to find and several places to intervene. Something like: "We don't have to pin down one cause. We can look at what is keeping the cycle turning, because that is where we can get a foot in." Turning depression into a process with an explanation tends to give patients some distance from it and a sense that it can be worked on.

The feeling of being trapped. Many patients describe feeling trapped or with no way out, and naming that directly can help more than an account of mechanism. It is worth saying that this is a recognised part of depression rather than a true measure of their options, and that the entrapment feeds the low mood as much as the other way round. The clinical task it points to is concrete: restoring a sense of movement, however small. Something like: "That trapped feeling is part of the depression itself, not an accurate picture of your situation, and our job is to find the first bit of room to move."

What management actually involves

A process maintained by several interacting loops will rarely respond to a single intervention, which fits what we see in practice: no one treatment works for everyone, and response varies widely. Management that follows the formulation tends to work on more than one loop at once. Restoring sleep and daily structure, reducing sustained stress load, rebuilding activity and reward, strengthening social connection and addressing practical concerns and problems all interrupt the cycle at different points, alongside psychological therapy or medication where appropriate.

On the choice between therapy and medication, the comparative evidence is reassuring and worth sharing with patients. Across direct comparisons, psychotherapy and antidepressants have broadly similar average effects, and combined treatment is often, though not always, better than either alone.[38] Cognitive behavioural therapy has the strongest evidence base but is not the only effective approach, and patient preference is a legitimate basis for choosing between options of similar average benefit if options are available. Medication need not be the default first step; a stepped approach matched to severity, with lower-intensity psychological options offered alongside or ahead of medication, is consistent with both the evidence and NICE guidance.

Medication and informed consent

Antidepressants help some patients, particularly in more severe or persistent depression, where average benefits are modest but meaningful for a proportion of people.[39] Given the uncertainty about mechanism and the variability in response, consent is more honest when it covers the likely benefits and their limits, possible adverse effects, the unpredictability of individual response, the alternatives, and the role of time and circumstances in recovery.

Presenting medication as correcting a known chemical imbalance is not supported by the evidence and can promote the deterministic beliefs that the explanation research warns against. Describing it as a treatment that may help shift a stuck state in the right direction is both more accurate and more useful. The companion antidepressant document develops this further.

Physical health

Depressive states sometimes overlap with physical illness, and as we know, conditions and substances that can mimic or contribute to depression include thyroid disease, anaemia, B12 or vitamin D deficiency, chronic pain, sleep disorders such as obstructive sleep apnoea, alcohol and recreational drugs, and some prescribed medications. A focused history and examination, with basic investigations where indicated, helps avoid missing a treatable contributor early on.

Risk and suicidality

Risk assessment is required in every depression consultation, and the process view helps here too. Suicidal thinking is better understood as a fluctuating state than a fixed trait, typically intensifying during acute distress and easing as mood and regulation improve. A useful frame is cognitive constriction, in which attention narrows onto present pain and the capacity to imagine change or a different future temporarily collapses, so that problems feel permanent and unsolvable even though that perception is itself part of the state.[40] This state does not always build slowly. It can descend within hours, sometimes minutes, often triggered by an acute blow such as humiliation, shame, a sudden loss or a public exposure, and it can do so in someone who is not chronically depressed at all. That is why acute distress around a precipitating event deserves to be taken seriously in its own right, not discounted because the person seemed well the day before; the narrowing, and the risk that travels with it, can happen quickly.

Because hopelessness is a symptom rather than a fact, communication that holds realistic hope without false reassurance can itself be protective, which is another reason the framing of prognosis matters. Single-occasion risk scores predict individual outcomes poorly; what helps more is an ongoing, collaborative appraisal of distress, intent, access to means, supports and protective factors, revisited over time. Of course, any expression of intent, a plan, or an inability to stay safe warrants prompt escalation through local pathways.

Conclusion

The story most patients carry, and that we as clinicians have often supplied, is that depression is a chemical imbalance, an inherited condition, or a fixed disease of the brain. None of these hold up when the evidence is examined. There is no consistent chemical deficiency, no depression gene, and no stable lesion that persists between episodes. What the science describes instead is a state: real biological changes that can profoundly affect

mood, thinking and function in the individual, yet show up only as small, non-specific and context-dependent differences when measured across groups, and that are largely reversible, arising through many converging pathways and held in place by self-reinforcing loops of sleep, stress, withdrawal and thought.

Depression remains serious, sometimes dangerous, and treatment remains essential. But understanding it as a process rather than a defect fits the evidence better, makes formulation central, and shapes the words we use. That last point is important. The explanations we give measurably affect how hopeful patients feel and how much agency they keep, and even how much empathy we extend to them. An account built around a changeable state does more good than one built around permanent damage. Being accurate about depression and being helpful to people experiencing it turn out to be the same task.

References

References are numbered in the order in which they first appear in the text.

1. Deacon BJ. (2013). The biomedical model of mental disorder: a critical analysis of its validity, utility, and effects on psychotherapy research. *Behaviour Research and Therapy*, 51, 846–854.
2. Moncrieff J, Cooper RE, Stockmann T, et al. (2022). The serotonin theory of depression: a systematic umbrella review of the evidence. *Molecular Psychiatry*, 28(8), 3243–3256.
3. Jauhar S, Arnone D, Baldwin DS, et al. (2023). A leaky umbrella has little value: evidence clearly indicates the serotonin system is implicated in depression. *Molecular Psychiatry*, 28, 3149–3152.
4. Sullivan PF, Neale MC, Kendler KS. (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry*, 157, 1552–1562.
5. Howard DM, Adams MJ, Clarke TK, et al. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, 22, 343–352.
6. Border R, Johnson EC, Evans LM, et al. (2019). No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. *American Journal of Psychiatry*, 176, 376–387.
7. Castrén E, Hen R. (2013). Neuronal plasticity and antidepressant actions. *Trends in Neurosciences*, 36(5), 259–267.
8. Schmaal L, Hibar DP, Sämann PG, et al. (2017). Cortical abnormalities in adults and adolescents with major depression based on brain scans from the ENIGMA consortium. *Molecular Psychiatry*, 22, 900–909.
9. American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Association.

10. Fried EI, Nesse RM. (2015). Depression is not a consistent syndrome: an investigation of unique symptom patterns in the STAR*D study.* Journal of Affective Disorders*, 172, 96–102.*
11. Goldberg D. (2011). The heterogeneity of “major depression”. *World Psychiatry*, 10, 226–228.
12. Kendler KS. (2016). The nature of psychiatric disorders. *World Psychiatry*, 15, 5–12.
13. Engel GL. (1977). The need for a new medical model: a challenge for biomedicine. *Science*, 196, 129–136.
14. Kendler KS. (2012). Levels of explanation in psychiatric and substance use disorders: implications for the development of an etiologically based nosology. *Molecular Psychiatry*, 17(1), 11–21.
15. Gilbert P, Allan S. (1998). The role of defeat and entrapment (arrested flight) in depression: an exploration of an evolutionary view. *Psychological Medicine*, 28(3), 585–598.
16. Taylor PJ, Gooding P, Wood AM, Tarrier N. (2011). The role of defeat and entrapment in depression, anxiety, and suicide. *Psychological Bulletin*, 137(3), 391–420.
17. Borsboom D, Cramer AOJ. (2013). Network analysis: an integrative approach to the structure of psychopathology. *Annual Review of Clinical Psychology*, 9, 91–121.
18. Dimidjian S, Barrera M, Martell C, et al. (2011). The origins and current status of behavioral activation treatments for depression. *Annual Review of Clinical Psychology*, 7, 1–38.
19. Eldar E, Rutledge RB, Dolan RJ, Niv Y. (2016). Mood as representation of momentum. *Trends in Cognitive Sciences*, 20(1), 15–24.
20. McEwen BS. (1998). Stress, adaptation, and disease: allostasis and allostatic load. *Annals of the New York Academy of Sciences*, 840, 33–44.
21. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. (2015). Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA Psychiatry*, 72, 603–611.
22. Pizzagalli DA. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, 10, 393–423.
23. Mayberg HS, Lozano AM, Voon V, et al. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron*, 45(5), 651–660.
24. McEwen BS. (2007). Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiological Reviews*, 87, 873–904.
25. Thayer JF, Lane RD. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of Affective Disorders*, 61(3), 201–216.
26. Dowlati Y, Herrmann N, Swardfager W, et al. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, 67, 446–457.

27. Miller AH, Raison CL. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, 16, 22–34.
28. Slavich GM, Irwin MR. (2014). From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychological Bulletin*, 140, 774–815.
29. Baglioni C, Battagliese G, Feige B, et al. (2011). Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders*, 135, 10–19.
30. Walker MP. (2017). *Why We Sleep: The New Science of Sleep and Dreams*. Scribner.
31. Felitti VJ, Anda RF, Nordenberg D, et al. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*, 14, 245–258.
32. Kessler RC. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, 48, 191–214.
33. Marmot M. (2005). Social determinants of health inequalities. *The Lancet*, 365, 1099–1104.
34. Hawkley LC, Cacioppo JT. (2010). Loneliness matters: a theoretical and empirical review of consequences and mechanisms. *Annals of Behavioral Medicine*, 40(2), 218–227.
35. Lebowitz MS, Ahn WK, Nolen-Hoeksema S. (2013). Fixable or fate? Perceptions of the biology of depression. *Journal of Consulting and Clinical Psychology*, 81(3), 518–527.
36. Lebowitz MS, Ahn WK. (2014). Effects of biological explanations for mental disorders on clinicians' empathy. *Proceedings of the National Academy of Sciences*, 111(50), 17786–17790.
37. Lebowitz MS, Ahn WK. (2015). Emphasizing the malleability of depression's biological basis: durable effects on perceived agency and prognostic pessimism. *Behaviour Research and Therapy*, 71, 125–130.
38. Cuijpers P, Sijbrandij M, Koole SL, et al. (2013). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. *World Psychiatry*, 12, 137–148.
39. Cipriani A, Furukawa TA, Salanti G, et al. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *The Lancet*, 391, 1357–1366.
40. O'Connor RC, Kirtley OJ. (2018). The integrated motivational–volitional model of suicidal behaviour. *Philosophical Transactions of the Royal Society B*, 373, 20170268.