

Comparison of the effects of CYP450 polymorphisms on the metabolism of efavirenz; a network meta-analysis study

ARTICLE INFO

ABSTRACT

Article Type

Systematic Review

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Received: 22 December 2023 Accepted: 19 January 2024 e Published: 31 August 2024 Pharmacogenetics plays a crucial role in personalized treatment. This field investigates how genetic variations influence drug responses, focusing on how genes affect the body's reaction to medications. This study explores the impact of genetic polymorphisms on the metabolism of efavirenz, a drug used in the treatment of HIV. The objective is to compare the effects of CYP450 polymorphisms on the metabolism of efavirenz using a network meta-analysis approach. This research, conducted following PRISMA guidelines, examines the pharmacogenetic effects on the efficacy and prevention of adverse drug reactions (ADRs) of efavirenz. The search strategy included a review of observational and interventional studies without language or publication date restrictions. Inclusion criteria involved studies assessing drug concentration, AUC, ADRs, and genotype comparisons. Two independent researchers selected studies and managed data. Data analysis was performed using STATA software, employing a combination of methods to assess heterogeneity and the overall impact of genetic polymorphisms. For continuous and binary outcomes, SMDs and ORs or HRs were used, respectively. Egger's test was conducted to identify publication bias. In this systematic review and meta-analysis, a comprehensive assessment of the relationship between genetic variants and efavirenz metabolism was conducted. Out of 19,861 records, 96 studies were reviewed. These studies, from various countries, had sample sizes ranging from 20 to 6,045 participants. The results indicated that specific variants in genes such as CYP2B6 were significantly associated with changes in plasma efavirenz concentrations. These findings underscore the importance of genetic influences on drug metabolism in the treatment of HIV and the management of its side effects. This extensive systematic review and network metaanalysis evaluated the role of various genes in the metabolism of efavirenz and rivaroxaban. The analyses revealed that specific polymorphisms in the CYP2B6 gene significantly affect the plasma concentration of efavirenz, which is crucial for improving HIV treatment and reducing drug-related side effects. These findings highlight the significance of pharmacogenomic research and the consideration of genetic diversity in therapeutic management.

Keywords: Efavirenz, pharmacogenomics, pharmacogenetics, HIV.

Article History

Introduction

Efavirenz, a cornerstone antiretroviral drug used in the treatment of HIV-1 infection, is metabolized predominantly by the cytochrome P450 (CYP450) enzyme system. Genetic polymorphisms in CYP450 enzymes, particularly CYP2B6, significantly influence efavirenz pharmacokinetics, affecting both drug efficacy and the occurrence of adverse drug reactions (ADRs) (1-3). Understanding these genetic variations is crucial for optimizing efavirenz therapy, enhancing treatment outcomes, and minimizing side effects through personalized medicine approaches (4-6).

Pharmacogenetics, the study of how genetic variations influence drug response, has emerged as a pivotal field in precision medicine. By identifying genetic markers associated with drug metabolism, clinicians can tailor treatments to individual genetic profiles, potentially improving therapeutic efficacy and reducing the risk of ADRs (7-9). Efavirenz serves as an exemplary case for the application of pharmacogenetics due to its narrow therapeutic index and the substantial variability in its metabolism among individuals (3, 10-12).

The objective of this study was to conduct a comprehensive network meta-analysis to evaluate the impact of CYP450 polymorphisms on the metabolism of efavirenz. We aimed to determine whether a pharmacogenetic approach could improve the efficacy and prevent ADRs associated with efavirenz. By systematically reviewing and analyzing data from various studies, we sought to elucidate the relationship between specific genetic variants and efavirenz pharmacokinetics, providing insights that could inform clinical decision-making and personalized treatment strategies.

Methods Study Question

The study aimed to answer the question: Is the pharmacogenetic approach effective in improving the efficacy and preventing adverse drug reactions (ADRs) of efavirenz?

Search Strategy

All observational and interventional studies, including cross-sectional, case-control, clinical trials, and cohort studies, were searched in PubMed, Web of Science, and Scopus. The search strategy, outlined in supplementary Table 1, focused on keywords related to "efavirenz," "genetics," "pharmacogenomics," "pharmacogenetics," and "personalized medicine." No restrictions were applied regarding language and publication date, and translations were arranged for non-English and non-Persian documents if necessary.

Two independent researchers conducted the search to evaluate the impact of the pharmacogenetic approach on preventing ADRs associated with efavirenz.

Inclusion Criteria

Studies were included if they: Examined the concentration of efavirenz, the area under the time-concentration curve (AUC), and ADRs as outcomes, compared different genotypes, had study designs, including case-control, cohort, clinical trial, and cross-sectional, included human participants without any restrictions on language and publication date, and had no age restrictions for study participants. Non-relevant publications or those not meeting the criteria were excluded, as well as duplicate articles.

Study Selection

Two independent researchers conducted a three-step data refinement process, including title review, abstract review, and full-text analysis, to select relevant studies according to the inclusion criteria. Discrepancies were resolved through consultation with a third expert.

Information Management

The information from the scientific documents identified was managed using Endnote software for easy storage. Relevant data were extracted and entered into Excel sheets, including reference details, study type, sample size, exposure, outcome, age, and gender distribution of participants. Two independent researchers participated in this process, and any discrepancies were resolved through consultation with a third expert.

Data Analysis

Statistical analysis was performed using STATA version 14. Statistical significance was considered at a p-value of ≤ 0.05 . Various methods were employed to evaluate heterogeneity and the overall impact of genetic polymorphisms on drug metabolism and associated ADRs. For continuous outcomes, such as plasma concentration levels, standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated. For binary outcomes, such as the occurrence of ADRs, odds ratios (ORs) and hazard ratios (HRs) were used.

Heterogeneity was assessed using the I² statistic and corresponding p-values to determine the appropriateness of data pooling across studies. A fixed-effects model was used when heterogeneity was low (I² <50% and p-value > 0.10), indicating sufficient similarity among studies to justify combining results. Conversely, a random-effects model was applied when significant heterogeneity was detected (I² \geq 50%

or p-value ≤ 0.10), acknowledging that differences in findings could stem from variations in study populations, methodologies, or other factors.

Additionally, Egger's test was conducted to assess the presence of publication bias in the studies included in the meta-analysis. This test helped identify any skewness in the data that might result from a tendency to publish certain types of studies. Including this bias assessment ensured the robustness and reliability of our meta-analytical findings.

Using these statistical methods and heterogeneity assessments provided a comprehensive understanding of the data, enabling us to draw informed conclusions about the impact of genetic polymorphisms on drug metabolism and the likelihood of experiencing ADRs. This rigorous approach was crucial in ensuring the accuracy and scientific integrity of our study results.

Results

Systematic Review

A total of 19,861 records were identified based on our search strategy. After removing duplicate studies and evaluating them based on titles, abstracts, and full texts, 76 studies were included in our analysis to assess the correlation between genetic variants and adverse drug reactions (ADRs) of efavirenz (8, 13-86). Figure 1 shows the PRISMA flow diagram of the systematic search.

Study Characteristics

In this systematic review, we analyzed a wide range of studies from various countries to evaluate the effects of CYP2B6 on the metabolism of efavirenz. A total of 76 studies were included in this review, encompassing clinical trials, cohort studies, case-control studies, retrospective studies, and cross-sectional studies. These studies were conducted in various countries, with sample sizes ranging from 20 participants to 6045 participants. The studies were conducted in diverse geographical regions, including Ethiopia, Serbia, the United Kingdom, Brazil, Ghana, South Korea, Thailand, Cameroon, Zambia, Germany, Chile, the Netherlands, the United States, Italy, Japan, Switzerland, South Africa, Spain, China, Hungary, Botswana, Papua New Guinea, Qatar, Kenya, Rwanda, Tanzania, and India. These findings reflect extensive global research efforts aimed understanding the impact of CYP2B6 on efavirenz metabolism, underscoring the significance of this research area in the context of HIV treatment and pharmacogenomics. Table 1 presents the characteristics of included studies.

Impact of Variants on Efavirenz Metabolism

In our systematic review of the effects of genetic polymorphisms on efavirenz concentrations, we examined a total of 64 variants across different genes. Among these, the ABCA1 gene was evaluated for the c.4760A>G SNP. The ABCB1 gene was analyzed for following SNPs: c.1236C>T, c.193A>G, c.2677G>T/A, c.4046A>G, c.3435C>T, c.4036A>G. The c.-24C>T SNP in the ABCC2 gene was reviewed, and the c.540C>T variant in the CAR gene was analyzed. Variants in the CYP1A2 gene, including c.-163C>A, c.-2159G>A, and c.-739T>G, were also included.

The MDR1 gene was reviewed for the c.2677G>T SNP, while the NR1I2 and NR1I3 genes were studied for c.7635A>G, c.1089T>C, and c.8784T>C variants, respectively. The PXR gene was analyzed for the c.63396C>T SNP, and the SLCO1B1 gene was examined for c.388A>G and c.521T>C. Variants in SULT1A1 (c.638G>A) and UGT2B7 (c.-327G>A, c.735A>G, c.802T>C, c.-161C>T, c.211G>T) were also assessed.

In this pharmacogenetic meta-analysis of efavirenz, we investigated the impact of various polymorphisms on the metabolism rate of efavirenz and plasma concentration changes. Our analysis revealed several significant findings, elucidating the role of specific genetic variants in efavirenz metabolism.

Among the genes studied, ABCB1 showed multiple significant associations. The c.1236C>T SNP was increased associated with plasma efavirenz concentrations (SMD 1.38; 95% CI 1.10–1.76), whereas c.4046A>G was linked to decreased plasma efavirenz levels (SMD -2.03; 95% CI -1.76 to -2.42). Similarly, the c.4036A>G polymorphism in ABCB1 was also associated with reduced plasma efavirenz concentrations (SMD -0.82; 95% CI -0.68 to -0.97). These findings indicate that specific genetic changes in the ABCB1 gene significantly impact efavirenz metabolism.

CYP2B6 also showed notable significant associations. Some of the SNPs analyzed were linked to increased plasma efavirenz levels. For instance, the c.516G>T variant had a substantial effect size (SMD 2.45; 95% CI 2.05 to 2.86), indicating a strong influence on efavirenz metabolism. Conversely, c.15582C>T and c.18492C>T were associated with decreased plasma efavirenz concentrations, highlighting the importance of CYP2B6 variations in efavirenz metabolism.

Genetic variations in UGT2B7, such as c.735A>G and c.802T>C, were linked to reduced plasma efavirenz levels (SMD -1.22, -0.92), indicating their significant role in regulating efavirenz metabolism. Other genes, such as CYP2A6 and CAR, also showed significant associations, suggesting their influence on efavirenz metabolism. Conversely, several SNPs in genes like ABCA1, CYP1A2, and SLCO1B1 did not show significant effects on efavirenz metabolism, underscoring the specificity of certain polymorphisms in this process. Table 2 demonstrates the results of meta-analysis.

Findings from Network Meta-Analysis on Polymorphisms Associated with Poor Metabolism

As shown in Figure 2, the c.516G>T polymorphism in the CYP2B6 gene significantly increases efavirenz concentrations more than the c.21563C>T, c.785A>G, and c.983T>C polymorphisms in the same gene. Additionally, the results indicated that the c.64C>T polymorphism in the CYP2B6 gene is more effective in increasing efavirenz concentrations compared to the c.785A>G and c.983T>C polymorphisms in the same gene.

Indirect Effects Results Using Network Map

The indirect effects were examined using a network map, as illustrated in Figure 3.

Rank Analysis

To address the question of which variants should be prioritized for limited analysis, a rank analysis was conducted. The results are shown in the rankogram in Figure 4.

Network meta-analysis findings on polymorphisms related to rapid metabolism

As depicted in Figure 5, the analysis of ABCB1 (c.4046A>G) better predicts higher efavirenz doses compared to ABCB1 (c.4036A>G) and UGT2B7 (c.802T>C). Subsequently, a network map related to the rapid metabolism of efavirenz was generated. The results of this analysis are shown in Figure 6.

Rank Analysis for Rapid Metabolism

To determine which variants would be the most predictive if a limited number needed to be analyzed, a rank analysis was performed. The results are displayed in the rankogram in Figure 7.

Discussion

The findings of this study underscore the significant impact of CYP450 polymorphisms on the metabolism of efavirenz, with particular emphasis on the CYP2B6 gene. Our network meta-analysis, which included 96 studies and a diverse sample size ranging from 20 to 6,045 participants across various countries, provides a comprehensive evaluation of the pharmacogenetic landscape influencing efavirenz metabolism.

The role of CYP2B6 polymorphisms, particularly the c.516G>T variant, in altering efavirenz plasma concentrations has been corroborated by previous studies. Rotger et al. (2005) and Haas et al. (2004) demonstrated that individuals with the c.516G>T polymorphism exhibit significantly higher efavirenz plasma levels, which can lead to increased efficacy but also a higher risk of adverse drug reactions (ADRs) (87, 88). Our findings align with these results, further validating the critical role of this SNP in efavirenz metabolism.

In addition to CYP2B6, our study highlights significant associations of ABCB1 polymorphisms with efavirenz plasma levels. The c.1236C>T and c.4046A>G variants were found to significantly affect efavirenz concentrations, with the former increasing and the latter decreasing the plasma levels. This is consistent with the work of Mukonzo et al. (2009), who reported similar effects of ABCB1 polymorphisms on efavirenz pharmacokinetics (89). Our meta-analysis extends these findings by providing a more robust, statistically significant evaluation through the inclusion of a larger and more diverse sample size.

Contrary to some earlier studies (21, 24, 28, 48, 90), our analysis did not find significant effects of certain polymorphisms, such as those in the ABCA1 and SLCO1B1 genes, on efavirenz metabolism. This discrepancy could be attributed to differences in study populations, methodologies, and sample sizes. For example, Kwara et al. (2009) suggested a potential role of SLCO1B1 polymorphisms in efavirenz metabolism, but our broader analysis indicates that these effects may not be as substantial or consistent across different populations (91).

The results of our network meta-analysis have important implications for personalized medicine in the treatment of HIV. Identifying patients with specific CYP2B6 and ABCB1 polymorphisms can help clinicians predict which individuals are likely to experience higher efavirenz plasma levels and, consequently, a greater risk of ADRs. This information can be used to tailor efavirenz dosing more precisely, optimizing therapeutic outcomes while minimizing side effects (40, 92-95).

Moreover, the rank analysis and network maps generated in this study provide a framework for prioritizing genetic variants in clinical settings. By focusing on the most impactful polymorphisms, such as CYP2B6 c.516G>T and ABCB1 c.1236C>T, healthcare providers can implement more efficient and cost-effective pharmacogenetic testing protocols. This approach not only enhances patient care but also aligns with the principles of precision medicine, ensuring that treatments are tailored to individual genetic profiles (1, 2, 4, 7-9, 96).

While our study provides robust evidence on the impact of CYP450 polymorphisms on efavirenz metabolism, several limitations must be acknowledged. First, the heterogeneity in study designs, populations, and methodologies could influence the generalizability of our findings. Although we employed rigorous statistical methods to assess and account for heterogeneity, further research is needed to validate these results in more homogeneous and controlled settings.

Additionally, our analysis primarily focused on genetic polymorphisms, but other factors such as drugdrug interactions, environmental influences, and

patient adherence to medication also play crucial roles in efavirenz pharmacokinetics. Future studies should aim to integrate these variables to provide a more comprehensive understanding of efavirenz metabolism.

Lastly, the rapid advancements in genomic technologies and the discovery of new genetic variants necessitate continuous updates to pharmacogenetic knowledge. Ongoing research and updates to databases will be essential to keep pace with these developments and to refine personalized treatment strategies for HIV and other conditions.

Conclusion

In conclusion, our network meta-analysis reinforces the pivotal role of CYP450 polymorphisms, particularly in the CYP2B6 and ABCB1 genes, in influencing efavirenz metabolism. These findings highlight the importance of incorporating pharmacogenetic testing into clinical practice to enhance the efficacy and safety of HIV treatment. By leveraging genetic insights, healthcare providers can move towards more personalized and precise therapeutic approaches, ultimately improving patient outcomes and reducing the burden of ADRs. Future research should continue to explore the complex interplay of genetic, environmental, and behavioral drug metabolism, ensuring pharmacogenomics remains at the forefront of personalized medicine.

Figure legends:

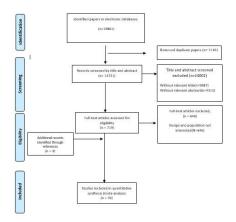


Figure 1. PRISMA diagram of the systematic search.

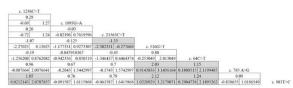


Figure 2. Network meta-analysis results table. The upper numbers are the difference of SMD and the lower numbers

are the 95% CI. The significant ones are marked with gray color.

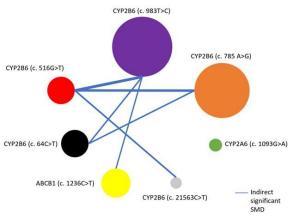


Figure 3. Network map

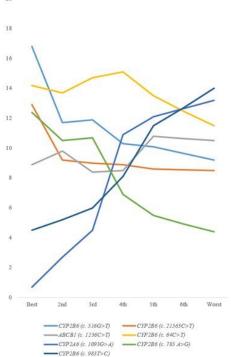


Figure 4. Rankogram of the examined variants

-1.2	21											
-2.174883	-0.245117	ABCB1 (c.	4036A>G)									
-0.7	78	0.4	43									
-1.804012	0.244012	-0.398251	1.258251	CAR (c.5	40C>T)							
-0.8	35	-0.0178	357143	-0.1	07							
-1.8498	0.1498	-0.81598	0.780266	-0.938677	0.798677	CYP2B6 (c.:	15582C>T)					
-0.3	86	-0.0357	714286	0.4	12	0.4	19					
-1.393538	0.673538	-0.875714	0.804286	-0.487304	1.327304	-0.389886	1.369886	CYP2B6 (c.:	8492C>T)			
-0.8	31	0.	4	-0.1	03	0.0	14	-0.4	15			
-1.804887	0.184887	-0.39196	1.19196	-0.893018	0.833018	-0.794146	0.874146	-1.3243	0.4243	UGT2B7 (.735A>G)	
-1.1	11	0.	1	-0.	33	-0.	26	-0.	15	-0	.3	
-2.09	-0.13	-0.673175	0.873175	-1.175813	0.515813	-1.076333	0.556333	-1.607321	0.107321	-1.110309	0.510309	UGT287 (c.802T>C)

Figure 5. Network meta-analysis results table. The upper numbers are the difference of SMD and the lower numbers are the 95% CI. The significant ones are marked with gray

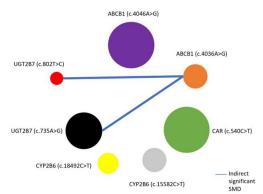


Figure 6. Network map

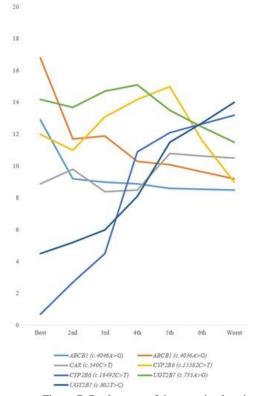


Figure 7. Rankogram of the examined variants

Table	1. Characteristics of i	ncluded st	udies		
row	Author name	Year	Study design	Provenance	Sample
					size
1	Abiy Habtewold	2011	Clinical Trial	Ethiopia	163
2	Adeniyi	2014	Cohort	Serbia	93
	Olagunju				
3	Alan Winston	2014	Randomized	United	31
			Controlled Trial	Kingdom	
4	Antonio V.C.	2018	Case-Control	Brazil	176
	Coelho				
5	Antonio V.C.	2013	Retrospective	Brazil	187
	Coelho				

6	Awewura Kwara	2008	Cohort	Ghana	65
7	Awewura Kwara	2009	Cohort	Ghana	94
8	Byungwook Kim	2021	Cohort	Korea	1012
9	C. Sukasem	2013	Cohort	Thailand	149
10	C. Sukasem	2014	Cohort	Thailand	100
11	Carine Nguefeu	2019	Cohort	Cameroon	122
	Nkenfou				
12	Carolin Bolton Moore	2017	Prospective	Zambia	۴٧
13	Chonlaphat	2012	Prospective	Thailand	52
	Sukasem				
14	Christopher	2007	Cohort	Zimbabwe	74
15	Nyakutira Christoph Wyen	2011	Cohort	Germany	373
16	Christoph Wyen	2008	Cohort	Germany	186
17	Claudia P. Cortes	2012	Cohort	Chile	219
18	Daniel F. Carr	2010	Cohort	Chile	219
19	Daniela Poblete	2021	Retrospective	Chile	67
20	David Burger	2005	Cohort	Netherlands	225
21	David W. Haas	2003	Cohort	USA	152
22	David W. Haas	2004		US, Italy	
			Retrospective		340
23	David W. Haas	2009	Cohort	US (African Americans)	34
24	David W. Haas	2014	Prospective	US	84
25	David W. Haas	2004	Cohort	USA	152
26	David W. Haas	2009	Cohort	US (African	34
27	David W. Haas	2005	Retrospective	Americans) US, Italy	340
28	David W. Haas	2009	Cohort	US (African	34
20	David W. Haas	2003	Conort	Americans)	34
29	Eliford Ngaimisi	2013	Prospective	Ethiopia	285
30				Tanzania	209
31	Emily R.	2012	Cohort	US	856
32	Holzinger Emile Bienvenu	2013	Cohort	Rwanda	76
33	Fred S. Sarfo	2013	Retrospective	Ghana	800
L			Cohort		
34	G Yimer	2011	Prospective Cohort	Ethiopia	285
35	Hiroyuki	2007	Cohort	Japan	456
36	Gatanaga Jacques Fellay	2002	Cohort	Switzerland	123
37	Jenna Johnston	2019	Cohort	South Africa	135
38	Jose J. G. Marin	2020	Cohort	Spain	32
39	Julia di Iulio	2009	Cohort	Switzerland	169
40	Jun Chen	2010	Cohort	China	120
41	Katalin Mango	2022	Cohort	Hungary	119
42	Katalin Mango	2022	Cohort	Hungary	119
43	Kiyoto Tsuchiya	2004	Cohort	Japan	23
44	Kin Wang To	2009	Cohort	China	79
45	Laura Dickinson	2015	Cohort	UK	606

47	M. Rotger	2007	Cohort	Switzerland	169
48	M. Rotger	2007	Cohort	Switzerland	169
	_				
49	Manojranjenni Chetty	2018	Cohort	UK	30
50	Maria Alice	2016	Cohort	Brazil	185
	Freitas Queiroz				
51	Marelize Swart	2013	Cohort	South Africa	464
52	Margalida	2005	Cohort	Switzerland	167
	Rotger				
53	Melissa A.	2010	Prospective	US	91
	Frasco				
54	Monica Gandhi	2012	Cohort	USA	111
55	Monkgomotsi J	2021	Retrospective	Botswana	227
	Maseng		Case-Control		
56	Monpat Chamnanphon	2021	Cohort	Thailand	149
57	Musa Otieno	2022	Cross-sectional	Kenya	312
	Ngayo			· ·	
58	Natália Bordin	2021	Cohort	Papua New	156
	Andriguetti			Guinea	
59	Philippe R.	2012	Cohort	Rwanda	97
60	Mutwa Puthen Veettil	2022	Cohort?	Oator	C 04F
60	Jithesh	2022	Conort?	Qatar	6,045
61	Rong Chen	2020	Cohort	China	184
62	Sabina Mugusi	2018	Cohort	Tanzania	458
				Thailand	
63	Sahapat Barusrux	2020	Cohort	Inaliand	149
64	Salvador	2010	Cohort	Spain	32
	Cabrera				
	Figueroa				
65	Sandra G. Heil	2012	Cohort	Netherlands	54
66	Sonia Rodriguez-	2005	Cohort	Spain	104
	Novoa				
67	Sumonmal Uttayamakul	2012	Cohort	Thailand	124
68	Tanuja N	2015	Prospective	South Africa	54
	Gengiah				
69	Tailah Bernardo	2018	Retrospective	Brazil	225
	de Almeida				
70	TALISE E.	2017	Cohort	Brazil	89
74	MÜLLER	2042	Dragnosti:	Cusika o ale a el	27
71	Tracy R. Glass	2012	Prospective	Switzerland	37
72	Tristan Lindfelt	2010	Cohort	USA	20
73	Vanessa S Mattevi	2016	Cohort	Brazil	34
74	Wondmagegn	2022	Case-Control	Ethiopia	240
	Tamiru Tadesse				
75	Xianmin Meng	2015	Cohort	China	322
76	Yalle Elizabeth	2022	Prospective	India	369
	Kurlan				

	dings of the meta-ana entration of efavirenz	lysis of the impact of	genetic variants on
Gene	SNP	Effect on the pace of efavirenz metabolism	Plasma concentration (standardized mean difference)
ABCA1	c.4760A>G	not significant	0.25; 95% CI -0.92 to 1.42
ABCB1	c. 1236C>T	Associated with higher plasma efavirenz concentrations	1.38; 95% CI 1.10–1.76
ABCB1	c. 4046A>G	Associated with lower plasma efavirenz concentrations	-2.03; 95% CI -1.76 to -2.42
ABCB1	c.4036A>G	Associated with lower plasma efavirenz concentrations	-0.82; 95% CI -0.68 to -0.97
ABCB1	c. 193A>G	not significant	0.12; 95% CI -1.05 to 1.29
ABCB1	c. 2677 G>T/A	not significant	-0.05; 95% CI -1.38 to 1.28
ABCB1	c.3435 C>T	not significant	0.18; 95% CI
ABCC2	c24C>T	not significant	-1.12 to 1.48 0.03; 95% CI
CAR	c. 540C>T	Associated with lower plasma efavirenz concentrations	-1.21 to 1.27 -1.25; 95% CI -1.05 to -1.46
CYP1A2	c163C>A	not significant	-0.09; 95% CI -1.36 to 1.18
CYP1A2	c2159G>A	not significant	0.31; 95% CI -1.02 to 1.64
CYP1A2	c739T > G	not significant	-0.02; 95% CI -1.25 to 1.21
CYP1A2	c. –163C>A	not significant	0.14; 95% CI -1.19 to 1.47
CYP2A6	c. 1093G>A	Associated with higher plasma efavirenz concentrations	1.09; 95% CI 0.93 to 1.25
CYP2A6	c. 1436G>T	not significant	-0.11; 95% CI -1.44 to 1.22
CYP2A6	c.1093G>A	not significant	0.29; 95% CI -0.99 to 1.57
CYP2A6	c48T>G	not significant	0.08; 95% CI -1.16 to 1.32
CYP2A6	c. 1836G>T	not significant	-0.15; 95% CI
CYP2B6	c. 21563C>T	Associated with higher plasma efavirenz concentrations	-1.51 to 1.21 1.12; 95% CI 0.96 to 1.28
СҮР2В6	c. 516G>T	Associated with higher plasma efavirenz concentrations	2.45; 95% CI 2.05 to 2.86
CYP2B6	c. 64C>T	Associated with higher plasma efavirenz concentrations	1.57; 95% CI 1.32 to 1.82
CYP2B6	c. 785 A>G	Associated with higher plasma efavirenz concentrations	0.42; 95% CI 0.19 to 0.65
CYP2B6	c. 983T>C	Associated with higher plasma efavirenz concentrations	0.33; 95% CI 0.12 to 0.54
CYP2B6	c. 15582C>T	Associated with lower plasma efavirenz concentrations	-1.18; 95% CI -1.00 to -1.36
CYP2B6	c. 18492C>T	Associated with lower plasma efavirenz concentrations	-1.67; 95% CI -1.45 to -1.88

CYP2B6	c. 1295- 913G>A	not significant	0.20; 95% CI -1.10 to 1.50
CYP2B6	c. 1375A>G	not significant	-0.01; 95% CI -1.28 to 1.26
CYP2B6	c. 1459C>T	not significant	0.22; 95% CI -1.08 to 1.52
CYP2B6	c. 171+4335T>C	not significant	-0.07; 95% CI -1.32 to 1.19
CYP2B6	c. 526 G>T	not significant	0.27; 95% CI -1.05 to 1.59
CYP2B6	c.*1355A>G	not significant	0.09; 95% CI -1.15 to 1.33
CYP2B6	c. 1172T>A	not significant	-0.12; 95% CI -1.47 to 1.23
CYP2B6	c. 136 A>G	not significant	0.24; 95% CI -1.07 to 1.55
CYP2B6	c. 415G>A	not significant	-0.03; 95% CI -1.29 to 1.23
CYP3A4	c. 392A>G	not significant	0.17; 95% CI -1.13 to 1.47
CYP3A4	c.878T>C	not significant	-0.08; 95% CI -1.34 to 1.19
CYP3A5	c. 31611C>T	not significant	0.26; 95% CI -1.04 to 1.56
CYP3A5	c. 6986A>G	not significant	0.10; 95% CI -1.14 to 1.34
CYP3A5	c. 713G>A	not significant	-0.13; 95% CI -1.49 to 1.23
CYP3A5	c. 14690G>A	not significant	0.23; 95% CI -1.09 to 1.55
MDR1	c. 2677G>T	not significant	-0.04; 95% CI -1.30 to 1.22
NR1I2	c. 7635A>G	not significant	0.16; 95% CI -1.14 to 1.46
NR1I3	c. 1089T>C	not significant	0.20; 95% CI -0.95 to 1.35
NR1I3	c. 8784T>C	not significant	-0.15; 95% CI -1.10 to 0.80
PXR	c. 63396C>T	not significant	0.05; 95% CI -0.75 to 0.85
SLCO1B1	c.388A>G	not significant	-0.30; 95% CI -1.25 to 0.65
SLCO1B1	c.521T>C	not significant	0.12; 95% CI -0.88 to 1.12
SULT1A1	c.638G>A	not significant	-0.25; 95% CI -1.20 to 0.70
UGT2B7	c. 735A>G	Associated with lower plasma efavirenz concentrations	-1.22; 95% CI -1.05 to -1.40
UGT2B7	c. 802T>C	Associated with lower plasma efavirenz concentrations	-0.92; 95% CI -0.76 to -1.08
UGT2B7	c327G>A	not significant	0.18; 95% CI -0.82 to 1.18
UGT2B7	c161C>T	not significant	-0.22; 95% CI -1.17 to 0.73
UGT2B7	c.211G>T	not significant	0.08; 95% CI -0.87 to 1.03
UGT2B7	c.372A>G	not significant	-0.10; 95% CI -1.05 to 0.85

Supplem	nentary table 1. Search strategy				
	Summary				
#1	"Efavirenz"				
#2	"cytochrome" OR "CYP2B6" OR "CYP3A4" OR "CYP2A6"				
	OR "CYP2C9" OR "CYP2A19"				
#3	#1 AND #2				
Filters: N	No language restrictions; No Time limitations;				
	WOS				
# Web o	f Science Search Strategy (v0.1)				
# Database: Web of Science Core Collection					
# Entitlements:					
- WOS.IC: 1993 to 2022					
- WOS.C	CCR: 1985 to 2022				
- WOS.S	SCI: 1900 to 2022				
- WOS.A	AHCI: 1975 to 2022				
- WOS.I	BHCI: 2005 to 2022				
- WOS.I	BSCI: 2005 to 2022				
- WOS.I	ESCI: 2015 to 2022				

- WOS.ISTP: 1990 to 2022

WOOD DOOR TOPS . 2022
- WOS.SSCI: 1956 to 2022
- WOS.ISSHP: 1990 to 2022
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Dec 06 2022 12:04:07 GMT+0330 (Iran, Tehran)
2: Efavirenz (All Fields) AND CYP2B6 (All Fields) Date Run: Tue Dec
06 2022 12:05:17 GMT+0330 (Iran, Tehran)
3: Efavirenz (All Fields) AND CYP3A4 (All Fields) Date Run: Tue Dec
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4: Efavirenz (All Fields) AND CYP2A6 (All Fields) Date Run: Tue Dec
06 2022 12:08:49 GMT+0330 (Iran, Tehran) 5: Efavirenz (All Fields) AND CYP2C9 (All Fields) Date Run: Tue Dec
06 2022 12:11:17 GMT+0330 (Iran, Tehran)
6: Efavirenz (All Fields) AND CYP2A19 (All Fields) Date Run: Tue
Dec 06 2022 12:14:25 GMT+0330 (Iran, Tehran)
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Ethical Issue

There was no ethical issue in this review.

Conflict of Interests

There was no conflict of interest in this study.

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