Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP2C19 and non-SSRI/non-TCA antidepressants

Beunk, L.; Nijenhuis, M.; Soree, B.; Boer-Veger, N.J. de; Buunk, A.M.; Guchelaar, H.J.; ... ; Westrhenen, R. van

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Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between *CYP2D6*, *CYP2C19* and non-SSRI/non-TCA antidepressants

Lianne Beunk[1], Marga Nijenhuis[2]✉, Bianca Soree[2], Nienke J. de Boer-Veger[3], Anne-Marie Buunk[4], Henk-Jan Guchelaar[5], Elisa J. F. Houwink[6], Arne Risselada[7], Gerard A. P. J. M. Rongen[8,9], Ron H. N. van Schaik[10], Jesse J. Swen[5], Daan Touw[11,12], Vera H. M. Deneer[13,14] and Roos van Westrhenen[15,16,17]

The Dutch Pharmacogenetics Working Group (DPWG) aims to facilitate pharmacogenetics implementation in clinical practice by developing evidence-based guidelines to optimize pharmacotherapy based on pharmacogenetic test results. The current guideline describes the gene-drug interaction between *CYP2D6* and venlafaxine, mirtazapine and duloxetine. In addition, the interaction between *CYP2C19* and mirtazapine and moclobemide is presented. The DPWG identified a gene-drug interaction that requires therapy adjustment for *CYP2D6* and venlafaxine. However, as the side effects do not appear to be related to plasma concentrations, it is not possible to offer a substantiated advice for dose reduction. Therefore, the DPWG recommends avoiding venlafaxine for *CYP2D6* poor and intermediate metabolisers. Instead, an alternative antidepressant, which is not, or to a lesser extent, metabolized by CYP2D6 is recommended. When it is not possible to avoid venlafaxine and side effects occur, it is recommended to reduce the dose and monitor the effect and side effects or plasma concentrations. No action is required for ultra-rapid metabolisers as kinetic effects are minimal and no clinical effect has been demonstrated. In addition, a gene-drug interaction was identified for *CYP2D6* and mirtazapine and *CYP2C19* and moclobemide, but no therapy adjustment is required as no effect regarding effectiveness or side effects has been demonstrated for these gene-drug interactions. Finally, no gene-drug interaction and need for therapy adjustment between *CYP2C19* and mirtazapine and *CYP2D6* and duloxetine were identified. The DPWG classifies *CYP2D6* genotyping as being "potentially beneficial" for venlafaxine, indicating that genotyping prior to treatment can be considered on an individual patient basis.

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INTRODUCTION

The study of effects of heritable genetic variation on drug response is referred to as pharmacogenetics (PGx). Personalized medicine, also known as precision medicine, can be achieved by using PGx information when prescribing medication. Knowledge of an individual's genetic background for drug metabolizing enzymes, drug transporters, receptors or effector proteins may be used to guide pharmacological treatment. Although the value of PGx is widely recognized, its implementation in daily clinical practice remains challenging [1], also in psychiatry [2, 3]. Barriers for implementation in clinical settings include the limited availability of therapeutic recommendations, the lack of awareness amongst clinicians, digital integration and decision support in electronic health records, and genotype test result interpretation.

The Royal Dutch Pharmacists Association (KNMP) has appointed the Dutch Pharmacogenetics Working Group (DPWG) in 2005, a multidisciplinary group consisting of (clinical) pharmacists, a psychiatrist, a general practitioner, clinical pharmacologists, clinical chemists and epidemiologists [4, 5]. The main objectives of the DPWG are to develop PGx informed therapeutic recommendations based on systematic literature review, and to assist physicians and pharmacists by integrating the recommendations into computerized

[1]Department of Clinical Chemistry, St Jansdal Hospital, Harderwijk, The Netherlands. [2]Royal Dutch Pharmacists Association (KNMP), The Hague, The Netherlands. [3]Pharmacy Boterdiep, Groningen, The Netherlands. [4]Pharmacy De Katwijkse Apotheek, Katwijk, The Netherlands. [5]Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, The Netherlands. [6]Department of Family Medicine, Mayo Clinic, Rochester, MN, USA. [7]Department of Clinical Pharmacy, Wilhelmina Hospital, Assen, The Netherlands. [8]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands. [9]Department of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, The Netherlands. [10]Department of Clinical Chemistry, Erasmus MC University Medical Center, Rotterdam, The Netherlands. [11]Department of Pharmaceutical Analysis, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands. [12]Department of Clinical Pharmacy & Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands. [13]Department of Clinical Pharmacy, Division Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands. [14]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands. [15]Department of Psychiatry, Parnassia Group, Amsterdam, Netherlands. [16]Institute of Psychiatry, Psychology&Neuroscience (IoPPN), King's College London, London, UK. [17]St. John's National Academy of health Sciences, Bangalore, India.
✉email: M.Nijenhuis@knmp.nl

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Table 1. The translation of *CYP2D6* and *CYP2C19* genotype to predicted phenotype.

Gene	Predicted phenotype	Patient genotype	Examples of genotypes[b]
CYP2D6	Normal metaboliser (NM)	Gene activity score[a] 1.25 through 2.5	*1/*1, *1/*10, *1/*41, *1 × 2/*41, *1/*41 × 2
	Intermediate metaboliser (IM)	Gene activity score[a] 0.25 through 1.0	*1/*4, *4/*10, *10/*41, *41/*41
	Poor metaboliser (PM)	Gene activity score[a] 0	*4/*4, *4/*6, *6/*6
	Ultra-rapid metaboliser (UM)	Gene activity score[a]≥2.75	*1 × 2/*1, *1 × 3/*1, *1 × 2/*10 × 3, *1/*10 × 7
CYP2C19	Normal metaboliser (NM)	Homozygous for fully functional allele or heterozygous for fully and increased functional allele	*1/*1, *1/*17
	Intermediate metaboliser (IM)	Heterozygous for a reduced functional or inactive allele	*1/*2, *1/*3, *2/*17, *3/*17
	Poor metaboliser (PM)	Homozygous or compound heterozygous for reduced functional or inactive alleles	*2/*2, *2/*3, *3/*3
	Ultra-rapid metaboliser (UM)	Homozygous for an increased functional allele	*17/*17

[a]The gene activity score of a genotype is determined by adding the gene activity scores of the alleles (see Supplementary Table 1A).
[b]The *-alleles mentioned in the table above are characterised by the following sequence variations:
*CYP2D6/CYP2C19**1: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations)
*CYP2D6**4: rs-number: rs3892097; NG_008376.3(NM_000106.6): c.506-1 G > A; protein sequence not available; NC_000022.11: g.42128945 C > T
*CYP2D6**6: rs-number: rs5030655; NM_000106.6: c.454del; NP_000097.3: p.(Trp152fs); NC_000022.11: g.42129084del
*CYP2D6**10: rs-number: rs1065852 and rs1135840; NM_000106.6: c.[100 C > T; 1457 G > C]; NP_000097.3: p.(Pro34Ser; Ser486Thr); NC_000022.11: g.[42130692 G > A; 42126611 C > G]
*CYP2D6**41: rs-numbers: rs16947, rs28371725 and rs1135840; NG_008376.3 (NM_000106.6): c.[886 C > T; 985 + 39 G > A; 1457 G > C]; NP_000097.3: p.(Arg296Cys;
protein not available; Ser486Thr); NC_000022.11: g.[42127941 G > A; 42127803 C > T; 42126611 C > G]
*CYP2C19**2: rs-number: rs12769205 and rs4244285; NC_000010.11(NM_000769.2): c.[332-23 A > G; 681 G > A]; NC_000010.11: g.[94775367 A > G; 94781859 G > A]
*CYP2C19**3: rs-number: rs4986893; NM_000769.2: c.636 G > A; NP_000760.1: p.(Trp212*); NC_000010.11: g.94780653 G > A
*CYP2C19**17: rs-number: rs12248560; NM_000769.2 c.−806 C > T; NP_000760.1: p.(Ile331Val); NC_000010.11: g.94761900 C > T.

systems for drug prescription, dispensing, and automated medication surveillance. This manuscript thus provides both the content required for enabling local translation of assay results into the predicted phenotype and for programming therapeutic recommendations into local clinical decision support systems. With the objective of implementing PGx into routine care, the DPWG has additionally developed the clinical implication score, which is given to every gene-drug interaction requiring therapy adjustment [6].

Recently, the DPWG guidelines were endorsed by the European Association of Clinical Pharmacology (EACPT) and Therapeutics and the European Association of Hospital Pharmacists (EAHP). In order to meet the public request for this information outside the Dutch healthcare system, the DPWG guidelines and future updates are published in the European Journal of Human Genetics [7].

CYP2D6 (*Cytochrome P450 family 2 subfamily D member 6*) and *CYP2C19* (*Cytochrome P450 family 2 subfamily C member 19*) are routinely genotyped in diagnostic laboratories. However, uncertainties about the relevance of *CYP2D6* and *CYP2C19* variants for treatment with venlafaxine, mirtazapine, moclobemide, and duloxetine hampered implementation in clinical practice. Therefore, the DPWG decided to develop a guideline for these gene-drug interactions, which is presented here. The choice for gene-drug interactions to be evaluated by the DPWG is outside the scope of this manuscript. Likewise, details on the clinical use of these drugs as well as the cost-effectiveness of PGx guided dosing are outside the scope of this guideline. The scientific evidence on the gene-drug interaction between *CYP2D6* and venlafaxine, mirtazapine, and duloxetine and between *CYP2C19* and mirtazapine and moclobemide is discussed. A summary of all references identified by the systematic review, which were used to develop this guideline, can be found in Supplementary Tables 1A through E.

DRUGS: VENLAFAXINE, MIRTAZAPINE, DULOXETINE, AND MOCLOBEMIDE

Venlafaxine is prescribed for the treatment of depressive disorder, anxiety disorders as generalized anxiety disorder, social anxiety and panic disorder, and off label for neuropathic pain [8]. Venlafaxine and its active metabolite O-desmethylvenlafaxine inhibit the reuptake of serotonin and noradrenaline and weakly inhibit the reuptake of dopamine. Common side effects of venlafaxine are nausea, headache, dry mouth, and sweating [9].

Mirtazapine is an atypical tetracyclic antidepressant that is prescribed for patients with major depressive disorder and off label also prescribed for sleeping problems [8]. It stimulates the release of noradrenaline by blocking presynaptic α2-adrenergic receptors, resulting in an increased release of serotonin. Mirtazapine also has strong antihistaminergic effect as it antagonizes histamine-H1-receptor, which results in a sedative effect. Increased sedation is thus a typical side effect of mirtazapine, in addition to increased appetite and weight [10].

Moclobemide is a reversible monoamine-oxidase A (MAO-A) inhibitor and hereby increases the concentration of serotonin, noradrenalin and dopamine in the synaptic cleft, which are all subject to metabolism by MAO-A. It is used for the treatment of episodes of depression in which vital functions are dysregulated [8]. Most common side effects include sleep disorders, nausea, dry mouth, dizziness and headache [11].

Duloxetine is prescribed for patients with a major depressive disorder, generalized anxiety disorder or diabetic peripheral neuropathic pain and off label for severe and chronic arthritic pain [8]. Like venlafaxine, duloxetine inhibits the reuptake of both serotonin and noradrenaline and also weakly inhibits the reuptake of dopamine. The pain reducing effect of duloxetine is probably caused by the strengthening of the descending inhibitory pain

pathways. Side effects of duloxetine include nausea, dry mouth, dizziness, sleepiness, and headache [12].

Venlafaxine, mirtazapine, moclobemide, and duloxetine are all extensively metabolized in the liver to both pharmacologically active and inactive metabolites by enzymes of the Cytochrome P450 superfamily as is discussed below [9–12].

GENE: *CYP2D6*

For *CYP2D6*, a detailed explanation of the gene and its variants can be found in Supplementary Material 1 as *CYP2D6* has been described as part of published DPWG guidelines [13]. For *CYP2D6*, alleles resulting in an inactive enzyme (gene activity score 0) (e.g. *4 and *6) or an enzyme with reduced activity (gene activity score 0.25 for *10 and 0.5 for the other reduced activity alleles (e.g. *41)) have been identified, as well as duplicated or multiplicated alleles (e.g. *1 × 2). A list of the most important allelic variants and their effect on the activity of the CYP2D6 enzyme (including rs-numbers and HGVS nomenclature) can be found in Supplementary Table 2A. The frequencies of allele groups with different gene activity scores and of separate alleles in different ethnic groups are presented in Supplementary Table 2B, C.

Based on *CYP2D6* genotype, patients can be translated into four predicted phenotypes: normal metaboliser (NM), intermediate metaboliser (IM), poor metaboliser (PM) or ultra-rapid metaboliser (UM). The different predicted phenotypes are defined based on the total gene activity score or gene activity score of the genotype. The DPWG defines NM as having a gene activity score of 1.25 through 2.5, IM as having a gene activity score of 0.25 through 1, PM as having a gene activity score of 0 and UM as having a gene activity score ≥ 2.75. The translation of genotype to phenotype is further defined in Supplementary Material 1 and summarized in Table 1. A comprehensive genotype to predicted phenotype translation can be found in Supplementary Table 2D, which can be used to program the translation of genotype results into predicted phenotypes in laboratory information systems.

GENE: CYP2C19

Since *CYP2C19* has extensively been described in a published DPWG guideline [14], a summary of the gene and its variants can be found in Supplementary Material 2. Alleles leading to absent, or reduced CYP2C19 enzyme activity have been identified (with the null alleles *2 and *3 as the most prevalent ones), as well as a genetic variant leading to slightly enhanced enzyme activity (*17). As a result, some individuals have a genetically determined absent or strongly reduced CYP2C19 enzyme activity (PM), due to homozygosity or compound heterozygosity of alleles leading to absent or reduced enzyme activity. Others have a genetically reduced CYP2C19 enzyme activity due to heterozygosity for such an allele (IM). A third group has a genetically enhanced CYP2C19 enzyme activity due to homozygosity for *17 (UM). See Table 1 for an overview.

A list of the most important allele variants and their effects on the enzyme activity of the CYP2C19 enzyme (including rs-numbers and HGVS nomenclature) can be found in Supplementary Table 3A. Supplementary Table 3B provides an updated overview of the frequencies of the most important alleles and predicted phenotypes in different populations. A complete genotype to predicted phenotype translation table, which can be used to programme the translation of genotype to predicted phenotypes in laboratory information systems, can be found in Supplementary Table 3C.

GENE-DRUG INTERACTION

Venlafaxine is mainly converted by CYP2D6 to the active metabolite O-desmethylvenlafaxine. Venlafaxine and O-desmethylvenlafaxine are primarily converted by CYP3A4 and CYP2C19 to the less active metabolite N-desmethylvenlafaxine [9]. Gene variants changing CYP2D6 activity are thus expected to affect exposure to venlafaxine and its active metabolite O-desmethylvenlafaxine, and as a result, the development of adverse effects and/or effectiveness of venlafaxine.

Mirtazapine is mainly converted by CYP2D6 and CYP1A2 to hydroxy metabolites [10]. These hydroxy metabolites have no significant pharmacological activity. Therefore, variant CYP2D6 activity is expected to affect exposure to mirtazapine, and as a result, the development of adverse effects and/or effectiveness of mirtazapine. Mirtazapine is mainly converted by CYP3A4 to N-desmethylmirtazapine [10], which pharmacological activity is 5-10 fold less than that of mirtazapine [15], and inactive N-oxide metabolites. The effect of *CYP3A4* variants is expected to be less than that of *CYP2D6* variants, because none of the main *CYP3A4* variants fully abolish enzyme activity. In addition, variation in CYP3A4 activity mostly has a non-genetic cause via substance-mediated inhibition or induction [16]. Because mirtazapine is not reported to be metabolised by CYP2C19 [10], it is not expected that variation in CYP2C19 activity has kinetic or clinical consequences. Therefore, mirtazapine might serve as a suitable alternative for patients with *CYP2C19* variants.

Moclobemide is converted by CYP2C19 and CYP2D6 of which altered CYP2C19 activity is reported to alter moclobemide exposure [11], and as a result, the risk for development of adverse effects and/or effectiveness. Moclobemide is a CYP2C19 inhibitor and therefore inhibits its own metabolism.

Duloxetine is converted to inactive metabolites by CYP1A2 and CYP2D6. Duloxetine is a moderate inhibitor of CYP2D6 [12]. Genetic variants changing CYP2D6 activity are expected to affect drug exposure, and as a result, the risk for development of adverse effects and/or effectiveness of duloxetine. Similarly as for *CYP3A4* and mirtazapine, the effect of *CYP1A2* genetic variants is expected to be smaller than that of *CYP2D6* variants for duloxetine due to the minor role of genetic causes on variation in *CYP1A2* activity [16].

SUPPORTING BODY OF EVIDENCE

A detailed description of the literature collection, assessment and preparation of the gene-drug monograph methods has previously been published [4]. In brief, a systematic review of literature was performed, relevant articles were summarized, and therapeutic recommendations were proposed by a KNMP scientist (from 2007 mainly MN). The performed search and the article selection strategy for each gene-drug combination are described in Supplementary Material 3. The quality of evidence was scored on a 5-point scale ranging from 0 (lowest – data on file) to 4 (highest – well performed controlled study or meta-analysis) and the impact of the clinical effect was scored on a 7-point scale ranging from AA# (positive effect) to F (highest negative effect). This clinical impact scale (AA#-F) runs parallel to the Common Terminology Criteria for Adverse Events (CTCAE); where CTCAE grade 5 severity is equal to clinical relevance score F (death) and CTCAE grade 1 severity is equal to clinical relevance score B. The clinical relevance score additionally includes the scores AA#, AA and A, since these do not exist in the CTCAE. These regard "Positive clinical effect", "No clinical or kinetic effect", and "A significant kinetic effect or a statistically significant, but not clinically relevant clinical effect", respectively. Two independent DPWG members checked the summary and scores of each article. Inconsistencies or disagreement were subsequently discussed with the entire DPWG that also made the final decision on therapeutic recommendations. The summaries, scores and references of the articles reviewed to devise this guideline can be found in Supplementary Table 1A–E. DPWG guidelines are in general checked for agreement with current evidence every 5 years and an updated version of the guideline is published if recommendations are adjusted.

Table 2. Therapeutic recommendations based on *CYP2D6* and *CYP2C19* phenotype for venlafaxine, mirtazapine, moclobemide, and duloxetine (if present).

Drug	Gene	Predicted phenotype	Therapeutic recommendation[a] (if present)[b]
Venlafaxine	*CYP2D6*	PM	It is not possible to offer adequately substantiated advice for dose reduction based on the literature. - avoid venlafaxine Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, (es)citalopram and sertraline. - if it is not possible to avoid venlafaxine and side effects occur: - reduce the dose - monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum. Furthermore, a reduced effectiveness of venlafaxine has been observed in depression patients with this gene variation.
		IM	It is not possible to offer adequately substantiated advice for dose reduction based on the literature. - avoid venlafaxine Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, (es)citalopram and sertraline. - if it is not possible to avoid venlafaxine and side effects occur: - reduce the dose - monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.
		UM	-
Mirtazapine	*CYP2D6*	All	-
Mirtazapine	*CYP2C19*	All	-
Moclobemide	*CYP2C19*	All	-
Duloxetine	*CYP2D6*	All	-

[a]In the pharmacotherapeutic recommendations, the normal dose is defined as the dose that would be given to the same patient if he or she had no gene variant.
[b]No pharmacotherapeutic recommendation: therapy adjustment is not required or beneficial for this phenotype-drug combination.
IM Intermediate metaboliser, *PM* Poor metaboliser, *UM* Ultra-rapid metaboliser.

GENERAL CONCLUSIONS OF EVIDENCE

CYP2D6-venlafaxine

It is reported that it is difficult to establish venlafaxine therapy that is both effective and well tolerated in patients with low O-desmethylvenlafaxine/venlafaxine ratios [17]. Both IM and PM are characterised by smaller ratios than the O-desmethylvenlafaxine/venlafaxine ratio > 4 showing precision in predicting venlafaxine responders/partial-responder (92%) and patients without venlafaxine-related adverse events (88%) in this study. Indeed, three studies including a combined group of 10 IM + PM, 49 PM and 3 PM, respectively, found a reduced effectiveness of venlafaxine therapy for IM + PM and PM. Also, three studies found an increase in side effects for PM (23 PM included) and one study reported that all five IM cases stopped venlafaxine treatment because of side effects. In addition, one study found a reduction in marked or severe side effects for the combined PM + IM + UM group. But this study did not find a difference when the groups were evaluated separately, so no effect was found for PM versus IM versus NM+gene activity score 1/0 versus UM. Based on these data and despite a small meta-analysis and other studies not confirming an effect of *CYP2D6* phenotype on response or side effects, the DPWG decided that a gene-drug interaction is present, and that therapy adjustment is required for PM and IM.

Clinical effects in UM (total of 27 UM) have only been assessed in five studies. Of these five studies, only one with 7 UM included reported a significant effect on therapeutic effectiveness. Two studies did not find an effect on adverse events. One study found a reduction in marked or severe side effects for PM + IM + UM but did not find an effect for PM versus IM versus (NM+gene activity score 1/0) versus UM. In addition, the observed 22% decrease in venlafaxine + O-desmethylvenlafaxine exposure is relatively low compared to the width of the therapeutic range. For these reasons, the DPWG decided that therapy adjustment is not required for UM.

Details on the included studies are provided in Supplementary Tables 1A and 4A.

CYP2D6-mirtazapine

A study with 3 PM and single dose administration found a longer duration of a dry mouth for PM. Two studies from the same group, one with 38 IM and one with 28 IM showed an increase in side effects and either a reduced or a better (or faster) effectiveness. However, the study with 38 IM did not find significant differences in plasma concentrations of mirtazapine between NM and IM, making it very unlikely that the observed differences in clinical outcomes were due to *CYP2D6* gene variants. The other study only determined effects during treatment initiation and the patient

group was not representative for patients normally treated with mirtazapine. In addition, a study with 27 PM or IM, a study with 1 PM, and 2 PM case reports found no (increase in) side effects for PM and IM on mirtazapine. No clinical effects were found for UM. Nine studies show alterations in dose-corrected steady state plasma concentration of mirtazapine with increased exposure observed for *CYP2D6* PM and IM and decreased exposure for UM, while five studies found no kinetic differences. Due to the effect of variant *CYP2D6* on mirtazapine pharmacokinetics, the DPWG concluded that there is a gene-drug interaction. Because there is insufficient evidence for a clinical effect of PM and no evidence for a clinical effect of IM and UM, the DPWG decided that adjustment of therapy is not required for patients with decreased or increased CYP2D6 activity. Details of included studies are provided in Supplementary Tables 1B, 4B.

CYP2C19-mirtazapine

None of the available studies, a study with 171 patients with the number of PM, IM and UM not mentioned, a study with 10 IM, and a case report with 1 PM, found an effect of *CYP2C19* phenotype on exposure, adverse effects, or effectiveness of mirtazapine (see Supplementary Tables 1C and 4C for details). The DPWG thus concluded that there is no evidence for a gene-drug interaction and no therapy adjustment is required for variant *CYP2C19* phenotype.

CYP2C19-moclobemide

The two available studies showed an increase in exposure or decrease in clearance of moclobemide in healthy *CYP2C19* PM volunteers (15 PM included). However, in case of repeated dosing, the exposure increase of approximately 1.5 times is modest. In addition, although the moclobemide exposure may deviate because of the altered *CYP2C19* metabolic capacity, this does not lead to an increased incidence of side effects or effectiveness, as far as is known. Because of the lack of evidence for a clinical effect, the DPWG concluded that adjustment of therapy is not required for this gene-drug interaction. Details are provided in Supplementary Tables 1D, and 4D.

CYP2D6-duloxetine

Convincing evidence for a clinical effect is lacking. The evidence for an effect on duloxetine response and adverse events in a study with 23 *CYP2D6* IM was not consistent in time and the observed difference was small and unlikely to be clinically significant. In two cases in which adverse events occurred in IM, there were also other risk factors that could explain these adverse events. Despite a very high duloxetine plasma concentration in another case, adverse events were lacking. A study with 23 IM found a lower duloxetine exposure in these patients than in NM, but two other studies with a total of 21 PM and 38 IM failed to show duloxetine clearance to differ from NM. For these reasons, the DPWG concluded that there is insufficient evidence for a gene-drug interaction and thus for a need to adjust treatment. Details are provided in Supplementary Tables 1E, and 4E.

PHARMACOTHERAPEUTIC RECOMMENDATIONS

The DPWG recommendation for therapy with venlafaxine in patients known to be *CYP2D6* PM and IM, and the absence of recommendations for the other investigated gene-drug combinations is summarized in Table 2. Supplementary Table 5A–E provides an overview of suggested pop-up or look-up texts for electronic prescribing systems for pharmacists and physicians. These can be used to program alerts into a clinical decision support system (CDSS). A brief description of the rationale for the therapeutic recommendation for venlafaxine in *CYP2D6* IM and PM is indicated below. More details are available in the third column of Supplementary Table 4A.

Usually, the DPWG calculates dose adjustments to optimize treatment based on the difference in drug exposure compared to NM. For venlafaxine, the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine is used to determine whether the plasma concentration lies within the therapeutic range, but side effects do not appear to be related to this sum. As it is not clear what the side effects are related to, it is not possible to calculate a dose reduction in such a way that the risk of side effects for PM and IM would be equal to the risk for NM. In addition, results for PM appear to indicate that the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine is not a good measure of the effectiveness for depression. Indeed, it is difficult to establish venlafaxine therapy that is both effective and well tolerated in patients with low O-desmethylvenlafaxine/venlafaxine ratios [17]. Thus, it is not possible to offer adequately substantiated advice for dose reduction based on the literature. Therefore, the DPWG recommends avoiding venlafaxine for *CYP2D6* PM and IM and instead prescribe antidepressants that are not, or to a lesser extent, metabolized by CYP2D6, including, for example, duloxetine, mirtazapine, (es)citalopram and sertraline. If it is not possible to avoid venlafaxine and side effects occur, the DPWG recommends reducing the dose and monitoring effect and side effects or checking the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, it is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained.

IMPLICATIONS FOR CLINICAL PRACTICE

Ongoing debate persists whether and which gene-drug interactions should be implemented into routine psychiatry. Points of debate include the amount of evidence that is necessary supporting effectiveness and cost-effectiveness of pre-emptive PGx testing and its reimbursement [18]. As a consequence, gene-drug interactions which are ready for implementation are hampered in application in clinical practice [1]. To overcome this inconclusiveness and to guide clinicians on whether or not to order relevant PGx genotyping tests prior to initiating pharmacotherapy, the DPWG has developed the Clinical Implication Score [6]. The DPWG Clinical Implication Score for a certain gene-drug interaction can be scored as: essential, beneficial, or potentially beneficial; these categories are specified in Supplementary Table 6A. The development of these categories and the systematic scoring criteria have been described previously elsewhere [6]. In brief, the implications for clinical practice are based on four criteria: (1) the clinical effect associated with gene–drug interaction, (2) the level of evidence supporting the associated clinical effect, (3) the number needed to genotype (NNG) in the Dutch population to prevent the clinical effect and (4) the availability of and type of PGx information in the drug label.

The scores provided for each of these criteria by the DPWG for actionable gene-drug interaction *CYP2D6*-venlafaxine can be found in Supplementary Table 6B. The DPWG concludes that pre-emptive genotyping of *CYP2D6* is potentially beneficial for venlafaxine therapy. This score indicates that *CYP2D6* genotyping prior to treatment with venlafaxine can be considered on an individual patient level. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline.

Since the Clinical Implication Score is only assigned for drug-gene pairs with therapeutic recommendations where pre-emptive genotyping might provide benefit, no score is assigned to *CYP2D6* and mirtazapine and duloxetine, and *CYP2C19* and mirtazapine and moclobemide.

DIFFERENCES BETWEEN AVAILABLE GUIDELINES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recently published a pharmacogenetic guideline for serotonin

reuptake inhibitor antidepressants including venlafaxine and duloxetine [19]. Differences between the CPIC and the DPWG methodology have previously been described in detail, which can explain possible differences between presented guidelines [20]. In addition, regional differences in health care between the United States/Canada and the Netherlands could result in differences in the DPWG and CPIC guidelines. Like the DPWG, the CPIC recommends the prescription of an alternative antidepressant not metabolized by CYP2D6 due to increased incidence of adverse effects for venlafaxine for *CYP2D6* PM. Comparably to the DPWG, the CPIC recommends no action for *CYP2D6* UM due to a lack of evidence on clinically relevant effects of reported pharmacokinetic changes. The CPIC also recommends no action for *CYP2D6* IM as they state that evidence on clinically relevant effects of a changed O-desmethylvenlafaxine/venlafaxine ratio is missing. However, the DPWG recommends action as the DPWG concludes that a clinical effect for *CYP2D6* IM can be substantiated as is discussed in the section "General conclusions of evidence". Finally, the CPIC concludes that data supporting a clinically relevant impact of *CYP2D6* gene variants is lacking for duloxetine and thus recommends no prescribing action, similar to the DPWG guideline. To the best of our knowledge, no other clinical guidelines regarding gene-drug interactions for mirtazapine and moclobemide are published in English.

Disclaimer

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

DATA AVAILABILITY

All data and material are either included in the Supplementary information or publicly available (i.e., the published articles, PubMed). The guidelines and background information are available on the website of the Royal Dutch Pharmacists Association (KNMP) [21]. The guidelines and background information will also be available on PharmGKB.org.

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AUTHOR CONTRIBUTIONS

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

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

This research involves a literature study and no human subjects, human material, or human data. Therefore, no approval by an ethics committee was needed.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Marga Nijenhuis.

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