

38 — Psychiatric Pharmacogenomics: Metabolism, Exposure and Variable Response

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

Abstract

Psychiatric drug response depends partly on exposure: a prescribed dose does not guarantee the same concentration or effect in every person. Genetic differences in drug-metabolizing enzymes, interactions, organ function and adherence can influence effectiveness and adverse effects. This is a concrete example of a biological explanation for apparent psychiatric treatment failure that can be investigated quantitatively.

Dose is an instruction; exposure is what reaches the body

Two patients receiving the same antidepressant may achieve different blood concentrations because of metabolic variation or interacting medications. Yet pharmacogenetic findings do not predict every dimension of response, and many variants have limited or drug-specific clinical usefulness. A genotype without a relevant substrate or clinical context should not be treated as a universal map of the mind. The stronger study would combine genotype, medication record, measured or inferred exposure, adverse-effect timing and clinical outcomes.

This creates a useful boundary for the oxalate hypothesis. If drug nonresponse is explained by abnormal drug exposure, blaming oxalate would not improve the account. If independently documented oxalate-related illness affects kidney function or medication handling, that would suggest a measurable interaction, not a direct chemical cause of every psychiatric symptom. Mechanistic psychiatry should embrace these distinctions instead of forcing all response variability into one favored theory.

A concentration is not an effect

Drug response depends on dose, absorption, liver metabolism, kidney function, interactions, receptor sensitivity, illness type and adherence. A poor metabolizer may experience higher exposure to a medication cleared through a relevant pathway; a rapid metabolizer may experience lower exposure. Even then, the relationship between plasma concentration and clinical improvement is not uniform. Psychiatric symptoms arise from complex networks, and drug effects cannot be predicted from one enzyme genotype alone.

What the guideline evidence supports

The Clinical Pharmacogenetics Implementation Consortium has published recommendations addressing CYP2D6, CYP2C19 and CYP2B6 relationships with selected serotonin-reuptake inhibitors. Its 2023 guideline also examined SLC6A4 and HTR2A but did not find sufficient evidence to support their routine clinical use for antidepressant prescribing. This is an important contrast: some genomic information helps with exposure and tolerability while other appealing variants do not add useful clinical prediction.

Confounding from clinical state

Drug interactions can inhibit or induce relevant pathways, creating a functional phenotype different from genotype alone. Liver disease, age, inflammatory illness and concurrent drugs can affect metabolism. An apparent pharmacogenetic mismatch may actually reflect an interacting prescription or an unsuitable diagnosis. Conversely, a medication that is metabolized predictably may still fail because the underlying disorder does not respond to its therapeutic mechanism.

The future of personalized prescribing

The most rigorous model integrates validated genotype–drug information with symptoms, side effects, prior response, relevant laboratory information and patient goals. It does not sell a genetic result as a complete explanation of someone's depression. The clinical value of a test lies in whether it changes a prescribing decision and improves an outcome, not how many genes appear on a report.

Prescribed dose is not identical to biological exposure

Two patients taking the same nominal psychiatric medication dose may experience different systemic exposure because of differences in absorption, metabolism, interactions and elimination. Genetic variation in enzymes such as CYP2D6 and CYP2C19 can influence the handling of selected medications, although the clinical importance depends on the specific drug and genotype. Age, liver disease, smoking, interacting medications and adherence also matter. This provides a useful challenge to the idea that an inadequate response automatically means the psychiatric diagnosis is wrong or the medication target is irrelevant. The patient may not have received the expected effective exposure—or may have experienced excess exposure and adverse effects.

A pharmacogenomic result is a modifier of probability, not a machine that predicts the ideal medication for every person. Many advertised broad combinatorial psychiatric tests have limitations in clinical validation, and evidence of improved outcomes is not uniform across products and settings. Guidelines for individual drug–gene pairs can be informative where a clinically actionable relationship has been established, but a generic “green/yellow/red” panel should not replace medication history, clinical response and shared decision-making. The consequence of a genotype depends on which treatment is being considered.

Metabolic state changes response independently of genotype

An acute inflammatory illness may alter drug metabolism, while gastrointestinal disease can influence absorption. Kidney or liver dysfunction can change elimination of certain agents or metabolites. Sleep, nutritional intake and concurrent medications may affect both efficacy and tolerability. These mechanisms complicate attempts to infer treatment resistance from one failed trial. A person whose medication exposure shifts during severe illness may appear to have a rapidly changing psychiatric disorder when part of the change reflects pharmacokinetics or adverse effects.

The oxalate-associated hypotheses are relevant only indirectly here unless a specific drug–oxalate interaction has been demonstrated. A patient with advanced oxalate-associated renal dysfunction may require careful review of drugs affected by renal clearance, but it would be unsupported to claim that elevated oxalate universally alters psychiatric drug metabolism. If a proposed interaction is important, the researcher should identify the drug, pathway, clinical dose and expected change in exposure. The presence of a broad terrain framework does not exempt a claim from pharmacological specificity.

A research design centered on function

An informative medication-response study could measure genotype when indicated, actual prescribed and taken doses, relevant drug concentrations where validated, medical comorbidity, adverse effects and meaningful outcomes. It should distinguish inadequate exposure from true pharmacodynamic nonresponse. An improvement in symptom score may coexist with disabling adverse effects; a successful treatment outcome requires considering functioning, sleep and patient priorities. Conversely, an unusual genotype without an actual treatment consequence may be interesting but clinically incidental.

The broader lesson is that molecular mechanisms matter most when they change what happens in real patients. Pharmacogenomics supports biological psychiatry because it illustrates a measurable pathway from individual physiology to treatment exposure. It also warns against excessive confidence in biomarkers divorced from context. The best terrain explanation uses molecular information to refine—not replace—clinical interpretation.

A genotype cannot diagnose a treatment response by itself

Suppose genetic testing suggests that a patient metabolizes a particular medication unusually quickly. This may help explain a low exposure at a standard dose, but the interpretation depends on adherence, competing drugs, clinical dose and whether the enzyme is actually important for that compound. Another patient may have a genotype associated with slower metabolism but take a dose that is appropriate and well tolerated. The meaningful question is whether genetic information changes the prediction of exposure or outcome in a validated way. Without that link, the result is a biological curiosity rather than a treatment plan.

The confounding role of systemic illness

Inflammation, liver impairment and renal dysfunction can influence medication effects through mechanisms not captured by the genetic test. A patient with serious oxalate-associated kidney disease might have altered clearance of certain agents, but the relevance is medication-specific and depends on actual renal function. It would be inaccurate to describe elevated urinary oxalate as a universal determinant of psychiatric drug effectiveness. The correct terrain model identifies the drug, metabolic or renal pathway, relevant tissue exposure and adverse-effect profile.

Testing causation with exposure measurements

Where therapeutic drug monitoring is clinically validated, measured concentrations can sometimes help distinguish inadequate exposure from pharmacodynamic nonresponse. Monitoring symptoms and adverse effects remains essential because concentration alone does not equal benefit. In research, genotype, measured exposure, clinical state and function should be linked prospectively, with attention to medication changes over time. A treatment-response theory becomes useful when it predicts a result more accurately than standard assessment and when acting on it improves outcomes in independent patients.

A particularly misleading situation occurs when multiple interacting medicines are changed together. If a patient improves, one cannot tell whether the relevant factor was genotype-guided dosing, removal of a pharmacokinetic interaction or a nonspecific effect of better adherence. Research designs should document the full medication regimen and ideally isolate the decision being tested. The existence of a biological explanation for variability does not mean that every genetic assay delivers useful information. Good pharmacogenomic practice respects both the strength of the drug-specific evidence and the practical consequences for the individual.

The most useful pharmacogenomic result is one that changes a concrete, evidence-based clinical decision. A genotype that predicts exposure to a particular medicine may justify closer monitoring or a different dosing strategy in appropriate circumstances. A broad prediction about mental health based on several unvalidated gene associations is a different proposition. Patients should be told which part of the report is clinically actionable and which part remains exploratory.

Conclusion

Pharmacogenomics is an example of biological precision grounded in exposure and mechanism. Its lesson is that causal explanation improves when the intermediate variable can actually be measured.

Selected readings

- Bousman et al., CPIC Guideline for Serotonin Reuptake Inhibitors (2023): <https://pubmed.ncbi.nlm.nih.gov/37032427/>