

37 — When Treatment-Resistant Depression Is Not Simply Depression

Treatment Resistance Reconsidered · Conceptual research article · No original clinical data presented

Abstract

Persistent depressive symptoms after apparently adequate treatment invite causal reassessment, but 'treatment resistance' is not itself an etiology. This paper proposes that some nonresponse reflects a mismatch between the intervention and the process maintaining the patient's disability—sleep disruption, pain, medical illness, drug exposure or a distinct psychiatric course. A more mechanistic classification might improve recovery without denying the value of established psychiatric care.

Treatment failure can have several non-equivalent meanings

A person who cannot tolerate an adequate medication dose has a different problem from someone who completes a sound trial with persistent symptoms. The same symptom score can conceal severe insomnia, cognitive slowing, grief, medication adverse effects or ongoing psychosocial stress. These differences matter because they alter what should be investigated and what an improvement would signify. A biologically informed review would examine the quality of prior treatment, diagnostic accuracy, comorbidity and actual functional outcomes before hypothesizing hidden toxins.

The oxalate hypothesis could become relevant if a patient has independently established metabolic abnormalities, but it cannot be inferred merely from antidepressant nonresponse. A persuasive study would prespecify an oxalate-positive subgroup and ask whether targeted management of its confirmed medical disorder changes independently rated outcomes compared with appropriate controls. Such evidence would add a causal tool rather than displace psychiatric treatments through assertion.

Resistance is a description, not a cause

A depression score that remains high after treatment establishes persistent symptoms; it does not specify why the treatment failed. Dose, duration, adherence, tolerability, drug interactions and access to appropriate psychotherapy may all matter. A trial interrupted by adverse effects is not equivalent to a fully adequate course that produces no improvement. Comorbid pain, insomnia, substance use or unresolved social stress may dominate clinical outcomes even if some depressive features respond.

Medical causes and modifying illness

Hypothyroidism, severe anemia, B12 deficiency, certain neurological disorders, inflammatory disease or medication effects may contribute to depression-like symptoms. True medical conditions should be investigated when history and examination support them, not assumed in every individual with persistent depression. Rare disorders such as Wilson disease, porphyria or autoimmune encephalitis become relevant through characteristic multisystem signs; broad testing without clinical clues can create incidental abnormalities and false confidence.

Psychological and social dimensions remain biological realities

Persistent trauma exposure, isolation, financial stress and sleep loss influence the patient's capacity to recover. Recognizing these factors does not reduce symptoms to weakness or imply that biochemical therapy is unnecessary. The point is that medication acts within an organism and a life, not in isolation. A patient receiving an appropriate drug while facing severe ongoing insomnia may remain unwell even if the drug's receptor effects are as expected.

A state-based interpretation with limits

The Institute's coherence model proposes examining energetic availability, regulatory flexibility and temporal organization as potential treatment moderators. That model has not been validated as a formal psychiatric stratification tool. It may nonetheless help organize questions about sleep, physiological illness and intervention burden. The alternative hypothesis is simply that the drug is not effective for that patient's disorder; any state-based theory must be able to admit this possibility.

Treatment resistance can be a property of the diagnosis rather than the person

A patient may be described as having treatment-resistant depression after insufficient response to appropriately selected treatments, yet the label itself does not explain why treatments failed. Some patients have bipolar depression misidentified as unipolar illness. Others have a prominent anxiety disorder, substance-related effects, chronic pain, sleep apnea, thyroid disease, neurological illness, medication interactions or severe psychosocial stress that changes response. Still others have genuinely difficult depressive illness despite accurate assessment. The purpose of examining the differential is not to deny psychiatric diagnoses but to recognize heterogeneity before attributing failure to an obscure biological cause.

The reliability of a treatment trial depends on dose, duration, adherence, tolerability and whether meaningful functional endpoints were monitored. A medication may appear ineffective because it was not taken consistently, because side effects dominated, or because the chosen outcome did not reflect the patient's central complaint. Conversely, repeated ineffective trials do not prove that all conventional mechanisms have been exhausted. Psychiatric diagnosis and treatment response involve probability and changing clinical information; they are not settled by a single blood panel or a broad "root cause" label.

Medical comorbidity can conceal distinct trajectories

Suppose a patient with long-standing fatigue, cognitive slowing and depressed mood also has a nutritional deficiency or clinically significant thyroid disorder. Correcting the medical problem may improve some symptoms, but the patient may still have a separate mood disorder. The two conditions can overlap without one wholly replacing the other. Sleep disorders are especially important because sleep impairment can sustain mood and cognitive symptoms while undermining the response to psychiatric treatment. Effective integrated care asks which symptoms belong to which mechanism and measures outcomes over time.

The proposed oxalate-psychiatry relationship is one candidate for future investigation in this context, particularly among patients with objective hyperoxaluria, malabsorption or oxalate-related kidney disease. Yet these patients may also have other nutritional and systemic problems. It would be premature to relabel treatment-resistant depression as hidden oxalate toxicity. The more credible research question is whether a characterized metabolic subgroup shows altered psychiatric outcomes after established causes and confounders are addressed.

How to make the assessment more rigorous

A structured review can examine the original diagnostic formulation, prior treatment adequacy, medications, sleep, substance use, relevant medical conditions and patient-defined functional goals. Tests should be guided by clinical suspicion rather than ordered indiscriminately. The quality of this review can be assessed: did the revised formulation lead to a different prediction, intervention or outcome? If not, the exercise may have added complexity without useful knowledge. A true biological differential must produce clinically discriminating information.

Longitudinal symptom and function tracking can be helpful, but time-series patterns alone are not proof of a causal pathway. Changes in diet, life circumstances and therapy often occur together. To evaluate an unconventional contributor such as oxalate, researchers should first document abnormal oxalate physiology and then determine whether it adds predictive value over standard clinical variables. The scientific aim is not to discredit psychiatry; it is to make treatment response less mysterious by identifying mechanisms that can actually be tested.

The paradox of adding more treatment to an uncertain formulation

After several medication trials, a clinician may face a choice between escalating treatment and revisiting the diagnosis. Both can be reasonable depending on the circumstances; what matters is whether the previous treatments were adequate and whether the patient's presentation contains evidence of a missed biological condition. New-onset cognitive decline, prominent sleep disturbance, unexplained neurological findings or a characteristic endocrine symptom pattern may justify a different workup. Yet repetitive testing without clinical indicators can create false leads and distract from established treatment options. The existence of an unexplained symptom does not justify assigning it to an unvalidated metabolic mechanism.

A study of residual symptom clusters

Research could distinguish patients whose primary remaining problem is low mood from those with disabling fatigue, cognitive deficits or sleep instability after partial treatment response. Medical comorbidities might be distributed differently across these groups, making a generic treatment-resistant label less useful. A documented oxalate disorder could be recorded as an exploratory variable, but an exposure hypothesis should be evaluated against established contributors such as sleep apnea, medications and nutritional deficiency. A positive association could motivate targeted investigation; a null finding would prevent costly misdirection.

Function is the indispensable outcome

Even when laboratory correction and mood improvement occur, the person may remain unable to perform normal activities. Rehabilitation, environmental change and other support can matter alongside biological treatment. Thus a mechanistic success should not be reported as complete reversal unless sustained function improves. The Institute's most promising contribution may be identifying interacting causes of incomplete recovery rather than promoting one new universal explanation for difficult psychiatric cases.

The revised formulation should also be evaluated prospectively. If a clinician identifies a previously unrecognized sleep disorder, the next question is whether its appropriate treatment improves the symptom domain it plausibly affects. If persistent depression remains, the original psychiatric diagnosis may still be valid and require ongoing treatment. A biologically informed approach can add an important causal contributor without turning diagnosis into an either-or contest between mental and physical illness. This is the standard that experimental oxalate hypotheses should eventually meet: additional explanatory power and improved

patient outcomes, not merely a new label for symptoms.

Conclusion

The intellectual advance is to treat treatment resistance as a question about mechanisms and adequacy, not a final diagnosis. The strongest controversial claims must change prediction and decision-making in a defined group.

Selected readings

- Raison et al., Inflammation and treatment-resistant depression: <https://doi.org/10.1001/2013.jamapsychiatry.4>
- CPIC antidepressant pharmacogenetics guideline: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10564324/>
- Heinrich and Grahm, Thyroid disease presenting as psychiatric illness: <https://pmc.ncbi.nlm.nih.gov/articles/PMC419396/>