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# Genetic and Epigenetic Factors Affecting Cytochrome P450 Phenotype and Their Clinical Relevance

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## 1. Introduction

Pharmacogenetics (or pharmacogenomics) studies the role of inherited and acquired genetic variation in drug response. Clinically relevant pharmacogenetic examples, mainly involving drug metabolism are known for decades, but the field was not evolved until the 1970s, when the discovery of the CYP2D6 polymorphism and its resultant effect on drug toxicity and response led to many observations of pharmacogenetic-based variations in pharmacokinetics. These and other discoveries and the subsequent ability to genotype led to the term pharmacogenetics. Today, as a consequence of sequencing and mapping of the human genome, pharmacogenetics is becoming the first drug discovery pipeline technology to affect the structure and economics of the pharmaceutical industry (Daly, 2010). During drug development, it is important to consider pharmacogenetic variation which could explain or even prevent discarding a drug candidate if appropriate genetic reasons are identified or when lack of response/occurrence of ADRs (adverse drug reactions) in drug therapy is experienced. Genetic variation is taken strongly into consideration also in clinic during individualized therapies. It helps to improve the number of responders and decrease the number of patients suffering from ADRs.

Beside genetic polymorphism there are other heritable phenotypic changes which play role in drug response that do not involve any alteration in nuclear DNA sequence, but affect gene transcription through DNA methylation, histone modification, miRNA regulation (called pharmacoepigenetic changes) (Berger et al., 2009). There are also non-heritable changes, which affect response to drugs, such as reactions to the environment, to drug-drug interactions through regulatory mechanisms (Tamási et al., 2003). Although fast, non-heritable responses, which alter signal transduction pathways affect the therapeutic outcome of a drug tremendously, pharmacogenetic and pharmacoepigenetic difference has to be taken also strictly into consideration in clinical practice.

In general one can envision important pharmacogenetic and pharmacoepigenetic variation

1. in genes responsible for pharmacokinetic properties of the drug (genes influencing absorption, distribution metabolism, elimination) or
2. in genes responsible for pharmacodynamic properties of the drug (genes affecting the pharmacologic effect of a drug) (Daly, 2010).

So far, it is apparent that heritable changes in genes encoding drug metabolizing enzymes often affects outcome in drug treatment to a high degree and the variability of the phase I enzymes plays major role in this respect, as evidenced by many studies (Spear et al., 2001; Ingelman-Sundberg, 2004a; Weinshilboum, 2003). In general it can be estimated that 20-25% of all drug therapies are influenced by such polymorphism to an extent that therapy outcome is changed. There are much fewer examples where the pharmacodynamic properties are influenced and it has clinical relevance (Ingelman-Sundberg, 2004b; Eichelbaum et al., 2006).

In this book chapter the polymorphic and epigenetic nature of phase I enzymes will be discussed and their role in therapy and clinic will be highlighted.

## 2. Pharmacogenetics

All genes encoding cytochrome P450 enzymes (CYPs) in families 1-3 are polymorphic. However, the functional importance of the variant alleles is not the same and the frequency of their distribution in different ethnic groups also differs. Polymorphisms of CYPs consist of single nucleotide polymorphisms (SNP), gene deletions, missense mutations, insertions, gene duplications and deleterious mutations creating inactive gene products. Furthermore amino acid changes might be introduced, which changes the substrate specificity of the enzyme. Mutations in intronic regions could also have relevance. An important aspect of drug metabolizing gene polymorphism would be copy number variation (CNV) where multiple functional gene copies of one allele can result in increased drug metabolism and absence of drug response at ordinary dosage. To order and standardize allelic variants, the CYP-allele nomenclature committee manages the naming and definition of CYP alleles, which are presented on an associated web site (<http://www.cypalleles.ki.se>). The homepage contains updated information regarding the nomenclature and properties of the variant alleles with links to the dbSNP database (<http://www.ncbi.nlm.nih.gov/projects/SNP/>) and relevant literature references. Based on the phenotype variability among drug metabolizers, the populations could be classified into four major groups:

1. the ultrarapid metabolizers (UM); with very high drug metabolizing capacity; usually carrying more than two active gene copies
2. the extensive metabolizers (EM); with high drug metabolizing capacity; usually carrying two active gene copies
3. the intermediate metabolizers (IM); with intermediate drug metabolizing capacity; usually carrying one functional and one defective allele, but may also carry two partially defective alleles
4. the poor metabolizers (PM); with slow, poor drug metabolizing capacity; usually lacking functional enzyme due to defective or deleted genes (Ingelman-Sundberg et al., 2007).

Taking CYP2D6-dependent metabolism as an example, the rate of metabolism for a certain drug can differ 1000-fold between phenotypes. Thus, the dosing required to achieve the same plasma levels of a drug metabolized mainly by CYP2D6, such as nortriptyline, differs 10-20-fold among individuals. Despite this extensive variation in metabolic capacity among patients, dosing is, at present, principally population based (i.e. doses are based on the plasma levels of the drug obtained on average in the population at a certain dosage), but not individual based.

- |  |   |
|--|---|
| <ul style="list-style-type: none"><li>• Lack or extended pharmacological effect</li><li>• Drug toxicity</li><li>• Lack of prodrug activation</li><li>• Increased effective dose</li><li>• Metabolism by alternative pathways</li></ul> | <ul style="list-style-type: none"><li>• Exacerbated drug-drug interactions</li><li>• Drug resistance</li><li>• Adverse drug reactions</li><li>• Idiosyncrasy</li><li>• Precarcinogen activation</li></ul> |
|--|---|

Box 1. Potential consequences of polymorphic drug metabolism.

CYP polymorphisms affect the response of individuals to drugs in many ways (see Box 1.) and it alters the therapeutic regimen of many diseases such as depression, psychosis, cancer, cardiovascular disorders, ulcer and gastrointestinal disorders, pain and epilepsy and many others. The problem is that the use of genotyping or genomic methods to inform clinical decisions about drug response are not widely practiced (Varmus, 2010) but it would be necessary, especially when drugs have narrow therapeutic indexes, when severe side effects occur or when the rate of non-responders is high. In recent years, the FDA has aggressively pursued drug-label modification when excess risk can be convincingly linked to a genetic marker. The FDA-mandated incorporation of pharmacogenomic information in drug labeling will remain an important step in the acceptance of pharmacogenomics in clinical practice (Wolf & Smith, 2000).

In the next section, relevant therapeutic areas where CYP polymorphism significantly influences the response of drugs or the incidence of adverse drug reactions will be presented.

## 2.1 Role of pharmacogenetics in therapies

At the present time, decisions about which medications to prescribe are made on a trial and error basis for many disorders. Under the pharmacogenomic paradigm, genetically based screening methods would allow the tailoring of drug therapy, drug selection and dosing according to an individual's ability to metabolize a drug. There are many disorders where it is already taken into consideration and applying information about the patient's genetic makeup has high impact on therapeutic outcome.

### 2.1.1 Cancer

Oncology is a field that is already being revolutionized by pharmacogenomics. Cancer pharmacogenomics is complicated by the fact that two genomes are involved: the germline genome of the patient and the somatic genome of the tumor. Chemotherapeutic drugs are very sensitive to genetic background, since in general they are unspecific drugs with narrow therapeutic indexes that result frequent severe or even fatal toxicities.

#### *Germline genetic variations in cancer cells*

*Tamoxifen.* Tamoxifen is an estrogen receptor modulator used in hormone receptor positive breast cancers. It has been suggested that CYP2D6 activity is required for the formation of endoxifen the active metabolite of tamoxifen (Jin et al., 2005). There are several studies proving that CYP2D6 PMs have worsened relapse-free time and disease-free survival rate, but they do not experience hot flashes at the same magnitude as compared with patients carrying the wild type allele. A similar loss of effectiveness is obtained as a result of enzyme inhibition (by serotonin reuptake inhibitors, antidepressants and other CYP2D6 inhibitors).

Another CYP enzyme, CYP2C19 has been shown to metabolize tamoxifen to its active form. Carriers of CYP2C19\*17 allele variants have been shown to exhibit a more favourable clinical outcome, since these patients activate tamoxifen in greater extent. This allele may be especially relevant for patients with low levels of CYP2D6 (Rodriguez-Antona et al., 2010).

*Cyclophosphamide.* Cyclophosphamide (CPA), a prodrug used in cancer therapy and for treatment of some autoimmune disorders is activated to 4-hydroxycyclophosphamide by CYP2C19, CYP2C9, CYP3A4 and CYP2B6. It has been shown that carriers of CYP2C19\*2 or CYP2B6\*5 had a significant lower CPA elimination and worse therapeutical outcome. CYP2B6 enzyme expresses also in the liver and it metabolizes ifosfamide, tamoxifen, procarbazine and thiotepa in the same manner as it activate CPA (Takada et al., 2004; Rodriguez-Antona et al., 2010).

*Tegafur.* Tegafur is also a prodrug which is activated to 5-fluorouracil by CYP2A6. Patients with CYP2A6\*4 or CYP2A6\*11 were poor metabolizer of this drug. Because other CYP enzymes influence the metabolism of tegafur (CYP3A4, CYP3A5, glutathione S-transferases) calculation of effective dose is difficult (Daigo et al., 2002).

*Thalidomide.* Bioactivation of thalidomide is dependent on metabolism by CYP2C19 (5-hydroxythalidomide). Another pathway producing arene oxid from thalidomide also exists and it is mediated by CYP1A1 and CYP2E1. It was reported that in multiple myeloma, response to thalidomide and dexamethasone parallel treatment was higher in CYP2C19 EMs than in PMs. The lower response rate observed in PMs is possibly due to the reduced activity to inhibit angiogenesis. Despite these facts there is no big influence of CYP2C19 polymorphism to treatment outcome (Vangsted et al., 2010).

#### *Somatic genetic variations in cancer cells*

CYP3A4 tumor expression could be somatically altered in specific tumors and it could be useful predictor for the effectiveness of drugs that are subject to CYP3A4 metabolism (for e.g. drug resistance in cancer tissue). Vincristine, CPA, etoposide treatments in lymphoma or docetaxel in breast cancer are all substrates of tumor CYP3A4 and their local metabolism could have therapeutical consequences due to their narrow therapeutical window. CYP2B1 is also overexpressed in breast cancer and there are several therapeutic approaches focusing on higher CYP2B1 metabolism in tumor cells than in other body cells (Rodriguez Antona et al., 2010).

### **2.1.2 Depression**

CYP2D6 and CYP2C19 metabolize virtually all of the antidepressants, many of which are also strong inhibitors of the enzyme.

#### *Antidepressants*

Tricyclic antidepressants (TCAs) are medications used to alleviate mood disorders, such as major depression dysthymia or anxiety disorders. CYP2D6 mediated metabolism of antidepressants leads to equally potent metabolites but the risk for side effects in poor metabolizers for CYP2D6 has been shown to be higher than in extensive metabolizers even if the sum of parent drug and metabolite was the same. Because of these adverse effects, in case of TCAs, there should be a dose adjustment depending on the patients genotype (for

e.g. single dose paroxetine is changing 10-fold in EMs compared to PMs) (Table 1.). Genotyping for *CYP2D6* in psychiatric patients is widely accepted and is more or less the only pharmacogenetic test used in clinical practice (Kirchheiner et al., 2004).

Drug	Dosing	Usual dose (mg)	EM (%)	IM (%)	PM (%)
<b>CYP2D6-dependent</b>					
<b>Amitriptyline</b>	M	150	120	90	50
	S	50	120	80	70
<b>Nortriptyline</b>	M	150	120	90	50
	S	50	140	70	50
<b>Imipramine</b>	M	150	130	80	30
	S	50	110	100	60
<b>Paroxetine</b>	M	20	110	90	70
	S	20	130	70	20
<b>Venlafaxine</b>	M	150	130	80	20
<b>CYP2C19-dependent</b>					
<b>Amitriptyline</b>	M	150	110	80	60
<b>Imipramine</b>	M	150	100	80	60
	S	50	100	90	70
<b>Clomipramine</b>	S	50	100	90	70

Table 1. M/S dosage recommendations of antidepressants for multiple-dosing or for beginning of treatment in relation to *CYP2D6* and *CYP2C19* polymorphism (M-maintenance treatment, S-single dose) (Kirchheiner et al., 2001).

*CYP2C19* polymorphism also influences the blood level of citalopram, amitriptyline and other antidepressants (Table 1.). Amitriptyline is demethylated to nortriptyline by *CYP2C19* which is further metabolised to nonactive metabolites. *CYP2C19* polymorphism alone does not affect the therapeutic outcome, since nortriptyline the metabolite is an active antidepressant, but side effects are different if the amitriptyline/nortriptyline balance is changing. The highest risk for ADRs occur when a patient is EM for *CYP2C19*, but PM for *CYP2D6*, since *CYP2C19* produces a high amount of nortriptyline, but there is no *CYP2D6* to metabolize it to inactive metabolites (Jornil et al., 2010).

#### *Serotonin reuptake inhibitors*

The pharmacokinetics of serotonin reuptake inhibitors (SSRIs) is complex, they are very lipid soluble, high clearance drugs subjected to multiple metabolic pathways.

*Fluoxetine.* Fluoxetine is metabolised to norfluoxetine, which is 20 times less potent SSRI than the original molecule. *CYP2D6* is responsible for R-norfluoxetine production and *CYP2C9* and *CYP2D6* produces S-norfluoxetine (Fuller et al., 1992). *CYP3A4* can also metabolise this drug, when *CYP2D6* becomes saturated (Margolis et al., 2000). Although genetic polymorphism influence greatly the level of fluoxetine, it is hard to predict the gene-concentration relationship because of several metabolic pathways.

*Paroxetine.* This drug is inactivated by *CYP2D6* (Bloomer et al., 1992). PMs for this enzyme tolerate much smaller dose than EMs (Table 1.). Single dose or multiple dosing makes

difference in paroxetine administration, because with chronic dosing metabolism is saturable and autophenocopy could occur (Laine et al., 2001).

### 2.1.3 Psychosis

Antipsychotic drugs are widely prescribed for a multitude of psychiatric conditions. CYP2D6 metabolizes many psychotropic drugs, including antipsychotics like haloperidol, thioridazine, perphenazine, chlorpromazine, risperidone, and aripiprazole.

Numerous authors suggested that genotyping for families of CYP enzymes (CYP2D6, CYP1A2) could potentially aid in prescribing antipsychotic drugs, since there are significant risks associated with their polymorphism, such as movement disorders (CYP1A2, CYP2D6), and cardiovascular adverse effects (CYP2D6) (Foster et al., 2007). CYP2D6 PMs had four time higher Parkinsonism like side-effects than EMs. Also, occurrence of other ADRs in response to treatment increased from CYP2D6 EMs to PMs. Furthermore, the duration of treatment was higher in PM patients, which increased the costs about 4000-6000\$ (Ingelman Sundberg, 2004b).

### 2.1.4 Epilepsy

Effective dosing of phenytoin is highly linked to CYP2C9 genotype. Patient carrying defective alleles show more frequently side effects for e.g. ataxia, diplopia and other neurological symptoms (Lee et al., 2002). Clobazam is also used in the treatment of epilepsy. This drug is metabolized to N-demethylclobazam, which is further processed by CYP2C19 to 4-hydroxydesmethylclobazam. In CYP2C19 PM patients there is an accumulation of N-demethylclobazam, which causes side effects such as drowsiness (Kosaki et al., 2004). Diazepam, another antiepileptic and anxiolytic is metabolized by CYP2C19 and CYP3A4. Both enzymes convert it to desmethyldiazepam. CYP2C19 produces two other metabolites also, oxazepam and temazepam (Andersson et al., 1994; Jung et al., 1997). PMs for CYP2C19 enzyme metabolize slower this drug and took longer to emerge from anesthesia than for EMs (Inomata et al., 2005). Although diazepam has a clear gene-concentration effect, it is not predictable for the dose because of the many other active metabolites produced and involvement of other CYP enzymes.

### 2.1.5 Pain

*Codeine.* Codeine and tramadol needs to be metabolized to its active forms (morphine or o-desmethyltramadol), before pain relieving effects are observed. Codeine is metabolised by CYP2D6 to its active metabolite, morphine, with CYP3A4 to norcodeine and with glucuronide transferase to codeine-6-glucuronide. CYP2D6 polymorphism affects greatly the present ratio of these metabolites, which means that PMs do not bioactivate enough codeine to morphine and EMs are at risk of CNS depression and other side effects due to elevated morphine production (Table 2.) (Leppert, 2011).

Gasche et al reported a patient who received oral codeine at daily dose of 75 mg and who experienced symptoms of morphine overdose (lack of consciousness, respiratory depression) after 4 days of treatment. The patient recovered after intravenous administration of naloxon. The cause of these symptoms was his CYP2D6 EM phenotype as genotyping showed 3 or

more functional alleles. The patient was concomitantly treated with claritromycin and voriconazole, both known inhibitors of CYP3A4 as confirmed by low CYP3A4 activity (Gasche et al., 2004)

Effects of metabolised codeine	EM	PM
Morphine conc. (% of codeine)	3.9%	0.17%
Analgesia	Yes	No
Pricking pain threshold	Increased	No effect
Tolerance thresholds to heat and pressure	Not altered	Not altered
Peak pain and discomfort during cold pressor test	Reduced	Not changed
Adverse effects	Yes	Yes

Table 2. Effects of codeine's active metabolite, morphine in relation to different CYP2D6 polymorphisms.

*Dihydrocodeine.* Dihydrocodeine (DHC) is a semi-synthetic analogue of codeine and it is used as analgetic, antitussive drug or for treatment of opioid addiction. DHC is metabolised to dihydromorphine (DHM) mostly by CYP2D6 (DHM percentage of a single oral DHC dose; 9%EM, 1% PM). Although DHM display greater affinity for opioid receptors than DHC, its pharmacological role in analgesic effect is not proven. Studies performed to date indicate that DHC analgesia is independent of CYP2D6 activity (Leppert, 2011).

*Tramadol.* Tramadol is a very usfull pain relief medication in neonates and infants. It is primary metabolized into its more active metabolite, O-demethyl tramadol by CYP2D6. EMs for CYP2D6 enzyme react better to tramadol treatment, pain treshold tests showed better tolerance of pain, than in PMs. PMs need approximately 30% higher tramadol doses than those with extensive CYP2D6 activity (EMs) (Ingelman-Sundberg et al., 2007).

### 2.1.6 Cardiovascular diseases

Genetic variation influences the dose of many cardiovascular drugs, because most of them has narrow therapeutic indexes. Cardiovascular diseases are treated with many different classes of drugs, such as antianginals, antihypertensives, antiarrhythmics, anticoagulants, antiaggregating agents, lipid lowering drugs, etc. Many of these drugs are metabolized through the polymorphic CYP2D6, CYP2C9 and CYP2C19 enzymes.

For example, the antianginal perhexiline metabolism is controlled by the polymorphic CYP2D6 enzyme. After perhexiline treatment a gene-dose effect has been observed; in poor metabolizers, perhexiline plasma concentrations can be very high (6-fold higher than in EMs after a single dose of perhexiline) which explains its hepatotoxic and neuropathic side effects. Determination of the ratio between perhexiline and its metabolite early in treatment may facilitate appropriate dose adjustment which may range from 10 mg in PMs to 500 mg in EMs (Cooper et al., 1984).

#### *Oral anticoagulants*

CYP2C9 and the C1 subunit of the vitamin K epoxide reductase (VKORC1) genotypes are associated with the variability in the overall pharmacodynamic responses to oral anticoagulants, such as warfarin, acenocoumarol and phenprocoumon. All three molecules have low therapeutic indexes and the dose required to produce a normal prothrombin time



is largely unpredictable. The consequences of under or over treating can be dire (thromboembolism or hemorrhage) (Gardiner & Begg, 2006).

*Warfarin.* S-Warfarin is 3- to 5-fold more potent than R-warfarin and its responsible for 70% of the overall anticoagulant effect. S-warfarin is mostly metabolized by CYP2C9 and in 1-1.5% by CYP4F2, whereas R-warfarin is metabolised by CYP3A4 and CYP1A2. Variations in genes central to warfarin activity (VKORC1, vitamin K reductase regulator (CALU) and gamma glutaryl carboxilase (GGCX)) are also polymorphic and they have to be taken into consideration during dose calculation (Table 3.).

Gene	Allele	Outcome
VKORC1	3673;G-1639A	GG (insensitive), GA (sensitive), AA (most sensitive)
GGCX	C>G	CC (less sensitive), CG (more sensitive), GG (most sensitive)
CALU	11G>A;R4Q	GG (less sensitive), GA (more sensitive), AA (most sensitive)
CYP4F2	C>T; V433M	CC (most sensitive), CT (more sensitive), TT (less sensitive)
CYP2C9	CYP2C9*2;R144C	CC (*1/*1, wild type), CT (*1/*2, IM), TT (*2/*2, PM)
	CYP2C9*3 ;I359L	AA (wild type), AC (-/*3, PM), CC(*3/*3, PM)
	CYP2C9*5	CC (wild type), CG (-/*5, PM), GG (*5/*5, PM)
	CYP2C9*6	AA (wild type), A(-/*6, PM), --(*6/*6, PM)

Table 3. Genes and their alleles that affect warfarin therapy. Various CYP alleles are just examples. The complete list could be found on the following homepage: <http://www.cypalleles.ki.se>.

Two common CYP2C9 allozymes have only a fraction of the level of enzyme activity of the wild type allozyme CYP2C9\*1: 12% for CYP2C9\*2 and 5% for CYP2C9\*3. Since VKORC1, CALU and GGCX genotype together with CYP2C9 and CYP4F2 genotype and factors such as age, body size may account just for 50-60% of the variability in warfarin dosing requirements, prothrombin time monitoring is still necessary during dose adjustment. But still, genotypization is recommended because of risk of side effects caused by the pharmacodynamic properties of warfarin (strong gene-dose relationship, strong dose-effect relationship and low therapeutic index). In 2010 the FDA revised the label on warfarin providing genotype-specific ranges of doses and suggesting that genotypes should be taken into consideration when the drug is prescribed (Wang et al., 2011; Takahashi et al., 1998).

*Acenocoumarol.* This drug is used in preference to warfarin in some countries, especially in Europe. R-Acenocoumarol is metabolized by several enzymes and produces most of the effect. S-Acenocoumarol is metabolized almost exclusively by CYP2C9 and although active, it contributes comparatively little because of its fast metabolism. The presence of one CYP2C9\*3 allele (PM) is associated with 20-30% lower acenocoumarol doses compared with wild type, whereas two alleles lead to very low dose requirements (1 mg/day instead of 2.5 mg/day) (Spreafico et al., 2002; Gardiner et al., 2006).

*Phenprocoumaron.* Phenprocoumaron exist as R and S-enantiomer and CYP2C9 is responsible for the elimination of the S form. This anticoagulant undergoes a large proportion of elimination via alternative pathways (e.g. renal and CYP3A4), so any relationship with the

CYP2C9 genotype may be less important than for warfarin or acenocoumarol (Toon et al., 1985).

#### *Antiplatelet agents*

*Clopidogrel.* Clopidogrel is an antiplatelet and it inhibits adenosine diphosphate (ADP)-stimulated platelet activation by binding irreversibly to a specific platelet receptor of ADP, P2Y<sub>12</sub>, thus inhibiting platelet aggregation.

Absorption of clopidogrel in the gut is opposed by the efflux pump P-glycoprotein, encoded by the *ABCB1* gene. Once absorbed, approximately 85% of the drug is converted to an inactive metabolite by the action of esterases. The remaining 15% must undergo a two-step transformation process to become active. The first step produces 2-oxo-clopidogrel and is catalyzed in varying proportions by the cytochromes CYP2C19, CYP1A2 and CYP2B6. The second step, which produces the reactive metabolite, can be catalyzed by CYP3A4/5, CYP2B6, CYP2C19 or CYP2C9. Among so many enzymes only genetic variation in CYP2C19 and *ABCB1* are associated with clopidogrel efficacy. As compared with subjects with no *CYP2C19* variant allele, subjects carrying one or two *CYP2C19* loss-of-function alleles have been shown to have lower plasma concentrations of the active metabolite of clopidogrel and a decrease in the antiplatelet effect of clopidogrel and an increased likelihood of cardiovascular event. In 2010, the FDA added a boxed warning to prescribing information for clopidogrel, stating that persons with a *CYP2C19* variant encoding a form of the enzyme associated with a low rate of metabolism might require dose adjustment or the use of a different drug (Simon et al., 2009; Ingelman-Sundberg et al., 2007).

#### *Antiarrhythmics*

Antiarrhythmia drugs are used to treat abnormal heart rhythms resulting from irregular electrical activity of the heart. Most antiarrhythmics are metabolized via CYP3A or CYP2D6 (Gardner et al., 2006).

*Propafenone.* Its enantiomers have equal sodium channel blocking activity, but S-propafenone is 100-fold more potent as a  $\beta$ -blocker (Kroemer et al., 1989a). Propafenone is metabolised via CYP2D6 to 5-hydroxypropafenone, which has sodium channel blocking activity similar to that of the racemic parent drug but less  $\beta$ -blockade and also by CYP1A2 and CYP3A4 to N-desalkylpropafenone (Kroemer et al., 1989b). Propafenone inhibits CYP2D6 strongly, with 70% phenocopying and R-propafenone inhibits the metabolism of the S-enantiomer. CYP2D6 status is generally thought to matter little for antiarrhythmic effect, but more for  $\beta$ -blockade and for side effects in central nervous system. Because of non linear pharmacokinetic and problems with active metabolites, enantiomers and phenocopying, it is hard to translate the proven gene-concentration ratio to clinically effective dose (Siddoway et al., 1987).

*Flecainide.* Flecainide is inactivated by renal elimination and in the liver by CYP2D6. Since the gene-effect relationships between CYP2D6 and flecainide seem minor, there is no need for clinical monitoring of this drug (Mikus et al., 1989).

*Mexiletine.* Mexiletine is a chiral, with the R-enantiomer having greater activity. It is metabolized to various metabolites by CYP2D6 and other enzymes. Due to CYP2D6, a minor gene-concentration effect seems to be present, but because of other elimination pathways it is not predictable for the dose (Labbe & Turgeon, 1999).

### *β-blockers*

Beta-blockers reduce the effects of the sympathetic nervous system on the cardiovascular system. These drugs are effective against high blood pressure, congestive heart failure, abnormal heart rhythms or chest pain. Their pharmacokinetic is very diverse; those which are metabolised by polymorph CYP enzymes are carvedilol, metoprolol, propranolol and timolol.

*Carvedilol.* Beside other metabolic pathways, CYP2D6 metabolizes carvedilol to its more potent β-blocker metabolite 4-hydroxyphenylcarvedilol. Polymorphism of CYP2D6 does not affect significantly the overall effect of this drug (Oldham & Clark, 1997).

*Metoprolol.* Metoprolol is a β<sub>1</sub>-selective blocker and is given as a racemate. Beside other pathways, metoprolol is under the control of CYP2D6. Metoprolol seems to have both consistent gene-concentration and gene-effect relationships in healthy volunteers, suggesting that dose reduction to 25% should occur in PMs or those phenocopied by other drugs (McGourty et al., 1985a).

*Propranolol.* Propranolol is metabolised by CYP2D6, but CYP2D6 polymorphism contributes little to variation in plasma concentration of this drug (Lennard et al., 1984).

*Timolol.* Timolol is a non selective β-blocker and is metabolised mainly by CYP2D6. Although the β-blocking effect can occur with very low level of the drug, it is not necessary to genotype before determining the dose of the drug (McGourty et al., 1985b).

### *Angiotensin II Blockers*

CYP2C9 metabolizes several antihypertensive angiotensin II receptor antagonists, such as losartan, irbesartan, candesartan or valsartan. Although losartan and candesartan are activated, irbesartan is metabolised by CYP2C9, there is no need for genotyping of the enzyme variants during the treatment (Gardiner et al., 2006).

## **2.1.7 Metabolic disorders**

### *Oral antidiabetics*

CYP2C9 is the main enzyme catalyzing the biotransformation of sulphonylureas such as tolbutamide, glyburine, glimepiride and glipizide. The total oral clearance of sulphonylureas has been shown to be 20% in PM persons of that in wild type, whereas the clearance in heterozygous carriers was between 50% and 80% of that of wild type genotype. Therefore, adverse effects of many oral antidiabetics may be reduced by CYP2C9 genotype-based dose adjustments (Gardiner et al., 2006).

## **2.1.8 Gastrointestinal disorders**

### *Proton pump inhibitors*

The PPIs undergo extensive hepatic biotransformation by the CYP system. The principal isoenzymes involved in the metabolism of the PPIs are CYP2C19 and CYP3A4 (Andersson et al., 1998; Pierce et al., 1996). CYP2C19 is the main enzyme involved in the metabolism of PPIs omeprazole, pantoprazole and lansoprazole and the CYP2C19 genotype is a strong

determinant of the acid inhibitory effect of these drugs. Higher doses of the PPIs should be used in homozygous EMs (e.g. 40 mg), and lower doses could be used in heterozygous EMs and PMs (e.g. 10 mg).

Eradication therapy		Eradication rate (%)			Av. cure rate (%)
		EM	IM	PM	
Dual therapy	Omeprazole/ Amoxicillin 20 mg 1x/500mg/two weeks 4x daily	30	60	100	63
	Omeprazole/ Amoxicillin 40 mg 1x/2000mg/one week 4x daily	33	30	100	54
	Rabeprazole/ Amoxicillin 10 mg 2x/500mg/two weeks 3x daily	60	92,2	92	80
Triple therapy	Omeprazole/ Amoxicillin/ Clarithromycin 40 mg 1x/1500mg/600 mg/one week 4x daily	81	94,5	100	92

Table 4. Dual and triple eradication therapy for *H. pylori* infection in relation to different CYP2C19 polymorphisms (Aoyama et al., 1999; Furuta et al., 2005).

Genotyping is also important in *Helicobacter pylori* eradication (Table 4.). If patients are confirmed as being PMs, dual therapy with PPI plus amoxicillin may be appropriate, as the eradication rate is likely to be high (>90%). This regimen has the advantage of being cheaper and less complex than triple therapy regimens. Individuals identified as homozygous EMs might be better to commence a triple drug regimen (PPI, amoxicillin and clarithromycin).

### 2.1.9 Infection

#### *Antiretrovirals*

*Efavirenz.* Efavirenz, a nonnucleoside reverse transcriptase inhibitor is an initial therapy during HIV infections. This drug is metabolised by CYP2B6 enzyme. In PMs for CYP2B6, efavirenz has been shown to be responsible for central nervous system side effects (sleep or mood disorders) and they also have increased risk for drug resistance (Rotger et al., 2005).

*Nelfinavir.* The protease inhibitor nelfinavir is metabolized mainly to nelfinavir hydroxy-t-butylamide by CYP2C9, which exhibits potent antiviral activity, and to other minor products by other CYPs that are inactive (Hirani et al., 2004). CYP2C9 polymorphism appears to have a clinical effect on nelfinavir, but the exact extent of the impact awaits additional clinical studies and confirmation. Nelfinavir is an inhibitor of CYP3A. Coadministration of nelfinavir and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug that could increase or prolong both their therapeutic and adverse effects (Niemi et al., 2003; Fulco et al., 2008).

### 2.1.10 Rheumatoid arthritis

Nonsteroid antiinflammatory drugs (NSAID) are commonly used for rheumatoid arthritis treatment and many of them are metabolised by the CYP2C9 enzyme. The low activity alleles of CYP2C9 (CYP2C9\*2, CYP2C9\*3) has been shown to influence the pharmacokinetics of ibuprofen, naproxen, diclofenac and celecoxib (Kircheiner & Brockmoller, 2005). From

these drugs, celecoxib and ibuprofen have extensive CYP2C9 metabolism (Kircheiner et al., 2002; Lundblad et al., 2006). In PM patients for CYP2C9 these two drugs have 2-7 fold longer effects and stronger gastrointestinal side effects (Martin et al., 2001).

### 3. Pharmacoeigenetics

Much of the interindividual variation in drug response has been addressed by pharmacogenetics and it is imperative for clinicians to consider during determination drug efficacy and reducing side effects. But it is important to note that many inherited and acquired discrepancies cannot be resolved only by sequencing the whole genome and identifying genetic variations, there are other heritable factors affecting the activity of a gene such as covalent modification of DNA and histones, DNA packaging around nucleosomes, chromatin folding and attachment to the nuclear matrix or miRNA regulation. These changes together are called epigenetic changes and with true genetics they show how genes might interact with their surroundings to produce a phenotype. It means that beside genetic information, epigenetic factors have to be also taken into consideration during determining variation in drug response. Beside individual variations, there could be a pharmacoeigenetic basis for other drug related effects, such as drug resistance (for e.g. doxorubicin resistance due to epigenetic regulation of ABCG2 transporter in cancer cells) (Calgano et al., 2008).

In the following section, an overview has been provided of new results in the field related to regulation by DNA methylation, histone modulation and miRNA, since they are topics of considerable current interest which may describe the large variation in expression seen for several important CYPs (Okino et al., 2006; Antilla et al., 2003; Dannenberg et al., 2006; Tamási et al., 2011).

#### 3.1 Epigenetic regulation

*DNA methylation.* DNA methylation occurs predominantly at CpG sites in the mammalian genome by the DNA methyltransferase (DNMT) enzymes. The majority of CpG pairs are chemically modified by the covalent attachment of a methyl group to the C<sub>5</sub> position of the cytosine ring (Tate & Bird, 1993; Calgano et al., 2008). Methylation of DNA is regarded as a means of regulating gene expression through two general mechanisms. First, DNA methylation of gene promoters may prevent the physical binding of some transcription factors to their DNA binding sites (Rountree et al., 2001). Second, the transcriptional silencing capability of DNA methylation may occur via indirect mechanisms involving changes in chromatin conformation. There is extensive evidence to support a functional role for promoter-CGI methylation in transcriptional repression (Weber et al., 2007; De Smet et al., 1999; Stein et al., 1982). DNA methylation of CpG-rich promoters of some genes correlates with tissue specific gene silencing (Futcher et al., 2002; Song et al., 2005). To date, several studies show altered DNA methylation of CYPs what could have importance in drug and endogen compound metabolism.

*Histone modification.* Posttranslational modifications such as phosphorylation, acetylation, methylation and ubiquitination on the N-termini of histones have been shown to play critical roles in gene regulation (Kouzarides, 2007). It is believed that the combination of modifications of the chromatin-associated histone and non-histone proteins, and the

interplay between these modifications create a marking system (“histone code”), which is responsible for compact DNA (heterochromatin) or more opened, transcriptionally active (euchromatin) configuration, that allows transcription (Jenuwein & Allis, 2001).

*miRNA regulation.* miRNAs, another part of the epigenetic machinery, are single-stranded RNA molecules of 21-24 nucleotides in length that arise from miRNA genes, which when transcribed, can promote posttranscriptional regulation by binding to 3'-untranslated regions (3'UTRs) of target mRNAs promoting their degradation and cleavage as miRNA/RISC complex (RISC-RNA Induced Silencing Complex) or interfering with their translation. Besides their direct influence on mRNA transcription, some miRNAs, defined as epi-miRNAs, have an indirect impact on gene transcription by affecting the epigenetic machinery, including DNA methyltransferases, histone deacetylases and other mechanisms (Fabbri et al., 2010). Post-transcriptional regulation by miRNA could be responsible for a portion of the significant amount of unexplained interindividual variability in CYP enzyme expression and activity.

The modified histones, methylated DNA sequences and miRNAs may interact in a synergistic manner, including methyl-CpG binding protein, nuclear receptor corepressor (NCoR), associated histone deacetylases, histone methyl transferases and epi-miRNAs to regulate gene expression (Yoon et al., 2003). The mentioned epigenetic changes affect the expression of drug metabolizing enzymes and with that ultimately affect the pharmacokinetic or pharmacodynamic properties of a drug.

### 3.2 Epigenetic regulation of P450s

*CYP1A1:* CYP1A1 is mainly involved in the metabolic activation of polycyclic aromatic hydrocarbons, which are common environmental pollutants. Important functional polymorphisms have been not described with this gene, but still there are several epigenetic processes which regulate CYP1A1.

Both hypermethylation (less active CYP1A1, slower metabolism of drugs) and hypomethylation (more active enzyme, higher metabolic rate) of CYP1A1 is described, mostly in cancer tissue. In prostate cells, CpG islands in CYP1A1 show segmented/selective methylation patterns: CpG sites from 1 to 36 are not methylated; this DNA region contains the CYP1A1 promoter and is responsible for correct initiation of gene transcription; CpG sites 37 to 90, which corresponds to the CYP1A1 enhancer region that mediates TCDD (2,3,7,8-Tetrachlorodibenzodioxin) inducibility, exhibits cancer cell-dependent hypermethylation and CpG sites 91 to 125 are commonly methylated, but known regulatory function has been not associated with this DNA region (Okino et al., 2006). Environmental factors, such as tobacco smoke have been shown to influence the DNA methylation of CYP1A1; smokers DNA were hypomethylated compared to non-smokers on the upstream regions, containing functional XREs. In addition, there was an inverse correlation between methylation and the number of cigarettes smoked daily. Cessation of smoking results in the methylation of CYP1A1 promoter being increased at 1-7 days after the last cigarette (Antilla et al., 2003). Although there was no correlation between ethoxyresorufin-O-deethylase (EROD) activity and the percentage of methylated DNA in a sample either in smokers or in nonsmokers, decrease in methylation caused significant higher CYP1A1 activity. A high inducibility of CYP1A1 has been connected with increased susceptibility to smoking-associated lung cancer (Kellermann et al., 1973; Stücker et al., 2000).

Chromatin structure has been suggested to play an essential role in *CYP1A1* transcription (Table 5). In the basal state, histone deacetylase 1 (HDAC1) is bound to the *CYP1A1* promoter and is released in concert with the recruitment of p300 upon benz[a]pyrene (B[a]P) ligand activation of the AHR. HDAC1 removal allows for several histone modification steps associated with the AHR-mediated induction of *CYP1A1* expression. Removal of HDAC1 is necessary, but not sufficient to activate *CYP1A1* expression (Schnekenburger et al., 2007).

miRNA regulation of *CYP1A1* is also known. miRNA regulation by miRNA-18b and miRNA-20b of *CYP1A1* was described by Wang and coworkers and a significant correlation was found between the mentioned miRNAs and *CYP1A1* expression (Wang et al., 2009).

	Methylation		Histon modification		miRNA	
	CpG region	Compound/disease	Modification	Compound/disease	miRNA	Tissue/ cell
<i>CYP1A1</i>	Enhancer/promoter	Cancer, tobacco smoke	Acetylation	B[a]P	Hsa-miR-18b, Hsa-miR-20b	Transformed lymphocytes
<i>CYP1B1</i>	Enhancer/promoter	Cancer	-	-	Hsa-miR-27b	Cancer
					Hsa-miR-124	Brain
<i>CYP2E1</i>	Region not described	Ethanol	-	-	Hsa-miR-378	HEK293
<i>CYP2W1</i>	1.exon/1.intron	Cancer	-	-	-	-
<i>CYP3A</i>	Enhancer/promoter	Cancer	Methylation	Rifampicin	Hsa-miR-27b	HEK293
					Hsa-miR-148a	Liver

Table 5. Epigenetic regulation of drug metabolism related P450s ("-" no data).

*CYP1B1*: *CYP1B1* activates various procarcinogens, metabolizes the antiestrogen tamoxifen, some flavonoids or benzpyrene derivatives. This enzyme is overexpressed in a variety of human tumor cells such as lung, breast, liver, gastrointestinal tract, and ovarian cancer (Murray et al., 1997). *CYP1B1* may be an important tumor marker, because it hydroxylates estrogens and activates many procarcinogens. *CYP1B1* enzyme could be methylated both on the promoter and on the enhancer of the gene. Promoter region contains the CpG sites of the core promoter region including SP1 binding sites and the enhancer region including AHR/ARNT (ARNT-Aromatic Hydrocarbone Receptor Nuclear Translocator) binding sites DRE2 and DRE3. Aberrant methylation in the *CYP1B1* gene affects binding of transcription factors and enhancer molecules. Because expression of *CYP1B1* is regulated by the methylation of its promoter/enhancer, this region may be a useful target for anticancer drugs and in preventive medicine (Tokizone et al., 2005).

Human *CYP1B1*, which is highly expressed in estrogen target tissues, catalyzes the 4-hydroxylation of 17-beta-estradiol. Tsuchiya and coworkers found an abundant amount of *CYP1B1* protein in breast cancerous tissue and they identified a near-perfect matching sequence with miR-27b in the 3'-untranslated region of human *CYP1B1*. Human *CYP1B1* is post-transcriptionally regulated by miR-27b (Tsuchya et al., 2006). Another brain-specific miRNA, miR-124, also downregulates *CYP1B1* directly and modulate all AHR target genes indirectly by binding to AHR receptor (Lim et al., 2005).

*CYP2E1*: CYP2E1 is involved in the metabolism of various drugs, such as halothane, enflurane, theophylline or isoniazid. Methylation of the CYP2E1 gene inhibits the expression of this enzyme in prenatal period (Vieira et al., 1998). In adult tissues the methylation pattern of CYP2E1 gene differs among various tissue types such as lung, kidney, placenta, liver and skin indicating that DNA methylation results in tissue-specific regulation (Vieira et al., 1996). CYP2E1 is metabolizing ethanol to its carcinogenic metabolite acetaldehyde. Even small doses of ethanol are able to change the methylation pattern of CYP2E1 and with that, increase its transcription. Higher CYP2E1 activity could have importance in cancerogenesis, since CYP2E1 is involved in bioactivation of other small-molecule precarcinogens (Ghanayem et al., 2007).

Mohri and coworkers recently found that miR-378 is involved in the post-transcriptional regulation of CYP2E1. The overexpression of miR-378 significantly decreased CYP2E1 protein levels and enzyme activity in the cells expressing CYP2E1, including 3'-UTR, but not in the cells expressing CYP2E1 without 3'-UTR, indicating that the 3'-UTR plays a role in the miR-378-dependent repression (Mohri et al., 2010). Chronically induced CYP2E1 with ethanol or other CYP2E1 inducers is a high-risk factor for esophageal and gastrointestinal cancers, which gives importance to investigate transcriptional and post-transcriptional CYP2E1 regulatory mechanisms, as basic targets in anticancer therapy.

*CYP2W1*: This enzyme has been shown to metabolise arachidonic acid and benzphetamine, as well as being able to metabolically activate several procarcinogens, including polycyclic aromatic hydrocarbon dihydrodiols, aflatoxin B1 or sterigmatocystin. CYP2W1 is expressed at relatively low levels (mRNA) in the human adult non-transformed tissues whereas the expression in colorectal cancer tissues was significantly higher (both at mRNA and protein levels) (Li et al., 2009; Edler et al., 2009). CYP2W1 gene expression appears to be governed by gene methylation. The CYP2W1 gene was shown to contain one functional CpG island in the exon 1-intron 1 region which was methylated in cell lines lacking CYP2W1 expression, but unmethylated in cells expressing CYP2W1 (Karlgren et al., 2007; Gomez et al., 2007).

*CYP3A*: These enzymes metabolise almost 50% of currently used drugs as well as endogenous and exogenous corticosteroids. Although CYP3A enzymes are not polymorphic enzymes interindividual variability is high due to epigenetic regulatory mechanisms.

Different DNA methylation pattern was found between primary hepatocytes and hepatocyte cell lines. HepG2 cells exhibit many cellular features of normal human hepatocytes, but also display characteristics resembling those of a cancerous or fetal hepatocyte. *CYP3A* expression in untreated HepG2 cells is fairly low, suggesting that their expression is reduced in these partially dedifferentiated cells. Dannenberg and coworkers were interested in determining whether CYP3A genes are regulated by DNA methylation in HepG2 cells. Their microarray experiments showed that after 5-aza-dC treatment (5-aza-2'-deoxycytidine, methylation inhibitor), expression of CYP3A4, CYP3A5 and CYP3A7 was 2-4-fold higher, suggesting the regulatory role of methylation with these CYPs (Dannenberg & Edenberg, 2006). Since CYP3A enzymes catalyse the transformation of many drugs, understanding their regulation would explain interindividual differences in drug response and would help to develop better personalized medicine.

CYP3A4 transcription is also regulated by a histone methyltransferase enzyme called protein arginine methyltransferase 1 (PRMT1). PRMT1 is required for the transcriptional



activity of CYP3A4 by pregnane X receptor (PXR). It is recruited to 5'-region of the CYP3A4 gene to methylate histone H4 as a response to the PXR agonist rifampicin (Xie et al., 2009). CYP3A4 is also regulated by constitutive androstane receptor (CAR) albeit it at a lower rate of expression. Assenat and coworkers reported that the synthetic glucocorticoid, dexamethasone, induces histone H4 acetylation at the proximal CAR promoter region, and indirectly affects CYP3A4 induction by regulating CAR expression (Assenat et al., 2004).

Until now, one miRNA, miR-27b, has been described to regulate CYP3A4 expression by binding to the miRNA response element (MRE) within the 3'UTR region of CYP3A4 mRNA (Pan et al., 2009). Some miRNAs, such as miR-148a, which is selectively and abundantly expressed in the liver, regulates other liver specific genes, for e.g., the human PXR. miR-148a binds to the 3'-UTR region of PXR mRNA, thereby decreasing synthesis of PXR protein. Since CYP3A4 is a target for PXR, miR-148a indirectly modulates the inducible and/or constitutive levels of CYP3A4 expression (Takagi et al., 2008). Another example of indirect modulation would be the vitamin D receptor (VDR). VDR also regulates CYP3A4 and VDR could be down-regulated with miR-27b (Mohri et al., 2010).

#### 4. Conclusion

Pharmacogenetics and pharmacoepigenetics is a scientific field which understands the role of an individual's genetic background in how well a medicine works, and also what side effects occur during drug administration. The development of pharmacogenetics/pharmacoepigenetics (for benefits and limitations see Box 2.) provides at least one mechanism for taking prescription away from its current empiricism and progressing towards more "individualised" drug treatment.

##### Benefits:

- Development of drugs based on a patient's genetic/epigenetic profile will maximise therapeutic effects, but decrease ADRs and other toxic effects
- More precise dose is calculated, if beside other factors, genetic background also counts
- Revival of older drugs with retrospective studies

##### Limitations:

- Identification of genes that may influence drug metabolism is very difficult, since more genes are involved in how someone reacts to a drug and these changes are small
- The interactions with other drugs or environmental factors need to be determined before any conclusions are made about the genetic influence on how the drug is working

Box 2. Potential benefits and limitations of pharmacogenetics/pharmacoepigenetics.

The clinical applicability of pharmacogenetic testing depends on the relative importance of each polymorphism in determining therapeutic outcome. Doctors need to be aware of whether a drug they are prescribing is subject to pharmacogenetic variability and they have to know how to use this knowledge. Routine genotyping or phenotyping before drug administration can be made for very few drugs today and we are still a long way from having a pharmacogenetic DNA chip that general practitioners can use to identify all the drugs to which any particular patient is sensitive. There are many issues against testing,

including specific factors that contaminate the signal, such as active metabolites/enantiomers, access and availability of the tests, complication for patients etc.

What have been changed as a result of pharmacogenetic knowledge until today is the drug-label modifications. There are more and more drug-labels where the pharmacogenetic consequence is highlighted (Table 6.). Drug labels may contain information on genomic biomarkers and can describe: drug exposure and clinical response variability, risk for adverse events, genotype-specific dosing, mechanisms of drug action, polymorphic drug target, disposition genes etc.

CYP enzymes	FDA-approved drugs with pharmacogenomic information in their labels
CYP2C9	Clopidogrel, Diazepam, Dextansoprazole, Drospirenone and Ethenyl Estradiol, Esomeprazole, Nelfinavir, Rabeprazole, Voriconazole
CYP2C19	Celexocib, Warfarin
CYP2D6	Aripiprazole, Atomoxetine, Carvedilol, Cevimeline, Clozapine, Codeine, Dextromethorphan and Quinidine, Doxepin, Fluoxetine, Fluoxetine and Olanzapine, Metoprolol, Propafenone, Propranolol, Protryptiline, Quinidine, Risperidone, Terbinafine, Tetrabenazine, Thioridazine, Timolol, Tiotropium, Tolterodine, Tramadol and Acetaminophen, Venlafaxine

Table 6. FDA-approved drugs with P450-related pharmacogenomic information in their labels (Taken from [www.fda.gov](http://www.fda.gov), updated 2011, July).

Another result of pharmacogenetic knowledge is including pharmacogenomics into clinical trials. Carlquist and Anderson reported that this year until May, a total of 158 pharmacogenomic clinical trials were listed at <http://www.clinicaltrials.gov>. Of those trials the three leading disease areas for which pharmacogenetic guided intervention is sought were cancer (37%), psychiatric disorders (13%), and anticoagulation/thrombosis (9%) (Carlquist & Anderson, 2011).

In addition to pharmacogenetics, it has been also predicted that DNA methylation, histone modification and RNA-mediated regulation also affects gene expression. Until now, cancer is the only disease, where pharmacoepigenetics of drug metabolizing enzymes seems to be important. Epigenetic changes influence sensitivity to chemotherapeutic drugs suggesting that epigenetic factors could serve as molecular markers predicting the responsiveness of tumors and other diseases to therapy.

Ultimately, it could be concluded that pharmacogenetics and pharmacoepigenetics explains in large extent individual variation of drug metabolising enzymes and hopefully these two factors together will help to work out more specific dosing protocols for drugs.

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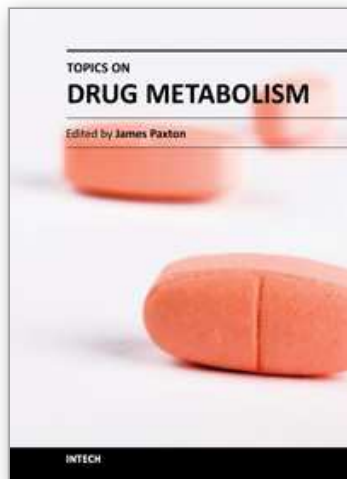
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## **Topics on Drug Metabolism**

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In order to avoid late-stage drug failure due to factors such as undesirable metabolic instability, toxic metabolites, drug-drug interactions, and polymorphic metabolism, an enormous amount of effort has been expended by both the pharmaceutical industry and academia towards developing more powerful techniques and screening assays to identify the metabolic profiles and enzymes involved in drug metabolism. This book presents some in-depth reviews of selected topics in drug metabolism. Among the key topics covered are: the interplay between drug transport and metabolism in oral bioavailability; the influence of genetic and epigenetic factors on drug metabolism; impact of disease on transport and metabolism; and the use of novel microdosing techniques and novel LC/MS and genomic technologies to predict the metabolic parameters and profiles of potential new drug candidates.

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