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SYSTEMATIC REVIEW

Impact of Genetic Polymorphisms on Phenytoin Pharmacokinetics and Clinical Outcomes in the Middle East and North Africa Region

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Abstract

Background Genetic polymorphisms are known to influence outcomes with phenytoin yet effects in the Middle East and North Africa region are poorly understood.

Objectives The objective of this systematic review was to evaluate the impact of genetic polymorphisms on phenytoin pharmacokinetics and clinical outcomes in populations originating from the Middle East and North Africa region, and to characterize genotypic and allelic frequencies within the region for genetic polymorphisms assessed.

Methods MEDLINE (1946–3 May, 2017), EMBASE (1974–3 May, 2017), Pharmacogenomics Knowledge Base, and Public Health Genomics Knowledge Base online databases were searched. Studies were included if genotyping and analyses of phenytoin pharmacokinetics were performed in patients of the Middle East and North Africa region. Study quality was assessed using a National Institutes of Health assessment tool. A secondary search identified studies reporting genotypic and allelic frequencies of assessed genetic polymorphisms within the Middle East and North Africa region.

Results Five studies met the inclusion criteria. *CYP2C9*, *CYP2C19*, and multidrug resistance protein 1 C3435T variants were evaluated. While *CYP2C9*2* and *3* variants significantly reduced phenytoin metabolism, the impacts of *CYP2C19*2* and *3* variants were unclear. The multidrug resistance protein 1 CC genotype was associated with drug-resistant epilepsy, but reported impacts on phenytoin pharmacokinetics were conflicting. Appreciable variability in minor allele frequencies existed both between and within countries of the Middle East and North Africa region.

Conclusions *CYP2C9* decrease-of-function alleles altered phenytoin pharmacokinetics in patients originating from the Middle East and North Africa region. The impacts of *CYP2C19* and multidrug resistance protein 1 C3435T variants on phenytoin pharmacokinetic and clinical outcomes are unclear and require further investigation. Future research should focus on the clinical outcomes associated with phenytoin therapy.

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Key Points

In patients originating from the Middle East and North Africa region, phenytoin metabolism was significantly decreased by genetic polymorphisms of the cytochrome P450 (CYP) 2C9 enzyme; the impacts of *CYP2C19* and multidrug resistance protein 1 C3435T polymorphisms were unclear.

The impacts of genetic polymorphisms on clinical outcomes associated with phenytoin are not well described in the literature and warrant further investigation.

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1 Introduction

Since the discovery of its anticonvulsant properties in 1938 [1], phenytoin has been widely used for both the acute management and chronic prevention of seizures [2, 3]. Its primary mechanism in treating and preventing seizures is through preferential binding to inactivated sodium channels, which inhibits neuronal generation of sustained high-frequency bursts of action potentials [4]. Phenytoin has a narrow therapeutic index, with 40–80 μmol/L (10–20 mg/L) being the recommend therapeutic range; however, this is often difficult to achieve due to wide interpatient variability in dose response and concentrations achieved from a given dose, as well as the capacity-limited metabolism of phenytoin [5, 6].

Factors such as patient body size and composition, serum albumin levels, comorbid disease states, and drug–drug interactions have been shown to contribute to the interpatient variability of the effect of phenytoin. Additionally, genetic polymorphisms of enzymes and transporters targeting phenytoin pharmacokinetics have been recognized as a significant contributor to the exhibited interpatient variability [5–7]. Evidence linking the cytochrome P450 (CYP) 2C9 polymorphism to the concentration of phenytoin has led to the development of guidelines tailoring the initial dose of phenytoin based on the *CYP2C9* genotype [7–9]. Though not as well studied, there is evidence to suggest that polymorphisms of *CYP2C19* may also significantly impact the concentration of phenytoin and warrant dosage adjustments [7, 10]. Additional enzymes and drug transporters have been investigated, but the implications of these polymorphisms are not well established [7, 11].

Cited studies investigating the impact of genetic polymorphisms on the pharmacokinetics and pharmacodynamics of phenytoin have predominantly been conducted in patients of European, Indian, and East Asian origin; however, few studies have been conducted in patients originating from the Middle East and North Africa (MENA) region [11, 12]. As a result of migration and significant admixture of European, Asian, and African populations dating back over thousands of years, the MENA region has a unique genetic diversity, with great variability in minor allelic frequencies (MAF) of genetic polymorphisms [13–15]. Even within the MENA region itself, there is great diversity. For example, while populations of Arabic and Iranian origin have both European and African ancestry, those of Iranian origin also have a significant level of Asian admixture [15]. Furthermore, as a result of consanguinity, some countries within the MENA region may exhibit relatively less genetic diversity [15]. Therefore, results of previous studies conducted in patients of different ethnic origins are not readily generalizable, and a focused review of the literature addressing genetic polymorphisms and the associated implications regarding phenytoin in individuals originating from the MENA region is warranted.

The primary objective of this systematic review was to evaluate the impact of genetic polymorphisms on phenytoin pharmacokinetics, specifically in populations originating from the MENA region. Secondary objectives were to evaluate the impact of genetic polymorphisms on clinical outcomes associated with phenytoin therapy, as well as to characterize the genotypic and allelic frequencies of each polymorphism identified in the primary search within the MENA region.

2 Methods

2.1 Search Strategy

A comprehensive search of the MEDLINE (1946–May 2017), EMBASE (1974–May 2017), Pharmacogenomics Knowledge Base (PharmGKB), and Public Health Genomics Knowledge Base (PHGKB) online databases was conducted to identify existing literature addressing the primary research question. An example of the search terms and Boolean connectors used in MEDLINE is outlined in the Appendix, and is reflective of the search strategy used in EMBASE. References of pertinent studies were also searched manually to identify additional studies not identified in the electronic search. For each polymorphism assessed in the studies that met the inclusion criteria, a secondary search was conducted to identify the reported variant MAF, specifically within the MENA region.

2.2 Selection of Studies

Studies were eligible for inclusion if participants originated from the MENA region, received at least one dose of phenytoin with a subsequent pharmacokinetic analysis, and were genotyped for a polymorphism that may impact phenytoin pharmacokinetics. Although understanding the impact of genetic polymorphisms on clinical outcomes associated with phenytoin therapy was a secondary objective of this review, eligible studies were not required to report on clinical outcomes. Two reviewers (RD, KW) screened potentially relevant studies by title and abstract, and then by full text to exclude any studies that did not fulfill the inclusion criteria. For the review regarding variant MAF, studies were included if participants originated from the MENA region and were genotyped for one or more of the polymorphisms assessed in the primary review.

2.3 Data Extraction and Management

Data from each included study were extracted and tabulated. Extracted data included: author, year of publication, study population (country of origin, practice setting, inclusion and exclusion criteria), sample size, study design, genetic polymorphism(s) assessed, phenytoin dosing, assay methods for phenytoin serum concentrations and genotyping, MAF of the genetic polymorphism(s), as well as final study results. For studies also including participants from outside of the MENA region, only data regarding participants who originated from the MENA region were extracted.

Similarly, for studies included in the review of variant MAF, the following data were extracted: author, country of origin, sample size, genetic polymorphism(s) assessed, as well as the computed genotypic and allelic frequencies. If studies eligible for inclusion also reported data from participants originating outside of the MENA region, only data on participants who originated from the MENA region were extracted.

2.4 Quality Assessment

The quality of each study included in the primary review was assessed by two reviewers (RD, KW) using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, from the National Institutes of Health, National Heart, Lung, and Blood Institute [16].

2.5 Data Synthesis

Data extracted from the included studies were assessed descriptively. If two or more studies reported the genotypic or allelic frequency of a given polymorphism, data from all studies were reported. The highest and lowest frequencies extracted for each polymorphism were assessed to estimate variants' MAF range within the MENA region.

3 Results

3.1 Study Selection

A total of five studies fulfilled the inclusion criteria for this review, as depicted in Fig. 1. Of the 30 articles screened for eligibility, ten were excluded for subjects not originating from the MENA region [17–26], seven were excluded for phenytoin concentrations not being assessed [27–33], five were excluded for both subjects not originating from the MENA region and phenytoin concentrations not being assessed [34–38], one was excluded for genetic polymorphisms not being assessed [39], and two

were excluded for being poster abstracts [40, 41]. Between the five included studies, CYP2C9*1, *2, and *3; CYP2C19*1, *2, and *3; and multidrug resistance protein 1 [MDR1, also known as ATP-binding cassette sub-family B member 1 (ABCB1)] C3435T polymorphisms were evaluated. The study population, phenytoin regimen, and genetic polymorphism(s) assessed varied between studies; summaries of each study are provided in Table 1.

Upon assessment, each of the five studies was rated to be of poor quality. The ratings of each study against the 14 quality assessment tool criteria are summarized in Table 2. Factors contributing to poor quality ratings included: unclear descriptions of study subject selection, introducing potential for selection bias; insufficient reporting of study subjects' baseline characteristics; relatively small sample sizes, limiting the power to assess the impact of polymorphic genotypes with low frequencies; and absence of adjustments for potential confounders that could affect phenytoin pharmacokinetics (e.g., antiepileptic polytherapy, concomitant medications, comorbid medical conditions, or serum albumin levels) or clinical outcomes (e.g., seizure control at baseline, seizure etiology, or type of seizure).

A total of 82 studies were conducted within the MENA region and investigated the prevalence of CYP2C9, CYP2C19, and/or MDR1 variant alleles [27, 29, 42–121]. These studies were included in the secondary part of the review. Specific single nucleotide polymorphisms reviewed were: CYP2C9*1, *2, and *3; CYP2C19*1, *2, and *3; and MDR1 (ABCB1) C3435T. The study populations and computed genotypic and allelic frequencies for CYP2C9, CYP2C19, and MDR1 are summarized in Tables 3, 4, and 5, respectively.

3.2 CYP2C9

CYP2C9 accounts for 70–90% of phenytoin metabolism [122], with (S)-5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH) being the major resultant metabolite [5, 7]. Although up to 60 different CYP2C9 haplotypes have been identified, CYP2C9*2 and *3 are the two most common allelic variants [123, 124]. Both variants exhibit reduced functional activity, with losses of 29 and 94% enzymatic activity reported for CYP2C9*2 and *3, respectively, when compared with the wild-type genotype [125, 126]. Three of the included studies investigated CYP2C9 genotypes [42–44].

Aynacioglu et al. [42] genotyped all outpatients and healthy volunteers for CYP2C9, and phenotyped phenytoin through assessment of serum phenytoin and p-HPPH concentrations in a subset of 101 of the Turkish healthy volunteers. Twelve hours following a single dose of phenytoin, serum phenytoin concentrations differed

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of included studies [146]. *MENA* Middle East and North Africa, *PHT* phenytoin
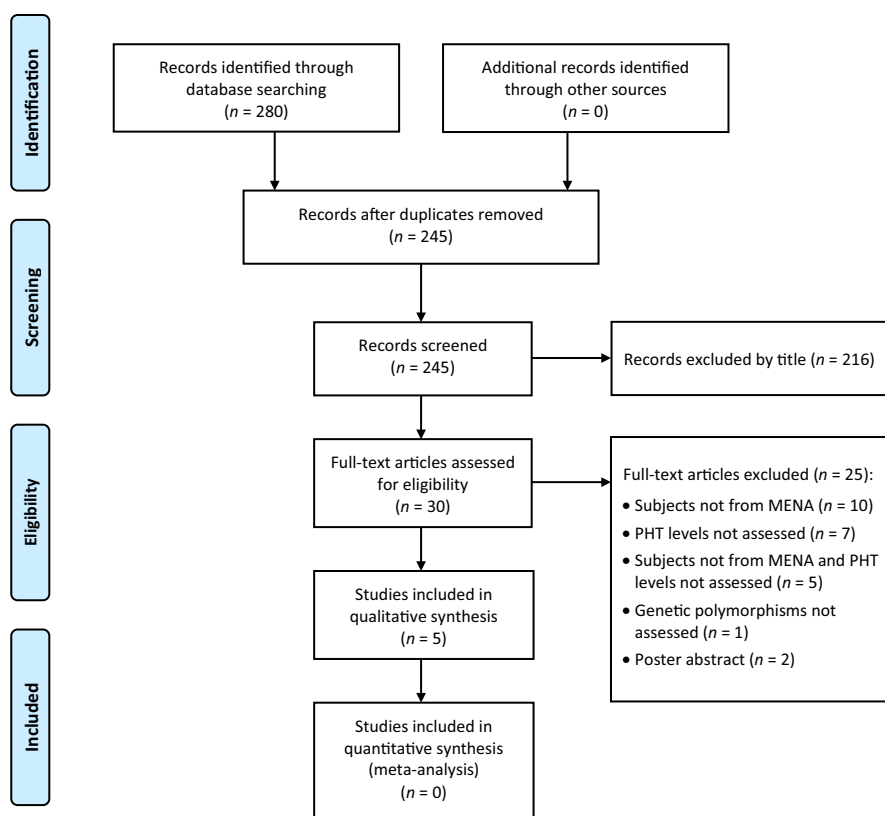
significantly across groups with 0, 1, and 2 loss of function mutations ($p < 0.001$). Study results indicated serum phenytoin concentration in the *CYP2C9*1/*1* wild-type genotype group was significantly lower when compared with *CYP2C9*1/*2*, *CYP2C9*1/*3*, and *CYP2C9*2/*2* genotype groups, with the difference in means being −1.36 mg/L ($p = 0.009$), −1.49 mg/L ($p = 0.001$), and −2.42 mg/L ($p = 0.02$), respectively. Accordingly, results also indicated the ratio of serum p-HPPH-to-phenytoin concentration of the *CYP2C9*1/*1* wild-type genotype group was significantly higher than that of *CYP2C9*1/*2*, *CYP2C9*1/*3*, and *CYP2C9*2/*2* genotype groups, with the difference in means being 0.17 ($p = 0.002$), 0.22 ($p < 0.0001$), and 0.29 ($p = 0.006$), respectively. Differences between wild-type and *CYP2C9*3/*3* genotypes were not compared statistically, as the latter was present in only one individual.

It was identified that data from the 96 healthy Turkish volunteers in the study conducted by Kerb et al. [43] were derived from the 101 volunteers of the Aynacioglu et al. study [42]. Thus, the results regarding influence of *CYP2C9* genotype on measured phenytoin concentrations and the p-HPPH-to-phenytoin ratio are reflected in the aforementioned results [42, 43]. Using these data in a multiple linear regression analysis, Kerb et al. determined that the number of polymorphic *CYP2C9* alleles accounted for 14.1% of variability in phenytoin serum concentrations

[43]. The final regression equation, which also included the number of *MDR1* C3435T alleles, had an $r^2 = 0.154$ ($p = 0.0002$).

Ozkaynakci et al. [44] reported data for 11 different combinations of *CYP2C9* and *CYP2C19* genotypes; therefore, the independent impact of the CYP2C9 genotype on serum phenytoin concentrations was difficult to discern. When compared with the *CYP2C9* and *CYP2C19* wild-type genotype group, *CYP2C9*1/*3, CYP2C19*2/*3* was the only genotype group with a serum phenytoin trough that was significantly different, with a mean concentration that was 20.47 mg/L higher than the wild-type genotype group ($p < 0.001$). The mean serum phenytoin trough of the *CYP2C9*1/*3, CYP2C19*2/*3* genotype group was also significantly higher than several other genotype groups (Table 1). Clinical outcomes associated with *CYP2C9* polymorphisms were not reported and therefore could not be assessed.

3.3 CYP2C19

CYP2C19 accounts for 10–30% of phenytoin metabolism, with greater metabolic contributions as CYP2C9 becomes saturated [122, 127]. CYP2C19 primarily forms the (*R*)-p-HPPH metabolite [5, 7]. Up to 35 different CYP2C19 haplotypes have been identified, of which *CYP2C19*2* and *3* are the two most common null alleles; presence of two

Table 1 Summary of studies assessing the impact of genetic polymorphisms on phenytoin pharmacokinetics and/or clinical outcomes

Study, year	Country/study population	PHT dosing regimen	Genotype(s)/reported allelic frequencies percentage	Pharmacokinetic outcomes	
Aynacioglu et al. [42]	Turkey Outpatients (n = 280); healthy volunteers (n = 218) PHT PK analysis in healthy volunteer subgroup (n = 101)	300 mg PO × 1 Sample collected 12-h post-dose	CYP2C9 Study population *1 = 79.4 *2 = 10.6 *3 = 10 Population included in PHT PK analysis: *1 = 81.7 *2 = 9.4 *3 = 8.9	Genotype CYP2C9*1/*1 CYP2C9*1/*2 CYP2C9*1/*3 CYP2C9*2/*2 CYP2C9*2/*3 CYP2C9*3/*3	Serum PHT, mean mg/L (95% CI) 4.16 (3.86–4.46) 5.52 (4.66–6.39) 5.65 (4.86–6.43) 6.58 (1.64–11.51) Not observed 5.92[a]
				Genotype CYP2C9*1/*1 CYP2C9*1/*2 CYP2C9*1/*3 CYP2C9*2/*2 CYP2C9*2/*3 CYP2C9*3/*3	p-HPPH/PHT ratio (95% CI) 0.43 (0.39–0.47) 0.26 (0.21–0.31) 0.21 (0.18–0.24) 0.14 (0.13–0.14) Not observed 0.02[a]
Kerb et al. [43]	Turkey Healthy volunteers (n = 96)	300 mg PO × 1 Sample collected 12-h post-dose	CYP2C9 *1 = 81.3 *2 = 10.1 *3 = 8.8 CYP2C19 *1 = 88.3 *2 = 11.7 MDR1 (ABCB1) C3435T C = 52.6 T = 47.4	Genotype CYP2C9*1/*1 CYP2C9*1/*2 CYP2C9*1/*3 CYP2C9*2/*2 CYP2C9*2/*3 CYP2C9*3/*3 CYP2C19*1/*1 CYP2C19*1/*2 CYP2C91*2/*2 MDR1 CC MDR1 CT MDR1 TT	Serum PHT, mean mg/L ± SD 4.20 ± 1.25 5.52 ± 1.43 5.54 ± 1.47 6.58 ± 1.99 Not observed 5.92[a] 4.73 ± 1.47 4.49 ± 1.68 4.40 ± 1.41 4.27 ± 1.74 4.85 ± 1.33 4.87 ± 1.36
				Multiple linear regression indicates the number of polymorphic CYP2C9 alleles and MDR1*T alleles account for 14.1 and 1.3% of the variability in phenytoin serum concentrations, respectively (r^2 = 0.154, p = 0.0002)	

Table 1 continued

Study, year	Country/study population	PHT dosing regimen	Genotype(s)/reported allelic frequencies percentage	Pharmacokinetic outcomes
Ebid et al. [46]	Egypt Epilepsy clinic outpatients taking PHT for partial ($n = 43$) or generalized tonic-clonic ($n = 57$) seizures; healthy volunteers from blood bank unit ($n = 50$) PHT phenotyping in epilepsy patients ($n = 100$)	Baseline dose 100 mg PO BID ≥1 year Dose adjustment at 3 months: if drug resistant and C_{tr} <10 mg/L: 150 mg PO TID If drug resistant and C_{tr} 10–14 mg/L: 100 mg PO TID If drug responsive and/or C_{tr} ≥15 mg/L: stop PHT and end follow-up C_{tr} collected pre-dose	*MDR1 (ABCB1) C3435T* Drug responsive C = 36.5 T = 63.5 Drug resistant C = 74.6 T = 25.4 Healthy volunteers C = 48 T = 52	(see below)

Pharmacokinetic outcomes

3-month evaluation ($n = 100$)

	Responsive, $n = 18$ (%)	Resistant, $n = 82$ (%)
Serum PHT C_{tr} mg/L		
<10	50	79.3
10 to <15	44.4	17.1
≥15	6.7	3.7
Genotype		
CC	0	48.8
CT	44.4	40.2
TT	55.6	11

6-month evaluation ($n = 79$)

	Responsive, $n = 19$ (%)	Resistant, $n = 60$ (%)
Serum PHT C_{tr}, mg/L		
<10	10.5	15
10 to <15	31.6	68.3
≥15	57.9	16.7
Genotype		
CC	26.3	58.3
CT	47.4	36.7
TT	26.3	5

AUC_{0-12h} area under the concentration–time curve from 0 to 12 h post-dose, *AVM* arteriovenous malformation, *BID* twice daily, *CBZ* carbamazepine, *CI* confidence interval, *Cl* clearance, *C_max* maximum plasma concentration, C_{tr} trough concentration, *CYP* cytochrome P450, *LTG* lamotrigine, *PHT* phenytoin, *p-HPPH* 5-(p-hydroxyphenyl)-5-phenylhydantoin metabolite, *PK* pharmacokinetic, *PO* orally by mouth, *SD* standard deviation, *SEM* standard error of the mean, *t½* half-life, *TID* three times daily, *T_max* time to *C_max*, *VPA* valproic acid

[a] From one individual, cannot calculate 95% CI, SD, or SEM

[b] Mean (SEM) reported

Table 2 Summary of methodological quality ratings of included studies[a]

Criteria	Aynacioglu et al. [42]	Kerb et al. [43]	Ozkaynakci et al. [44]	Alhazzani et al. [45]	Ebid et al. [46]
1. Research question or objective clearly stated	Yes	No	Yes	Yes	Yes
2. Study population clearly specified and defined	No	No	No	No	No
3. At least 50% of eligible persons participate	NR	NR	NR	NR	NR
4a. All subjects selected from same or similar population and same time period	CD	CD	CD	CD	CD
4b. Inclusion and exclusion criteria pre-specified and uniformly applied	NR	NR	Yes	Yes	Yes
5. Sample size justification, power description, or variance and effect estimate provided	No	No	No	No	No
6. Exposure[b] of interest measured prior to outcome(s) being measured	NA	NA	NA	NA	NA
7. Timeframe sufficient to see association between exposure[b] and outcome if it existed	Yes	Yes	Yes	Yes	Yes
8. Study examined different levels of exposure[b] as related to outcome	NA	NA	NA	NA	NA
9. Exposure[b] measures clearly defined, valid, reliable, and implemented consistently	Yes	CD	Yes	CD	Yes
10. Exposure[b] assessed more than once over time	NA	NA	NA	NA	NA
11. Outcome measures clearly defined, valid, reliable, and implemented consistently	Yes	CD	CD	CD	Yes
12. Outcome assessors blinded to participant exposure status	NA	NA	NA	NA	NA
13. Loss to follow-up after baseline was 20% or less	NA	NA	NA	NA	Yes
14. Key potential confounding variables measured and adjusted for statistically	No	No	No	No	No

CD cannot determine, *NA* not applicable, *NR* not reported

[a] Studies were rated against the 14 criteria of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, from the National Institutes of Health, National Heart, Lung, and Blood Institute [16]

[b] Exposure was defined as study participants' allelic make-up for the polymorphism of interest

null alleles results in a non-functional CYP2C19 enzyme [124, 125]. A third haplotype, *CYP2C19*17*, results in increased expression and activity of the enzyme [125]; however, this haplotype was not assessed in the included studies. Two of the included studies investigated *CYP2C19* genotypes [43, 44].

In the study conducted by Kerb et al. [43], the *CYP2C19* genotype did not significantly affect serum phenytoin concentration ($p = 0.52$) or p-HPPH-to-phenytoin ratio (p value not reported). As with CYP2C9, as a result of Ozkaynakci et al. [44] reporting the data for 11 different *CYP2C9* and *CYP2C19* genotype groups, it is difficult to distinguish the independent impact of *CYP2C19* genotype on serum phenytoin concentrations; therefore, no inferences can be made. As with CYP2C9, clinical outcomes were not reported and therefore could not be assessed.

3.4 MDR1 (ABCB1) C3435T

The *MDR1* (*ABCB1*) gene encodes for human P-glyco-protein, an efflux transporter of which phenytoin is a substrate [128, 129]. The *MDR1* C3435T polymorphism is a silent mutation that decreases transporter expression and alters substrate specificity [130, 131]; therefore, it has the potential to affect substrate absorption and tissue distribution. The resultant impact of this polymorphism on pharmacokinetic and pharmacodynamic outcomes of phenytoin therapy is unclear [7, 130, 132]. Three of the included studies investigated the *MDR1* C3435T polymorphism [43, 45, 46].

Kerb et al. [43] identified that the *MDR1* C3435T genotype did not significantly impact serum phenytoin concentration overall ($p = 0.064$), and the number of *MDR1* T alleles accounted for only 1.3% of the variability in serum phenytoin concentrations in their multiple regression analysis. As discussed previously, the final regression equation had an $r^2 = 0.154$ ($p = 0.0002$). When serum phenytoin concentrations were divided into quartiles (25th percentile: <3.79 mg/L, interquartile range: 3.79–5.79 mg/L, 75th percentile: >5.79 mg/L), the frequency distribution of MDR1 genotype indicated that the *MDR1 CC* genotype was more frequent in the 25th

Table 3 Genotypic and allelic frequencies of *CYP2C9* in the Middle East and North Africa region

References	Country	Study population	Sample size	Genotypic frequencies (%)						Allelic frequencies (%)		
				*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3	*1	*2	*3
[47]	Egypt	Healthy volunteers	247	66.4	19.0	11.7	2.4	0	0.4	81.8	11.9	6.3
[48]	Egypt	Healthy volunteers (n = 154), patients taking maintenance warfarin (n = 46)	200	81.5	4.5	8.5	4.5	0.5	0.5	88.0	7.0	5.0
[49]	Egypt	Warfarin-resistant patients	41	60.9	19.5	19.5	0	0	0	80.4	9.8	9.8
		Warfarin-responsive patients	30	73.3	20.0	6.7	0	0	0	86.7	10.0	3.3
[50]	Egypt	Patients taking maintenance warfarin	63	76.2	7.9	6.3	3.2	0	6.3	83.4	7.1	9.5
[51]	Egypt	Patients taking maintenance warfarin	84	83.3	NA	11.9	NA	NA	4.8	89.3	NA	10.7
[52]	Egypt[a]	Patients taking maintenance warfarin	207	62.6	17.4	11.8	1.0	4.1	1.0	74.2	11.1	8.5
[53]	Iran	Healthy volunteers	200	82.0	10.5	0	7.5	0	0	87.2	12.8	0
[54]	Iran	Healthy volunteers	50	82.0	12.0	6.0	0	0	0	91.0	6.0	3.0
		Patients taking maintenance valproic acid	68	80.9	11.8	4.4	1.5	1.5	0	89.0	8.1	2.9
[55]	Iran	Warfarin-sensitive patients	21	19.0	66.7	14.3	0	0	0	52.4	47.6	NA
		Patients with normal warfarin response	37	75.7	21.6	2.7	0	0	0	86.5	13.5	NA
[56]	Iran	Patients taking maintenance warfarin	100	39.0	41.0	9.0	2.0	9.0	0	64.0	27.0	9.0
[57]	Jordan	Healthy volunteers	263	62.7	21.7	12.2	1.9	1.5	0	79.7	13.5	6.8
[58]	Kuwait	Patients taking maintenance warfarin	108	69.4	21.3	6.5	0	2.8	0	83.4	12.0	4.6
[59]	Libya	Healthy volunteers	161	65.8	14.9	13.7	1.9	2.5	1.2	80.1	10.6	9.3
[60]	Libya	Patients taking maintenance VKA	231	60.6	22.5	10.0	2.2	3.9	0.9	76.8	15.4	7.8
[61]	Morocco	Low-dose acenocoumarol	20	55.0	25.0	5.0	10.0	0	5.0	70.0	22.5	7.5
		Medium-dose acenocoumarol	58	72.4	19.0	6.9	1.7	0	0	85.4	11.2	3.4
		High-dose acenocoumarol	36	94.4	2.8	0	2.8	0	0	95.8	4.2	0
[62]	Oman[a]	Patients taking maintenance warfarin	212	73.6	11.3	8.5	NA	2.4	0.9	84.2	6.8	6.4
[63]	Oman	Patients taking maintenance warfarin	189	80.4	12.7	5.8	1.1	0	0	89.6	7.5	2.9
[64]	Saudi Arabia	Healthy volunteers	131	68.7	26.7	4.6	0	0	0	84.3	13.4	2.3
[65]	Saudi Arabia	Healthy volunteers	192	64.1	17.2	13.0	2.1	2.1	1.6	79.2	11.7	9.1
[66]	Sudan[a]	Patients taking maintenance warfarin	203	71.9	8.9	0	0	0	0	84.0	4.9	0
[67]	Tunisia[a]	Healthy volunteers	258	61.6	19.4	13.2	2.7	3.1	0	77.9	14.0	8.1
[43]	Turkey	Healthy volunteers	96	66.7	13.5	15.6	3.1	0	1.0	81.2	9.9	8.9
[68]	Turkey	Healthy volunteers	64	64.0	14.1	15.6	3.1	0	3.1	78.9	10.2	10.9
[69]	Turkey	Healthy volunteers	85	68.2	11.8	14.1	3.5	1.2	1.2	81.2	10.0	8.8
[42]	Turkey	Healthy volunteers (n = 218), outpatients with variable diagnoses (n = 280)	499	61.7	18.0	17.2	1.0	1.1	0.8	79.4	10.6	10.0
[44]	Turkey	Outpatients of epilepsy clinic	102	78.4	14.7	6.9	0	0	0	89.2	7.4	3.4
[70]	Turkey[a]	Patients taking maintenance warfarin	205	60.0	18.0	13.7	1.5	3.9	1.0	76.8	12.7	9.8
[71]	Turkey	Patients taking maintenance warfarin	100	50.0	21.0	24.0	0	5.0	0	72.5	13.0	14.5
[72]	Turkey	Patients taking maintenance anticoagulant	292	56.5	23.0	8.6	3.0	7.2	1.7	72.2	18.2	9.6

CYP cytochrome P450, *NA* not assessed, *VKA* vitamin-K antagonist, *VPA* valproic acid

[a] Additional CYP2C9 alleles assessed; therefore, percentages do not add to 100%

percentile group ($p \leq 0.001$, χ^2 test). Moreover, while the presence of the *MDR1 TT* genotype reportedly had significant influence on p-HPPH-to-phenytoin ratio ($p < 0.026$), absolute values were not provided and there was considerable overlap in the depicted frequency distribution; therefore, clinical significance of this association cannot be inferred.

Alhazzani et al. [45] identified significant differences between the *CC*, *CT*, and *TT* genotypes (classified as extensive, intermediate, or poor metabolizers, respectively)

Table 4 Genotypic and allelic frequencies of *CYP2C19* in the Middle East and North Africa region

References	Country	Study population	Sample size	Genotypic frequencies (%)						Allelic frequencies (%)		
				*1/ *1	*1/ *2	*1/ *3	*2/*2	*2/ *3	*3/ *3	*1	*2	*3
[67]	Bahrain[a]	Healthy volunteers	75	33.3	33.3	NA	8.0	NA	NA	53.3	26.0	NA
[47]	Egypt	Healthy volunteers	247	78.5	20.2	0.4	0.8	0	0	88.9	10.9	0.2
[73]	Egypt	Male agricultural workers	120	93.3	5.8	NA	0.8	NA	NA	96.2	3.8	NA
[74]	Gaza Strip	Children with hematological malignancy	52	80.8	15.4	1.9	1.9	0	0	89.4	9.6	1.0
		Healthy volunteers	200	86.5	6.5	1.5	3	0.5	2.0	90.5	6.5	3.0
[53]	Iran	Healthy volunteers	200	75.0	22.0	0	3.0	0	0	86.0	14.0	0
[75]	Iran[a]	Healthy volunteers	180	41.7	18.3	NA	2.2	NA	NA	65.3	13.1	0
[27]	Iran	Healthy volunteers of Baluch descent	140	78.6	20.0	0.7	0	0	0.7	88.9	10.0	1.1
[76]	Iran	Patients with erosive reflux esophagitis	82	70.7	24.3	3.7	1.3	0	0	84.8	13.4	1.8
[56]	Iran	Patients taking maintenance warfarin	99	76.8	21.2	0.1	0	0.1	0	87.9	11.1	1.0
[77]	Iran	Patients taking clopidogrel for elective PCI	112	NR						89.0	10.1	0.9
[78]	Iran	Patients with PCI for CAD	43	72.1	23.3	NA	4.7	NA	NA	83.7	16.3	NA
[79]	Iran	Patients with in-stent restenosis while taking appropriate DAPT for PCI	50	86.0	14.0	NA	0	NA	NA	93.0	7.0	NA
		Patients without in-stent restenosis while taking DAPT for PCI	50	92.0	8.0	NA	0	NA	NA	96.0	4.0	NA
[80]	Israel	Healthy volunteers	140	70.7	25.0	1.4	2.9	0	0	83.9	15.4	0.7
[81]	Israel	Volunteers of Yemenite descent	36	77.8	19.4	0	2.8	0	0	87.5	12.5	0
		Volunteers of Bedouin descent	50	76.0	20.0	2.0	2.0	0	0	87.0	12.0	1.0
[57]	Jordan	Healthy volunteers	158	78.5	18.4	0	3.2	0	0	87.7	12.3	0
[82]	Jordan	Healthy male volunteers	78	74.4	19.2	0	6.4	0	0	84.0	16.0	0
[67]	Kuwait[a]	Healthy volunteers	100	41.0	35.0	NA	3.0	NA	NA	61.5	22.0	NA
[83]	Lebanon	Healthy volunteers	161	75.8	20.5	0.6	3.1	0	0	86.3	13.4	0.3
[84]	Saudi Arabia[a]	Healthy volunteers	201	40.3	14.4	NA	0.005	NA	NA	62.9	11.2	NA
[85]	Saudi Arabia	Healthy military recruits	97	NR						87.0	13.0	0
[86]	Saudi Arabia	Patients taking clopidogrel for ACS	90	67.0	3.0	0	32.0	0	0	67.8	32.2	0
[67]	Tunisia[a]	Healthy volunteers	258	47.3	12.8	NA	0.3	NA	NA	69.8	8.9	0
[43]	Turkey	Healthy volunteers	94	78.1	16.7	NA	3.1	NA	NA	88.3	11.7	0
[87]	Turkey	Healthy volunteers	404	76.0	22.3	0.7	1.0	0	0	87.5	12.1	0.4
[44]	Turkey	Outpatients of epilepsy clinic	102	55.9	17.6	10.8	5.9	9.8	0	70.1	19.6	10.3
[88]	Turkey[a]	Children, 2–18 years old	244	44.3	12.3	0	1.2	0	0	65.6	10.0	0
[89]	Turkey	Patients taking clopidogrel for ICVD	51	70.6	25.5	0	3.9	0	0	83.3	16.7	0

ACS acute coronary syndrome, *CAD* coronary artery disease, *CYP* cytochrome P450, *DAPT* dual anti-platelet therapy, *ICVD* ischemic cerebrovascular disease, *MACE* major adverse cardiac event, *NA* not assessed, *NR* not reported, *PCI* percutaneous coronary intervention

[a] Additional CYP2C19 alleles assessed; therefore, percentages do not add to 100%

for the pharmacokinetic parameters of maximum plasma concentration ($p < 0.01$), area under the plasma concentration–time curve from 0 to 12 h post-dose ($p < 0.01$), half-life ($p < 0.01$), and clearance ($p < 0.01$) using one-way analysis of variance. However, post-hoc analyses were not performed to identify which genotypes differed significantly for these parameters. There was no difference between genotype groups for the parameter of time to maximum plasma concentration ($p > 0.05$). The reported values for each genotype are presented in Table 1. Moreover, a significant association between the *MDR1* C3435T genotype and phenytoin response was reported. Non-responders (i.e., phenytoin-resistant patients) had a higher frequency of the *T* allele ($\chi^2 = 9.76$, $p = 0.0017$) and,

Table 5 Genotypic and allelic frequencies of *MDR1* (*ABCB1*) C3435T in the Middle East and North Africa region

References	Country	Study population	Sample size	Genotypic frequencies (%)			Allelic frequencies (%)	
				CC	CT	TT	C	T
[46]	Egypt	Healthy volunteers	50	24.0	48.0	28.0	48.0	52.0
		Patients with drug-responsive epilepsy	37	13.5	46.0	40.5	36.5	63.5
		Patients with drug-resistant epilepsy	63	55.6	38.1	6.3	74.6	25.4
[90]	Egypt	Patients taking clopidogrel for ACS or PCI who experienced MACE	84	39.3	47.6	13.1	63.1	36.9
		Patients taking clopidogrel for ACS or PCI who did not experience MACE	106	37.7	44.3	17.9	59.9	40.1
[91]	Egypt	Patients taking maintenance warfarin	84	29.8	54.8	15.4	57.1	42.9
[92]	Egypt	Patients with hypercholesterolemia	50	38.0	40.0	22.0	58.0	42.0
[93]	Egypt	Patients taking imatinib for newly diagnosed Philadelphia chromosome-positive CML	100	44.0	47.0	9.0	67.5	32.5
[94]	Egypt	Healthy child volunteers	35	28.6	48.6	22.9	47.1	52.9
		Children with immune thrombocytopenia	48	8.3	62.5	27.1	67.6	32.4
[95]	Iran	Patients admitted for primary care	933	31.6	64.5	3.9	49.1	50.9
[96]	Iran	Healthy volunteers	200	23.5	45.0	31.5	46.0	54.0
		Patients with drug-responsive epilepsy	200	16.0	40.0	44.0	36.0	64.0
		Patients with drug-resistant epilepsy	132	25.7	41.7	32.6	46.6	53.4
[97]	Iran	Iranian Azeri Turkish volunteers	92	19.6	53.3	27.2	46.2	53.8
		Iranian Azeri Turkish patients with Behçet's disease	69	18.8	46.4	34.8	42.0	58.0
[98]	Iran	Healthy female volunteers	200	70.5	25.0	4.5	83.0	17.0
		Female patients with breast cancer	100	75.0	16.0	9.0	83.0	17.0
[99]	Iran	Healthy female volunteers	54	18.5	55.6	25.9	47.0	53.0
		Female patients with breast cancer	50	20.0	54.0	26.0	46.3	53.7
[100]	Iran	Healthy female volunteers	77	15.6	58.4	26.0	44.8	55.2
		Female patients with breast cancer	106	15.1	53.7	31.1	42.0	58.0
[101]	Jordan	Healthy volunteers	100	17.0	50.0	33.0	42.0	58.0
[102]	Jordan	Patients of ear, nose, and throat clinic	251	16.3	48.2	35.4	40.4	59.6
[103]	Jordan	Patients receiving methotrexate for RA	159	37.7	45.3	17.0	60.4	39.6
[104]	Jordan	Healthy female volunteers	150	26.7	43.3	30.0	48.3	51.7
		Female patients with breast cancer	150	45.3	41.3	13.3	66.0	34.0
[105]	Lebanon	Children with ALL	127	27.6	44.1	28.3	49.6	50.4
[106]	Morocco	Healthy volunteers	100	39.0	51.0	10.0	64.5	35.5
[107]	Saudi Arabia	Healthy volunteers	179	35.2	45.2	19.6	57.8	42.2
[108]	Saudi Arabia	Healthy female volunteers	100	93.0	5.0	2.0	95.5	4.5
		Female patients with breast cancer	100	73.0	11.0	16.0	78.5	21.5
[45]	Saudi Arabia	Patients with PHT-responsive epilepsy	25	80.0	20.0		88.0	12.0
		Patients with PHT-resistant epilepsy	25	52.0	48.0		70.0	30.0
[43]	Turkey	Healthy volunteers	96	29.2	46.9	24.0	52.6	47.4
[109]	Turkey	Healthy volunteers	107	27.1	41.1	31.8	47.7	52.3
[110]	Turkey	Healthy volunteers	174	28.2	46.0	25.9	51.1	48.9
		Patients with CBZ-responsive epilepsy	53	30.2	54.7	15.1	57.5	42.5
		Patients with CBZ-resistant epilepsy	44	29.5	59.1	11.4	59.1	40.9
[29]	Turkey	Children with drug-responsive epilepsy	83	26.5	45.8	27.7	49.4	50.6
		Children with drug-resistant epilepsy	69	24.6	43.5	31.9	46.4	53.6
[111]	Turkey	Patients receiving fentanyl for spinal anesthesia	83	28.9	54.2	16.9	56.0	44.0

Table 5 continued

References	Country	Study population	Sample size	Genotypic frequencies (%)			Allelic frequencies (%)	
				CC	CT	TT	C	T
[112]	Turkey	Patients with normal CAG	85	27.1	41.2	31.8	47.6	52.4
		Patients with CAD found on CAG	113	27.4	48.7	23.9	51.8	48.2
[113]	Turkey	Healthy male volunteers	102	26.5	49.0	24.5	51.0	49.0
		Male individuals with primary infertility	192	27.6	57.3	15.1	56.3	43.7
[114]	Turkey	Healthy volunteers	130	25.4	44.6	30.0	47.7	52.3
		Patients with familial Mediterranean fever	142	16.9	59.9	23.2	46.8	53.2
[115]	Turkey	Healthy volunteers	250	27.2	42.4	30.4	48.4	51.6
		Patients with familial Mediterranean fever	309	20.4	55.3	24.3	48.1	51.9
[116]	Turkey	Patients with familial Mediterranean fever	41	3.7	54.2	43.4	29.2	70.8
[117]	Turkey	Renal transplant recipients taking tacrolimus	92	30.4	47.8	21.7	54.3	45.7
[118]	Turkey	Renal transplant recipients taking cyclosporine who did not develop gingival hyperplasia	114	27.2	44.7	28.1	49.6	50.4
		Renal transplant recipients taking cyclosporine who developed gingival hyperplasia	40	32.5	37.5	30.0	51.3	48.7
[119]	Turkey	Patients taking clozapine who did not develop agranulocytosis	91	29.7	53.8	16.5	56.6	43.4
		Patients taking clozapine who developed agranulocytosis	10	20.0	60.0	20.0	50.0	50.0
[120]	Turkey	Patients with non-small-cell lung cancer	79	24.1	62.0	13.9	55.1	44.9
[121]	Turkey	Healthy volunteers	150	NR			52.3	47.7
		Patients with colorectal cancer	103	NR			61.2	38.8

ACS acute coronary syndrome, *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CAD* coronary artery disease, *CAG* coronary angiography, *CBZ* carbamazepine, *CML* chronic myeloid leukemia, *MACE* major adverse cardiac event, *NA* not assessed, *NR* not reported, *PCI* percutaneous coronary intervention, *PHT* phenytoin, *RA* rheumatoid arthritis

accordingly, the *CT* or *TT* genotypes ($\chi^2 = 4.37$, $p = 0.036$). The odds ratio (OR) calculated from the identified frequencies was significant for the allelic frequency [OR 3.14; 95% confidence interval (CI) 1.42–7.05], but not for the genotypic (OR 3.69; 95% CI 0.90–5.81).

Ebid et al. [46] did not identify a significant association between drug resistance or responsiveness and phenytoin concentrations overall, but reported associations between the *MDR1 CC* genotype and the likelihood of drug-resistant patients having serum phenytoin trough concentrations below or in the lower half of therapeutic range at the 3- and 6-month evaluations. Whether the *MDR1* C3435T genotype influences the efficacy and toxicity of phenytoin in epilepsy management was also explored. Overall, patients who were drug resistant (i.e., had seizure recurrence in the preceding 3 months) were more likely to have the *MDR1 CC* genotype than the *MDR1 TT* genotype when compared with patients responsive to therapy (55.5 vs. 13.5%, $\chi^2 = 24.99$; $p < 0.0001$). Moreover, as would be expected, within the drug-resistant group, seizures occurred at higher frequency in patients with serum phenytoin trough <10 mg/L, with average seizure frequencies of 4.4 and 3.7 at 3 and 6 months, respectively ($p < 0.0001$).

3.5 Genotypic and Allelic Frequencies Within the MENA Region

Variant MAF of *CYP2C9*, *CYP2C19*, and *MDR1 (ABCB1)* C3435T have been investigated in a variety of settings and study populations across the MENA region. Studies from 11 different countries were identified for both *CYP2C9* and *CYP2C19*, and seven countries for *MDR1 (ABCB1)* C3435T; study populations and computed genotypic and allelic frequencies for each polymorphism are summarized in Tables 3, 4, and 5, respectively. Overall, there was appreciable variability in MAF both between and within countries of the MENA region for each of *CYP2C9*, *CYP2C19*, and *MDR1 (ABCB1)* C3435T. For example, in studies assessing subjects of Turkish origin, the reported *CYP2C19*3* MAF ranged from 0 to 10.3% [43, 44, 87–89].

4 Discussion

The purpose of this systematic review was to evaluate the role of genetic polymorphisms on phenytoin pharmacokinetics and clinical outcomes specifically in populations

originating from the MENA region, and to characterize assessed polymorphism variant MAF within the region. Recognizing and understanding factors that contribute to interpatient variability in pharmacokinetics, pharmacodynamics, and associated clinical outcomes is essential to providing patient-individualized pharmacotherapy and disease management. In the management of epilepsy and seizure disorders, the significant role of genetic polymorphisms as one such factor has received increasing recognition, with phenytoin being an antiepileptic drug of particular interest, owing to its unique pharmacokinetic and pharmacodynamic profile [5, 6, 17–26, 35, 38–46, 127, 133, 134]

4.1 CYP2C9

Findings of the studies included in this review indicate that the reduced functional capacity of CYP2C9 enzymes with CYP2C9*2 and CYP2C9*3 variant alleles results in significantly higher serum phenytoin concentrations [42–44]. This difference was significant after only a single dose of phenytoin in healthy volunteers included in the studies by Aynacioglu et al. [42] and Kerb et al. [43]. Although the absolute difference between the wild-type genotype and those with one or two reduced function alleles was only in the range of 1.32–2.42 mg/L, owing to the reduced functional capacity of enzymes with variant alleles, it is reasonable to surmise that the absolute difference in phenytoin concentrations would likely be of clinical significance with repeat dosing [5]. This notion is supported by an in-vitro study of CYP2C9 polymorphisms, wherein *2 and *3 allelic variants decreased maximal velocity by 29 and 79%, respectively, and while the *2 variant did not affect the Michaelis constant, the *3 variant increased it fourfold [126].

Ozkaynakci et al. [44] reported a statistically significant difference between the wild-type and CYP2C9*1/*3, CYP2C19*2/*3 genotype groups. However, five of the 11 reported genotype groups had frequencies of only 0.98–2.94%, which likely limited the power of the study to detect differences between the wild-type and other genotype groups. Moreover, patients were required to have been taking phenytoin for only 7 days. Therefore, it is possible that some patients were not yet at steady state when phenytoin trough concentrations were drawn, and that absolute differences in concentrations would be statistically and/or clinically significant over time [5]. This is especially noteworthy in those with CYP2C9*2 or *3 alleles, in whom reduced functional capacity may significantly prolong the time necessary to achieve steady-state concentrations [5, 46]. As well, patients were not on a fixed dose of phenytoin; therefore, knowing the mean dose

within each genotype group or having a serum concentration adjusted for mean dose in each genotype group would allow for assessment of this as a potential confounder. Although the impact of polytherapy was explored, the study was underpowered to appropriately assess this outcome. Thus, these results do not provide a clear demonstration of the impact of CYP2C9*2 and *3 allelic variants on phenytoin pharmacokinetics.

The impact of CYP2C9 variants have been more clearly demonstrated in studies conducted in non-MENA populations. In a cohort of Japanese pediatric patients, when controlling for CYP2C19 polymorphisms, patients with the CYP2C9*1/*3 genotype required phenytoin maintenance doses that were 37.3% lower than those with the wild-type genotype to achieve target concentrations of 15–20 mg/L [10]. Similarly, in a sample of Dutch patients, those with at least one CYP2C9*2 or *3 allele required phenytoin maintenance doses that were 37% lower to achieve target concentrations of 10–20 mg/L [24]. A study of patients originating from India indicated that those with the CYP2C9*1/*3 genotype were more likely than the wild-type genotype to have serum phenytoin concentrations >20 mg/L (OR 4.8; 95% CI 1.89–12.17; p 0.001), despite receiving comparable maintenance doses of phenytoin (5.4 vs. 5.1 mg/kg/day; $p = 0.16$) [133]. In addition to the impact of CYP2C9 polymorphisms on phenytoin pharmacokinetics in non-MENA populations, it also had an effect on phenytoin safety outcomes. A case-control study of Thai patients demonstrated that, when on comparable maintenance phenytoin doses, patients with the CYP2C9*1/*3 genotype were more likely to develop phenytoin-induced severe cutaneous adverse reactions (i.e., Stevens–Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms) within 12 weeks of initiating therapy than those with the wild-type genotype (OR 14.52; 95% CI 1.18–∞; p 0.044) [134]. This association is supported by findings of a meta-analysis conducted in Asian populations, wherein the CYP2C9*3 allele was associated with an increased risk of phenytoin-induced severe cutaneous reactions (OR 11.0; 95% CI 6.2–18.0; $p < 0.00001$) [17]. Furthermore, in a case-control study of Tamilian patients, when adjusting for phenytoin maintenance dose, patients with the CYP2C9*1/*3 genotype were significantly more likely to experience phenytoin-induced neurological toxicity (e.g., ataxia, slurred speech, lethargy, nystagmus) when compared with wild-type genotype (adjusted OR 15.3; 95% CI 5.8–40.3; p 0.0001) [22].

Ultimately, the significant impact of CYP2C9*2 and *3 allelic variants on phenytoin pharmacokinetics and risk of adverse effects when standard doses are administered has led to development of genotype-specific recommendations.

It is suggested that initial doses of phenytoin be reduced by 25% in patients with one variant allele (i.e., CYP2C9*1/*2 or *1/*3) and by 50% in patients with two variant alleles (i.e., CYP2C9*2/*2, *2/*3 or *3/*3) [8].

4.2 CYP2C19

Results of this review suggest that CYP1C19*2 and *3 allelic variants, on their own, did not significantly impact the pharmacokinetics of phenytoin. In the single-dose study by Kerb et al. [43], using the same rationale as discussed with CYP2C9, although CYP2C19*1/*2 and *2/*2 genotypes were not associated with significantly different phenytoin serum concentrations, owing to the non-functional nature of *2 alleles, it is possible that statistically and clinically differences would arise after repeat dosing [5].

For results regarding CYP2C19 reported by Ozkaynakci et al. [44], previously discussed limitations affecting interpretation of results regarding CYP2C9 also apply. Both studies included in this review were likely underpowered to assess the impact of CYP2C19 polymorphisms specifically. Moreover, because CYP2C19 accounts for only 10–30% of phenytoin metabolism [122, 127], decreased or loss of functional capacity may be less likely to significantly affect phenytoin serum concentrations when compared with CYP2C9 allelic variants with reduced function.

Evidence from studies conducted in non-MENA populations suggest that CYP2C19 allelic variants may significantly impact pharmacokinetics of phenytoin. In the previously described Japanese cohort, those with CYP2C9 wild-type genotype and one variant CYP2C19 allele (i.e., CYP2C19*1/*2 or *1/*3) required phenytoin doses 13.1% lower than patients with wild-type genotypes of both CYP2C9 and CYP2C19 to achieve target concentrations ($p < 0.01$), while those with two variant CYP2C19 alleles (i.e., CYP2C19*2/*2, *2/*3, or *3/*3) required doses 28.1% lower ($p < 0.001$) [10]. Regarding clinical outcomes, in the study conducted in Tamilian patients, when adjusting for maintenance dose, patients with CYP2C19*2/*2 genotype were significantly more likely to experience phenytoin-induced neurological toxicity when compared with wild-type genotype (adjusted OR 3.0; 95% CI 1.3–7.0; p 0.01) [22]. Evidence from studies assessing both CYP2C9 and CYP2C19 genotypes suggest additive impact on phenytoin concentrations when variant genotypes of both enzymes are present [20, 22]. Although official guidelines have not been developed for dosage adjustments in patients with CYP2C19 allelic variants, recommendations for both pediatric and adult patients have been suggested based on the combination of both CYP2C9 and CYP2C19 genotypes [10, 20].

4.3 MDR1 (ABCB1) C3435T

The reported impact of the MDR1 C3435T genotype on phenytoin pharmacokinetics in this review was inconsistent, and results in all three studies [43, 45, 46] may have been confounded because of aforementioned factors such as concomitant medications, comorbid conditions, and serum albumin levels, among other patient-specific factors.

Kerb et al. [43] reported no significant association between MDR1 genotype and serum phenytoin concentrations overall. Although post-hoc analysis identified a significant association between the MDR1 CC genotype and serum phenytoin concentrations in the 25th percentile, the association is likely of limited clinical significance because of the narrow concentration range defined by the three classes of low, medium, and high. Unlike CYP2C9 and CYP2C19, transporters encoded by MDR1 are not involved in phenytoin metabolism; therefore, it is unclear whether repeat dosing over time would significantly impact the observed degree of difference in phenytoin serum concentrations between genotype groups. Moreover, although presence of MDR1 T alleles accounted for 1.3% of variability in phenytoin serum concentrations, the clinical relevance of this is questionable, especially considering the final regression equation could account for only 15.4% of observed variability [43].

In contrast, results reported by Alhazzani et al. [45] indicate all pharmacokinetic parameters, with the exception of time to maximum plasma concentration, were significantly affected by the MDR1 C3435T genotype. In the absence of post-hoc analyses of the one-way analysis of variance, which genotypes significantly differed for these parameters cannot be confirmed; however, the results trend toward the MDR1 CC genotype group being different. Of note, the classification of extensive, intermediate, and poor metabolizer to describe the MDR1 C3435T genotype is misleading, as proteins encoded by MDR1 are involved in substrate absorption and distribution, not metabolism [129–131]. The trend of increased maximum plasma concentration, area under the plasma concentration–time curve from 0 to 12 h post-dose, half-life, and clearance in subjects with one or more T alleles holds face validity, as this variant is associated with lower levels of transporter expression [130], which, at the level of the intestine, would result in less phenytoin being effluxed from systemic circulation back into the intestinal lumen. The distributions of responders and non-responders across the extensive, intermediate, and poor metabolizer categories were not reported; therefore, associations between the MDR1 C3435T genotype, phenytoin pharmacokinetics, and resultant clinical outcomes could not be assessed.

The clinical significance of the association between serum phenytoin level and *MDR1* C3435T genotype reported by Ebid et al. [46] is unclear. Specifically, at the 3-month evaluation, there was no significant association between phenytoin responsiveness and serum concentration overall, while at the 6-month evaluation, a 'higher' concentration in the drug-responsive group was not defined and whether or not weight adjusting the doses mitigated reported differences was not explored.

Reported associations between the *MDR1* C3435T genotype and drug resistance reported in this review are conflicting [45, 46]. Historically, associations between drug-resistant epilepsy and overexpression of transporters encoded by *MDR1* have been reported [135–137]. Despite this, several limitations must be considered when interpreting the clinical outcomes reported by Ebid et al. [46]. Foremost, distribution of seizure type within the drug-responsive and drug-resistant groups was not reported, nor adjusted for in the results. This is notable, as there is evidence to suggest phenytoin may aggravate generalized seizures [3]. Additional potential confounders, such as baseline seizure control and concomitant antiepileptic drugs, were also not adjusted for. It is unclear if appropriate corrections were made for multiple statistical analyses; thus, it is possible that identified associations were the result of chance.

The association of *MDR1* C3435T genetic polymorphisms and drug-resistant epilepsy in general (as opposed to phenytoin specifically) was assessed within Iranian patients [33]. The *MDR1 CC* wild-type genotype was significantly more frequent in drug-resistant patients, and associations were also made with adult age and female sex; however, the latter two associations may have resulted from performing multiple statistical analyses. The investigators attempted to address confounders such as baseline etiology and seizure type through univariate analyses; however, because baseline characteristics were so different between study groups, residual confounding likely remained [33]. Two studies conducted in Turkish patients with seizure disorders did not find a significant association between the *MDR1* C3435T genotype and drug resistance [29, 110]. More recently, a meta-analysis of studies conducted in Asian, Caucasian (under which populations originating from the MENA region were classified), and Indian populations investigated the role of *MDR1* gene haplotypes in antiepileptic drug response [132]. Initial results indicated that the presence of the T variant of *MDR1* C3435T may be associated with lower rates of drug resistance. Once corrected for multiple statistical analyses, there was no significant association overall, but a significant association remained in Caucasian patients (*T* vs. *C* allele, OR 0.83; 95% CI 0.71–0.96; *p* = 0.01) [132]. One hypothesis regarding inconsistency in positive associations

found between *MDR1* genotypes and responsiveness to antiepileptic drugs is that the gene falls within a significant block of high linkage disequilibrium [138]. Therefore, it is possible that the associations identified are not the result of the *MDR1* polymorphism itself, but to an alternative gene within the linkage disequilibrium block [138].

4.4 Genotypic and Allelic Frequencies Within the MENA Region

Variability in genotypic and allelic frequencies of *CYP2C9*, *CYP2C19*, and *MDR1* C3435T both between and within the MENA countries for which data were identified was not unexpected. Key factors contributing to this variability were likely small sample sizes and selective patient populations in whom many of the studies were conducted. The allelic frequencies of *CYP2C9*2* and *3*, as well as *CYP2C19*2* and *3* were comparable to those reported for Middle Eastern populations [139, 140]. Similar population data for the *MDR1* C3435T polymorphism were not available for comparison, nor were comparative data specific to North Africa populations.

Ethnicity significantly affects distributions of variants [124] and contributes to differences in MAF reported for populations outside of the MENA region for each of *CYP2C9* [48, 50, 53, 57, 65, 67, 70, 139], *CYP2C19* [27, 53, 57, 67, 140], and *MDR1* C3435T [132, 141, 142]. This emphasizes the importance of population-specific studies assessing genetic polymorphisms.

4.5 Limitations

This review has several limitations that must be considered when interpreting the results. Foremost, in the primary analysis, only three different countries within the MENA region were represented by study populations, with three of five studies being in subjects of Turkish origin. The genotypic diversity across MENA countries as well as the small sample size of the included studies, therefore limit the generalizability of this review. Moreover, only three of the five studies were conducted in patients with seizure disorder, of which only one assessed clinical outcomes, thereby limiting ability to make clinical inferences. The two healthy volunteer studies (which used data from the same subjects) were based on a single dose of phenytoin; therefore, they did not reflect the potential impact of genetic polymorphisms on the steady-state pharmacokinetics of phenytoin or the influence of the non-linear capacity-limited metabolism of phenytoin. Furthermore, all five studies had poor methodological quality and were likely not powered to compare differences between genotypes and alleles of relatively low frequencies. Regarding the review of genotypic and allelic frequencies, the small

select study populations and resultant variability in frequency estimates limit generalizability.

4.6 Future Directions

Identified limitations of this review highlight the need for future studies to investigate the impact of genetic polymorphisms on the pharmacokinetics of phenytoin and associated clinical outcomes, specifically in patients with epilepsy and seizure disorders. Although the impacts of CYP2C9*2 and *3 allelic variants on phenytoin metabolism and the risk of adverse effects have been recognized and dosage modification guidelines developed [8, 9], the potential impacts of CYP2C19*2 and *3 allelic variants have not been established and warrant further investigation. Moreover, owing to the limitations of individual studies, the association between the MDR1 C3435T genotype and drug-resistant epilepsy as well as phenytoin pharmacokinetics remains to be elucidated. To address these questions, future studies must be appropriately powered to assess differences between genotypes of low frequencies, and account for known confounding factors. Furthermore, studies should be designed to look at both pharmacokinetic and clinical outcomes once phenytoin concentrations have achieved a steady state. If possible, studies should be conducted in patient populations originating from countries of the MENA region that have not yet been assessed.

Future research may also focus on investigating the prevalence of the HLA-B*15:02 allele and its impact on the risk of phenytoin-induced severe cutaneous adverse reactions (i.e., Stevens–Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms) in populations originating within the MENA region. The presence of this allele has been associated with an increased risk of phenytoin-induced severe cutaneous adverse reactions [38, 143–145], resulting in pharmacogenetic guidelines recommending against the use of phenytoin in patients who are HLA-B*15:02 carriers [8].

5 Conclusion

Results of this review indicate the reduced functional capacities of CYP2C9*2 and *3 allelic variants significantly decrease phenytoin metabolism in patients originating from the MENA region. The impacts of CYP2C19 and MDR1 C3435T polymorphisms on phenytoin pharmacokinetics and clinical outcomes in this population are unclear and require further investigation. Future research should focus on better understanding the impact of genetic polymorphisms on clinical outcomes associated with phenytoin therapy.

Appendix: MEDLINE search strategy

1. MENA.mp.
2. exp Africa, Northern/ or "Middle East and North Africa".mp. or exp Middle East/
3. Afghanistan.mp. or exp Afghanistan/
4. Bahrain.mp. or exp Bahrain/
5. Djibouti.mp. or exp Djibouti/
6. Egypt.mp. or exp Egypt/
7. Algeria.mp. or exp Algeria/
8. Iran.mp. or exp Iran/
9. exp Iraq/ or Iraq.mp.
10. Israel.mp. or exp Israel/
11. Jordan.mp. or exp Jordan/
12. Kuwait.mp. or exp Kuwait/
13. Lebanon.mp. or exp Lebanon/
14. Libya.mp. or exp Libya/
15. Morocco.mp. or exp Morocco/
16. Oman.mp. or exp Oman/
17. Palestine.mp.
18. West Bank.mp.
19. Gaza.mp.
20. Qatar.mp. or exp Qatar/
21. Saudi Arabia.mp. or exp Saudi Arabia/
22. Somalia.mp. or exp Somalia/
23. exp South Sudan/ or exp Sudan/ or Sudan.mp.
24. Syria.mp. or exp Syria/
25. Tunisia.mp. or exp Tunisia/
26. exp Turkey/ or Turkey.mp.
27. United Arab Emirates.mp. or exp United Arab Emirates/
28. Yemen.mp. or exp Yemen/
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. Polymorphism.mp. or exp Polymorphism, Genetic/ or exp Polymorphism, Single Nucleotide/
31. Pharmacogenetics.mp. or exp Pharmacogenetics/
32. Pharmacogenomics.mp.

33. cytochrome p450.mp. or exp Cytochrome P-450 Enzyme System/
34. CYP2C9.mp. or exp Cytochrome P-450 CYP2C9/
35. CYP2C19.mp. or exp Cytochrome P-450 CYP2C19/
36. CYP3A4.mp. or exp Cytochrome P-450 CYP3A/
37. CYP2B6.mp. or exp Cytochrome P-450 CYP2B6/
38. CYP1A2.mp. or exp Cytochrome P-450 CYP1A2/
39. CYP2E1.mp. or exp Cytochrome P-450 CYP2E1/
40. CYP2C8.mp. or exp Cytochrome P-450 CYP2C8/
41. exp Cytochrome P-450 CYP2A6/ or CYP2A6.mp.
42. exp Glucuronosyltransferase/ or UGT.mp.
43. UGT1A1.mp.
44. UGT1A4.mp.
45. UGT1A6.mp.
46. UGT1A9.mp.
47. P-glycoprotein.mp. or exp P-Glycoprotein/
48. multi drug resistance protein.mp. or exp Multidrug Resistance-Associated Proteins/ or exp ATP-Binding Cassette Transporters/
49. exp P-Glycoproteins/ or exp P-Glycoprotein/ or MDR1.mp.
50. ABCB1.mp.
51. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52. phenytoin.mp. or exp Phenytoin/
53. antiepileptic.mp. or exp Anticonvulsants/
54. exp Epilepsy/ or epilepsy.mp.
55. 52 or 53 or 54
56. 29 and 51 and 55

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