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Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C9* and *HLA-B* Genotypes and Phenytoin Dosing: 2020 Update

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Conflicts of Interest

EJP is a consultant for Biocryst. She is section editor for drug allergy (uptodate) and is co-director of IIID, Pty Ltd that holds a patent for *HLA-B*57:01* testing for abacavir hypersensitivity. She holds a provisional patent for *HLA-A*32:01* testing for vancomycin-induced DRESS. All other authors declared no competing interests for this work.

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Abstract

Phenytoin is an antiepileptic drug with a narrow therapeutic index and large inter-patient pharmacokinetic variability, partly due to genetic variation in *CYP2C9*. Furthermore, the variant allele *HLA-B*15:02* is associated with an increased risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in response to phenytoin treatment. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for the use of phenytoin based on *CYP2C9* and/or *HLA-B* genotypes (updates on cpicpgx.org).

Keywords

Phenytoin; HLA-B; CPIC; CYP2C9; pharmacogenetics; fosphenytoin; Stevens-Johnson syndrome; toxic epidermal necrolysis

Introduction

The purpose of this guideline is to provide information for the interpretation of human leukocyte antigen B (*HLA-B*) and/or cytochrome P450 2C9 (*CYP2C9*) genotype test results to guide use and/or dosing of phenytoin. Guidelines for phenytoin use and cost effectiveness of genetic testing are outside the scope of this report. This guideline updates the 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C9* and *HLA-B* Genotypes and Phenytoin Dosing (1). CPIC guidelines are periodically updated at www.cpicpgx.org.

Focused Literature Review

We reviewed literature focused on *CYP2C9* and *HLA* variation and phenytoin use (details in Supplemental Material). Evidence is summarized in Tables S1 and S2.

Genes: *HLA-B* and *CYP2C9*

Background—This guideline discusses *HLA-B* and the risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with phenytoin and *CYP2C9* as it relates to phenytoin metabolism and dosing. Updated *CYP2C9* allele function assignments are provided using the activity score system.

HLA-B: *HLA-B* is part of a gene cluster designated as the human major histocompatibility complex (MHC) located on the short arm of chromosome 6. The cluster contains three classes (I, II and III). MHC class I contains three genes: *HLA-A*, *HLA-B* and *HLA-C*. These genes encode a cell surface protein that binds peptides generated by proteolysis and extruded from proteasomes. The presentation of these cell surface peptides enables the immune

system to distinguish self-proteins from foreign proteins (see Supplement for further discussion).

HLA genes, specifically *HLA-B*, are among the most highly polymorphic genes in the human genome. *HLA* polymorphisms were previously ascertained serologically, but DNA sequencing methods have identified genetic variability in the *HLA* region with greater precision. More than 7,000 *HLA-B* alleles, many of which differ by more than one nucleotide from each other, were deposited to the World Health Organization Nomenclature Committee for Factors of the HLA System (<http://hla.alleles.org>). Each allele is designated by the gene name followed by an asterisk and up to an eight-digit (four pairs) identifier, which gives information about the allele type (designated by the first two digits) followed by the specific protein subtypes (second set of up to 6 digits). The first four digits typically differ in at least one amino acid substitution and give the most important functional information. For more information on the description of the current *HLA* allele nomenclature see <http://hla.alleles.org/nomenclature/naming.html> and a previous CPIC guideline (2). This guideline discusses only the *HLA-B*15:02* allele as it relates to the phenytoin-induced cutaneous adverse drug reactions, including SJS and TEN.

CYP2C9.: The hepatic CYP2C9 enzyme system metabolizes many clinically relevant drugs, including phenytoin (<http://www.pharmgkb.org/pathway/PA145011115>). The *CYP2C9* gene is highly polymorphic, with at least 61 variant alleles and multiple suballeles (see **CYP2C9 Allele Definition Table** in references (3, 4); <https://www.pharmvar.org/gene/CYP2C9> (5)). Each *CYP2C9* star (*) allele is defined by one or more single nucleotide polymorphisms (SNPs) or nucleotide deletions that may alter enzyme activity. The two most common variants with decreased enzyme activity are *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) (6). *CYP2C9* allele and diplotype frequencies differ between racial/ethnic groups ((7); **CYP2C9 Frequency Table** (3, 4)). *In vitro* and clinical studies suggest that *CYP2C9* decreased function and no function alleles generate variant enzymes with activities that are substrate-dependent (**CYP2C9 Allele Functionality Table** (3, 4)). Therefore, assigning function to *CYP2C9* alleles requires careful evaluation of individual drugs.

Genetic Test Interpretation

HLA-B.: Clinical genotyping test results for *HLA-B*15:02* are interpreted as “positive” if one or two copies of *HLA-B*15:02* are present or “negative” if no copies of *HLA-B*15:02* are found. *HLA-B* alleles do not affect the pharmacokinetics or pharmacodynamics of phenytoin. Phenotype assignments for *HLA-B*15:02* genotypes are summarized in Table 1. *HLA-B*15:02* is most prevalent in East Asian and Central/South Asian populations with allele frequency ranging from 1% to over 20%. *HLA-B*15:02* is less frequent in European populations (0–1%) and was not detected in several sub-Saharan African populations (**HLA-B Frequency Table** (3, 4, 8)).

CYP2C9.: Most clinical laboratories reporting *CYP2C9* genotype use the star (*) allele nomenclature and may interpret the patient’s predicted metabolizer phenotype based on the combination of *CYP2C9* alleles (diplotype) (Table 2; **CYP2C9 Diplotype to Phenotype Table** (3, 4)). Not all *CYP2C9* allelic variants may be tested, and this influences the

accuracy of the genotype-based dose prediction. Misclassification occurs primarily in individuals of Asian or African ancestry who carry decreased function *CYP2C9* alleles other than *2 or *3 (***CYP2C9* Frequency Table** (3, 4)). An activity value is assigned to each *CYP2C9* allele ranging from 0 to 1 (i.e. 0 for no function, 0.5 for decreased function, and 1.0 for normal function). Activity values are summed to calculate the activity score (AS) of a diplotype (3, 4). The *CYP2C9* AS is translated into phenotypes as follows: individuals with an AS of 0 or 0.5 are poor metabolizers (PMs), those with a score of 1 or 1.5 are intermediate metabolizers (IMs), and those with a score of 2 are normal metabolizers (NMs) (Table 2; ***CYP2C9* Diplotype to Phenotype Table** (3, 4)). Of note, as there are no known increased function alleles for *CYP2C9*, no ultrarapid or rapid *CYP2C9* metabolizer phenotypes currently exist. Reference laboratories providing clinical *CYP2C9* genotyping may use various methods to assign phenotypes. Thus, before making phenytoin therapeutic decisions, we strongly advise referring to the online ***CYP2C9* Diplotype to Phenotype Table** (3, 4) that lists of all possible *CYP2C9* diplotypes and phenotype assignments.

Of note, Table 2 denotes a change to the previous (2014) genotype to phenotype translation tables for diplotypes containing *CYP2C9**2 and other decreased function alleles (see Supplement for details). The *CYP2C9**2/*2 diplotype (AS=1) is now translated into the IM phenotype group (originally translated to PM). This change is based on data for multiple substrates (flurbiprofen, celecoxib, phenytoin, and warfarin) showing a similar effect of *CYP2C9**1/*3 (AS=1) and *CYP2C9**2/*2 on metabolic ratio and dose requirements (warfarin) (9–11). Furthermore, *CYP2C9**3 and alleles with a similar clinical effect and function are classified as ‘no function’ alleles with a value of 0 for AS calculation. This is based on *CYP2C9**3/*3, which represents the diplotype with the lowest metabolic activity and slowest pharmacokinetic clearance. Other alleles with similarly low function have also been classified as ‘no function’ (see ***CYP2C9* Allele Functionality Table** (3, 4)).

Available Genetic Test Options—See Supplement and the Genetic Testing Registry (<https://www.ncbi.nlm.nih.gov/gtr/>) for more information on commercially available clinical testing options.

Incidental findings—While multiple autoimmune diseases are associated with *HLA-B* alleles, *HLA-B**15:02 has not been reproducibly associated with these or other non-drug induced diseases (12). No diseases have been linked to genetic variations in *CYP2C9*, except for a small study that associated *CYP2C9**2 and *3 variants and phenytoin with a higher frequency of cerebellar atrophy (13).

Other Considerations—Not applicable

Drugs: Phenytoin and Fosphenytoin

Phenytoin and its prodrug fosphenytoin are commonly used treatments for both focal and generalized convulsive status epilepticus. Phenytoin is indicated for control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (14). Once

a mainstay of treatment, phenytoin's complex dosing and propensity for side effects and drug-drug interactions have led to a decline in its use.

Phenytoin dosing is complex owing to its nonlinear dose accumulation pharmacokinetics and requirements for adjustments based on patient weight, sex, and age (see Supplementary Material and Figures S1 and S2). Outpatient therapy is generally initiated at 5–7 mg/kg/day in adults (slightly higher in children) and may be given once daily (or twice daily in children). The starting dose must be lower in the setting of hepatic impairment. Careful dose adjustments must then be made to stabilize drug concentrations within the targeted therapeutic range (typically 10–20 mcg/mL). In urgent situations such as status epilepticus, intravenous loading doses of 15–20 mg/kg are given over 1–3 mg/kg/min or 50 mg/min, whichever is slower, with cardiac monitoring (14), followed by intravenous or oral maintenance doses, as above. Acute dose-related side effects include sedation, ataxia, dizziness, nystagmus, nausea, and cognitive impairment. The drug is highly allergenic, and rashes ranging from mild eruptions to life-threatening hypersensitivity reactions may be seen. *HLA-B*15:02* is associated with phenytoin-induced SJS and TEN. Sub-acutely, hematologic and hepatic toxicity can occur. Hepatic toxicity is likely a hypersensitivity reaction and is usually accompanied by rash (15), while the hematologic toxicity may reflect leukopenia or pancytopenia. Suicide ideation/behavior has also been linked to phenytoin (two-fold greater risk than placebo), as described in the Food and Drug Administration (FDA) label (14).

Because of the narrow therapeutic index of the drug, initial maintenance dose selection is important. Higher plasma concentrations increase the probability of toxicity (16). However, nonlinear saturable pharmacokinetics, *CYP2C9* autoinduction and *CYP2C9* pharmacogenetics complicate dose-selection. The *CYP2C9* PM phenotype and *CYP2C9* drug interactions, such as concomitant use with voriconazole, can significantly increase phenytoin exposure (17). Variability in protein binding, primarily related to changes in albumin concentrations, can confound the relationship of therapeutic drug monitoring, unless unbound drug concentrations are assayed (18). Use of phenytoin for outpatient therapy has declined in the last decade owing to its potential for drug interactions, chronic metabolic effects including bone loss, and the aforementioned pharmacokinetic difficulties that make phenytoin dose adjustments challenging (see Supplement for further discussion).

Linking genetic variability to variability in drug-related phenotypes—Substantial evidence links *CYP2C9* and *HLA-B*15:02* genotypes with phenotypic variability (see Tables S1 and S2). Application of a grading system that evaluates the relationship between genetic variation and phenotypic variability produces consistent, high quality evidence. The evidence presented in the Supplement text and in Tables S1 and S2 provides the basis for the dosing recommendations in Table 3. In this guideline, all clinical recommendations were based on evidence graded at either High (Evidence includes consistent results from well-designed, well-conducted studies) or Moderate (Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence).

Therapeutic Recommendations

HLA-B*15:02 and CYP2C9 dosing recommendations. Table 3 summarizes the dosing recommendations for phenytoin based on genotype-derived *HLA-B*15:02* and *CYP2C9* phenotypes. If both *HLA-B*15:02* and *CYP2C9* genotypes are known, consider the *HLA-B*15:02* genotype first, then *CYP2C9* genotype (Figure 1; Table 3).

HLA-B*15:02 recommendations. If a patient is phenytoin-naïve and *HLA-B*15:02* positive, the patient has an increased risk of SJS/TEN and the recommendation is to consider using an anticonvulsant other than phenytoin unless the benefits of treating the underlying disease clearly outweigh the risks (see Table 3). Carbamazepine and oxcarbazepine should also be avoided if a patient is *HLA-B*15:02* positive (19). Alternative medications such as eslicarbazepine acetate and lamotrigine have limited evidence linking SJS/TEN with the *HLA-B*15:02* allele. These alternatives to phenytoin should be chosen with caution (see Supplement for details). With standard dosing, phenytoin-induced SJS/TEN usually develops within the first 4–28 days of therapy (20–22). Therefore, patients who have evidence of adherence and continuous dosing of phenytoin or fosphenytoin for longer than 3 months without the development of cutaneous reactions are at low risk of hypersensitivity events related to phenytoin in the future, regardless of *HLA-B*15:02* status (Figure 1; Table 3). The FDA warning for phenytoin states “Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*15:02* due to the increased risk of SJS/TEN in patients of Asian ancestry (14)”. The evidence linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated primarily in individuals of Asian ancestry as the frequency of *HLA-B*15:02* is very low in other populations (see **HLA-B Frequency Table** (3, 4)). However, this allele may also occur in other populations throughout the world that have yet to be studied, and patients may be unaware of, or fail to disclose, Asian ancestry in their families (23, 24).

If a patient is phenytoin-naïve and *HLA-B*15:02* negative, the patient has a normal risk of phenytoin-induced SJS/TEN and the recommendation is to use phenytoin with dosage adjustments based on *CYP2C9* genotype (if known) or standard dosing guidelines (if *CYP2C9* genotype is unknown). However, an *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN (see Supplement for additional guidance).

CYP2C9 recommendations. Phenytoin and fosphenytoin dose should first be adjusted according to a patient’s clinical characteristics. The recommended phenytoin initial or loading and maintenance doses do not need adjustments based on genotype for *CYP2C9* NMs and IMs with an AS of 1.5. Available evidence does not clearly indicate the extent of dose reduction needed to prevent phenytoin-related toxicities in *CYP2C9* IMs with an AS of 1.0 and PMs with an AS of 0 or 0.5. Furthermore, multiple case studies have observed that *CYP2C9* PMs are at increased risk for exposure-related phenytoin toxicities, and multiple studies have observed an association between the *CYP2C9*3* allele and SJS/TEN (25–27). Although carriage of the *CYP2C9*3* allele is insufficient to predict phenytoin-induced SJS/TEN, these and other data suggest that the risk of SJS/TEN is dose-related and provide an additional rationale for reducing phenytoin dose in *CYP2C9* PMs (28). Thus, our recommendations are conservative given the variability surrounding phenytoin dosing.

Based on the doses reported in the pharmacokinetic and pharmacogenetic studies mentioned above (29–31) and in Table S2, a typical initial or loading dose followed by at least a 25% reduction in the recommended starting maintenance dose may be considered for CYP2C9 IMs with AS of 1.0. Subsequent maintenance doses should be adjusted based on therapeutic drug monitoring and response. For CYP2C9 PMs, use a typical initial or loading dose then consider at least a 50% reduction of starting maintenance dose with subsequent maintenance doses adjusted based on therapeutic drug monitoring and response.

Pediatrics.: Much of the evidence (summarized in Table S1) linking *HLA-B*15:02* to phenytoin-induced SJS/TEN was generated in both children and adults. Therefore, the above recommendation is made regardless of *CYP2C9* genotype, individual age, race or ancestry. For pediatric patients who are CYP2C9 IMs or PMs, dose adjustment as described in Table 3 with therapeutic drug monitoring is recommended. While limited data are available for effects of *CYP2C9* alleles on phenytoin metabolism in pediatric patient populations, there is no compelling data to indicate that *CYP2C9* polymorphisms will affect phenytoin metabolism differently in children compared to adults. As such, the pediatric recommendation is extrapolated using adult data. Special considerations in neonates and older pediatric patients, including a high degree of dose variability and dosage forms, and evidence from pediatric populations is included in the supplement (see Pediatrics section of the Supplement for details).

Other considerations

HLA.: *HLA-B*15:02* is linked to SJS and TEN but not to a predisposition for other phenytoin-induced cutaneous ADRs such as mild maculopapular eruptions (MPE) or drug hypersensitivity syndrome (HSS) (32). Other *HLA-B* alleles have also been associated with phenytoin-induced drug reactions with eosinophilia and systemic symptoms (DRESS) and are associated with hypersensitivity reactions to other drugs (26, 33). CPIC guidelines are available for *HLA-B*15:02* and *HLA-A*31:01* and carbamazepine- and oxcarbazepine-induced SJS and TEN (2, 19). Although the structural similarity between phenytoin and carbamazepine and the shared association of the *HLA-B*15:02* allele with SJS and TEN might suggest cross-reactivity with *HLA-A*31:01*, no association between *HLA-A*31:01* and phenytoin-induced SJS and TEN has been presently found. CPIC guidelines are also available for *HLA-B*57:01* and abacavir-induced hypersensitivity reactions and *HLA-B*58:01* and allopurinol-induced severe cutaneous adverse reactions (2, 19, 34).

CYP2C9.: Because of its potent CYP-inducing properties, phenytoin can contribute to a large number of drug interactions, especially involving increased metabolism of other agents with subsequent decrease in their plasma concentrations (35). A full discussion of these is beyond the scope of this guideline, but agents prominently and significantly affected include antineoplastic and immunosuppressive agents, lipid-lowering agents, psychotropics, oral contraceptives, antifungals and warfarin. Furthermore, inhibitors of CYP2C9 can cause phenytoin overexposure and toxicity. Although there are several potent CYP2C9 enzyme inhibitors such as fluconazole and amiodarone, other less potent drugs can produce significant elevations in phenytoin plasma concentrations. Therefore, it is important to

interpret the results of pharmacogenetic testing in the context of other co-administered drugs.

CYP2C9 genetic variation does not account for all observed pharmacokinetic variability in phenytoin metabolism. Some studies suggest that variants in other genes also contribute to altered phenytoin metabolism (e.g., *CYP2C19*, *CYP1A1*, and *EPHX1*; see (36) for a review) and combined genetic analysis might improve the prediction of phenytoin metabolism (29, 30). However, these studies evaluating the effect of multiple gene variation and phenytoin dose requirements are limited and have not been replicated. Consequently, this guideline on genotype-directed phenytoin dosing is limited to *CYP2C9*.

Implementation of this Guideline: The guideline supplement and CPIC website (<https://cpicpgx.org/guidelines/guideline-for-phenytoin-and-cyp2c9-and-hla-b/>) contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* in the Supplemental Material).

Recommendations for Incidental Findings—Case reports have identified cross-reactions to lamotrigine and other anti-epileptic drugs in the presence of *HLA-B*15:02* (see Supplemental Material for further discussion). However, larger replication studies are warranted.

CYP2C9 metabolizes substrates from several drug classes, including nonsteroidal anti-inflammatory drugs (NSAIDs) and oral hypoglycemics. Patients with enhanced sensitivity to warfarin may have a decreased capacity to metabolize phenytoin owing to the presence of one or more *CYP2C9* variant alleles (37).

Potential Benefits and Risks for the Patient

The potential benefit for patients with existing *CYP2C9* and/or *HLA-B*15:02* genotype information is avoidance of adverse effects in patients who are *CYP2C9* IMs (AS of 1.0) and *CYP2C9* PMs by making significant reductions in their initial maintenance dose or by selecting alternative agents for patients who carry *HLA-B*15:02*. A potential risk is that phenytoin therapy may have been needlessly avoided in patients who may not have developed SJS/TEN; however, this risk is mitigated because alternatives to phenytoin with comparable effectiveness exist. Another potential risk would be an error in genotyping. Also, many commercially available genotyping tests do not detect all known alleles or *de novo* variants (for example *HLA-B* alleles in the same B75 serotype family as *HLA-B*15:02*). Other *HLA* alleles are not well characterized, resulting in uncertainty when predicting the phenotype for some genetic test results. Since an *HLA-B*15:02* negative test does not eliminate the risk of phenytoin-induced SJS/TEN and since genetic tests may not detect rare *CYP2C9* variants, a patient with a high ADR risk could be prescribed phenytoin or a patient with reduced *CYP2C9* activity could be prescribed a higher than needed phenytoin dose. Moreover, because not all phenytoin-induced adverse events are attributed to *HLA-B*15:02* or *CYP2C9* metabolizer status, particularly in non-East and Central/South

Asian populations, clinicians should carefully monitor all patients according to standard practices.

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

The application of genotype-based dosing is most appropriate when initiating phenytoin maintenance therapy. Obtaining genetic information after months of drug therapy is less informative, given that the drug dose may have already been adjusted based on therapeutic drug monitoring. As with all diagnostic tests, genetic tests are only one of several pieces of clinical information that should be considered before initiating and maintaining drug therapy.

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 variation 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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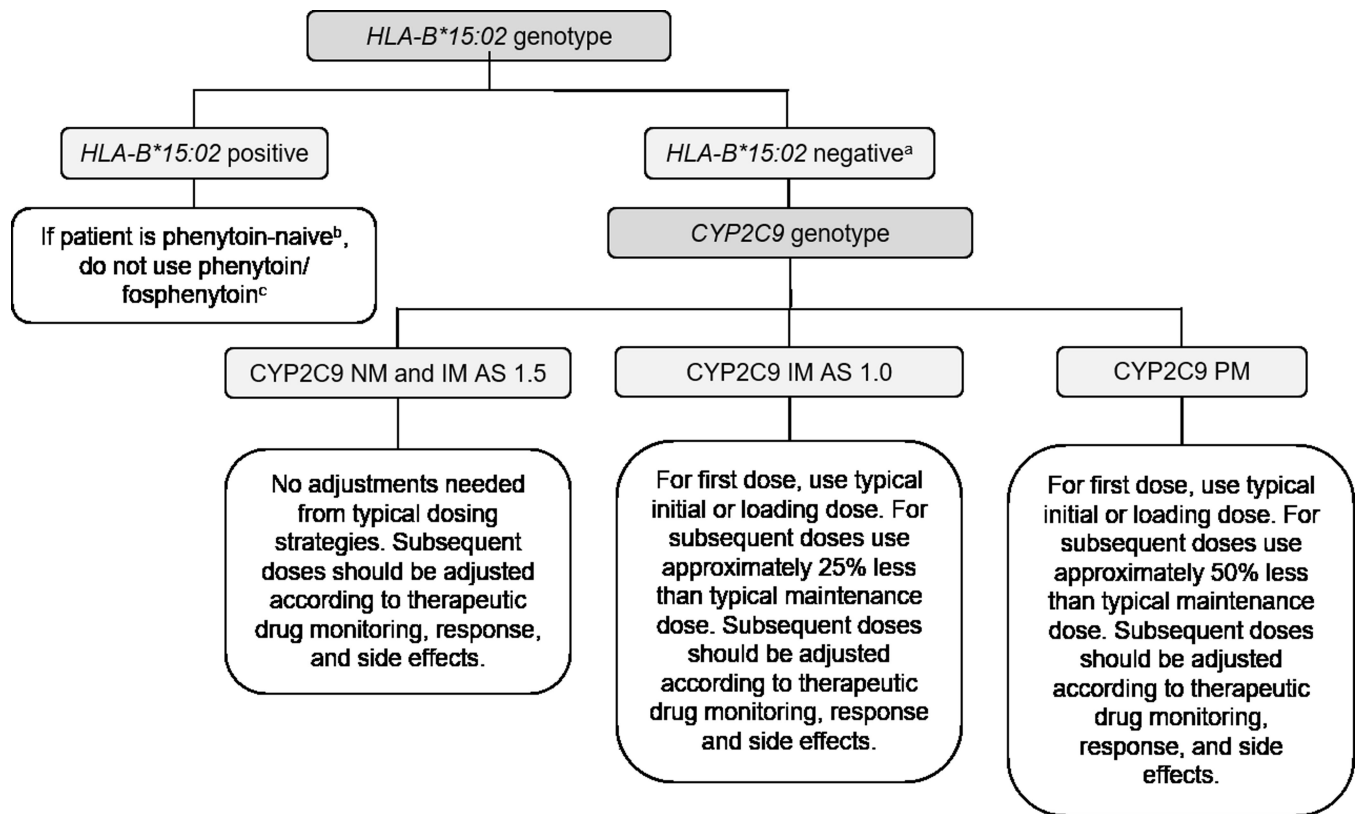


Figure 1. Algorithm for suggested clinical actions based on *HLA-B*15:02* and *CYP2C9* genotype. NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; AS, Activity Score

^aAn *HLA-B*15:02* negative test does not completely eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.

^bIf the patient has previously used phenytoin continuously for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4–28 days), and cases usually occur within three months of dosing.

^cOther aromatic anticonvulsants, including eslicarbazepine, lamotrigine, and phenobarbital, have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.

Table 1.

Assignment of likely HLA-B phenotypes based on genotypes

HLA Phenotype	Genotype	Examples of diplotypes
HLA-B*15:02 negative	Homozygous for an allele other than <i>HLA-B*15:02</i>	<i>*X/*X</i> Where *X = any <i>HLA-B</i> allele other than <i>HLA-B*15:02</i> .
HLA-B*15:02 positive	Heterozygous or homozygous variant	<i>*15:02/*X</i> , <i>*15:02/*15:02</i> Where *X = any <i>HLA-B</i> allele other than <i>HLA-B*15:02</i> .

Table 2.

Assignment of likely CYP2C9 phenotypes based on genotypes

CYP2C9 Phenotype ^{a,b}	Activity Score	Genotypes	Examples of Diplotypes
Normal Metabolizer	2	An individual carrying two normal function alleles	*1/*1
Intermediate Metabolizer	1.5 1	An individual carrying one normal function allele plus one decreased function allele; OR one normal function allele plus one no function allele OR two decreased function alleles	*1/*2 *1/*3, *2/*2
Poor Metabolizer	0.5 0	An individual carrying one no function allele plus one decreased function allele; OR two no function alleles	*2/*3 *3/*3

^a Assignment of allele function and associated citations can be found at <https://www.pharmgkb.org/page/cyp2c9RefMaterials> (see **CYP2C9 Allele Definition Table** and **CYP2C9 Allele Functionality Table** in references (3, 4)). For a complete list of CYP2C9 diplotypes and resulting phenotypes, see the **CYP2C9 Diplotype to Phenotype Table** in references (3, 4).

^b See the **CYP2C9 Frequency Table** in references (3, 4) for population-specific allele and phenotype frequencies.

Table 3. Recommended dosing of phenytoin/fosphenytoin based on *HLA-B*15:02* and *CYP2C9* phenotype/genotype

<i>HLA-B*15:02</i> Phenotype	CYP2C9 Phenotype	Implication	Therapeutic Recommendation	Classification of Recommendation	Considerations
<i>HLA-B*15:02</i> positive	Any CYP2C9 phenotype	Increased risk of phenytoin-induced SJS/TEN	If patient is phenytoin-naïve, do not use phenytoin/fosphenytoin. Avoid carbamazepine and oxcarbazepine.	Strong	Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, and phenobarbital, have weaker evidence linking SJS/TEN with the <i>HLA-B*15:02</i> allele; however, caution should still be used in choosing an alternative agent.
<i>HLA-B*15:02</i> negative	CYP2C9 NM	Normal phenytoin metabolism	If the patient has previously used phenytoin continuously for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of phenytoin in the future. The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4–28 days), and cases usually occur within three months of dosing.	Optional	Previous tolerance of phenytoin is not indicative of tolerance to other aromatic anticonvulsants.
<i>HLA-B*15:02</i> negative	CYP2C9 IM AS 1.5	Slightly reduced phenytoin metabolism; however, this does not appear to translate into increased side effects.	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An <i>HLA-B*15:02</i> negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
<i>HLA-B*15:02</i> negative	CYP2C9 IM AS 1.0	Reduced phenytoin metabolism; Higher plasma concentrations will increase probability of toxicities.	No adjustments needed from typical dosing strategies. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An <i>HLA-B*15:02</i> negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Moderate	
<i>HLA-B*15:02</i> negative	CYP2C9 PM	Reduced phenytoin metabolism; Higher plasma concentrations will increase probability of toxicities.	For first dose, use typical initial or loading dose. For subsequent doses, use approximately 25% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response and side effects. An <i>HLA-B*15:02</i> negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Moderate	
<i>HLA-B*15:02</i> negative	Indeterminate	n/a (not applicable)	For first dose, use typical initial or loading dose. For subsequent doses use approximately 50% less than typical maintenance dose. Subsequent doses should be adjusted according to therapeutic drug monitoring, response, and side effects. An <i>HLA-B*15:02</i> negative test does not eliminate the risk of phenytoin-induced SJS/TEN, and patients should be carefully monitored according to standard practice.	Strong	
<i>HLA-B*15:02</i> negative			n/a	No recommendation	n/a