

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.

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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 pre-morbid 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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developed, the concept of formally using pharmacogenetics to guide therapy can only be clinically 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 includ-

ing *CYP1A2*, *CYP2A6*, *CYP2B6*, *CYP3A4*, -5, and -7 or phase-II enzymes in psychopharmacology was considered to be either too moderate or controversial.

The cytochrome P450 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_{tss}), 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_{ss}) 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:

$$\begin{aligned} (AUC_{PM} + AUC_{EM})/2 &= AUC_{IM} \\ AUC_{PM} &= 2AUC_{IM} - AUC_{EM} \end{aligned}$$

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 advisable 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 P450 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, setipiline, 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 tranilcypromine, 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 P450 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

	<i>Not any data</i>	<i>In vitro data only</i>	<i>Renal excretion, mainly</i>	<i>Phase-II enzymes, mainly</i>	<i>CYP1A2, CYP2B6 or CYP3A4, mainly</i>	<i>In vivo studies on polymorphic enzymes CYP2D6, CYP2C19, CYP2C9</i>
Antidepressant drugs	Iprindole Isocarboxacid Setiptiline Viloxazine	Amineptine Amoxapine Dibenzipine Doxepin Dothiepin Lofepamine Protriptyline	Milnacipran	Phenelzine Tranlycypromine	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 Trifluoperidol 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

^aDrugs 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_{1ss} 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 biotransforma-

tion 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).

Stereoselective metabolism by CYP2D6 was reported in trimipramine metabolism towards the less active L-trimipramine⁶⁸ and for doxepin, CYP2D6 polymorphisms had influence only on clearance of the less active E-isomer.⁵⁹ For these two tricyclics, dose adjustments should be based on the active drug compound (active enantiomers or isomer plus demethylated metabolite).

An extremely high clearance was described for a few CYP2D6 ultrarapid metabolizers from studies with nortriptyline and desipramine. For nortriptyline, one ultrarapid metabolizer carrying 13 active *CYP2D6* genes was included, which caused the very high mean of clearance in this group.^{61,123} However, the 1–10% carriers of a *CYP2D6* gene-amplification allele found in Caucasian populations usually carry only one gene duplication and should get moderately higher doses as calculated above and as illustrated in Figures 2 and 3.

In Figure 1, dose adjustments calculated from the data of Table 2 of all studies on tricyclic antidepressants and *CYP2D6* polymorphisms are depicted in relation to the number of EMs or PMs studied. As can be seen in the figure, despite small sample sizes, different studies come to very similar results for dose adjustments. CYP2D6 PMs seem to be dosed correctly with approximately half of an average dose of tricyclic antidepressants.

Selective serotonin reuptake inhibitors Some selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, fluvoxamine, and paroxetine are potent inhibitors of CYP2D6 activity. Therefore, multiple dosing causes decreased CYP2D6-mediated metabolism of the drugs themselves, and conversion from extensive to slow metabolizer phenotype and from ultrarapid to extensive metabolism was described.^{124–127} Unfortunately, these studies for fluoxetine and fluvoxamine describing conversion from higher to lower enzyme activity have studied the effect of enzyme inhibition only in one genotype group^{40,127} and could therefore not be used in our dose calculation approach.

Genotype-based dose adjustments might be necessary for paroxetine (Table 2), but less for fluoxetine and fluvoxamine; moreover, caution has to be paid to drug interactions. These drugs are strong inhibitors of CYP2D6, and therefore, differences in pharmacogenetic parameters are substantially decreasing under multiple dosing conditions^{72,75} (Table 2). For paroxetine, undetectable drug concentrations are described in one ultrarapid metabolizer carrying at least three functional *CYP2D6* genes. For sertraline and citalopram, no influence of *CYP2D6* polymorphisms on pharmacokinetic parameters was detected.

Other antidepressants For other antidepressants (bupropion, maprotiline, mianserin, mirtazapine, moclobemide, nefazodone, reboxetine, venlafaxine), no general assessment on polymorphic drug metabolism can be made.

Bupropion is a substrate of CYP2B6 and apparently not influenced by *CYP2D6* polymorphisms.⁷⁶ In about 100 subjects, no major effects of CYP2B6 genotypes on bupropion pharmacokinetics were identified.¹⁹

There are contradictory data regarding the effects of CYP2D6 polymorphisms on metabolism of the tetracyclic antidepressant maprotiline: while in a patient group receiving monotherapy with 150 mg maprotiline, no differences in steady-state concentrations were detected due to the debrisoquine metabolizer status,⁷⁷ a study with healthy volunteers receiving 100 mg maprotiline over 7 days, revealed differences similar to those detected in tricyclics.⁷⁸

For mianserin, CYP2D6 mediates enantioselective hydroxylation of the more active S-(+) mianserin. For dose adjustments, the sum of S-(+)-mianserin and the active desmethylmianserin was taken (Table 2).

For the racemic drug mirtazapine, S-(+)-mirtazapine clearance significantly depends from CYP2D6 genotype, but no CYP2D6 effect on R(-)-mirtazapine clearance was found.¹²⁸ Achiral analysis did not reveal CYP2D6 genotype-related differences.⁸² Further clinical studies are warranted on the impact of CYP2D6 on mirtazapine clinical effects and adverse events, which differ between both enantiomers.

For moclobemide, nefazodone, reboxetine, and trazodone, CYP2D6 polymorphisms do not seem to have a major influence on metabolism in humans.^{37,83–86,129,130}

Venlafaxine is a chiral drug with both enantiomers transformed by CYP2D6 to the equipotent O-desmethyl-venlafaxine.^{88,90,131} Thus, the active drug moiety, sum of parent drug and metabolite is not much changed by the *CYP2D6* genotype. However, a higher risk for cardiotoxic events and severe arrhythmia was reported in four patients admitted to a cardiologic unit who all were PMs, according to CYP2D6 function.⁸⁷ Dose adjustments based on parent drug alone would lead to 60% reduction of the average dose for PMs.

Figure 2 shows the differential doses of antidepressants needed because of polymorphisms of *CYP2D6* as the weighted mean (weighted according to the sample sizes in the studies) of single-study data given in Table 2. Dose adjustments are given for poor, intermediate, extensive, and ultrarapid (UM) metabolizers of CYP2D6. For the UM group, extrapolation was made assuming a linear gene-dose effect according to the calculation methods given above. If possible, data on active moiety of the drug (sum of parent drug and active metabolites) after multiple dosing were taken and if more studies exist, mean dose adjustments were calculated. The figure shows that the amount of dose adjustment varies for substrate to substrate, and that clinically relevant differences in dosages are supported by existing data.

Table 2 Dose adjustments according to CYP2D6 genotype

Drug	Study conditions and parameters measured					Numbers	Extrapolated dose adjustments				References
							UM	EM	IM	PM	
	Measured Parameter	Dose (mg)	Dosage	Participants	UM/EM/IM/PM	UM (%)	EM (%)	IM (%)	PM (%)		
Tricyclic antidepressants											
Amitriptyline	P	CL	50	SD	Volunteers	0/2/4/3		124	74	67	46
		CL	50	SD	Volunteers	0/5/3/3		123	85	57	47
	P + DM	AUC	75	SD	Volunteers	0/4/0/3		120	86	52	48
		Css	150	MD	Patients	0/11/0/4		111	92	73	49
Clomipramine	P	CL	100	SD	Volunteers	15/0/10		115	90	65	50
	P + DM	Css	150	MD	Patients	0/35/0/1		125	83	41	51
		Css	200	MD	Patients	0/15/0/5		112	92	72	52
		Css	75	MD	Patients	0/19/0/3		122	85	48	52
		Css	125	MD	Patients	0/21/0/2		118	88	59	52
Desipramine	P	AUC	25	SD	Volunteers	0/5/0/4		136	76	16	53
		AUC	25	SD	Volunteers	0/8/0/6		130	80	29	54
		CL	100	SD	Volunteers	0/6/6/6		131	106	19	55
		CL	100	SD	Volunteers	6/6/0/0	247	130			56
		Css	100	MD	Patients	0/29/0/2		125	83	42	57
		Css	100	MD	Patients	0/4/5/0		166	37	21 [#]	58
Doxepin	P + DM		75	SD	Volunteers	0/8/8/8		127	82	36	59
Imipramine	P	CL	100	SD	Volunteers	0/6/6/6		110	108	64	55
	P + DM	Css	100	MD	Patients	0/28/0/2		131	79	28	60
Nortriptyline	P	AUC	25	SD	Volunteers	6/5/5/5	254	149	50	42	61
		AUC	29	SD	Volunteers	0/2/3/2		128	73	59	62
		CL	29	SD	Volunteers	0/2/4/2		130	74	54	63
		Css	150	MD	Patients	0/7/13/1		119	96	53	64
		AUC	25	SD	Volunteers	0/10/5/0		133	72	49 [#]	65
		Css	15–120	MD	Patients	0/7/6/0		138	66	43 [#]	66
Trimipramine	P + DM		75	SD	Volunteers	0/8/7/6		150	60	13	67
	D-P + D-DM	Css	300–400	MD	Patients	0/25/0/1		131	91	51	68
SSRIs											
Citalopram	P	AUC	40	MD	Volunteers	0/10/0/8		101	100	98	69
Fluoxetine	P + DM	AUC	60	SD	Volunteers	0/6/0/6		119	87	56	70
		AUC	20	SD	Volunteers	0/9/0/10		107	96	84	71
			20	MD	Patients	0/8/0/3		(99	100	101)	72
Fluvoxamine	P	AUC	50	SD	Volunteers	0/10/0/5		108	95	82	73
		AUC	50	SD	Volunteers	0/10/0/4		129	81	33	74
		AUC	100	MD	Volunteers	0/8/0/2		(94	104	113)	75
Paroxetine	P	AUC	30	MD	Volunteers	0/9/0/8		114	90	66	38
Sertraline	P	AUC	50	SD	Volunteers	0/10/0/10		100	100	99	71
Other antidepressants											
Bupropion	P	Css	300	MD	Patients	0/4/0/3		(104	97	90)	76
Maprotiline	P	Css	150	MD	Patients	0/75/0/5		(100	100	100)	77
		AUC	100	MD	Volunteers	0/6/0/6		127	82	36	78
Mianserin	S-P	Css	30	MD	Patients	0/14/1/0		153	52	31 [#]	79

Table 2 (Continued)

Drug	Study conditions and parameters measured					Numbers	Extrapolated dose adjustments				References
	Measured	Parameter	Dose (mg)	Dosage	Participants		UM/EM/IM/PM	UM (%)	EM (%)	IM (%)	
	P + DM	AUC	30	SD	Volunteers	2/8/0/5	319	114	91	68	80
	S-P + DM	Css	10–360	MD	Patients	0/21/7/1		114	90	74	81
Mirtazapine	P	AUC	15	SD	Volunteers	0/7/0/7		(99	101	102)	82
Moclobemide	P	AUC	600	MD	Volunteers	0/2/0/2		(92	107	121)	83
		Css	450	MD	Volunteers	0/22/0/5		(92	107	121)	84
Nefazodone	P	AUC	400	MD	Volunteers	0/10/0/10		(105	97	90)	85
Trazodone	P	Css	150	MD	Patients	0/46/8/0		(110	93	80)	86
Venlafaxine	P	CL	19	MD	Volunteers	0/8/0/6		130	80	30	87
		AUC	31	SD	Volunteers	0/8/4/0		163	41	23 [#]	88
		AUC	19	SD	Volunteers	0/6/0/6		145	91	37	89
P + DM	Css	225	MD	Patients	2/22/6/3	186	109	86	68	90	
Antipsychotics											
Aripiprazole	P + DM	AUC	No data	SD	Volunteers	No data		113	92	70	Drug information ⁹¹
Clozapine	P	AUC	10	SD	Volunteers	0/10/0/5		(94	104	113)	
Flupentixol	cis-P	Cl	12	MD	Patients	0/45/36/3		116	86	74	92
Haloperidol	P	AUC	5	SD	Volunteers	0/13/0/13		(117	89	61)	93
		CL	4	SD	Volunteers	0/6/0/6		119	87	55	94
		Css	10–40	MD	Patients	0/11/0/1		(108	96	83)	95
		Css	2–24	MD	Patients	5/106/56/5	126	107	97	76	96
		Css	12	MD	Patients	0/22/6/0		120	87	54 [#]	97
		Css	3–20	MD	Patients	0/5/15/0		(131	73	51 [#])	98
		Css	12	MD	Patients	0/60/7/0		114	91	67 [#]	99
		Css	1.5–36	MD	Patients	0/25/13/0		(107	95	85 [#])	100
		Css	12	MD	Patients	0/28/4/0		118	88	58 [#]	101
Css	1–80	MD	Patients	0/76/34/0		(108	94	84 [#])	102		
Levomepromazine	P	AUC	100	SD	Volunteers	0/6/0/3		(100	100	100)	103
Olanzapine	P	AUC	7.5	SD	Volunteers	0/12/0/5		(92	107	122)	104
	P	Css	5–10	MD	Patients	0/13/0/4		122	105	61	105
Perazine	P	Cl	320	MD	Patients	3/71/53/8	117	110	91	86	92
Perphenazine	P	AUC	6	SD	Volunteers	0/6/0/6		129	80	31	106
		Css	15	MD	Patients	0/56/0/8		118	88	59	107
Pimozide	P	AUC	6	SD	Volunteers	0/7/0/5		(102	99	95)	108
Risperidone	P P + OHM	CL	1	SD	Volunteers	0/9/1/2		141	80	22	109
		AUC	1	SD	Volunteers	0/3/0/2		108	95	82	110
		Css	6	MD	Patients	0/39/0/3		106	96	87	111
		Css	1–8	MD	Patients	0/17/22/0		122	82	62 [#]	112
		Css	6	MD	Patients	0/20/4/0		127	77	55 [#]	113
Thioridazine	P	AUC	25	SD	Volunteers	0/13/0/6		130	80	30	114
		Css	100	MD	Patients	0/18/0/2		115	90	65	115
		Css	20–500	MD	Patients	3/47/19/5	140	130	80	30	116
Zuclopenthixol	P	CL	6	SD	Volunteers	0/6/0/6		123	84	45	117
		Css	4–32	MD	Patients	0/12/0/58		116	90	64	118
		CL	8–22	MD	Patients	0/8/9/3		120	87	53	119

Table 2 (Continued)

Drug	Study conditions and parameters measured				Numbers	Extrapolated dose adjustments				References
	Measured Parameter	Dose (mg)	Dosage	Participants		UM/EM/IM/PM (%)	UM (%)	EM (%)	IM (%)	
Zuclopenthixol-decanoat	P + DM	Css	100–400MD	Patients	0/35/13/4		116	89	70	120

Measured: Measured drug component in the studies, if available, the active moiety was taken. P + DM: Parent drug + demethylated metabolite; S-P: S-enantiomer; E-P: E-stereoisomer; OHM: hydroxy-metabolite.

Parameter: Pharmacokinetic parameter taken for calculation (CL: clearance; AUC: area under the concentration time curve; C_{ss}: concentration at steady state).

Dose (mg): The doses given in the clinical studies are depicted. In cases where different doses were given to patients, the dose range is shown.

UM (%), EM (%), IM (%), PM (%): Percents of dose adaptations from an average 'common' dose are given for each genotype group and each study calculated as given in the text section 'data calculation for dose adjustments'.

Dosage: This column indicates whether pharmacokinetic parameters are from a single-dose study (SD) data or from multiple dosing (MD).

Participants: Either healthy volunteers or patients taking part in the study.

Number UM/EM/IM/PM: Number of participants for each genotype group.

Extrapolated dose recommendations from studies where differences were statistically not significant are printed in parenthesis. No dose adjustments based on CYP2D6 genotype are recommended based on these studies; the percentages are solely given for completeness of this quantitative metaanalysis. If intermediate metabolizers have not been tested ($n = 0$ in the column number UM/EM/IM/PM), a linear extrapolation was performed: $(AUC_{PM} + AUC_{EM})/2 = AUC_{IM}$; equation for $AUC_{PM} = 2AUC_{IM} - AUC_{EM}$.

The symbol # marks studies in Asian populations where carriers of the genotype *CYP2D6*10/*10* are considered equivalent to intermediate metabolizers, and true functionally deficient metabolizers are extrapolated.

Impact of CYP2D6 polymorphisms on dosing of antipsychotics

The influence of CYP2D6 polymorphisms on antipsychotic drug metabolism was studied in humans for aripiprazole, clozapine, flupentixol, haloperidol, levomepromazine, olanzapine, perazine, perphenazine, pimozide, risperidone, thioridazine, and zuclopenthixol.

Differences in pharmacokinetic parameters resulting in dose adjustments are depicted in Table 2, and dose recommendations according to the results from the studies in each substance are expressed in Figure 3.

The recently released antipsychotic drug aripiprazole was studied for polymorphic CYP2D6 metabolism prior to marketing, and 60% higher exposure to the total active moieties (parent drug and dehydroaripiprazole) was detected in PMs compared to EMs (aripiprazole drug information) (Table 2). Similar dose variations were detected for flupentixol as well as for perazine in a naturalistic study with schizophrenic patients receiving different doses.⁹²

For thioridazine, a recent study within patients reports a large difference in pharmacokinetics resulting in 30% of the average dose in PMs,¹¹⁶ which corresponds to the data from a study in healthy volunteers administering single doses,¹¹⁴ but is in contrast to another study in patients where smaller differences were found.¹¹⁵ For dose recommendations, the weighted mean of the dose adjustment was

taken from the two studies in patients (with multiple doses) according to the number of PMs (Figure 3).

For haloperidol, differences in drug metabolism lead to 60–70% of the average dose for PMs^{94,96} and two studies did not report significant differences at all.^{93,95} However, a significant higher risk for extrapyramidal side effects in PMs was observed, probably due to higher levels of reduced haloperidol. Patients with UM genotype had the worst clinical outcome measured by the positive and negative symptoms scale.⁹⁶

For perphenazine, thioridazine, and zuclopenthixol, pharmacokinetic differences due to CYP2D6 genotype decreased under steady state compared to single-dose studies (30–40% decrease with PM single dose, and 60–70% with multiple dosing) and risperidone with 20% for PMs according to single dose and no significant differences for multiple doses due to an active CYP2D6-generated metabolite.

For olanzapine, a single-dose study in healthy volunteers failed to show CYP2D6-mediated differences, whereas in a patient study, steady-state concentrations differed according to the *CYP2D6* genotype.¹⁰⁵ Our own data indicated the same trend (Kirchheiner *et al.*, unpublished).

For zuclopenthixol, the only study evaluating depot medication and CYP2D6 genotype revealed that CYP2D6 PMs should get only 70% of an average dose.¹²⁰ Consequently, particularly at the beginning of antipsychotic treatment, knowledge about the poor

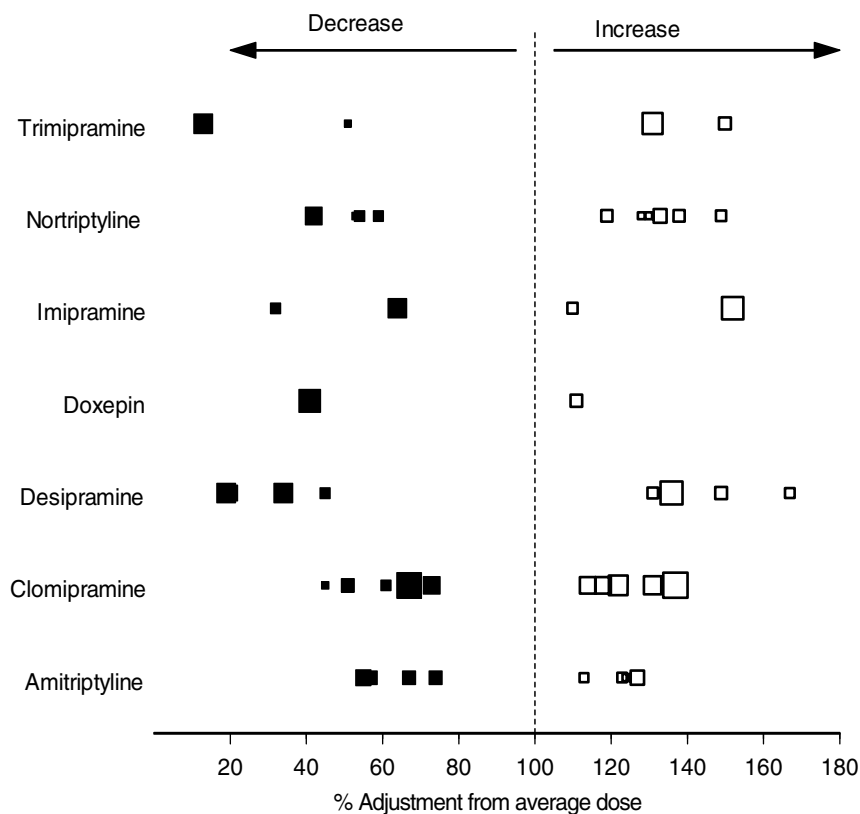


Figure 1 Dose adjustments for *CYP2D6* PMs and EMs for tricyclic antidepressant drugs in relation to sample size. PMs are defined as carriers of zero active *CYP2D6* gene and EMs are defined as carriers of two active *CYP2D6* genes. Filled black boxes indicate how much doses would have to be decreased in genotypically identified poor metabolizers according to data of the single studies and open boxes indicate how much doses would have to be increased in carriers of two active *CYP2D6* genes. As can be seen, there is a good agreement of the different studies with respect to the possible therapeutic consequences.

metabolizer status might help to reduce adverse events by initiation therapy with lower doses in this subgroup of the population.

Impact of *CYP2C19* polymorphisms

When compared to *CYP2D6* polymorphisms, substantially fewer studies were conducted evaluating *CYP2C19*-mediated differences in drug metabolism (Table 3). Since *CYP2C19* poor metabolizers are more frequent in Asiatic populations (13–23% in contrast to 2–5% in Caucasians^{132,133}), several studies of Table 3 were conducted in Japanese individuals.

In general, *CYP2C19* seems to be involved in demethylation biotransformation reactions of tricyclic antidepressants as was shown for amitriptyline, clomipramine, doxepin, imipramine, and trimipramine (Table 3 and Figure 4). For these drugs, PMs seem to be adequately adjusted with about 60% of the average dose and EMs with 110%. The same dose adjustments seem to be adequate for moclobemide and citalopram.

Impact of *CYP2C9*

Carriers of the alleles *CYP2C9*2* and **3* have lower enzyme activity compared with carriers of the wild-

type allele (*CYP2C9*1*), and a *CYP2C9*4* allele with completely deficient enzyme activity was found in a single African-American subject.¹⁴³ *CYP2C9*2* and **3* alleles have frequencies of about 12 and 8% in Caucasians (our own data on 1010 Caucasians), but *CYP2C9*2* is rare in Asian populations.

All currently existing data show only a minor contribution of *CYP2C9* polymorphisms for interindividual pharmacokinetic variability of tricyclic antidepressants: data on amitriptyline are based on *in vitro* studies only, a small difference in kinetics between carriers of *CYP2C9*1/*1* and **3/*3* was shown for trimipramine and doxepin.^{59,67}

Clinical impact of pharmacogenetic testing for polymorphic drug metabolism

Although differences in the pharmacokinetic parameters due to polymorphic metabolism are relatively well characterized with a surprisingly good between-study concordance (Tables 2 and 3, and Figure 1), the impact of those variations on therapeutic outcomes and incidence and severity of adverse drug reactions are not as well documented. Few studies provide quantitative data on adverse drug reactions.^{49,57,80,87,137,144} Higher risk for antidepressant

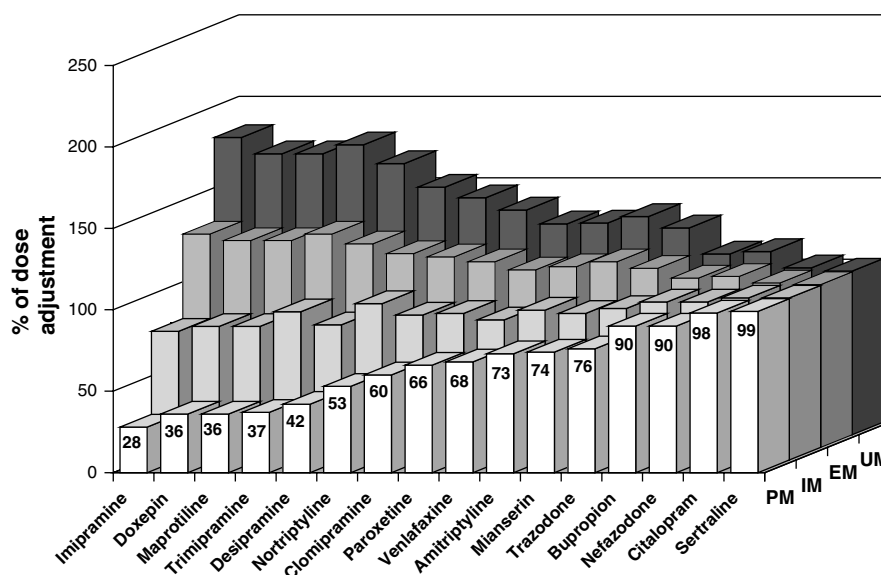


Figure 2 CYP2D6-mediated quantitative influences on pharmacokinetics of antidepressant drugs expressed as percent dose adjustments: CYP2D6 PM (white), IM (gray), EM (dark gray), UM (black). Dose adjustments were calculated according to the data given in Table 2. If data on active drug moiety (consisting on active principle metabolite + parent drug of active enantiomers of a racemic drug) were given, dose recommendations were based on these data only (other studies not providing so detailed information were not incorporated). If more than one study was integrated, the weighted mean for the dose adjustment was taken according to the number of poor metabolizers in each study. Data on mirtazapine, moclobemide, fluoxetine, and maprotiline were not shown in the figure, since no dose adjustment based on CYP2D6 can be recommended at present.

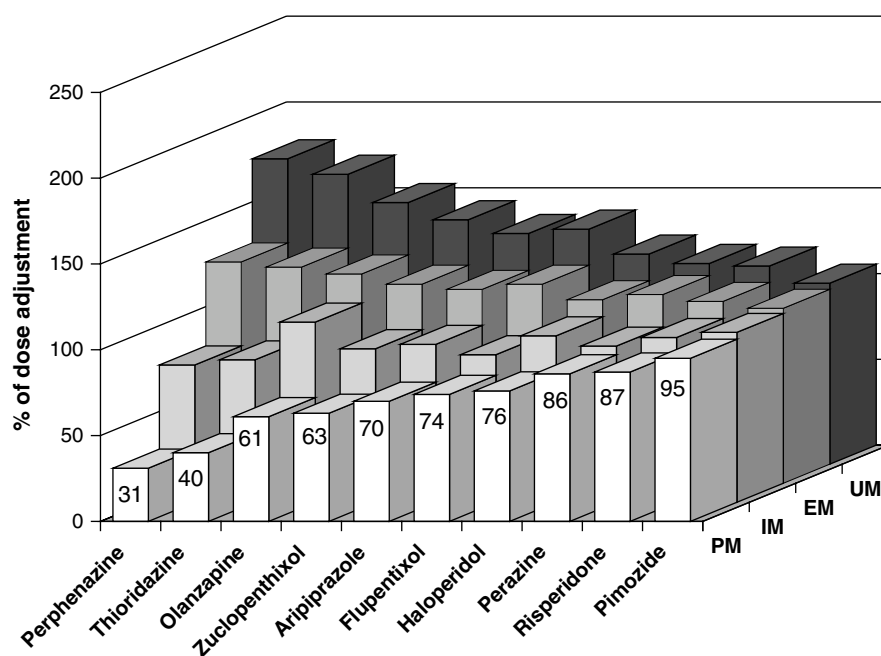


Figure 3 CYP2D6-mediated quantitative influences on pharmacokinetics of antipsychotic drugs expressed as percent dose adaptations: CYP2D6 PM (white), IM (gray), EM (dark gray), UM (black).

induced seizures was reported in relation to CYP2D6 activity¹⁴⁵ and several studies showed a relationship between extrapyramidal side effects of antipsychotic drugs and CYP2D6 polymorphisms.^{96,146–156} However, compared to the large efforts made to evaluate

pharmacokinetic differences due to CYP polymorphisms, few prospective studies on benefit of phenotyping or genotyping for therapeutic outcome have been conducted so far. It was estimated from retrospective assessments that patients with psychiatric disorders

Table 3 CYP2C19-based dose adjustments: bioequivalent doses were calculated from differences in AUC, clearance or steady-state trough concentrations

Drug	Study conditions and parameters measured					Numbers	Extrapolated dose adjustments			References
	Measured	Parameter	Dose (mg)	Dosage	Participants		EM (%)	IM (%)	PM (%)	
Tricyclic antidepressants										
Amitriptyline	P	Css	25–225	MD	Patients	4/19/7	104	94	59	133
	P + DM	AUC	50	SD	Volunteers	4/2/6	98	98	92	134
		Css	150	MD	Patients	11/0/1	109	81	53	49
Clomipramine	P	Css	10–250	MD	Patients	18/25/8	110	79	62	135
		1/CL	100	SD	Volunteers	19/0/6	106	88	71	50
Doxepin	P	1/CL	75	SD	Volunteers	8/7/7	105	91	48	59
Imipramine	P	1/CL	100	SD	Volunteers	11/0/5	(105	91	77)	136
	P + DM	Css	70	MD	Patients	5/0/5	105	90	75	137
		Css	50	MD	Patients	5/0/23	108	83	58	138
Trimipramine	D-P + D-DM	Css	350	MD	Patients	25/0/1	(114	73	31)	68
	P + DM	1/CL	75	SD	Volunteers	8/7/7	100	48	58	67
SSRIs										
Citalopram	P	AUC	40	MD	Volunteers	10/0/6	108	84	61	69
Fluoxetine	P	AUC	40	SD	Volunteers	4/4/6	113	72	39	139
	P + DM	AUC	40	SD	Volunteers	4/4/6	100	100	100	139
Fluvoxamine	P	AUC	100	SD	Volunteers	9/0/4	(101	97	93)	140
Sertraline	P	AUC	100	SD	Volunteers	6/0/6	105	90	75	141
Other antidepressants										
Maprotiline	P	Css	150	MD	Patients	78/0/2	(100	100	100)	77
Mianserin	P	AUC	30	SD	Volunteers	10/0/5	(92	117	142)	80
Moclobemide	P	1/CL	300	SD	Volunteers	8/0/7	112	77	42	37
		1/CL	600	MD	Volunteers	8/0/7	107	86	65	37
Antipsychotics										
Clozapine	P	AUC	10	SD	Volunteers	10/0/5	(104	91	78)	80
Zotepine	P	1/CL	25	SD	Volunteers	7/0/7	(104	93	82)	142

Measured: Measured drug component in the studies, if available, the active moiety was taken. P + DM: Parent drug + Desmethyl-metabolite; D-P + D-DM: D-enantiomer of parent drug and metabolite.

Parameter: Pharmacokinetic parameter taken for calculation (CL: clearance; AUC: area under the concentration time curve; Css: concentration at steady state).

Dose (mg): The doses given in the clinical studies are depicted. In cases where different doses were given to patients, the dose range is shown.

EM (%), IM (%), PM (%): Percents of dose adaptations from an average ‘common’ dose are given for each genotype group and each study calculated as given in the text section ‘data calculation for dose adjustments.’

Dosage: This column indicates whether pharmacokinetic parameters are from a single-dose study (SD) data or from multiple dosing (MD).

Participants: Either healthy volunteers or patients taking part in the study.

Number EM/IM/PM: Number of participants for each genotype group.

Extrapolated dose recommendations from studies where differences were statistically not significant are printed in parenthesis. No dose adjustments based on CYP2C19 genotype are recommended based on these studies and the percentages are solely given for completeness of this quantitative metaanalysis. Note that in some instances paradoxical dose recommendations would be derived from these insignificant relationships.

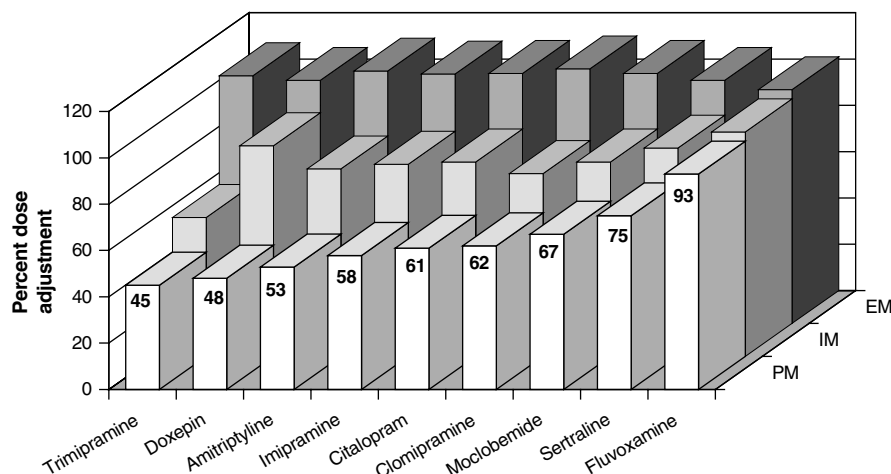


Figure 4 *CYP2C19*-mediated quantitative influences on pharmacokinetics of antidepressant drugs expressed as percent dose adaptations: *CYP2C19* PM (white), IM (gray), EM (dark gray).

who are poor or ultrarapid metabolizer of *CYP2D6* cost US\$ 4000–6000 more per year than extensive metabolizers.^{157,158} The next step is to perform prospective controlled analyses on the benefit of genotyping in drug therapy: one group should receive therapeutic recommendations according to genotype, whereas the other group should be treated as usual.

Dose reduction might take place by prolongation of the dosing interval and/or by reducing the single dose. Due to first-pass metabolism, dose adjustments may be smaller in i.v. than in oral doses as shown recently by a study on trimipramine.¹⁵⁹ However, the validity of these calculated dose adaptations (Figures 2–4) for dose recommendations remains to be tested.

Pharmacodynamics: polymorphisms in neurotransmitter transporters, receptors, and other drug targets

As pharmacokinetic factors explain only a small part of the variability in therapeutic response, efforts have to concentrate on variations within target molecules in the brain. Thus far, mostly dopaminergic and serotonergic receptors and transporters have been studied in patients as predictors of the response to psychotropic drug therapy (Table 4). Systematic exploration of other transmitter systems, of downstream intracellular signaling molecules, of neurotrophic factors and their receptors is a major goal of the next few years.

Serotonergic system

Serotonin transporter

Role in antidepressant drug therapy The molecular mechanism of antidepressant drug action involves inhibition of the neuronal serotonin transporter. One apparently functional polymorphism in the 5'-upstream regulatory region of this gene is a 44-base

pair (bp) insertion/deletion resulting in a long (l) and a short (s) variant, the latter resulting in two-fold decreased expression and transport activity *in vitro*.^{191,192} Several studies have reported a better response to SSRIs in individuals carrying two (l)-alleles of the 44-bp insertion/deletion polymorphism in the regulatory region of the serotonin transporter (SERT).^{168,169,171–175,193} Two studies had contradictory results.^{165,170} This discrepancy might be due to ethnic differences: the (s)-allele frequency is much higher in Orientals than in Caucasians (79 vs 42%),¹⁹⁴ and both studies showing an association of the (s) allele with better response were conducted in Oriental patients. However, Yu *et al*,¹⁶⁹ who also studied an Asian population, found data similar to the European studies. Thus, ethnicity does not provide a clear explanation of the discrepancies and further studies are required for confirmation.

Increased circulating prolactin levels, used as a surrogate parameter of antidepressant drug action, were reported to be higher in individuals carrying the (l)-allele.^{166,167} In Figure 5, effect size of the studies is depicted in relation to sample size. One would expect from such plots a symmetric convergence of the effect towards the overall mean with increasing sample size. None of the authors has given a specific solution how the knowledge about differences in response depending on SERT genotype should be used in psychiatric practice. A rational approach would be to prefer primarily noradrenergic agents or tricyclics in carriers of the s/s genotype; however, this requires confirmation in a clinical study.

Another polymorphism is located in intron 2 of the SERT gene. It is a variable number of tandem repeats (VNTR) polymorphism resulting in three frequent alleles containing 9, 10, and 12 copies of the VNTR element. The VNTR was shown to act as strong positive transcriptional regulatory element for SERT in mouse embryonic rostral hindbrain and the (l)-allele containing 12 copies had the strongest

Table 4 Genetic data correlated with antidepressant treatment response

Gene	Polymorphism	Drug	Scales	Time to response (weeks)	Number	Response predictive genotype	Effect-size (odds ratio or decrease in rating score)	Significance	Reference
HTR2A	His452Tyr 102T>C	Various	HAMD-17/CGI	4	173	Tyr/Tyr	No data	NS	160
		Various	HAMD-17/CGI	4	173	CC	No data	0.02	160
	-1420C>T	Fluvoxamine/ paroxetine	HAMD-21	6	340	TT	1.9	NS	161
		Fluvoxamine/ paroxetine	HAMD-21	6	340	CC	1.3	NS	161
	-1438G>A	Fluvoxamine	MADRS	6	54	AA	0.8	NS	162
HTR6	267C>T	Venlafaxine, fluoxetine	HAMD	4	34	TT	No data	NS	163
SERT	17-bp VNTR	Fluvoxamine	MADRS	6	66	12/12	1.3	NS	164
		Various SSRI	HAMD-17	6	120	12/12	32	0.0001	165
	44-bp ins/del	Clomipramine	Prolactin increase	No data	14	l/l	126 vs -7.2 mIU × h/l	0.02	166
		Fenfluramine	Prolactin increase	No data	14	l/l	3-fold vs 1.6-fold	0.045	167
		Fluoxetine	HAMD-17/ GAS	18	51	l/l	48 vs 31% (1.5)	0.01	168
		Fluoxetine	HAMD	No data	121	l/l	5.59	0.013	169
		Fluvoxamine	MADRS	6	54	l/l + l/s	0.2	0.01	170
		Fluvoxamine	HAMD	6	53	l/l + l/s	85 vs 50% (1.7)	<0.0001 ^a	171
		Fluvoxamine + pindolol	HAMD-21	6	155	l/l	83 vs 65% (1.3)	0.03	172
		Nortriptyline	HAMD-17	12	95	l/l	0.7	NS	173
		Paroxetine	HAMD-17	12	95	l/l	49 vs 30% (1.6)	0.028	173
		Paroxetine	HAMD-21	4	58	l/l	72 vs 42% (1.7)	<0.0001	174
		Sleep deprivation	Increase of VAS-mood	0.1	68	l/l	1.6-fold vs 1.1-fold (1.5)	0.05	175
		Various SSRI	HAMD-17	6	120	l/l	0.6	0.02	165
Various	HAMD-17/CGI	4	104	l/l	1	NS	160		
ACE	Ins/Del	Various	HAMD-17	4	99	D/D, D/I	14.6 vs 22.6*	<0.0001	176
		Venlafaxine, fluoxetine	HAMD-21/CGI	4	35	D/D, D/I	50 vs 50%	NS	177
DRD2	Ser311Cys	Fluvoxamine, paroxetine	HAMD-21	6	364	Ser/Cys	1.5	NS	178
DRD3	Ser9Gly	Sleep deprivation	HAMD-6/VAS	0.1	52	Gly/Gly	1.1	NS	179
DRD4	48-bp repeat	Fluvoxamine/ paroxetine	HAMD-21	6	364	Homozygous *5, *6, *7, *8	0.5	NS	178
		Sleep deprivation	Increase of VAS mood	0.5	124	*7/*7	1.5-fold vs 1.2	NS	180
GNAS1	131T>C	Various	HAMD-17/CGI	4	212	C/C	No data	NS	181
GNB3	825C>T	Various	HAMD-17	4	88	T/T	54 vs 33%	0.012	182
		Fluvoxamine, paroxetine	HAMD	6	590	T/T	1.8	0.009	183
MAOA	Promoter VNTR	Fluvoxamine	MADRS	6	54	*3/*3	2.9	NS	184
		Fluvoxamine/ paroxetine	HAMD-21	6	278	ss	1.5	NS	161

Table 4 (continued)

Gene	Polymorphism	Drug	Scales	Time to response (weeks)	Number	Response predictive genotype	Effect-size (odds ratio or decrease in rating score)	Significance	Reference
TPH	218A>C	Fluvoxamine	HAMD	6	121	C/C	5.3	0.001	185
		Fluvoxamine	MADRS	6	54	C/C	0.8	NS	184
		Paroxetine	HAMD-21	4	121	C/C	2.1	0.001	186
NOS	276C>T	Fluoxetine	HAMD	4	110	C/C	0.8	NS	187
β 1AR	Gly389Arg	Various	HAMD-17	4	259	C/C	38 vs 24%	0.05	188
IL-1b	-511C>T	Fluoxetine	HAMD	4	119	T/T	1.9	NS	189
BDNF	Val166Met	Fluoxetine	HAMD	4	152	Met/Met	1.1	NS	190

VNTR, Variable number of tandem repeats; Ins/Del, Insertion/Deletion; 5'-UTR, 5' untranslated region.

Scale: Rating scale used for response assessment: HAMD-21 or HAMD-17: Hamilton depression scale with either 21 or 17 items; CGI: clinical global impression scale; VAS: visual analogue scale for mood disorders; GAS: global assessment scale; MADRS: Montgomery and Aasberg depression rating scale.

Effect size: If data available, odds ratio was calculated or taken from the studies or the ratios of the decrease in rating scores (in%) or mean end rating score * were taken. ** in one case, visual analogue scales (VAS) measuring mood were used and effect size was expressed as increase in VAS.

^aP-value is based on s/s genotype group compared to both, the l/l and the s/l group together. NS = nonsignificant.

transcriptional inducing ability.¹⁹⁵ Two studies assessed the predictive value on antidepressant response of this VNTR, but an initially described association with an odds ratio of 32 of the (l) 12 allele with better response to SSRIs¹⁶⁵ was not replicated.¹⁶⁴ Studies on the association of adverse drug reactions and SERT polymorphisms show that there is a positive association with the risk of switching to mania, but no correlation to antidepressant-caused nausea.^{196,197} Fluoxetine-induced insomnia appeared to be greater in carriers of the s/s genotype.¹⁹⁸

Role in antipsychotic drug therapy Newer antipsychotics appear to exert their effects partially through the serotonergic systems making the SERT a logical candidate gene for prediction of antipsychotic drug response. One study showed a better response to clozapine in carriers of the (l)-allele (Table 5). For various typical antipsychotics, in 684 patients, no differences in drug response were observed in relation to SERT genotype.¹⁹⁹

Adverse effects of antipsychotics have also been related to SERT polymorphisms. A slightly higher frequency of the SERT l/l genotype was observed in patients suffering from tardive dyskinesia with an odds ratio of 1.9; however, differences were not statistically significant.²⁰⁰ Clozapine-induced weight gain was not associated with the SERT promoter polymorphism either.²⁰¹

Serotonin receptors

Role in antidepressant drug therapy Serotonin (5-HT) receptor genes are further candidate genes for the prediction of antidepressant response. Several studies

have shown that paroxetine induces downregulation of the 5-HT_{2A} receptor,^{202,203} which has been reported to be overexpressed in depressed patients.²⁰⁴

Three polymorphisms have been described in the 5-HT_{2A} gene: a silent point mutation 102T>C that is completely linked to a -1438G>A promoter polymorphism, and a polymorphism in the coding region causing a His452Tyr amino-acid substitution. A better treatment response to antidepressants in patients with one or two C-alleles of the 102T>C polymorphism was reported as compared to T/T homozygotes.¹⁶⁰ In contrast, no significant association between the completely linked -1438G>A polymorphism and therapeutic response to fluvoxamine was observed.¹⁶²

A severe adverse drug effect related to the serotonin system is the serotonin syndrome characterized by serotonin-related side effects with symptoms such as mental status changes, agitation, myoclonus, hyperreflexia, tremor, and diarrhea.²⁰⁵ Impaired drug metabolism of serotonergic drugs caused by genetic deficiency of drug-metabolizing enzyme activity, as well as genetic factors in serotonergic neurotransmission, might be involved, but serotonin receptor polymorphisms have not been systematically analyzed in this context.

Role in antipsychotic drug therapy Even though the mechanisms of action of clozapine are incompletely elucidated, it appears that in comparison to typical neuroleptics, this atypical antipsychotic drug has more effects at the level of serotonergic systems and less on dopaminergic systems.²⁰⁶ Serotonin receptor (5-HT_{2A}, 5-HT_{2C}, 5-HT_{3A}, 5-HT_{5A}, 5-HT₆) polymorphisms were studied as predictors of the

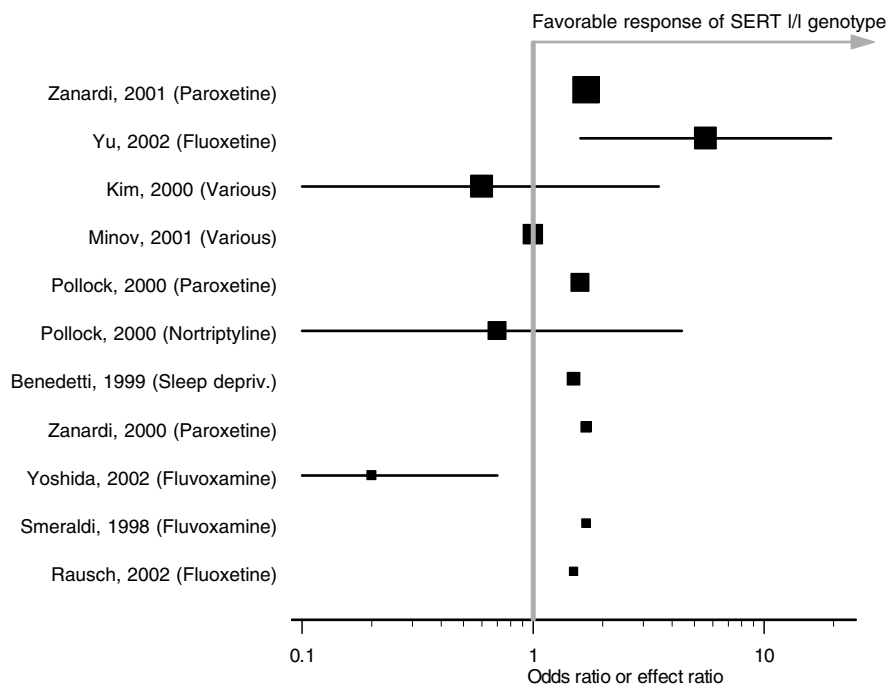


Figure 5 Impact of the SERT promoter 44-bp insertion/deletion polymorphism on the response to antidepressant medication. The odds ratios to respond to medication or effect ratios (ratio of responders with the I/I genotype over responders with other genotypes) are shown. If data were available, 95% confidence limits of the odds ratios were calculated and shown as horizontal lines. In such plots, the between-study variation should be as smaller as larger the sample size of the studies is. In addition, one expects that the scatter is symmetric around the common mean of all studies and asymmetry suggests publication bias.

therapeutic response to clozapine. In Figure 6, studies on serotonin receptor polymorphisms as predictors of clozapine response are depicted in relation to effect size and sample sizes. In cases where ≥ 3 studies on the same polymorphism have been performed, studies are ordered by sample size. The true impact of a polymorphism as a predictor for response is dependent, if this result is reproduced in several independent studies. Nevertheless, a possibility of publication bias has to be considered. A first hint for possible publication bias is deviation from the theoretically expected pattern in the funnel plots where studies should converge with increasing sample size. The weighted mean of the odds ratios of all studies on 5-HT_{2A} receptor genotypes was 1.7, thus predicting only a minor influence of this gene on clozapine response (Table 5).

Two studies on antipsychotic response to various antipsychotics other than clozapine did not show any correlation to 5-HT_{2A} receptor genotype.^{240,241}

For 5-HT receptor subtype 2C, one study reported significant better clozapine response in individuals carrying the Ser allele of the Cys23Ser variant,²²⁹ but subsequent studies failed to reproduce this observation.^{220,225,230,231} The 5-HT receptor variants have also been studied as predictors of antipsychotic drug adverse events including tardive dyskinesia, weight gain, and malignant neuroleptic syndrome, but mostly without significant results (Table 6).

Serotonin biosynthesis

Tryptophan hydroxylase is the rate-limiting enzyme of serotonin biosynthesis.^{185,186} One polymorphism (218A>C) located in a possible transcription factor-binding site may influence gene expression.²⁸⁰ Significant associations with response to SSRIs were reported in individuals carrying the C variant of the A218C polymorphism.^{185,186} Recently, it has been elucidated that tryptophan hydroxylase expressed in the brain is coded by a gene (TPH2) different from that coding for peripherally expressed tryptophan hydroxylase (TPH1)²⁸¹ and animals in which TPH1 was knocked out had normal central tryptophan hydroxylase. Thus, the older polymorphisms data will have to be reanalyzed and an analysis of the TPH2 gene regarding medically relevant polymorphisms has to be performed. Regeneration of serotonin from 5-methoxytryptamine is mediated by polymorphic human CYP2D6; this drug-metabolizing enzyme is therefore also directly involved in serotonin homeostasis.²⁸²

Dopaminergic system

Dopamine receptors

Dopamine receptors are classified according to their signal transduction pathways and sequence homology into the dopamine D1-like receptors (DRD1 and DRD5) and the dopamine D2-like receptors (DRD2,

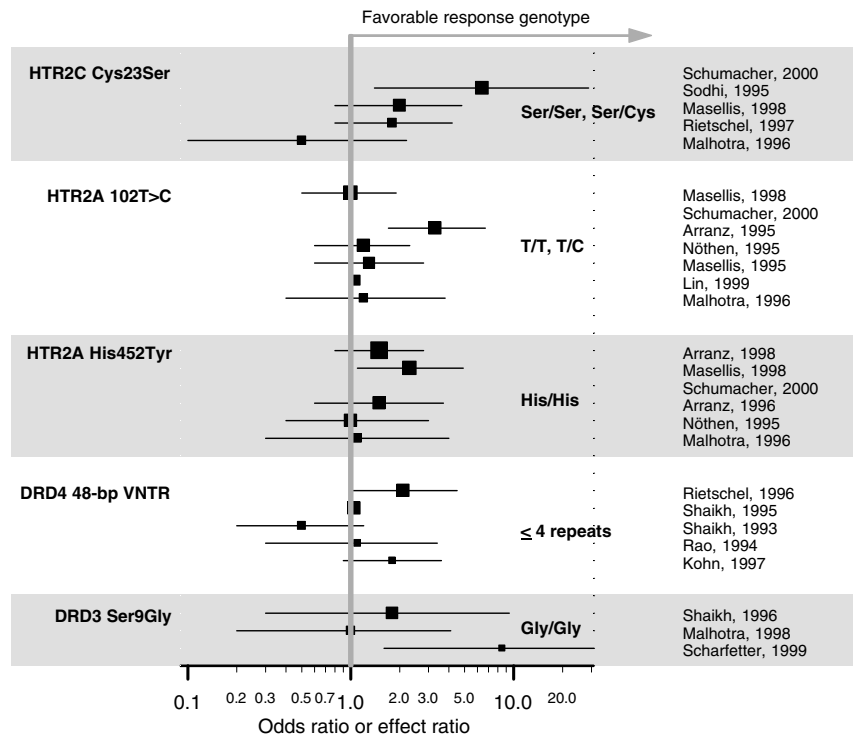


Figure 6 Serotonin 5HT_{2A} and 5HT_{2C} and dopamine D₃ and dopamine D₄ receptor polymorphisms as predictors of clozapine response. Only polymorphisms for which more than one study has been published are included in this figure. The squares indicate the odds ratio to have a favorable therapeutic response if the allele combination indicated in the figure exists and the horizontal lines show the 95% confidence intervals of these odds ratios.

DRD3, and DRD4). Numerous polymorphisms have been described in all five receptors,^{283,284} but functional effects of most variants appear to be moderate. Variants resulting in completely deficient expression of DRD4²⁸⁵ are very rare.

Role in antidepressant drug therapy Dopamine receptor genes might be less involved in antidepressant drug action, and so far, all studies resulted in odds ratios around 1 when testing the predictive value for antidepressant treatment response of dopamine receptor variants (Table 4).

Role in antipsychotic drug therapy For dopamine receptor D2 (DRD2), two alleles A1 and A2 exist, of which allele A1 appeared to be associated with lower dopamine D2 receptor density in the brain and with diminished dopaminergic activity.^{286,287} However, data on the medical impact of these polymorphisms are controversial. Three amino-acid substitutions in the DRD2 are apparently functionally relevant²⁸⁸ but these are rare, and conclusive clinical data are missing. Numerous other noncoding polymorphisms have been identified including two promoter polymorphisms (−241A>G and deletion −141C) but again, consistent data indicating a clinical impact are missing (Table 6).

One recently performed meta-analysis on pharmacogenetics of tardive dyskinesia involved data from 780 patients from different populations (mostly

Caucasian, but also African American and Ashkenazi) confirmed contribution of the dopamine receptor D3 (DRD3) Ser9Gly polymorphism with an odds ratio of 1.33 for carriers of the Gly variant;²⁵² however, in epidemiology, such small odds ratios are usually interpreted with caution. In Figure 7, the odds ratio or effect sizes of the studies on the role of the DRD3 Ser9Gly polymorphism in tardive dyskinesia are depicted in relation to sample sizes. As illustrated in Figure 7, the biggest effects were seen in the small studies and these effects were apparently not replicated in the larger studies. One explanation for this trend may be publication bias meaning that small studies with the opposite effect might also exist but have never been submitted for publication.⁴²

Dopamine D4 receptor (DRD4) polymorphisms have been studied as predictors of the response to the DRD4 ligand clozapine, but the results on a 16-amino-acid VNTR polymorphism were contradictory (Table 5).^{214–218}

For typical (ie predominantly dopamine D-2 antagonistic) antipsychotics, only few studies were found on dopamine receptor genes (DRD2, DRD3, and DRD4).^{210,289–293} Most results were negative findings for response prediction. One study observed a slight over-representation of the DRD3 Ser9Gly amino-acid exchange (allele *2) in patients with poor response to antipsychotics, particularly in the non-Ashkenazi, Israeli schizophrenics.²⁹⁰

Table 5 Genetic polymorphisms as predictors of the response to clozapine

Functional class	Gene	Polymorphism	Scales	Time to response (weeks)	Response predictive genotype	Significance	Effect size	Number	Reference
Adrenoceptor	ADRA1A	Arg492Cys	GAS	12	Cys/Cys	NS	1.7	289	207
		ADRA2A	1291C>G	BPRS	8	G/G	NS	12 vs 9 ^a	97
		1291C>G	GAS	12	G/G	NS	1	289	207
		261G>A	GAS	12	A/A, G/A	NS	1.7	289	207
Dopamine receptor	DRD1	Promoter	BPRS	5	22	0.05	30 vs 0%	15	209
	DRD2	141C Ins/Del	GAS	>6	Ins/Del	NS	1.5	151	210
	DRD3	Ser9Gly	BPRS	6 months	Gly/ Gly + Ser/ Gly	0.006	8.5	32	211
			BPRS	10 weeks	Gly/Gly	NS	1	68	212
	DRD4	12-bp VNTR	GAS	>3 months	Gly/Gly	NS	1.8	133	213
			Clinical impression	16 (±13) months	*2/*2	NS	1.8	37	214
		48-bp VNTR	No data	70 days	*2/*2	NS	1.4	149	215
			BPRS	15 weeks	Alleles with $n \leq 4$ TR	NS	1.1	29	216
			Clinical impression	16 (±13) months	$\leq 4/7$	NS	1.8	37	214
			Clinical impression	70 days	$\leq 4/7$	NS	2.1	149	215
			Change in GAS	>3 months	$\leq 4/7$	NS	23 vs 22	147	217
			GAS	>2 months	Alleles with $n \leq 4$ TR	NS	0.5	64	218
		13-bp del	Clinical impression	70 days	del/ins	NS	1.9	149	215
		Gly11Arg	Clinical impression	70 days	Gly/Gly	NS	2.2	149	215
Serotonin transporter	SerT	44-bp ins/del	Decrease in BPRS	>8 weeks	l/l	NS	55 vs 70%	90	219
Serotonin receptor	HTR2A	1438A>G	BPRS/CGI	>6 months	G/A + A/A	NS	1	181	220
			GAS	>3 months	G/A + A/A	0.002	2.5	274	221
		His452Tyr	BPRS/CGI	>6 months	His/His	0.04	2.3	181	220
			BPRS	10 weeks	His/His	NS	1.1	70	222
			GAS	No data	His/His	NS	1.5	153	223
			Clinical impression	>28 days	His/His	NS	1.1	146	224
			Clinical impression	>28 days	His/His	NS	No data	163	225
			GAS	>3 months	His/His	NS	1.5	274	221
		102T>C	BPRS/CGI	>6 months	T/T + C/T	NS	1	181	220
			Decrease in BPRS	>8 weeks	T/T + C/T	NS	68 vs 70%	97	226
			BPRS	10 weeks	T/T + C/T	NS	1.2	70	222
			GAS	12 weeks	T/T + C/T	0.001	3.3	149	227
			Clinical impression	>28 days	T/T + C/T	NS	1.2	146	224
			Clinical impression	>28 days	T/T + C/T	NS	No data	163	225
		Thr25Asn	BPRS	>6 months	T/T + C/T	NS	1.3	126	228
			Clinical impression	>28 days	Thr/Asn	NS	1	146	224
	HTR2C	Cys23Ser	BPRS/CGI	>6 months	Ser/Ser + Ser/Cys	NS	2	139	220
Clinical impression			>28 days	Ser/Ser + Ser/Cys	NS	No data	163	225	

Table 5 (Continued)

Functional class	Gene	Polymorphism	Scales	Time to response (weeks)	Response predictive genotype	Significance	Effect size	Number	Reference
			GAS	> 3 months	Ser/Ser + Ser/Cys	0.002	6.4	162	229
			BPRS	10 weeks	Ser/Ser + Ser/Cys	NS	0.5	66	230
			Clinical impression	> 28 days	Ser/Ser + Ser/Cys	NS	1.8	76	231
		330G>T, 244C>T	Clinical impression	> 28 days	Ser/Ser + Ser/Cys	NS	No data	163	225
	HTR3A	178C>T, 1596A>G	GAS	> 3 months	T178-G1596, C178-A1596	NS	1.1	266	232
	HTR3B	CA repeat	GAS	> 3 months	2/2	NS	1.7	266	232
	HTR5A	-19G>C	GAS	> 3 months	G/G	NS	1.4	269	233
		12A>T	GAS	> 3 months	A/A	NS	1.6	269	233
	HTR6	267C>T	Decrease in BPRS	> 8 weeks	T/T	0.04	51 vs 30%	99	234
			BPRS/CGI	> 6 months	T/T	NS	1.8	185	235
Histamine receptor	HRH1	Several	GAS	> 3 months	Several	NS	No difference	158	236
	HRH2	Several	GAS	> 3 months	Several	NS	No difference	158	236
		1080G>A	Clinical impression	> 28 days	G/G	NS	No data	163	225
Glutamate receptor	GRIN2B	2664C>T	BPRS	> 8 weeks	T/T	NS	2.1	100	237
Neurotrophic factor	BDNF	Val66Met	BPRS	> 8 weeks	Val/Val	NS	1.5	93	238
Apolipoprotein	APOE	Epsilon 4 allele	Decrease in BPRS	> 8 weeks	Carrier of epsilon 4	NS	36 vs 31%	95	239

Ins/Del, Insertion/Deletion; 5'-UTR, 5' untranslated region.

Scale: Rating scale used for response assessment: BPRS: brief psychiatric rating scale; CGI: clinical global impression scale; clinical impression: subjective clinical impression, without validated rating scale; GAS: global assessment scale; Time: time until response was defined.

Effect size: If data available, odds ratio was calculated or taken from the studies. Unless, mean percent decrease in rating score or mean end rating score was taken.

^aIn one study, mean absolute decrease in BPRS was given, since data on BPRS baseline were not available. Sign.: statistical significance (P-value). NS = nonsignificant.

Norepinephrinergic system

Antidepressant efficacy is mediated not only by serotonin reuptake inhibition, but also by inhibition of the norepinephrine uptake. Norepinephrine reuptake inhibitors (NRIs) with variable selectivity are desipramine, lofepramine, viloxazine, maprotiline, oxaprotiline, and reboxetine. Several genetic variants have been identified in the human norepinephrine transporter gene; however, no association has been found so far between those polymorphisms and either bipolar disorder and schizophrenia.²⁹⁴ It has not yet been studied if genetic polymorphisms in the norepinephrine transporter gene have influence on antidepressant drug response especially of the NRIs.

Candidate genes beyond the neurotransmitter axes

Antidepressant response

Associations with response to various antidepressant drugs were observed with the ACE 287-bp insertion/deletion polymorphism,^{176,177} with the G-protein $\beta 3$ subunit (GNB3).¹⁸² Both genes play an important role in regulation of blood pressure, and there is a well-known relationship between depression and cardiovascular disease. In turn, depression is a major risk factor for the development of coronary artery disease. In fact, it was shown recently by the authors, that the same allelic combination of ACE and GNB3 that have

Table 6 Genetic data on adverse drug reactions (ADR)

Type of ADR	Gene	Polymorphism	Drug	Scales	Variant at risk	Significance	Effect size	Sample size	Author	
Tardive dyskinesia	DRD2	TaqIA	Typical antipsychotics	AIMS	A2/A2	0.001	5	83	242	
			Various	AIMS	A2/A2	NS	1.5	200	243	
		Ser311Cys	Various	AIMS	Cys/Cys, Ser/Cys	NS	1.3	200	243	
				AIMS	Cys/Cys, Ser/Cys	NS	1.4	317	244	
			Various	AIMS	Ins/Ins	NS	1.9	200	243	
		-141C Ins/Del Nine SNPs	Various	AIMS	EPS/BARS/AIMS	Haplotypes	NS	1	665	245
			Various	AIMS	EPS/BARS/AIMS	Haplotypes	NS	1	665	245
		DRD3	Ser9Gly	Various	No data	Gly/Gly	NS	2.5	71	246
				Typical antipsychotics	AIMS	Gly/Gly	0.002	14 vs 4 (3.5)	112	247
				Various	TDRS	Gly/Gly	NS	0.5	157	248
	Various			AIMS	Gly/Gly	0.018	6.5	100	249	
	Various			AIMS	Gly/Gly	NS	1	131	250	
	Various			AIMS	Gly/Gly	0.014	0.4	115	251	
	Various			AIMS	Gly/Gly	0.012	0.8	317	244	
	Various			Several	Gly/Gly	0.02	1.33	780	252	
	Various			AIMS/EPS	Gly/Gly	0.02	0.7	116	253	
	Various			AIMS	Gly/Gly	0.028	6.1	113	254	
	Various			AIMS	Gly/Gly	NS	0.2	94	255	
	Various			AIMS	Gly,CYP17A2	0.03	12.2 vs 3.7	113	256	
	DRD3 + Cyp17			Ser9Gly	Various	AIMS	Gly,CYP17A2	0.03	12.2 vs 3.7	113
		Various	AIMS		Gly,CYP17A2	0.03	12.2 vs 3.7	113	256	
		Various	AIMS		Gly,CYP17A2	0.03	12.2 vs 3.7	113	256	
		Various	AIMS		Gly,CYP17A2	0.03	12.2 vs 3.7	113	256	
Various		AIMS	Gly,CYP17A2		0.03	12.2 vs 3.7	113	256		
Various		AIMS	Gly,CYP17A2		0.03	12.2 vs 3.7	113	256		
Various		AIMS	Gly,CYP17A2		0.03	12.2 vs 3.7	113	256		
Various		AIMS	Gly,CYP17A2		0.03	12.2 vs 3.7	113	256		
HTR2A	102T>C	Atypical antipsychotics	AIMS	C/C,C/T	NS	1.3	136	257		
		Various	AIMS	C/C,C/T	0.038	2.1	221	258		
		Various	AIMS	C/C,C/T	0.01	2.5	121	259		
		Various	AIMS	C/C,C/T	0.01	2.5	121	259		
	His452Tyr	Atypical antipsychotics	AIMS	His/His	NS	2.2	136	257		
		Various	AIMS	His/His	NS	1.3	120	259		
	1437A>G	Atypical antipsychotics	AIMS	G/G	NS	1.1	136	257		
		Various	AIMS	G/G	0.01	2.5	121	259		
HTR2C	697G>C 759C>T Cys23Ser	Various	AIMS	C allele	>0.05	2.8	92	260		
		Various	AIMS	T allele	NS	2.4	92	260		
		Various	AIMS	Ser/Ser + Ser/Cys	0.03	2.1	115	261		
HTR6 SerT ACE OPRM1	267C>T 44bp Del 287bp Ins/Del 118A>G	Various	AIMS	C/C	NS	1	173	262		
		Various	AIMS	I/I	NS	1.9	188	200		
		Various	AIMS/EPS	I/I	NS	1.4	113	263		
		Various	AIMS	118A allele	0.04	1.8	216	264		

Table 6 (Continued)

Type of ADR	Gene	Polymorphism	Drug	Scales	Variant at risk	Significance	Effect size	Sample size	Author
	OPRD1	921T>C	Various	AIMS	921 T allele	NS	1	216	264
	SOD	Ala9Val	Various	AIMS	Val/Val	0.04	4.1	192	265
			Various	AIMS	Val/Val	NS	1.4	101	266
			Various	AIMS	Val/Val	NS	1.4	94	255
	ESR1	PvuII/XbaI	Various	AIMS	P/P	NS	0.6	180	267
Hypersalivation	ADRA2A	1291C>G	Clozapine	UKU hypersalivation	C/C	NS	1.5	97	208
Weight gain	HRH1	Glu349Asp	Clozapine	BMI	Glu/Asp	NS	4.3 vs 2.3	88	268
	SerT	Several	Clozapine	BWC	I/I	NS	2.1 vs 2.5	93	201
	HTR2A	102T>C	Clozapine	BWC	CC	NS	1.5 vs 2.6	93	201
	HTR2C	68G>C	Clozapine	BWC	CG	NS	2.0 vs 2.4	93	201
		-759C>T	Clozapine	BWC	CC	NS	0.7	80	269
			Clozapine	Change in BMI	CC	0.02	1.1 vs 0.3	32	270
			Chlorpromazine/ Risperidone	BWC	CC	0.001	6	117	271
	HTR6	267C>T	Clozapine	BWC	TT	NS	1.5 vs 2.4	93	201
Nausea	SerT	44bpDel	Fluvoxamine	UKU nausea	I/I	NS	2.6	66	197
	VNTR	VNTR	Fluvoxamine	UKU nausea	12/12	NS	2	66	197
	TPH	218A>C	Fluvoxamine	UKU nausea	CC	NS	0.5	66	197
Mania	SerT	44bp Del	Antidepressants	Mania	s/s	0.002	7.9	56	196
	VNTR	VNTR	Antidepressants	Mania	12/12	NS	2.1	54	196
Akathisia	DRD3	Ser9Gly	Typical antipsychotics	BARS	Gly/Gly	0.02	8.1	150	272
Insomnia	SerT	44bpDel	Fluoxetine	Insomnia	s/s	0.005	12	36	198
Unspecific	DRD4	12bp repeat, 13bpDel, Gly11Arg, 48bp repeat	Clozapine	Various	Various	NS	1	149	215
	HTR2A	102T>C	Paroxetine	Adverse event index rating	C/C	0.001	64 vs 49	122	273
	HTR2C	Cys23Ser	Clozapine	ECG abnormalities	Ser, Cys	NS	1	152	231
Neuroleptic malignant syndrome	DRD2	TaqI A Polym	Various	NMS	A1/A1, A1/A2	0.04	10.5	153	274
			Various	NMS	A1/A1, A1/A2	NS	1	182	275
		Ser311Cys	Various	NMS	Gly/Gly	NS	3	180	276
		141C Ins/Del	Various	NMS	Ins/Del, Del/Del	NS	0.6	180	276

HTR2A	1354C>T 74C>A	Various Various	NMS NMS	C/T C/C	NS NS	No data No variant	200 200	²⁷⁷ ²⁷⁷
HTR1A	659G>T	Various	NMS	G/G	NS	No variant	200	²⁷⁷
COMT	Val158Met	Various	Smooth pursuit	Met/Met	0.005	0.2	73	²⁷⁸
DRD3	Ser9Gly	Various	Fixation disturbance	Ser/Ser	0.02	4	119	²⁷⁹

VNTR: Variable number of tandem repeats; Ins/Del, Insertion/Deletion; 5'-UTR, 5' untranslated region; MTR, mitochondrial targeting sequence.

Scale: AIMS: abnormal involuntary movement scale; EPS: Simpson Angus rating scale for extrapyramidal side effects; UKU: Urdvalg for kliniske undersogelser (UKU) side effects rating scale; BMI: body mass index; BWC: body-weight change; BARS: Barne's akathisia rating scale; HSIDS: Hillside Simpson Dyskinesia Scale; TDRS: tardive dyskinesia rating scale.

Effect size: If data available, odds ratio was calculated or taken from the studies. Unless mean percent decrease in rating score or mean end rating score was taken.

Sign.: statistical significance (P-value). NS = nonsignificant.

No variant: No variant allele was found in the study (only wild type).

been shown to increase the risk for myocardial infarction²⁹⁵ increase the vulnerability for depressive disorder.²⁹⁶

The reason why most genetic variability within pharmacodynamic elements did not turn out to be highly predictive of favorable antidepressant treatment response might be that most studies focused on short-time effects of antidepressants such as changes in the serotonin- or noradrenaline-pathways. There is growing evidence that long-term antidepressant treatment enhances structural changes in neuroplasticity, and genes involved in neurotrophic signaling cascades, might act as antidepressant targets.²⁹⁷ Future studies on genetic variability in antidepressant treatment response should focus on these systems, which in fact could be the common final pathway of different antidepressant strategies (irrespective of whether the drug used is primarily serotonergic or noradrenergic).

Antipsychotic response

Methylenetetrahydrofolate reductase (MTHFR) gene was studied in relation to antipsychotic drug therapy.²⁹⁸ A missense mutation (677C>T) in the MTHFR gene was previously found to be associated with schizophrenia,²⁹⁹ and a significant over-representation of the T allele in responders to antipsychotic therapy was found compared to nonresponders.²⁹⁸

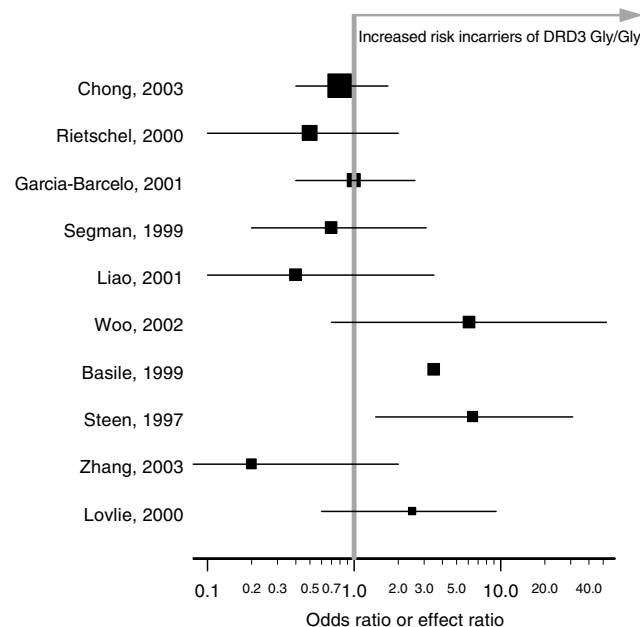


Figure 7 Impact of the DRD3 Ser9Gly polymorphism for the risk to develop tardive dyskinesia during treatment with typical antipsychotics. The squares indicate the risk of carriers of the Gly/Gly genotype to develop tardive dyskinesia and the horizontal lines depict the 95% confidence intervals of these odds ratios. Although some studies with small sample size indicated a relevant impact of this DRD3 polymorphism, a review of all published studies does not indicate that the DRD3 polymorphism predicts tardive dyskinesia.

Catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO) enzymes are involved in metabolic inactivation of several neurotransmitters. Within the COMT gene, a G to A transition at codon 158 resulting in a Val158Met amino-acid exchange is responsible for 3–4-fold lower enzyme activity in Met/Met carriers compared to wild type.³⁰⁰ For the MAO gene, a VNTR located in the upstream regulatory region was described to affect enzyme activity with lower activity in carriers of only three repeat elements in comparison to four.³⁰¹ Both functional polymorphisms were studied with regard to antipsychotic drug response, and the Met/Met genotype of the COMT gene was found to be associated with nonresponse to at least two antipsychotic drugs. The MAO gene promoter polymorphism showed an additional synergistic effect with a six-fold higher risk to be a nonresponder found in patients with genotypes predicting low activity of both enzymes than in patients with the wild-type genotype combination (COMT Met/Met and MAO 3/3 vs COMT Val/Val and MAO 4/4, odds ratio 6.1).³⁰²

BDNF is involved in the neurodevelopment of dopaminergic-related systems. A dinucleotide repeat polymorphism is located 1040bp upstream of the transcriptional site.³⁰³ Allele distribution differed significantly in treatment-responding patients compared to refractory patients with an excess of (L)-alleles (172–176bp) in the treatment responders.³⁰⁴ Another polymorphism is located in the coding region and causes a Val166Met amino-acid substitution. In human subjects, the Met allele was associated with poorer episodic memory, and abnormal hippocampal activation.³⁰⁵ The response to clozapine was studied in patients with regard to the Val166Met polymorphism but no association was found.²³⁸

Polymorphisms in free radical detoxification might be particularly relevant for adverse events caused by haloperidol, which has reactive metabolites. An association of a polymorphism in manganese superoxide dismutase (SOD2) was found to be associated with tardive dyskinesia,²⁶⁵ but replication failed.²⁶⁶

Hypersalivation is a common side effect of clozapine, which might be caused by its β 2-adrenoceptor-blocking effects.³⁰⁶ Thus, genetic polymorphisms within the β 2-adrenoceptor gene might be associated with altered susceptibility to hypersalivation; however, no association has been observed so far.²⁰⁸

There are several additional adverse drug reactions, for which susceptibility caused by genetic mechanisms are not yet elucidated. A variety of psychotropic drugs are associated with cardiac side effects, in particular with iatrogenic prolongation of the QT interval of the electrocardiogram, which in turn is associated with torsade-de-pointes arrhythmia. Tricyclic antidepressants, such as imipramine and amitriptyline, and phenothiazine antipsychotics, such as thioridazine, inhibit cardiac potassium channels.³⁰⁷ Individual risk for drug-induced prolongation of the QT interval was shown to be related to genetic variants in genes encoding cardiac K⁺-

channels, such as the HERG gene encoding for a K⁺ channel subunit.³⁰⁸

Several recently published studies on schizophrenia focus on susceptibility genes for schizophrenia, which have shared effects on synapses, such as glutamatergic, GABAergic, cholinergic, and monoaminergic synapses.³⁰⁹ Polymorphisms in these genes (eg neuregulin, dysbindin, COMT, D-amino acid oxides (DAAO), regulator of G-protein signaling 4 (RGS4), and proline dehydrogenase (PRODH) may be candidates for prediction of antipsychotic therapeutic response, and will certainly be addressed in future studies.

Integrated multigene and multifactorial approaches

Promising efforts have been made to test for the best predictive value of combinations of polymorphisms in context of genetic prediction of response to clozapine. A set of six from 19 genetic polymorphisms was extracted showing the strongest association with clozapine response in a sample of 200 patients;³¹⁰ however, the exciting finding of 76% success in the prediction of clozapine response could not be replicated by others in a sample of 163 schizophrenic patients.²²⁵ This illustrates the major problem of type I error adjustment in pharmacogenomic studies. Usually, it is a rational and necessary approach to consider multiple candidate genes and to consider their gene–gene and gene–environment interactions, but this exploratory approach results in substantial increases in the type I error.

As drug response is just as complex a phenotype as disease susceptibility, it is probable that genetic variability will derive not only from genotypes in the translated gene regions, but also from variability in gene expression and regulation. Genetic mechanisms on the level of drug metabolism and transport as well as in drug target structures such as neurotransmitter receptors and transporter molecules have to be systematically studied for their predictive value in terms of antidepressant drug response. This is a necessary foundation for the development of clearcut therapeutic strategies. Individualized medicine is the overall goal of pharmacogenetic research. A systematic pharmacogenomic approach for optimization of antidepressant drug treatment is based on several levels: (1) identifying and validating the candidate genes involved in drug response, (2) developing a commercially viable pharmacogenetic test system for bedside-testing of patients' individual response profiles, and (3) providing guidelines for pharmacogenetic-based individualized drug therapy in the form of therapeutic strategy flow-charts and genotypic specific dose recommendations.

Conclusions

Pharmacogenetic knowledge will only be translated into daily clinical decision-making when it becomes

scientifically possible to provide relatively specific therapeutic recommendations. Therefore, this review intended to integrate pharmacogenetic results from clinical studies on drug response and pharmacokinetic variability into dose adjustments and therapeutic strategies. In terms of pharmacokinetic variability, quantitative dose adjustments based on genotypes can already be calculated for many antidepressants and antipsychotics. However, the actual outcome and benefit of pharmacogenetic individualization of drug therapy will have to be supported by future prospective studies, leading to dose recommendations that will then have to be validated.

The pharmacodynamic aspects of psychotropic drug action, including the functional consequences of polymorphisms in neurotransmitter receptors, transporters, and molecules involved in signal transduction, cannot yet be easily translated into treatment recommendations. This is partly due to difficulties in replication of findings from association studies in prospective trials from diverse populations, and also might be due to the key problem of multigenetic influences. Rather than large effects given by single polymorphisms, multigenetic interactions and gene-environment interactions will have to be considered. Therefore, in the future, haplotype analyses and multigenetic analyses with sufficient power (adequate sample size and high quality of phenotypic data) might reveal the genotypes that predict clinical responses, including susceptibility to adverse drug reactions. We are optimistic that progress in this field will integrate excellence in clinical research and phenotypic characterization, genomic science, and bioinformatics to yield in the not-too-distant future a body of reliable data that will eventually guide clinical pharmacology and medical practice.

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