Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* Genotype and Use of Ondansetron and Tropisetron

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The 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonists are used in the prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting. *CYP2D6* polymorphisms can influence the metabolism of some of these drugs (i.e., ondansetron and tropisetron), thereby affecting drug efficacy. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for ondansetron and tropisetron based on *CYP2D6* genotype (updates at www.pharmgkb.org and cpicpgx.org).

The purpose of this guideline is to provide information to allow the interpretation of clinical *CYP2D6* genotype tests so that the results can be used to guide use of the 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonists, ondansetron and tropisetron. Detailed guidelines for use of ondansetron and tropisetron as well as analyses of cost-effectiveness are beyond the scope of this document. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are periodically updated at https://cpicpgx.org/guidelines/ and http://www.pharmgkb.org.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2D6* genotype and ondansetron, granisetron, tropisetron, palonosetron, and ramosetron use was conducted (details in **Supplementary Material** online).

GENE: *CYP2D6*

CYP2D6 is highly polymorphic with over 100 known allelic variants and subvariants identified (http://www.cypalleles.ki.se/cyp2d6.htm; ***CYP2D6* Allele Definition Table 1**). *CYP2D6* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups and significant differences in allele frequencies have been observed (***CYP2D6* Frequency Table 1**). The most commonly reported alleles are categorized into functional groups as follows: Normal function (e.g., *CYP2D6*1* and **2*), decreased function (e.g., *CYP2D6*9*, **10*, and **41*), and no function (e.g., *CYP2D6*3-*6*).[1–3] Because *CYP2D6* is subject to deletions, gene duplications, or multiplications, many clinical laboratories also report copy number variations. *CYP2D6*5* represents a gene deletion (no function allele), whereas gene duplications and multiplications are denoted by "xN" (e.g., *CYP2D6*1xN* with xN representing the number of *CYP2D6* gene copies). Alleles carrying two or more normal function gene copies are categorized as alleles with increased function.

The combination of alleles is used to determine a patient's diplotype. Each functional group is assigned an activity value ranging from 0–1 (e.g., 0 for no; 0.5 for decreased function, and 1.0 for normal function).[3] **Supplementary Table S1** online describes the activity score values assigned to selected alleles. If an allele contains multiple copies of a functional gene, the value is multiplied by the number of copies present. Thus, the *CYP2D6* activity score is the sum of the values assigned to each allele, which typically ranges from 0–3 but may exceed 3 in rare cases.[3]

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Table 1 Assignment of likely CYP2D6 phenotypes based on diplotypes

Likely phenotype	Activity score	Genotypes[a]	Examples of *CYP2D6* diplotypes
CYP2D6 Ultrarapid Metabolizer (~1–2% of patients)[b]	>2.0	An individual carrying duplications of functional alleles	**1/*1xN*, **1/*2xN*, **2/*2xN*[c]
CYP2D6 Normal Metabolizer (~77–92% of patients)	2.0–1.0[d]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele or combinations of duplicated alleles that result in an activity score of 1.0–2.0	**1/*1*, **1/*2*, **1/*4*, **1/*5*, **1/*9*, **1/*41*, **2/*2*,**41/*41*
CYP2D6 Intermediate Metabolizer (~2–11% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*10*,**4/*41*, **5/*9*
CYP2D6 Poor Metabolizer (~5–10% of patients)	0	An individual carrying only no functional alleles	**3/*4*,**4/*4*, **5/*5*, **5/*6*

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.
[a]Assignment of allele function and citations for allele function can be found https://www.pharmgkb.org/page/cyp2d6RefMaterials (***CYP2D6* Allele Definition Table** and ***CYP2D6* Allele Functionality References Table 1**). [b]See the ***CYP2D6* Frequency Table 1** for race-specific allele and phenotype frequencies or see Gaedigk *et al*.[4] [c]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see **Supplementary Data** for additional information on how to translate diplotypes into phenotypes. [d]Patients with an activity score of 1.0 may be classified as IMs by some reference laboratories.

The CYP2D6 activity score relates to the phenotype classification system as follows (***CYP2D6* Allele Definition Table 1**): patients with an activity score of 0 are poor metabolizers (PMs), those with a score of 0.5 are considered intermediate metabolizers (IMs), and those with a score of 1.0, 1.5, or 2.0 represent normal metabolizers (NMs). Patients with a score >2.0 are classified as ultrarapid metabolizers (UMs). It should be noted that reference laboratories providing clinical *CYP2D6* genotyping might use varying methods to assign phenotypes. Therefore, it is advisable to note a patient's *CYP2D6* diplotype and to calculate an activity score before making therapeutic decisions about ondansetron or tropisetron therapy.

Genetic test interpretation

Clinical laboratories rarely sequence through the *CYP2D6* gene or interrogate every known variant position. Instead, they typically test for variants that are used to determine high frequency allele haplotypes using the star-allele (*) nomenclature system, found at The Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se). **Supplementary Table S1** online and tables found on the PharmGKB website[1] contains a list of *CYP2D6* alleles, the specific combination of variants that can be used to determine the allele, functional status, and frequency across major ethnic populations, as reported in the literature.

Genetic test results are reported as diplotypes, or the combination of the maternal and paternal alleles (e.g., *CYP2D6*1/*2*). Phenotypes are assigned based on the reported *CYP2D6* diplotype, as summarized in **Table 1**.[4]

The limitations of genetic testing as described here include: (1) rare variants are often not detected; (2) known star (*) alleles not tested for will not be reported, and, instead, the patient will be reported as a **1*; and (3) tests are not designed to detect unknown or *de novo* variants. **Supplementary Data** online (Genetic Test Interpretation Section) contains additional information regarding *CYP2D6* genetic test interpretation and phenotype assignment.

Available genetic test options

See **Supplementary Material** online and www.ncbi.nlm.nih.gov/gtr/ for more information on commercially available clinical testing options.

Incidental findings

Currently, there are no diseases or conditions consistently linked to the variation in the *CYP2D6* gene independent of drug metabolism and response.

Other considerations

Not applicable.

DRUGS: ONDANSETRON AND TROPISETRON

Background

Ondansetron and tropisetron, highly specific and selective members of the 5-HT_3 receptor antagonists, are used in the prevention of chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting.[5] The 5-HT_3 receptor antagonists suppress nausea and vomiting by selectively binding to 5-HT_3 receptors centrally and peripherally, thereby preventing serotonin-mediated emetogenic signaling and exhibit a steep dose-response curve.[6–8] The 5-HT_3 receptor antagonist class is the cornerstone of prophylactic therapy for moderately to highly emetogenic chemotherapy and radiotherapy.[9] All of the medications in this class have been shown to be effective in the prevention of nausea and vomiting; the main differences between these drugs are due to variations in pharmacokinetic and pharmacodynamic considerations. The 5-HT_3 receptor antagonists are generally well tolerated. Mild headache, constipation, and transient elevations in liver enzymes are common side effects. Ondansetron has also been associated with cardiac adverse events such as corrected QT prolongation[9] (see "Other Considerations" section).

Ondansetron is metabolized to four inactive metabolites by multiple CYP enzymes, including CYP3A4, CYP1A2, and CYP2D6, followed by glucuronide conjugation to metabolites not clinically relevant for pharmacologic activity.[10,11] Tropisetron is extensively metabolized by CYP2D6 to inactive metabolites and further

Table 2 Dosing recommendations for ondansetron and tropisetron based on *CYP2D6* genotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]	Consideration for alternative 5-HT_3 receptor antagonists antiemetics[b]
CYP2D6 Ultrarapid Metabolizer	Increased metabolism to less active compounds when compared to NMs and is associated with decreased response to ondansetron and tropisetron (i.e., vomiting)	Select alternative drug not predominantly metabolized by CYP2D6 (i.e., granisetron).[c]	Moderate	Dolasetron, palonosetron, and ramosetron are also metabolized by CYP2D6. Limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide use of these drugs.
CYP2D6 Normal Metabolizer	NM	Initiate therapy with recommended starting dose.[c]	Strong	
CYP2D6 Intermediate Metabolizer	Very limited data available for CYP2D6 IMs	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	
CYP2D6 Poor Metabolizer	Very limited data available for CYP2D6 PMs	Insufficient evidence demonstrating clinical impact based on *CYP2D6* genotype. Initiate therapy with recommended starting dose.[c]	No recommendation	

5-HT_3, 5-hydroxytryptamine type 3; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.
[a]Rating scheme described in the **Supplementary Material** online. [b]Clinical Pharmacogenetics Implementation Consortium strength of recommendation: no recommendation. See rating scheme described in the **Supplementary Material** online. [c]Drug-drug interactions and other patient characteristics (e.g., age, renal function, and liver function) should be considered when selecting alternative therapy.

conjugated to glucuronides and sulfates.[11,12] Other 5-HT_3 receptor antagonists, including dolasetron, palonosetron, and ramosetron, are also metabolized via multiple CYP enzymes.[13–15] CYP3A4 is majorly involved in the demethylation of granisetron to 9′-desmethylgranisetron,[16] whereas CYP1A1 is preferentially responsible for the formation of 7-hydroxygranisetron, the main metabolite of granisetron.[17]

Linking genetic variability to variability in drug-related phenotypes

There is evidence linking the *CYP2D6* genotype with phenotypic variability in efficacy of ondansetron and tropisetron (see **Supplementary Table S2** online). Application of a grading system to evidence linking *CYP2D6* genotypic variations to phenotypic variability in response to these two drugs indicates an acceptable quality of evidence (**Supplementary Table S2** online). This body of evidence, rather than randomized clinical trials involving pharmacogenetic testing, provides the basis for the ondansetron dosing recommendations in **Table 2**. Although the evidence to support this recommendation is limited, the recommendation is supported by the quality of these studies, the evidence to support increased metabolism of ondansetron and tropisetron (and many other CYP2D6 substrates) in CYP2D6 UMs,[18] and the fact that there are suitable alternatives to ondansetron and tropisetron that are not affected by metabolism by CYP2D6.[5,19] Although other CYP enzymes contribute to ondansetron metabolism, there are substantial data to support a major role of CYP2D6 in the metabolism of ondansetron.[10,11,13]

Decreased antiemetic effect (i.e., vomiting) of ondansetron and tropisetron when used for postoperative or chemotherapy-induced nausea and vomiting has been observed in CYP2D6 UMs.[20,21] Candiotti *et al.*[20] genotyped 250 female patients undergoing general anesthesia who received 4 mg ondansetron 30 min before extubation. CYP2D6 UMs had the highest incidence of vomiting (45%) as compared to NMs (15%).[20] However, there was no difference in the incidence of vomiting between CYP2D6 IMs and PMs as compared with NMs. In addition, Kaiser *et al.*[21] found similar results in patients (n = 270) receiving tropisetron or ondansetron for chemotherapy-induced nausea and vomiting. The evidence review yielded no studies describing any substantial impact of CYP2D6 PM status on ondansetron adverse events; however, one study reports that CYP2D6 PMs treated with ondansetron had the fewest episodes of vomiting.[21] Although CYP2D6 PMs had higher serum concentrations of tropisetron than all other patients measured 6 h after administration, no dose reduction is recommended per US Food and Drug Administration (FDA) labeling.

Dosage recommendations/therapeutic recommendations

Table 2 summarizes the therapeutic recommendations for ondansetron and tropisetron based on CYP2D6 phenotype. Gene duplication has been shown to be associated with higher metabolism and clearance of ondansetron resulting in lower area under the plasma concentration-time curve.[18,22] This translates clinically into a decreased response to ondansetron and tropisetron, specifically increased risk of vomiting in CYP2D6 UMs.[20,21] If the *CYP2D6* genotype is known, alternative 5-HT_3 receptor antagonist antiemetics not metabolized by CYP2D6 (e.g., granisetron) should be considered in CYP2D6 UMs. Although dolasetron, palonosetron, and ramosetron are also

metabolized by CYP2D6 (**Supplementary Table S3** online), limited evidence is available regarding the utilization of *CYP2D6* genetic variation to guide use of these drugs.

The strength of this recommendation is based on the evidence provided in **Supplementary Table S2** online and the availability of suitable antiemetics not metabolized by CYP2D6. Currently, there are limited published data to support a recommendation in CYP2D6 IMs and PMs. Of note, the prescribing information for i.v. Zofran states, based on unpublished data, that the pharmacokinetics of i.v. ondansetron did not differ between CYP2D6 PMs and CYP2D6 NMs.[23]

At the time of this writing, there are no data available on CYP2D6 genotype's effect on ondansetron or tropisetron response in the pediatric patient populations, although there is no reason to suspect that *CYP2D6* genetic variation will affect this drug's metabolism differently in children compared with adults. Because CYP2D6 catalytic activity in neonates (<1 month old) depends strongly on developmental aspects,[24] the impact of CYP2D6 in this patient population might be different than adults or older children.

Recommendations for incidental findings

Not applicable.

Other considerations

The syndrome of congenital prolongation of the QT interval of the electrocardiogram is associated with a risk of potentially fatal polymorphic ventricular tachycardia, which is commonly referred to as torsades de pointes. Drugs that prolong the QT interval, such as ondansetron, should generally be avoided in patients with this diagnosis, as well as in those patients considered borderline. In September 2011, the FDA issued a safety communication reporting a change to the medication label by adding a warning to avoid ondansetron use in patients with congenital long QT syndrome (http://www.fda.gov/Drugs/DrugSafety/ucm271913.htm). The alert also recommended electrocardiogram monitoring for patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking concomitant medications that prolong the QT interval. In June 2012, the FDA issued another safety communication reporting changes to the ondansetron label regarding i.v. dosing (http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm). This alert recommended that no single i.v. dose should exceed 16 mg. The alert noted new evidence suggesting that QT prolongation is dose dependent. Therefore, in patients for whom genetic testing indicates intermediate or poor CYP2D6 metabolism, potentially elevated blood levels of ondansetron would suggest these patients might be at an even greater risk for torsades de pointes even with the 16 mg maximum dose.[25,26] However, there are no clinical data demonstrating greater QT prolongation in CYP2D6 PMs.

CYP2D6 genetic variants do not account for all variations observed for ondansetron or tropisetron response. In addition to specific patients factors (such as smokers vs. nonsmokers and male vs. female), other genes have been implicated in the response to ondansetron, including the adenosine triphosphate-binding cassette subfamily B member 1 gene (*ABCB1*)[27,28] and the genes for the serotonin 5-HT_3A and 5-HT_3B receptors.[19,28,29] Genetic variation in *CYP3A5* has been found to influence concentrations of R-ondansetron; however, to date, there are no data to support how *CYP3A5* variation impacts antiemetic efficacy in individuals taking ondansetron and tropisetron.[18] However, one study has found that variations in *CYP3A5* and *CYP1A1* impact systemic clearance and exposure of granisetron in pregnant women.[30] Additional studies are needed to elucidate the role of variation in these genes in antiemetic therapy.

Implementation resources for this guideline. The guideline supplement contains resources that can be used within electronic health records to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see the "Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support" sections of the **Supplementary Material** online). Clinical implementation resources include cross-references for drug and gene names to widely used terminologies and standardized nomenclature systems, workflow diagrams, a table that translates genotype test results into a predicted phenotype with genetic test interpretation, and example text for documentation in the electronic health record and point-of-care alerts.

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of using *CYP2D6* genotype to guide ondansetron and tropisetron use is that patients with genotypes that are associated with a decreased response (e.g., CYP2D6 UMs) may be identified and alternative antiemetics administered. At this time, the evidence does not justify increasing the dose in CYP2D6 UMs because dose adjustments based on CYP2D6 UMs have not been studied and a detailed recommendation of dosing for the different CYP2D6 phenotypes is missing. Additionally, there is a single i.v. dose maximum of 16 mg in the FDA labeling that might prevent increases in dosing in certain situations. *CYP2D6* genotyping is reliable when performed in qualified laboratories (e.g., CLIA-certified). However, as with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction, along with the presence of a rare genomic variant not tested for, which could have long-term adverse health implications for patients.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Rare *CYP2D6* variants may not be included in the genotype test used and patients with rare variants may be assigned a "wild-type" (*CYP2D6*1*) genotype by default. Thus, an assigned "wild-type" allele could potentially harbor a no or decreased function variant. Furthermore, it is important that the genetic testing platform include testing for gene copy number to identify CYP2D6 UMs. Caution should be used regarding molecular diagnostics of *CYP2D6* gene copy-number variation because commercially available genotyping results may differ between diagnostic laboratories depending on assay design. Like all diagnostic tests, *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider when making their therapeutic choice

for each patient. Furthermore, several other factors cause potential uncertainty in the genotyping results and phenotype predictions. These are discussed in detail in the **Supplementary Data** online.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

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Additional Supporting Information may be found in the online version of this article.

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CONFLICT OF INTEREST

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