ARTICLE

Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between *CYP2D6*, *CYP3A4* and *CYP1A2* and antipsychotics

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The Dutch Pharmacogenetics Working Group (DPWG) aims to facilitate pharmacogenetics implementation in clinical practice by developing evidence-based guidelines to optimize pharmacotherapy. A guideline describing the gene-drug interaction between the genes *CYP2D6*, *CYP3A4* and *CYP1A2* and antipsychotics is presented here. The DPWG identified gene-drug interactions that require therapy adjustments when respective genotype is known for *CYP2D6* with aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol, and for *CYP3A4* with quetiapine. Evidence-based dose recommendations were obtained based on a systematic review of published literature. Reduction of the normal dose is recommended for aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol for *CYP2D6*-predicted PMs, and for pimozide and zuclopenthixol also for *CYP2D6* IMs. For *CYP2D6* UMs, a dose increase or an alternative drug is recommended for haloperidol and an alternative drug or titration of the dose for risperidone. In addition, in case of no or limited clinical effect, a dose increase is recommended for zuclopenthixol for *CYP2D6* UMs. Even though evidence is limited, the DPWG recommends choosing an alternative drug to treat symptoms of depression or a dose reduction for other indications for quetiapine and *CYP3A4* PMs. No therapy adjustments are recommended for the other *CYP2D6* and *CYP3A4* predicted phenotypes. In addition, no action is required for the gene-drug combinations *CYP2D6* and clozapine, flupentixol, olanzapine or quetiapine and also not for *CYP1A2* and clozapine or olanzapine. For identified gene-drug interactions requiring therapy adjustments, genotyping of *CYP2D6* or *CYP3A4* prior to treatment should not be considered for all patients, but on an individual patient basis only.

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INTRODUCTION

The study of effects of heritable genetic variation on drug response is referred to as pharmacogenetics (PGx). 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 lack of guidelines on the interpretation of genotype test results, drug-specific sensitivity towards altered metabolic activity and the limited availability of therapeutic recommendations. The Royal Dutch Pharmacists Association (KNMP) has appointed the Dutch Pharmacogenetics Working Group (DPWG) in 2005 [4, 5]. The DPWG develops evidence-based drug-specific PGx-guided therapeutic recommendations based on systematic literature review, of which the identity of included guidelines is based on the need for them in clinical practice. In addition, it implements these recommendations into computerized systems used nationwide for medication prescription, dispensing and monitoring. Gene variants are generally grouped based on reported activity, but variant activity is often substrate specific, resulting in different impact of variant activity on varying drugs [6]. In addition, genotyping laboratories report different activities for some reported gene variants. Therefore, the DPWG aims to

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determine the pharmacological relevance of gene variants and draft genotype to phenotype translations for each reviewed gene. Together, this potentially stimulates uptake in clinical practice. 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), *CYP3A4 (Cytochrome P450 family 3 subfamily A member 4)* and, in some cases, *CYP1A2* (*Cytochrome P450 family 1 subfamily A member 2)* are routinely genotyped in diagnostic laboratories. However, uncertainties about determined variants and their relevance for antipsychotic treatment hampered implementation in clinical practice. Therefore, the DPWG decided to develop a guideline for these gene-drug interactions, which is presented here. Firstly, background information of the covered antipsychotics and genetic variation in *CYP2D6, CYP3A4* and *CYP1A2* is provided. Next, the scientific evidence on the gene-drug interaction between these genes and antipsychotics is discussed. Finally, the developed therapeutic recommendations for clinicians and clinical decision support systems are provided.

ANTIPSYCHOTIC DRUGS

Typical antipsychotics, including flupentixol, fluphenazine, haloperidol, pimozide and zuclopenthixol, block dopamine D2 receptors and are effective for the treatment of positive symptoms of psychotic disorders, as hallucinations and delusions. However, negative symptoms, including lack of initiative, energy, movement and emotion and cognitive problems, respond much less favorable to treatment with these antipsychotics. In addition, these drugs can have major adverse effects, especially extrapyramidal symptoms. Next to blocking the D2 receptors, atypical antipsychotics, including aripiprazole, brexpiprazole, clozapine, olanzapine, quetiapine and risperidone also block serotonin receptor 5-HT2A. Use of atypical antipsychotics is in general associated with a lower risk of extrapyramidal symptoms and in general better treatment of negative symptoms of psychotic disorders. Atypical antipsychotics are also prescribed for the treatment of other psychiatric disorders, including bipolar disorders, and as add-on therapy in major depressive disorder. However, the use of atypical antipsychotics can cause a range of adverse effects, including metabolic syndrome. Thus, although antipsychotics are prescribed to treat disruptive psychiatric disorders, the prevalence and severity of adverse effects require close monitoring of patients and also often result in adherence problems.

GENE: *CYP2D6*

For *CYP2D6*, a detailed explanation of the gene and its variants can be found in Supplementary Material 1A as *CYP2D6* has previously been described elsewhere as part of published DPWG guidelines [8]. The translation of genotype to phenotype is summarized in Table 1. Recently, an international consensus has been reached on genotype to phenotype translation for *CYP2D6* [9]. As a result, the DPWG adapted the enzyme activity score of *10-allele to 0.25, which, as a matter of fact, does not result in a change in the translation of genotype to predicted phenotype. The international consensus also allocates a gene dose of 2.5 to the ultra-rapid metabolizer (UM) phenotype. Consequently, when both a reduced functional and fully functional allele are present, the normal metabolizer (NM) phenotype will be predicted when the reduced functional allele is duplicated while the UM phenotype will be predicted when the fully functional allele is duplicated. Therefore, determination of the identity of the duplicated allele is required to perform the genotype to phenotype translation. However, the identity of the duplicated allele is currently not identified and reported by most of the Dutch laboratories that perform genotyping in clinical practice. The DPWG thus decided to postpone this change until the majority of Dutch laboratories report allele-specific duplications.

GENE: *CYP3A4*

CYP3A4 encodes the Cytochrome P450 family 3 subfamily A member 4 enzyme and is located on chromosome 7q22.1. Transcription variant 1 (NC_000007.14) has 13 exons [10]. *CYP3A4* is a highly polymorphic gene and contains 862 variants [11], from which over 30 *CYP3A4* alleles and 30 suballeles have been identified [12]. It has been determined that allelic variant *CYP3A4**22 results in reduced translation and therefore reduced enzymatic activity in the liver. CYP3A4-mediated hydroxylation of testosterone is reduced by approximately a factor 2.5 in carriers of the *22 allele [13] and this allele explains 12% of the variation in CYP3A4 activity worldwide [13]. As a result, the French National Network of Pharmacogenetics (RNPGx) recommends, besides *CYP3A5**3, retrospective genotyping of *CYP3A4**22 to explain the need for adapting the dose of CYP3A4-substrate immunosuppressive drugs including tacrolimus [14]. *18-allele also has a substrate-dependent reduced activity, whilst three other variants (*6, *20, and *26) have an inactivating gene variation [12]. In addition, in vitro indications of reduced activity have been found for six gene variants [12]. Supplementary Table 2A gives an overview of the most frequently occurring alleles with their HGVS nomenclature and metabolic capacity. Of note, the latest version of PharmVar [12] does not report the functional impact of *CYP3A4* alleles.

So far as can be determined from the data that are currently available, there is little variation between ethnic groups in the frequency of occurrence of the *CYP3A4**22 allele. The frequency for African-Americans and for Chinese individuals from the USA is in the same range as the frequency for Caucasians [15], with a reported allele frequency of 3.2-10.6% in the Dutch population [16–19]. *20 appears to occur almost exclusively in Spaniards and Latin-Americans [20] and *16 also appears to occur only in certain countries [20–22]. A multitude of alleles with known decreased activity or unknown activity are rare in all populations with a minor allele frequency (MAF) < 0.1% [23]. A frequency table of the predicted phenotype and the alleles *22, *20, and *16 in different ethnic groups is included in Supplementary Table 2B.

Translation of genotype to phenotype

Based on *CYP3A4* genotype, the DPWG decided to group patients into three predicted phenotypes: NM, intermediate metabolizer (IM) and poor metabolizer (PM). As the remaining activity of alleles with reduced activity has not been quantified properly and inactive alleles are not very common, the DPWG proposed predicted phenotypes for *CYP3A4* that currently do not distinguish between alleles with reduced or absent activity. NMs have a normal metabolic capacity with two alleles encoding normal activity, IMs have a reduced metabolic capacity (one allele with reduced or absent activity and one allele with normal activity; i.e., *1/*22) and PMs have a severely reduced metabolic capacity (two alleles with absent or reduced activity; i.e., *22/*22). The proposed translation of genotype to phenotype is depicted in Table 1. An extensive genotype to predicted phenotype translation can be found in Supplementary Table 2C, which can be used to program the translation of genotype results into predicted phenotypes in laboratory information systems.

Table 1. The translation of *CYP2D6*, *CYP3A4* and *CYP1A2* genotype to predicted phenotype or genotype group.

Gene	Phenotype/genotype group	Patient genotype[a]	Examples of genotypes[b]
CYP2D6	Normal metabolizer (NM)	Gene dose 1.25 through 2.5	*1/*1, *1/*10, *1/*41, *1 × 2/*41, *1/*41 × 2
	Intermediate metabolizer (IM)	Gene dose 0.25 through 1.0	*1/*4, *4/*10, *10/*41, *41/*41
	Poor metabolizer (PM)	Gene dose 0	*4/*4, *4/*6, *6/*6
	Ultra-rapid metabolizer (UM)	Gene dose ≥2.75	*1 × 2/*1, *1 × 3/*1, *1 × 2/*10 × 3, *1/*10 × 7
CYP3A4	Normal metabolizer (NM)	Homozygous or compound heterozygous for fully functional alleles	*1A/*1A, *1B/*1B, *1A/*1B
	Intermediate metabolizer (IM)	Heterozygous for a reduced functional or inactive allele	*1A/*22, *1B/*16
	Poor metabolizer (PM)	Homozygous or compound heterozygous for reduced functional or inactive alleles	*22/*22, *16/*22, *16/*16
CYP1A2	*1 F/*1 F	Homozygous for the allele with increased inducibility *1 F	*1 F/*1 F
	*1 A/*1 F	Compound heterozygous for a fully functional allele and allele *1 F with increased inducibility	*1 A/*1 F, *1B/*1 F
	Normal metabolizer (NM)	Homozygous or compound heterozygous for fully functional alleles	*1 A/ *1 A, *1 A/*1B, *1B/*1B
	*1 C heterozygous	Compound heterozygous for the reduced functional allele *1 C and a fully functional or increased inducible allele	*1 A/*1 C, *1B/*1 C, *1 C/*1 F
	*1 C/*1 C	Homozygous for the allele with reduced functionality *1 C	*1 C/*1 C
	Intermediate metabolizer (IM)	Compound heterozygous for a reduced or non-functional allele other than *1 C and a fully functional or increased inducible allele	*1 A/*1 K, *1B/*3
	Poor metabolizer (PM)	Homozygous for a reduced or non-functional allele other than *1 C or compound heterozygous for reduced or non-functional alleles	*1 C/*1 K, *1 K/*1 K, *1 K/*3, *3/*3

[a]The gene dose or gene activity score of a genotype is determined by adding the gene doses of the alleles (see Supplementary Table 1A).
[b]The *-alleles mentioned in the table above are characterized by the following sequence variations:
*CYP2D6**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].
*CYP3A4**1B: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations).
*CYP3A4**1 A: rs-number: rs2740574; NM_017460.6:c.-392G > A; protein sequence not changed; NC_000007.13:g.99382096 C > T.
*CYP3A4**16: rs-numbers: rs2740574 and rs12721627; NM_017460.6:c.[-392G > A; 554 C > G]; NP_059488.2:p.(Thr185Ser); NC_000007.13:g.99366093 G > C; 99382096 C > T].
*CYP3A4**22: rs-numbers: rs2740574 and rs35599367; NG_008421.1(NM_017460.6):c.[-392G > A; 522-191 C > T]; protein sequence not available (splice defect); NC_000007.13:g.99366316 G > A; 99382096 C > T].
*CYP1A2**1A: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations).
*CYP1A2**1B: rs-number: rs2470890; NM_000761.4:c.1548 T > C; NP_000752.2:p.(Asn516 =); NC_000015.10:g.74755085 T > C.
*CYP1A2**1 C: rs-number: rs2069514; no cDNA notation available; protein sequence not changed; NC_000015.9:g.75038220 G > A.
*CYP1A2**1 F: rs-number: rs762551; NC_000015.9(NM_000761.4):c.-9-154C > Ab; protein sequence not changed; NC_000015.9:g.75041917 C > A.
*CYP1A2**1 K: rs-numbers: rs762551, rs12720461 and rs2069526; NC_000015.9(NM_000761.4):c.[-10 + 103 T > G; -10 + 113 C > T; -9-154C > Ab]; protein sequence not changed; NC_000015.9:g.[75041341 T > G; 75041351 C > T; 75041917 C > A].
*CYP1A2**3: rs-numbers: rs56276455 and rs2470890; NM_000761.4:c.[1042 G > A; 1548 T > C]; NP_000752.2:p.(Asp348Asn; Asn516 =); NC_000015.10:g.[74751854 G > A; 74755085 T > C].

GENE: *CYP1A2*

CYP1A2 encodes the Cytochrome P450 family 1 subfamily A member 2 enzyme and is located on chromosome 15q24.1 and transcription variant 1 (NC_000015.10) has 7 exons [24]. *CYP1A2* is a polymorphic gene and contains 780 variants [25], from which over 20 *CYP1A2* alleles and 40 suballeles have been identified or predicted [26]. Suballele *1 F is reported to have a higher inducibility [26], but some studies found no effect of *1 F on metabolism [27–29]. Various suballeles including *1 C, *1 K and *7 lead to decreased enzyme activity, whereas *3, *4, *6 encode decreased gene expression in vivo [26]. Supplementary Table 3A gives an overview of the most frequently occurring alleles, including the HGVS nomenclature, translated to metabolic capacity.

The *1 F suballele is a common allele with a frequency of 44-73% [23]. Suballeles with decreased enzyme activity *1 C and *1 K have an allele frequency ranging from 0 to 27% in various populations [30, 31], with *1 C having a low allele frequency of 2.3% in the Dutch population [32, 33]. These large differences in allele *1 C gene variant frequencies may contribute to the differences in CYP1A2 activities found between various ethnic groups. A frequency table of the gene variants *1 F and *1 C, the most important gene variants, is included in Supplementary Table 3B.

Translation of genotype to genotype group or predicted phenotype

The *CYP1A2**1 F allele is the most common allele in the Dutch population and 43% of the Dutch population carries genotype *1 F/*1 F. Therefore, no guidelines are developed for this genotype, genotype *1 F/*1 F is instead used as the reference genotype for the development of this guideline. The DPWG

decided to group patients into six other genotype groups or predicted phenotypes based on genotype: *1 A/*1 F, NM, *1C-heterozygote, *1 C/*1 C, IM and PM. *1 A/*1 Fs have one fully functional allele and one *1F allele with increased inducibility while NMs have normal metabolic capacity with two functional alleles. Of the alleles with reduced activity, *1 C is the most common while the other alleles with reduced or absent activity occur so rarely that they are usually not detected in studies. For this reason, separate genotype groups were designed for *1 C. *1C-heterozygotes have one *1 C allele and one fully functional or increased inducible allele, while *1 C/*1 Cs are homozygous for the *1 C allele with reduced activity. Lastly, IMs have reduced metabolic capacity (one allele with reduced or absent activity except *1 C combined with one allele with normal or increased inducible activity) and PMs have severely reduced metabolic capacity (two alleles with reduced or absent activity not including *1C). The translation of genotype to genotype group or phenotype is depicted in Table 1. An extensive genotype to genotype group or predicted phenotype translation can be found in Supplementary Table 3C.

GENE-DRUG INTERACTION

Most antipsychotic drugs are metabolized by CYP2D6, CYP3A4 and CYP1A2. The metabolic pathway is outlined in short below, and discussed in detail by others [34]. Aripiprazole and risperidone are converted by CYP2D6 to active metabolites dehydroaripiprazole and 9-hydroxyrisperidone, respectively. Brexpiprazole, pimozide and zuclopenthixol are mainly converted by CYP2D6 to inactive metabolites. Haloperidol is primarily metabolized via glucuronidation and to a lesser extent by CYP2D6, CYP3A4 and carbonyl reduction. The enzymes involved in flupentixol metabolism are unknown, but it was believed that CYP2D6 plays an important role. Quetiapine is mainly converted by CYP3A4 to the inactive metabolite quetiapine sulfoxide and to N-desalkylquetiapine (norquetiapine). N-desalkylquetiapine is active, but seems to have mainly antidepressive activity. In addition, quetiapine and N-desalkylquetiapine are metabolized by CYP2D6 to a limited extent to active 7-hydroxymetabolites. Clozapine is primarily metabolized by CYP1A2 to the active, but clinically irrelevant, metabolite N-desmethylclozapine (norclozapine) with a minor metabolic role of other CYP enzymes, including CYP2D6. Lastly, olanzapine is primarily metabolized by UGT and CYP1A2 and to a far lesser extent by CYP2D6 and CYP3A4.

Based on the drug metabolism described above, gene variants changing CYP2D6 activity are expected to affect exposure, and as a result, the development of adverse effects and/or effectiveness of aripiprazole, brexpiprazole, flupentixol, haloperidol, pimozide, risperidone, and zuclopenthixol, whereas a minor or no effect is expected for clozapine, olanzapine, and quetiapine. Gene variants changing CYP3A4 activity are expected to affect quetiapine exposure and gene variants changing CYP1A2 activity clozapine and olanzapine exposure. The effect of *CYP3A4* and *CYP1A2* variants is expected to be smaller than that of *CYP2D6* variants, because none of the *CYP3A4* and *CYP1A2* variants fully abolish enzyme activity. In addition, variation in CYP3A4 and CYP1A2 activity mostly has a non-genetic cause via substance-mediated inhibition or induction.

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 selection strategy and performed search for each gene-drug combination is described in Supplementary Material 1B. The quality of evidence was scored on a 5-point scale ranging from 0 (lowest) to 4 (highest) 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 "Significant kinetic effect or not clinically relevant effect", respectively. Two independent DPWG members checked the summary and scores for quality of evidence and for clinical impact of each article. Inconsistencies or disagreement were subsequently discussed with the entire DWPG that also made the final decision on therapeutic recommendations. 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.

GENERAL CONCLUSIONS OF EVIDENCE

The summaries, scores, and references of the articles reviewed to devise this guideline can be found in Supplementary Tables 4, 5, and 6 of which a brief description is given below. Detailed rationales for the conclusions of evidence and the kinetic and clinical consequences for each predicted phenotype or genotype group are provided in Supplementary Tables 7, 8, and 9.

CYP2D6—aripiprazole

Multiple studies found a correlation between *CYP2D6*-predicted phenotype and plasma concentration of the sum of aripiprazole and the active metabolite dehydroaripiprazole. This effect was most pronounced for *CYP2D6*-predicted PMs and there were indications for a higher risk of adverse effects. The AUC was changed to a limited degree for IMs and UMs; there is insufficient or no evidence that this resulted in a different risk of adverse effects or reduced clinical effect.

CYP2D6—brexpiprazole

Only one study investigating the pharmacokinetic consequences of *CYP2D6* phenotype has been published. This study showed a non-significant increase of dose-corrected area under the concentration-time curve (AUC) of brexpiprazole without development of adverse effects for six IM patients. The drug label reports increased plasma concentration in PM and recommend a corresponding dose decrease. The accompanying European Public Assessment Report mentions slightly changed plasma concentrations for IMs and UMs, but does not recommend dose adaptation for these phenotypes.

CYP2D6—clozapine

A small effect of predicted CYP2D6 activity on the plasma concentration of clozapine was observed in one study, while multiple studies reported no differences in plasma concentrations between *CYP2D6* phenotypes. Multiple studies showed no increase in adverse effects, including the development of agranulocytosis, for PM, IM and UM patients. In addition, no effect of *CYP2D6* predicted phenotype on clinical response was found for PMs and IMs. Therefore, the DPWG concluded that therapy adjustment is not required.

CYP2D6—haloperidol

Haloperidol plasma concentrations were increased for *CYP2D6* PMs and IMs in multiple studies. One study with five PMs reported a higher score for extrapyramidal symptoms and one PM case with serious adverse effects is described. No clinically significant effects were found for IM. For *CYP2D6* UMs, haloperidol concentration

was decreased. A study with five UMs included found the lowest rate of improvement of symptoms for UM patients compared to other phenotypes.

CYP2D6—pimozide

One study showed a decreased pimozide clearance for *CYP2D6* PMs and IMs. Two studies confirmed an increased exposure in PMs, although it did not reach significance in these studies. However, pimozide can cause the rare, but serious, exposure-dependent adverse event QT prolongation.

CYP2D6—risperidone

The majority of kinetic studies showed an effect of *CYP2D6* phenotype on the exposure of risperidone and its active metabolite 9-hydroxyrisperidone. A large study involving 90 PMs, 91 IMs and 35 UMs found an increase in the percentage of patients with therapy failure for PMs and UMs, but not IMs, compared to NMs. Multiple smaller studies showed contradicting results regarding response and prevalence of adverse effects for all diverging phenotypes.

CYP2D6 – zuclopenthixol

Increased plasma concentrations and decreased oral clearance have been observed in multiple studies for PMs and IMs, while reduced serum concentration for UMs has been reported in one study. Although only supported by an increased number of dose changes in 11 IMs, these changes in plasma concentration are likely to increase the risk of side effects for PMs and IMs and reduce effectiveness for UMs.

CYP2D6—flupentixol, olanzapine or quetiapine

In general, the majority of included studies reported no pharmacokinetic differences between *CYP2D6* phenotypes for flupentixol, olanzapine and quetiapine. In addition, convincing evidence for a clinical effect is lacking according to the DPWG. Therefore, the DPWG concluded that there is no interaction between *CYP2D6* and these antipsychotics, confirming quetiapine to be a possible alternative antipsychotic in patients with *CYP2D6* gene variants.

CYP3A4—quetiapine

Only one study with 207 NMs, 29 IMs and 2 PMs is available on the evaluation of this gene-drug pair that showed highly increased serum concentration of quetiapine for PMs and slightly increased level for IMs. The impact of the PM phenotype was large and therefore likely to have clinical consequences, i.e., an increase in adverse effects. Supratherapeutic serum concentrations of quetiapine occurred significantly more often in patients carrying the *22 allele. Pharmacokinetic differences were large between PM and NM patients and minor between IM and NM patients. For example, the dose-corrected serum concentration was a factor 3.2 higher for PM and a factor 1.2 for IM compared to NM. In addition, the formation of the active metabolite N-desalkylquetiapine, which is probably responsible for the antidepressant effect, is expected to be strongly reduced for PMs. Thus, even though the evidence is limited with only one included pharmacokinetic study with 31 *CYP3A4**22 carriers, the DPWG concluded that a therapeutic recommendation is appropriate for patients with a known *CYP3A4**22/*22 genotype.

CYP1A2—clozapine or olanzapine

The majority of studies on the consequences of *CYP1A2* predicted phenotypes and genotype groups found no significant pharmacokinetic effect for clozapine or olanzapine. In addition, the majority of studies on the clinical consequences did not find differences in adverse effects or response between predicted phenotypes and genotypes groups. Moreover, the clinical effects were generally not substantiated by corresponding pharmacokinetic effects. Therefore, the DPWG must conclude that there is no gene-drug interaction between *CYP1A2* and clozapine or olanzapine.

PHARMACOTHERAPEUTIC RECOMMENDATIONS

The DPWG therapeutic recommendations to optimize therapy with antipsychotics in patients known to have a variant *CYP2D6* or *CYP3A4* phenotype are summarized in Table 2. The decision whether a gene-drug interaction is actionable was based on several criteria. Phenotype-drug pairs are considered actionable when clinical effects have been identified or are highly likely based on the strength of pharmacokinetic effect and exposure-clinical effect correlation. In general, a gene-drug interaction was considered actionable for a variant phenotype when (1) negative clinical effects, (2) kinetic effects for drugs with small therapeutic windows or (3) a large kinetic effect related to the width of the therapeutic window were observed. In cases of doubt, the decision was based on the clinical knowledge of DPWG members. The DPWG calculated dose adjustments to optimize treatment based on the difference in drug exposure compared to NMs (see Supplementary Tables 7 and 8 for details). The DPWG recommends a reduction of the (maximum) dose as specified in Table 2 for aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol for *CYP2D6* PMs and for pimozide and zuclopenthixol for *CYP2D6* IMs. For haloperidol and *CYP2D6* UMs, the DPWG recommends a dose increase by 1.5 times or an alternative drug. The DPWG also recommends an alternative drug or dose titration according to the maximum dose for the active metabolite paliperidone for risperidone prescription to *CYP2D6* UMs. For zuclopenthixol and *CYP2D6* UMs, it is recommended to try a dose increase of maximally 1.5 times the normal dose if the effectiveness is insufficient. Lastly, for *CYP3A4* PMs and quetiapine, the DPWG recommends a reduction to 30% of the normal dose for indications other than depression and choosing an alternative drug for the indication depression. No therapy adjustments are required for non-mentioned *CYP2D6* or *CYP3A4* phenotypes, because the clinical effects are minor or not present.

Supplementary Tables 10, 11, and 12 provide 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).

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 and cost-effectiveness of pre-therapeutic PGx testing and its reimbursement [35]. As a consequence, drug-gene pairs which are ready for implementation are hampered in application in clinical practice [1]. In an effort to overcome this inconclusiveness and to direct clinicians on whether or not to order relevant PGx genotyping tests prior to initiating therapy, the DPWG has developed the Clinical Implication Score. Only gene-drug interactions which are actionable are subject to receiving a Clinical Implication Score [36]. Because therapeutic recommendations are lacking for *CYP2D6*-clozapine, *CYP2D6*-flupentixol, *CYP2D6*-olanzapine, *CYP2D6*-quetiapine, *CYP1A2*-clozapine and *CYP1A2*-olanzapine, pre-therapeutic genotyping provides no benefit. The DPWG Clinical Implication Score for a certain gene-drug pair can be scored as: essential, beneficial or potentially beneficial; these categories are clarified in Supplementary Table 13A. The development of these categories and the systematic scoring criteria are discussed elsewhere [36]. In brief, the implications for clinical practice are based on: (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 and (4) the availability of and type of PGx information in the drug label.

Table 2. Summary of the therapeutic recommendations based on *CYP2D6* and *CYP3A4* phenotype for antipsychotics.

Drug	Gene	Phenotype	Therapeutic recommendation[a] (if present)[b]
Aripiprazole	*CYP2D6*	PM	Administer no more than 10 mg/day or 300 mg/month (68-75% of the normal maximum dose of aripiprazole).
Brexpiprazole	*CYP2D6*	PM	Use half of the normal dose.
Haloperidol	*CYP2D6*	PM	Use 60% of the normal dose.
	CYP2D6	UM	Use 1.5 times the normal dose or choose an alternative. Antipsychotics that are not metabolized by CYP2D6 - or to a much lesser extent - include, for example, flupentixol, penfluridol, quetiapine, olanzapine or clozapine.
Pimozide	*CYP2D6*	PM	Use no more than the following doses (50% of the normal maximum dose): - 12 years and older: 10 mg/day - younger than 12 years: 0.05 mg/kg per day to a maximum of 2 mg/day.
	CYP2D6	IM	Use no more than the following doses (80% of the normal maximum dose): - 12 years and older: 16 mg/day - younger than 12 years: 0.08 mg/kg per day to a maximum of 3 mg/day.
Risperidone	*CYP2D6*	PM	- Use 67% of the normal dose. - If problematic side effects originating in the central nervous system occur despite this reduced dose, then reduce the dose further to 50% of the normal dose.
	CYP2D6	UM	Choose an alternative or titrate the dose according to the maximum dose for the active metabolite (paliperidone) (oral 12 mg/day for adults and children from 15 years of age weighing at least 51 kg and 6 mg/day for children from 15 years of age weighing less than 51 kg; intramuscular 75 mg per 2 weeks).
Zuclopenthixol	*CYP2D6*	PM	Use 50% of the normal dose.
	CYP2D6	IM	Use 75% of the normal dose.
	CYP2D6	UM	There is insufficient information available to make a dose recommendation. If the effectiveness is insufficient: try a dose increase. Do not exceed 1.5 times the normal dose.
Quetiapine	*CYP3A4*	PM	- Indication depression: Choose an alternative. Aripiprazole appears to be less dependent on CYP3A4 for metabolism. Olanzapine is not metabolized by CYP3A4. - Other indications: Use 30% of the normal dose.

IM intermediate metaboliser, *PM* poor metaboliser, *UM* ultra-rapid metaboliser.

[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 combinations. This is also true for all genotype groups/phenotypes for the following gene-drug combinations: *CYP2D6*-clozapine, *CYP2D6*-flupentixol, *CYP2D6*-olanzapine, *CYP2D6*-quetiapine, *CYP1A2*-clozapine, and *CYP1A2*-olanzapine.

The scores provided for each of these criteria by the DPWG for actionable gene-drug interactions can be found in Supplementary Table 13B. The DPWG concludes that pre-therapeutic genotyping is potentially beneficial for aripiprazole, brexpiprazole, haloperidol, pimozide, risperidone and zuclopenthixol and *CYP2D6* and for quetiapine and *CYP3A4*. All gene-drug interactions were scored in this category due to lack of severe clinical effects (at least CTCAE Grade 3) in users of these drugs with a variant phenotype. This score indicates that pre-therapeutic PGx analysis for all patients treated with aforementioned antipsychotics is not recommended by the DPWG. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline. In addition, genotyping prior to treatment could be considered on an individual patient basis. The DPWG considers issues with multiple antipsychotics or other CYP2D6/CYP3A4-metabolized drugs as the main criterium to consider *CYP2D6/CYP3A4* genotyping. Other factors including decreased renal function and relevant comedication could also be weighted for each individual to determine the appropriateness of genotyping.

DIFFERENCES BETWEEN AVAILABLE GUIDELINES

To the best of our knowledge, no other clinical guidelines regarding gene-drug interactions for antipsychotics are published in English. To prioritize the order of guidelines for gene-drug interactions, The Clinical Pharmacogenetics Implementation Consortium (CPIC) assigns levels to gene-drug interactions. CPIC ranked the guideline regarding *CYP2D6* and antipsychotics a B, indicating that prescribing action is recommended [37], but the CPIC has so far not published this guideline.

The drug labels approved by the United States Food and Drug Administration (FDA) of aripiprazole, brexpiprazole and clozapine were included in the systematic reviews and recommend dose reduction for *CYP2D6* PMs [38]. Interestingly, the literature review of the DPWG showed only a minor contribution of *CYP2D6* phenotype to the variation in clozapine exposure without clinical consequences, which caused the DPWG to decide that therapy adjustment is not required.

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 healthcare 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) (Pharmacogenetic Recommendation Text. Available from: https://www.knmp.nl/). The guidelines and background information will also be available on PharmGKB.org.

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AUTHOR CONTRIBUTIONS

LB drafted the manuscript and contributed to interpretation of results. JvW supervised drafting of the manuscript and contributed to conceiving the work and interpretation of the results. MN contributed to conceiving the work and interpretation of the results, and performed the data extraction. BS drafted and published English versions of clinical decision support texts. NBV, AB, HG, EH, AR, GR, RvS, JS, DT, RvW, and VD contributed to conceiving the work and interpretation of the results. In addition, all authors 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 appropriately investigated and resolved.

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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.

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