

When Treatment-Resistant Depression Is Not Simply Depression

ABSURD HEALTH INSTITUTE · 2026-10-16 · Clinical differential and conceptual analysis

Abstract

Treatment-resistant depression is often operationally defined by insufficient response to multiple adequate antidepressant trials. That definition is useful but heterogeneous. Inadequate exposure, unrecognized bipolar disorder, substance use, sleep disorders, medical illness, psychosocial adversity and genuine drug nonresponse can produce the same label. The distinction matters because escalating a treatment that is mismatched to the underlying problem may add burden without improving function.

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.

Conclusion

Treatment resistance should trigger disciplined reassessment, not automatic distrust of psychiatric diagnosis or medication. An integrated differential protects against both missed medical illness and endless searches for a hidden toxin when a primary psychiatric disorder is the correct explanation.

Selected readings

- Raison et al., Inflammation and treatment-resistant depression
- CPIC antidepressant pharmacogenetics guideline
- Heinrich and Grahm, Thyroid disease presenting as psychiatric illness