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Published in:
European Journal of Human Genetics

DOI:
10.1038/s41431-021-01004-7

Publication date:
2022

ARTICLE

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

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The Dutch Pharmacogenetics Working Group (DPWG) guideline presented here, presents the gene-drug interaction between the genes *CYP2C19* and *CYP2D6* and antidepressants of the selective serotonin reuptake inhibitor type (SSRIs). Both genes' genotypes are translated into predicted normal metabolizer (NM), intermediate metabolizer (IM), poor metabolizer (PM), or ultra-rapid metabolizer (UM). Evidence-based dose recommendations were obtained, based on a structured analysis of published literature. In *CYP2C19* PM patients, escitalopram dose should not exceed 50% of the normal maximum dose. In *CYP2C19* IM patients, this is 75% of the normal maximum dose. Escitalopram should be avoided in UM patients. In *CYP2C19* PM patients, citalopram dose should not exceed 50% of the normal maximum dose. In *CYP2C19* IM patients, this is 70% (65–75%) of the normal maximum dose. In contrast to escitalopram, no action is needed for *CYP2C19* UM patients. In *CYP2C19* PM patients, sertraline dose should not exceed 37.5% of the normal maximum dose. No action is needed for *CYP2C19* IM and UM patients. In *CYP2D6* UM patients, paroxetine should be avoided. No action is needed for *CYP2D6* PM and IM patients. In addition, no action is needed for the other gene-drug combinations. Clinical effects (increase in adverse events or decrease in efficacy) were lacking for these other gene-drug combinations. DPWG classifies *CYP2C19* genotyping before the start of escitalopram, citalopram, and sertraline, and *CYP2D6* genotyping before the start of paroxetine as "potentially beneficial" for toxicity/effectivity predictions. This indicates that genotyping prior to treatment can be considered on an individual patient basis.

European Journal of Human Genetics (2022) 30:1114–1120; https://doi.org/10.1038/s41431-021-01004-7

INTRODUCTION

Pharmacogenomics (PGx) encompasses the notion that genetic variation can lead to variation in drug response. This shifts "one-size fits all" pharmacotherapy towards "tailor-made" pharmacotherapy. Although PGx is widely acknowledged, its implementation in daily clinical practice remains challenging [1]. One of the barriers preventing implementation in daily clinical practice was the lack of clear guidelines on how to interpret and apply PGx test results. To resolve this barrier, the Royal Dutch Pharmacists Association (KNMP) established the Dutch Pharmacogenetics Working Group (DPWG) in 2005 [2]. The main objectives of the DPWG are (1) to develop PGx informed therapeutic recommendations based on systematic literature review, and (2) to assist physicians and pharmacists by integrating the recommendations into computerized systems for drug prescription, dispensing, and automated medication surveillance. The DPWG is a multidisciplinary group in which (clinical) pharmacists, physicians, clinical pharmacologists, clinical chemists and epidemiologists are represented. Recently, the DPWG guidelines were endorsed by the European Association of Clinical Pharmacology and Therapeutics and the European Association of Hospital Pharmacists. The DPWG guidelines and future updates will be published in the European

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Received: 9 July 2021 Revised: 12 October 2021 Accepted: 2 November 2021
Published online: 16 November 2021

Journal of Human Genetics, in order to meet the public request for this information also outside the Dutch health care system.

This guideline presents the gene-drug interaction between *CYP2D6* and *CYP2C19* and antidepressants of the selective serotonin reuptake inhibitor type (SSRIs). First, it describes background information regarding genetic variation in the genes *CYP2D6* and *CYP2C19*. Second, the evidence for gene-drug interactions between *CYP2D6* and *CYP2C19* and individual SSRIs is presented (Supplementary Tables 1–9), as is the clinical implication score for these gene-drug interactions (*Implications for clinical practice section*). Finally recommendations are compared to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines [3].

Drugs: selective serotonin reuptake inhibitors

SSRIs are licensed for several indications, such as the treatment of depression, anxiety disorders, and obsessive-compulsive disorders. The mechanism of action of SSRIs mostly relies on the inhibition of reuptake of serotonin by the serotonin transporter (SERT). This is thought to be responsible for the antidepressant effect. However, treatment response and remission is only present in one third of the patients [4], while in addition antidepressant drugs may also lead to side effects, such as agitation, headache, gastro-intestinal symptoms as vomiting or diarrhoea, and (rarely) serotonergic syndrome. Selection of an appropriate antidepressant drug is, to a great extent, still empirical based [5]. Whether there is sufficient effect or presence of side effects, relies among others on the metabolism of the SSRI by the Cytochrome P450 system.

Citalopram is a racemic mixture of S- and R-citalopram, whereby escitalopram (the S-enantiomer) is the active enantiomer. Citalopram and escitalopram are primarily metabolized by CYP2C19 and to a lesser extent by CYP3A4 to an inactive metabolite.

Fluoxetine is metabolized extensively to the active and equipotent metabolite norfluoxetine by CYP2D6. CYP2C9, CYP2C19, and CYP3A4 are, possibly, also involved. Fluoxetine and norfluoxetine are potent inhibitors of CYP2D6, moderate inhibitors of CYP2C9, and mild to moderate inhibitors of CYP2C19 and CYP3A4.

Paroxetine is a potent antagonist of SERT and is metabolized by CYP2D6 and CYP3A4 to inactive metabolites. In addition, it is a potent inhibitor of CYP2D6.

Fluvoxamine is converted by CYP2D6 and to a lesser extent by CYP1A2. Fluvoxamine is a strong inhibitor of CYP1A2, a moderate inhibitor of CYP2C19 and CYP3A4, and a weak inhibitor of CYP2D6.

Sertraline is metabolized to N-desmethylsertraline by CYP2C19, CYP2B6, and to a far lesser extent by CYP2C9, CYP3A4, and CYP2D6. Sertraline does not significantly inhibit CYP enzymes.

Gene: CYP2C19 (Cytochrome P450 family 2 subfamily C member 19)

CYP2C19, formulated as *Cytochrome P450 family 2 subfamily C member 19*, is located on chromosome 10q23.33, has 9 exons, and a total size of approximately 120 kb. It encodes the metabolic enzyme CYP2C19 and is expressed in the liver, duodenum, small intestine, stomach and gall bladder [6]. With over 30 different allele variants in *CYP2C19* being identified and described in the literature [7–9], each allele variant is indicated with an asterisk and a number, with *1 being the wild type allele. Except for *2, *3 and *17, the prevalence of individual variants is low. The *2- and *3-alleles are null alleles, leading to an inactive CYP2C19 enzyme. In contrast, the *17-allele results in an increased CYP2C19 enzyme activity. Supplementary Table 10A lists the most important allele variants and their predicted effect on the enzyme activity of the CYP2C19 enzyme (including rs-numbers and HGVS nomenclature).

The frequency of the various *CYP2C19* variant alleles and the associated phenotypes varies significantly between nations and ethnic groups [10]. The *2-allele has a frequency of ~15% in White and African populations, while in Asian populations the frequency is ~30%. The *3-allele has a very low frequency in White and African populations and a frequency of 5–11% in Asian populations. As a result, 12–23% in Asian populations as well as 1–7.5% in White and African populations have a complete CYP2C19 deficiency (*CYP2C19* poor metabolizers (PM)). In contrast, the frequency of the *17-allele is 18–27% in White and African populations and 1–4% in Asian populations [10–12], resulting in a percentage of 3–7% in White and African populations and 0–0.2% in Asian populations being *CYP2C19*17 homozygotes (ultra-rapid metabolizers (UM)). Supplementary Table 10B provides an overview of the frequencies of the alleles most important for genotyping in different populations.

Translation of genotype to predicted phenotype

The DPWG defines patients with one allele leading to a CYP2C19 enzyme with diminished or no activity as *CYP2C19* intermediate metabolizers (IM), and patients homozygous or compound heterozygous for such alleles as *CYP2C19* PMs. The *CYP2C19* IM phenotype includes patients compound heterozygous for a *17-allele and an allele leading to a CYP2C19 enzyme with no or diminished activity, because the effect of the *17-allele on enzyme activity has been shown to be small and not to compensate for the effect of a null allele. For the same reason, the DPWG decided to include the *1/*17 genotype in the *CYP2C19* normal metabolizer (NM) phenotype (see Supplementary Material 1A for a detailed rationale). Therefore, the DPWG only assigns *17/*17 to a separate genotype, i.e., *CYP2C19* UM.

The genotype to predicted phenotype translation is summarized in Table 1. A complete genotype to predicted phenotype translation table, which can be used to programme the translation of genotype results into predicted phenotypes in laboratory information systems, can be found in Supplementary Table 11.

Gene: CYP2D6 (Cytochrome P450 family 2 subfamily D member 6)

For *CYP2D6*, a detailed explanation of the gene and its variants can be found in Supplementary Materials 1B as *CYP2D6* has previously been described elsewhere as part of the DPWG guidelines [13]. In addition, a list of the most important allele variants and their effect on the enzyme activity of the CYP2D6 enzyme (including rs-numbers and HGVS nomenclature) can be found in Supplementary Table 12A, whereas Supplementary Table 12B provides an overview of the frequencies of the alleles most important for genotyping in different populations. The genotype to predicted phenotype translation is summarized in Table 1. A complete genotype to predicted phenotype translation table, which can be used to programme the translation of genotype results into predicted phenotypes in laboratory information systems, can be found in Supplementary Table 13.

Gene-drug interaction

Pharmacological mechanism. CYP2D6 and CYP2C19 are major metabolizing enzymes for SSRIs. Increased enzyme activity of CYP2C19 is expected to lower plasma concentrations of escitalopram, citalopram, and sertraline, therefore potentially hampering the antidepressant effect. On the other hand, decreased enzyme activity of CYP2C19 is associated with increased plasma concentrations of escitalopram, citalopram, and sertraline. The increased plasma concentrations may result in SSRI-induced side effects.

Increased enzyme activity of CYP2D6 is expected to lower plasma concentrations of paroxetine, fluoxetine, and fluvoxamine, therefore potentially decreasing the antidepressant effect. On the other hand, decreased enzyme activity of CYP2D6 is associated with increased plasma concentrations of paroxetine, fluoxetine, and fluvoxamine. The increased plasma concentrations may result in SSRI-induced side effects. However, as the therapeutic ranges of SSRIs are relatively broad and the preferred 70% SERT occupancy,

Table 1. Translation of genotype to predicted phenotype for CYP2C19 and CYP2D6.

Gene	Examples of diplotypes	Genotypes	Predicted phenotypes
CYP2C19	*1/*1, *1/*17	Two normal function alleles or one normal function and one increased function allele.	Normal metabolizer
	*1/*2, *1/*3, *2/*17, *3/*17	One no or decreased function allele in combination with either one normal function allele or one increased function allele.	Intermediate metabolizer
	*2/*2, *2/*3, *3/*3	Two no or decreased function alleles.	Poor metabolizer
	*17/*17	Two increased function alleles.	Ultrarapid metabolizer
CYP2D6	*1/*1, *1/*41, *1/*41×3[a]	Gene dose[b] 1.5–2.5	Normal metabolizer
	*1/*4, *41/*41, *4/*41	Gene dose[b] 0.5–1	Intermediate metabolizer
	*4/*4, *4/*5	Gene dose[b] 0	Poor metabolizer
	*1/*1×2, *1/*2×2, *2×3/*4, *1/*41×4[a]	Gene dose[b] ≥ 3	Ultrarapid metabolizer

The *-alleles mentioned in the table above are characterized by the following sequence variations:
*CYP2C19**1: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations).
*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.−806C > T; NP_000760.1: p.(Ile331Val); NC_000010.11: g.94761900 C > T.
*CYP2D6**1: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations).
*CYP2D6**2: rs-numbers: rs16947 and rs1135840; NM_000106.6: c.[886 C > T; 1457 G > C]; NP_000097.3: p.(Arg296Cys; Ser486Thr); NC_000022.11: g.[42127941 G > A; 42126611 C > G].
*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**5: *CYP2D6* full gene deletion.
*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 sequence not available; Ser486Thr); NC_000022.11: g.[42127941 G > A; 42127803 C > T; 42126611 C > G].
[a]x2 denotes a gene duplication, x3 a gene triplication and x4 a gene quadruplication.
[b]The gene dose is 1 for an allele encoding a fully functional enzyme, 0.5 for an allele encoding a reduced activity enzyme and 0 for an allele encoding an inactive enzyme.

which should be achieved for optimal clinical outcome, seems to occur at relatively low doses [14, 15], changes in plasma concentrations might not have clinical consequences.

For paroxetine and fluoxetine specifically, differences in clinical effect and/or prevalence of side effects between *CYP2D6* genotypes is expected to be relatively small. This is because of the strong inhibitory effect of these drugs on CYP2D6, in which phenotypes change from NM to PM during chronic dosing [16, 17].

Supporting body of evidence

A detailed description of the methods used for literature collection, assessment and preparation of the gene-drug monograph has previously been published elsewhere [2, 18]. In brief, a systematic review of literature was performed, relevant articles were summarized, and therapeutic recommendations were proposed by a scientist of the Royal Dutch Pharmacists Association (predominantly MN from 2007). The performed search and selection strategy can be found in Supplementary Material 1C. Each article was provided with two scores: (1) the level of evidence and (2) the clinical impact. The level of evidence was scored using a five-point scale ranging from 0 to 4, with 0 being the lowest (data on file) and 4 being the highest (published controlled studies of good quality or meta-analyses). The impact of the clinical effect was scored using a seven-point scale ranging from AA# to F, with AA# indicating a positive effect and F indicating the highest negative effect. The criteria used to develop these scores have been published in detail previously [2, 18]. The clinical impact scale runs parallel to the Common Terminology Criteria for Adverse Events (CTCAE), with CTCAE grade 5 severity being equal to the clinical relevance score F (death) and CTCAE grade 1 severity being equal to the clinical relevance score B. Clinical relevance scores AA#, AA and A are defined as a positive clinical effect, no kinetic or clinical effect, and a kinetic effect or not clinically relevant effect, respectively, as these do not exist in the CTCAE.

The summaries and scores of the articles reviewed to devise this guideline can be found in the Supplementary Table 1 through 9. The summary and scores of each article were checked by two independent DPWG members. The DPWG made the final decision on the therapeutic recommendations.

General conclusions of evidence

Detailed rationales for the conclusions of evidence and the kinetic and clinical consequences for each predicted phenotype are provided in Supplementary Table 14 through 22. A brief description is given below.

CYP2C19 – *Escitalopram*. A study showed an increase in therapy failure for PM and UM (increase in the percentage of patients switched to another antidepressant). For this reason, the DPWG decided to recommend therapy adjustment for UM.

As IM and PM lead to a distinct increase in escitalopram plasma concentration and so in the risk of escitalopram-induced QT prolongation, a decision was made to recommend to lower the maximum dose in IM and PM patients to compensate for this plasma concentration increase. Details are provided in Supplementary Table 14, the summaries of reviewed articles in Supplementary Table 1.

CYP2C19 – *Citalopram*. As a study found a positive correlation between QT_c interval and dose, it was decided to recommend to lower the maximum dose in IM and PM patients to compensate for the plasma concentration increase in these patients. For UM, no warning is issued for the gene-drug interaction, as there were no significant clinical effects reported. Details are provided in Supplementary Table 15, the summaries of reviewed articles in Supplementary Table 2.

CYP2C19 – *Sertraline*. For sertraline, the *CYP2C19* phenotype was shown to affect sertraline exposure, but no clinical consequences were reported. The DPWG recommends a decrease in the

maximum dose for PM patients, due to the relative high increase in concentration compared to the therapeutic range. Because of the smaller effect in IM and UM patients, the DPWG decided that there was not enough evidence to recommend an adjustment of therapy for these patients. Details are provided in Supplementary Table 16, the summaries of reviewed articles in Supplementary Table 3.

CYP2D6 – *Paroxetine*. For most *CYP2D6* UM patients, the plasma concentration at steady state was below the detection limit and therapeutic efficacy was lacking. As a precaution, the DPWG recommends selecting an alternative. As no clinical effects were reported for IM and PM, no action is required for these gene-drug interactions. Details are provided in Supplementary Table 17, the summaries of reviewed articles in Supplementary Table 4.

CYP2D6 – *Fluoxetine*. Studies found an effect of *CYP2D6* phenotype on the conversion of fluoxetine to its active metabolite, but no effect on the sum of the plasma concentrations of the active substances, response and side effects. Thus, no adjustment of therapy is needed for these gene-drug interactions. Details are provided in Supplementary Table 18, the summaries of reviewed articles in Supplementary Table 5.

CYP2D6 – *Fluvoxamine*. Studies found a not very strong effect of the *CYP2D6* phenotype on fluvoxamine exposure and no effect on response and side effect. For this reason, the DPWG decided that no adjustment of therapy is needed for these gene-drug interactions. Details are provided in Supplementary Table 19, the summaries of reviewed articles in Supplementary Table 6.

CYP2C19 – *Fluvoxamine,* CYP2D6 – *Escitalopram/citalopram, and* CYP2D6 – *Sertraline*. No gene-drug interactions are expected for these three gene-drug combinations. Indeed, the systematic reviews confirmed that there is no or insufficient evidence to support a gene-drug interaction for these three combinations. This confirms the suitability of these drugs as possible alternatives for other SSRIs in patients with a *CYP2C19* or *CYP2D6* variant, respectively. Details are provided in Supplementary Table 20 through 22, the summaries of reviewed articles in Supplementary Table 7 through 9.

Pharmacotherapeutic recommendations

The DPWG recommendations for therapy with SSRIs in patients known to have an aberrant *CYP2C19* or *CYP2D6* metabolizer status is summarized in Table 2. A more detailed version of the recommendations, including their rationale, is provided in Supplementary Tables 14 through 22. A brief version is indicated below.

The DPWG calculates dose adjustments to optimize treatment based on the difference in exposure with NM. Calculated dose adjustments are subsequently 'rounded off' to make application in clinical practice more feasible.

In terms of escitalopram and *CYP2C19* UM, the DPWG decided to recommend an alternative antidepressant, because the data to calculate a dose increase were not sufficiently reliable.

For PM, the DPWG recommends a dose reductions to 50% of the normal maximum dose based on the median of the calculated dose adjustment of 54% and the statement in the SmPC of a 50% dose adjustment. For IM, the DPWG recommends a dose reduction to 75% of the normal maximum dose based on a calculated weighted mean of 68%. For prevention of higher plasma concentrations in PM and IM than in NM, only the maximum dose of escitalopram has to be reduced. See Supplementary Table 14 for details.

In terms of citalopram and *CYP2C19* PM, the DPWG recommends a dose reduction to 50% of the normal maximum dose based on the 48% calculated from the AUC increase reported by the FDA. The dose reduction based on our own data was considered insufficiently reliable due to the wide variation between the 6 studies (46–108%) and the low number of total PM ($n = 32$).

For IM, the DPWG recommends a dose reduction to 75% and 65–70% of the normal maximum dose for the tablets and the drops, respectively, based on a calculated weighted mean of 71% of the normal dose. For prevention of higher plasma concentrations in PM and IM than in NM, only the maximum dose of escitalopram has to be reduced. See Supplementary Table 15 for details.

In terms of sertraline and *CYP2C19* PM, the DPWG recommends a dose reduction to 37.5% of the normal dose, based on a calculated dose adjustment of 34%. However, as the initial dose for children and certain indications for adults is the lowest commercially available strength of 25 mg, the recommendation for a dose decrease is limited to the maximum dose. See Supplementary Table 16 for details.

In terms of paroxetine and *CYP2D6* UM, the DPWG recommends selecting an alternative antidepressant. A dose adjustment could not be calculated because the plasma concentration was below the detection limit in 71% of the UM patients. See Supplementary Table 17 for details.

No therapy adjustments are needed for other gene-drug and phenotype-drug combinations. Supplementary Table 23A through I gives an overview of suggested pop-up texts for electronic prescribing systems for pharmacists and physicians. These can be used to programme alerts into the clinical decision support system.

Implications for clinical practice

Ongoing debate persists whether and which single-drug gene pairs should be implemented into routine care. Points of debate include the amount of evidence that is necessary supporting effectiveness of pre-therapeutic genotyping, cost-effectiveness of PGx testing in the pre-therapeutic setting and its reimbursement [19, 20]. As a consequence drug-gene pairs which are ready for implementation are hampered in the uptake into the clinical practice [1, 21]. In an effort to overcome this inconclusiveness and to direct clinicians on whether or not to order relevant PGx genotyping tests before initiating therapy, the DPWG has developed the clinical implication score. The pre-therapeutic PGx results for a certain drug-gene pair can be scored as: essential, beneficial, or potentially beneficial. The development of these categories and the systematic scoring criteria are discussed elsewhere [22]. In brief, the implications for clinical practice are based on a list of four criteria: the clinical effect associated with the gene-drug interaction, the level of evidence supporting the clinical effect, the effectiveness of the intervention in preventing the clinical effect (i.e., the number needed to genotype) and the PGx information included in the drug-label. The scores provided for each of these criteria by the DPWG can be found in Supplementary Table 24.

As a results, the DPWG concludes pre-therapeutic PGx analysis of *CYP2C19* to be potentially beneficial for citalopram, escitalopram, and sertraline. In terms of *CYP2D6*, pre-therapeutic PGx analysis is considered to be potentially beneficial for paroxetine. This score indicates that genotyping prior to treatment can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline.

Because therapeutic recommendations are lacking for the other gene-drug combinations, pre-therapeutic genotyping provides no benefit for these gene-drug combinations. For this reason, the clinical implication score (with scores ranging from potentially beneficial to essential) is not applicable to these gene-drug combinations.

The DPWG recommendation to consider genotyping on an individual patient basis before initiation of citalopram,

Table 2. Summary therapeutic recommendations based on CYP2C19 and CYP2D6 phenotype for escitalopram, citalopram, sertraline, paroxetine, fluoxetine, and fluvoxamine.

Drug	Gene	Phenotype	Therapeutic recommendation (if present)[a]
Escitalopram	*CYP2C19*	PM	Do not exceed the following doses (50% of the standard maximum dose): - Adults up to 65 years: 10 mg/day - Adults 65 years or older: 5 mg/day
		IM	Do not exceed the following doses (75% of the standard maximum dose): - Adults <65 years: 15 mg/day - Adults 65 years or older: 7.5 mg/day
		UM	Avoid escitalopram. Antidepressants that are not metabolized or that are metabolized to a lesser extent by CYP2C19 are, for example, paroxetine or fluvoxamine.
Citalopram	*CYP2C19*	PM	Do not exceed the following daily doses (50% of the standard maximum dose): - Adults up to 65 years: 20 mg as tablets or 16 mg as drops, - Adults 65 years or older: 10 mg as tablets or 8 mg as drops
		IM	Do not exceed the following daily doses: - Adults up to 65 years: 30 mg as tablets or 22 mg as drops, - Adults 65 years or older: 15 mg as tablets or 10 mg as drops
		UM	-
Sertraline	*CYP2C19*	PM	Do not give doses exceeding 75 mg/day. Guide the dose by response and side effects and/or sertraline plasma concentration.
		IM	-
		UM	-
Paroxetine	*CYP2D6*	PM	-
		IM	-
		UM	Avoid paroxetine. Antidepressants that are not metabolized by CYP2D6, or to a lesser extent, include for example citalopram or sertraline.
Fluoxetine	*CYP2D6*	PM	-
		IM	-
		UM	-
Fluvoxamine	*CYP2D6*	PM	-
		IM	-
		UM	-
Fluvoxamine	*CYP2C19*	PM	-
		IM	-
		UM	-
Escitalopram/Citalopram	*CYP2D6*	PM	-
		IM	-
		UM	-
Sertraline	*CYP2D6*	PM	-
		IM	-
		UM	-

PM: poor metabolizer, *IM:* intermediate metabolizer, *UM:* ultrarapid metabolizer.
[a]No pharmacotherapeutic recommendation: therapy adjustment is not required or beneficial for this phenotype-drug combinations.

escitalopram, sertraline, and paroxetine correlates reasonably well with and can give direction to the recommendation of the Dutch Association for Psychiatry. According to the Dutch Association for Psychiatry, pre-therapeutic genotyping is not recommended, even though it can be considered in patients that already experienced side effects or inefficacy with psychotropic drug use [23].

Differences between available guidelines

To the best of our knowledge, only pharmacogenetics guidelines by the DPWG and the CPIC do concern SSRI. The comparison of the methodologies for grading scientific evidence and strength of the recommendations between the CPIC and DPWG are described elsewhere [24, 25].

For the phenotype-drug combination *CYP2C19* UM – citalopram, the CPIC (2015) does recommend to choose an alternative for citalopram, whereas for *CYP2C19* UM – sertraline, *CYP2D6* PM – paroxetine, and *CYP2D6* PM – fluvoxamine, the CPIC (2015) does recommend to optimize the dose or choose an alternative. However, the DPWG states that no action is required for these phenotype-drug combinations. The difference in recommendation for *CYP2C19* UM – citalopram can be explained because the DPWG considers the *1/*17 genotype not different enough from the *1/*1 genotype to assign it a separate phenotype, whereas UM + *1/*17 was CPICs definition of UM in 2015. This consideration by the DPWG is based on studies that demonstrated that the effect of *17 is 1) smaller than that of one additional fully functional allele and 2) not correcting the effect of one null allele [26, 27]. Due to

the broader definition of UM, the CPIC (2015) recommends an alternative drug for escitalopram in an additional 26–30% of patients in the Netherlands (*CYP2C19* *1/*17) (calculation based on the observed allele frequencies in Dutch Whites).

For *CYP2C19* IM and PM patients, a reduction to 65–75% and 50% of the normal maximum dose, respectively, is recommended by the DPWG for escitalopram and citalopram. However, the CPIC (2015) solely recommends a 50% reduction of the escitalopram/citalopram starting dose for PM patients.

For *CYP2C19* PM patients, the DPWG recommends to not exceed 75 mg/day of sertraline, whereas the CPIC (2015) recommends a consideration of a 50% reduction of the starting dose or an alternative drug. The DPWG does not recommend action in *CYP2C19* UM patients, whereas the CPIC (2015) recommends to start with the recommended starting dose, but to consider an alternative drug if the patient does not respond to the recommended maintenance dose.

For *CYP2D6* PM patients, the CPIC (2015) recommends to select an alternative drug for paroxetine or, when paroxetine use is warranted, to consider a 50% dose reduction of the starting dose and titrate to response. The DPWG recommends no action. Although the DPWG agreed to the international consensus which allocates gene dose 2.5 to UM [28], at the moment, most Dutch genotyping laboratories cannot distinguish between *1×2/*41 (gene dose 2.5) and *1/*41×2 (gene dose 2), making allocating these genotypes to different predicted phenotypes very impractical.

For *CYP2D6* PM patients, the CPIC (2015) recommends a consideration of a 25–50% reduction of the recommended starting dose of fluvoxamine and titration to response. Otherwise, it recommends an alternative drug not metabolized by CYP2D6. The DPWG recommends no action.

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 KNMP.nl and will be available on PharmGKB.org.

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ACKNOWLEDGEMENTS

We want to thank Anna de Goede for performing the systematic reviews before April 2007 and Mandy van Rhenen for performing the systematic reviews for CYP2C19/(es)citalopram in 2013 and 2015, CYP2D6/(es)citalopram in 2016, and paroxetine in 2014 and 2016. In addition, we want to thank Leonora Grandia for initiating the pharmacogenetics subject within the Royal Dutch Pharmacists Association and

leading this until May 2012. The U-PGx consortium received funding from the European Community's Horizon 2020 Programme under grant agreement No. 668353 (U-PGx). The DPWG received funding from the Royal Dutch Pharmacists Association.

AUTHOR CONTRIBUTIONS

All authors have contributed to the conception and/or design of the work that led to the submission, the acquisition of data, and/or played an important role in the interpretation of the results. In addition, all authors drafted or revised the manuscript and approved the final version as well as agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropiately investigated and resolved.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

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

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41431-021-01004-7.

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