

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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Authors: Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands.

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Sciences (UIPS), Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands 3 4 2024 8 2024 32 8 467900 903 911 11 8 2023 30 1 2024 19 2 2024 01 08 2025 01 08 2025 02 08 2024 01 08 2025 © The Author(s), under exclusive licence to European Society of Human Genetics 2024. Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law. 2024 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.