

Bile-Acid Signaling and Affective Symptoms: Toward a Phenotype-Stratified Model

Abstract

Bile acids are not merely intestinal detergents; they are endogenous metabolites that act through multiple nuclear and membrane receptors, interact with the gut microbiota, and participate in metabolic and neuroimmune signaling. Human observational studies associate altered bile-acid profiles with depressive symptoms, while animal studies implicate receptor-dependent mechanisms. Yet the direction of effect differs by bile-acid species, tissue, receptor and concentration. This paper proposes a phenotype-stratified research model that distinguishes impaired secretion, altered microbial biotransformation, metabolic liver disease and cholestatic accumulation from one another. It recommends separating total bile-acid concentration from individual species and testing longitudinal relationships with validated affective outcomes, liver indices, gastrointestinal symptoms, and medication exposures. The model rejects the inference that historical “black bile” corresponds to a defined pathological substance responsible for depression, or that stimulation of biliary flow is a validated antidepressant therapy. Rather, it specifies which mechanistic pathways could be evaluated, how causal inference might be improved, and how apparently contradictory receptor findings may be reconciled. The objective is to transform an intuitively appealing hepatobiliary hypothesis into a discriminating, falsifiable neurogastroenterological research program.

Background and the legitimate physiological question

Contemporary bile-acid biology extends far beyond fat emulsification. Cholesterol-derived primary bile acids are synthesized in the liver, conjugated, secreted into the intestine and modified by gut microorganisms; most are recirculated through the enterohepatic system. Their molecular identity and concentration influence signaling through the nuclear farnesoid X receptor (FXR), the G-protein-coupled bile acid receptor TGR5/GPBAR1, and additional pathways. These receptors participate in metabolic, inflammatory and endocrine regulation, providing several plausible links between intestinal physiology and the central nervous system [1–3].

The source manuscripts from which this paper originates argue that altered bile physiology may contribute to emotional symptoms. That observation identifies a worthwhile research question but is too broad as a causal explanation. “Poor bile flow,” “bile deficiency,” cholestasis, disrupted microbial metabolism and abnormal circulating bile-acid composition are not synonymous exposures. They can lead to different—and sometimes opposing—physiological states. Precision requires that each be defined and measured separately.

A 2025 mini-review in the *American Journal of Pathology* and a subsequent mechanistic review in the *International Journal of Molecular Sciences* describe associations between bile acids, affective disorders and neuroimmune functions [1,2]. These publications mean the existence of a bile-brain connection is no longer an untouched claim of novelty. A publishable contribution must instead sharpen phenotypes, distinguish clinical and preclinical findings, and advance a falsifiable strategy unavailable from unqualified assertions about “stagnation.”

Mechanistic pathways and contradictory signals

First, the intestinal route is indirect. The microbiota alters bile-acid composition, while bile acids regulate microbial selection, intestinal barrier properties and gut hormone secretion. Signals arising in the gut may then affect systemic immunity, vagal pathways and metabolic status. It would nevertheless be incorrect to assume that every change in the fecal or circulating bile-acid pool reaches the brain as an active ligand. Systemic and central concentrations, receptor access and blood-brain barrier physiology are critical uncertainties [1,3].

Second, receptor effects are context-sensitive. Experimental manipulation of FXR and TGR5 has produced changes in depressive-like behaviors in animals, but biological responses vary with receptor distribution and experimental model. Reports that FXR deletion is protective in some stress paradigms coexist with data suggesting that activation of a relevant FXR-associated pathway by chenodeoxycholic acid may be beneficial in another model [2,4]. One explanatory possibility is that tissue-specific effects and ligand concentration matter more than binary “more bile” versus “less bile.” This must be tested rather than presumed.

Third, bile-acid species differ in hydrophobicity, receptor affinity and inflammatory effects. A concentration that produces protective signaling under one circumstance may contribute to epithelial or endothelial injury in another. Reviews document that cholestatic or excessively elevated circulating bile acids can have adverse effects, while selected derivatives exhibit neuroprotective actions in preclinical studies [2,3]. Therefore, total serum bile acids alone should not be treated as a linear index of mental health.

Fourth, species differences complicate translation. Humans and rodents possess substantially different primary bile-acid pools and conjugation patterns, with corresponding receptor pharmacology differences [3]. Rodent behavioral results generate hypotheses but cannot establish efficacy in major depressive disorder.

Human evidence: what has and has not been demonstrated

One translational study reported lower plasma chenodeoxycholic acid (CDCA) in a group of 142 patients with major depressive disorder than in 148 healthy participants, and found normalization among clinical remitters but not nonremitters after antidepressant treatment. Parallel mouse work examined FXR and inflammasome-related signaling [4]. Such results establish an interesting association and mechanistic direction of inquiry, not proof that a low CDCA concentration caused depression or that supplementing bile acids would treat it.

Bile-acid profiles may be influenced by medications, liver disease, dietary intake, circadian timing, stool transit, microbiome composition, body mass and the depression itself. Reverse causation is particularly plausible: depression can change appetite, gastrointestinal motility, sleep and adherence to medication, which may alter metabolomic measurements. Single-time-point case-control studies cannot confidently establish temporal order.

Moreover, psychiatric disorders cannot be reduced to a single biochemical deficiency. Even if a biologically defined subgroup exists, it must be identified prospectively and its response measured against appropriate comparison groups. Clinical care already requires attention to mood symptoms regardless of whether a hepatobiliary biomarker has been identified.

Proposed phenotype-stratified causal model

We propose four nonexclusive biliary phenotypes as hypotheses for investigation rather than existing validated clinical categories. Phenotype A is cholestatic accumulation, defined by concordant clinical and biochemical measures of impaired bile excretion. Phenotype B is altered microbial transformation with relatively preserved hepatobiliary indices but an atypical secondary-to-primary bile-acid spectrum. Phenotype C is a metabolic-inflammatory phenotype with altered bile-acid signaling in the context of insulin resistance or liver metabolic disease. Phenotype D is a symptomatic digestive or malabsorption phenotype in which bile-acid handling and nutrient absorption require distinct investigation.

An essential prediction is that these phenotypes will not show the same directions of association with depression scores. For example, an adverse correlation for a hydrophobic secondary bile acid in cholestasis would not refute potential benefits from a separate bile-acid derivative in another phenotype. A study treating all cases as a single “bile blockage” class would obscure this heterogeneity.

The model should include a directed causal graph with potential confounders—dietary change, medication, hepatic injury, microbiome differences and severity of illness—specified before data collection. Prespecified outcomes would include validated depression scale scores, longitudinal relapse or remission, fatigue and sleep outcomes, objective bile-acid speciation, and liver-related laboratory indices. Imaging or physiological testing should be performed only when clinically indicated, not as indiscriminate screening.

Studies capable of disproving the model

A prospective cohort could collect standardized fasting-state plasma bile-acid profiles and repeated affective symptom assessments over six to twelve months, controlling for medication changes, liver disease, body mass, diet and circadian variables. If bile-acid species fail to predict subsequent symptom changes beyond covariates, the model would lose causal plausibility.

A second design could compare bile-acid speciation and stool microbial enzyme capacities in carefully phenotyped patients with and without co-occurring gastrointestinal disease. The prediction would be that particular species or metabolite ratios—not total bile acids—display reproducible interactions with symptom clusters. Negative replication would meaningfully weaken the claim.

Finally, a treatment hypothesis should only follow strong evidence linking a modifiable pathway to a clinically important outcome. Bile-acid sequestration, receptor agonism and other interventions carry organ-specific risks and should not be repurposed as mood treatment outside appropriate research or approved indications. Mechanistic plausibility alone is not sufficient for random clinical use.

Limitations and conclusion

This is a conceptual proposal built on a targeted, nonsystematic reading of relevant literature, not a quantitative synthesis. It does not establish that bile stagnation causes depression, that fasting normalizes a uniquely beneficial bile-acid state, or that altering bile flow can replace effective psychiatric therapies. Historical humoral theory can motivate a historical study but is not a molecular diagnosis.

The central advance is specificity: the hypothesis concerns measured bile-acid species, defined host states, receptor-dependent signaling, temporal relations and clinically meaningful affective outcomes. Those variables can be studied, challenged and potentially disproved. Replacing metaphor with measurable biological distinctions is a prerequisite to discovering whether a tractable biliary depression subtype exists.

Selected references

- [1] Evidence and Mechanism of Bile Acid-Mediated Gut-Brain Axis in Anxiety and Depression. *Am J Pathol.* 2025;195:163–173. doi:10.1016/j.ajpath.2024.10.019.
- [2] Research Progress on the Mechanism of Bile Acids and Their Receptors in Depression. *Int J Mol Sci.* 2025;26:4023. doi:10.3390/ijms26094023.
- [3] Gut-Brain Axis and Bile Acid Signaling: Linking Microbial Metabolism to Brain Function and Metabolic Regulation. *Int J Mol Sci.* 2025;26:12167. <https://www.mdpi.com/1422-0067/26/24/12167>.
- [4] The FXR mediated anti-depression effect of CDCA underpinned its therapeutic potentiation for MDD. 2023. PubMed PMID:36584576.
- [5] Gut microbial metabolites in depression: understanding the biochemical mechanisms. 2019. PMCID:PMC6780009.
- [6] Beyond metabolic messengers: Bile acids and TGR5 as pharmacotherapeutic intervention for psychiatric disorders. *Pharmacol Res.* 2025;211:107564. doi:10.1016/j.phrs.2024.107564.