Pharmacogenetic Testing in Psychiatry

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What is pharmacogenetic testing?

Pharmacogenetic testing looks at genetic variations that can impact an individual's response to psychiatric medications. Some genes influence how quickly the body metabolizes medications (pharmacokinetics), while other genes impact how medications act in the body, including their effects in the brain (pharmacodynamics).

Genetic variations in metabolizer status

- Poor metabolizer - Having inactive copies of certain genes can lead to slower metabolism of medications, higher blood levels, and increased side effects. For example, 7-10% of people have inactive CYP2D6 genes and metabolize CYP2D6 substrates like antidepressants and antipsychotics poorly.
- Extensive metabolizer - Having normal copies of metabolic genes leads to expected rates of medication metabolism and typical blood levels. Most people (90-93%) are extensive metabolizers for enzymes like CYP2D6.
- Ultrarapid metabolizer - Having extra copies of metabolic genes leads to faster than normal metabolism and lower medication blood levels. For CYP2D6, 2-5% of people are ultrarapid metabolizers.

Commercially available tests

Most commercial pharmacogenetic tests bundle together analyses of many genes. The most heavily marketed tests include GeneSight, Genomind, and Genecept. However, these tests combine some clinically useful genetic tests with many others that are not evidence-based. Reliability between different labs is also a concern. Professional guidelines do not recommend using any of these tests at this time.

Individual genetic testing

Ordering specific pharmacokinetic genes like CYP2D6 or CYP2C19 may be warranted in certain situations, like when a patient has unusual medication sensitivity. However, pharmacodynamic gene testing is not currently evidence-based.

Clinical situations when testing may help

- Your patient has unusual sensitivity to medication side effects, which could indicate poor metabolizer status
- Your patient has had multiple ineffective medication trials, in which case testing may identify if drugs are being metabolized too quickly

FDA recommendations

The FDA suggests genetic testing in specific situations with certain psychiatric medications, and these situations are outlined in the following table.

Pharmacogenetic Recommendations From the FDA

	Medication	Gene	Risk	Action
Testing Required	Carbamazepine (and possibly oxcarbazepine)	HLA-B*1502	Stevens-Johnson syndrome (SJS)	In patients of Asian descent, test is required before starting carbamazepine and recommended (but not required) before oxcarbazepine; a positive result in this population means they are 80 times more likely to develop SJS on carbamazepine and 30 times more likely on oxcarbazepine
	Pimozide	2D6	Arrhythmias	Test is required before dosing pimozide above 4 mg/day (or 0.05 mg/kg/day in children) because of risk of arrhythmias; in poor metabolizers, wait 14 days between dose adjustments
Testing Recommended[1]	Thioridazine	2D6	Arrhythmias	Contraindicated in poor metabolizers
	Citalopram	2C19	Arrhythmias	Max dose of 20 mg/day in poor metabolizers
	Deutetrabenazine	2D6	Arrhythmias	Max dose 18 mg BID in poor metabolizers (must be divided BID)
	Valbenazine	2D6	Arrhythmias	Lower the dose by 50% and divide it twice a day in poor metabolizers
Adjust Dose if Testing Results Are Known	Atomoxetine, clozapine, perphenazine, venlafaxine, vortioxetine, and various tricyclics (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	2D6	Various	Lower the dose by 50% in poor metabolizers; for clozapine and tricyclics, adjust based on serum levels; for venlafaxine, keep in mind that the active metabolite (desvenlafaxine) will be low in poor metabolizers and high in rapid metabolizers
	Aripiprazole, brexpiprazole, iloperidone	2D6, 3A4	Various	Lower the dose by 50% in poor metabolizers at either enzyme, or by 75% if both enzymes are poor
	Flibanserin	3A4	Syncope	Lower the dose in poor metabolizers

[1]In these cases, the FDA does not require the test but does require dose adjustment if the test was done and an abnormality found (a slightly inconsistent recommendation). Sources: www.cpicpgx.org/genes-drugs; www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

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