ARTICLE

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Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of *CYP2C9, HLA-A* and *HLA-B* with anti-epileptic drugs

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By developing evidence-based pharmacogenetics guidelines to optimize pharmacotherapy, the Dutch Pharmacogenetics Working Group (DPWG) aims to advance the implementation of pharmacogenetics (PGx). This guideline outlines the gene-drug interaction of *CYP2C9* and *HLA-B* with phenytoin, *HLA-A* and *HLA-B* with carbamazepine and *HLA-B* with oxcarbazepine and lamotrigine. A systematic review was performed and pharmacotherapeutic recommendations were developed. For *CYP2C9* intermediate and poor metabolisers, the DPWG recommends lowering the daily dose of phenytoin and adjust based on effect and serum concentration after 7–10 days. For *HLA-B*15:02* carriers, the risk of severe cutaneous adverse events associated with phenytoin, carbamazepine, oxcarbazepine, and lamotrigine is strongly increased. For carbamazepine, this risk is also increased in *HLA-B*15:11* and *HLA-A*31:01* carriers. *For HLA-B*15:02*, *HLA-B*15:11* and *HLA-A*31:01* positive patients, the DPWG recommends choosing an alternative anti-epileptic drug. If not possible, it is recommended to advise the patient to report any rash while using carbamazepine, lamotrigine, oxcarbazepine or phenytoin immediately. Carbamazepine should not be used in an *HLA-B*15:02* positive patient. DPWG considers *CYP2C9* genotyping before the start of phenytoin "essential" for toxicity prevention. For patients with an ancestry in which the abovementioned HLA-alleles are prevalent, the DPWG considers *HLA-B*15:02* genotyping before the start of carbamazepine, phenytoin, oxcarbazepine, and lamotrigine "beneficial", as well as genotyping for *HLA-B*15:11* and *HLA-A*31:01* before initiating carbamazepine.

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INTRODUCTION

Pharmacogenetics (PGx) is the study of how genetic variation affects individual medication response. The goal of PGx is to optimize drug therapy and to prevent adverse drug reactions by using this knowledge to guide drug selection and (starting) dose, resulting in safer and more cost-effective pharmacotherapy. Despite its widespread recognition, the implementation of PGx into daily clinical practice remains challenging [1, 2]. To aid clinicians with the implementation of PGx, the Royal Dutch Pharmacists Association (KNMP) established the Dutch Pharmacogenetics Working Group (DPWG) in 2005 [3]. Its goals are to develop PGx informed therapeutic dosing recommendations based on systematic literature review, as well as assist pharmacists and physicians by integrating these recommendations into computerized systems for drug prescription, dispensing, and automated medication surveillance. This guideline serves a dual purpose: it provides the information required for the translation of PGx assay results into the predicted phenotype, and it provides guidance for programming therapeutic recommendations into local clinical decision support systems. For every gene-drug interaction requiring therapy adjustment, the DPWG has additionally provided a clinical implication score, to encourage implementing PGx testing into routine care [4]. The objective of this score is to direct clinicians on whether to order relevant PGx genotyping tests prior to initiating therapy.

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The DPWG is a multidisciplinary group consisting of (clinical) pharmacists, physicians, clinical pharmacologists, epidemiologists, toxicologists, and clinical chemists. The DPWG guidelines are endorsed by the European Association of Clinical Pharmacology and Therapeutics (EACPT), and the European Association of Hospital Pharmacists (EAHP) [5, 6]. To meet the public demand from outside the Dutch health care system, the DPWG guidelines are published in the European Journal of Human Genetics [7–13].

This manuscript presents the gene-drug interactions associated with anti-epileptic drugs. This includes the gene-drug interactions of *CYP2C9* with phenytoin, *HLA-A* with carbamazepine, and *HLA-B* with carbamazepine, lamotrigine, oxcarbazepine, and phenytoin. This guideline starts with background information on the included drugs and on genetic variation in the *CYP2C9, HLA-A* and *HLA-B* genes. Furthermore, the evidence retrieved from a systematic literature search on the gene-drug interactions is presented. A summary of all used references can be found in Supplementary Tables 1–5. Finally, the therapeutic recommendations and the clinical implication scores of the actionable gene-drug interactions are provided and recommendations are compared to other guidelines.

DRUGS: ANTI-EPILEPTIC DRUGS (CARBAMAZEPINE, LAMOTRIGINE, OXCARBAZEPINE, AND PHENYTOIN)

Carbamazepine, lamotrigine, oxcarbazepine, and phenytoin are mainly prescribed for treatment of epilepsy, including the treatment of tonic-clonic seizures and partial seizures. Carbamazepine and phenytoin are also used for the treatment of trigeminal neuralgia and carbamazepine is also used as mood stabilizer in the treatment of bipolar disorder. Phenytoin is primarily metabolized by CYP2C9 and to a lesser extent by CYP2C19 and is characterized by non-linear pharmacokinetics due to saturation of CYP2C9. Due to autoinduction, phenytoin steady state concentrations are reached after 2–3 weeks.

All four anti-epileptic drugs can cause cutaneous adverse drug reactions (cADRs) which are partly HLA associated. These cADRs range from mild reactions such as maculopapular rash to potentially fatal severe cutaneous adverse reactions (SCARS) such as the Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) [14]. Carbamazepine can induce SJS/TEN (in 0.25% of the Han Chinese from Taiwan users and 0.005% of European users) and DRESS (in 0.05% of both Chinese and European users). In 2019, the incidence of phenytoin-induced SJS/TEN and DRESS were estimated to be 0.01–0.1% [15]. The incidence of lamotrigine induced SJS/TEN and DRESS is 0.1% and <0.01%, respectively, while for oxcarbazepine these incidences are estimated at <0.01% and 0.01–0.1% [16, 17].

GENE: *CYP2C9*

CYP2C9, formally known as Cytochrome P450 family 2 subfamily C member 9, is situated on chromosome 10q23.33, has 9 exons, and a size of ~51 kb. It encodes the metabolic enzyme CYP2C9 and is expressed in the liver, duodenum, and small intestine [18]. Over 60 different allelic variants are identified. Each variant is denoted with an asterisk and a number, with *1 designated the wildtype allele. The Pharmacogenomics Working Group of the Association for Molecular Pathology (AMP) has recommended a minimum panel of variant alleles to be tested (Tier 1). These include *CYP2C9* *2, *3, *5, *6, *8, and *11 [19]. *CYP2C9* *2, *5, *8 and *11 alleles result in a decreased enzyme activity, while *3 and *6 result in an inactive or almost inactive enzyme. In Caucasian and Asian populations, *2 and *3 have a relatively high prevalence while *5, *6, *8 and *11 are more prevalent in African populations. Supplementary Table 6 lists the most important allele variants and their predicted effect on the enzyme activity of the CYP2C9 enzyme (including rs-numbers and HGVS nomenclature) and Supplementary Table 7 provides an overview of the frequencies of these alleles.

DISTINGUISHED GENOTYPES AND GENOTYPE GROUPS (PREDICTED PHENOTYPES)

Based on the metabolic capacity of CYP2C9, the DPWG distinguishes three metaboliser phenotypes. Because the metabolic capacity of the two most common alleles, *2 and *3, differs significantly, the intermediate and poor metabolisers are further subdivided based on the presence of these or other alleles, see Table 1. Patients with two alleles with reduced activity are defined as poor metabolisers. This includes, ranked by decreasing metabolic capacity, *2/*2, *2/*3, *3/*3, and also includes two alleles with reduced activity of which at least one allele is no *2 or *3 (PM OTHER). Patients with one allele with reduced enzyme activity, and one allele with normal enzyme activity are categorized as intermediate metabolisers. These are subdivided into (first two ranked according to decreasing metabolic capacity) *1/*2, *1/*3 and IM OTHER, where the allele with reduced function is neither *2 nor *3. The complete "genotype to distinguished genotype (group)/ predicted phenotype translation table", which can be used to program the translation of genotype results into predicted phenotypes in laboratory information systems, can be found in Supplementary Table 8.

GENE: HLA-A AND HLA-B

The *Human Leukocyte Antigen (HLA)* genes are situated on chromosome 6. *HLA-A* is located on chromosome 6p22, while *HLA-B is* located on chromosome 6p21. HLA class I proteins, including HLA-A and HLA-B, are present on almost all cells. Their primary role is to present peptides derived from intracellular proteins to cytotoxic (CD8+) T-cells. HLA-A and HLA-B proteins are involved in the development of delayed hypersensitivity reactions such as SJS/TEN and DRESS. The specific HLA allele is dependent on the drug used. For carbamazepine, oxcarbazepine, lamotrigine and phenytoin, the systematic literature review showed that the *HLA-B*15:02* allele is involved (see the section "General conclusion of evidence"). Besides, for carbamazepine, also *HLA-A*31:01* and *HLA-B*15:11* are involved. The *HLA-A*31:01*, *HLA-B*15:02*, *HLA-B*15:11* sequences are described in GenBank [20–22]. HLA variants cannot be described using HGVS-nomenclature as no allele in the highly polymorphic HLA genes has been assigned the wildtype allele. Only minimal amounts of HLA are required to generate an immune response, suggesting the absence of a gene-dose effect. Therefore, the DPWG does not distinguish between individuals who are heterozygous or homozygous for HLA alleles (see Table 1 and Supplementary Table 8). The *HLA-B*15:02* allele is mostly common in South and East Asian populations except for Japan (see Supplementary Table 9). In other populations such as Caucasian or African populations this allele is rare. *HLA-A*31:01* is prevalent globally. *HLA-B*15:11* is rare in most populations but is more prevalent in East Asian populations.

GENE-DRUG INTERACTION

CYP2C9—phenytoin

Polymorphisms in the *CYP2C9* gene lead to an enzyme with reduced activity. This may increase the plasma concentration and may also lead to an increased risk of phenytoin side effects such as ataxia, nystagmus, slurred speech, or sedation. An overview of the phenytoin metabolism and excretion is depicted in Fig. 1 [23, 24].

HLA—carbamazepine, lamotrigine, oxcarbazepine, phenytoin

HLA proteins have an essential role in the pathogenesis of delayed hypersensitivity reactions such as (SJS/TEN) and DRESS. These hypersensitivity reactions have been observed for carbamazepine, lamotrigine, oxcarbazepine, and phenytoin. Because specific HLA alleles are involved in drug hypersensitivity reactions and it cannot be predicted which, both the specific HLA allele or alleles involved and the likelihood they confer for a hypersensitivity reaction

Table 1. Distinguished genotypes and genotype groups or predicted phenotypes (pharmacogenetic contraindications) for *CYP2C9* and *HLA*.

Gene	Genotype groups/phenotypes predicted based on genotype (pharmacogenetic contraindications)	Genotype group description	Examples of genotypes
CYP2C9	*1/*1	Two alleles with normal enzyme activity	*1/*1, *1/*9
	*1/*2	*2 and one allele with normal enzyme activity	*1/*2
	*1/*3	*3 and one allele with normal enzyme activity	*1/*3
	IM OTHER (intermediate metaboliser, other genotype)	One allele with decreased enzyme activity other than *2 and *3 and one allele with normal enzyme activity	*1/*8, *1/*11
	*2/*2	Two *2 alleles	*2/*2
	*2/*3	One *2 and one *3 allele	*2/*3
	*3/*3	Two *3 alleles	*3/*3
	PM OTHER (poor metaboliser, other genotype)	Two alleles with decreased enzyme activity, of which at least one other than *2 or *3	*2/*8, *3/*11, *8/*11
HLA-A	*3101 positive	Heterozygous or homozygous carrier of HLA-A*31:01	*31:01/*31:01, *01:01/*31:01, *02:01/*31:01
	*3101 negative	No carrier of HLA-A*31:01	*01:01/*01:01, *01:01/*02:01, *02:01/*02:01,
HLA-B	*1502 positive	Heterozygous or homozygous carrier of HLA-B*15:02	*15:02/*15:02, *07:02/*15:02, *08:01/*15:02
	*1502 negative	No carrier of HLA-B*15:02	*07:02/*07:02, *07:02/*08:01, *08:01/*08:01
	*1511 positive	Heterozygous or homozygous carrier of HLA-B*15:11	*15:11/*15:11, *07:02/*15:11, *08:01/*15:11
	*1511 negative	No carrier of HLA-B*15:11	*07:02/*07:02, *07:02/*08:01, *08:01/*08:01

The alleles mentioned in the table above are characterized by the following sequence variations: *CYP2C9**1: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations). *CYP2C9**2: rs-number: rs1799853; NM_000771.4: c.430C > T; NP_000762.2: p.Arg144Cys; NC_000010.11: g.94942290C > T. *CYP2C9**3: rs-number: rs1057910; NM_000771.4: c.1075A > C; NP_000762.2: p.Ile359Leu; NC_000010.11: g.94981296A > C. *CYP2C9**8: rs-number: rs7900194; NM_000771.4: c.449G > A; NP_000762.2: p.Arg150His; NC_000010.11: g.94942309G > A. *CYP2C9**9: rs-number: rs2256871; NM_000771.4: c.752A > G; NP_000762.2: p.His251Arg; NC_000010.11: g.94949217A > G. *CYP2C9**11: rs-number: rs28371685; NM_000771.4: c.1003C > T; NP_000762.2: p.Arg335Trp; NC_000010.11: g.94981224C > T. *HLA-A*31:01*: the *HLA-A*31:01* sequence is described in GenBank: M84375.1. *HLA-B*15:02*: the *HLA-B*15:02* sequence is described in GenBank: D50293.1. *HLA-B*15:11*: the *HLA-B*15:11* sequence is described in GenBank: D50294.1.

should be derived from literature. Alleles consistently and repeatedly showing an association in literature with hypersensitivity for the anti-epileptic drug (see Supplementary Tables 2–5), were identified as being involved and are elaborated on in this manuscript.

SUPPORTING BODY OF EVIDENCE

A thorough description of the methods used for the preparation of this guideline, including literature search, assessment and therapeutic recommendations has been described previously [3, 25]. In summary, a systematic review of the literature was performed after which relevant articles were summarized. Based on the summarized information, a scientist of the Royal Dutch Pharmacists Association (KNMP) (mainly MN) proposed therapeutic recommendations which were reviewed and approved by the entire DPWG. The literature searches can be found in the Supplementary Material. All included publications were scored for level of evidence and clinical relevance. For the level of evidence, a five-point scale was used with 0 being the lowest possible quality and 4 being the highest quality, i.e., high quality meta-analyses or studies. The impact of the clinical effect was scored using a seven-point scale ranging from AA$^{\#}$ to F. This clinical impact scale (AA$^{\#}$-F) runs parallel to the Common Terminology Criteria for Adverse Events (CTCAE); where CTCAE grade 1 severity is equal to clinical relevance score B and CTCAE grade 5 severity is equal to the clinical relevance score F (death). The clinical relevance score additionally includes the scores AA$^{\#}$, AA, and A. AA$^{\#}$ is defined as a positive clinical effect, e.g., better efficacy, AA as no kinetic or clinical effect, and A as a kinetic effect or not clinically relevant effect, e.g., an asymptomatic bradycardia. The summaries and scores of the articles can be found in Supplementary Tables 1–5. Two independent DPWG members checked the summary of all articles and their scores. In a meeting with all members of the DPWG, all summaries and scores were discussed. If scores differed, consensus was reached within this meeting and a score was agreed upon.

GENERAL CONCLUSIONS OF EVIDENCE

CYP2C9-phenytoin

A total of 36 articles and two Summaries of Product Characteristics were included in the systematic review. Multiple human studies found an increased incidence of side effects for *CYP2C9**1/*3, *1/*2, *2/*2, *2/*3 and *3/*3. There was one case of *6/*6 (PM OTHER) with side effects on phenytoin. One study found an IM OTHER patient with an 1.8 fold increase in dose- and weight-corrected phenytoin trough concentrations. Based on these data, the DPWG decided that the *CYP2C9*-phenytoin interaction requires a therapeutic recommendation for all variant genotypes and predicted phenotypes. Details are provided in Supplementary Table 10 and the summary of reviewed articles in Supplementary Table 1.

HLA-phenytoin

Phenytoin-induced SJS/TEN occurs more frequently in the first 3 months after initiating therapy in *HLA-B*15:02* carriers. The calculated risk of phenytoin-induced SJS/TEN in patients with HLA-

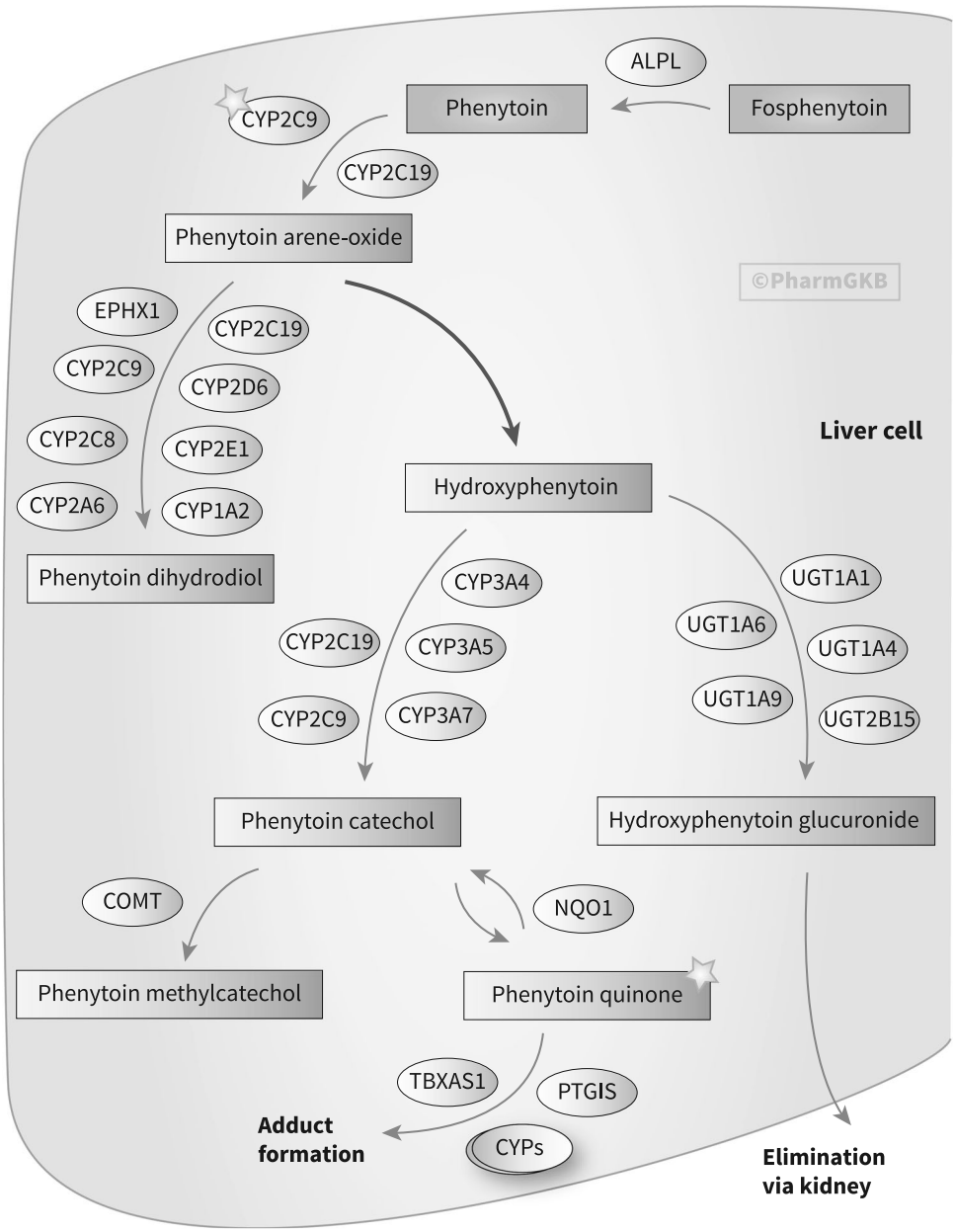

Fig. 1 Overview of phenytoin metabolism and excretion. The purple rectangles depict drugs while the purple/yellow rectangles depict the metabolites as formed by the genes depicted as ovals [23, 24].

B*1502 is 0.65%. Four meta-analyses of 10, 7, 4 and 2 case-control studies respectively found an increased risk of SJS/TEN in *HLA-B*15:02* carriers (OR = 3.5–4.3) while one meta-analysis with 2 case-control studies found no effect. Three meta-analyses of 5, 3 and 2 case-control studies found no effect of *HLA-B*15:02* on the risk of DRESS. Out of ten case-control studies with at least 10 cases of phenytoin-induced serious cutaneous adverse side effects, 4 found an increased risk in *HLA-B*15:02* carriers for serious cutaneous adverse side effects. Because life-threatening adverse events should be avoided, if possible, even if both the incidence and the risk increase are low, the DPWG decided that a warning is necessary. Details are provided in Supplementary Table 11 and the summary of reviewed articles in Supplementary Table 2.

HLA-carbamazepine

Carbamazepine can induce SJS/TEN and DRESS. The risk of carbamazepine-induced SJS/TEN is strongly increased the first 3 months after initiating therapy in patients with the *HLA-B*15:02* allele. The risk of carbamazepine-induced SJS/TEN in these patients is 1.8–7.7%. Six meta-analyses showed that the *HLA-B*15:02* allele strongly increased the risk for carbamazepine-induced SJS/TEN (OR = 27–138). In addition, one study in Han Chinese showed that excluding *HLA-B*1502* positive patients from therapy with carbamazepine, resulted in reduction of the incidence of carbamazepine-induced SJS/TEN from 0.23 to 0%. For this reason, the DPWG concluded that that therapy adjustment is required for this gene-drug interaction. Although an association was found between *HLA-B*15:02* and SJS/TEN induced by phenytoin, lamotrigine and oxcarbazepine, the risk for SJS/TEN in *HLA-B*15:02*-positive users was ~10-fold higher for carbamazepine than for the other three anti-epileptic drugs.

Patients carrying *HLA-A*31:01* have an increased risk for DRESS and SJS/TEN in the first 3 months of use. The risk of DRESS in patients carrying *HLA-A*31:01* is 0.89%. Seven meta-analyses (2 for

Table 2. Pharmacotherapeutic recommendations.

Drug	Gene	Genotype-(group) or phenotype	Therapeutic recommendation
Phenytoin	CYP2C9	*1/*2	- The loading dose does not need to be adjusted. - For the other doses, use 75% of the standard dose and assess the dose based on effect and serum concentration after 7–10 days. - Advise the patient to report side effects (such as ataxia, nystagmus, slurred speech, sedation or rash).
		*1/*3	- The loading dose does not need to be adjusted. - For the other doses, use 70% of the standard dose and assess the dose based on effect and serum concentration after 7–10 days. - For patients with gene variant HLA-B*1502, take the extra increase in the risk of life threatening cutaneous adverse events into account while weighing the risks of phenytoin against the benefits. - Dose reduction probably does not lower this risk. - Advise the patient to report side effects (such as ataxia, nystagmus, slurred speech, sedation or, especially in Asian patients, rash).
		*2/*2	- The loading dose does not need to be adjusted. - For the other doses, use 50% of the standard dose and assess the dose based on effect and serum concentration after 7–10 days. - Advise the patient to report side effects (such as ataxia, nystagmus, slurred speech, sedation or rash).
		*2/*3	- The loading dose does not need to be adjusted. - For the other doses, use 50% of the standard dose and assess the dose based on effect and serum concentration after 7–10 days. - Advise the patient to report side effects (such as ataxia, nystagmus, slurred speech, sedation or rash).
		*3*3	- The loading dose does not need to be adjusted. - For the other doses, use 40% of the standard dose and assess the dose based on effect and serum concentration after 7–10 days. - For patients with gene variant HLA-B*1502, take the extra increase in the risk of life threatening cutaneous adverse events into account while weighing the risks of phenytoin against the benefits. - Dose reduction probably does not lower this risk. - Advise the patient to report side effects (such as ataxia, nystagmus, slurred speech, sedation or, especially in Asian patients, rash).
		IM OTHER	- The loading dose does not need to be adjusted. - For the other doses, use 70–75% of the standard dose and assess the dose based on effect and serum concentration after 7–10 days. - Advise the patient to report side effects (such as ataxia, nystagmus, slurred speech, sedation or rash).
		PM OTHER	- The loading dose does not need to be adjusted. - For the other doses, use 40–50% of the standard dose and assess the dose based on effect and serum concentration after 7–10 days. - Advise the patient to report side effects (such as ataxia, nystagmus, slurred speech, sedation or rash).
	HLA-B	HLA-B*1502 positive	- Carefully weigh the risk of SJS/TEN against the benefits. - Avoid phenytoin if an alternative is possible. - Carbamazepine carries a 10-fold higher risk of SJS/TEN for these patients and is therefore not an alternative. - A comparable risk has been reported for lamotrigine as for phenytoin. The same applies for oxcarbazepine, but the most severe forms (SJS/TEN overlap and TEN) are not observed with oxcarbazepine. - if it is not possible to avoid phenytoin, advise the patient to report any skin rash immediately.
Carbamazepine	HLA-B	HLA-B*1502 positive	- Avoid carbamazepine. - Phenytoin, lamotrigine and oxcarbazepine also pose an increased risk of SJS/TEN in these patients, but the final risk is 5–10-fold lower for these medicines than for carbamazepine. Furthermore, in the case of oxcarbazepine, the most severe forms (SJS/TEN overlap and TEN) have not been observed.
		HLA-B*1511 positive	- Carefully weigh the risk of SJS/TEN against the benefits - Avoid carbamazepine if an alternative is possible. - If it is not possible to avoid carbamazepine, advise the patient to report any skin rash immediately.
	HLA-A	HLA-A*3101 positive	- Carefully weigh the risk of DRESS and SJS/TEN against the benefits - Avoid carbamazepine if an alternative is possible. - If it is not possible to avoid carbamazepine, advise the patient to report any skin rash immediately.

Table 2. continued

Drug	Gene	Genotype-(group) or phenotype	Therapeutic recommendation
Oxcarbazepine	HLA-B	HLA-B*1502 positive	- Carefully weigh the risk of SJS against the benefits. - Avoid oxcarbazepine if an alternative is possible. - Carbamazepine carries a 10-fold higher risk of SJS/TEN in these patients and is therefore not an alternative. - In these patients, phenytoin and lamotrigine carry a similar risk of SJS/TEN as oxcarbazepine, but more severe forms of SJS/TEN (SJS/TEN overlap and TEN) are also observed with these medicines. Therefore, they are also not suitable as alternatives. - If it is not possible to avoid oxcarbazepine, advise the patient to report any skin rash immediately.
Lamotrigine	HLA-B	HLA-B*1502 positive	- Carefully weigh the risk of SJS/TEN against the benefits. - Avoid lamotrigine if an alternative is possible. Carbamazepine carries a much higher risk of SJS/TEN in these patients and is therefore not an alternative. - A similar risk has been reported for phenytoin as for lamotrigine. The same applies to oxcarbazepine, but the most severe forms (SJS/TEN overlap and TEN) have not been observed with oxcarbazepine. - If it is not possible to avoid lamotrigine, advise the patient to report any skin rash immediately.

DRESS, 3 for SJS/TEN, 1 for maculopapular exanthema (MPE) and 1 for all cutaneous adverse events) and a meta-analysis of genome wide association studies (GWAS) for severe cutaneous adverse events (DRESS, SJS/TEN or acute generalized exanthematous pustulosis (AGEP)) showed that this allele increased the risk for carbamazepine-induced cutaneous adverse events. The meta-analyses found the strongest effect for DRESS (OR = 10.2–13.2 for all ethnicities and OR = 24.1 for Europeans). For SJS/TEN, the OR was 3.9–8.0 (7.9 for Europeans). For all severe cutaneous adverse events, the OR was 8.0 in Europeans. For MPE and all cutaneous adverse events, the OR was respectively 7.2 and 9.5. In addition, one study in Japanese showed that excluding the 17.7% *HLA-A*3101* carriers from therapy with carbamazepine, resulted in reduction of the incidence of carbamazepine-induced cutaneous adverse events from 3.4% to 2.0%. Although the positive predictive value for DRESS is not high, the increase in risk is considerable and life-threatening adverse events should be avoided if possible. For these reasons, the DPWG concluded that therapy adjustment is useful for the *HLA-A*31:01*-carbamazepine interaction.

Also patients with the *HLA-B*15:11* allele have an increased risk of SJS/TEN in the first 3 months after initiating therapy. The risk of carbamazepine-induced SJS/TEN in *HLA-B*15:11* carriers is estimated to be 0.18–4.8%. Two meta-analyses showed that this allele increased the risk for carbamazepine-induced SJS/TEN (OR = 14–17). Because the increase in risk is considerable and life-threatening adverse events should be avoided if possible, the DPWG concluded that therapy adjustment is useful for the *HLA-B*15:11*-carbamazepine interaction. Details are provided in Supplementary Table 12 and the summary of reviewed articles in Supplementary Table 3.

HLA-lamotrigine

The incidence of lamotrigine-induced SJS/TEN is 1 in 1000 users. For *HLA-B*15:02* carriers, this risk is 2.4–7.9 fold increased resulting in a risk for *HLA-B*15:02* carriers of 0.24–0.79%. Four meta-analyses, of which two identical (with a total of 12, 17, 17 and 54 Asian SJS/TEN cases per meta-analysis), one case-control study with 28 Iranian SJS/TEN cases, and two pooled case-control studies with a total of 7 Han Chinese SJS/TEN cases showed that carriership of this allele increased the risk of lamotrigine-induced SJS/TEN. A meta-analysis of two studies with a total of 7 Han Chinese SJS/TEN cases and four case-control studies with respectively 22, 7, 6, and 6 Chinese SJS/TEN cases, did not find an increased risk for *HLA-B*15:02* carriers. Although the evidence for this gene-drug interaction is not strong, the DPWG considers it to be sufficient. Because life-threatening adverse events should be avoided if possible, even if both the incidence and the risk increase are low, the DPWG decided that a warning is necessary. Details are provided in Supplementary Table 13 and the summary of reviewed articles in Supplementary Table 4.

HLA-oxcarbazepine

Oxcarbazepine-induced SJS occurs more often in patients with *HLA-B*15:02*. The calculated risk of oxcarbazepine-induced SJS in patients with *HLA-B*15:02* is 0.73%. Two case-control studies (with 20 and 3 cases of SJS respectively) and a meta-analysis of the largest case-control study and a case description revealed that this allele increased the risk of oxcarbazepine-induced SJS (OR = 26–81, with the OR decreasing with increasing number of cases investigated). In addition, 4 of the 7 reported Asian cases with oxcarbazepine-induced SJS were carriers of *HLA-B*15:02*. Oxcarbazepine induced SJS/TEN appeared somewhat less severe than SJS/TEN induced by other aromatic anti-epileptic drugs. The specified cases all concerned SJS. Descriptions of cases with TEN or with SJS/TEN-overlap were lacking.

A meta-analysis of 3 case-control studies with 23 SJS and 6 DRESS cases showed an increase in the risk of SJS or DRESS (OR = 18). The relatively low OR in this study is possibly caused by the inclusion of the DRESS cases. The study from which these cases originated, did find an association of *HLA-B*15:02* with SJS, but not with DRESS. Although the evidence for this gene-drug interaction is not very strong, the DPWG considers it to be sufficient. Because severe adverse events requiring hospitalization should be avoided if possible, even if the incidence is low, the DPWG decided that a warning is necessary. Details are provided in Supplementary Table 14 and the summary of reviewed articles in Supplementary Table 5.

PHARMACOTHERAPEUTIC RECOMMENDATIONS

An overview of the DPWG therapeutic recommendations for the anti-epileptic drugs carbamazepine, lamotrigine, oxcarbazepine, and phenytoin is presented in Table 2. A more detailed version of the recommendations, including their rationale and clinical consequences is provided in Supplementary Tables 10–14.

CYP2C9-phenytoin

For *CYP2C9* intermediate and poor metabolisers the DPWG recommends lowering the daily dose to 70–75% and 40–50% of

the normal dose respectively and to adjust the dose based on effect and serum concentration after 7–10 days. The DPWG calculates dose adjustments to optimize treatment based on the difference in exposure with normal metabolisers. Calculated dose adjustments are subsequently "rounded off" to make application in clinical practice more feasible. Dose adjustments are calculated based on (dose-corrected) AUC or steady-state plasma concentrations of phenytoin, or based on the dose needed to achieve plasma concentrations within the therapeutic range. Due to the longer half-life in patients with a CYP2C9 variant, it will take longer to reach steady-state. For this reason, the DPWG recommends measuring plasma concentrations in patients with a CYP2C9 variant 7–10 days after treatment start or dose adjustment, instead of the normal 4–5 days lag time for therapeutic drug monitoring.

HLA—carbamazepine, oxcarbazepine, lamotrigine, and phenytoin

For *HLA-B*15:02* positive patients, the recommendation for carbamazepine is to select an alternative. If possible, selecting an alternative is also recommended for *HLA-A*31:01* and *HLA-B*15:11* after carefully weighing the risk of DRESS and SJS/TEN against the benefits of using carbamazepine. Although an association was found between *HLA-B*1502* and SJS/TEN induced by phenytoin, lamotrigine and oxcarbazepine, the risk for SJS/TEN in *HLA-B*15:02*-positive users of these anti-epileptic drugs was ~10-fold lower compared to *HLA-B*15:02*-positive users of carbamazepine. In addition, the most severe forms (SJS/TEN-overlap and TEN (both with more than 30% skin detachment) have not been observed for oxcarbazepine. For lamotrigine, oxcarbazepine, and phenytoin the recommendation is therefore to choose an alternative, if an alternative is possible. If an alternative is not possible, it is recommended to advise the patient to report any rash immediately.

Supplementary Tables 15–19 present an overview of suggested pop-up or look-up texts for electronic prescribing systems for pharmacists and physicians that can be used to program alerts into the clinical decision support system (CDSS). The guidelines and background information are available on KNMP.nl [26].

IMPLICATIONS FOR CLINICAL PRACTICE

There is ongoing discussion regarding the selection of pharmacogenetic tests for drug-gene pairs that should be implemented in routine health care. Points of debate include the strength of evidence that is necessary supporting the effectiveness and cost-effectiveness of pre-therapeutic genetic testing and reimbursement [27, 28]. To overcome this inconclusiveness and to assist clinicians in in their decision-making process regarding the necessity of PGx testing prior to initiating a new therapy, the DPWG has developed the clinical implementation score. The pre-therapeutic PGx results for a certain actionable drug-gene pair can be scored as: essential, beneficial, or potentially beneficial. The development of these categories and the systematic scoring criteria have been previously discussed [4]. In short, implications for clinical practice are based on a list of four criteria: the clinical effect associated with the gene-drug interaction, the level of evidence supporting the clinical effect, the effectiveness of the intervention in preventing the clinical effect (including the number needed to genotype) and the PGx information included in the drug-label. The criteria of the clinical implication score and the scores provided for each of these criteria by the DPWG can be found in Supplementary Table 20.

CYP2C9—phenytoin

The DPWG considers *CYP2C9* genotyping of patients before starting phenytoin maintenance therapy to be essential for drug safety. They recommend performing genotyping to guide dose selection before maintenance therapy has been initiated.

HLA—phenytoin, *HLA*—lamotrigine and *HLA*—oxcarbazepine

The DPWG considers *HLA-B*15:02* genotyping of patients of Asian descent, other than Japanese, before starting phenytoin, lamotrigine and/or oxcarbazepine to be beneficial for drug safety. The DPWG advises to consider genotyping these patients before (or directly after) drug therapy has been initiated to guide drug selection.

HLA—carbamazepine

The DPWG considers *HLA-B*15:02* genotyping of patients of Asian descent, other than Japanese, *HLA-A*31:01* genotyping, and *HLA-B*15:11* genotyping of patients of Han Chinese, Korean, Thai, or Japanese descent before starting carbamazepine to be beneficial for drug safety. It is advised to consider genotyping these patients before (or directly after) drug therapy has been initiated to guide drug selection. Based on the clinical implication score *HLA-B*15:02* genotyping was scored as "essential". However, the DWPG decided to downgrade the score, because there might not be an equivalent alternative for carbamazepine and because of the low positive predictive value of *HLA-B*15:02* for severe cutaneous adverse events. Therefore, pre-therapeutic genotyping will not only diminish severe adverse events but will also strongly increase the number of patients who are falsely denied a commonly used drug for the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder.

DIFFERENCES BETWEEN AVAILABLE GUIDELINES

To the best of our knowledge, for oxcarbazepine and phenytoin, only the DPWG and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have formulated pharmacogenetics guidelines. For carbamazepine, the DPWG, CPIC as well as the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) have a guideline available.

CPIC

Differences between CPIC and DPWG methodology, the conversion of genotype to phenotype, and the recommendations have previously been described in detail [29, 30]. The current DPWG and CPIC guidelines for phenytoin differ regarding the therapeutic recommendations of *CYP2C9*. For patients with *1/*2 or IM OTHER: DPWG recommends to reduce the maintenance dose to 75% and 70–75% of the normal dose respectively while CPIC recommends no adjustments for these patients [31]. CPIC recommends to use ~75% of the normal dose as maintenance dose for *1/*3, *2/*2 and IM OTHER while DPWG recommends respectively 70%, 50% and 70–75%. CPIC recommends 50% of the regular maintenance for *2/*3, *3/*3 and *CYP2C9* PM OTHER while the DPWG recommends respectively 50%, 40% and 40–50% of the regular maintenance dose. CPIC indicates that if both *HLA-B*15:02* and *CYP2C9* genotypes are known, the *HLA-B*15:02* genotype should be considered first, then *CYP2C9* genotype. However, if you follow the opposite order, the route is longer, but the final result is the same. The CPIC and DPWG guidelines on oxcarbazepine and carbamazepine are similar, with the exception of a DPWG recommendation for carbamazepine and *HLA-B*15:11*, whereas CPIC does not due to lack of data [32]. In addition, the CPIC recommendation for *HLA-B*15:02* is less stringent ("if possible, choose an alternative" instead of "choose an alternative"). Also, CPIC does not have a guideline for lamotrigine and *HLA* because of limited evidence.

CPNDS

The CPNDS gives the same recommendation in *HLA-B*15:02* positive patients as the DPWG, but a more stringent recommendation in

*HLA-A*31:01* positive patients ("choose an alternative" instead of "if possible, choose an alternative") [33].

The CPNDS recommends genotyping for *HLA-B*15:02* and *HLA-A*31:01* for all carbamazepine naïve patients prior to initiation of the pharmacotherapy. For *HLA-B*15:02* this recommendation is classified as level A (strong) and for *HLA-A*31:01* as level B (moderate) [33]. This recommendation is stronger than the DPWG recommendation to consider genotyping the patient before (or directly after) drug therapy has been initiated.

Disclaimer

The Pharmacogenetics Working Group of the KNMP (DPWG) formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendationcannot be followed due to practical restrictions, e.g., therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

DATA AVAILABILITY

All data and material are either included in the Supplementary Information or publicly available (i.e., the published articles, PubMed). The guidelines and background information are available on KNMP.nl [26] and will be available on PharmGKB.org.

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AUTHOR CONTRIBUTIONS

LENM drafted the manuscript. MN performed most of the literature searches and article summaries and suggested clinical decision support texts. HJG supervised drafting of the manuscript and contributed to conceiving the work and interpretation of the results. BS had the clinical decision support texts translated in English and published them. NBV, AB, EJFH, AR, GAR, RHNS, JJS, DT, and RW contributed to conceiving the work and interpretation of the results. VHMD led the meetings in which the DPWG decided about the article summaries and clinical decision supports texts and contributed to conceiving the work and interpretation of the results. In addition, all authors revised the manuscript and approved the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

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