LEADING ARTICLE

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Therapeutic Drug Monitoring and Pharmacogenetic Tests as Tools in Pharmacovigilance

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Abstract

Therapeutic drug monitoring (TDM) and pharmacogenetic tests play a major role in minimising adverse drug reactions and enhancing optimal therapeutic response. The response to medication varies greatly between individuals, according to genetic constitution, age, sex, co-morbidities, environmental factors including diet and lifestyle (e.g. smoking and alcohol intake), and drug-related factors such as pharmacokinetic or pharmacodynamic drug-drug interactions. Most adverse drug reactions are type A reactions, i.e. plasma-level dependent, and represent one of the major causes of hospitalisation, in some cases leading to death. However, they may be avoidable to some extent if pharmacokinetic and pharmacogenetic factors are taken into consideration.

This article provides a review of the literature and describes how to apply and interpret TDM and certain pharmacogenetic tests and is illustrated by case reports. An algorithm on the use of TDM and pharmacogenetic tests to help characterise adverse drug reactions is also presented. Although, in the scientific community, differences in drug response are increasingly recognised, there is an urgent need to translate this knowledge into clinical recommendations. Databases on drug-drug interactions and the impact of pharmacogenetic polymorphisms and adverse drug reaction information systems will be helpful to guide clinicians in individualised treatment choices.

In the future, significant advances in drug therapy may not be due to the development of new drugs or drug classes but to the development and integration of our understanding of inter-individual differences that occur during treatment with certain medicines. Inter-individual variability in drug responses concerning efficacy, tolerability and safety is not only determined by patient factors, such as sex, age, genetic background and co-morbidity, but also by environmental factors that include concomitant

medication, smoking, diet and culturally driven ideas, such as an individual's belief in treatment and cure.

This multifactor variability in drug response is affected not only by pharmacokinetics, i.e. drug disposition (absorption, distribution, metabolism and excretion [ADME]) and plasma concentration, but also pharmacodynamics, i.e. the interaction of the drug with its target site (such as receptors, neurotransmitter transporters, and enzymes). This interplay between pharmacokinetic and pharmacodynamic factors significantly affects how patients respond to treatment. Examples of pharmacodynamic factors include interactions between drugs acting on the same neurotransmitter system leading to, e.g. serotonin syndrome or extrapyramidal symptoms (EPS), or else pharmacogenetic polymorphism of neurotransmitter transporters or receptors resulting in a modified response.

Tools enabling the clinician to get a better picture of the fate of prescribed drugs in the body include therapeutic drug monitoring (TDM) and specific pharmacogenetic tests that examine the function of metabolising enzymes, particularly those of the cytochrome P450 (CYP450) family.

Although some of the factors affecting individual drug responses have been known for some time, e.g. pharmacogenetic polymorphisms of metabolic enzymes[1-4] (reviewed by Ingelman-Sundberg,[5] Meyer[6] and Wilkinson[7]) or pharmacokinetic drug-drug interactions, this information is not often used in the context of daily clinical routine. This lack of pharmacokinetic/pharmacogenetic understanding or consideration might be due to the fact that individuals with the same drug disposition might still have a different clinical response. This leads to complex, hard-to-interpret, data, which is often missing important variables. Thus, one patient with a high drug plasma concentration may experience an adverse drug reaction whilst another, with a similarly high drug plasma concentration, will not. Only when the interplay between pharmacokinetic and pharmacodynamic reactions is known does the whole picture emerge.

Furthermore, prospective trials assessing the benefits of TDM and pharmacogenetic tests are scarce, and there is also an urgent need for well designed pharmacoepidemiological studies.

The majority of adverse drug reactions are drug-level dependent (type A reactions)[8-11] and are, therefore, at least partly avoidable. A meta-analysis from 1998[12] involving 39 studies in US hospitals showed the overall yearly incidence of serious adverse events was 6.7%, whereas fatal adverse drug reactions involved 0.32% of hospitalised patients. Similar figures have been found in more recent studies in Europe;[13,14] a French study examining the incidence of hospital visits as a result of adverse drug reactions found 85% of these reactions were preventable.[15] Calculations in the US show that 2.2 million in-patients experience serious adverse drug reactions per year, with 100 000 patients dying as a result. These figures suggest that adverse drug reactions are the fourth to sixth leading cause of death in hospital and that they represent a serious medical and financial problem.[13,16-21] Pharmacovigilance could therefore be an area where TDM and pharmacogenetic tests could be of major benefit.

To minimise serious adverse drug reactions in cancer chemotherapy, TDM of cytotoxic drugs that have narrow therapeutic indices, like methotrexate or mercaptopurine, can be helpful. As with other antimetabolites, mercaptopurine is not active *per se* and needs to be activated intracellularly to 6-thioguanine nucleotides. Mercaptopurine methylation by the polymorphic thiopurine S-methyltransferase (TPMT) reduces the availability of intracellular mercaptopurine for conversion to thioguanine; lack of TPMT functional activity leads to toxic concentrations of active metabolites and life-threatening myelotoxicity.

The importance of genetic polymorphisms and drug-drug interactions in relation to therapeutic response and susceptibility to adverse drug reactions is becoming increasingly acknowledged.[22,23] Regulatory authorities and the pharmaceutical industry are making considerable efforts to shift their attention from groups of patients towards the individual. Guidelines for the submission of new drug applica-

tions are constantly changing, and several national regulatory bodies have refined their requirements to include pharmacogenetic information.[24] Although pharmacogenetics is important, consideration of other biological factors, such as age, sex and disease, coupled with lifestyle and environmental characteristics should also be taken into account. These factors mostly influence the pharmacokinetic parameters (ADME) that control the amount of drug reaching the target site.

As illustrated by some examples concerning clozapine,[25-27] selective serotonin reuptake inhibitors (SSRIs)[28] and other drugs[29-31] used in psychiatry, the application of pharmacogenetic tests for both pharmacodynamic (e.g. receptor proteins and neurotransmitter transporter proteins) and pharmacokinetic (e.g. CYP450 and drug transporters) variables is becoming more popular. However, pharmacogenetic tests for pharmacodynamic parameters have not yet been validated in clinical practice and will therefore be only briefly considered in this article.

This article, therefore, describes the use of TDM and pharmacogenetic tests in psychiatry, infectious diseases, transplant medicine, cardiology, oncology and epilepsy, where these instruments are used to optimize pharmacological treatments.[32-39] The emphasis will be on genetically determined pharmacokinetic variations; pharmacodynamic factors are equally important, but currently not fully understood.

The literature was reviewed using keyword searches of primarily MEDLINE/EMBASE and public Internet sources. Search terms included 'pharmacogenetics', 'genetic polymorphisms', 'therapeutic drug monitoring', 'plasma level monitoring', 'drug safety', 'pharmacovigilance', 'side effect', 'adverse drug reaction', 'ethnicity', 'ethnic', 'drug interaction' and 'interaction'. In addition, manual searches were performed of the bibliographies of selected articles. Patients described in the illustrative case reports have all given written informed consent for publication of case details.

1. Type A Adverse Drug Reactions: Drug-Concentration-Dependent

Type A reactions are predictable. They are common and tend to be dose-related and less serious than those that are aberrant effects, the so-called type B reactions. They can usually be treated by reducing the dose of the drug and tend to occur as a result of one of the following circumstances: (i) the individual may have received more of a drug than is customarily required; (ii) the individual may have received a conventional amount of the drug, but may metabolise or excrete the drug unusually slowly, leading to drug levels that are too high; and (iii) the individual may have normal drug levels, but for some reason is overly sensitive to them.

Type A reactions can also occur in response to secondary drug pharmacology (i.e. an action different from the drug's therapeutic actions but still explainable from its known pharmacology).[40] These can be detected and quantified during the clinical development of the drug in a population of a few thousand patients who are adequately monitored. Examples include: bronchospasm due to β-adrenoceptor antagonists, attributable to the blockade of β_2-adrenergic bronchial receptors; amnesia due to benzodiazepines; gastrointestinal bleeding due to nonsteroidal anti-inflammatory drugs; and cardiac adverse effects due to conventional antipsychotics.[41]

Type A adverse drug reactions are more common than type B reactions, accounting for >80% of all reactions.[9,42] Table I compares examples of type A and type B reactions.

2. Inter- and Intra-Individual Variations in Drug Plasma Levels

Plasma levels are determined by pharmacokinetic parameters (ADME) that control the amount of drug reaching the site of action. Drug-transporting proteins (e.g. P-glycoprotein) and most important drug-metabolising enzymes (e.g. CYP450) are relevant factors determining the pharmacokinetic profile. Drugs may be metabolised by many different sequential and/or competitive chemical processes comprising phase I metabolic reactions (oxidation,

Table I. Classification of adverse drug reactions

Type A
Overdose/toxicity
For example, nephrotoxicity and coma caused by elevated aminoglycoside and benzodiazepine concentrations, respectively
Side effects
For example, constipation caused by chronic opioid use
Secondary or indirect effects
Related to drug alone: e.g. disturbance of vaginal flora due to antibiotic use
Related to both disease and drug: e.g. ampicillin rash in association with Epstein-Barr virus
Drug interactions
For example, terfenadine (now withdrawn from the market) in combination with ketoconazole can result in torsade de pointes caused by elevated terfenadine levels; combination of fluvoxamine and clozapine can result in delirium due to very high clozapine plasma levels
Type B
Intolerance
For example, tinnitus caused by small doses of aminosalicylic acid
Allergic (hypersensitivity or immunological)
Result of an immune response to a drug, e.g. penicillin-induced urticaria
Pseudoallergic (non-immunological)
Immediate, generalised reaction involving mast cell mediator release, e.g. respiratory symptoms induced by nonsteroidal anti-inflammatory drugs
Idiosyncratic
Unexpected response to a drug and differing from its pharmacological actions; not related to an allergic mechanism, e.g. anticonvulsant hypersensitivity syndrome reaction (characterised by fever, cutaneous eruption and internal organ involvement)

reduction and hydrolysis) and/or phase II reactions (e.g. glucuronidation and acetylation).

Drugs that enter target organs via the cell membrane are usually lipophilic. When metabolised, they generally acquire a polar group in a first step (or phase I), and while in a second step (or phase II) they are made hydrophilic by conjugation to be easily excreted; this step often results in detoxification. Not all drugs go through both phases.

Inter- and intra-individual variations in plasma levels depend on biological variables and on lifestyle and environmental factors. Figure 1 illustrates examples of factors influencing plasma levels and subsequently the risk of developing an adverse drug reaction.

2.1 Drug-Metabolising Enzymes in Phase I

The most important drug-metabolising enzymes are the phase I enzymes belonging to the CYP450 enzyme family, which also metabolise the largest number of drugs.[47,48] Other phase I enzymes include alcohol dehydrogenases, flavin monooxygenases, esterases and monoamine oxidases.

The CYP450 enzyme system comprises >200 enzymes in about a dozen families. These enzymes exist in plants and animals and oxidise endogenous and exogenous compounds, in general making them less active and preparing them for phase II metabolism (e.g. glucuronidation) and finally for excretion. More than 50 CYP450 enzymes have been identified in humans, but only six of them, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4, metabolise >90% of all drugs.[49,50] There is a growing interest in CYP2B6, which plays a clinically important role for several drugs (e.g. bupropion, efavirenz and methadone).[51-53]

CYP450 enzymes display high catalytic specificity for distinct metabolic reactions but have broad substrate specificity. Specificity is sometimes concentration-dependent, e.g. with haloperidol, which at low plasma concentrations is mainly metabolised by CYP2D6 and at high plasma concentrations mainly by CYP3A.[54] In the case of some racemic drugs such as fluoxetine or citalopram, enantioselective metabolism has been found.[55]

Figure 2 shows the relative importance of the different CYP450 enzymes in drug metabolism. Two of the six main CYP450 enzymes are dominant: CYP3A4 and CYP2D6. CYP3A4 has low substrate specificity and is involved in the metabolism of about half of all drugs. It plays an important role in the gut as well as in the liver. Wilkinson[7] reviewed the intestinal and hepatic functions of CYP3A, i.e. first-pass metabolism, and their effect on the bioavailability of drugs. The activity of CYP3A varies markedly between individuals, and it seems that this variation is due to a multiple gene effect rather than single-gene polymorphisms. Drug interactions further enhance these effects. CYP2D6 accounts for just 2% of the total liver CYP450 content, and yet is involved in about 20–25% of

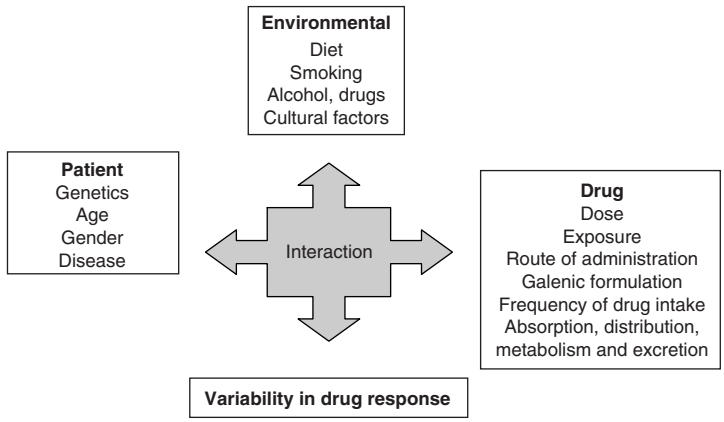

Fig. 1. Factors that contribute to variability in drug response.[43-46]

drug metabolism. As a high-affinity, low-capacity enzyme, it can be very sensitive to enzyme inhibition, leading to important increases in substrate concentration. Many cardiovascular, psychotropic and opioid drugs are CYP2D6 substrates. Since these drugs often have a narrow therapeutic index, caution and, where possible, TDM are advised.

2.1.1 Genetic Polymorphisms

Pharmacogenetics describes hereditary factors influencing the response to drug treatment (therapeutic effect and potential adverse effects), either dealing with the fate of drugs in the body (pharmacokinetics) or the interaction of the drug with the body at the target site (pharmacodynamics, e.g. neurotransmitter transporter polymorphism). The term 'pharmacogenetics' was introduced as early as 1959 by F. Vogel[57] and, in 1962, W. Kalow published the first book on pharmacogenetics.[58] Pharmacogenomics deals with the genome-wide assessment of the effect of drugs.[59] The term 'genetic polymorphism' usually refers to genetic loci for which variants occur with a frequency of at least 1%.[60] Genetic polymorphisms of drug-metabolising enzymes and their consequences for the patient were first identified in the late 1970s and 1980s.[2,4,61] Weinshilboum[62] has overviewed the development of the pharmacogenetics of drug metabolism, and more detailed information on pharmacogenetics in general can be found in textbooks and reviews.[63-66]

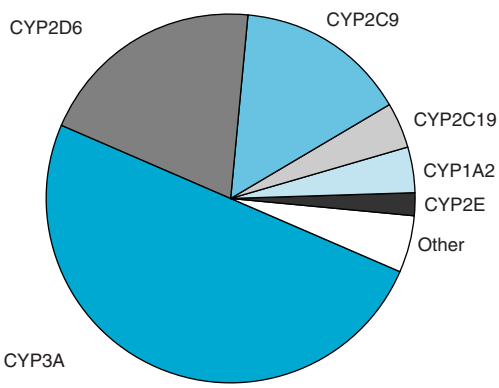

Fig. 2. Relative importance of the different CYP450 enzymes in drug metabolism.[56]

Individual genetic disposition determines the activity of drug-metabolising enzymes, and the number of active alleles in a gene determines, to a great extent, how much enzyme will be produced. Among the CYP450 enzymes, CYP2D6 and CYP2C19 show a polymodal distribution of activity in the population. From a phenotypic point of view, four types of drug metabolisers have been identified, which are not found with all drug metabolising CYP450 enzymes. 'Poor metabolisers' have a low- or no-enzyme activity, 'intermediate metaboliser' a reduced activity, 'extensive metabolisers' a normal activity and 'ultra-rapid metabolisers' a very high activity. Poor metabolisers have no functional alleles, intermediate metabolisers are heterozygous for an active and an inactive allele (or allele with reduced activity) or have two alleles with reduced

activity, extensive metabolisers are wild-type with two active alleles and ultra-rapid metabolisers (only described for CYP2D6) have an amplification of functional alleles (3–13 copies),[61,67,68] although this does not explain all the ultra-rapid metaboliser phenotypes.[69,70]

The prevalence of the different types of metabolisers varies between ethnic groups. It is important to note that ethnicity not only encompasses genetics but also environmental factors and is different from race.[71-73] Environmental factors might explain differences in treatment response between ethnic groups living in their country of origin and those who have emigrated. For more details on ethnicity, drug disposition and drug response see a review by Xie et al.[71] Inter-ethnic variability is an important factor in drug safety, and many drug regulatory authorities request appropriate clinical trials in different ethnic populations.

In a study of clozapine,[74] it was observed that Asian patients needed a lower dosage to reach the same plasma level as Caucasians, even after correcting for body mass index, sex and other confounding factors, such as smoking and caffeine consumption. This might indicate an important inter-ethnic variation in clozapine pharmacokinetics. Clozapine metabolism seems to be slower in the Asian population compared with the Caucasian population. This slower clozapine metabolism might reflect a lower CYP1A2 activity (CYP1A2 being a major metabolic pathway of clozapine), which has previously been described.[75] CYP2C19 is also involved in the biotransformation of clozapine,[76] and the frequency of poor metabolisers is higher among Asians than Caucasians.[77] Further pharmacodynamic differences concerning the likelihood of therapeutic response or adverse effects are discussed by Matsuda et al.[78]

Table II gives an overview of the estimated prevalence of the most relevant CYP450 polymorphisms in ethnic populations.

A study by Bertilsson et al.[112] in 1992 compared the metabolic activity of the CYP2D6 enzyme with the debrisoquine test and found that the Chinese population had an overall slower metabolism, but had fewer poor metabolisers, than the Swedish population. This can be explained by a high percentage of carriers of *CYP2D6**10 alleles with reduced metabolic activity due to an unstable enzyme. For example, in a pharmacogenetic study with venlafaxine, its area under the plasma concentration-time curve (AUC) was five times larger in homozygous *CYP2D6**10 carriers than in carriers of wild-type alleles.[113]

For CYP2D6, a trimodal activity distribution (poor metabolisers; intermediate and extensive metabolisers; and ultra-rapid metabolisers) has been described by Bertilsson et al.[114,115] To reach therapeutic plasma levels of nortriptyline, poor metabolisers would need a daily dosage of 10–20mg, intermediate and extensive metabolisers 100–200mg and ultra-rapid metabolisers ≥500mg. This idea of genotype-based dose adjustment has been further developed by Kirchheiner et al.[30,116,117] Figure 3 illustrates the schematic genotype-based plasma level differences and therapeutic consequences, assuming that, with a standard dose, poor and ultra-rapid metabolisers have an increased risk of intoxication or insufficient therapeutic response, respectively.[117]

The importance of CYP2D6 polymorphism arises from the fact that its substrates are typically cardiovascular and psychoactive drugs, many of them having a narrow therapeutic index and being intended for long-term use. Among the psychotropic medications, tricyclic antidepressants[114] and some older typical antipsychotics such as thioridazine are known to bear a high risk for cardiotoxic events. Additionally, severe arrhythmia was reported with venlafaxine in four patients admitted to a cardiological unit who were all CYP2D6 poor metabolisers.[118] In general, poor metabolisers are at higher risk of exposure to toxic plasma concentrations of a drug and subsequent development of an adverse drug reaction. Table III and table IV illustrate this with two case reports. Codeine is a prodrug that has to be metabolised via CYP2D6 to become the active compound morphine. Several cases of opioid adverse effects have been reported in ultra-rapid metabolisers.[119,120] Figure 3 and figure 4 il-

Table II. Estimate of the prevalence of relevant cytochrome P450 polymorphisms in various ethnic populations

Enzyme	Ethnicity	Poor metaboliser	Ultra-rapid metaboliser
CYP1A2[a]	Various	Rare[79-81]	Induction polymorphism[26,27,81-83] Clinical relevance unclear
CYP2C9	Caucasian[84-86]	1–10%	None
	Asian[87,88]	0–2%	None
	African[89]	Up to 4%	None
CYP2C19	Caucasian,[86,90] African,[91] Saudi Arabian [92] and Turkish[93]	1–5%	None
	Asian[94-97]	13–23%	None
CYP2D6	Asian[6,90]	1–2%	Up to 2%
	Turkish[93]		5–10%
	African[6,91] and African American	2–4%	2%
	Caucasian[86,98-102]	5–7%	1–2% North Europe 5–10% South Europe
	Saudi Arabian[92,103]		20%
	Ethiopian		Up to 29%
	Asian[104]	Carrier of an allele with reduced activity[105-107]	Up to 50% (*CYP2D6**10)
	African[91]	Carrier of an allele with reduced activity[105-107]	Up to 30% (*CYP2D6**17)
CYP3A5	Caucasian[108]	About 70%	None
	African American[108]	About 40%	None
	Japanese[109]	30–40%	None
	Chinese[110]	About 50%	None
CYP3A4[b]	Various[111]	Wide variability in metabolic capacity, only very few functional polymorphisms have been identified	Wide variability in metabolic capacity, only very few functional polymorphisms have been identified

a Inter-individual variability of CYP1A2 metabolic capacity is wide, with a bi- or tri-modal distribution depending on the population; only a few functional genes have been identified to date.

b Inter-individual variability in CYP3A4 metabolic capacity is wide, but no bi- or multimodal distribution has been found, most probably indicating that several genes contribute to the function.

lustrate plasma concentration variations in relation to the therapeutic window.

Polymorphic CYP2C19 is important in the metabolism of proton-pump inhibitors. Marked differences in drug plasma levels occur between extensive metabolisers and poor metabolisers treated with lansoprazole or omeprazole, and these concentrations are reflected in unequal changes in gastric pH.[123,124] In this case, polymorphisms are not so much associated with adverse drug reactions, but rather with differences in treatment response.[125-127]

For S-warfarin, a clear relationship between CYP2C9 genotype and coagulation time has been found,[128,129] making genotype-based dose recommendations feasible in order to avoid bleeding or over-coagulation.[130]

CYP1A2 polymorphisms have been examined in clinical studies with clozapine.[26,131] Although the C→A polymorphism has been associated with a very high inducibility of CYP1A2 in certain studies, this effect has not been consistent and further studies are currently being analysed.

The uni-modal distribution of large inter-individual variability of CYP3A activity suggests multigene effects. Some functional polymorphisms have been detected, often at low frequencies, and their contributing effects to overall CYP3A activity is low.[108,111,132]

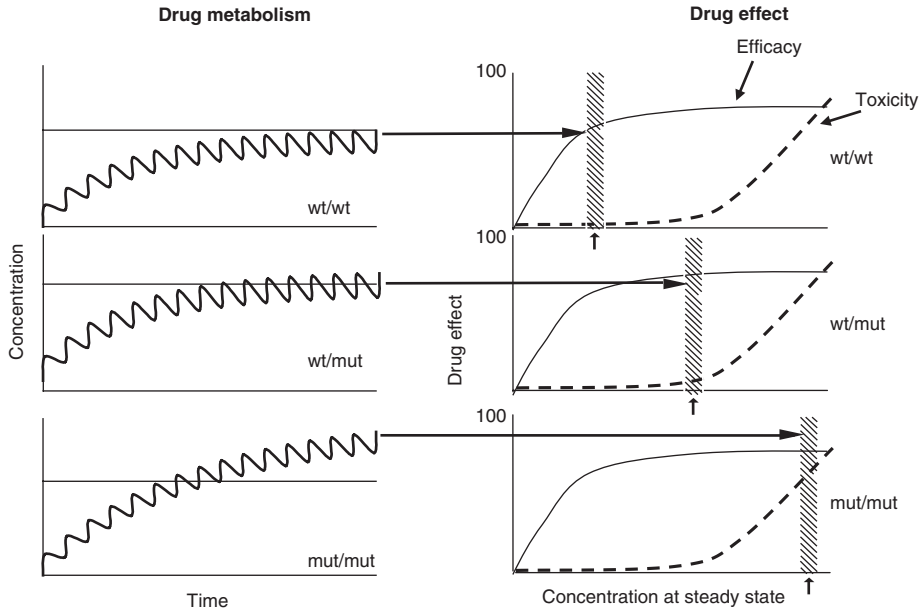

Fig. 3. Schematic illustration of genotype-based plasma concentration differences and therapeutic consequences.[56] The bar in the right part represents drug concentration at a steady state with a standard dose for a normal (no or very low toxicity risk and good efficacy), an intermediate (higher toxicity risk) and a poor metaboliser (high toxicity risk). **mut/mut** = homozygous with two mutant alleles and strongly reduced or no metabolic capacity; **wt/mut** = heterozygous with one active and one mutant allele and reduced metabolic function; **wt/wt** = 'wild type', with two active alleles and normal metabolic function.

Table V shows examples of pharmacogenetic polymorphisms that increase the risk of severe adverse drug reactions.

Polymorphic drug-metabolising enzymes represent some of the most common inheritable risk factors associated with adverse drug reactions.[140-144] However, it is difficult to identify simple monogenic associations between an adverse drug reaction and a single polymorphic drug-metabolising enzyme. Therefore, the concept of 'combinatorial pharmacogenetics', as proposed by Wilke et al.,[145] will probably yield more results as it seeks to characterise genetic variations that affect reactions to drugs within the complex metabolic networks of the human body by using novel high-dimensionality analysis methods.

Table III. Case 1

A 46-year-old patient with profound psychotic depression received treatment with clomipramine 300 mg/day and quetiapine 700 mg/day after previous treatment failures with venlafaxine, mirtazapine, clotiapine and lorazepam. His mood improved, but he experienced multiple adverse effects including hypotension, tachycardia, dizziness, sweating and liver function abnormalities. It was revealed that the plasma levels of both quetiapine and clomipramine were more than three times higher than the recommended therapeutic range.[121] Genotyping showed *CYP2D6* deficiency and phenotyping indicated a very low CYP3A activity. Treatment with quetiapine was stopped and clomipramine was reduced to 75 mg/day (bringing plasma levels within the recommended therapeutic range), after which the adverse effects, with the exception of liver abnormalities, abated and the patient was discharged.[122]

2.1.2 Pharmacokinetic Drug-Drug Interactions

Drug-drug interaction means a change in drug activity/effect as a result of the presence of another

Table IV. Case 2

A 45-year-old severely depressed female patient was treated with venlafaxine 375 mg/day and flupentixol 4 mg/day. Her mood improved but she began to experience strong inner agitation and tremors. After 2 weeks, objective hair loss was observed. The plasma levels of venlafaxine plus its active metabolite were found to be extremely high (2285 ng/mL; recommended range 195–400 ng/mL[121]). Phenotyping revealed that the patient was a poor metaboliser of CYP2D6. The dose of venlafaxine was reduced stepwise, and when the plasma concentration reached twice the upper limit of the recommended range, the hair loss stopped.

Table V. Examples of pharmacogenetic CYP450 polymorphisms and associated potential risks for serious adverse drug reactions[6,133]

Polymorphism	Potential serious adverse drug reactions
CYP2C9 PM	Phenytoin intoxication;[134,135] over anticoagulation with warfarin[128,136] or similar anticoagulation drugs; bleeding or hypoglycaemia with tolbutamide or glipizide[137,138]
CYP2C19 PM	Barbiturate intoxication; over-sedation with diazepam
CYP2D6 PM	Proarrhythmic and other toxic effects with antiarrhythmics; QT interval prolongation/torsade de pointes and anticholinergic delirium with tricyclic antidepressants in PMs; extrapyramidal symptoms with typical antipsychotics in PMs[139]
CYP2D6 UM	Opioid intoxication with codeine in UMs[119]

PM = poor metaboliser; **UM** = ultra-rapid metaboliser.

drug. This can represent a serious risk factor in drug safety. Both pharmacodynamic and pharmacokinetic drug interactions must be considered in combination therapy.

Pharmacodynamic interactions are due to the influence of drug A on drug B at the target site of drug action (i.e. end organ or receptor site). Examples of serious complications are the serotonin syndrome, resulting from a combination of several serotonin agonistic drugs (e.g. SSRI plus the analgesic tramadol or the anorectic sibutramine),[146-148] and delirium caused by a combination of drugs with anticholinergic properties. Pharmacodynamic interactions are not easily measured *in vivo*.

Pharmacokinetic interactions are due to the effect of drug A on drug B's movement through the body. Alterations can occur during absorption, distribution, metabolism and elimination. They are expressed by a change in the expected concentration of one or both substances at the target site, and often also in the blood. TDM is therefore a very valuable instrument in controlling the effect of a pharmacokinetic drug interaction, even if it is not a direct measure of the drug concentration at the target site. The usefulness of TDM may be limited in a situation where drug transport through the blood brain barrier shows high inter-individual variability and is determined by active transport mechanisms.[149,150] Information on mechanisms of metabolic interactions can be found in textbooks[151] or other literature.[7,152]

Drugs can be substrates for one or several metabolic enzymes, which contribute to their biotransformation using major and minor pathways. This is important when estimating the consequences of inhibition or induction of one of these pathways. The extent of an interaction is dependent on the baseline enzyme activity. No inhibition occurs in people with almost no enzyme activity (e.g. in the situation of a genetic deficiency of this enzyme), while the inhibitory effect may be pronounced in people with high baseline activity.

It is not an easy task to estimate the interaction potential of a particular combination therapy. Numerous tables exist that list drugs as substrates and inhibitors/inducers for different metabolic enzymes, mostly CYP450 enzymes. Many do not differentiate between major and minor pathways, and many translate *in vitro* results into *in vivo* data, which can lead to misinterpretation. Clozapine *in vitro* is metabolised by almost all relevant CYP450 enzymes. However, *in vivo*, it appears that CYP1A2 is the major pathway; CYP2C19 and CYP3A4 are probably involved in a concentration-dependent manner, whereas CYP2D6 plays a negligible role.[76,131,153-155]

Predicting *in vivo* interactions from *in vitro* data is difficult; a number of reviews have been published on the impact of various factors on the accuracy of such an extrapolation and on prediction models.[156-162] Some drug-interaction lists give the interaction potential of drug classes, such as found for the SSRIs, but SSRIs form a very heterogeneous group especially concerning their CYP450 enzyme inhibiting properties. Fluvoxamine is a potent inhibitor of CYP1A2, but not of CYP2D6. Paroxetine and fluoxetine are potent inhibitors of CYP2D6, but not of CYP1A2, and so forth. Table VI indicates websites with clinically relevant information on drug interactions, CYP450 and other drug-metabolising and transporter systems.

Since the extent of a specific drug-drug interaction is not easy to predict, TDM should be used in drug combinations where affected drugs have a nar-

Table VI. Examples of websites providing information on drug-drug interactions, CYP450 enzymes and drug-transporting proteins[a]

http://medicine.iupui.edu/flockhart
http://www.genemedrx.com/
http://www.themedicalletter.com/
http://www.druginteractioninfo.org/
http://www.mediQ.ch/ (in German)
http://www.cypalleles.ki.se
http://www.mhc.com/PGP/index.html
http://www.aidsinfonyc.org/tag/science/pgp.html

a Accessed 2006 Aug 7.

row therapeutic index. Figure 4 shows that the clinical consequences strongly depend on the therapeutic index of the drug. It would not be wise to avoid combinations when they appear to be of little risk and are promising from a therapeutic point of view. However, inhibition can last for several weeks after discontinuation of the inhibiting agent, as is the case with fluoxetine and especially its metabolite norfluoxetine, which has a very long elimination half-life. In cases of a rapid change of medication from fluoxetine to another serotonergic compound, an increased risk for serotonergic adverse effects, including serotonin syndrome,[163-166] has been reported.

For drugs with active metabolites, the active moiety has to be considered, especially when the active metabolite is formed by the affected enzyme. In a study of 12 patients with schizophrenia,[168] risperidone was shown to be inhibited by paroxetine in a dose-dependent manner. Dosages of paroxetine 10, 20 or 40 mg/day resulted in a 3.8- to 9.7-fold increase in the concentration of risperidone. The concentration of the 'active moiety' (risperidone plus 9-OH-risperidone) was not significantly increased by low dosages of paroxetine, but a 1.8-fold increase occurred after paroxetine 40 mg/day. However, EPS scores also rose significantly with paroxetine 20 mg/day.

Modulation of drug metabolism can be enantioselective, as is the case for warfarin, methadone, some antidepressants (e.g. venlafaxine, citalopram and mirtazapine) and other substances.[52,55,169-176] Since, in many cases, the effect of each enantiomer is distinct, it is important to know which metabolic pathway is affected. With warfarin, for example, S-warfarin exerts the main anticoagulation effect and is inhibited by CYP2C9 inhibitors such as fluconazole and amiodarone. In contrast, drugs such as omeprazole that affect R-warfarin metabolism, only

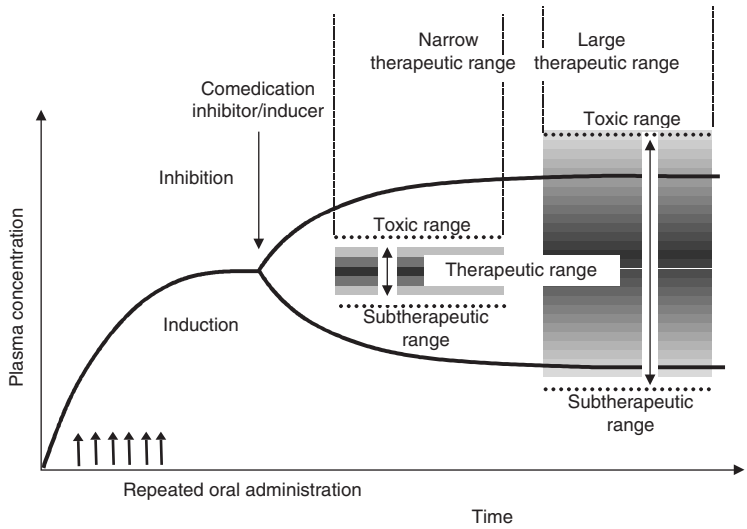

Fig. 4. The importance of a drug-drug interaction or drug metabolising enzyme polymorphism depends on the therapeutic index.[167] Inhibition of a certain strength leads to a plasma concentration increase, which with a drug with a narrow therapeutic range may lead to a toxic reaction, whereas with a drug with a wide therapeutic range this increase is tolerated.

moderately increase the anticoagulation effect.[177,178]

Table VII and table VIII illustrate typical examples of an inhibition and an induction interaction and the utility of TDM to avoid serious adverse drug reactions.

Adding fluvoxamine to clozapine treatment can increase plasma levels of clozapine by up to 10-fold,[27,180-184] which can be highly effective[27,181-183,185] but is not without risk of intoxication (drowsiness, epileptic seizures, delirium and cardiac problems). Regular TDM control during the treatment switching period is necessary, as well as an immediate adaptation of the clozapine dose. It is important to remember that the extent of the inhibitory effect is dependent on the baseline metabolic activity of the enzyme to be blocked and on the dose of the blocking agent.[186,187] Another effect will be a shift of the concentration relationship between the parent compound clozapine and the metabolite norclozapine, which might represent a certain advantage in the tolerability of the treatment, since norclozapine seems to be more sedative. It has also been postulated that combination therapy with fluvoxamine causes less weight gain than monotherapy with clozapine alone.[181]

In addition, it should be noted that an inhibitory effect occurs as soon as the inhibitor is introduced and disappears as soon as the interacting compound is eliminated from the body, which implies that the time course depends on the elimination half-lives of the drugs (and metabolites) implicated in the interaction.

Table VII. Case 3

A 48-year-old smoker with chronic schizophrenia was treated with a very high dosage of clozapine (1200 mg/day) in order to obtain plasma levels within the recommended range of 350–600 ng/mL and to attain a therapeutic response (the patient was phenotyped as a rapid CYP1A2 metaboliser due to a high smoking-related CYP1A2 inducibility). After 2 years of this high-dose treatment, he experienced several grand mal epileptic attacks. It was hypothesised that the use of such a high dose of clozapine produced high peak plasma levels, which could be a risk factor for his epileptic attacks. Treatment was therefore changed to a combination of the strong CYP1A2 inhibitor fluvoxamine (150 mg/day) plus clozapine 125 mg/day, in order to decrease peak plasma levels, while maintaining the trough levels. The therapeutic response remained stable and trough plasma levels stayed within the same range as those observed with high-dose clozapine treatment; however, the patient did not experience any further epileptic fits.[27,179]

Table VIII. Case 4

A 38-year-old patient with a history of drug abuse, psychotic episodes and HIV infection was admitted to hospital in an aggressive psychotic state. Treatment with a high dose of zuclopenthixol 400mg depot, diazepam 60 mg/day and methadone 90 mg/day improved his condition. Because of his HIV infection he subsequently received lamivudine and efavirenz. Five days after starting the new HIV treatment, the patient deteriorated rapidly and became highly aggressive again. TDM of methadone showed a decrease in the methadone concentration to 55% of the baseline value, resulting in methadone withdrawal symptoms. HIV treatment with efavirenz was stopped and the patient recovered after about 1 week; the methadone plasma levels concomitantly returned to baseline values. A better alternative would have been a stepwise increase in the methadone dose together with multiple daily dosing and TDM.

Case 4 and similar published cases[188,189] demonstrate a drug-inducing effect leading to methadone withdrawal. Efavirenz[190] and nevirapine[191] are strong inducers of CYP3A4 and CYP2B6, major pathways in the metabolism of methadone. The induction process takes time, since more new enzyme has to be synthesised. As a rule of the thumb, the induction effect can generally be expected after 1 week, and the full effect might take several weeks. This has to be kept in mind when applying TDM. When an inducer is removed from treatment,[192] plasma levels of the substrate will increase with about the same lag time until a new equilibrium is reached.

Table IX lists examples of typical substrates, inhibitors and inducers for the most relevant CYP450 enzymes in drug metabolism. This information can also be found in handbooks[193] and on websites (table VI).

2.1.3 Other Factors

Individual drug response is also dependent on factors such as age, sex, organ (especially renal and hepatic) function, comorbidity and lifestyle or environmental factors such as diet or smoking. These factors certainly affect CYP450 enzyme function, but glucuronidation and the expression of drug transporters also appear to be sensitive.

Table IX. Examples of typical substrates, inhibitors and inducers for the most relevant CYP450 enzymes in drug metabolism

Enzyme	Substrates	Inhibitors	Inducers
CYP1A2	Clozapine, caffeine, theophylline, tacrine, tricyclic antidepressants (some), zolmitriptan	Ciprofloxacin, fluvoxamine	Omeprazole, rifampicin, ritonavir, smoking
CYP2C9	Phenytoin, S-warfarin, acenocoumarol, tolbutamide, glipizide, torasemide, losartan, fluvastatin, several NSAIDs	Flucanozol, sulfaphenazole	Phenobarbital, rifampicin
CYP2C19	Citalopram, diazepam, mephenytoin, moclobemide, omeprazol	Fluoxetine, fluvoxamine, omeprazole, ritonavir	Phenobarbital, rifampicin
CYP2D6	Many anti-arrhytmics, β-adrenoceptor antagonists and psychotropic drugs, codeine, dextromethorphan, tramadol	Buproprion, cimetidine, fluoxetine, paroxetine, metoclopramide, quinidine	Probably none
CYP3A	Azole antifungals, astemizole, calcium channel antagonists, carbamazepine, cisapride, citalopram, clozapine, ciclosporin, haloperidol, macrolide antibiotics, methadone, midazolam, mirtazapine, mianserin, olanzapine, protease inhibitors, quetiapine, sirolimus, HMG-CoA reductase inhibitors, steroids, tacrolimus, terfenadine, tricyclic antidepressants (some)	Ciprofloxacin, diltiazem, grapefruit juice, norfloxacin, norfluoxetine, itraconazol, ketoconazole, macrolide antibiotics	Carbamazepine, efavirenz, phenobarbital, phenytoin, rifampicin, ritonavir, hypericum

Smoking

Smoking induces CYP1A2, which means that smokers are likely to have lower plasma levels of CYP1A2 substrates than non-smokers. Importantly, it is the tar particles in the smoke, rather than nicotine, that are responsible for this effect. A similar effect is also seen when consuming barbecued meat, for instance. Smoking also slightly induces glucuronidation, as seen with codeine.[194] Environmental and genetic factors can produce either synergistic or antagonistic effects. It appears that there is also a genetic polymorphism for inducibility (e.g. by tobacco smoke) of CYP1A2.[79,82]

Smoking cessation in patients on drugs such as clozapine, olanzapine, tacrine or theophylline, which are mainly metabolised by CYP1A2, can lead to drug intoxication. Several cases have been described for clozapine and olanzapine,[195-197] with adverse drug reactions including seizures, heavy sedation, cardiac problems and delirium. The induction effect of smoking seems to have a mean elimination half-life of about 39 hours (range 27–54 hours);[192] a new steady state could be expected after about 2 weeks. de Leon[196] suggests a mean dose correction factor of 1.5 for a change in smoking behaviour. In individual patients, however, smoking cessation may lead to a more marked increase in plasma levels. Other authors refer to mean correction factors of up to 5.[26,198] A stepwise dose reduction with TDM control is strongly recommended.

Food

Recently there has been increased awareness that grapefruit juice can have an important interaction with as many as 40 orally administered drugs.[199-201] In particular, interaction with certain HMG-CoA reductase inhibitors (statins), such as simvastatin, atorvastin and lovastatin, can lead to serious complications such as rhabdomyolysis.[200,202] Some antihypertensive drugs, when taken with grapefruit juice, might also have a higher risk of adverse drug reactions (e.g. felodipine or nifedipine resulting in excessive vasodilatation). Special attention is advised for drugs with a narrow therapeutic index, such as the immunosuppressant ciclosporin or the antimalarial agent halofantrine. For certain drugs (e.g. ciclosporin in the Sandimmune® formulation), very high individual differences in bioavailability exist and; therefore, it is difficult to predict the magnitude of an interaction. TDM is therefore very valuable and routinely used. The type of interaction consists mostly of an increase in drug plasma levels,

seen in either the AUC or the maximum plasma concentration. The main mechanism is inhibition of the intestinal CYP3A4 pathway, but inhibition of P-glycoprotein might play a role as well. Saito et al.[199] recently reviewed pharmacokinetic interactions with citrus juices (mainly grapefruit) and provide more insight into possible mechanisms of action.

Interactions with other food constituents (caffeine, cabbage, chargrilled food, water cress and others)[203,204] exist but, with the exception of clozapine and caffeine,[205,206] seem to play a less important role.

Age and Sex

Divergent responses to drug treatment are often observed between elderly, young and adult populations. In children, some clinical studies indicate that higher doses (on a weight-adjusted basis) compared with adults are often needed to reach therapeutic drug concentrations.[207,208] This seems to be based on an increased clearance of the drug in younger children. In contrast, in elderly patients, impaired renal and sometimes hepatic function often leads to a decrease in drug elimination and reduced drug metabolism, respectively; therefore, dose adjustment may be necessary.[209,210] It is also probable that the therapeutic index of some drugs in some elderly individuals is narrower, because of an increased sensitivity to drugs.[211]

Men and women often differ in their response to drug treatment. Sex differences in subjective tolerability might account for part of this,[212] but biological factors are certainly also important.[213] An extensive overview of sex-specific factors such as body build, hormonal transitions, diet and other environmental or cultural factors in relationship to antipsychotic therapy was recently published.[214] The author concludes that, for a given dose, the mean plasma level in men tends to be lower than in women, suggesting, therefore, that women need lower doses than men. Another review[215] concludes that the adverse drug reaction risk for women is about 1.5-fold greater than that for men and discusses sex-based differences in pharmacokinetic and pharmacodynamic factors. Data from a naturalistic dynamic cohort study looking at 165 psychiatric inpatients with a severe adverse drug reaction showed that women (n = 79) were more likely to have unexpectedly high plasma drug levels than men (n = 82) [36% vs 22%[216]]. This sex difference has been demonstrated previously.[217] The use of TDM rather than the adoption of a standard recommended dose could help optimise individual doses of therapeutic agents.

Pronounced sex differences are, for example, described for clozapine[218,219] and olanzapine,[220] both of which are mainly metabolised by CYP1A2. Perry et al.[218] developed a clozapine dosing model comprising the variables: dose, smoking status and sex. To reach therapeutic plasma levels, male smokers may need twice the dose required by female non-smokers (figure 5).

Sex differences are also observed in drug metabolising enzymes and drug transporter proteins.[221,222] Men appear to have higher CYP1A2 activity and maybe also higher CYP2E1 activity, as well as of some increased activity for UGT and P-gp uridine 5′-diphosphate glucuronosyltransferases (UGTs) and drug transporter P-glycoprotein, whereas women may have higher CYP2D6 activity.[223] Of course there are other physiological differences between women and men; women have generally lower body weight and organ size, a higher percentage

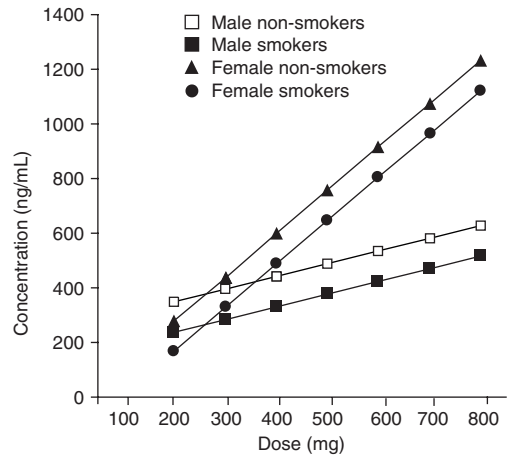

Fig. 5. Sex-related dose differences for clozapine (reproduced from Perry et al.[218] with permission from Society of Biological Psychiatry).

Table X. Case 5

A 54-year-old obese diabetic female non-smoker with chronic schizophrenia was treated with a stable clozapine dose and stable plasma levels in the therapeutic range (350–600 ng/mL) for several months. She became drowsy and partly disoriented during a symptom-free episode of pericarditis. Without any change in dose, plasma clozapine levels increased by a factor of 2.5 from pre-percarditis levels.

of body fat, a lower glomerular filtration rate and, in general, a slower gastric motility than men.[224]

In general, however, sex-based pharmacokinetic differences account for only subtle changes in drug response; sex-based pharmacodynamic processes such as QTc interval prolongation seem to be more important.[222]

Co-morbidity

The effect of renal or hepatic insufficiency on the fate of a drug may be dramatic, but it depends on the means of elimination. It is not widely appreciated that plasma levels of CYP1A2 substrates can vary in the presence of an inflammatory process. This is illustrated in table X.

Similar cases, mainly with respiratory infections such as pneumonia, have been reported.[225,226] The hypothesis is that cytokines (e.g. interleukin-6) inhibit CYP1A2 activity.[227] Several animal studies have shown that different CYP450 enzymes are down-regulated during sepsis[228] or after endotoxin-induced inflammation,[229,230] but the mechanism for this reduction is still unclear. It can also be hypothesised that an increase of binding to α_1-acid glycoprotein, an acute-phase protein reactant, contributed in case 5 to an increase in plasma levels of clozapine and a decrease in the volume of distribution.

Other examples exist where comorbidity has a major influence on drug metabolism and therefore an impact on drug safety. N-acetyl-transferase (NAT) activity is determined by inherited as well as acquired factors such as liver disease or AIDS. In these patients, genotyping alone does not sufficiently predict acetylator phenotype. The discrepancy between predicted and observed acetylator phenotype in AIDS patients may reach up to 35%.[231] Patients with AIDS show the slow acetylator phenotype more often, which, in general, predicts a higher incidence of cutaneous reactions of the immunoallergic type. Patients with AIDS have a higher incidence of hypersensitivity reactions,[232] and the danger of the potentially fatal Stevenson-Johnson syndrome should be taken into consideration. Finally, inhibition of NAT activity by the multiple drugs received by HIV patients could also contribute to a slower acetylator phenotype.

2.2 Drug-Metabolising Enzymes in Phase II

In phase II conjugation reactions, a drug is conjugated with hydrophilic molecules, usually resulting in an inactive and easily excretable compound. An exception is the 6-glucuronide of morphine, which retains pharmacological activity for steric reasons. The role of the different isozymes implicated in the biotransformation of individual drugs has been less well studied than that of the CYP450 enzymes. Members of this system are UGTs, sulphotransferase (ST), gluthatione S-transferase (GST), NAT and thiopurine methyltransferase (TPMT). UGTs are the most important phase II enzymes, both in quantity and variety of substrates conjugated. Many drugs initially undergo a phase I step by CYP450, followed by a second step in which they are glucuronidated. Some benzodiazepines such as lorazepam, oxazepam and temazepam are directly glucuronidated. UGTs, similar to CYP450 enzymes, are sensitive to enzyme inhibition and induction, and UGT substrates can be metabolised by one or more UGTs. Despite the fact that many drugs are glucuronidated, precise information on substrates, inhibitors and inducers is not as accurate as that for the CYP450 enzymes. Many data stem from *in vitro* experiences, and have still to be studied *in vivo*.[233-237]

2.2.1 Uridine 5′-Diphosphate Glucuronosyltransferases

UGTs are human enzymes involved in phase II metabolism of toxic endogenous compounds (e.g. bilirubin) and/or exogenous compounds (e.g. drugs, pesticides and carcinogens). These compounds are metabolised and excreted in the bile and urine.[238] Six of the 16 human UGTs have been shown to demonstrate genetic polymorphism (UGT1A1,

UGT1A6, UGT1A7, UGT2B4, UGT2B7 and UGT2B15).[238,239] However, the main clinical significance involves defects in UGT1A1 resulting in decreased enzyme activity and Gilbert syndrome (UGT1A1*28 promoter mutations[238,240]), a mild disease characterised by episodes of jaundice caused by unconjugated hyperbilirubinaemia in the absence of liver disease. This mutation seems also to be of specific importance and clinical significance for the occurrence of prolonged jaundice in neonates. Large inter-ethnic prevalence differences have been demonstrated.[240-242]

UGT1A1 polymorphisms may also lead to variations in glucuronidation of drugs and subsequently to unexpected toxicity. In poor metabolisers of UGT1A1, irinotecan can lead to treatment-limiting diarrhoea and to immunotoxicity.[243,244] However, the effects of UGT polymorphisms seem, in general, to be far less pronounced than those of CYP450 isozymes,[234] and the clinical significance of UGT1A6, UGT1A7 and UGT2B15 polymorphisms remains to be proven.

The UGTs appear to play an important role in the metabolism and interaction potential of antiepileptic drugs. Lamotrigine and valproic acid are typical substrates. Amongst the older drugs, carbamazepine, phenobarbital, phenytoin and primidone are inducers of one or more UGTs; of the newer drugs, oxcarbazepine and lamotrigine have been shown to induce this class of enzymes. This metabolic pathway is responsible for the decrease of thyroid hormone levels in many patients taking these drugs.[245]

A highly relevant clinical interaction between the anticonvulsants valproic acid and lamotrigine[246] seems to be the consequence of glucuronidation inhibition. Caution is advised in administering lamotrigine in this combination, since rapid dose increase is a risk factor for severe skin reactions.[247] TDM can be helpful in adjusting the dose.

2.2.2 N-Acetyltransferase-1 and -2

NATs are polymorphically expressed enzymes involved in phase II drug metabolism. Various therapeutically important drugs, as well as toxic chemicals in the environment (e.g. diesel exhaust and tobacco smoke), undergo acetylation, potentially influencing the efficacy of drug treatment and the risk of adverse drug reactions. Exposure-related health hazards and diseases[248,249] may be associated with NAT polymorphisms. Drugs metabolised by NATs comprise compounds that bear arylamine or hydrazine moieties. Examples of NAT1 or NAT2 substrates are shown in table XI.

Differences in therapeutic efficacy between slow and rapid acetylating individuals are of minor importance. However, adverse drug reactions are influenced or determined by the actual capacity for acetylating drugs. The consequences of this include altered kinetics of specific drug substrates, drug-drug interactions resulting from altered kinetics, and idiosyncratic adverse drug reactions.[250] Early reports of isoniazid-induced neuropathies[251] were the first examples of adverse drug reactions in connection with the slow acetylator phenotype; more examples are to be found in table XII.

In patients with a high clinical risk of severe adverse effects, genotyping and/or phenotyping of NAT variants is advisable. The approximate percentage of slow acetylators differs between ethnic populations (table XIII). Predicting NAT phenotypes by genotyping tests is possible, with a correlation of 95%.[232] However, the acetylation type may

Table XI. Drugs metabolised by N-acetyltransferase[232]

Acebutolol
Aminobenzoic acid
Aminoglutethimide
Amonafide
Amrinone
Aminosalicylic acid
Benzocaine
Caffeine
Clonazepam
Dapsone
Declopramide
Dipyrone
Hydralazine
Isoniazid
Nitrazepam
Phenelzine
Procainamide
Sulfonamides

Table XII. Examples of clinically relevant adverse effects in slow acetylators[232]

Isoniazid in tuberculosis: up to 50% of patients have adverse events such as peripheral neural disturbances; some also experience hepatotoxicity
Sulfonamides: hypersensitivity, haemolytic anaemia and lupus-like syndromes
Procainamide: hypotension and systemic lupus
Hydralazine: hypotension, tachycardia, flush and headache
Clonazepam in epilepsy: ataxia, dizziness and slurred speech

be only one of the risk factors that contributes to an adverse drug reaction. The positive predictive value of pharmacogenetic tests for NAT1 and NAT2 phenotypes in relation to the risk of serious adverse drug reactions is unknown, thus making dose titration and TDM important tools in their prevention of adverse drug reactions.

2.2.3 Thiopurine Methyltransferase

TPMT is involved in the phase II metabolism of thiopurine drugs used in the treatment of acute leukaemia and other autoimmune conditions such as rheumatoid arthritis, myasthenia gravis and inflammatory bowel disease.[252,253] The molecular basis for polymorphic activity has been well defined.[254] It is estimated that 1 in 300 Caucasians has a complete deficiency and 11% are intermediate metabolisers, whereas 1 in 2500 Asians is a poor metaboliser.[255] TPMT substrates include azathioprine, mercaptopurine and tioguanine. Patients who are poor or intermediate metabolisers are prone to serious haematopoietic adverse effects when treated with thiopurine drugs[35,256,257] and therefore require reduced doses. The adverse effects are due to high intracellular levels of tioguanine nucleotides.[252,258] Screening for abnormal TPMT genotypes or phenotypes prior to treatment with thiopurine medication has become standard procedure in some centres. Patients with a TPMT deficiency need only about 10% of the normal dose of thiopurine drugs.[259,260]

2.3 Drug-Transporting Proteins

Recent investigations indicate that drug transporters, such as P-glycoprotein and organic anion-transporting polypeptides (OATP), in the intestinal mucosa and the blood brain barrier are also relevant for the pharmacokinetic variability of many drugs.[149,150,261-266]

P-glycoprotein, coded by the *ABCB1* gene, is an adenosine triphosphate (ATP)-dependent efflux pump for xenobiotic compounds with broad substrate specificity. It plays an important role in drug absorption, disposition and excretion, and is found in several organs such as the gut, liver, gonads, kidneys and brain. Reported genetic polymorphisms of *ABCB1* show high inter-ethnic variability and appear to play a role similar to that of drug-metabolising enzymes.[267-270] P-glycoprotein function can be influenced by drugs, food, smoking status, age and sex. If P-glycoprotein function is induced or inhibited, absorption of drugs that are P-glycoprotein substrates will be affected. Interestingly, P-glycoprotein and CYP3A4 are often co-expressed in the same cells, and they share a large number of substrates and modulators (inhibitor and inducers). The disposition of such drugs is influenced by both drug transport and metabolism, and the interaction with a modulator acting on both systems will multiply the effect; e.g. ciclosporin is a substrate of CYP3A4 and P-glycoprotein, whereas hypericum (St John's wort) is an inducer of both.

With regard to the occurrence of wanted or unwanted clinical effects, the contribution of drug transporters is less well understood than that of drug-metabolising enzymes. Digoxin is a typical P-glycoprotein substrate with a narrow therapeutic index that can be affected by P-glycoprotein inhibition or induction. Certain phenotypes of P-glycoprotein can lead to increased plasma levels of digoxin[270,271] and to serious adverse drug reactions. Another example is the P-glycoprotein substrate

Table XIII. Estimate of the prevalence of N-acetyltransferase-2 slow acetylators in various ethnic populations[6,23]

Ethnicity	Prevalence (%)
Egyptian	92
Caucasian	50–59
Black African	50–60
African American	41
Chinese	20
Japanese	8–10

Table XIV. Examples of P-glycoprotein substrates and modulators

Substrates	
Aldosterone, amitryptiline, amoxicillin, carbamazepine, ciprofloxacin, citalopram, cortisol, corticosteroids, ciclosporin, colchicine, dexamethasone, digoxin, domperidone, doxorubicin, erythromycin, estradiol, fexofenadine, irinotecan, lansoprazole, lovastatin, loperamide, morphine, nelfinavir, odansetron, phenytoin, quetiapine, quinidine, ranitidine, risperidone, ritonavir, saquinavir, tacrolimus, terfenadine, topiramate, trimipramine, verapamil, vinblastine, vincristine	
Inhibitors	
Amiodarone, amitryptiline, atorvastatin, bromocriptine, carbamazepine, carvedilol, clarithromycin, ciclosporin, disulfiram, erythromycin, felodipine, fentanyl, fluoxetine, fluphenazine, fluvoxamine, grapefruit juice, garlic, green tea, haloperidol, ketoconazol, lansoprazole, levothyroxine sodium, midazolam, nelfinavir, omeprazole, paroxetine, progesterone, propranolol, quinidine, ritonavir, saquinavir, sertraline, simvastatin, spironolactone, tamoxifen, trimipramine, verapamil	
Inducers	
Aminosalicylic acid, clotrimazole, doxorubicin, efavirenz, hypericum, phenobarbital, rifampicin, trazodone	

loperamide, a potent opiate anti-diarrhoeal drug that has limited access to the brain due to P-glycoprotein activity. When combined with the P-glycoprotein inhibitor quinidine, it can enter the brain and cause respiratory depression[272] without any change in loperamide plasma levels. Further examples of P-glycoprotein substrates and modulators are shown in table XIV.

Besides efflux transporter systems such as P-glycoprotein, influx systems also exist such as the one involving OATP transporter proteins. OATPs primarily pump drugs into cells from a region of high concentration to one of low concentration, e.g. from the intestinal lumen to the plasma. Similar to P-glycoprotein, they are expressed in different organs including the intestine, liver, kidneys and brain. Genetic polymorphisms are recognised, as are modulators (inhibition by drugs and food), but information on their clinical relevance is very limited. OATP substrates include digoxin, enalapril, fexofenadine, hydrocortisone, pravastatin and ritonavir. A review on the role of drug transporters in drug interactions has been published recently.[266]

3. Therapeutic Drug Monitoring in Pharmacovigilance

TDM is based on the hypothesis that the concentration of a drug in the blood (plasma or serum) reflects the concentration at the target site better than the given dose. TDM is also based on the assumption that there is a definable relationship between plasma concentration and clinical effects (therapeutic effect, adverse effects and toxicity).

In psychiatry, these relationships have been investigated mainly for lithium, tricyclic antidepressants and antipsychotic drugs, the latter with inconsistent results.[273-283] Methodological shortcomings of numerous studies might be responsible for the lack of an evident relationship between concentration and therapeutic effects or adverse effects.[284-288] However, systematic reviews and meta-analyses[289] based on adequately designed studies have produced convincing evidence. A correlation between plasma levels, dopamine D_2 receptor occupancy and EPS has been demonstrated for antipsychotic medications, e.g. haloperidol.[290,291] For drugs with a wide therapeutic index, such as SSRIs, TDM is used mainly as a basis to adjust doses for special populations such as the elderly, patients with hepatic impairment or those with a known pharmacogenetic polymorphism affecting the prescribed drug.[292] TDM in psychiatry was introduced in the 1960s and 70s[293,294] and is still the only available means of estimating drug concentrations in the brain. Other techniques such as nuclear magnetic resonance spectroscopy have only recently been developed,[295] and it is not expected that this will be readily available and/or used on a routine basis in the near future.

TDM is an established tool for immunosuppressive agents such as ciclosporin, tacrolimus, sirolimus and everolimus in transplant medicine, permitting sufficient blood levels to prevent rejection, but avoiding adverse effects.[37]

TDM has shown its clinical utility in other disease areas, e.g. epilepsy.[39] Since the treatment of epilepsy aims to prevent or reduce the number of

Table XV. List of indications for therapeutic drug monitoring (TDM) in relation to pharmacovigilance

Pharmacovigilance of type A adverse drug reactions
Monitoring of substances with a narrow therapeutic window
Combination therapy with a drug-drug interaction potential
Known hepatic or renal insufficiency
Known pharmacogenetic polymorphisms (drug metabolising enzymes and transporter proteins)
Pharmacotherapy in special patient populations (e.g. the elderly, children and pregnant women)
Problems occurring after switching between different preparations of the same compound (e.g. original preparation vs generic)
Intoxication
Monitoring optimal individual plasma level ("TDM nouveau"[296])
Monitoring compliance

seizures, there is no direct measure to control the pharmacological effect.

A disease area where TDM might be beneficial is oncology, especially for drugs used in long-term treatment. Cytotoxic drugs have a narrow therapeutic index, definable by plasma levels but not by dose, and lack simple markers of pharmacological effects to monitor treatment. Elevated plasma concentrations of cytotoxic drugs can provoke serious adverse effects including myelotoxicity and cytotoxicity; cytotoxic drugs, therefore, would be good candidates for TDM. However, methotrexate is the only agent that is routinely monitored in most treatment centres. One complication is that cytotoxic drugs are often used in combination therapies, where the concentration-effect relationship is not the same as when a drug is used alone.[35] Ideally, TDM of cytotoxic drugs should be combined with measurement of polymorphic enzyme activities, e.g. for TPMT (section 2.2), dehydropyrimidine dehydrogenase (DPD) and methylene tetrahydrofolate reductase (MTHFR).

Table XV outlines situations where TDM is useful in relation to drug safety. The priority of the indications depends on the medical specialty. In psychiatry, monitoring of substances with a narrow therapeutic index, especially when used in long-term treatments, and compliance control are probably dominant. In other clinical areas, TDM in particularly vulnerable patient populations may be most important. TDM also gains importance in the presence of unexpected adverse drug reactions. Compliance control by TDM can also be indicated in pharmacovigilance, as adverse drug reactions are sometimes reported by non-compliant patients.

In order to get interpretable results that can lead to informed dose adjustment based on measured plasma levels, appropriate preparation for TDM is mandatory.[297] Key parameters are the timing of blood sampling, information on co-medications, dose and time of administration.

Reference plasma levels are generally based on trough steady-state concentrations. Blood should therefore be collected at least 4–5 drug elimination half-life periods after any change in dose and during the terminal elimination phase after drug intake. In clinical practice, the appropriate sampling time for most drugs is immediately before the next (morning) dose (12–24 hours after the last dose). In an outpatient setting, it can be problematic to measure trough levels. If for any reasons blood sampling is done <12 hours after drug intake, it is crucial to indicate the time of administration of the last dose to enable interpretation of the results. The difference between peak and trough levels can be very important (figure 6). In patients treated with an intramuscular depot preparation of an antipsychotic drug, blood should be sampled immediately before the next injection and also during steady-state conditions (often only reached after 2–4 months).[298]

For TDM of antimicrobial treatment with aminoglycoside antibiotics, tuberculostatic drugs and others, different rules for blood sampling may apply. In order to control the bacteriostatic effect, the maximum concentration of a drug in plasma is as important as the trough level, which is determined to prevent toxicity. The peak concentration is deter-

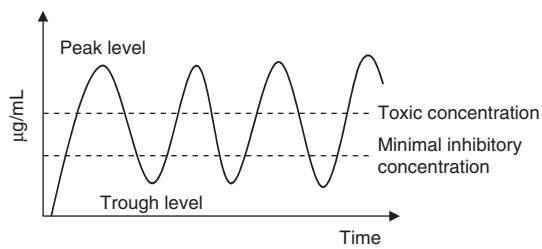

Fig. 6. Peak and trough plasma levels in antimicrobial treatment.

mined immediately after the end of the infusion for conventional treatment with intravenous aminoglycosides, whereas for an orally administered drug, such as rifampicin, the maximum plasma concentration 2 hours post-administration is usually the most informative.[299]

Technical recommendations given by the laboratory must be considered when blood is collected for TDM (e.g. correct anticoagulant, conditions for mailing and the influence of light and temperature). With the exception of immunosuppressants (measured in whole blood samples with EDTA additive), the preferred material is serum or plasma (i.e. blood containers without additives or with EDTA or heparin, respectively). With few exceptions, psychotropic drugs are stable in serum or plasma for at least 24 hours.[300] Some antimicrobial agents are not very stable in human serum and therefore have to be frozen for transport.[299]

The quality of the analysis may be considerably influenced by interactions with co-administered drugs or drug metabolites. Precise information on co-medications may help the laboratory to identify analytical problems associated with such interactions. In addition, information on co-medications is essential for interpretation of the results, as is the reason for the request and information on treatment duration, dose, time of ingestion, sex and age of the patient and, if possible, diagnosis and co-morbidities.

In 2004, the first consensus guidelines for TDM of psychopharmacological agents were published by the interdisciplinary TDM group of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP).[121] These guidelines are designed to assist clinicians and laboratories involved in TDM of psychotropic drugs. The guidelines cover indications for TDM, levels of recommendation based on the literature, practical guidelines for correct use and, very importantly, give reference plasma levels for the therapeutic window, as well as expected dose-dependent plasma levels under steady-state conditions. When therapeutic ranges could not be established, the target ranges correspond to the normally observed plasma levels at therapeutic doses.

Consensus guidelines also exist for determination of the immunosuppressant drugs ciclosporin,[301] tacrolimus,[302] mycophenolate[303] and sirolimus,[304] but are apparently lacking for such an important group as the anticonvulsants. Practical TDM guidelines have also been published for antiretroviral drugs.[305,306] TDM of antibiotics can be helpful in complex treatment situations such as tuberculosis; normal or usual concentrations for given doses, together with guidelines for special patient populations, have been published.[299]

Sometimes, however, individual optimal serum concentrations seem to be preferred over consensus values, especially for long-term and combination treatments.[296,307]

In the difficult treatment situation of relative overdose (e.g. due to a pharmacogenetic polymorphism or a drug-drug interaction), it is useful to know toxic plasma levels. These are far from known for all drugs, especially newer drugs, which generally have larger therapeutic indexes. Some large listings of therapeutic and toxic drug concentrations exist,[308,309] which have been generated by reviewing case reports of intoxication where drug concentrations have been measured.

Laboratories vary in the presentation of results including different use of units (e.g. nmol/L, μmol/L, ng/mL and μg/L). Conversion tables can be found in the literature (e.g. in consensus guidelines[121]) or obtained from TDM laboratories. For clinically complex situations, it may be advisable to involve a laboratory that offers pharmacological consultations.

TDM is a valid tool to optimise pharmacotherapy, but it does not replace clinical judgement. Since the majority of adverse drug reactions are dose-dependent, measuring drug plasma levels seems to be a highly rational approach to help prevention of these reactions, to reveal possible causes and, subsequently, to take steps to adjust drug treatment.

4. Pharmacogenetic Tests as a Tool in Pharmacovigilance

Depending on the particular drug metabolising enzyme or transporting protein, phenotyping and/or genotyping methods are now available. Phenotyping and genotyping differ in their clinical significance. Phenotyping generally represents a 'state marker', which is influenced by environmental factors such as co-medications, food and smoking status; genotyping, however, may be considered as a 'trait marker'. Phenotyping carries the advantage of indicating the metabolic situation of the patient at a specific moment, and allows its evolution to be followed. Among its disadvantages, however, are the fact that a test substance has to be ingested and that many phenotyping probes lack specificity.[310] Phenotyping is carried out most frequently with test probes specific for certain isozymes, such as debrisoquine, sparteine or dextromethorphan for CYP2D6, caffeine for CYP1A2, midazolam for CYP3A, mephenytoin or omeprazol for CYP2C19 and flurbiprofen for CYP2C9. When several enzymes are to be tested, a 'phenotyping cocktail' may be advantageous.[311-313] However, depending on the assay method used, the risk of analytical interference may be high in the presence of co-medications and their metabolites.

The clear advantage of genotyping is that it represents a 'trait marker', and that the result is not influenced by environmental factors, meaning that it needs to be performed only once in a person's lifetime. However, the functional significance of many genotypes remains to be clarified.[310,314] A DNA probe is extracted from a non-centrifuged whole blood sample. Some laboratories also work with material such as buccal swabs or saliva samples, for which the sampling procedures are less invasive and therefore might be better accepted by some patients. Different kinds of procedures are then used to analyse the DNA and its genes. Most laboratories analyse only a limited number of gene alleles (i.e. the most common ones). Recently, microarray-based genotyping devices, known as 'gene chips', have been introduced to the market. They are powerful analysers of many alleles of more than one gene in a very short period of time. A short lag time between collecting a DNA probe and obtaining the results is an important prerequisite if genotyping is to be done before initiating treatment. The current drawback, however, is the high cost of the instrumentation and each chip.

In the case of CYP2D6 substrates, low-plasma concentrations may be explained by an ultra-rapid metabolism, but genotyping identifies only about 30% of ultra-rapid metabolisers, the ones who present an allele amplification,[61,67,68] and phenotyping tests are not selective enough to clearly distinguish between ultra-rapid metabolisers and extensive metabolisers (and intermediate metabolisers) since there is no clear-cut trimodal distribution of CYP2D6 phenotypes. Besides allele amplification, there most probably exists another mechanism for ultra-rapid metabolic function.[69,70]

Kirchheiner et al.[117] recommend pharmacogenetic tests for drugs where a ≥2-fold difference in AUC (for the active moiety) has been observed between poor metabolisers and ultra-rapid or extensive metabolisers and/or for which the relative risk for an adverse drug reaction or therapy failure is ≥2-fold. Ensom et al.[310] propose extending pharmacogenetic testing before prescribing a drug to more different drugs than currently (mercaptopurine, azathioprine, thioguanine) done. They also see a potential to partly replace conventional TDM by pharmacogenetic testing. However, pharmacogenetic testing combined with TDM remains probably the ideal solution in many cases.

Finally, pharmacogenetic tests should also be considered from an ethical point of view. Issues such as informed consent, the right of the patient (and their biological relatives) to understand the results and its consequences, data privacy and equality of treatment are not unique to pharmacogenetic tests and must be considered. More in-depth discussion about ethical issues in pharmacogenetics is available in other publications.[59,315-319]

5. Pharmacovigilance Studies

Few studies have examined the relationship between pharmacovigilance and pharmacogenetic

polymorphisms. Phillips et al.[23] conducted a systematic literature review of adverse drug reaction studies published between 1995 and 2000. The selection comprised 18 studies and 22 variant alleles of drug-metabolising enzymes (CYP1A2, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, UGT2 and NAT2) were identified. Twenty-seven drugs frequently associated with adverse drug reactions, of which 59% are metabolised by at least one polymorphic enzyme, were identified. Most of these drugs belonged to cardiovascular, antibiotic, psychiatric or analgesic classes. Conversely, only 7–22% of randomly selected drugs are known to be metabolised by a polymorphic enzyme. The authors concluded that drug therapy based on individual genetic make-up could significantly reduce the occurrence of adverse drug reactions.

To determine the potential clinical relevance of CYP2D6 polymorphisms on therapeutic outcome, a retrospective assessment of the frequency of CYP2D6 polymorphisms (genotyped) in a psychiatric inpatient population (n = 100) was conducted by de Leon et al.[320,321] The main finding, although only borderline statistically significant, was an over-representation of poor metabolisers; there was a 14% incidence of CYP2D6 poor metabolisers compared with an expected incidence of 7% in the general population. The authors concluded that CYP2D6 poor metabolisers might have a higher risk of being admitted to a psychiatric hospital. When considering only the 45% of patients taking medication primarily metabolised by CYP2D6, a trend towards a greater number of adverse drug reactions was detected. The medical costs of poor metabolisers were $US4000 to $US6000 higher per year than those of extensive metabolisers. The total duration of hospitalisation was also longer for CYP2D6 poor metabolisers (24 vs 17 days), but this was not statistically significant. In order to determine if CYP2D6 genetic deficiency significantly alters the duration of hospitalisation and costs, it was calculated that 1500–2000 patients would need to be evaluated over at least 1 year.

Rau et al.[322] showed, in a retrospective study, a significant over-representation of CYP2D6 poor metabolisers among patients who had experienced an adverse drug reaction with an antidepressant metabolised by CYP2D6. Another retrospective study in a psychiatric hospital, by Tamminga et al.,[323] assessed the influence of polymorphic CYP2D6 drug metabolism on the utilisation of psychotropic drugs. Patients with impaired CYP2D6 metabolism received fewer CYP2D6-dependent drugs, and furthermore, the average duration of prescription was significantly lower. Poor metabolisers were more prone to Parkinson-like effects, as evidenced by the co-prescription of anti-Parkinson drugs. Similarly, Mulder et al.[324] showed that CYP2D6 polymorphism was associated with more frequent switching and dose adjustments in patients taking psychotropic medication, which might reflect an association with unsatisfactory treatment response.

In a clinical trial involving 325 patients treated with risperidone, de Leon et al.[325] showed that CYP2D6 poor metabolisers had a higher risk of adverse drug reactions, and that this also led to more patients withdrawing from the study. Similar findings were reported by Brockmöller et al.[326] with haloperidol. Some small studies have found a link between EPS, mainly tardive dyskinesia, and CYP450 polymorphisms, but most lack sufficient power to detect significant differences in adverse drug reaction rates due to pharmacogenetic polymorphisms.[327,328] Kapitany et al.[139] genotyped 45 patients with chronic schizophrenia for CYP2D6 and found that patients heterozygous for a deficient allele were at a higher risk of developing tardive dyskinesia compared with patients with two wild-type alleles. Similarly, in a small naturalistic study, Reggiani et al.[329] found a correlation between CYP2D6 poor metabolisers and the risk of dystonia and parkinsonism in patients receiving neuroleptics and antidepressants.

For the antidepressant amitriptyline, Steimer et al.[330] found in a clinical trial involving 50 patients with depression a highly significant difference in adverse drug reaction risk between carriers of two functional CYP2D6 alleles and carriers of only one functional allele. In a naturalistic study, Grasmäder

et al.[331] observed a significant influence of CYP2D6 genotype on drug plasma levels of mainly newer antidepressants, but this had no significant influence on drug safety, probably because of the good tolerability of these drugs.

In the area of cardiovascular drugs, Wuttke et al.[332,333] retrospectively studied patients having experienced pronounced adverse drug reactions with metoprolol. CYP2D6 poor metabolisers showed a 5-fold relative risk of developing adverse drug reactions.

Basile et al.[334] studied the relationship between the C→A polymorphism of the gene for CYP1A2 (*CYP1A2**F), which is believed to influence the inducibility of this enzyme. Eighty-five patients with schizophrenia were assessed for the severity of tardive dyskinesia and were genotyped for CYP1A2. Patients with the genotype CC (less inducible CYP1A2 variant) were at a significantly higher risk of developing tardive dyskinesia than patients with the AC or AA genotype. This effect was further compounded when only the patients who smoked were evaluated. Tiwari et al.[335] studied patients with schizophrenia in North India and found an increased severity of tardive dyskinesia among carriers of the *CYP1A2*C* (G>A) variant allele, but no association with *CYP1A2*1F* polymorphism. Increased risk of developing tardive dyskinesia has also been related to dopamine D_3-receptor polymorphism.[336,337]

Kirchheiner et al.[30,116,117] determined dosing recommendations for antidepressant treatment for the different genotypes and phenotypes of CYP2C19 and CYP2D6 based on pharmacokinetic differences between poor, intermediate, extensive and ultrarapid metabolisers. However, extensive clinical studies are needed to verify their hypotheses. The authors proposed various study designs[117] to answer questions regarding the potential medical and economic value of pharmacogenetic tests.

A dynamic cohort study was conducted in psychiatric inpatients with severe, mainly serious, adverse drug reactions, with an emphasis on plasma levels of the medication involved.[216] The study was based on the following hypothesises: (i) most adverse drug reactions are dose-dependent; (ii) plasma levels of a particular drug are a better reflection of brain concentration than the dose; and (iii) plasma levels are dependent on the pharmacogenetic status of the patient. Over a 3-year period, 250 cases of adverse drug reactions were collected. In approximately 25% of these cases, drug plasma levels were at least 20% above the given reference ranges.[121] A gender difference was also observed; females more often had elevated blood concentrations compared with males. In addition, drug plasma levels regularly exceeded 200% over the maximal recommended reference value, suggesting the presence of a particular pharmacogenetic phenotype for a metabolising enzyme in some patients. A matched controlled follow-up study combining TDM with pharmacogenetic tests for relevant CYP450 enzymes is currently in progress.

6. Algorithm

TDM and pharmacogenetic tests can help to elucidate adverse drug reactions and establish better tolerated individualised treatment regimens for patients who have experienced a drug concentration-dependent adverse reaction in the past (e.g. because of a pharmacogenetic polymorphism). As a result of our clinical experience, we propose the algorithm in figure 7. It reflects the current availability of tests in clinical practice. Pharmacogenetic polymorphisms of transporting and receptor systems are not currently taken into account, since these tests are still the object of research. Knowledge about these will refine the possibility to find causes for inter-individual variations in drug response.

Phillips et al.[23] have proposed a clinician's checklist for reducing adverse drug reactions related to pharmacogenetic polymorphisms. Pharmacogenetic testing is recommended in particular circumstances, especially when an adverse drug reaction has occurred and no alternative medicine is available. It is difficult to identify additional gains from pharmacogenetic testing, as no clinical studies have linked pharmacogenetic variants with clinical outcomes. The example given by Phillips et al.[23] describes warfarin therapy with a high incidence of

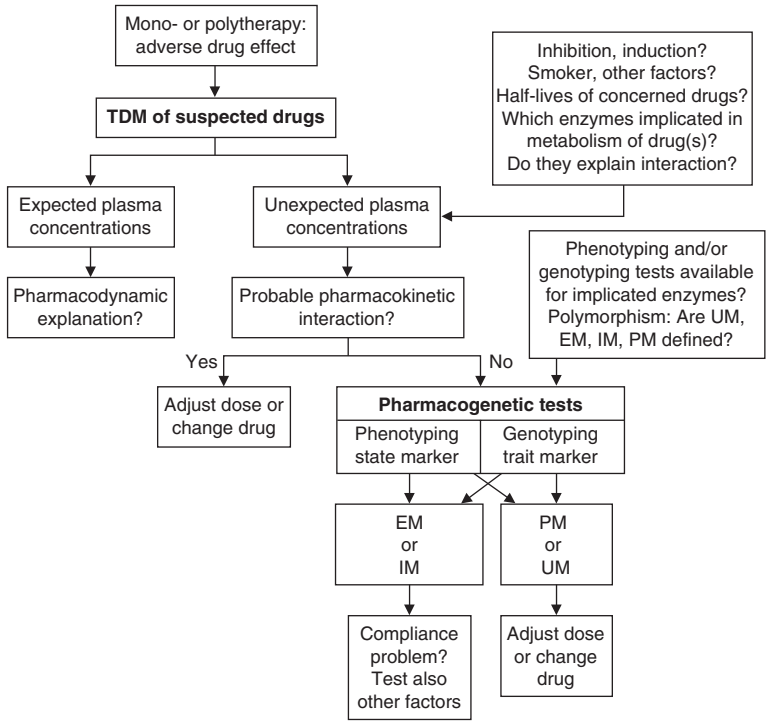

Fig. 7. Algorithm for the use of therapeutic drug monitoring (TDM) and pharmacogenetic tests of drug metabolising enzymes in pharmacovigilance.[43,337] **EM** = extensive metaboliser; **IM** = intermediate metaboliser; **PM** = poor metaboliser; **UM** = ultra-rapid metaboliser.

adverse drug reactions and a relatively high incidence of CYP2C9 (the main catalysing enzyme of warfarin) poor metabolisers. Although several studies have found an association between CYP2C9 genotype and adverse drug reactions,[128,136,338] none has yet suggested the advantage of CYP2C9-adjusted warfarin dosing over assessing individual blood coagulation times.

7. Discussion

Personalised medicine seems very attractive, certainly for the individual patient, but at present we are unable to predict the benefits for a wider patient population. Clinical studies in this field require large numbers of patients, and in order to make informed decisions on the value of routine pharmacogenetic testing and TDM the combined efforts of academia, governments and the pharmaceutical industry are necessary.

Understanding drug response in the individual is complex. Even more complex are the analysis and interpretation of population-based toxicogenetic data. In order to detect previously unrecognised gene-gene interactions in the context of drug toxicity, large scale clinical trials will have to be analysed, with new high-quality computational methods such as 'multifactor dimensionality reduction'.[145,339]

Wilkinson[7] discussed the reasons for not using extensive genotyping in clinical practice despite the fact that information on potential adverse drug reaction risk is readily available. Many adverse drug reactions emerging in a poor metaboliser phenotype are undesirable but rarely life-threatening, only a small portion of the population is affected and, on most occasions, an alternative medication exists. In other instances (e.g. with anticoagulants and hypoglycaemic drugs), surrogate markers can guide drug dosing. Ingelman-Sundberg[340] estimated that predictive genotyping for CYP2D6 would be beneficial

in treatment, with about 30–40% of CYP2D6 substrates or 7–10% of all drugs being used clinically.

Similarly, Phillips et al.[23] have proposed criteria to evaluate the potential impact of pharmacogenetic information on reducing adverse drug reactions: (i) the medical need, taking into account the prevalence of adverse reactions caused by a drug, the prevalence of variant alleles, the severity of the reactions and the availability of current methods for monitoring the reactions; (ii) the clinical utility, i.e. the association between the adverse drug reaction and the variant alleles and the predictability of the genotypic assay for a substantial portion of the patient population; and (iii) the ease of use and the availability of an assay that rapidly and inexpensively detects the variant alleles and the ability of the clinicians to interpret the result and adjust drug treatment.

Veenstra et al.[341] have similarly identified five criteria for cost-effective use of pharmacogenetics, emphasising the need to carefully select appropriate drug candidates. They assess the potential cost effectiveness of pharmacogenetic interventions in different situations. The greatest cost effectiveness would include screening for TPMT polymorphism using a commercially available test because, if undetected, the clinical consequences are severe. In contrast, there is only an intermediate benefit with screening for CYP2C9 poor metabolisers in patients needing warfarin since clinical monitoring is feasible, and indeed mandatory.

There are very few cost-effectiveness calculations for TDM. One study with nortriptyline showed that patients who received TDM-guided dosing could be discharged earlier from hospital and returned to work earlier, than those dosed without TDM.[342] Another study[343] calculated significant savings in treatment with tricyclic antidepressants when TDM was used, primarily due to the avoidance of adverse drug reactions. A Swedish group investigated the cost effectiveness of newer antidepressants in elderly patients.[344] TDM led to dose reduction with sustained clinical efficacy, resulting in 38% net drug cost reduction. However, more cost-effectiveness studies are required for TDM in different treatment areas. Potential pitfalls, with respect to the doctor's non-adherence to the TDM-based recommended dosing, have to be taken into account.[345] TDM analyses in addition to clinical surveillance should result in positive therapeutic results.

TDM is increasingly being combined with pharmacogenetic tests.[30,314] Genotype-based dose adjustments are ideally followed by TDM since most genotype-based dose recommendations are based on calculations rather than clinical data. Genotyping and phenotyping procedures are still relatively expensive,[346] but preliminary data exist showing that psychiatric patients who are poor metabolisers or ultra-rapid metabolisers of CPY2D6 have treatment costs that are $US4000 to $US6000 higher than those of extensive metabolisers.[321] Tools to assess cost effectiveness of pharmacogenetic testing need to be further developed.[341]

8. Conclusion

The usefulness of TDM varies depending on the clinical situation and the particular drug involved. In common with other diagnostic tests, TDM should only be requested when there is evidence that the result will provide an answer to a specific question. Pharmacogenetics holds promise as a valuable screening tool for identifying patients who may be predisposed to the risk of an adverse drug reaction. Both TDM and pharmacogenetic tests are useful for causality assessments in a number of adverse drug reaction situations. Routine TDM and/or pharmacogenetic testing recommendations cannot be made based upon currently available data, except for drugs that have an established therapeutic index. More controlled studies are necessary to understand the role of elevated plasma concentrations and pharmacogenetic polymorphisms in the development of an adverse drug reaction.

Although an increasing number of reports on pharmacogenetically based differences in drug response have been published, there is an urgent need to translate this information into clinical recommendations.[347] Databases on drug-drug interactions, the

impact of pharmacogenetic polymorphisms and adverse drug reaction information systems[348] will be helpful to guide clinicians in individualised treatment choices. It may be advantageous for the clinician to involve a laboratory offering pharmacological consultation on TDM and pharmacogenetic test results.

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