Translating pharmacogenetics to primary care

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Pharmacogenetics: From Bench to Byte

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Despite initial enthusiasm [1–3], the use of pharmacogenetics has remained limited to investigation in only a few clinical fields such as oncology and psychiatry [4–8]. The main reason is the paucity of scientific evidence to show that pharmacogenetic testing leads to improved clinical outcomes [9,10]. Moreover, for most pharmacogenetic tests (such as tests for genetic variants of cytochrome P450 enzymes) a detailed knowledge of pharmacology is a prerequisite for application in clinical practice, and both physicians and pharmacists might find it difficult to interpret the clinical value of pharmacogenetic test results. Guidelines that link the result of a pharmacogenetic test to therapeutic recommendations might help to overcome these problems, but such guidelines are only sparsely available. In 2001, an early step was taken to develop such guidelines for the therapeutic use of antidepressants, and these included *CYP2D6*-related dose recommendations drawn from pharmacokinetic study data [11]. However, the use of such recommendations in routine clinical practice remains difficult, because they are currently outside the ambit of the clinical environment and are not accessible during the decision-making process by physicians and pharmacists, namely the prescription and dispensing of drugs.

It was for these reasons that the Royal Dutch Association for the Advancement of Pharmacy established the Pharmacogenetics Working Group (PWG) in 2005. In this 15-member multidisciplinary working group, clinical pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists, and toxicologists are represented. The objective of the PWG is to develop pharmacogenetics-based therapeutic (dose) recommendations on the basis of a systematic review of literature, and to assist the drug prescribers as well as the pharmacists by integrating the recommendations into computerized systems for drug prescription and automated medication surveillance. The recommendations do not indicate patients who are eligible for genotyping, but merely aim to optimize drug use in the small but ever-increasing group of patients whose genotypes are known.

In the Netherlands, computerized drug prescription and automated medication surveillance are well organized, and the majority of general practitioners as well as nearly all the community and hospital pharmacists use such a system [12]. Most of these automated medication systems use the G-standard, an extensive electronic drug database [13]. The therapeutic (dose) recommendations composed by the PWG are incorporated into the G-standard, thereby directly linking the pharmacogenetics-based therapeutic (dose) recommendations to the decision-making process. The first recommendations were released with the October 2006 edition of the G-standard. To our knowledge, the PWG initiative is the first to integrate pharmacogenetic test results and therapeutic (dose) recommendations into automated medication surveillance systems to be applied nationwide. In this article, we describe the procedures followed by the PWG for structured pharmacogenetic data collection, assessment, and subsequent synthesis of therapeutic (dose) recommendations. Furthermore, we report the first 26 defined recommendations included in the G-standard.

STRUCTURED ASSESSMENT OF GENE-DRUG INTERACTIONS

Scope

The scope of the PWG comprises the compilation of therapeutic (dose) recommendations on the basis of gene–drug interactions. It was decided to commence with the polymorphisms that affect pharmacokinetics. A list of polymorphic enzymes involved in phases I and II of the metabolic process, including an overview of drug substrates, was compiled. The criteria for inclusion were: (i) that the enzyme is known to play an important role in the metabolic process in vivo, and (ii) that data relating to the gene–drug interaction are available in the published literature. The following sources were used for assessing whether these criteria were fulfilled:

- PubMed (http://www.ncbi.nlm.nih.gov)
- Website (http://medicine.iupui.edu/flockhart/table.htm, http://www.genemedrx.com, http://www.druginteractioninfo.org, http://www.themedicalletter.com)
- Drug interaction textbook [14]
- Pharmacogenetics textbook [15]

Data collection

For each drug, a systematic search of PubMed and Frisbee (a bibliography of Dutch medical literature) [16] was carried out. The articles included in the reference lists were individually screened for additional material or papers. Wherever information relating to gene–drug interaction was present in the European Public Assessment Report, the manufacturer was asked to provide further details. Review articles, studies involving non-human subjects and in vitro experiments were excluded.

Data assessment

For data assessment, a method earlier described was adapted [13]. Two core parameters were defined:

- Level of evidence of the gene–drug interaction. This indicates the quality of the evidence found in literature for the gene–drug interaction, and was scored on a five-point scale with a range from 0 (lowest evidence) to 4 (highest evidence) (Table 3.1) [17].
- Clinical relevance of the potential adverse drug event, decreased therapeutic response, or other clinical effect resulting from the gene–drug interaction.

The clinical relevance was scored on a seven-point scale derived from the National Cancer Institute's Common Toxicity Criteria [18]. A clinical or pharmacokinetic effect

Table 3.1 Assigned levels of evidence

	Criteria for assigning levels of evidence
4	Published controlled studies of good quality[a] relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints
3	Published controlled studies of moderate quality[b] relating to phenotyped and/or genotyped patients or healthy volunteers, and having relevant pharmacokinetic or clinical endpoints
2	Published case reports, well documented, and having relevant pharmacokinetic or clinical endpoints. Well documented case series
1	Published incomplete case reports
	Product information
0	Data on file
-	No evidence

[a]The study is deemed to be of "good quality" if:
(i) the use of concomitant medication with a possible influence on the phenotype is reported in the manuscript.
(ii) other confounders are reported (e.g., smoking status).
(iii) the reported data are based on steady-state kinetics.
(iv) the results are corrected for dose variability.
[b]Wherever one or more of these "good quality" criteria were missing, the quality of the study was considered to be "moderate."

that was not statistically significant was classified as AA (lowest impact), whereas death, for example, was classified as F (highest impact) (Table 3.2). At every level of this point scale, new events are added after assessment by the PWG.

Status report and therapeutic (dose) recommendation

For each of the assessed gene–drug interactions, a status report was prepared that presented an overview of key findings from selected articles from the published literature, along with the scores representing level of evidence and clinical relevance. Based on these scores, each gene–drug interaction was coded with the highest scored level of evidence and clinical relevance. After a final assessment of the information presented in the status report, a decision was made whether or not a therapeutic (dose) recommendation was required. These recommendations could include (i) a dose adjustment, (ii) advice on therapeutic strategy (e.g., the advice for therapeutic drug monitoring or a warning for increased risk of adverse drug event or diminished therapeutic efficacy), or (iii) the recommendation to select an alternative drug. In order to clarify how the PWG had arrived at the final therapeutic (dose) recommendation, a concise rationale was provided.

A specific procedure was followed in the preparation of the status report. After data collection, the level of evidence and clinical relevance of each article were independently

Table 3.2 Classification of clinical relevance

Classification of clinical relevance	
AA	Clinical effect (NS) Kinetic effect (NS)
A	Minor clinical effect (S): QTc prolongation (<450 ms ♀, <470 ms ♂), INR increase <4.5 Kinetic effect (S)
B	Clinical effect (S): short-lived discomfort (<48 h) without permanent injury, for example, reduced decrease in resting heart rate, reduction in exercise tachycardia, diminished pain relief from oxycodone and ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance, etc.)
C	Clinical effect (S): long-standing discomfort (48–168 h) without permanent injury, for example, increase risk of failure of therapy with tricyclic antidepressants or atypical antipsychotic drugs: extrapyramidal side effects, parkinsonism: ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects, e.g., dizziness).
D	Clinical effect (S): long-standing effect (>168 h), permanent symptom or invalidating injury, for example, failure of prophylaxis of atrial fibrillation; deep vein thrombosis
E	Clinical effect (S): Increased risk of failure of lifesaving therapy; expected bone marrow depression
F	Clinical effect (S): death; arrhythmia; unexpected bone marrow depression

ADE, adverse drug event; INR, international normalized ratio; NS, not statistically significant difference; S, statistically significant difference.

scored by two PWG members. In order to prevent interobserver variation, a seven-member subgroup of the PWG discussed the scores of each selected paper and composed a preliminary status report. This preliminary report was then evaluated by the complete PWG during one of its three-monthly meetings, resulting in the final consensus-based status report and inclusion into the G-standard.

Calculation of dose adjustments

The calculation of dose adjustments was based on four rules:

- Pharmacokinetic data only from papers with a level of evidence of 3 or 4 were used.
- Data from selected papers reporting both statistically significant and not statistically significant differences were used. Results showing differences that were not statistically significant were considered as having been caused by limited sample size per genotype. Dose recommendations were calculated only if statistically significant data were available, so as to rule out the possibility of making dosage calculations from data generated purely by chance.

- Dose calculations were based on the sum of parent drug and active metabolites for atomoxetine (4-hydroxyatomoxetine), clomipramine (desmethylclomipramine), imipramine (desipramine), nortriptyline (10-hydroxynortriptyline), propafenone (5-hydroxypropafenone), risperidone (9-hydroxy-risperidone), and venlafaxine (O-desmethylvenlafaxine).
- For prodrugs, pharmacokinetics of the active metabolite were used (e.g., morphine when codeine is used for analgesia).

We assumed that currently used standard doses are representative for extensive metabolizers. For calculating dose adjustments for the CYP2D6 PM phenotype (D_{PM}), we started by making a dose adjustment calculation from each selected paper from the published literature, using the formula below:

$$D_{PM}\,(\%) = (AUC_{EM} / AUC_{PM}) \times 100\%$$

After calculating dose adjustments from the data in each individual paper, a final dose recommendation was calculated as the population size-weighted mean of the individual dose adjustments:

$$D_{PM}\,(\%) = \frac{(N_{(a)} \times D_{PM(a)}) + (N_{(b)} \times D_{PM(b)}) + (N_{(c)} \times D_{PM(c)}) + \ldots + (N_{(x)} \times D_{PM(x)})}{N_{(a)} + N_{(b)} + N_{(c)} + \ldots + N_{(x)}}$$

N = number of subjects with corresponding phenotype in article a, b, c, … x

Dose recommendations of drugs for other genotypes and phenotypes were calculated using analogous equations, except in the case of prodrugs (e.g., codeine for analgesia) and drugs with metabolites whose contribution to the clinical effect is unknown (e.g., tamoxifen).

Consequences for automated medication systems

On the basis of the information collated in the status report, the PWG classified the gene–drug combination according to whether or not there was interaction between gene and drug (interaction: yes/no) and whether or not any alerts that were generated had to be tagged for action (action: yes/no). Wherever action is required, the alert with the therapeutic (dose) recommendation appears on the screen during prescription and dispensing (Figure 3.1). Where no action is required, the alert is only logged in the system.

Alerts will be generated only if a certain gene–drug combination occurs. Therefore, the recording of a patient's genotype in the computerized drug prescription or automated medication surveillance system is a prerequisite for the generation of an alert. The classifications and their consequences for the computerized drug prescription and automated medication surveillance system have been described earlier [13]. Four different types of alerts, each with its own text, are provided by the PWG; a prescriber

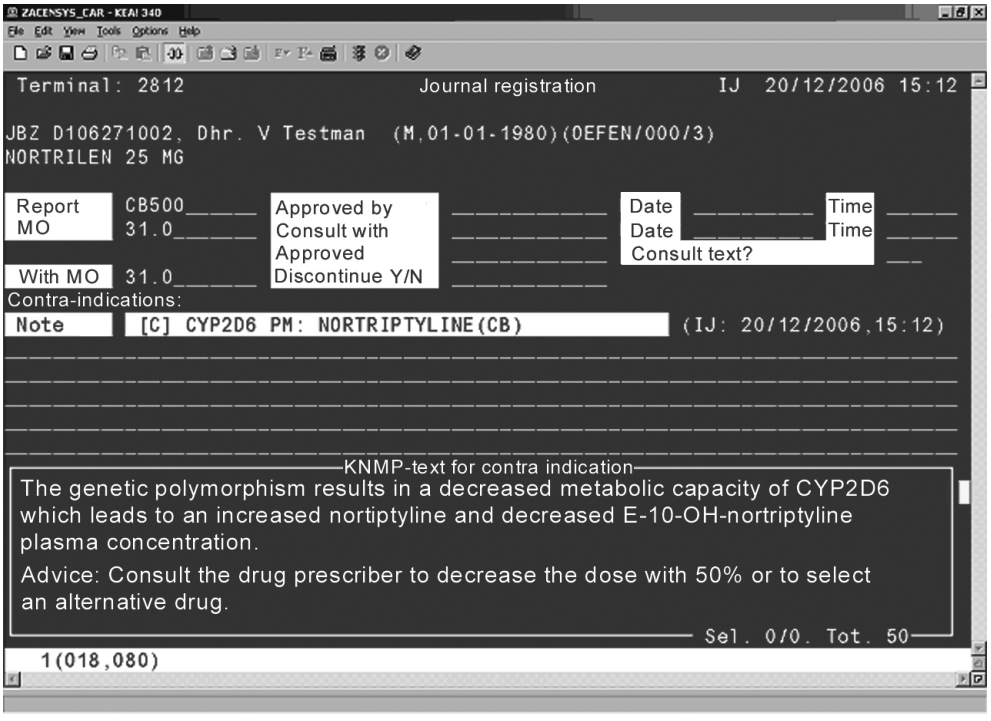

Figure 3.1 Typical alert generated by automated medication surveillance after prescription of nortriptyline to a patient known to be a poor metabolizer of CYP2D6 (translated from Dutch).

text, a pharmacy counter text, a hospital text, and a background text. Each of these is specifically designed to meet the requirements of its user. After a prescription has been issued by a physician (prescriber text), the prescription is transferred to the pharmacy either electronically or physically (by the patient). In the Netherlands, the prescription is then processed electronically by a pharmacy assistant (pharmacy counter text in a pharmacy, hospital text in a hospital setting), and the prescribed drug is dispensed. Prescriptions are checked for medication errors by the pharmacist (background text in community pharmacy, hospital text in hospital).

Composed therapeutic (dose) recommendations

To date, we have used this method of assessment for 85 genotype/phenotype–drug combinations comprising 26 drugs (Table 3.3, please note that the table in this thesis contains the information for 53 drugs from the updated 2011 Cinical Pharmacology & Therapeutics paper). The assessed drugs were substrates for CYP2D6 (n = 21), CYP2C19 (n = 1), CYP2C9 (n = 3), and UGT1A1 (n = 1). After assessment of the literature,

Table 3.3 Updated results for *CYP2D6*, *CYP2C9*, *CYP2C19*, *UGT1A1*, *TPMT*, *HLA-B44*, *HLA-B*5701*, *CYP3A5*, *VKORC1*, *Factor V Leiden*, *DPYD*

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
CYP2D6							
Amitriptyline	459	PM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g. citalopram, sertraline) or monitor amitriptyline and nortriptyline plasma concentration	[26-28]
		IM	3	C	Yes	Reduce dose by 25% and monitor plasma concentration or select alternative drug (e.g. citalopram, sertraline)	[26-31]
		UM	3	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g. citalopram, sertraline) or monitor (E-10-hydroxy)amitriptyline plasma concentration	[28,32,33]
Aripiprazole	124	PM	4	C	Yes	Reduce maximum dose to 10 mg/day (67% of the maximum recommended daily dose)	[34-37]
		IM	4	A	Yes	No	[35,38-40]
		UM	—	—	Yes	No	—
Atomoxetine	10,081	PM	3	B	Yes	Standard dose. Dose increase probably not necessary, be alert to ADE	[41-46]
		IM	4	A	Yes	No	[47]
		UM	—	—	Yes	Insufficient data to allow calculation of dose adjustment. Be alert to reduced efficacy or select alternative drug (e.g. methylphenidate, clonidine)	—
Carvedilol	135	PM	4	B	Yes	No	[48,49]
		IM	4	A	Yes	No	[50-54]
		UM	—	—	Yes	No	—
Clomipramine	272	PM	4	C	Yes	Reduce dose by 50% and monitor (desmethyl) clomipramine plasma concentration	[55-60]
		IM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Monitor (desmethyl)clomipramine plasma concentration	[57,61,62]

		UM	2	C	Yes	Select alternative drug (e.g. citalopram, sertralin) or monitor (desmethyl)clomipramine plasma concentration	[63,64]
Clozapine	297	PM	4	AA	No	No	[65-69]
		IM	4	AA	No	No	[66,69]
		UM	4	AA	No	No	[68,69]
Codeine	453	PM	4	B	Yes	Analgesia: Select alternative drug (e.g. acetaminophen, NSAID, morphine not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief Cough: No	[70-80]
		IM	3	A	Yes	Analgesia: Select alternative drug (e.g. acetaminophen, NSAID, morphine not tramadol or oxycodone) or be alert to symptoms of insufficient pain relief Cough: No	[71,81]
		UM	3	F	Yes	Analgesia: Select alternative drug (e.g. acetaminophen, NSAID, morphine not tramadol or oxycodone) or be alert to ADE Cough: Be extra alert to ADE due to increased morphine plasma concentration	[70,82-85]
Doxepin	76	PM	3	F	Yes	Reduce dose by 60%. Adjust maintenance dose in response to (nor)doxepin plasma concentration	[32,86-89]
		IM	3	A	Yes	Reduce dose by 20%. Adjust maintenance dose in response to (nor)doxepin plasma concentration	[88]
		UM	3	A	Yes	Select alternative drug (citalopram, sertraline), or increase dose by 100%. Adjust maintenance dose in response to (nor)doxepin plasma concentration	[87]
Duloxetine	0[b]	PM	0	AA	Yes	No	[90]
		IM	—	—	Yes	No	—
		UM	—	—	Yes	No	—

Table 3.3 continues on next page

Table 3.3 – Continued

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
Flecainide	145	PM	4	A	Yes	Reduce dose by 50%, record ECG, monitor plasma concentration	[91-95]
		IM	3	A	Yes	Reduce dose by 25%, record ECG, monitor plasma concentration	[96,97]
		UM	—	—	Yes	Record ECG and monitor plasma concentration or select alternative drug (e.g. sotalol, disopyramide, quinidine, amiodarone)	—
Flupenthixol	0	PM	—	—	No	No	—
		IM	—	—	No	No	—
		UM	—	—	No	No	—
Haloperidol	1,411	PM	4	C	Yes	Reduce dose by 50% or select alternative drug (e.g. pimozide, flupenthixol, fluphenazine, quetiapine, olanzapine, clozapine)	[98-105]
		IM	4	A	Yes	No	[98-102,106-114]
		UM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Be alert to decreased haloperidol plasma concentration and adjust maintenance dose in response to haloperidol plasma concentration or select alternative drug (e.g. pimozide, flupenthixol, fluphenazine, quetiapine, olanzapine, clozapine)	[98,99]
Imipramine	268	PM	4	C	Yes	Reduce dose by 70% and monitor imipramine and desipramine plasma concentration	[57,115-119]
		IM	4	A	Yes	Reduce dose by 30% and monitor imipramine and desipramine plasma concentration	[115,117, 119]
		UM	4	A	Yes	Select alternative drug (e.g. citalopram, sertraline) or increase dose by 70% and monitor imipramine and desipramine plasma concentration	[117,119]

Metoprolol	1,966	PM	4	C	Yes	*Heart failure*: Select alternative drug (e.g. bisoprolol, carvedilol) or reduce dose by 75% *Other indications:* Be alert to ADE (e.g. bradycardia, cold extremities) or select alternative drug (e.g. atenolol, bisoprolol)	[120-135]
		IM	4	B	Yes	*Heart failure:* Select alternative drug (e.g. bisoprolol, carvedilol) or reduce dose by 50% *Other indications:* Be alert to ADE (e.g. bradycardia, cold extremities) or select alternative drug (e.g. atenolol, bisoprolol)	[121-125,127, 132,133, 135-140]
		UM	4	D	Yes	*Heart failure*: Select alternative drug (e.g. bisoprolol, carvedilol) or titrate dose to max. 250% of the normal dose in response to efficacy and ADE *Other indications:* Select alternative drug (e.g. atenolol, bisoprolol) or titrate dose to max. 250% of the normal dose in response to efficacy and ADE	[123,125-128]
Mirtazapine	333	PM	3	B	Yes	No	[32,55,141-145]
		IM	3	A	Yes	No	[144,146]
		UM	3	A	Yes	No	[32,141,143]
Nortriptyline	270	PM	3	C	Yes	Reduce dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	[147-152]
		IM	4	C	Yes	Reduce dose by 40% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	[147-149, 151,153-157]
		UM	3	C	Yes	Select alternative drug (e.g. citalopram, sertraline) or increase dose by 60% and monitor nortriptyline + 10-hydroxynortriptyline plasma concentrations	[64,148, 149,153]
Olanzapine	201	PM	3	AA	No	No	[158-160]
		IM	3	AA	No	No	[159,161, 162]
		UM	—	—	No	No	—

Table 3.3 continues on next page

Table 3.3 – Continued

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
Oxycodone	78	PM	3	B	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (not tramadol or codeine) or be alert to symptoms of insufficient pain relief	[163-167]
		IM	3	AA	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (not tramadol or codeine) or be alert to symptoms of insufficient pain relief	[165]
		UM	1	A	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (not tramadol or codeine) or be alert to ADE (e.g. nausea, vomiting, constipation, respiratory depression, confusion, urinary retention)	[168]
Paroxetine	633	PM	4	A	Yes	No	[144,169-176]
		IM	4	A	Yes	No	[144,170, 176-179]
		UM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g. citalopram, sertraline)	[169,173, 175, 176, 180]
Propafenone	257	PM	4	C	Yes	Reduce dose by 70%, record ECG, monitor plasma concentration	[181-190]
		IM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g. sotalol, disopyramide, quinidine, amiodarone)	[190-193]
		UM	3	D	Yes	Insufficient data to allow calculation of dose adjustment. Adjust dose in response to plasma concentration and record ECG or select alternative drug (e.g. sotalol, disopyramide, quinidine, amiodarone)	[184,190]

Risperidone	1,721	PM	4	D	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g quetiapine, olanzapine, clozapine) or be extra alert to ADE and adjust dose to clinical response	[194-200]
		IM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g quetiapine, olanzapine, clozapine) or be extra alert to ADE and adjust dose to clinical response	[198,199, 201-209]
		UM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g quetiapine, olanzapine, clozapine) or be extra alert to decreased response and titrate dose in response to clinical effect and ADE	[198-200, 210]
Tamoxifen	5,020	PM	4	E	Yes	Increased risk for relapse of breast cancer. Consider aromatase inhibitor for postmenopausal women	[211-221]
		IM	4	E	Yes	Increased risk for relapse of breast cancer. Avoid concomitant use of CYP2D6 inhibitors. Consider aromatase inhibitor for postmenopausal women	[212,214-222]
		UM	4	A	Yes	No	[217,222]
Tramadol	968	PM	4	B	Yes	Select alternative drug (not oxycodone or codeine) or be alert to symptoms of insufficient pain relief	[223-236]
		IM	4	B	Yes	Be alert to decreased efficacy. Consider dose increase. If response is still inadequate select alternative drug (not oxycodone or codeine) or be alert to symptoms of insufficient pain relief	[223-225, 233,236-238]
		UM	3	C	Yes	Reduce dose by 30% and be alert to ADE (e.g. nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) or select alternative drug (e.g. acetaminophen, NSAID, morphine not oxycodone or codeine)	[224,231, 236,239, 240]

Table 3.3 continues on next page

Table 3.3 – Continued

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
Venlafaxine	251	PM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g. citalopram, sertraline) or adjust dose to clinical response and monitor (O-desmethyl)venlafaxine plasma concentration	[241-247]
		IM	4	C	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g. citalopram, sertraline) or adjust dose to clinical response and monitor (O-desmethyl)venlafaxine plasma concentration	[243-246, 248-250]
		UM	4	A	Yes	Be alert to decreased venlafaxine and increased O-desmethylvenlafaxine plasma concentration. Titrate dose to max 150% of the normal dose or select alternative drug (e.g. citalopram, sertraline)	[243,245]
Zuclopenthixol	231	PM	4	A	Yes	Reduce dose by 50% or select alternative drug (e.g. flupenthixol, quetiapine, olanzapine, clozapine)	[251-255]
		IM	4	A	Yes	Reduce dose by 25% or select alternative drug (flupenthixol, quetiapine, olanzapine, clozapine)	[252-254]
		UM	—	—	Yes	Insufficient data to allow calculation of dose adjustment. Be alert to low zuclopenthixol plasma concentrations or select alternative drug (flupenthixol, quetiapine, olanzapine, clozapine)	—
CYP2C9							
Acenocoumarol[a]	6,811	*1/*2	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	[256-274]
		*2/*2	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	[256-261, 263-274]
		*1/*3	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	[256-275]

		*2/*3	4	F	Yes	Check INR more frequently after initiating or discontinuing NSAIDs	[257-275]
		*3/*3	4	F	Yes	Check INR more frequently during dose titration and after initiating or discontinuing NSAIDs	[256-259, 263, 267-270, 272,275, 276]
Glibenclamide	86	*1/*2	3	AA	Yes	No	[277-281]
		*2/*2	3	AA	Yes	No	[277,279]
		*1/*3	3	B	Yes	No	[277-280]
		*2/*3	3	AA	Yes	No	[277,279, 281]
		*3/*3	3	A	Yes	No	[279,281]
Gliclazide	912	*1/*2	3	AA#	Yes	No	[282-284]
		*2/*2	3	AA#	Yes	No	[282,284]
		*1/*3	3	AA#	Yes	No	[282-285]
		*2/*3	3	AA#	Yes	No	[282]
		*3/*3	3	AA#	Yes	No	[282]
Glimepiride	442	*1/*2	3	AA	Yes	No	[277,278, 281,283]
		*2/*2	4	AA	Yes	No	[277]
		*1/*3	4	AA#	Yes	No	[277,278, 281,283, 286,287]
		*2/*3	3	D	Yes	No	[277,278, 281]
		*3/*3	3	D	Yes	No	[281,287]
Phenprocoumon[a]	1,802	*1/*2	4	F	Yes	No	[264-267, 288-296]
		*2/*2	4	F	Yes	Check INR more frequently	[264-267, 289-294, 296]

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Table 3.3 – Continued

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
		*1/*3	4	F	Yes	No	[265-267, 288-294, 296]
		*2/*3	4	F	Yes	Check INR more frequently	[265-267, 288-292, 294, 296]
		*3/*3	4	D	Yes	Check INR more frequently	[289-292, 294]
Phenytoin	1,354	*1/*2	4	A	Yes	Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation)	[297-303]
		*2/*2	4	A	Yes	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation)	[297-299, 301-303]
		*1/*3	4	D	Yes	Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7-10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation)	[297-300, 303-311]
		*2/*3	4	A	Yes	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation)	[298,302]
		*3/*3	4	D	Yes	Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7-10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation)	[297,299-301,311-315]

Tolbutamide	544	*1/*2	3	A	Yes	No	[277,316-320]
		*2/*2	3	A	Yes	No	[277,316, 318,319]
		*1/*3	3	B	Yes	No	[277,316-322]
		*2/*3	3	A	Yes	No	[277,319, 320]
		*3/*3	3	A	Yes	No	[319-321]
CYP2C19							
Citalopram / Escitalopram	2,396	PM	4	A	Yes	No	[323-330]
		IM	4	A	Yes	No	[323-325, 327,330, 331]
		UM	4	A	Yes	Monitor plasma concentration and titrate dose to max. 150% in response to efficacy and ADE or select alternative drug (e.g. fluoxetine, paroxetine)	[324,332]
Clopidogrel	11,785	PM	4	F	Yes	Increased risk for reduced response to clopidogrel. Consider alternative drug. Prasugrel is not or to a much smaller extent metabolized by CYP2C19 but is associated with an increased bleeding risk compared to clopidogrel	[333-351
		IM	4	F	Yes	Increased risk for reduced response to clopidogrel. Consider alternative drug. Prasugrel is not or to a much smaller extent metabolized by CYP2C19 but is associated with an increased bleeding risk compared to clopidogrel	[323-353]
		UM	3	A	Yes	No	[333,340-342,354]

Table 3.3 continues on next page

Table 3.3 – Continued

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
Esomeprazole	975	PM	4	AA#	Yes	No	[355-364]
		IM	4	AA#	Yes	No	[355-363, 365]
		UM	—	V	Yes	*Helicobacter pylori eradication:* increase dose by 50-100%. Be extra alert to insufficient response *Other:* Be extra alert to insufficient response. Consider dose increase by 50-100%	—
Imipramine	541	PM	3	A	Yes	Reduce dose by 30% and monitor plasma concentration of imipramine and desipramine or select alternative drug (e.g. fluvoxamine, mirtazapine)	[118,366-371]
		IM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g. fluvoxamine, mirtazapine)	[118,367-370]
		UM	—	—	Yes	No	—
Lansoprazole	2,304	PM	4	AA#	Yes	No	[372-394]
		IM	4	AA#	Yes	No	[372-393, 395,396]
		UM	—	—	Yes	*Helicobacter pylori eradication:* increase dose by 200%. Be extra alert to insufficient response. *Other:* Be extra alert to insufficient response. Consider dose increase by 200%	—
Moclobemide	31	PM	3	A	Yes	No	[397-399]
		IM	—	—	Yes	No	—
		UM	—	—	Yes	No	—
Omeprazole	2,522	PM	4	AA#	Yes	No	[356,378, 380,383, 384,386, 389,400-414]

		IM	4	AA#	Yes	No	[356,378, 380,383, 384,386, 389,396, 400-404, 406-410, 412-415]
		UM	3	A	Yes	*Helicobacter pylori eradication:* increase dose by 100-200%. Be extra alert to insufficient response *Other:* Be extra alert to insufficient response. Consider dose increase by 100-200%	[416-418]
Pantoprazole	829	PM	3	AA#	Yes	No	[361,419-423]
		IM	3	AA#	Yes	No	[361,365, 415,420-423]
		UM	3	AA	Yes	*Helicobacter pylori eradication:* increase dose by 400%. Be extra alert to insufficient response *Other:* Be extra alert to insufficient response. Consider dose increase by 400%	[423]
Rabeprazole	2,239	PM	4	AA#	Yes	No	[359,377, 382,384, 386,389, 401,405, 406,410, 413,419, 424-435]
		IM	4	AA	Yes	No	[359,377, 382,384, 386,389, 401,406, 410,413, 424-428, 430-434]
		UM	—	—	Yes	No	—

Table 3.3 continues on next page

Table 3.3 – Continued

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
Sertraline	26	PM	3	C	Yes	Reduce dose by 50%	[32,436]
		IM	3	A	Yes	Insufficient data to allow calculation of dose adjustment. Be extra alert to ADE (e.g. nausea, vomiting, diarrhea)	[436]
		UM	—	—	Yes	No	—
Voriconazole	314	PM	3	A	Yes	Monitor serum concentration	[437-446]
		IM	3	A	Yes	Monitor serum concentration	[437,438, 441, 444-446]
		UM	3	A	Yes	No	[443,445]
UGT1A1							
Irinotecan	3,883	*1/*28	3	F	Yes	No	[447-473]
		*28/*28	3	E	Yes	*Dose > 250 mg/m²:* Reduce initial dose by 30%. Increase dose in response to neutrophil count *Dose ≤ 250 mg/m²:* No dose adjustment	[447,448, 450-460, 462, 464-470,472-479]
TPMT							
Azathioprine / Mercaptopurine	2,853	PM	4	F	Yes	Select alternative drug or reduce dose by 90%. Increase dose in response of hematologic monitoring and efficacy	[480-492]
		IM	4	E	Yes	Select alternative drug or reduce dose by 50%. Increase dose in response of hematologic monitoring and efficacy	[480,481, 483,484, 486,487, 489-491, 493-502]
Thioguanine	792	PM	2	F	Yes	Select alternative drug. Insufficient data to allow calculation of dose adjustment	[503,504]
		IM	3	D	Yes	Select alternative drug. Insufficient data to allow calculation of dose adjustment	[505-508]

HLA-B44							
Ribavirine	130	HLA-B44 negative	4	C	Yes	No	[509]
*HLA-B*5701*							
Abacavir	3,791	HLA-B*5701 positive	4	E	Yes	Select alternative drug	[510-523]
CYP3A5							
Tacrolimus	1,302	*1/*1	4	B	Yes	No	[524-536]
		*1/*3	4	D	Yes	No	[524-537]
VKORC1							
Acenocoumarol[a]	776	CT	4	A	Yes	No	[258,275, 538-540]
		TT	4	A	Yes	Check INR more frequently	[258,275, 538-540]
Phenprocoumon[a]	391	CT	4	D	Yes	No	[294,539]
		TT	4	D	Yes	Check INR more frequently	[294,539]
Factor V Leiden							
Estrogen containing oral contraceptive	7,441	FVL homozygous	3	D	Yes	*Positive (family)history of thrombotic events:* Avoid estrogen containing OC and select alternative (e.g. copper intrauterine device or progestin-only contraceptive) *Negative (family)history of thrombotic events:* Avoid additional risk factors (e.g. obesity, smoking etc.)	[541-548]
		FVL heterozygous	4	D	Yes	*Positive (family)history of thrombotic events:* Avoid estrogen containing OC and select alternative (e.g. copper intrauterine device or progestin-only contraceptive) *Negative (family)history of thrombotic events:* Avoid additional risk factors (e.g. obesity, smoking etc.)	[541-545, 547-560]

Table 3.3 continues on next page

Table 3.3 – Continued

Drug	Subjects (n)	Genotype or phenotype	Level of evidence	Clinical relevance	Gene-drug interaction	Therapeutic (dose) recommendation	References
DPYD							
Fluorouracil / Capecitabine	3,733	PM	3	F	Yes	Select alternative drug. Tegafur is not a suitable alternative because this drug is also metabolized by DPD	[561-569]
		IM	3	F	Yes	Reduce dose by 50% or select alternative drug. Tegafur is not a suitable alternative because this drug is also a substrate for DPD. Increase dose in response to toxicity and efficacy	[561-567, 569-580]
Tegafur/uracil combination	0[b]	PM	3	AA	Yes	Select alternative drug. Fluorouracil or capecitabine are not suitable alternatives because both are also metabolized by DPD	[581]
		IM	3	AA	Yes	No	[581]

Level of evidence: assigned level of evidence (0–4) for the gene–drug interaction. If scored "—" no data was retrieved with the literature search.
Clinical relevance: assigned level of clinical relevance (AA–F) for the gene–drug interaction. If scored "—" no data were retrieved with the literature search. Positive clinical effects were scored as AA#.
ADE, adverse drug event; ECG, electrocardiogram; FVL, factor V Leiden; IM, intermediate metabolizer; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; OC, oral contraceptive; PM, poor metabolizer; UM, ultrarapid metabolizer.
CYP2C19 IM, *1/*2, *1/*3, *17/*2, *17/*3; CYP2C19 PM, *2/*2, *2/*3, *3/*3; CYP2C19 UM, *17/*17; CYP2D6 IM, patients carrying two decreased-activity (*9, *10, *17, *29, *36, *41) alleles or carrying one active (*1, *2, *33, *35) and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele, or carrying one decreased-activity (*9, *10, *17, *29, *36, *41) allele and one inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) allele; CYP2D6 PM, patients carrying two inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) alleles; CYP2D6 UM, patients carrying a gene duplication in absence of inactive (*3-*8, *11-*16, *19-*21, *38, *40, *42) or decreased-activity (*9, *10, *17, *29, *36, *41) alleles; DPD PM, patients carrying two inactive (*2A, *3, *7, *8, *10, *11, *12, *13, 496A>G, IVS10-15T>C, 1156G>T, 1845G>T) alleles, two decreased-activity (*9B, *10) alleles, or one inactive (*2A, *3, *7, *8, *10, *11, *12, *13, 496A>G, IVS10-15T>C, 1156G>T, 1845G>T) and one decreased-activity (*9B, *10) allele; DPD IM, patients carrying one active (*1, *4, *5, *6, *9A) allele and one inactive (*2A, *3, *7, *8, *10, *11, *12, *13, 496A>G, IVS10-15T>C, 1156G>T, 1845G>T) or decreased-activity (*9B, *10) allele. For the inactive *DPYD* alleles *3, *7, *8, *11, *12, *13, 1156G>T, 1845G>T and decreased-activity *DPYD* alleles *9B, *10, toxicity has been described in case reports but has not been confirmed in independent studies or pharmacokinetic analyses. TPMT IM, patients carrying one active (*1, *1S, *1A) and one inactive (*2, *3A-*3D, *4-*18) allele; TPMT PM, patients carrying two inactive (*2, *3A-*3D, *4-*18) alleles.
[a]Therapeutic (dose) recommendations for acenocoumarol and phenprocoumon solely based on *CYP2C9* genotype without knowledge of *VKORC1* status. Advice based on situation in the Netherlands. [b]Therapeutic (dose) recommendation based on information from the Summary of Product Characteristics.

therapeutic (dose) recommendations were composed for 17 of the 26 drugs. It was decided that for four of the drugs (clozapine, duloxetine, flupenthixol, and olanzapine) no gene–drug interaction was present and therefore no therapeutic (dose) recommendation was required. For aripiprazole, tamoxifen, acenocoumarol, phenprocoumon, and voriconazole, although a gene–drug interaction was present, no therapeutic (dose) recommendation was made.

Overview and caveats

We have developed a method to interpret the results of structured assessment of gene–drug interactions, and translate them into therapeutic recommendations. These recommendations have been included in the G-standard since October 2006, and are applied in clinical practice for patients whose genotype is known. The availability of these guidelines as part of most computerized drug prescription and automated medication surveillance systems in the Netherlands will facilitate the use of pharmacogenetic information in therapeutic decision-making. Recommendations relating to other drugs such as sulfonylureas, angiotensin II receptor blockers, and proton pump inhibitors, are currently under evaluation and will be released along with future three-monthly updates.

Many of the studies that were assessed did not have pharmacogenetics as their primary objective, and this resulted in underpowered studies. Even where pharmacogenetics was the primary study objective, the assessed endpoints were mostly pharmacokinetic; also, the results related to single-dose experiments in healthy volunteers and was therefore not representative of daily clinical practice. A third limitation was the frequent use of specific study populations such as Asians, involving the investigation of genotypes which occur only rarely in Caucasian populations. In particular, there is a dearth of data relating to intermediate and ultrarapid metabolizers. Because we did not allow extrapolation of dose recommendations if a phenotype was not present in the studied population, only a few dose recommendations could be calculated for ultrarapid and intermediate metabolizers. The number of research papers per gene–drug combination retrieved during our searches and eligible for assessment was lower than we had expected, varying from 0 to 21. For nortriptyline, a widely used example for demonstrating the possible impact of pharmacogenetics, only 10 original papers were found eligible for assessment. These findings demonstrate that there remains a need for more studies to provide data on the clinical consequences of pharmacogenetics. These studies should be adequately designed with regard to sample size and clinically relevant endpoints [19]. Also, initiatives such as the cataloging of pharmacogenetic information, introduced by the Pharmacogenomics and Pharmacogenetics Knowledge Base (http://www.pharmgkb.org/), are a valuable approach to providing research studies with adequate power to demonstrate the clinical relevance of pharmacogenetics.

Currently there is only limited evidence to justify prospective pharmacogenetic testing or population-wide screening. The justification for such testing and screening will depend upon the availability of sufficient data demonstrating that pharmacogenetic testing actually improves clinical outcome and is cost-effective [20]. Producing such evidence presents a significant challenge. Long-term monitoring of the clinical outcome of the PWG dose recommendations might provide such data. However, there are indications that patients with non-wild-type genotypes are more often prone to an aberrant drug response. Therefore, we chose to formulate therapeutic recommendations for the situation where the patient's genotype is known. Currently, the infrastructure for genotyping is available only in a limited number of centers and needs to be expanded or made accessible for other centers [4,21].

Obviously, tests for single polymorphisms that affect pharmacokinetics may account for only part of the variability in drug response, and the pharmacogenetic tests that are currently available cannot replace other methods for dose individualization such as therapeutic drug monitoring [22,23]. We have described only genetic polymorphisms that affect the pharmacokinetics of a drug. The available literature on polymorphisms that affect pharmacodynamics, and the implications of these effects, is limited and sometimes contradictory [24,25].

In summary, our initiative to develop pharmacogenetics-based therapeutic (dose) recommendations and to make them accessible during electronic drug prescription and automated medication surveillance represents an important step forward toward the application of pharmacogenetic information in daily patient care.

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