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Nijenhuis, M.; Soree, B.; Jama, W.O.M.; Boer-Veger, N.J. de; Buunk, A.M.; Guchelaar, H.J.; ... ; Risselada, A.

ARTICLE

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Dutch pharmacogenetics working group (DPWG) guideline for the gene-drug interaction of *CYP2D6* and *COMT* with atomoxetine and methylphenidate

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

Pharmacogenetics (PGx) studies the effect of heritable genetic variation on drug response. Clinical adoption of PGx has remained limited, despite progress in the field. To promote implementation, the Dutch Pharmacogenetics Working Group (DPWG) develops evidence-based guidelines on how to optimize pharmacotherapy based on PGx test results. This guideline describes optimization of atomoxetine therapy based on genetic variation in the *CYP2D6* gene. The CYP2D6 enzyme is involved in conversion of atomoxetine into the metabolite 4-hydroxyatomoxetine. With decreasing CYP2D6 enzyme activity, the exposure to atomoxetine and the risk of atomoxetine induced side effects increases. So, for patients with genetically absent CYP2D6 enzyme activity (*CYP2D6* poor metabolisers), the DPWG recommends to start with the normal initial dose, bearing in mind that increasing this dose probably will not be required. In case of side effects and/or a late response, the DPWG recommends to reduce the dose and check for sustained effectiveness for both poor metabolisers and patients with genetically reduced CYP2D6 enzyme activity (*CYP2D6* intermediate metabolisers). Extra vigilance for ineffectiveness is required in patients with genetically increased CYP2D6 enzyme activity (*CYP2D6* ultra-rapid metabolisers). No interaction was found between the *CYP2D6* and *COMT* genes and methylphenidate. In addition, no interaction was found between *CYP2D6* and clonidine, confirming the suitability of clonidine as a possible alternative for atomoxetine in variant *CYP2D6* metabolisers. The DPWG classifies *CYP2D6* genotyping as being "potentially beneficial" for atomoxetine. *CYP2D6* testing prior to treatment can be considered on an individual patient basis.

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INTRODUCTION

Pharmacogenetics (PGx) studies the effect of heritable genetic variation on drug response. Because polymorphisms in pharmacogenetic loci can affect drug response, dose and drug selection based on these polymorphisms can improve safety and (cost-)effectiveness of pharmacotherapy. PGx guided pharmacotherapy constitutes one of the first clinical applications of genomics in medicine. However, clinical adoption of PGx has remained limited, despite scientific and clinical progress in the field. Implementation barriers have been previously reported [1]. Part of these barriers have been overcome in the past years, including the lack of clear guidelines on how to interpret and apply PGx test results.

The Royal Dutch Pharmacists Association (KNMP) established the Dutch Pharmacogenetics Working Group (DPWG) in 2005 to overcome this barrier [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. 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

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

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DPWG has additionally developed the clinical implication score, which is given to every gene-drug interaction requiring therapy adjustment [3]. The objective of this score is to direct clinicians on whether or not to order relevant PGx genotyping tests before initiating therapy. Recently, the DPWG guidelines were endorsed by the European Association of Clinical Pharmacology and Therapeutics (EACPT) and the European Association of Hospital Pharmacists (EAHP) [4, 5]. Other initiatives such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) were also established to promote implementation of PGx [6, 7].

The DPWG is a multidisciplinary group in which (clinical) pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists and toxicologists are represented. From 2005 onwards, the DPWG has systematically executed risk analyses for 108 gene-drug combinations resulting in 63 guidelines providing therapeutic recommendations for one or more variant phenotypes [8, 9]. Available DPWG guidelines and future updates will be published in an effort to provide transparency of their development and to fulfil the public demand for their publication [10–12].

This guideline describes the dose optimization of atomoxetine to reduce side effects in patients with genetically diminished CYP2D6 activity (*CYP2D6* poor and intermediate metabolisers). In addition, this guideline substantiates the need for extra vigilance for ineffectiveness in patients with genetically increased CYP2D6 activity (*CYP2D6* ultra-rapid metabolisers). Finally, the guideline substantiates the lack of a clinically significant interaction between methylphenidate and the *CYP2D6* and *COMT* gene, and between clonidine and *CYP2D6*. This manuscript provides an overview of the guideline development and summarizes the pharmacotherapeutic recommendations. 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 *gene-drug interaction* section includes background on the pharmacological mechanism of the interaction. In addition it also includes a list of the most prevalent *CYP2D6* and *COMT* variants associated with altered enzyme activity and the method developed by DPWG for local genotype-phenotype translation. This information may be useful for laboratories to select and/or design a *CYP2D6* or *COMT* assay and subsequently determine the patients' predicted phenotype based on the genotype results. Subsequently, the literature review supporting the *CYP2D6*-atomoxetine interaction and the lack of interactions for methylphenidate and clonidine is described and the DPWG guideline is presented. A summary of all references identified by the systematic review, which were used to develop this guideline, can be found in Supplementary Tables 1 through 3.

DRUGS: ATOMOXETINE, METHYLPHENIDATE, CLONIDINE

Atomoxetine and methylphenidate are commonly used drugs for the treatment of attention-deficit/hyperactivity disorder (ADHD) [13–17]. Clonidine is another treatment option for ADHD [13–15, 18]. Occurrence of side effects and lack of efficacy [13–18] can limit drug adherence, and therefore methods to reduce these would be valuable.

Atomoxetine is a non-stimulant ADHD drug that inhibits noradrenaline reuptake [16]. Atomoxetine is used when first-line treatment with psychostimulants such as methylphenidate or dexamphetamine is ineffective, discontinued due to side effects, contraindicated, or when 24 h effectiveness is required [13, 14, 16]. The onset of action for atomoxetine (4–8 weeks) is significantly slower than for psychostimulants (30–60 min) [13, 14, 16, 17].

Psychostimulants inhibit the reuptake of both dopamine and noradrenaline [13, 14]. Because of their efficacy and quick onset of action, psychostimulants are first-choice drugs for the treatment of ADHD in both children and adults [13–15, 17]. Within this group methylphenidate is mostly used first [13, 14, 17].

Clonidine is an agonist of the α2-adrenergic and can be used off-label for ADHD [13, 18]. It is less effective for treating ADHD than psychostimulants or atomoxetine [13, 18] and affects hyperactivity and impulsivity more than the cognitive symptoms [18]. However, it can be used as a drug of choice for patients with both ADHD and tics or comorbid sleep disorders, aggression and (oppositional defiant) behavioural problems [13, 14, 18]. Use of clonidine is often hampered by its sedative and hypotensive side effects [13, 14, 18].

GENE: CYTOCHROME P450 2D6 (*CYP2D6*)

For *CYP2D6*, a detailed explanation of the gene and its variants can be found in Supplementary Material 1 and Supplementary Tables 4A through C, 5a as *CYP2D6* has previously been described elsewhere as part of published DPWG guidelines [11]. The translation of genotype to phenotype is summarized in Table 1. Recently, a universal consensus has been reached on genotype to phenotype translation for *CYP2D6* [19]. As a result, the DPWG adapted the enzyme activity score of the *10-allele from 0.5 to 0.25, which does not result in any change in the translation 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, most of the Dutch laboratories that perform genotyping in clinical practice do currently not report which allele is duplicated. The DPWG thus decided to postpone this change until the majority of Dutch laboratories report allele-specific duplications.

GENE: CATECHOL-O-METHYLTRANSFERASE (*COMT*)

COMT is located on chromosome 22q11.21, has 8 exons, and a total size of approximately 28 kb [20]. It has two transcription start sites and therefore encodes two proteins: a long membrane-bound variant and a soluble variant in the cytoplasm which is 50 amino acids shorter [20]. Amino acid numbering usually follows the numbering of the long membrane-bound variant. The encoded COMT enzyme is involved in the catabolism of catecholamines, such as dopamine and noradrenaline in nerve cell synapses. It inactivates catecholamines by methylation. COMT is especially important for the dopamine level in the prefrontal cortex, as this area contains only few dopamine transporters that remove dopamine from the synaptic cleft. Because high levels of dopamine in the prefrontal cortex act as a negative feedback signal to dopamine in other parts of the brain, COMT probably also has an indirect effect on dopamine levels elsewhere in the brain [21].

The *COMT* polymorphism p.(Val158Met) results in a thermolabile enzyme and 2–4x lower enzyme activity, which raises the dopamine concentration mainly in the prefrontal cortex [22, 23]. This change is associated with improvements in functions such as attention, organisation and planning and may also have an effect on impulsiveness. This may influence subcortical dopaminergic neurotransmission due to prefrontal dopaminergic negative control over this neurotransmission. The HVGS nomenclature of the p.(Val158Met) variant is included in the legend of Table 1.

Ethnic diversity exists in the frequency of the *COMT* p.(Val158Met) variant [24, 25]. The prevalence of wildtype and variant is about equal in Whites. In the Netherlands, 30% is homozygous for the p.(Val158Met) variant and 50% is heterozygous [26]. Homozygotes for the wildtype make up the smallest population at 20%. In East-Asians and Africans, the frequency of the p.(Val158Met) variant is distinctly lower than in Whites. South-Asians and South Americans seem to have an intermediate p.(Val158Met) frequency. Supplementary Table 6 provides an overview of the p.(Val158Met) frequencies in different populations.

Table 1. Assignment of *CYP2D6* phenotypes and *COMT* genotype groups based on genotypes.

Gene	Predicted phenotype (i.e. based on genotype)/ assigned genotype group name	Genotype[a]	Examples of genotypes[b]
CYP2D6	Normal metaboliser (NM)	Gene dose 1.25 through 2.5	*1/*1, *1/*10, *1/*41, *1 × 2/*41, *1/*41 × 2
	Intermediate metaboliser (IM)	Gene dose 0.25 through 1.0	*1/*4, *4/*10, *10/*41, *41/*41
	Poor metaboliser (PM)	Gene dose 0	*4/*4, *4/*6, *6/*6
	Ultra-rapid metaboliser (UM)	Gene dose ≥2.75	*1 × 2/*1, *1 × 3/*1, *1 × 2/*10 × 3, *1/*10 × 7
COMT	Val/Val (wild type)	Homozygous wildtype for p.(Val158Met)	
	Val/Met	Heterozygous for p.(Val158Met)	
	Met/Met	Homozygous for p.(Val158Met)	

[a]The gene dose or gene activity score of a genotype is determined by adding the gene doses of the alleles (see Supplementary Table 5).
[b]x2 denotes gene duplication, x3 and x7 denote gene multiplication (resulting in 3 and 7 gene copies respectively).
The *-alleles and *COMT* variant mentioned in the table above are characterised by the following sequence variations:
*1: defined as the allele without variations affecting enzyme activity (in clinical practice as the allele without any of the determined variations).
*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.
*6: rs-number: rs5030655; NM_000106.6: c.454del; NP_000097.3: p.(Trp152fs); NC_000022.11: g.42129084del.
*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].
*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].
p.(Val158Met) (membrane isoform numbering): rs-number: rs4680; NM_000754.3: c.472 G > A; NP_000745.1: p.Val158Met; NC_000022.11: g.19963748 G > A.

Distinguished genotype groups

Three genotypes/genotype groups are distinguished: heterozygotes and homozygotes of p.(Val158Met) and wildtype genotypes (see Table 1). A genotype to distinguished genotype (group) translation table, which can be used to programme this translation in laboratory information systems, can be found in Supplementary Table 5B.

GENE-DRUG INTERACTION

Atomoxetine is primarily metabolised by CYP2D6 to 4-hydroxyatomoxetine [27]. This metabolite is equipotent to atomoxetine, but circulates in much lower concentrations in the plasma [27]. To a much lower extent, atomoxetine is metabolised by the enzyme CYP2C19 and other iso-enzymes to the inactive metabolite N-desmethylatomoxetine [27]. For this reason, exposure to atomoxetine (and thus the active moiety of atomoxetine) is expected to be higher in *CYP2D6* poor and intermediate metabolisers and lower in *CYP2D6* ultra-rapid metabolisers. This might result in a higher incidence of adverse events and a lower effectiveness, respectively.

Methylphenidate is mainly converted by the carboxylesterase CES1A1 and hydrolysis to the major metabolite α-phenyl-2-piperidine acetic acid (also known as ritalinic acid) [23, 28]. This metabolite is inactive. So, unlike atomoxetine therapy, methylphenidate therapy is not expected to be affected in patients with *CYP2D6* gene variants.

Methylphenidate inhibits the reuptake of dopamine and noradrenaline in the central nervous system, while the COMT enzyme inactivates catecholamines, such as dopamine and noradrenaline in nerve cell synapses, by methylation. For this reason, the *COMT* p.(Val158Met) variant, resulting in lower COMT enzyme activity, might increase side effects and effectiveness of methylphenidate.

Clonidine is excreted for 70% via urine (primarily in unchanged form: 40–60% of the dose) and for 20% via faeces [29]. It is not known which enzyme is responsible for the formation of the most important metabolite p-hydroxyclonidine [29]. Because a considerable portion of clonidine is excreted unchanged, CYP2D6 is not expected to have a large effect - if any - on clonidine therapy. Thus clonidine might be a possible alternative for atomoxetine in patients with *CYP2D6* gene variants.

LITERATURE REVIEW AND GENE-DRUG MONOGRAPH PREPARATION

A detailed description of the methods used for literature collection, assessment and preparation of the gene-drug monograph has previously been published elsewhere [2, 8]. 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 (mainly MN). The strategy for choosing gene-drug combinations and performing searches can be found in Supplementary Material 2. Each article was provided with two scores: (1) quality of evidence and (2) clinical impact. 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). The criteria used to develop these scores have been published in detail previously [2, 8]. 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 "Kinetic effect or not clinically relevant effect", respectively. The summaries of articles, and their respective scores, reviewed to devise this guideline can be found in the Supplementary Tables 1 through 3. 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 CONCLUSION OF EVIDENCE

Atomoxetine and *CYP2D6*

In the systematic review performed for atomoxetine and *CYP2D6*, all 8 kinetic studies and the Summary of Product Characteristics showed the plasma concentrations of atomoxetine in *CYP2D6* poor metabolisers to be much higher and/or those in *CYP2D6* intermediate metabolisers to be higher than in *CYP2D6* normal metabolisers. This was also true in studies in which the dose was adjusted based on efficacy and side effects. However, only a limited

Table 2. Pharmacotherapeutic recommendations[a] for the different genotype group-ADHD drug combinations (if present).

ADHD drug	Gene	Predicted phenotype (based on genotype) or assigned genotype group name	Pharmacotherapeutic recommendation (if present)[b]
Atomoxetine	*CYP2D6*	Poor metaboliser (PM)	- Start with the normal initial dose, bearing in mind that an increase in this dose probably will not be required - Advise the patient to report side effects (such as decreased appetite, vomiting, abdominal pain, constipation, insomnia, early waking, drowsiness, irritability, pupil dilation and itching) - If the medicine is effective, but side effects occur: reduce the dose and check whether the effect is conserved The plasma concentration of atomoxetine is a factor of 8–11 times higher for PM than for NM at the same dose.
		Intermediate metaboliser (IM)	- In the event of side effects occurring and/or a response later than 9 weeks: reduce the dose and check whether the effect is conserved The plasma concentration of atomoxetine is a factor of 2–3 times higher for IM than for NM at the same dose.
		Ultra-rapid metaboliser (UM)	- Be extra alert to reduced efficacy of the treatment - Advise the patient to report an inadequate effect - An alternative can be selected as a precaution Clonidine is not metabolised by CYP2D6.
Clonidine	*CYP2D6*	Poor metaboliser (PM)	-
		Intermediate metaboliser (IM)	-
		Ultra-rapid metaboliser (UM)	-
Methylphenidate	*CYP2D6*	Poor metaboliser (PM)	-
		Intermediate metaboliser (IM)	-
		Ultra-rapid metaboliser (UM)	-
Methylphenidate	*COMT*	Val/Met	-
		Met/Met	-

[a]Pharmacotherapeutic recommendation are for both adults and children, because literature does not point to a difference in effect of genotype groups between adults and children.
[b] – = no pharmacotherapeutic recommendation: no genotype group-drug interaction has been found.

increase in side effects was reported in 8 studies and in the Summary of Product Characteristics, probably due to the wide therapeutic range of atomoxetine (see Supplementary Tables 1, 7 for details). As a result, it is generally not necessary to reduce the dose for *CYP2D6* poor and intermediate metabolisers to such an extent that the plasma concentrations become identical to those for *CYP2D6* normal metabolisers. Atomoxetine is not effective in all patients. There are indications that the percentage of patients for whom atomoxetine is not effective decreases with increasing plasma concentrations of atomoxetine [30]. A higher plasma concentration can therefore also have a favourable effect. As an increase in side effects was also found for *CYP2D6* intermediate and poor metabolisers when the dose was adjusted based on efficacy and side effects, the DPWG decided that the *CYP2D6*-atomoxetine interaction necessitates a therapeutic recommendation for intermediate and poor metabolisers.

Hardly any data have been published about consequences for *CYP2D6* ultra-rapid metabolisers. For 1 ultra-rapid metaboliser, a decrease in atomoxetine exposure by approximately two thirds was found compared to the average for 7 normal metabolisers (see Supplementary Tables 1, 7 for details). Due to the risk of reduced efficacy, the DPWG decided that a therapeutic recommendation is also required for ultra-rapid metabolisers.

Literature did not point to a difference in the effect of variant *CYP2D6* metabolisers between adults and children.

Methylphenidate and *CYP2D6*

The systematic review performed for methylphenidate and *CYP2D6* only retrieved one article showing no effect of *CYP2D6* gene variants on methylphenidate exposure (see Supplementary Tables 2, 8 for details). For this reason, the DPWG concluded that there is no *CYP2D6*-methylphenidate interaction. Thus, the observed variance in side effects and efficacy in patients treated with methylphenidate cannot be explained by genetically changed CYP2D6 activity. In theory, methylphenidate could be used as an alternative for atomoxetine in patients with *CYP2D6* variants. However, because methylphenidate is one of the first-choice ADHD drugs and atomoxetine second choice, for most patients on atomoxetine methylphenidate will not be an option.

Methylphenidate and *COMT*

In the systematic review performed for methylphenidate and *COMT*, 8 of the 11 studies investigating the effect of *COMT* p.(Val158Met) on efficacy of methylphenidate in patients with ADHD did not find a significant effect (see Supplementary Tables 3, 9 for details). In two of these eight studies the significance of the effect disappeared after correction for multiple testing. The results of the remaining three studies are conflicting. One study with 112 ADHD patients found a better (or faster) response for p.(Val158Met) carriers, one study with 122 ADHD patients found a worse response for p.(Val158Met) carriers and one study with 514 patients found a better response for heterozygotes, but not for p.(Val158Met) homozygotes. A meta-analysis of 7 studies with a total of 699 patients found a worse response for p.(Val158Met) carriers. However, this meta-analysis overestimates the effect by using a fixed-effects model despite high heterogeneity between the studies. Thus, this meta-analysis provides no evidence for a statistically significant effect.

Of two studies investigating the effect on adverse events, a study with 107 ADHD patients found no effect and a study with 82 ADHD patients found a decrease in irritability for p.(Val158Met) carriers (see Supplementary Tables 3, 9 for details).

Because the effects of *COMT* p.(Val158Met) on efficacy are mostly negative or contradictory and because the results on

adverse events are not confirmed, the DPWG concludes that there is not enough evidence for a gene-drug interaction and therefore no need for therapy adjustment in patients with the *COMT* p.(Val158Met) variant.

So, the observed variance in side effects and efficacy in patients treated with methylphenidate cannot be explained by genetically changed COMT activity either. In addition, a general search on methylphenidate and gene variants performed in 2017, did not identify any more promising candidate genes than *COMT* (data not shown). Either very few studies were found or results of studies were contradictory. So, it seems that the variance in methylphenidate side effects and efficacy is either caused by non-genetic factors or by interactions with multiple genes with each of the genes having a small effect.

Clonidine and *CYP2D6*

No articles were retrieved in the systematic search for clonidine and *CYP2D6*. Therefore, the DPWG concluded that there are no indications for a gene-drug interaction and that clonidine is a possible alternative for atomoxetine in patients with *CYP2D6* gene variants.

PHARMACOTHERAPEUTIC RECOMMENDATIONS

The DPWG recommendation for therapy with atomoxetine in patients known to have a variant *CYP2D6* metaboliser status and the absence of recommendations for the other investigated gene-drug combinations is summarized in Table 2.

A brief description of the rationale for the therapeutic recommendation for atomoxetine in patients with a variant *CYP2D6* metaboliser status is indicated below. More details are available in the third column of Supplementary Table 7.

For *CYP2D6* poor metabolisers, three studies and the SmPC indicated that atomoxetine exposure was 8- to 11-fold higher than in normal metabolisers. Four studies and the SmPC showed these changes to be associated with a significantly increased frequency of side effects, including amongst others, insomnia, decreased appetite and weight loss, depression, and tremor, although a small study did not find an effect. An increase in side effects was also found when the dose was adjusted based on efficacy and side effects. One study found an increased efficacy in *CYP2D6* poor metabolisers, but two other studies did not. The American Summary of Product Characteristics provides a recommendation for dose adjustment in poor metabolisers or when used in combination with a *CYP2D6* inhibitor: start with the standard initial dose, but only increase this dose if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. The DPWG decided to adopt this dose recommendation. The DPWG further decided to add that, if the initial dose is not well tolerated but results in symptom improvement, it should be determined whether efficacy can be maintained when lowering the dose.

For *CYP2D6* intermediate metabolisers, six studies indicated that atomoxetine exposure was 2- to 3-fold higher than in normal metabolisers but, due to the wide therapeutic range of atomoxetine, this appears to have only a limited influence on the side effects. Out of five studies investigating side effects in intermediate metabolisers, one involving adults found a limited increase in the number of patients with dry mouth and sleep disorders (OR = 1.6 and 1.7). Three small studies did not find a significant difference in side effects for intermediate metabolisers. In the fifth study, 6 out of 10 patients who experienced side effects and/or had a late response at a standard dose were intermediate metabolisers. A dose reduction in two of these intermediate metabolisers (to 1.14 mg/kg per day and 0.42 mg/kg per day) resulted in a reduction of side effects while maintaining efficacy. For this reason, if side effects occur, the DPWG recommends to check whether efficacy can also be achieved at a lower dose. The DPWG recommends the same in case of a late response. Because low exposure is unlikely to be the cause of a late response in *CYP2D6* intermediate metabolisers, the dose might have been titrated upwards too much at the time a response occurs.

For *CYP2D6* ultra-rapid metabolisers no clinical data are available. As a precaution, the DPWG therefore recommends to be alert of reduced efficacy due to the lower plasma concentration of atomoxetine.

Supplementary Tables 10 through 13 present 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 the clinical decision support system (CDSS). The guidelines and background information are available on KNMP.nl [9] and will be available on PharmGKB.org.

IMPLICATIONS FOR CLINICAL PRACTICE

At the moment, consensus is lacking about whether and which gene-drug pairs should be implemented into routine care. The lack of consensus includes the required amount of evidence supporting effectiveness of pre-emptive genotyping, the cost-effectiveness of PGx guided therapy and reimbursement of PGx testing [31, 32]. This lack of consensus seems to have hindered implementation of gene-drug pairs which seem ready for implementation [1, 33]. In an effort to diminish this inconclusiveness and to guide clinicians on whether or not to order relevant PGx genotyping tests before starting therapy, the DPWG has developed the clinical implication score. The pre-emptive 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 [3]. In brief, the implications for clinical practice are based on a list of four criteria regarding the following: 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 (which includes 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 14.

As a result, the DPWG has concluded the clinical implication score of *CYP2D6*-atomoxetine to be "potentially beneficial" for the prevention of side effects and for drug efficacy. This score indicates that *CYP2D6* genotyping prior to treatment with atomoxetine can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guidelines.

Because therapeutic recommendations are lacking for methylphenidate in patients with a variant *CYP2D6* metaboliser status and in patients with the *COMT* p.(Val158Met) variant, and for clonidine in patients with a variant *CYP2D6* metaboliser status, pre-emptive genotyping of *CYP2D6* and *COMT* provides no benefit for these drugs. For this reason, the clinical implication score (with scores ranging from potentially beneficial to essential) is not applicable to methylphenidate and clonidine.

DIFFERENCES BETWEEN AVAILABLE GUIDELINES

To the best of our knowledge, the only other available guideline regarding a gene-ADHD drug interaction is the guideline on *CYP2D6* and atomoxetine from CPIC [34]. Differences between CPIC and DPWG methodology have previously been described in detail [7].

The main difference between the CPIC and DPWG guidelines on atomoxetine is that CPIC puts much more emphasis on the possibility of the normal starting dose being too low than DPWG. The reason for this difference is that DPWG considers the registered dose for patients without a gene variant to be adequate, whereas according to CPIC even the maximum registered dose might be too low to reach therapeutic concentrations (peak concentrations ≥200 ng/ml) in all NM. Whereas the DPWG recommendation indicates that the

normal starting dose will probably suffice for *CYP2D6* poor metabolisers, CPIC recommends doubling the starting dose in adults in case of no clinical response and in the absence of adverse events. In addition, CPIC recommends a further dose increase guided by plasma concentration if response remains inadequate and plasma concentration 2–4 h after dosing is <200 ng/ml. For children, CPIC recommends the latter when response and side effects are absent after 2 weeks. CPIC recommends a dose reduction only in case of unacceptable side effects.

Another difference is that DPWG gives the same recommendation for all IM, whereas CPIC gives separate recommendations for IM with gene dose 1 and IM with gene dose 0.25–0.75. The DPWG recommendation for IM is to reduce the dose and check whether the effect is maintained in case of side effects and/or a response later than 9 weeks. In contrast, CPIC indicates that doses greater than the registered maximum dose for adults and the registered target dose for children may be needed to achieve target concentrations in IM with gene dose 1, and recommends to treat IM with gene dose 0.25–0.75 the same as PM.

For UM, DPWG does not recommend a dose increase, but recommends to be alert on reduced efficacy and suggests choosing an alternative as a precaution. CPIC recommends the same for UM as for IM with gene dose 1, i.e. indicates that doses greater than the registered maximum dose for adults and the registered target dose in children may be needed to achieve target concentrations.

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 [9] and will be available on PharmGKB.org.

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AUTHOR CONTRIBUTIONS

MN performed most of the literature searches and article summaries, suggested clinical decision support texts, and drafted the manuscript. AR supervised drafting of the manuscript and contributed to conceiving the work and interpretation of the results. BS had the clinical decision support texts translated in English and published them. WOMJ collected data required for the *CYP2D6* genotype-phenotype translation for implementation into clinical decision support systems. NBV, AB, HJG, EJHF, GAR, RHNS, JJS, DT, JW, and RW contributed to conceiving the work and interpretation of the results. VHMD led the meetings in which the DPWG decided about the article summaries and clinical decision supports texts and contributed to conceiving the work and interpretation of the results. In addition, all authors revised the manuscript and approved the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

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

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