

40 — Could Biological State Determine Treatment Response?

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

Abstract

Psychiatric treatment may work differently depending on the patient's current biological state, even when diagnoses are the same. This paper argues that sleep, inflammation, organ function, medication exposure and circadian timing can modify the impact of a given intervention. The strong version of the claim is predictive: a measurable state should identify which treatment will work better for whom and when.

Moderator is a stronger claim than vague context

Saying that patients differ biologically is trivial. The meaningful experiment tests whether a particular baseline variable interacts with a treatment effect rather than merely predicting poor outcomes in everyone. For example, severe sleep disruption may reduce the ability to participate in psychotherapy, but the study must distinguish a general severity marker from a true modifier of comparative treatment benefit. That requires randomized treatment comparisons, repeated physiology measures and predefined interaction tests.

Oxalate handling can be included only when there is a measured reason to suspect it. If renal or inflammatory oxalate disease meaningfully changes drug clearance, fatigue or treatment capacity, the relevant pathway can be modeled. The claim does not require delaying urgent evidence-based treatment until a theoretical state score is optimized. A state-aware system should improve timing and safety, not invent prerequisites that prevent care.

The intervention enters a context

Drug distribution, receptor adaptation, learning, behavioral practice and stress responses occur within a patient whose physiology changes across time. Severe insomnia may worsen attention and emotional regulation, undermining psychotherapy participation. Inflammatory disease can increase fatigue and pain. Sedating medications may produce different burdens depending on occupational demands or respiratory illness. These effects can influence perceived improvement without meaning that the underlying treatment mechanism is wrong.

Why temporal sequencing sometimes matters

An acutely suicidal or psychotic patient may need rapid evidence-based treatment before attempts at broad lifestyle stabilization. Another patient with nonurgent chronic symptoms may benefit from addressing sleep apnea, substance use or endocrine dysfunction while continuing psychiatric care. State-sensitive treatment is therefore about determining urgency, contraindications and capacity, not insisting that every patient complete a nutritional program before receiving medication or psychotherapy.

Falsifiable possibilities

The model could predict that particular baseline measures—sleep variability, specific inflammatory profiles, medication exposure or functional reserve—moderate response to a defined therapy. This is a different claim from saying such variables cause the psychiatric syndrome. A valid state model would outperform simpler explanations, show reproducibility and improve actual decisions. If it does not, it should remain a descriptive clinical heuristic rather than a diagnostic scoring system.

The risk of ideological overreach

Systems language can become as reductionist as receptor language when used carelessly. Assigning every failed treatment to a hidden global state simply protects a favored theory from contradiction. A mature framework acknowledges that certain targeted drugs work exceptionally well, some patients require long-term maintenance and some therapies fail despite apparently favorable systemic conditions.

State and trait are not interchangeable

Genetic predisposition and relatively stable individual characteristics influence psychiatric vulnerability, but momentary biological state also matters. Sleep, immune activity, endocrine transitions, nutritional status, stress and medication exposure change over time. A treatment delivered during acute insomnia or systemic illness may have a different apparent effect from the same treatment after stabilization. This creates the hypothesis that some variability in treatment response reflects the interaction between a therapy and the patient's current physiological state rather than only the correctness of the psychiatric diagnosis.

This idea is attractive because it is broadly compatible with adaptive physiology. However, it becomes scientifically empty if “state” means any unmeasured factor invoked after an intervention fails. A useful model must specify which variables are important, how they are measured and which direction of change is expected. For example, the prediction that documented sleep restoration alters a particular cognitive outcome is testable; the statement that “terrain optimization improves everything” is not. A model may be multi-dimensional without being vague.

Why timing and sequencing could matter

Suppose a patient has depression and severe untreated sleep apnea. Improving breathing and sleep may change daytime energy and cognitive function, potentially allowing more accurate assessment of residual mood symptoms. Conversely, an acute infection could reduce tolerability of a medication through changes in metabolism or activity. These are examples of the general principle, not evidence that every psychiatric treatment should be postponed until physiology is “perfect.” For high-risk psychiatric conditions, timely effective care is essential, and medical optimization should proceed alongside treatment rather than serving as a barrier to it.

The oxalate hypothesis offers a potential additional state variable in selected people with confirmed hyperoxaluria or systemic oxalate disease. A research program could test whether oxalate burden predicts treatment response beyond renal function, sleep, nutrition and inflammatory illness. A finding that high urinary oxalate is associated with poor response would remain observational; a more compelling result would identify a plausible intermediary and reproduce the relationship in independent cohorts. Without such evidence, oxalate status should not be promoted as a validated tool for choosing psychiatric treatments.

The difficulty of measuring a whole organism

Wearable devices and repeated symptom reports can capture changes in sleep, heart rate, activity and subjective experience. These data may identify meaningful fluctuations, but they can also create patterns through sampling noise, device error and ordinary daily variation. A physiological network model must respect those limits. The strongest approach combines objective measures with clear clinical outcomes and prespecified hypotheses rather than treating every correlation as meaningful.

A state-dependent treatment model may ultimately help explain why some patients improve only after an apparently unrelated medical condition is addressed. It may also show that many proposed terrain variables do not add predictive power beyond existing clinical information. Either outcome is valuable. The main contribution is to make biological timing and context explicit while retaining the primacy of patient safety, appropriate diagnosis and sustained function.

The false promise of a universal readiness score

An integrated data platform might combine sleep, heart rate variability, activity and self-reported symptoms to infer how ready a patient is for a particular intervention. Such a tool could be helpful for longitudinal description but would not automatically be a validated predictor of psychiatric treatment response. Wearable measurements vary in reliability across situations, and physiological correlations can arise from shared causes or simple daily routines. If an algorithm recommends changing care, its predictions should be evaluated against meaningful outcomes in independent samples before clinical deployment.

A clear experiment in state-dependent response

Imagine a study that enrolls patients with a defined psychiatric diagnosis and measures severe sleep disruption before treatment. The hypothesis is that restoring sleep in parallel with standard care changes the treatment trajectory compared with standard care alone. The design could test whether sleep improvement mediates a particular functional outcome, while accounting for the fact that treatments themselves may improve sleep. A parallel experimental hypothesis might concern objectively measured inflammatory disease. Each must identify its target variable and primary outcome in advance. Otherwise a general claim that “terrain determines response” can accommodate any result and therefore predicts little.

Where oxalate might enter the future model

A selected patient subgroup with proven hyperoxaluria could be studied for an additional effect of biochemical burden, particularly if concurrent renal or gastrointestinal illness is present. The key question would be whether oxalate measurements add predictive value after sleep, medication, mood severity and medical comorbidity are accounted for. If not, oxalate should not become a treatment-selection biomarker merely because it fits a preferred narrative. If yes, the finding would justify mechanistic and intervention studies. This is the difference between an adaptive hypothesis and a clinical decision rule.

The proposed data architecture should also include missingness and measurement error. People may stop logging symptoms during their worst periods, creating a falsely optimistic trend. Wearables may misclassify sleep or movement under unusual conditions. A model trained on incomplete data can learn the pattern of who reports rather than the pattern of who improves. An honest state-dependent treatment study would define how missing observations are handled, assess clinical relevance and validate predictions beyond the population from which they were derived. Technology can improve systems medicine only when its measurements remain tethered to reality.

Conclusion

The controversial prospect is a psychiatry organized partly around dynamic physiological states rather than stable diagnostic labels. It will earn credibility only if those state measurements improve actual treatment selection.

Selected readings

- Bousman et al., CPIC antidepressant pharmacogenetics: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10564324/>
- Raison et al., Inflammatory biomarkers and differential response: <https://doi.org/10.1001/2013.jamapsychiatry.4>