

Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6 and CYP2C19 and tricyclic antidepressants.

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Publication year: 2026

Journal: European journal of human genetics : EJHG

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Society: Dutch Pharmacogenetics Working Group

Origin country: Netherlands

DOI: 10.1038/s41431-025-02008-3

PMID: 41526670

Source: <https://pubmed.ncbi.nlm.nih.gov/41526670/>

Eur J Hum Genet Eur J Hum Genet 1300 ejhg 9302235 European Journal of Human Genetics 1018-4813 1476-5438 Nature Publishing Group PMC12963449 PMC12963449.1 12963449 12963449 41526670 10.1038/s41431-025-02008-3 2008 1 Article Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction between CYP2D6 and CYP2C19 and tricyclic antidepressants <http://orcid.org/0009-0009-5008-244X> Kleine Schaars Kristian 1 2 3 <http://orcid.org/0000-0001-7476-6867> Nijenhuis Marga M.Nijenhuis@knmp.nl 4 Soree Bianca 4 de Boer-Veger Nienke J. 5 Buunk Anne-Marie 6 Guchelaar Henk-Jan 7 <http://orcid.org/0000-0002-9927-7266> Houwink Elisa J. F. 8 Risselada Arne 9 Rongen Gerard A. P. J. M. 10 11 van Schaik Ron H. N. 12 <http://orcid.org/0000-0002-3965-5552> Swen Jesse J. 7 <http://orcid.org/0000-0002-1429-4789> Touw Daan 13 14 Deneer Vera H. M. 15 16 <http://orcid.org/0000-0003-2298-9924> van Westrhenen Roos 1 2 17 18 1 <https://ror.org/002wh3v03> grid.476585.d 0000 0004 0447 7260 Outpatient Clinic Pharmacogenetics Amsterdam, Parnassia Group, Amsterdam, The Netherlands 2 <https://ror.org/044hshx49> grid.418011.d 0000 0004 0646 7664 Centre for Human Drug Research, Leiden, The Netherlands 3 <https://ror.org/05xvt9f17> grid.10419.3d 0000000089452978 Leiden University Medical Center, Leiden, The Netherlands 4 <https://ror.org/00gdw7f12> grid.489189.5 0000 0001 0708 7338 Royal Dutch Pharmacists Association (KNMP), The Hague, The Netherlands 5 <https://ror.org/017b69w10> grid.416468.9 0000 0004 0631 9063 Department of Clinical Pharmacy, Martini Hospital, Groningen, The Netherlands 6 Pharmacy De Katwijkse Apotheek, Katwijk, The Netherlands 7 <https://ror.org/05xvt9f17> grid.10419.3d 0000000089452978 Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands 8 <https://ror.org/02qp3tb03> grid.66875.3a 0000 0004 0459 167X Department of Family Medicine, Mayo Clinic, Rochester, MN USA 9 Department of Clinical Pharmacy, Wilhelmina Hospital, Assen, The Netherlands 10 <https://ror.org/05wg1m734> grid.10417.33 0000 0004 0444 9382 Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands 11 <https://ror.org/05wg1m734> grid.10417.33 0000 0004 0444 9382 Department of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, The Netherlands 12 <https://ror.org/018906e22> grid.5645.2 0000 0004 0459 992X Department of Clinical Chemistry, Erasmus MC University Medical Center, Rotterdam, The Netherlands 13 <https://ror.org/012p63287> grid.4830.f 0000 0004 0407 1981 Department of Pharmaceutical Analysis, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands 14 <https://ror.org/03cv38k47> grid.4494.d 0000 0000 9558 4598 Department of Clinical Pharmacy & Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands 15 <https://ror.org/0575yy874> grid.7692.a 0000 0000 9012 6352 Department of Clinical Pharmacy, Division Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands 16 <https://ror.org/04pp8hn57>

grid.5477.1 0000 0000 9637 0671 Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands 17 <https://ror.org/0220mzb33> grid.13097.3c 0000 0001 2322 6764 Institute of Psychiatry, Psychology&Neuroscience (IoPPN), King's College London, London, UK 18 <https://ror.org/03qvzj64> grid.482756.a St. John's National Academy of Health Sciences, Bangalore, India 12 1 2026 3 2026 34 3 508954 379 386 21 3 2025 8 12 2025 17 12 2025 01 03 2027 07 03 2026 07 03 2026 © The Author(s), under exclusive licence to European Society of Human Genetics 2026. 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. 2026 The Dutch Pharmacogenetic Working Group (DPWG) aims to integrate pharmacogenetics into clinical practice by creating evidence-based guidelines to optimize pharmacotherapy based on genetic tests. The current guideline describes the gene–drug interactions between CYP2D6 and CYP2C19 and various tricyclic antidepressants (TCAs). For CYP2D6 poor metabolisers (PM), dose reductions are advised for amitriptyline (reduction to 60% of the normal dose), clomipramine (reduction to 50% of the normal dose for the indication depression or in case of side effects at the normal dose for the other indications), doxepin (reduction to 40% of normal dose), imipramine (30% of the normal dose), and nortriptyline (40%). For CYP2D6 intermediate metabolisers (IM) reduced dose is also recommended for amitriptyline (75%), clomipramine (70%), doxepin (80%), imipramine (70%), and nortriptyline (60%). Also, CYP2D6 ultra-rapid metabolisers (UM) require tailored dose adjustments: amitriptyline (1.6 times the normal dose), clomipramine (1.5 times), doxepin (2 times), imipramine (1.7 times), and nortriptyline (1.7 times). Additionally, alternative drugs may be needed for CYP2D6 UM due to potential safety concerns. For CYP2C19 PM, a 70% dose reduction is advised for imipramine. For CYP2C19 IM, no action is required for TCAs. For CYP2C19 UM, an alternative medication is recommended for clomipramine prescribed for anxiety and obsessive-compulsive disorder (OCD). The DPWG classifies CYP2D6 genotyping for all five TCAs and CYP2C19 genotyping for clomipramine in patients with anxiety disorders or OCD, and for imipramine as being “potentially beneficial”. Genotyping prior to treatment can be considered on an individual patient basis.