

Psychiatric Pharmacogenomics: Metabolism, Exposure and Variable Response

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Abstract

Genetic variation in drug-metabolizing enzymes can change exposure to selected psychiatric medications. CYP2D6, CYP2C19 and CYP2B6 offer clinically actionable examples for certain antidepressants. Yet pharmacogenomics cannot reliably identify the one correct psychiatric drug for every patient, and commercial panels sometimes conflate well-supported pharmacokinetic findings with weaker claims about pharmacodynamic outcome prediction. This paper distinguishes the levels of evidence.

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.

Conclusion

Psychiatric pharmacogenomics is a genuine but bounded form of precision medicine. It illustrates why specific molecular insights and broad systems reasoning should complement rather than displace each other.

Selected readings

- Bousman et al., CPIC Guideline for Serotonin Reuptake Inhibitors (2023)