Molecular Psychiatry (2004) 9, 442–473

www.nature.com/mp

FEATURE REVIEW

Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response

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Genetic factors contribute to the phenotype of drug response. We systematically analyzed all available pharmacogenetic data from Medline databases (1970–2003) on the impact that genetic polymorphisms have on positive and adverse reactions to antidepressants and antipsychotics. Additionally, dose adjustments that would compensate for genetically caused differences in blood concentrations were calculated. To study pharmacokinetic effects, data for 36 antidepressants were screened. We found that for 20 of those, data on polymorphic *CYP2D6* or *CYP2C19* were found and that in 14 drugs such genetic variation would require at least doubling of the dose in extensive metabolizers in comparison to poor metabolizers. Data for 38 antipsychotics were examined: for 13 of those *CYP2D6* and *CYP2C19* genotype was of relevance. To study the effects of genetic variability on pharmacodynamic pathways, we reviewed 80 clinical studies on polymorphisms in candidate genes, but those did not for the most part reveal significant associations between neurotransmitter receptor and transporter genotypes and therapy response or adverse drug reactions. In addition associations found in one study could not be replicated in other studies. For this reason, it is not yet possible to translate pharmacogenetic parameters fully into therapeutic recommendations. At present, antidepressant and antipsychotic drug responses can best be explained as the combinatorial outcome of complex systems that interact at multiple levels. In spite of these limitations, combinations of polymorphisms in pharmacokinetic and pharmacodynamic pathways of relevance might contribute to identify genotypes associated with best and worst responders and they may also identify susceptibility to adverse drug reactions.
Molecular Psychiatry (2004) **9,** 442–473. doi:10.1038/sj.mp.4001494
Published online 23 March 2004

Keywords: pharmacogenetics; pharmacogenomics; antidepressant; dose recommendation; antipsychotic; cytochrome *P*450

The need for predictive pharmacogenetics-based therapeutic recommendations

Major depressive disorder, schizophrenia, and related disorders are among the most important causes of death and disability worldwide.[1] These disorders are highly prevalent, chronic or recurrent conditions with a substantial impact on public health. Antidepressant drugs are the standard of care for clinical depression; likewise, antipsychotics are the standard treatment for schizophrenia. Despite the availability of a wide range of different drug classes, about 30–50% of patients will not respond sufficiently to acute treatment, regardless of the initial choice of standard psychiatric medication.[2–5] For example, in randomized controlled trials in major depressive disorder, after 6–8 weeks, only 35–45% of the patients treated with standard doses of the most commonly prescribed antidepressants return to premorbid levels of functioning without any significant depressive symptoms.[6,7] There is consequently a considerable need to increase efforts in maximizing clinical outcomes in major psychiatric disorders. The identification of genetic factors underlying drug response is among the most promising areas of research in molecular medicine.

Large genetic variability has been described in drug metabolism, in drug effects, and genetic modulators of the response to drug treatment. However, it is not yet possible to use genetic tools to identify an individual's likelihood of responding to a treatment and thereby to individualize drug therapy by choosing the best medication and dosage. While faster and more effective methods for genetic testing are being

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Received 31 October 2003; revised 22 January 2004; accepted 02 February 2004

developed, the concept of formally using pharmacogenetics to guide therapy can only be clinical applicable when there is reliable ability to predict clinical outcomes. Blood typing for the A, B, O system may serve as an analogy of how specific therapeutic products are administered after being specifically guided by a laboratory genetic test. Similarly, specific clinical guidelines in psychopharmacology have to be developed to clarify in which situations and with which consequences the results of individual pharmacogenetic tests may be applicable for therapy.

This review covers methods for data extraction from pharmacogenetic studies and for aggregating such information into concise and usable therapeutic recommendations. This concept is nearly established with respect to polymorphisms in pharmacokinetic pathways, but use of genetic testing of neurotransmitter transporter and receptor variants for therapeutic decisions, is still incipient. Rapid advances in molecular analytical tools will soon allow very rapid and inexpensive genotyping; however, pharmacogenetics will only be used as a diagnostic tool in clinical practice, if precise and specific treatment options and guidelines based on genetic testing can be provided.

Methods of pharmacogenetics data extraction and dose calculation

Literature research

Data on antidepressant and antipsychotic genotype-dependent pharmacokinetics published in Medline and Embase databases were searched using word combinations of 'cytochrome', 'debrisoquine', 'sparteine', 'dextromethorphan', 'mephenytoin', 'polymorph*', 'metabolizer', 'ultrarapid', 'antidepressant', 'antipsychotic' in combination with 36 generic names of commonly used antidepressants and 38 antipsychotics. Data on therapeutic response and adverse drug reactions of antidepressants and antipsychotics in relation to genetic parameters were retrieved from current Medline using search combinations 'antidepressant', 'polymorphism', 'antipsychotic', 'genetic', 'response', 'tardive dyskinesia', and 'adverse drug reactions'. Studies on inherited susceptibility factors for depression and schizophrenia were not included, because the focus of this work was on the phenotype of drug response, not on the elucidation of the genetic basis of disease susceptibility. Data were classified according to gene polymorphisms studied, sample size, time interval for response measurement, clinical outcome parameters, and surrogate parameters (rating scales for response, documentation of adverse drug reactions).

With respect to pharmacokinetically relevant polymorphisms, only data from human studies with healthy volunteers or patients were included. Data on the *in vitro* biotransformation of antidepressants and antipsychotics have been reviewed elsewhere.[8–12]

Studies were restricted to those providing data on effects of genetic polymorphisms in *CYP2D6, CYP2C19*, or *CYP2C9*. The functional impact of other polymorphisms in drug-metabolizing enzymes including CYP1A2, CYP2A6, CYP2B6, CYP3A4, -5, and -7 or phase-II enzymes in psychopharmacology was considered to be either too moderate or controversial.

The cytochrome *P*450 enzyme 1A2 partially catalyzes biotransformation of clozapine, olanzapine, and some other antipsychotics;[10] however, it remains questionable how much of the interindividual variability in CYP1A2 activity is explained by genetic polymorphisms.[13 15] Some data exist on higher drug concentrations and higher risks for tardive dyskinesia in schizophrenic patients who are smokers and carriers of CYP1A2 genotypes with reduced inducibility (C/A polymorphism at position 734 in intron 1 and G/A polymorphism at position −2964 in the 5′-flanking region of CYP1A2), but those results have not been fully replicated.[16–18] Polymorphisms in CYP2B6 might be relevant for the antidepressant bupropion, but the differences due to genotype are small.[19] Polymorphisms in the CYP3A enzyme family were not considered, since CYP3A4 genetic variants have little effects on function or are rare in most populations.[20] Whether or not the polymorphisms in CYP3A5 and CYP3A7 play a medically relevant role is questionable since expression levels are low and a psychotropic drug selectively metabolized by either CYP3A5 or CYP3A7, but not by CYP3A4, still remains to be identified.[21]

Studies using CYP inhibiting substances such as quinidine to mimic poor metabolizer status were not included. Studies were classified based on whether they were conducted in patients or healthy volunteers, single or multiple dosage, existence of data on active metabolites/active moiety of the drug, sample size, and available pharmacokinetic parameters. For dose adjustments, dose-related pharmacokinetic parameters such as trough concentrations at steady state (C_{ss}), area under the concentration–time curve (AUC), or total drug clearance (Cl) were used. Data on metabolic ratios (MR) in urine or plasma could not be used since these parameters are not linearly correlated with dose.

As many psychotropic drugs are metabolized to equally active metabolites,[22] some studies provide data on both metabolite and parent drug, and thus the whole active moiety was taken into consideration. In Tables 2 and 3, data of all studies are shown and the substances measured in the respective studies are indicated. In Figures 2–4, dose adjustments calculated as the weighted mean from the single studies were depicted for each substance and data of the active moiety were taken if available.

Metabolic polymorphisms

Classification of metabolizer groups The homozygous carriers of two *CYP2D6* genes coding for functional enzymes are termed extensive metabolizers (EM; genotypes: **1/*1, *1/*2, *2/*2*) and carriers of one duplication allele (**2 × 2 or *1 × 2*) plus one deficient allele (eg **3, *4; *5, *6*) were also classified as extensive metabolizers. Heterozygous carriers of only one active allele were termed

intermediate metabolizers and homozygous or compound homozygous carriers of two deficient alleles were termed poor metabolizers. Ultrarapid metabolizers identified by genotype were carriers of any combination of one *CYP2D6*1* or one *CYP2D6*2* gene duplication in combination with another active allele (genotypes: **2 × 2/*1, *1 × 2/*1*).[23,24] *CYP2D6* alleles **9, *10, *17*, and **41* were also classified as active alleles but with intermediate to low activity.[25] In Africans, the *CYP2D6*17* allele is frequent and causes greatly decreased (but not deficient) enzyme activity. This has to be considered if genotyping is used to predict metabolic phenotype in African populations.[26] In Orientals, the *CYP2D6*10* allele causing decreased (but not deficient) enzyme activity is prevalent with an allele frequency of about 50%. Heterozygous carriers of **10* may be in the higher activity range of the IM group and homozygous carriers (*CYP2D6*10/*10*) may be at the lower activity range.[27] The poor metabolizer genotype with two deficient alleles is very rarely found in Orientals (<1%); therefore, studies in Japanese, Chinese or Korean individuals are mostly focused on intermediate and extensive metabolizers of substrates of CYP2D6. Studies analyzing the impact of the *CYP2D6*10* genotypes are marked by a number sign (#) in Table 2, and for these studies PM genotype data are extrapolated from data in IMs and EMs.

For CYP2C19, the following classifications of metabolic phenotype based on genotype were made: extensive metabolizer: genotype **1/*1*; intermediate: heterozygous carrier of one inactive *CYP2C19* allele (**2, *3*) and poor metabolizer as homozygous combination of two deficient *CYP2C19* alleles. Most studies did not provide data on intermediate metabolizers. In these cases, a linear gene–dose relationship was assumed and a mean AUC of those of the PMs and EMs was used to calculate dose adjustments for heterozygous carriers of deficient alleles.

Phenotyping with debrisoquine or dextromethorphan for CYP2D6 and *S*-mephenytoin for CYP2C19 was considered equivalent to genotyping. Classification by phenotype was based on the usual urinary metabolic ratio antimodes of 12.6 for testing with debrisoquine and 0.3 for testing with dextromethorphan.[28,29]

Data calculation for dose adjustment To adapt doses according to genotypes, data on clearance (Cl), area under concentration–time curve (AUC) or trough concentrations at steady state (C_{tss}) in the respective genotype groups were used to calculate internal exposure to the drugs. It was assumed that the average dose recommended for the whole population can be regarded as the weighted mean of subpopulation-specific doses.[30] For CYP2D6 about 7–10% of Caucasians are poor metabolizers, 40% are intermediate (heterozygous carriers), and 50% are extensive metabolizers.[31] Thus, the average dose (D_{av}) usually recommended in Caucasian populations can be regarded as

$$D_{av} = 0.1D_{PM} + 0.4D_{IM} + 0.5D_{EM} \quad (1)$$

where D_{PM}, D_{IM} and D_{EM} represent the optimal dose for the groups of poor metabolizers, intermediate metabolizers, and extensive metabolizers. The empirically gained average dose (D_{av}) can be set as 100%. Then, percentages of dose adaptations (reductions or elevations) for each genotype are obtained. The genotype-specific dose differences can be expressed by pharmacokinetic parameters from the patient or volunteer pharmacokinetic/pharmacogenetic studies analyzed here (Tables 1 and 2):

$$D_{PM}/D_{EM} = Cl_{PM}/Cl_{EM} \quad (2)$$

and

$$D_{IM}/D_{EM} = Cl_{IM}/Cl_{EM} \quad (3)$$

Then, Equations (2) and (3) can be substituted into (1):

$$D_{EM}(\%) = 100/(0.1Cl_{PM}/Cl_{EM} + 0.4Cl_{IM}/Cl_{EM} + 0.5)$$

When D_{EM} is obtained, D_{PM} and D_{IM} can be calculated from (2) and (3). If no data on intermediate metabolizer are available, linear gene–dose effects were assumed and Cl_{IM} was estimated as 0.5 $(Cl_{PM} + Cl_{EM})$.

For CYP2D6, gene duplications lead to the so-called ultrarapid metabolizer type (UM). Only few studies were found concerning UMs and these were mostly single case reports. We usually assumed a linear gene–dose effect. Thus, the UM genotype with three active alleles would be correctly dosed with the EM-dose plus (difference between EM and IM doses):

$$D_{UM} = D_{EM} + (D_{EM} - D_{IM}) = 2D_{EM} - D_{IM} \quad (4)$$

As explained above, in most studies from Asiatic populations only data on CYP2D6 EMs and IMs are available. For calculation of dose recommendations, a linear gene–dose effect was assumed and the AUC in PMs was estimated as follows:

$$(AUC_{PM} + AUC_{EM})/2 = AUC_{IM}$$
$$AUC_{PM} = 2AUC_{IM} - AUC_{EM}$$

For CYP2C19, genotype frequencies of approximately 3% PM, 27% IM and 70% EM as known in Caucasian populations were used.[32] The equation for CYP2C19 corresponding to Equation (1) would be

$$D_{av} = (0.03D_{PM} + 0.27D_{IM} + 0.7D_{EM}) \quad (5)$$

and Equations (2) and (3) from above were applied accordingly. In the tables, tentative therapeutic recommendations are given as percentual adjustments from the standard dose. Intentionally, no milligram-doses were given since the standard dose may differ depending on factors such as disease severity, age, gender, body weight, and ethnicity. When applying our dose recommendation tables in

ethnic groups other than Caucasians, it is advisible to calculate the dose adjustments based on the standard dose used in that population. Ethnic differences in the response to a drug are not only due to differences in the frequencies of drug metabolic enzyme polymorphisms, but also due to differences in nutrition, other lifestyle factors, and the effects of various other genotypes on the pharmacodynamic site of drug action.

Limitations of dose adjustments based on CYP2D6 or CYP2C19 genotype An approach using the principles of bioequivalence has been described above. However, drug concentration differences due to genotype are not exactly the same as drug concentration differences due to different preparations of a drug because the active metabolites also contribute to the overall drug effect or are responsible for adverse drug reactions.[22,33] Whenever possible, we based dose adjustments on the active moiety of drug exposure consisting of parent drug and active metabolites if prevalent in considerable concentrations.

Many psychotropic drugs are administered as racemates and the enantiomers may undergo differential biotransformation, have different receptor binding profiles and different side effects,[34,35] but pharmacologic activities of the specific enantiomers are frequently unknown in humans: enantiomers have been in most cases only tested in animals or *in vitro*. Therefore, dose recommendations might not be able to take the differential activity of enantiomers into account.

Some psychotropic drugs show saturation kinetics in the common dose-range. For clomipramine, desipramine, fluvoxamine, haloperidol, paroxetine, trimipramine, dose adjustments are only applicable in the dose ranges used in research studies, which is often much lower than clinical dosages.

Data from single dose experiments cannot be extrapolated to long-term drug therapy as saturation pharmacokinetics, irreversible enzyme blockade, or enzyme up- or downregulation might change the outcome under multiple dosing.[36–38] Enzyme inhibition by the substrate itself was described to convert genotypic extensive metabolizers of CYP2D6 substrates to phenotypically poor metabolizers in antidepressant drug therapy.[39–41]

Drug target polymorphisms

Data analysis We included all available studies concerning response to therapy and adverse drug reactions. We did not include studies on genetic polymorphisms as risk factors for the genetic susceptibility to mental illness. Essential parameters in this meta-analysis were sample size (power of the study), effect size and statistical significance. Effect size was either the odds ratio (if therapy response or adverse events were dichotomized) or the effect ratio (if response was presented on a continuous scale in the respective size). *Effect ratio* was the ratio of the response criterion in the group with the variant at risk divided by the response criterion in the complementary group. Funnel plots were used to assess for possible publication bias (Figures 5–7).[42] Such funnel plots illustrate the relationship between sample size of clinical trials and the study outcome. From statistical theory, it is expected that the odds ratio or the effect ratio converging to the true values if sample size of studies becomes larger and individual study data should scatter randomly around the overall mean of all studies, unless there is selective publication.

Pharmacokinetic phase: dose adjustments based on polymorphisms in cytochrome *P*450 enzymes

Examination of research on metabolism of 36 antidepressants and 38 antipsychotics was conducted (Table 1). For 20 antidepressants, data on *CYP2D6* or *CYP2C19* polymorphisms from pharmacokinetic studies in humans were found.

For iprindole, isocarboxacid, setiptiline, and viloxazine, no data on polymorphic drug metabolism were found. Elimination mainly via conjugation reactions (glucuronidation, acetylation, sulfatation) and subsequent renal excretion was described for phenelzine and tranylcypromine, and elimination via renal excretion of the unchanged compound was described for milnacipran.

For several tricyclic antidepressants, no data on the specific enzymes involved in hydroxylation or demethylation reactions were available, and apparently the impact of genetic polymorphisms for biotransformation of these drugs has not been studied. However, structural similarity to other tricyclics such as imipramine implicates that CYP2D6 and CYP2C19 might be involved in metabolism of these tricyclics, as well.

Tianeptine as well as reboxetine seem to be mainly metabolized by CYP3A4 in humans and genetic polymorphisms of CYP2D6, CYP2C19 and CYP1A2 enzymes are unlikely to cause relevant pharmacokinetic variability of these antidepressants.[9]

The new atypical antidepressant duloxetine is a potent inhibitor of CYP2D6 *in vivo* and a CYP2D6 substrate *in vivo*.[43] It therefore seems probable that *CYP2D6* genetic polymorphisms have a major impact on elimination of this drug, but this has not yet been studied in detail.

CYP2D6 or *CYP2C19* polymorphisms were studied for the metabolism of 13 antipsychotic drugs (Table 1). Other elimination pathways than cytochrome *P*450 enzymes are important for following antipsychotics: sulpiride and amisulpride (renal excretion), raclopride (glucuronidation, sulfatation), zotepine (flavin-mono-oxygenases involved). CYP3A4 is the main enzyme involved in the metabolism of bromperidole, iloperidone, perospirone, quetiapine, and ziprasidone.[8,44] For chlorpromazine, remoxipride, and sertindole, only *in vitro* data exist on involvement of

Table 1 List of antidepressant and antipsychotic drugs screened for polymorphic metabolism

	Not any data	*In vitro data only*	*Renal excretion, mainly*	*Phase-II enzymes, mainly*	*CYP1A2, CYP2B6 or CYP3A4, mainly*	*In vivo studies on polymorphic enzymes CYP2D6, CYP2C19, CYP2C9*
Antidepressant drugs	Iprindole Isocarboxacid Setiptiline Viloxazine	Amineptine Amoxapine Dibenzipine Doslepine Dothiepin Lofepramine Protriptyline	Milnacipran	Phenelzine Tranylcypromine	Bupropion Tianeptine Reboxetine	Amitriptyline Citalopram Desipramine Doxepin Duloxetine Fluoxetine Fluvoxamine Imipramine Maprotiline Mianserin Mirtazapine Moclobemide Nefazodone[a] Nortriptyline Paroxetine Sertraline Trazodone Trimipramine Venlafaxine
Antipsychotic drugs	Benperidol Chlorprotixen Fluphenazine Fluspirilen Mazapertine Nemonapride Pipamperon Promethazine Prothipendyl Trifluperidol Triflupromazine	Chlorpromazine Remoxipride Sertindole Melperone	Amisulpride Sulpiride	Raclopride	Bromperidol Iloperidone Perospirone Quetiapine Ziprasidone Clozapine	Aripiprazole Clopenthixol Clozapine[a] Flupenthixol Haloperidol Levomepromazine[a] Olanzapine Perazine Perphenazine Pimozide[a] Risperidone Thioridazine Zotepine Zuclopenthixol

[a]Drugs that are minor substrates of CYP2D6 or CYP2C19 according to *in vivo* studies.

CYP2D6.[8] Remoxipride and sertindole were withdrawn from the market due to adverse drug reactions (aplastic anemia and arrhythmia). Melperone is described as potent inhibitor of CYP2D6 but studies on impact of CYP2D6 polymorphisms on melperone metabolism are not yet available.[45]

Studies on polymorphic metabolism by CYP2D6

Table 2 summarizes all human studies found for antidepressants and antipsychotics: information on poor and extensive metabolizers of CYP2D6 are shown and percents of dose adjustments were calculated from AUC, Cl, or C_{tss} as described above. There is good concordance of the quantitative effects on pharmacokinetic parameters among various studies.

Impact of CYP2D6 polymorphisms on dosing of antidepressants

Tricyclic antidepressants The group of tricyclic antidepressants undergoes similar biotransformation actions in the liver with CYP2D6 catalyzing hydroxylation reactions,[49–51,68,121,122] whereas demethylation of the parent drug is mediated by CYP2C19. Both metabolites are pharmacologically active and the demethylated metabolites are partially tricyclic drugs by themselves such as nortriptyline and desipramine, which are desmethyl-metabolites of amitriptyline and imipramine, respectively. For dose adjustments, the active drug moiety consisting of the sum of parent drug + demethylated metabolite was used if available from the studies. The desmethyl-metabolite-drugs nortriptyline and desipramine are mainly hydroxylated to less active or inactive metabolites,[63,121] in consequence, dose adjustments were calculated taking the parent drug alone.

Differences in the internal exposure to the drug (AUC) due to genotypes were mostly similar when comparing single-dose or multiple-dose studies (Table 2).

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