13 Metabolism of Psychotropic Drugs

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13.1 SUMMARY

The major depressive disorder schizophrenia and related disorders are among the most important causes of death and disability worldwide [1]. These disorders are highly prevalent, typically chronic or recurrent conditions with a substantial impact on public health. Therapy with antidepressant drugs is the standard of care for clinical depression; likewise, therapy with antipsychotics is required for schizophrenia.

The most important enzymes in psychotropic drug metabolism are the cytochrome P450 enzymes CYP2D6, CYP2C19, or CYP2C9. The functional impact of other drug-metabolizing enzymes including CYP1A2, CYP2A6, CYP2B6, CYP3A4, -5, and -7 or phase II enzymes in psychopharmacology is less, but some agents are cleared predominantly by these latter pathways.

The metabolism of psychotropic drugs may be assessed by *in vitro* studies and/or with *in vivo* pharmacokinetic studies. The clinical importance of drug metabolism is mainly determined by alteration of the individual activity of a relevant drug-metabolizing enzyme. This is frequently the case in drug–drug interactions, leading to enzyme inhibition or enzyme induction. Alternatively, individual patient

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factors, such as pharmacogenetic polymorphisms, may contribute to variability in CYP isozyme activity.

Owing to the discrepancy between *in vitro* predictions of CYP-mediated metabolism and *in vivo* results on drug exposure, drug metabolism from *in vivo* studies will be preferentially presented in this chapter. A multitude of clinical metabolism data for psychotropic drugs exists because of the recognized importance of individual differences in drug exposure in clinical practice. As many psychotropic drugs are metabolized to equally active metabolites [2], more than one CYP isoform may be important in metabolism and exposure data of both metabolite and parent drug have to be taken into account. For many antidepressants or antipsychotic drugs, therapeutic drug monitoring is practiced regularly.

In the following pages, specific metabolism of antidepressant and antipsychotic drugs will be presented for the main CYP enzymes such as CYP2D6, CYP2C19, CYP2C9, and CYP1A2 (Table 13.1). Further, those metabolic pathways that are not typically used will be described for specific psychotropics. Special focus will be paid on the impact of genetically caused variations in enzyme activity and on drug–drug interactions, leading to changes in enzyme activity and drug metabolism (Table 13.2).

13.2 PSYCHOTROPIC DRUGS WITH METABOLISM BY CYP2D6

13.2.1 Antidepressants

13.2.1.1 Tricyclic Antidepressants. Depending on the amine side chain, tricyclic antidepressants (TCAs) can be classified into tertiary TCAs and secondary TCAs. Tertiary TCAs include amitriptyline, clomipramine, doxepin, trimipramine, and imipramine; and secondary TCAs include desipramine, nortriptyline, and protriptyline. Tertiary TCAs are first demethylated into secondary TCAs, which are further hydroxylated and conjugated. In the liver, CYP2D6 mediates the hydroxylation reactions [3–7] and CYP2C19 is responsible for demethylation of the parent drug. In certain cases, CYP3A4 may also act as a minor pathway for oxidative metabolism. Both hydroxylated and demethylated metabolites are pharmacological active, and the demethylated metabolites are tricyclic drugs in themselves, for example, nortriptyline and desipramine (desmethyl metabolites of amitriptyline and imipramine, respectively). Nortriptyline and desipramine are mainly hydroxylated to less active or inactive metabolites [5,8]. For dose adaptation, the sum of pharmacologically active moieties (parent drug + demethylated metabolite) must be taken into account if data are available from therapeutic drug monitoring.

Stereoselective metabolism by CYP2D6 has been reported for trimipramine metabolism toward the less active L-trimipramine [6]. For doxepin, CYP2D6 polymorphisms affects only the clearance of the less active E-isomer [9]. For these two tricyclics, dose adjustments are usually based on the active drug compound (active enantiomers or isomer plus demethylated metabolite).

For several TCAs, no data on the specific enzymes involved in hydroxylation or demethylation reactions are available. However, structural similarity to other tricyclics such as imipramine implicates that CYP2D6 and CYP2C19 might be involved in metabolism of these tricyclics also.

An extremely high clearance was described for a few CYP2D6 ultrarapid metabolizers (UM) from studies with nortriptyline and desipramine, which are heavily

TABLE 13.1 List of Psychotropic Drugs and their Metabolic Pathways (Modified and Extended from [59])

	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, and CYP2C9
Antidepressant drugs	Iprindole Isocarboxzcid 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	Chlorpromazine Remoxipride	Amisulpride Sulpiride	Raclopride	Bromperidol Iloperidone	Aripiprazole Clopenthixol

(*continued overleaf*)

TABLE 13.1 (*Continued*)

	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, and CYP2C9
	Fluphenazine Fluspirilen Mazapertine Nemonapride Pipamperon Promethazine Prothipendyl Trifluperidol Triflupromazine	Sertindole Melperone			Perospirone Quetiapine Ziprasidone Clozapine	Clozapine[a] Flupenthixol Haloperidol Levomepromazine[a] Olanzapine Perazine Perphenazine Pimozide[a] Risperidone Thioridazine Zotepine Zuclopenthixol
Anxiolytic drugs	—	—	—	Lorazepam Oxazepam Temazepam	Alprazolam Buspirone Clonazepam Flunitrazepam Midazolam Triazolam	Diazepam
Psychostimulants	—	—	—	—	Armodafinil Modafinil	Amphetamines Atomoxetine Methylphenidate

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

TABLE 13.2 Psychotrophics Causing Clinically Relevant Drug–Drug Interactions Via CYP Inhibition

Inhibitory Potency	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Strong[a]	Fluvoxamine	—	—	Bupropion Fluoxetine Paroxetine	—
Moderate[b]	—	—	—	Duloxetine Moclobemide Sertraline	Nefazodone
Weak[c]	Moclobemide	Fluvoxamine	Fluvoxamine Fluoxetine Moclobemide Modafinil	Chlorpromazine Citalopram Clomipramine Clozapine Doxepin Escitalopram Fluphenazine Haloperidol Levomepro-mazine Perphenazine Pimozide Risperidone Venlafaxine	Fluvoxamine Fluoxetine Paroxetine

[a]Greater than fivefold increase in AUC or >80% decrease in clearance.
[b]Two- to fivefold increase in AUC or 50–80% decrease in clearance.
[c]1.25- to 2-fold increase in the plasma AUC, 20–50% decrease in clearance or *in vitro* data only.

dependant on CYP2D6 for their metabolism. For nortriptyline, one UM carrying 13 active CYP2D6 genes was included, which was responsible for the very high mean of clearance in this group [10,11]. The frequency of CYP2D6 gene duplications varies between 10% and 50% in certain ethnic populations, including Eastern African, Arabian, and Pacific populations. In Europe, the UM phenotype is relatively rare at ~1–5% [12].

TCAs are known inhibitors of CYP1A2, CYP2C19, and CYP2D6, although the rank order varies between individual drugs. Nortriptyline and desipramine are usually considered as the least problematic of TCAs in terms of drug interactions since they are weak inhibitors of CYP2D6. The tertiary amine TCAs potently inhibit both CYP1A2 and 2 C19 and are therefore more complicated to use with other drugs.

13.2.1.2 Selective Serotonin Reuptake Inhibitors. Some SSRIs (selective serotonin reuptake inhibitors) such as fluoxetine and paroxetine are potent inhibitors of CYP2D6 activity. These drugs also rely on CYP2D6 for their own oxidative metabolism. Therefore, multiple dosing causes decreased CYP2D6-mediated metabolism of the drugs themselves. Multiple dosing of these agents can also convert extensive metabolizers (EMs) of CYP2D6 into slow metabolizers [13–16]. Besides CYP2D6, paroxetine inhibits CYP2B6 quite strongly and causes a fourfold increase in plasma concentration of desipramine, a drug metabolized both via CYP2B6 and 2D6, when coadministrated

[17]. Fluoxetine and its long-lived metabolite norfluoxetine are formed by CYP2D6 but also via other CYPs (2 C9, 2 C19, and 3A4). Owing to these alternative metabolic pathways, the plasma levels of fluoxetine are not usually affected by selective CYP inhibitors. Both fluoxetine and norfluoxetine are potent inhibitors of CYP2D6. However, fluoxetine and norfluoxetine inhibit also other CYPs besides CYP2D6. They have been shown to increase the concentrations of risperidone (a substrate of CYP2D and 3A4) when concomitantly used.

Sertraline and its active metabolite desmethylsertraline are partially metabolized by CYP2D6. Sertraline is considered to be a potent inhibitor of CYP2D6 when its daily doses exceed 150 mg. For sertraline and citalopram, no influence of CYP2D6 polymorphisms on pharmacokinetic parameters have been detected [13,18].

13.2.1.3 Other Antidepressants. Bupropion is primarily cleared by CYP2B6 and its metabolites are known to be potent inhibitors of CYP2D6. After treatment, phenotypically EMs of CYP2D6 appear pharmacokinetically similar to poor metabolizers (PMs) [19,20]. Thus, care should be exercised when bupropion is used concomitantly with drugs metabolized by CYP2D6, especially those with a narrow therapeutic index. In about 100 subjects, no major effects of CYP2B6 genotypes on bupropion pharmacokinetics were identified [21].

There are contradictory data regarding the effects of CYP2D6 poor metabolism status on the tetracyclic antidepressant maprotiline. Patients receiving monotherapy with 150 mg maprotiline showed no differences in steady state concentrations because of the debrisoquine metabolizer status [22]. A study with healthy volunteers receiving 100 mg maprotiline over seven days revealed differences similar to those detected in tricyclics [23].

For mianserin, CYP2D6 mediates enantioselective hydroxylation of the more active *S*-(+)-mianserin. For the racemic drug mirtazapine, *S*-(+)-mirtazapine clearance significantly depends on CYP2D6 activity but no such effect on *R*-(−)-mirtazapine clearance was found [24]. For moclobemide, reboxetine, and trazodone, CYP2D6 polymorphisms do not seem to have a major influence on metabolism in humans [25–30].

Venlafaxine is a chiral drug with both enantiomers transformed by CYP2D6 to the equipotent *O*-desmethylvenlafaxine [31–33]. A higher risk for cardiotoxic events and other adverse drug effects may exist in individuals lacking CYP2D6 activity [34]. Cases of severe arrhythmias have been reported in four patients treated with venlafaxine who all were CYP2D6 PMs [35]. On the other hand, efficacy was improved in individuals with high CYP2D6 activity in a metaanalysis of four studies [36].

13.2.2 CYP2D6 in the Metabolism of Antipsychotics

The influence of CYP2D6 polymorphisms on antipsychotic drug metabolism has been studied in humans for aripiprazole, clozapine, flupentixol, haloperidol, levomepromazine, olanzapine, perazine, perphenazine, pimozide, risperidone, thioridazine, and zuclopenthixol. The antipsychotic drug aripiprazole was studied for polymorphic CYP2D6 metabolism before marketing, and a 60% higher exposure of the total active moieties (parent drug and dehydroaripiprazole) was detected in PMs compared to EMs (aripiprazole product insert). In an observative study with schizophrenic patients receiving different doses, similar dependence on the genetically defined CYP2D6 phenotype was detected for flupentixol as well as for perazine [37].

For thioridazine, a recent study has revealed a 30% higher drug exposure in individuals who are CYP2D6 PMs [38]. This result corresponds to data from a study in healthy volunteers administering single doses of the drug [39], but it is in contrast to another study where smaller differences were found [40].

For haloperidol, CYP2D6 deficiency leads to a 60–70% lower clearance indicating that CYP2D6 is a principal pathway [9,41] but other studies have not reported significant CYP2D6 differences [42,43]. A significantly higher risk for extrapyramidal side effects in PMs was observed probably because of higher levels of the metabolite, the reduced form of haloperidol. Patients with UM genotype had the worst clinical outcome measured by the positive and negative symptoms scale which might be due to subtherapeutic haloperidol concentrations [9].

For perphenazine, thioridazine, and zuclopenthixol, steady state plasma drug concentrations decreased and resulting pharmacokinetic parameters were affected relative to those following single dose administration because of autoinhibition of CYP2D6. For olanzapine, although CYP1A2 is mainly involved in metabolism, in a comparative clinical study, steady state concentrations were correlated with CYP1A2 activity (influenced by smoking) but not by the CYP2D6 genotype [44]. Because zuclopenthixol is only metabolized partly via CYP2D6 and is also sulfoxidated and glucuronidated, CYP2D6 genotype seems to be less important [45].

Hydroxylation of risperidone at the 9-position is the most important metabolic pathway mediated mainly by CYP2D6 [46–49]. The total sum of plasma risperidone and 9-OH risperidone (paliperidone) is usually used as a determinant for risperidone pharmacological activity in therapeutic drug monitoring [50]. Since the sum of risperidone and 9-OH risperidone does not differ between CYP2D6 PMs and EMs, CYP2D6 polymorphism was hypothesized not to be important [50–53]. However, several studies have found an impact on 9-OH-risperidone plasma levels and CYP2D6 activity on risperidone effects. For example, in a recent report with children with pervasive developmental disorder treated with risperidone, serum prolactin level was positively correlated with the number of functional *CYP2D6* genes and serum 9-OH risperidone [54]. This and other studies have led to the proposal that the plasma profile for CYP2D6 PMs (characterized by higher risperidone than 9-OH risperidone concentrations) may be more "toxic" than for other phenotypes [55]. Accordingly, in one large study of adverse drug effects in 360 patients, PMs had more than a threefold increased risk (odds ratio, OR = 3.4) for significant risperidone adverse drug reaction (ADRs) and a sixfold increased risk of discontinuing risperidone (OR = 6.0) because of ADRs than EMs [56]. Thus, in the case of risperidone, clinicians should consider treating CYP2D6 PMs with an alternative antipsychotic drug or careful dosing under plasma concentration monitoring.

13.2.3 CYP2D6 in the Metabolism of Psychostimulants and Atomoxetine

Methylphenidate and amphetamines have a complex metabolism in which CYP2D6 has been postulated to play only a minimal role. In the case of atomoxetine, CYP2D6 is the principle enzyme responsible for the elimination of this drug, and atomoxetine itself is not known to inhibit any CYP. CYP2D6 metabolizer status affects the efficacy and tolerability of atomoxetine treatment, and coadministration of potent inhibitors of CYP2D6 results in altered pharmacokinetics similar to CYP2D6 PMs [57,58]. Thus, potent inhibitors of CYP2D6 (e.g., paroxetine and fluoxetine) should be coadministrated with caution and careful monitoring of the treatment should be exercised.

13.3 IMPACT OF CYP2C19

There are currently over 50 available medications that are primarily metabolized by the CYP2C19 enzyme. The 2C19 substrate medications include widely used pharmaceuticals, such as most of the proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, and pantoprazole), proguanil, and phenytoin, and some commonly prescribed psychotropic medications. A number of antidepressants are metabolized primarily or partially by CYP2C19, including amitriptyline, clomipramine, citalopram, and escitalopram [59]. In contrast, doxepin, imipramine, nortriptyline, sertraline, and moclobemide have substantial, but not exclusive, 2C19 substrate metabolic clearance.

Sertraline is metabolized by five cytochrome P450 enzymes (i.e., CYP2D6, CYP2C9, CYP2B6, CYP2C19, and CYP3A4). Consequently, the inhibition of any single CYP does not result in a major change in the pharmacokinetics of sertraline. However, CYP2C19 PMs have been shown to have higher serum levels of sertraline at a standard dose than do normal metabolizers. CYP2C19 phenotype may be of relevance for the clinical outcome of sertraline treatment, but thus are no unambiguous recommendations for dose adjustments available. The inhibition of CYP2B6 is reported to have a similar effect. The contribution of CYP2C9 and CYP3A4 to sertraline metabolism is minimal unless there is impaired CYP2C19 and CYP2B6 metabolic activity. The major metabolite of sertraline, desmethylsertraline, is a weak serotonin transporter reuptake inhibitor and does not have an important clinical pharmalogical effect. Venlafaxine is minimally metabolized by the 2C19 isozyme.

The 2C19 isozyme plays a relatively circumscribed role in the metabolism of antipsychotic medication. It is substantially involved in the metabolism of clozapine and plays a minimal role in the metabolism of thioridazine. The 2C19 isozyme plays a primary role in the metabolism of diazepam. Diazepam is metabolized predominantly by 2C19 to nordiazepam, and then by 3A4 to oxazepam, which is then conjugated and excreted in urine. Diazepam is also metabolized to temazepam and then to oxazepam via CYP3A4. Although diazepam clearance has been shown to be decreased in CYP2C19 PMs or when inhibitors of CYP2C19 are concomitantly administrated, the clinical impact is generally considered to be relatively small. The role of CYP2C19 in the metabolism of other benzodiazepines has not been well demonstrated.

13.4 IMPACT OF CYP2C9

13.4.1 Antidepressants

The cytochrome P450 2C9 gene (CYP2C9) codes for an enzyme that facilitates the oxidation of about 100 medications. These include drugs with a narrow therapeutic index, such as warfarin and phenytoin, as well as many of the nonsteroidal inflammatory drugs (NSAIDs). CYP2C9 is a polymorphically expressed enzyme, and some of the SNPs (single nucleotide polymorphisms) within this gene have been identified as contributors to the wide interindividual variation in the pharmacokinetics of certain drugs. The main variant alleles **2* and **3* are present in roughly 35% of Caucasian population, but they are much less prevalent in Asian and black populations.

Amitriptyline and fluoxetine are substantially metabolized by CYP2C9, and this CYP can play an important role in clearance if other metabolic pathways are

nonfunctional. Amitriptyline is demethylated by both CYP2C9 and CYP3A4 to produce nortriptyline, an active metabolite [60]. All existing data show only a minor contribution of CYP2C9 toward the interindividual pharmacokinetic variability of TCAs. Data on amitriptyline is based on *in vitro* studies only, and a small difference in kinetics between carriers of CYP2C9**1/*1* and **3/*3* was shown for trimipramine and doxepin [61]. Amitriptyline is known to be an inhibitor of CYPs, 1A2, 2C19, and 2D6.

Fluoxetine is metabolized primarily via N-demethylation by CYP2D6. Demethylation results in the production of norfluoxetine, which is also biologically active. Fluoxetine is metabolized secondarily by CYP2C9. Given the slow elimination of fluoxetine and the subsequent required secondary clearance of norfluoxetine, fluoxetine has the longest functional half-life of any SSRI antidepressants. In addition to its own metabolism by CYP2D6, fluoxetine is a suicide CYP2D6 inhibitor, which means that a strong and long-lasting CYP2D6 inhibition takes place after several doses of fluoxetine; and as a result, it may participate in drug interactions with other drugs that are metabolized by CYP2D6.

13.5 OTHER ENZYMES OR METABOLIC PATHWAYS

13.5.1 CYP1A2

There are over 40 currently available drugs that are primarily metabolized by the 1A2 isozyme. These include some commonly prescribed psychotropic medications such as antipsychotics clozapine and olanzapine and antidepressants fluvoxamine and mirtazapine. The 1A2 enzyme also plays an important secondary role in the metabolism of other psychotropic drugs when their primary pathways are not functional. This is the case with several TCAs. Besides psychotropics, CYP1A2 has a pivotal role in the metabolism of caffeine, theophylline, naproxen, tacrine, tizanidine, and some triptans such as frovatriptan and zolmitiptan. CYP1A2 is also responsible for metabolic activation of polycyclic aromatic hydrocarbons found in cigarette smoke.

The induction of CYP1A2 by smoking results in increased metabolic clearance and necessitates higher doses to achieve effective pharmacotherapy for drugs relying CYP1A2 [62]. During smoking cessation, the CYP1A2 activity will decrease and accumulation of parent drug will take place if dosing is not adjusted accordingly. Monitoring serum levels of drugs with narrow therapeutic indices (e.g., clozapine) during these transition periods is strongly recommended. The average plasma concentration of clozapine in smokers is about 50% of nonsmokers at the same dose. Seven to 12 cigarettes per day are necessary for maximal induction [63]. Schizophrenia patients smoke up to three times more than the general population and more than most psychiatric patients. When psychiatric hospital units were mandated to become nonsmoking in the United States, newly admitted patients who were smokers and who were taking clozapine had altered clearance of clozapine as CYP1A2 induction "wore off" during an extended stay. An opposite effect occurred on discharge. Many other psychotropics have been shown to have decreased concentrations in smokers: alprazolam, chlorpromazine, duloxetine, fluvoxamine, haloperidol, mirtazapine, olanzapine, and thioridazine.

13.5.1.1 Antidepressant Medications. The only antidepressant that is metabolized primarily by the CYP1A2 enzyme is the SSRI fluvoxamine. It has no active metabolites. It is a pan-CYP inhibitor, and it potently inhibits CYP1A2. Fluvoxamine has shown to raise serum clozapine concentrations drastically (about two- to threefold) whereas ciprofloxacin, a less potent inhibitor of CYP1A2 has a much weaker effect on clozapine metabolism. A recent study suggests that initiating treatment with 50 mg/day of fluvoxamine plus 100 mg/day of clozapine can be utilized with careful monitoring of levels [63].

Additionally, several other antidepressants including duloxetine, clomipramine, and imipramine [64–66] are substantially metabolized by the CYP1A2 enzyme. Mirtazapine and amitriptyline are minimally metabolized by CYP1A2, but the CYP1A2 genotype may be important for the metabolism of these antidepressants if their primary enzymes are inactive.

Duloxetine is an antidepressant that blocks the reuptake of serotonin and norepinephrine. It has also been reported to have an analgesic effect in patients with pain related to diabetic peripheral neuropathy. In addition to CYP1A2, CYP2D6 plays a role in the metabolism of duloxetine [67]. To a lesser extent, duloxetine blocks reuptake of dopamine at the receptors.

Clomipramine is a TCA that has been widely used for the treatment of obsessive-compulsive symptoms. In addition to CYP1A2, clomipramine is metabolized by CYP2C19, CYP3A4, and CYP2D6.

Mirtazapine is an antidepressant with a tetracyclic chemical structure that enhances both noradrenergic and serotonergic neurotransmission. In addition to CYP1A2, mirtazapine is metabolized by CYP2D6 and CYP3A4 [68]. Amitriptyline is a TCA that inhibits serotonin and noradrenaline reuptake almost equally. The major metabolic pathway for amitriptyline is primarily demethylation via CYP2C19 and results in the active metabolite, nortriptyline. Alternative minor pathways for the metabolism of amitriptyline are primary hydroxylation by CYP2D6 and demethylation by CYP1A2, CYP2C9, and CYP3A4 [69].

13.5.1.2 Antipsychotic Medications. The cytochrome P450 enzyme 1A2 catalyzes biotransformation of several antipsychotics [70]. Clozapine and olanzapine are predominantly metabolized by the CYP1A2 enzyme, and chlorpromazine is substantially metabolized by CYP1A2. Thioridazine and haloperidol are minimally metabolized by CYP1A2.

Clozapine was the first atypical antipsychotic. It has one major metabolite, which is also pharmacologically active. CYP1A2 is primarily responsible for clozapine metabolism. However, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 can provide alternative metabolic pathways. Olanzapine is an atypical antipsychotic that is primarily metabolized by CYP1A2 and secondarily by CYP2D6 and is further glucuronidated by uridine diphosphate glucuronosyltransferase (UGTs). Olanzapine does not inhibit or induce the CYP system. Induction of CYP1A2 by cigarette smoking is known to lead to reduced olanzapine concentrations and inhibition of CYP1A2 by fluvoxamine is known to increase olanzapine plasma levels. This latter drug interaction has been used as the basis for a strategy of increasing the concentration of olanzapine in smokers by administering nontherapeutic low dose fluvoxamine to smokers taking olanzapine [71]. Concomitant use of olanzapine with UGT-inhibitor probenecid and a wide spectrum inducer, carbamazepine, has shown

to reduce and increase its clearance, respectively [72,73]. Chlorpromazine was the first phenothiazine used to treat psychotic patients and has minimal effect on the serotonergic pathways. It is metabolized by both CYP1A2 and CYP2D6.

Haloperidol is a typical antipsychotic drug. It is primarily metabolized by CYP3A4 and CYP2D6. However, CYP1A2 also contributes to haloperidol's metabolism, as has been demonstrated by evaluating patients who have received a CYP1A2 inhibitor and subsequently experienced increased serum levels of haloperidol [74].

Thioridazine is a phenothiazine that is a racemic compound with two enantiomers. Both enantiomers are metabolized by CYP2D6, but the CYP1A2 metabolism becomes important for patients who are taking thioridazine and who are poor 2D6 metabolizers.

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 with contradictory results [75–77].

13.5.1.3 Other Drugs. Melatonin, melatonin receptor agonist, ramelteon (used as a treatment for insomnia), and melatonin analog, agomelatine (used as an antidepressant) rely mainly on CYP1A2 for their metabolism. Coadministration with fluvoxamine has shown to lead to significantly increased plasma levels of these drugs [78,79].

13.5.2 Drugs Metabolized by CYP2B6, CYP3A4, and Other Pathways

13.5.2.1 Antidepressants. CYP2B6 is the main metabolic enzyme in bupropion metabolism, and polymorphisms in CYP2B6 may be relevant for bupropion, but the differences due to genotype are small [21]. Certain non-nucleoside reverse transcriptase inhibitors (efavirenz, nelfinavir) and viral protease inhibitors (ritonavir) have been shown to inhibit bupropion metabolism, but convincing documentation concerning the clinical relevance of this interaction is currently lacking.

13.5.2.2 Antipsychotics. For iprindole, isocarboxazid, setiptiline, and viloxazine, elimination occurs mainly via conjugation reactions (glucuronidation, acetylation, and sulfation). The specific phase II enzymes catalyzing these reactions are not known. Renal excretion is the principle route for phenelzine tranylcypromine, and milnacipran. Tianeptine as well as reboxetine seem to be mainly metabolized by CYP3A4 [80]. Buspirone is metabolized by CYP3A4 to the active metabolite, 1-(2-pyrimidinyl)-piperazine (1-PP) [81]. Inhibitors of CYP3A4, for example, diltiazem, erythromycin, grapefruit juice, itraconazole, and nefazodone have shown to greatly increase plasma buspirone concentrations and side effects. Coadministration of buspirone and CYP3A4 inhibitors should be preferably avoided, or the dose of buspirone should be greatly reduced during the concomitant treatment. Buspirone is also vulnerable to potent CYP3A4 inducers such as rifampan and others.

Elimination pathways other than those involving cytochrome P450 enzymes are important for the following antipsychotics: sulpiride, amisulpride, paliperidone (renal excretion), raclopride (glucuronidation, sulfation), and zotepine (flavin-monooxygenases involved). CYP3A4 is the main enzyme involved in metabolism of bromperidole, iloperidone, perospirone, and quetiapine [82,83]. Ziprasidone is metabolized primarily by aldehyde oxidase with a minor contribution of CYP3A4. Wakefulness-promoting drugs armodafinil and modafinil are metabolized mainly

by CYP3A4 and glucuronide conjugation. For chlorpromazine, remoxipride, and sertindole, only *in vitro* data exist on involvement of CYP2D6 [83]. Remoxipride and sertindole were withdrawn from the market because of adverse drug reactions (aplastic anemia and arrhythmia), but sertindole was recently been reintroduced to the European market. Melperone is described as potent inhibitor of CYP2D6, but studies on impact of variability in CYP2D6 activity (through genetic polymorphisms) on melperone metabolism do not yet exist [84].

13.6 CONCLUSIONS

Twenty years ago, a clinician would not have been able to anticipate possible drug interactions involving psychotropics. There has been an avalanche of data about these drugs since then. With the help of the information about the metabolism of psychotropics in this chapter, clinicians are now in a much better position to "predict" possible drug interactions. Further, the information about what drugs demonstrate P450 cytochromal genetic variations provide guidance to clinicians in deciding who would be candidates for P450 CYP genetic testing.

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