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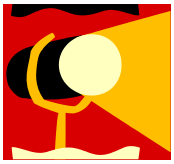
Spotlight on CYP450 Enzymes: Introduction to Common Inhibitors and Inducers Used in Psychiatry



The Cytochrome P450 (CYP450) genes analyzed by the Genecept Assay® and utilized by G-DIG (Genomind Drug Interaction Guide)™ can have significant influence on medication serum levels and treatment effects. These CYP450 phenotypes affect drug efficacy and adverse events; metabolizer status is dependent on genetic variability within these enzymes.

Most psychiatric drugs are metabolized by one of the following CYP450 enzymes: 1A2, 2B6, 2C9, 2C19, 2D6, 3A4/5. Consequently, there are many opportunities for interactions. Complicating the problem is the fact that some drugs act as inhibitors or inducers of these enzymes, interfering with the metabolism of concurrent medications. Various SSRIs are established inhibitors of CYP2D6 and CYP2C19, decreasing the enzyme's ability to metabolize tricyclic antidepressants or some antipsychotics.[1] A study by Bramness et al. showed that drug exposure (area under the plasma concentration-time curve [AUC]) and drug accumulation of the muscle relaxer carisoprodol was dependent on both CYP2C19 genotype and CYP2C19 concurrent inhibitors.[2] Poor Metabolizers (PM) and Intermediate metabolizers (IM) had higher exposure to carisoprodol compared to Normal metabolizers (NM). The AUC was greater in IM's who were taking oral contraceptives, known CYP2C19 inhibitors. The AUC values were 11.3 mg*h/L(NM); 16.3 (IM); 26.0 (IM + Inhibitor); 42.7 (PM). The authors calculated that carisoprodol would accumulate to the greatest extent in the IM + Inhibitor group and PM group.

The FDA defines the strength of inhibitors and inducers based on the amount by which they change the area under the plasma concentration-time curve (AUC) of CYP450 enzyme substrates (see Table 1).[3] The AUC represents the total amount of drug exposure in a defined amount of time. Because inhibitors act on the CYP450 enzyme and not directly on concurrent drugs, inhibitors *increase* the AUC of the concurrent drug; conversely, inducers of a particular CYP450 enzyme result in *decreased* AUC of concurrent drugs metabolized by the same enzyme.

Table 1. FDA Definitions of Strong, Moderate, and Weak Inhibitors/Inducers, adapted from Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

	Percent Change in AUC	
Strength	Inhibitors (Increase)	Inducers (Decrease)
Strong	>5-fold	≥80%
Moderate	≥2 - <5-fold	≥50% to <80%
Weak	≥1.25 to <2-fold	≥20% to <50%

The Genecept Assay provides information regarding a number of common drugs defined by the FDA as strong inhibitors or inducers, many of which are antidepressants. Paroxetine and bupropion are strong inhibitors of CYP2D6. Fluoxetine also strongly inhibits CYP2D6, but only moderately inhibits CYP2C19. Another SSRI, fluvoxamine, is a strong inhibitor of CYP1A2 and CYP2C19. Other antidepressants include Nefazodone, which is a strong inhibitor of CYP3A4/5. Carbamazepine, an anticonvulsant, strongly induces CYP2B6 and CYP3A4/5, while the stimulant-like drug modafinil is a moderate inducer of CYP3A4/5.[1]

Due to frequent psychiatric co-morbidities, it is not uncommon for patients to be prescribed multiple psychoactive medications. G-DIG, the Genomind Drug Interaction Guide, was developed to evaluate the potential interactions of co-administered drugs based on patient metabolizer phenotypes, enhancing the ability to select optimal treatment regimens. This tool is complimentary to all clinicians who use the Genecept Assay and provides a personalized drug-gene-environment interaction profile.

References

1. Tanaka, E. and S. Hisawa, *Clinically significant pharmacokinetic drug interactions with psychoactive drugs: antidepressants and antipsychotics and the cytochrome P450 system*. 1999: Oxford, UK. p. 7-16.
2. Bramness, J.G., et al., *The CYP2C19 genotype and the use of oral contraceptives influence the pharmacokinetics of carisoprodol in healthy human subjects.* Eur J Clin Pharmacol, 2005. **61**(7): p. 499-506.
3. FDA, *U.S. Food and Drug Administration. (2016). Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Retreived from:* *https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm* 2016.