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Clinical Implementation of Pharmacogenetics: More Than One Gene at a Time

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Abstract

Tricyclic antidepressant (TCA) clinical pharmacogenetic implementation guidelines for *CYP2D6* and *CYP2C19* genotypes highlight the importance of both genes. However, studies of the combined impact of the two genes are sparse, limiting the ability to make strong recommendations based on both genes. The warfarin pharmacogenetics literature highlights the strength of a multigenic approach for discovery and clinical implementation. For optimal impact and interpretation, investigators are encouraged to conduct studies in the context of previously well-defined pharmacogenetics markers.

TCAs rank among our older drugs, and they have a long history of use in depression. Although their primacy for the treatment of depression has been overtaken by selective serotonin reuptake inhibitors, they have continued use in depression and for treatment of neuropathic pain.

It has been recognized since the early 1980s that cytochrome P450 2D6 (*CYP2D6*) plays a major role in metabolism of the TCAs and that genetic polymorphisms in the *CYP2D6* gene have substantial impact on the pharmacokinetics of TCAs, leading to differential efficacy or toxicity based on *CYP2D6* genotype.¹ The literature on the impact of *CYP2D6* genotype on TCAs has continued to grow over the ensuing decades. In the mid-1990s associations between *CYP2C19* genotype and TCA pharmacokinetics and response began to emerge, with most studies on the influence of this gene published since 2000 (ref. 1). There are now many studies linking *CYP2D6* and/or *CYP2C19* genotype to TCA pharmacokinetics and response.

This issue of *Clinical Pharmacology & Therapeutics* contains the most recent set of guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC), focused on TCAs and clinical use of *CYP2D6* and *CYP2C19* genotypes to guide TCA use or dosing.¹ These guidelines contain a comprehensive review of this large and complex literature, which includes data on many TCAs and their associations with *CYP2D6* and *CYP2C19*. This new guideline provides specific recommendations regarding use or dosing of TCAs based on *CYP2D6* genotype–inferred phenotype, *CYP2C19* genotype–inferred

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CONFLICT OF INTEREST

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phenotype, and a supplemental recommendation table that considers both *CYP2D6* and *CYP2C19* phenotype together (TCA CPIC guidelines Supplementary Table S19).¹ Dosing recommendations based on genotypes for either *CYP2D6* or *CYP2C19* in isolation are useful because some patients will have genotype determined for just one of those two genes and CPIC guidelines are intended to assist clinicians' dosing decisions based on the assumption that genotype(s) for one or more genes are already in hand.

Many of the dosing recommendations based on either *CYP2D6* or *CYP2C19* alone are classified as "strong" recommendations, on the basis of the strength of the literature supporting those recommendations. However, the recommendations based on both genes are classified only as "optional" because they have a more modest literature base. Assuming that the effects of variant genotypes are additive (and not redundant), dosing based on results for both *CYP2D6* and *CYP2C19* phenotypes would be preferable, provided that both genes are adequately typed in a patient.

Unfortunately, many of the TCA pharmacogenetics studies that underlie the TCA CPIC guidelines considered only *CYP2D6* or *CYP2C19*, or, when both genes were studied, one was not evaluated in the context of the other. Such approaches to pharmacogenetics research will ultimately limit clinical translation because it is expected that many drugs will have important influences associated with more than one gene. If pharmacogenetics is to have the greatest possible impact on clinical practice, pharmacogenetics researchers must move away from a focus on single genes. And once a gene has been documented to be clearly associated with a drug's pharmacokinetics or response, then studies of other genes should include the previous genes in the analysis.

Warfarin, the subject of a previous CPIC guideline,² provides insight into multigenic approaches for pharmacogenetics research and clinical implementation. The influence of *CYP2C9* genotype on warfarin dose requirements and bleeding was first recognized in 1999; as a result of that first report, many investigators undertook warfarin pharmacogenetic studies, building large cohorts of stably treated warfarin patients, with warfarin dosing and clinical information, and collection of genetic samples. The gene encoding the protein target of warfarin, *VKORC1*, was first described in a *Nature* paper in February 2004. Following this publication, sequencing of the gene in warfarin-treated patients was rapidly undertaken in the existing warfarin pharmacogenetics cohorts, leading to the discovery of common polymorphisms that explain up to 25% of the variability in warfarin dose requirement, substantially more than the *CYP2C9* contribution.² The first article describing this association was published online in September 2004,³ only 7 months after the original publication describing the gene. By the end of 2006, there were 24 original-research publications in the literature describing the association of *VKORC1* polymorphisms with warfarin dose requirement. The rapid explosion in the literature on this topic was largely attributed to investigators utilizing warfarin pharmacogenetic data sets they had previously accrued, or were building, based on the earlier *CYP2C9* findings. Importantly, these studies considered the impact of *VKORC1* in the context of *CYP2C9* genotype. As such, it is very clear that both genes are important and essentially additive in their effects; moreover, the contribution of each gene to warfarin dose requirements has been clearly defined in the CPIC-recommended dosing algorithms and in the dosing table in the US Food and Drug Administration–approved product label for warfarin.²

The impact of utilizing existing warfarin pharmacogenetics data sets and building on existing pharmacogenetics knowledge was later confirmed with the discovery of the influence of *CYP4F2* on warfarin dose requirement.⁴ This association was first described in 2008 in analyses that controlled for *CYP2C9* and *VKORC1* genotype, and again there was a rapid response in the literature of publications describing this association in the context of

CYP2C9 and *VKORC1* genotype. Of note is that genome-wide association studies that followed the original description of the *CYP4F2*-warfarin association found that the *CYP4F2* signal reached genome-wide significance only after controlling for *CYP2D6* and *VKORC1* genotype.⁵ This highlights the importance of conducting pharmacogenetic studies in the context of well-defined pharmacogenetic markers, so that the additional impact of the new gene can be placed in the context of the existing pharmacogenetics literature for that drug. More important, it suggests that discoveries of additional pharmacogenes may actually be enhanced by consideration of known pharmacogenetic markers.

It is unfortunate that the literature is lacking in tests of the contribution of both *CYP2C19* and *CYP2D6* to TCA dosing, with analyses considering them together. Perhaps the TCA literature has suffered in this regard because it was built over a very long time frame (before either gene was even cloned or identified), and, although TCAs continue to be widely used, they have been off patent for many years and interest in other antidepressant classes has superseded that in TCAs. Nonetheless, unless such data are available, it may be difficult to fully realize the potential for pharmacogenetic-guided treatment with TCAs. Until such data exist, clinicians who have genotype data for both genes will have to recognize the limitations in the literature for considering both genes to make decisions about TCA use or dosing.

Adequately powered clinical studies designed to test response to medications are difficult to conduct and expensive, and it is unrealistic to consider conducting a new clinical study each time a new gene of interest is identified. Therefore, the pharmacogenetics research community must ensure that our pharmacogenetics resources are utilized to their fullest potential. This includes use of existing data sets to define the pharmacogenetic influence of genes of interest as they arise. The value of utilizing existing pharmacogenetics data sets has been clearly defined with warfarin. We encourage investigators holding TCA pharmacogenetics data sets to conduct studies and analyses that will provide a clearer picture of the combinatorial impact of *CYP2D6* and *CYP2C19* genotypes. Such studies, which are relatively inexpensive, will facilitate clinical translation of TCA pharmacogenetics. Availability of these data will be an important advance for the clinical translation of these data.

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References

1. Hicks JK, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants. *Clin. Pharmacol. Ther.* 2013; 93:402–408. [PubMed: 23486447]
2. Johnson JA, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C9* and *VKORC1* genotypes and warfarin dosing. *Clin. Pharmacol. Ther.* 2011; 90:625–629. [PubMed: 21900891]
3. D'Andrea G, et al. A polymorphism in the *VKORC1* gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. *Blood.* 2005; 105:645–649. [PubMed: 15358623]
4. Caldwell MD, et al. *CYP4F2* genetic variant alters required warfarin dose. *Blood.* 2008; 111:4106–4112. [PubMed: 18250228]

5. Takeuchi F, et al. A genome-wide association study confirms *VKORC1*, *CYP2C9*, and *CYP4F2* as principal genetic determinants of warfarin dose. *PLoS Genet.* 2009; 5:e1000433. [PubMed: 19300499]