Using pharmacogenetics guidelines when prescribing: What's available

Vicki L. Ellingrod, PharmD, FCCP, and Kristen M. Ward, PharmD

Ms. C, age 45, has a history of generalized anxiety disorder, which has been controlled for the past 6 weeks with extended-release (ER) venlafaxine, 37.5 mg/d. Previous medication trials included fluvoxamine, 300 mg/d, for 2 weeks; paroxetine, 20 mg/d, for 1 week; sertraline, 100 mg/d, for 1 week; and citalopram, 20 mg/d, for 2 weeks. For each trial, Ms. C was unable to tolerate standard doses because of substantial adverse effects; she complained that her anxiety would significantly worsen with each course of treatment. Although the adverse effects would eventually subside with continued treatment, they appeared to be the dose-limiting factor for treatment, even when much lower doses were started.

Ms. C's son recently suggested that she undergo pharmacogenomics testing, and she brings in the results of this testing. The report states that Ms. C has cytochrome P450 (CYP) pharmacogenotypes CYP2D6 *5/*9, CYP2C19 *2/*3, CYP2C9 *2/*2, and CYP1A2 *1A/*1F. Ms. C wants to know if these results explain some of the issues she has had with previous medication trials, and if these results mean that she should be taking a different medication.

Dr. Ellingrod is Associate Dean for Research and John Gideon Searle Professor of Clinical and Translational Pharmacy, College of Pharmacy; and is Professor of Psychiatry and Adjunct Professor of Psychology, Associate Director, Michigan Institute for Clinical and Health Research, and Director of the Education and Mentoring Group, University of Michigan College of Pharmacy and School of Medicine, Ann Arbor, Michigan; and is the Savvy Psychopharmacology Department Editor of the Current Psychiatry Editorial Board. Dr. Ward is Clinical Lecturer, College of Pharmacy, University of Michigan, Ann Arbor, Michigan.

Disclosures

The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

The human genome project was a vast, international effort to sequence the entire human genome[1] and identify individual differences in drug response, which serves as the basis for pharmacogenomics. Since completion of the human genome project in the early 2000s, the field of pharmacogenomics has advanced, and using pharmacogenomic testing to make therapeutic decisions for medication management is becoming commonplace.[2] Although this critical change to how medicine is practiced is exciting, implementation of pharmacogenomics into practice has been varied.[2] Therefore, having an understanding of the resources available to guide pharmacogenomics into practice is critical, because the FDA now lists >160 medications that include specific pharmacogenomics information within their package insert.[3]

continued

Practice Points

- The **Clinical Pharmacogenomics Implementation Consortium (CPIC) was developed to facilitate useful interpretation of pharmacogenomics** data when making clinical decisions.
- The **Pharmacogenomics Knowledge Base (PharmGKB) and the Pharmacogenomics Research Network (PGRN) are other valuable resources** for understanding the impact of available pharmacogenomics information on patient care.
- **Free online educational resources related to the principles of pharmacogenomics**, as well as additional resources necessary for systematic implementation, are available from CPIC, PharmGKB, PGRN, and other sources.

Vicki L. Ellingrod, PharmD, FCCP
Department Editor

Savvy Psychopharmacology is produced in partnership with the College of Psychiatric and Neurologic Pharmacists
cpnp.org
mhc.cpnp.org (journal)

Table 1

CPIC gene/drug combinations with guidelines for psychiatry[a]

Gene	Drug(s)
CYP2D6	Amitriptyline, fluvoxamine, nortriptyline, paroxetine, clomipramine, desipramine, doxepin, imipramine, trimipramine
CYP2C19	Amitriptyline, citalopram, escitalopram, clomipramine, doxepin, imipramine, trimipramine, sertraline
HLA-B	Carbamazepine

[a]As of April 2017

CPIC: Clinical Pharmacogenomics Implementation Consortium; CYP: cytochrome P450; HLA-B: human leukocyte antigen complex B

Source: Reference 5

Clinical Point

Investigators found that 1 out of 4 pharmacogenomic test results had a potential clinically actionable outcome

Table 2

Ms. C's genotypes and phenotypes

Genotype	Phenotype
CYP2D6 *5/*9	CYP2D6 intermediate metabolizer
CYP2C19 *2/*3	CYP2C19 poor metabolizer
CYP2C9 *2/*2	CYP2C9 poor metabolizer
CYP1A2 *1A/*1A	CYP1A2 extensive metabolizer

CYP: cytochrome P450

Source: Reference 6

CPIC provides guidance for implementing pharmacogenomics

In 2000, the National Institutes of Health established the Pharmacogenomics Knowledge Base (PharmGKB) and the Pharmacogenomics Research Network (PGRN). These 2 resources provide information from cutting-edge research on genomic variation and therapeutic and adverse events, as well as practical implementation of this research.[4] As part of their partnership, PharmGKB and PGRN established the Clinical Pharmacogenomics Implementation Consortium (CPIC), which has begun to provide clinical practice guidelines for implementing pharmacogenomic results. Although CPIC does not advocate for pharmacogenomics testing as a standard, it recognizes that this testing is becoming more commonplace, and therefore its guidelines can help clinicians make rational prescribing decisions.[4]

In a recent partnership among several PGRN members, investigators found that 1 out of 4 pharmacogenomic test results had a potential clinically actionable outcome.[2] There are currently >43 gene/drug pairs for which CPIC has provided guidelines; however, >200 other gene/drug pairs are being evaluated.[5]

Table 1[5] lists the current CPIC gene/drug combinations with accompanying published guidelines that are pertinent to psychiatry. For each of these guidelines, experts reviewed the available literature to provide graded therapeutic recommendations: A ("preponderance of evidence is high or moderate in favor of changing prescribing"), B ("preponderance of evidence is weak with little conflicting data"), and C and D ("evidence levels can vary").[4] Looking at the specific genotypes for Ms. C, we can use the information within the CPIC to assign a drug metabolism phenotype for her genotype combinations (***Table 2***).[6]

Consider additional resources

In addition to those from the CPIC, guidelines have been developed by other scientific groups, such as the Dutch

Pharmacogenetics Working Group and the European Pharmacogenomics Implementation Consortium. Although most of these guidelines are concordant with CPIC, differences exist, which makes it important to be aware of all available resources.

As well as working on the CPIC guidelines, PGRN investigators also provide numerous free online educational resources related to the principles behind pharmacogenomics, including additional resources necessary for systematic implementation. Examples include tables that outline all possible diplotypes (genotypes) for genes in the guidelines and how these are related to the metabolic phenotypes.[2,4] Drug metabolizing phenotypes, for example, often are described as poor, intermediate, extensive, and ultra-rapid; in this system, metabolizing ability labeled as poor is less-than-average, and ultra-rapid describes greater-than-average ability. The extensive phenotype is considered average. The data files on the CPIC Web site also can be used as resources to "double check" interpretation results for the diplotype phenotype combinations currently available from various pharmacogenomics companies.[7]

Based on Ms. C's presentation, as well as information from the CPIC guidelines, we expect that she might experience substantial adverse effects from most selective serotonin reuptake inhibitors and tricycle antidepressants because of her intermediate metabolizer status for CYP2D6 and poor metabolizer status for CYP2C19. The CPIC's recommendation for using paroxetine and fluvoxamine in patients with a CYP2D6 intermediate metabolism phenotype is to initiate the recommend starting dose, but acknowledge that reduced metabolic capacity through CYP2D6 may result in higher blood levels and greater probability of adverse drug reactions. For a patient with the CYP2C19 poor metabolizer phenotype, the recommendation is to reduce the starting dose of citalopram or sertraline by 50%, or to prescribe a drug that is not metabolized by CYP2C19.[8] Therefore, this pharmacogenomic information may help us understand why Ms. C is unable to tolerate these medications.

Although the CPIC guidelines do not address venlafaxine, the PharmGKB Web site contains literature supporting CYP2D6 as important in venlafaxine metabolism. Current recommendations from the Dutch Pharmacogenetics Working Group Guidelines[9] are to either use a non–CYP2D6 metabolized medication or to adjust the dose to clinical response. Because Ms. C has been taking venlafaxine ER for the last 6 weeks and is taking a relatively low but effective dose, our recommendation is to continue current therapy.

It is also important to consider drug interactions when interpreting pharmacogenomic test results. In Ms. C's case, the impact of a CYP2D6 intermediate metabolism phenotype would be increased if she also was taking a strong CYP2D6 inhibitor such as bupropion. Pharmacogenomics is another clinical tool and discontinuation of an effective treatment that is adequately tolerated should not be done based on pharmacogenomics recommendations alone.

continued

Related Resources

- Clinical Pharmacogenomics Implementation Consortium. https://cpicpgx.org.
- Dutch Pharmacogenetics Working Group. https://www.pharmgkb.org/page/dpwg.
- European Pharmacogenomics Implementation Consortium. http://www.eu-pic.net.

Drug Brand Names

Amitriptyline • Elavil	Escitalopram • Lexapro
Bupropion • Wellbutrin, Zyban	Fluvoxamine • Luvox
Carbamazepine • Tegretol	Imipramine • Tofranil
Citalopram • Celexa	Nortriptyline • Pamelor
Clomipramine • Anafranil	Paroxetine • Paxil
Desipramine • Norpramin	Sertraline • Zoloft
Doxepin • Silenor, Sinequan	Trimipramine • Surmontil
	Venlafaxine ER • Effexor

Clinical Point

Drug metabolism phenotypes are described as poor, intermediate, extensive, and ultra-rapid; extensive is considered average

Clinical Point

An effective treatment should not be discontinued based solely on pharmacogenetics recommendations

References

1. Collins FS, Patrinos A, Jordan E, et al. New goals for the U.S. Human Genome Project: 1998-2003. Science. 1998;282(5389): 682-689.
2. Luzum JA, Pakyz RE, Elsey AR, et al; Pharmacogenomics Research Network Translational Pharmacogenetics Program. The Pharmacogenomics Research Network Translational Pharmacogenetics Program: outcomes and metrics of pharmacogenetic implementations across diverse healthcare systems. Clin Pharmacol Ther. 2017;102(3):502-510.
3. U.S. Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labeling. https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm. Updated October 3, 2017. Accessed October 23, 2017.
4. Caudle KE, Gammal RS, Whirl-Carrillo M, et al. Evidence and resources to implement pharmacogenetic knowledge for precision medicine. Am J Health Syst Pharm. 2016; 73(23):1977-1985.
5. Clinical Pharmacogenomics Implementation Consortium. Genes-drugs. https://cpicpgx.org/genes-drugs. Updated October 2, 2017. Accessed October 23, 2017.
6. PharmGKB. PGx gene-specific information tables. https://www.pharmgkb.org/page/pgxGeneRef. Accessed October 27, 2017.
7. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2012;92(4):414-417.
8. Hicks JK, Bishop JR, Sangkuhl K, et al; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharmacol Ther. 2015;98(2): 127-134.
9. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte—an update of guidelines. Clin Pharmacol Ther. 2011;89(5):662-673.