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## WHAT IS THE ROLE OF CYP GENOTYPING IN PSYCHIATRY?

#### Abstract

Aim of this article was to summarize the available evidence on the role of genetic variants of the cytochrome P450 (CYP) enzyme system in the metabolism and clinical response to the most commonly used psychotropic drugs. The clinical implications of CYP genotyping procedures in psychiatry were also critically evaluated. Genetic polymorphisms of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 have been reported to cause large interindividual differences in the serum concentrations of many drugs used in psychiatry, in particular antidepressants and antipsychotics. However, the influence of CYP variants on pharmacokinetic parameters of psychotropic drugs has not been associated so far with consistent results on a clinical level, that is, in terms of therapeutic effect and adverse events. Genotyping for allelic variants of CYP2D6 and CYP2C19 can be used to personalize dosing for outliers, i.e., poor metabolizers or ultrarapid metabolizers. Recommendations from practice guidelines describing CYP2D6 and CY2C19 genotyping for dosing some antidepressants and antipsychotics have been recently developed. Genotyping for CYP2D6 and CYP2C19 is currently performed only when issues relating to efficacy, such as non-response, or safety, such as severe adverse effects, occur. In order to better personalize treatment in psychiatry, the best approach is to integrate CYP2D6 and CYP2C19 genotyping and therapeutic drug monitoring (TDM). At present, genotyping for CYP1A2, CYP2B6, CYP2C9 and CYP3A4 may be of interest in an academic context, but has limited clinical utility in psychiatry.

**Key words:** Cytochrome P-450 enzyme system, pharmacogenetics, psychotropic drugs, genotyping.

## Introduction

Psychiatric disorders are a leading cause of disability worldwide and despite important pharmacological advances, are still difficult to diagnose and treat. As with most therapeutic agents, clinical response to psychotropic drugs varies considerably among patients treated with the same dose: from no response at all to severe adverse drug reactions (ADRs). In addition to psychological and social implications, this variability results from the interaction of genetic, personal (e.g., age, sex, diseases) and environmental (e.g., smoking, diet, alcohol habits, concomitant medications) factors that produce interindividual differences in pharmacokinetics and pharmacodynamics<sup>1</sup>.

Pharmacogenetics is the discipline studying the genetic basis leading to individual variation in drug response<sup>2</sup>. Genetic factors may influence drug response at the level of drug-metabolizing enzymes, drug transporters, drug targets and other biomarker genes<sup>3</sup>. One of the man goals of modern drug therapy has been the identification of these gene variants. This has been frequently described as "individualized" or "personalized medicine". On the other hand, the term pharmacogenomics has a broader meaning and consists of the study of the entire spectrum of

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Edoardo Spina espina@unime.it genes that determine drug response, including the assessment of the diversity of human genome sequence and its clinical consequences<sup>2</sup>.

Genetically determined variability in drug metabolism may result in interindividual differences in the pharmacokinetics and plasma/serum concentrations of a given drug. Over the past decades, several polymorphisms associated with drug metabolism have been identified <sup>3</sup>. As most psychotropic agents undergo extensive hepatic metabolism, predictable variations in genes encoding drug-metabolizing enzymes may account for differences in drug efficacy and safety in psychiatric disorders<sup>4</sup>.

The present article reviews the available evidence illustrating the role of genetic variants of the cytochrome P450 (CYP) enzyme system, the most important phase I drug-metabolizing enzymes, in the pharmacokinetics and clinical response to the most commonly used psychotropic drugs and critically evaluates the implications of CYP genotyping techniques in psychiatry. Articles for this review were obtained from a PubMed search with no time limit. Only articles published in peer-reviewed journals were included, while meeting abstracts were excluded.

## The cytochrome P450 (CYP) enzyme system

Most psychotropic medications are highly lipophilic substances and therefore undergo significant biotransformation in the liver. Hepatic metabolism converts non-polar (lipid soluble) drugs into one or polar (hydrophilic) metabolites, this facilitating their elimination in urine or bile. The metabolism of psychotropic drugs involves phase I oxidative reactions, catalyzed via CYP enzymes, followed by phase II glucuronide conjugation, which occurs through UDP-glucuronosyltransferases (UGT)<sup>5</sup>.

The CYP system consists of a superfamily of more than 50 heme-containing mono-oxygenases, located in the membranes of the smooth endoplasmic reticulum in the liver and in many extrahepatic tissues, which are responsible for the phase I oxidative reactions of many drugs, nutrients, environmental toxins and endogenous substances (i.e., steroids, fatty acids, prostaglandins)<sup>36</sup>. Interestingly, these enzymes are also expressed in the brain suggesting a role in the regulation of physiological homoeostasis by biotransformation of endogenous substrates<sup>7</sup>. They are classified into families and subfamilies according to similarities in their amino acid sequence, with each enzyme being designated as CYP followed by a number indicating the family, a letter indi-

cating the subfamily, and another number denoting the specific isoform<sup>8</sup>. The human genome comprises 57 CYP genes divided into 18 families and 44 subfamilies according to sequence homology. The CYP 1 to 3 families are involved in phase I drug metabolism, whereas CYPs 4 to 51 are associated with endobiotic metabolism <sup>3</sup> <sup>8</sup>. CYP1A2, CYP2B6, CYP2C9, CYP2C19, CY-P2D6 and CYP3A4 are the isoforms which play a major role in the metabolism of therapeutic agents <sup>36</sup>. Other CYP isoforms contributing to drug metabolism include CYP2A6, CYP2C8 and CYP2E1. Each CYP isoform is a specific gene product and possesses a characteristic but relatively broad spectrum of substrate specificity. The greater part of CYP isoforms metabolize several drugs and the majority of drugs are metabolized by more than one CYP isoform. There is a significant variability in the expression and activity of CYP isoenzymes as a result of genetic, but also environmental factors.

The human CYP genes are highly polymorphic. A genetic polymorphism is defined as a stable variation in a given locus of the genetic sequence, which is detected in 1% or more of a specific population<sup>2</sup>. These polymorphisms reflect gene insertions and deletions, gene duplications, copy number variations, and single nucleotide polymorphisms (SNPs). Mutations or polymorphisms in genes coding for CYP isoforms can result in enzyme variants with higher, lower or no activity, or occasionally the total absence of the enzyme. These variants may explain a large portion of the manifold interindividual variability in drug metabolism and, therefore, can lead to differences in plasma/serum concentrations and therapeutic response to the administered medications. According to Ingelman-Sundberg et al.<sup>3</sup>, the phenotypes associated with these genetic variants may be classified into four major groups:

- the poor metabolizers (PM), lacking functional enzymes due to defective or deleted genes;
- the intermediate metabolizers (IM), usually carrying 1 functional and 1 defective allele, but may also carry 2 partially functional alleles;
- the extensive metabolizers (EM), carrying 2 functional genes;
- the ultrarapid metabolizers (UM), with more than 2 active genes encoding a certain P450.

The activity of CYP enzymes can be evaluated by the use of phenotyping and/or genotyping tests<sup>9</sup>. Phenotyping procedures require the administration of a single dose of a probe compound to an individual, followed by quantification of urinary or serum concentrations of the drug and its major metabolite(s). The ratio of parent drug/ metabolite (metabolic ratio, MR) can be considered a proxy of activity of the enzyme responsible for the formation of that metabolite and is often used to describe an individual's phenotype. Test drugs for in vivo phenotyping of CYP isoenzyme activity include the following: caffeine for CYP1A2, bupropion for CYP2B6, tolbutamide for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6 and midazolam for CYP3A4<sup>10</sup>. Genotyping on the other hand is effected out through molecular genetic testing. This allows the detection and characterization of allelic variants for the genes coding for the polymorphic enzymes. The main advantage of a genotyping test is that it represents a trait marker which is not influenced by environmental factors. The test can be performed in any situation and its result lasts a lifetime.

The clinical significance of a CYP polymorphism is related to a number of factors, such as the pharmacological and toxic activity of the parent compound and/or its metabolite(s), the therapeutic index of the drug and the overall contribution of the polymorphic pathway to the total clearance of the drug. The clinical consequences of polymorphic genes for drugmetabolizing enzymes may be more notable for subjects who are at the extremes of metabolic capacity such as the homozygous for defective genes (PMs) or those with duplicated or amplified functional genes (UMs). While PMs may achieve high plasma/serum concentrations of a drug given at a standard dose with possible risk of an exaggerated response, the UMs may not reach optimal levels and this might account for lack of therapeutic effect. The CYP polymorphisms associated with the greatest clinical implications involve CYP2C9, CYP2C19 and CYP2D6. Phenotyping and/or genotyping should allow the identification of patients at risk of inefficacy or toxicity and offer tools to individualize drug prescription. In recent years, the major CYP isoenzymes have been characterized at the molecular level and their various substrates, inhibitors and inducers have been identified<sup>511</sup>. As shown in Table I, the majority of com-

monly used psychotropic drugs are metabolized by

Table I. Cytochrome P450 isoforms and psychotropic drugs as substrates, inhibitors or inducers. Modified from Spina - de Leon<sup>4</sup>.

| CYP<br>isoform   | Psychotropic drugs  |  |               |  |
|------------------|---|--|---------------|--|
|                  | Substrates  | Inhibitors*  | Inducers*     |  |
| CYP1A2           | Antidepressants: tricyclics (demethylation), fluvoxamine,<br>trazodone, duloxetine, mirtazapine, agomelatine<br>Antipsychotics: haloperidol, thioridazine, clozapine,<br>olanzapine, asenapine  | Fluvoxamine (potent)   | Carbamazepine |  |
| CYP2B6           | Antidepressants: bupropion  |  | Carbamazepine |  |
| CYP2C9           | Antidepressants: fluoxetine<br>Mood stabilizers: valproic acid<br>Hypnotics: zolpidem, zopiclone  | Fluoxetine (moderate)<br>Fluvoxamine (moderate)<br>Valproic acid (weak)  | Carbamazepine |  |
| CYP2C19          | Antidepressants: tricyclics (demethylation), sertraline, citalopram, escitalopram, moclobemide<br>Anxiolytics: diazepam, clobazam   | Fluvoxamine (potent)<br>Fluoxetine (moderate)  | Carbamazepine |  |
| CYP2D6           | Antidepressants: tricyclics (hydroxylation), fluoxetine,<br>fluvoxamine, paroxetine, citalopram, escitalopram,<br>venlafaxine, mirtazapine, duloxetine, vortioxetine<br>Antipsychotics: haloperidol, chlorpromazine,<br>fluphenazine, perphenazine, thioridazine, zuclopenthixol,<br>pimozide, clozapine, olanzapine, risperidone, iloperidone,<br>aripiprazole, brexpiprazole  | Fluoxetine (potent)<br>Paroxetine (potent)<br>Sertraline (moderate)<br>Duloxetine (moderate)<br>Bupropion (moderate)<br>Thioridazine (potent)<br>Perphenazine (potent)<br>Asenapine (weak) |               |  |
| CYP3A4           | Antidepressants: tricyclics (demethylation), sertraline,<br>citalopram, escitalopram, venlafaxine, mirtazapine,<br>trazodone, reboxetine, vilazodone<br>Antipsychotics: haloperidol, thioridazine, pimozide,<br>clozapine, quetiapine, risperidone, iloperidone, aripiprazole,<br>brexpiprazole, ziprasidone, lurasidone, cariprazine<br>Anxiolytics: alprazolam, midazolam, triazolam<br>Mood stabilizers: carbamazepine | Fluoxetine (moderate)<br>Fluvoxamine (moderate)  | Carbamazepine |  |
| * Inducers and i | nhibitors are restricted to psychotropic drugs  |  |               |  |

CYP enzymes and some may also act as inhibitors or inducers of one or more of these isoforms, thus resulting in metabolically-based drug interactions<sup>4</sup>.

## Role of CYP isoforms in the metabolism and clinical response to psychotropic drugs

The most relevant CYP isoforms involved in the metabolism of psychiatric drugs include CYP1A2, CY-P2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Polymorphism of genes encoding for these enzymes result in different rates of psychotropic drug metabolism potentially increasing the risk for adverse effects or reducing therapeutic response. The currently known evidence of the impact of genetic variants of the major CYP isoforms on the metabolism and pharmacological response to psychotropic medications is described.

## CYP1A2

CYP1A2 is an isoform accounting for about 10-15% of total hepatic CYPs<sup>12</sup>. The CYP1A2 gene has been mapped on to chromosome 15q24.1 <sup>3</sup>. So far, more than 21 variant alleles and a series of subvariants (\*1B to \*21) of the CYP1A2 gene have been identified <sup>6</sup>. While some variants show decreased activity (\*1C, \*1K, \*8, \*11, \*15 and \*16), the variant \*1F is associated with increased inducibility among smokers<sup>6</sup>. The large interindividual variability in CYP1A2 activity may be partly due to environmental factors such as inhibitors (i.e., ciprofloxacin and fluvoxamine) or inducers (i.e., carbamazepine and cigarette smoking). CYP1A2 plays a significant role in the metabolism of a variety of clinically important drugs, including theophylline, caffeine, phenacetin, propranolol, tacrine and a number of antidepressants and antipsychotics <sup>12</sup>.

### Antidepressants

The biotransformation of several antidepressants is partially mediated by CYP1A2. This enzyme has been shown to contribute to the demethylation of TCAs <sup>13</sup>. Together with CYP2D6, CYP1A2 is involved in the metabolism of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. In this respect, some studies have reported an effect of smoking (an inducer of CYP1A2) on fluvoxamine disposition <sup>14</sup> <sup>15</sup>. CYP1A2 is also the main enzyme responsible for the metabolism of the new antidepressant agomelatine <sup>16</sup>. Consistent with this, the use of agomelatine is contraindicated in patients taking fluvoxamine, a potent CYP1A2 inhibitor <sup>16</sup>. In addition, CYP1A2 contributes to the biotransformation of duloxetine <sup>17</sup>, mirtazapine <sup>18</sup> and trazodone <sup>19</sup>. To our knowledge, no pharmacogenetic study has so far evaluated the effect of CYP1A2 gene variants on the pharmacokinetics of these antidepressants.

### Antipsychotics

CYP1A2 is involved in the biotransformation of the first-generation antipsychotics haloperidol and thioridazine<sup>20</sup>. On the other hand, CYP1A2 plays a major role in the metabolism of the newer antipsychotics clozapine<sup>21</sup>, olanzapine<sup>22</sup> and asenapine<sup>20</sup>.

The major metabolic pathways of clozapine include the demethylation to norclozapine, mediated by CY-P1A2, CYP2C19, and CYP3A4, and the oxidation to clozapine N-oxide, mediated by CYP3A4<sup>21</sup>. In a study of schizophrenic patients, the CYP1A2 genetic polymorphisms \*1*F* and \*1*D* did not affect significantly clozapine clearance <sup>23</sup>. Higher serum concentrations of clozapine and norclozapine have been observed in patients carrying two *CYP1A2* variants associated with reduced enzyme activity (–3860A, –2467del, –163C, –739G, and/or –729T), compared with those with one or none<sup>24</sup>.

Olanzapine is primarily metabolized via direct N-glucuronidation, mediated by UGT1A4, and N-demethylation, catalyzed by CYP1A2<sup>22</sup>. Studies investigating the impact of CYP1A2 on the pharmacokinetics of olanzapine produced conflicting results<sup>25-27</sup>. On the other hand, in a study of schizophrenic patients treated with olanzapine, subjects with the *CYP1A2\*1F/\*1F* genotype had 22% lower (dose and bodyweight adjusted) serum olanzapine concentrations compared to *CYP1A2\*1A* carriers<sup>28</sup>.

The new antipsychotic asenapine is cleared through oxidative metabolism, primarily by CYP1A2, and by direct glucuronidation <sup>20</sup>.

Based on the available evidence, routine genotyping for CYP1A2 allelic variants is not yet indicated in psychiatry.

## CYP2B6

CYP2B6 represents a relatively small proportion (about 2-6%) of the total hepatic CYPs <sup>6</sup> <sup>12</sup>. The *CY*-*P2B6* gene is located at chromosome 19 between 19q12 and 19q13.2 and is highly polymorphic <sup>3</sup>. The variant alleles *CYP2B6\*6*, *CYP2B6\*16* and *CYP2B6\*18* are associated with lower expression/ activity, while the allele *CYP2B6\*4* appears to be associated with increased activity. CYP2B6 plays an important role in the metabolism of the anticancer drugs cyclophosphamide and ifosfamide, the anti-HIV agents efavirenz and nevirapine, the anesthetics propofol and ketamine, the antiparkinsonian drug selegiline, the atypical antidepressant and smoking cessation agent bupropion, and the  $\mu$ -opioid agonist methadone<sup>6</sup>. The activity of CYP2B6 may be affected by inhibitors, such as clopidogrel and ticlopidine, and inducers, including carbamazepine and rifampicin.

According to *in vitro* studies, CYP2B6 is the main enzyme responsible for the metabolism of bupropion <sup>29</sup>. In a study of healthy volunteers, bupropion total clearance was higher in carriers of the allele *CYP2B6\*4* compared to carriers of wild-type allele \*1 <sup>30</sup>. In a genotype-guided study of 42 healthy subjects, Benowitz et al. <sup>31</sup> found that *CYP2B6\*6* and \*18 gene variants were associated with approximately 33% reduced concentrations of hydroxybupropion at steady-state, with no effects on concentrations of bupropion or other metabolites.

At present, genotyping for CYP2B6 has no clinical utility in psychiatry.

## CYP2C9

CYP2C9 is largely represented in human liver where it corresponds to approximately 20% of the hepatic total CYP content <sup>32</sup>. The CYP2C9 gene is located at chromosome 10q24 in a densely packed region also containing genes encoding other CYP2C subfamily members such as CYP2C8, CYP2C18 and CYP2C19<sup>3</sup>. CYP2C9 exhibits genetic polymorphisms and, to date, more than 35 allelic variants have been described <sup>32</sup>. The two more common variants associated with reduced enzyme activity are CYP2C9\*2 and CYP2C9\*3. There are significant inter-ethnic differences in the frequency of these two variants<sup>3</sup>. CY-P2C9\*2 and CYP2C9\*3 are mainly present in Caucasians at a frequency of 11% and 7% respectively, while frequencies are lower in Africans. CYP2C9\*2 has indeed not been detected in Asians<sup>6</sup>.

CYP2C9 is primarily involved in the biotransformation of a variety of therapeutic agents including nonsteroidal anti-inflammatory drugs, oral antidiabetics, diuretics, angiotensin II receptor antagonists, anticancer drugs, oral anticoagulants (e.g., S-warfarin) and antiepileptics (e.g., phenobarbital and phenytoin). On the other hand, CYP2C9 plays only a minor role in the metabolism of a number of psychotropic drugs, namely TCAs, fluoxetine, valproic acid, and the Zdrugs zolpidem and zopiclone <sup>32</sup>. Genotyping for CYP2C9 is not likely to have any clinical use in psychiatry.

## **CYP2C19**

CYP2C19 is expressed at relatively low levels in human liver. The CYP2C19 gene is located on chromosome 10q24.1-q24.3 and is highly polymorphic with at least 35 allelic variants and subvariants (\*1B to \*34) identified so far <sup>33</sup>. CYP2C19\*1, the wild-type allele encoding a fully functional enzyme, is present in double or single copy in EMs (homozygotes or heterozygotes, respectively). CYP2C19 PMs are carriers of null alleles CYP2C19\*2 and CYP2C19\*3. The prevalence of CYP2C19 PMs is about 2 to 5% in Caucasians but up to ~25% in Asians. There is a marked inter-ethnic variation in the distribution of these two variant alleles <sup>33 34</sup>. The allelic frequency of CYP2C19\*2 has been shown to be 15% in Africans, 29-35% in Asians, 12-15% in Caucasians and 61% in Oceanian peoples. CYP2C19\*3 is mainly found in Asians (5-9% in Asians, less than 0.5% in Caucasians). A CYP2C19 gene variant (CYP2C19\*17), associated with increased gene transcription and thus a higher metabolism of CYP2C19 substrates has been described <sup>35</sup>. Its frequency varies guite broadly between different ethnic groups, being 18% among Swedes and 4% in Chinese.

CYP2C19 is responsible for the oxidative metabolism of some widely used drugs such as proton pump inhibitors, clopidogrel and various psychotropic medications including some TCAs, SSRIs and benzodiazepines<sup>3 12 36</sup>. Many studies have investigated the relationship between the CYP2C9 genetic polymorphism and the pharmacokinetics of these drugs, but only a few have examined its possible influence on clinical outcomes.

#### Antidepressants

It is well documented that CYP2C19 is the major enzyme involved in the demethylation of tertiary TCAs amitriptyline, imipramine and clomipramine to secondary amines, but other CYPs, namely CYP2C9, CYP3A4 and CYP1A2, may also contribute <sup>13</sup>. Two studies in depressed Japanese patients reported higher plasma concentrations of imipramine in CY-P2C19 PMs as compared to EMs <sup>37 38</sup>. Pharmacokinetic investigations in Japanese <sup>39</sup> and Caucasian psychiatric patients <sup>40 41</sup> found that steady-state serum concentrations of amitriptyline were higher in subjects with two *CYP2C19*-mutated alleles (\*2,\*3) as compared to subjects with wild-type genotype. Doseand weight-adjusted steady-state concentrations of clomipramine were 41% and 76% higher in patients with two mutated CYP2C19 alleles than individuals carrying one defective CYP2C19 allele or none, respectively <sup>42</sup>. Two studies involving a large sample of depressed patients documented that subjects homozygous for CYP2C19\*17, the variant associated with higher enzyme activity, had lower plasma concentrations of amitriptyline 43 and imipramine 44 compared with CYP2C19\*1/\*1 individuals. Dosing recommendations for TCAs based on CYP2C19 genotyping have been suggested and summarized in Table I<sup>45-47</sup>. With regard to SSRIs, CYP2C19 is the most important isoform responsible for the demethylation of sertraline to an almost inactive metabolite. A single-dose pharmacokinetic study in healthy subjects reported that the area under the curve (AUC) of sertraline was 41% higher in CYP2C19 PMs compared with EMs<sup>48</sup>. Citalopram and escitalopram are metabolized primarily by CYP2C19 and CYP3A4 and, to a lesser extent, by CYP2D6<sup>49</sup>. A population pharmacokinetic study in Chinese patients reported that the oral clearance of citalopram in CYP2C19 PMs was 43 and 33% lower compared with the homozygous and heterozygous EMs, respectively <sup>50</sup>. In a study involving 166 patients treated with escitalopram, the serum concentrations of escitalopram were 42% lower in patients homozy-gous for *CYP2C19\*17* and 5.7-fold higher in subjects homozygous for defective *CYP2C19* alleles, compared with the *CYP2C19\*1/\*1* subgroup <sup>51</sup>. Despite this correlation, the influence of CYP2C19 variants on the clinical outcome with sertraline, citalopram and escitalopram is presumably low, due to the large therapeutic window of these antidepressants.

Based on this evidence, the CYP2C19 genetic polymorphism appears to play only a marginal role on the pharmacokinetics and clinical response to newer antidepressants, so the usefulness of CYP2C19 genotyping techniques as a guide for dose individualization is probably limited. Nevertheless, Hicks et al. <sup>52</sup> suggested dosing recommendations for CYP2C19 and SSRIs (Tab. II).

#### Other psychotropic drugs

CYP2C19 plays a role in the complex metabolism of clozapine. In this respect, higher serum clozapine concentrations have been described in CYP2C19 PM patients than in those with other CYP2C19 geno-

**Table II.** Pharmacogenetic guidelines using CYP2C19 and CYP2D6 genotyping for dosing psychiatric drugs. Based on refs. <sup>45-47 52 78 79</sup>.

| Psychotropic drug  | Recommendations  |  |  |
|--|--|--|--|
| TCAs   | CYP2D6 PMs: avoid TCAs or ↓ dose by 50% and use TDM to adjust dosing.<br>CYP2D6 UMs: avoid TCAs.<br>CYP2C19 PMs and amitriptyline: ↓ dose by 50% and use TDM to adjust dosing<br>CYP2C19 UMs and amitriptyline: select another antidepressant not metabolized by CYP2C19 |  |  |
| Citalopram, escitalopram and sertraline                                    | CYP2C19 PMs: select another antidepressant or ↓ dose by 50% and use TDM to adjust dosing CYP2C19 UMs: select another antidepressant  |  |  |
| Fluoxetine, fluvoxamine and paroxetine                                     | CYP2CD6 PMs: select another antidepressant or ↓ dose by 50% and use TDM to adjust dosing (Hicks et al. 2015) CYP2C19 UMs: select another antidepressant  |  |  |
| Venlafaxine  | CYP2D6 PMs: select another antidepressant or use venla-<br>faxine TDM<br>CYP2D6 UMs: increase dose by a factor of 1.5  |  |  |
| Aripiprazole, haloperidol, risperidone and zuclopenthixol                  | CYP2D6 PMs: ↓ dose by 50% or select another antipsy-<br>chotic<br>CYP2D6 UMs: be alert to diminished serum concentrations<br>or prescribe another antipsychotic.   |  |  |
| Long-acting intramuscular aripiprazole                                     | CYP2D6 PMs: ↓ dose to 75%*   |  |  |
| Pimozide   | If prescribing > 4 mg/day in adults, CYP2D6 genotyping is<br>required by the US prescribing information because 4 mg/<br>day is the maximum recommended dose in CYP2D6 PMs.  |  |  |
| <sup>1</sup> Inducers and inhibitors are restricted to psychotropic drugs. |  |  |  |

types <sup>53</sup>. Further studies are needed to evaluate the impact of CYP2C19 genetic polymorphism on clozapine disposition.

Some benzodiazepines, including diazepam and clobazam, are extensively metabolized by CYP2C19, with partial contribution from CYP2C18, CYP3A4, and CYP2B6<sup>54</sup>.

## CYP2D6

CYP2D6 is the most important polymorphic enzyme involved in drug metabolism but accounts for less than 5% of the hepatic total CYP content<sup>12</sup>. The gene encoding for CYP2D6 is located in position 22q13.1 and is highly polymorphic. Currently more than 100 allelic variants and subvariants have been identified, and there are substantial interethnic differences in allele frequencies 55. While some variants encode an inactive enzyme or no enzyme at all, others consist of gene duplication. Therefore, CYP2D6 activity may range from complete deficiency to ultrarapid metabolism and individuals are classified as PMs, IMs, EMs or UMs according to their inherited genetic profile. PMs lack CYP2D6 activity and represent approximately 3 to 10% of Caucasians, but only 1 to 2% of East Asians. Among EMs, the catalytic activity varies largely, and a subgroup of subjects with extremely high enzyme activity has been classified as UMs. Four major mutated alleles, CYP2D6\*3, CYP2D6\*4, CYP2D6\*5 and CYP2D6\*6, account for 90-95% of the PM alleles in Caucasians. Alleles with duplication or multiduplication of a functional CYP2D6\*2 gene are associated with increased CYP2D6 activity: the frequency of this condition varies from 1-2% in Swedes to up to 7-10% in Spaniards and Southern Italians. Most of the CYP2D6 UMs probably have 3 active copies but as many as 13 copies have been described. A comprehensive worldwide study provided CYP2D6 UM frequencies of 1-5% in Caucasians, 40% in northern Africa and > 20% in Oceania  $^{56}$ .

Differently from other CYPs, CYP2D6 is not inducible, and thus genetic mutations are largely responsible for the interindividual variation in enzyme expression and activity. On the other hand, the activity of CYP2D6 can be inhibited by several drugs including quinidine, perphenazine, thioridazine, fluoxetine and paroxetine, resulting in clinically significant drug interactions <sup>5</sup>.

CYP2D6 plays an important role in drug metabolism, being partially or entirely responsible for the oxidative biotransformation of commonly prescribed drugs such as antidepressants, antipsychotics, opioids, antiemetics, antiarrhythmics, beta-blockers, tamoxifen and atomoxetine <sup>55 57.</sup>

#### Antidepressants

Most antidepressants including TCAs, SSRIs and other newer agents are metabolized, at least in part, by CYP2D6<sup>57</sup>.

TCAs are first-generation agents with a relatively narrow therapeutic index. Clinical effects of TCAs appear to be correlated with their serum concentrations 58. TCAs include tertiary amines (amitriptyline, imipramine, clomipramine) and secondary amines (nortriptyline, desipramine). Tertiary amines are demethylated to secondary amines, while both tertiary and secondary are further hydroxylated to active metabolites. It is well documented that the hydroxylation reactions of TCAs are catalyzed by CYP2D6, whereas N-demethylation is catalyzed by CYP2C19 and, to a lesser extent, by CYP1A2, CYP2C9 and CYP3A4<sup>13</sup>. The best correlation between CYP2D6 genotype and pharmacokinetics and steady-state serum concentrations has been observed for the secondary amines nortriptyline and desipramine. On the other hand, the impact of CYP2D6 genotype on the elimination kinetics of tertiary amines is lower presumably due to the involvement of multiple CYP isoforms in their biotransformation. Several investigations in healthy subjects found significant differences in the pharmacokinetic parameters of TCAs between CYP2D6 PMs and EMs<sup>13 57</sup>. In general, CYP2D6 PMs reach higher peak serum concentrations, and have lower clearances and longer half-lives as compared with CYP2D6 EMs. Interestingly, Dalen et al. 59 showed that the number of active CYP2D6 gene copies had a strong impact on the pharmacokinetics of nortriptyline in healthy subjects. Earlier pharmacokinetic studies in depressed patients had documented a significant correlation between CYP2D6 activity and steady-state serum concentrations of imipramine 60, nortriptyline 61 or desipramine 62. The relevance of CYP2D6 variants on clinical outcomes in patients treated with TCAs is documented by several ADR cases with increased serum TCA concentrations in CYP2D6 PMs or therapeutic failure associated with decreased concentrations in CYP2D6 UMs<sup>13</sup>.

SSRIs are currently the most widely used antidepressant drugs. Different from TCAs, SSRIs have a wide therapeutic index and no evident correlation between serum levels and clinical outcome has been demonstrated <sup>63</sup>. Therefore, genetically dependent interindividual differences in their elimination have probably a limited clinical relevance. CYP2D6 plays a major role in the biotransormation of fluoxetine and paroxetine, and contributes to that of fluvoxamine and citalopram/escitalopram<sup>63</sup>. Fluoxetine is N-demethylated to the active metabolite norfluoxetine primarily by CYP2D6 and, to a lesser extent, by CYP2C9, CY-P2C19 and CYP3A4<sup>49</sup>. Some studies in depressed patients treated with fluoxetine reported significantly lower steady-state serum concentrations of fluoxetine (and norfluoxetine) in CYP2D6 EMs than in PMs 64 65, whereas other reported an effect of genotype only on S-enantiomer metabolism 66 67. Paroxetine is extensively metabolized in the liver by CYP2D6 with additional contribution of CYP3A4<sup>49</sup>. A number of pharmacokinetic investigations in depressed patients have documented an association between CYP2D6 genotype and steady-state serum concentrations of paroxetine <sup>64 68 69</sup>. CYP2D6 and CYP1A2 are the major CYP isoforms involved in the metabolism of fluvoxamine. Studies evaluating the possible correlation between CYP2D6 genetic polymorphisms and pharmacokinetic parameters of fluvoxamine produced conflicting results suggesting that the contribution of CYP2D6 to the overall clearance of fluvoxamine is probably marginal <sup>70</sup> <sup>71</sup>. As previously mentioned, CYP2D6 plays only a minor role in the biotransformation of citalopram and escitalopram<sup>49 63</sup>.

Polymorphic CYP2D6 is also involved in the metabolism of antidepressants of the SNRI class. The demethylation of venlafaxine to the active metabolite O-desmethylvenlafaxine is primarily mediated by CYP2D6 72 73. In theory, as venlafaxine and its metabolite have similar pharmacological properties, the clinical implications of polymorphic venlafaxine metabolism should not be particularly relevant. However, symptoms of cardiotoxicity (palpitation, shortness of breath, arrhythmia) were reported in four CYP2D6 PM patients while treated with venlafaxine <sup>74</sup>. The SNRI duloxetine is extensively metabolized in the liver primarily by CYP1A2 and, to a lesser extent, by CYP2D6 17. Different CYPs including CYP2D6, CY-P1A2 and CYP3A4 mediate the biotransformation of mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA) 18. The multimodal antidepressant vortioxetine is extensively metabolized in the liver by CYP2D6 with additional participation of several CYP isoforms <sup>75</sup>. As PMs achieve twice the plasma concentrations of EMs, they should receive a maximum vortioxetine dosage of 10 mg/day<sup>75</sup>.

In conclusion, several lines of evidence indicate that most antidepressants are metabolized, at least in part, by the polymorphic CYP2D6. This explains the significant interindividual variability in serum concentrations of these agents and the interactions observed when these drugs are used in combination with other substrates or inhibitors of the enzyme. The clinical significance of this association is most pronounced for TCAs, since have a narrow therapeutic index and their effects are concentration-dependent. Patients with a decreased ability to eliminate these drugs, either because of a genetic or environmentally-induced deficiency in CYP2D6, are at risk of developing severe adverse effects with conventional doses. Conversely, UMs with duplicated or multiduplicated CYP2D6 genes could require higher than normal doses for optimal treatment. A number of studies have shown a higher incidence of UMs among nonresponders to antidepressants primarily metabolized by CYP2D6, in particular TCAs and SSRIs 76 77. As a result, genotyping for CYP2D6 may be used to supplement the measurement of serum TCA concentrations when aberrant metabolic capacity (poor or ultrarapid) is suspected. On the other hand, the impact of CYP2D6 polymorphisms on clinical outcome in patients treated with newer antidepressants remains to be seen. Specific CYP2D6 genotype-based dose recommendations for a number of antidepressants have been recently developed and described in Table II 45-47 52 78 79.

#### Antipsychotics

Polymorphic CYP2D6 is responsible for the oxidative metabolism of various first- and second-generation antipsychotics <sup>20 57 80 81</sup>.

Concerning first-generation compounds, studies in both patients and healthy volunteers have demonstrated that CYP2D6 is the major enzyme involved in the biotransformation of perphenazine 82 83 and zuclopenthixol 82. The metabolism of haloperidol and thioridazine is mediated by both CYP2D6 and CYP3A4<sup>84 85</sup>. Interestingly, patients with CYP2D6 PM phenotype have been reported to reach higher serum concentrations of haloperidol than EMs 86-88. A study involving 76 psychiatric patients documented that dose-corrected serum thioridazine concentrations were 1.8- and 3.8-fold higher (p < 0.01 for both) in subjects with one or no active CYP2D6 alleles, respectively, compared with those with two or more functional alleles 88. CYP2D6 plays a major role in the metabolism of pimozide and PMs reach higher serum concentrations than EMs. As the occurrence of pimozide-induced arrhythmias is concentration dependent, the US prescribing information recommends CYP2D6 genotyping for prescribing pimozide doses > 4 mg/day  $^{90}$  (Tab. II).

The second-generation antipsychotic risperidone is converted by CYP2D6 and, to a lesser extent, by CY-P3A4 to the active metabolite 9-hydroxyrisperidone or paliperidone, which has a similar potency compared with the parent drug in terms of dopamine receptor affinity. Pharmacokinetic studies in patients treated with risperidone found that the ratio of risperidone to 9-hydroxyrisperidone concentrations at steady-state is strongly associated with the CYP2D6 genotype, with the highest ratios in PMs and the lowest in UMs; nevertheless the sum of the active moieties was substantially comparable among the various genotype groups <sup>91 92</sup>. It may be assumed that CYP2D6 genetic polymorphism have no relevant clinical implications for risperidone metabolism as decreased 9-hydroxyrisperidone production would be compensated for by higher serum levels of the parent drug, risperidone. However, a number of studies described a higher incidence of ADRs, including lengthening of QTc interval and parkinsonism, in CYP2D6 PM patients, presumably reflecting pharmacological differences between parent drug and metabolite <sup>93-96</sup>. Aripiprazole is metabolized by CYP2D6 and CYP3A4 to dehydroaripiprazole, an active metabolite with pharmacological properties similar to the parent drug. Aripiprazole is the major moiety in systemic circulation, while dehydroaripiprazole represents roughly 40% of aripiprazole exposure. Patients with the CYP2D6 PM phenotype have an 80% increase in aripiprazole blood levels and a 30% decrease in dehydroaripiprazole levels, resulting in a 60% higher exposure to the total active moieties; the elimination half-life of aripiprazole and dehydroaripiprazole was found to increase significantly in PMs <sup>20</sup>. Based on the US and EU prescribing information, long-acting aripiprazole should be administered at monthly doses of 400 mg in average individuals <sup>97</sup>. However, this dose should be reduced to 300 mg in CYP2D6 PMs and 200 mg in CYP2D6 PMs taking CYP3A4 inhibitors. On the other hand, CYP2D6 plays only a minor role in the metabolism of clozapine and olanzapine. Accordingly, a number of studies found no differences in steady-state serum concentrations of both antipsychotics in the various phenotype groups <sup>23 24 27 98 99</sup>.

Many studies have investigated the relationship between CYP2D6 polymorphisms, steady-state serum concentrations, and therapeutic and adverse effects of various antipsychotic drugs <sup>20 81</sup>. Results may be considered controversial partly due to differences in methodology (e.g., retrospective and prospective open-label studies as well as case-control studies), small sample size and heterogeneity of studied populations. Grossman et al. <sup>100</sup> examined the influence of 25 genetic variants of drug metabolizing enzymes in a subgroup of patients (n = 750) who were enrolled in the large CATIE study; these patients were treated with olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine. None of the variants investigated (including CYP2D6) showed a significant association with dosing, efficacy or overall tolerability.

In conclusion, there is a significant body evidence suggesting a relationship between CYP2D6 genetic polymorphisms and the pharmacokinetic parameters of many antipsychotics such as perphenazine, haloperidol, pimozide, risperidone and aripiprazole. On the other hand, findings on the association between polymorphic CYP2D6 and response to these antipsychotics are not in agreement. Therefore, recommendations for antipsychotics dose adjustments based on CYP2D6 are not likely to be made in the near future, although published recommendations exist for some antipsychotics (Tab. II).

## CYP3A4

CYP3A4 is the most abundant CYP isoform, accounting for about 30% of total CYP in the human liver and 70% in the small intestine<sup>3</sup>. The gene encoding for CYP3A4 is located on chromosome 7g21-g22.1 along with the other members of the CYP3A sub-family (CYP3A4, CYP3A5, CYP3A7 and CYP3A43). Several polymorphisms of CYP3A4 have been identified, but most are extremely rare and occur as heterozygotes with the wild-type allele, while others have no demonstrable effect on substrate metabolism<sup>12</sup>. Only the variants CYP3A4\*6, CYP3A4\*17, CYP3A4\*20 and CYP3A4\*22 display functional variability with decreased activity, whereas CYP3A4\*18A is associated with increased activity<sup>3</sup>. The activity of CYP3A4 may be increased by potent inducers such as rifampin and antiepileptic inducers. A number of drugs including ketoconazole, itraconazole, erythromycin and troleandomycin, act as potent CYP3A4 inhibitors. Grapefruit juice is also a known inhibitor of CYP3A4.

CYP3A4 is involved in the biotransformation of over 50% of therapeutic agents. Drugs primarily metabolized by CYP3A4 include immunosuppressants (e.g., cyclosporin and tacrolimus), non-sedating antihistamines (e.g., terfenadine and astemizole), calcium antagonists (e.g., diltiazem, verapamil, nifedipine and other dihydropyridines), cholesterol lowering drugs (e.g., simvastatin and lovastatin), antiarrhythmics (e.g., amiodarone and quinidine), and several steroids (e.g., cortisol, ethinylestradiol and levonorgestrel) <sup>12</sup>. CYP3A4 plays an important role also in psychopharmacotherapy as it contributes to the biotransformation of various antidepressants (TCAs, sertraline, citalopram, escitalopram, venlafaxine, mirtazapine and reboxetine), antipsychotics (haloperidol, pimozide, clozapine, quetiapine, risperidone, aripiprazole, ziprasidone, lurasidone and brexpiprazole), mood stabilizers (carbamazepine) and benzodiazepines (e.g., alprazolam, midazolam and triazolam).

CYP3A4 is primary involved the metabolism of the newer antipsychotics quetiapine and lurasidone. To date, there is limited evidence of an association between these variants and antipsychotic response. A recent study in 238 patients treated with quetiapine found that dose-corrected serum concentrations of quetiapine were 67% higher (p = 0.01) in carriers of the CYP3A4\*22 allele (\*1/\*22 and \*22/\*22, n = 31) than in wild-type patients (n = 207)<sup>101</sup>.

CYP3A4 is the major enzyme responsible for the epoxidation of carbamazepine, an antiepileptic agent also used as a mood stabilizer. In study involving 90 patients with epilepsy patients, the *CYP3A4\*1B* was associated with lower carbamazepine clearance <sup>102</sup>. There is no known clinical use for genotyping for CY-P3A4 in psychiatry.

# Clinical usefulness of CYP genotyping procedures in psychiatry

Pharmacological treatment can be personalized by basing drug selection and dose on the needs of the individual <sup>1</sup>. CYP genotyping is one factor on which such personalized medicine can be based. CYP genotyping is currently performed only when issues relating to efficacy, such as non-response, or safety, such as ADRs or abnormal TDM, arise. However, advances in genotyping technology and the increasing affordability of associated costs are making it more likely that CYP genotyping is carried out even before psychiatric medication is prescribed <sup>103</sup>.

Some CYPs, namely CYP1A2, CYP2B6, CYP2C9 and CYP3A4, may be of interest for research in psychiatry, but are of limited clinical use for many reasons:

- there is little scientific evidence regarding these CYPs, and such evidence is rarely replicated, and therefore validated;
- 2) it is not clear what the relationship between phenotype and genotype may be;
- the impact of genetic variations in these CYPs is not likely to be more significant than environmental factors.

On the other hand, genotyping for CYP2D6 and CY-P2C19 may be useful in psychiatry in certain clinical situations. A summary of the pharmacogenetic guidance for CYP2C19 and CYP2D6 as well as associated dosing regimens of selected psychiatric drugs is found in Table II <sup>46 47 52</sup>.

Psychiatric medication such as antidepressants are prescribed not only by psychiatrists but also by general practitioners. However, prescribers require training in order to have the expertise needed to make use of genotyping to improve efficacy and safety outcomes. This is particularly true when prescribing TCAs and when treating rare subjects who are PMs for both CYP2C19 and CYP2D6 (< 1/1000). Such persons lack both CYPs and are expected to be unable to metabolize TCAs as well as the newer antidepressants<sup>104</sup>.

Clinicians need to be familiar with current genotyping methods and the next generation of sequencing technologies. Samer et al. <sup>105</sup> describe currently applied methods available for the most common CYP genotyping required by psychiatrists, that is, of CY-P2D6 and CYP2C19. The AmpliChip CYP450 Gene-Chip is the best-studied tool used to carry out such genotyping <sup>79 106</sup>.

One obstacle to the use of genotyping is the large variety of genotyping methods and outputs for CY-P2D6 and CYP2C19 provided by clinical laboratories. It may be advisable for prescribers to use the services of one laboratory and familiarize themselves with the strengths and limitations of the methods used for genotyping. Even though CYP2D6 and CYP2C19 genotype-phenotype relationships are relatively wellknown, the existence of rare new alleles is still coming to light. As a matter of fact, a recent review 107 indicates that the vast majority of genetic variations at the CYP genes may be very rare. It is not clear how much these rare variations can impact clinical practice but combining CYP genotyping and therapeutic drug monitoring (TDM) may be the current answer to this uncertainty. In summary in our opinion, to correctly interpret CYP2D6 or CYP2C19 genotyping, prescribers require a complete drug history and ideally also TDM results.

Novel sequencing technologies have permitted the description of variations in the human genome in ways that were not possible until recently, and this has helped understand the role of rare variations in drug response <sup>108</sup>. Nevertheless, CYPs are not idea for novel sequencing methods due to their genomic complexity <sup>109</sup>. In addition, rare CYP variants may be particularly significance in African populations where

there is notable discordance between CYP genotypes and phenotypes <sup>110</sup>.

As genetic technology rapidly advances, the cost of genetic testing in general, and of CYP genotyping in particular, is drastically falling. A recent review in pharmacogenomics found two types of cost studies (cost-effectiveness studies and cost-utility studies) but no corresponding published study in psychiatry<sup>111</sup>. It was easier to probe the cost-effectiveness of CYP testing in psychiatry when the old antipsychotics and antidepressants were the main drugs prescribed in psychiatry, because these drugs have a narrow therapeutic window and are highly dependent on CYP2D6 and CYP2C19 for their metabolism<sup>112</sup>. The newer psychiatric drugs have wider therapeutic windows and more varied metabolic pathways, making it difficult to complete cost studies in CYP genotyping. Therefore, large prospective studies aiming to deliver "proof of concept" outputs as well as describe the cost-benefit ratio CYP genotyping in psychiatry are unlikely to be conducted, as these are very expensive.

In order to personalize drug dosing, prescribers should take into consideration also environmental (inhibitors and inducers) and personal (e.g., age, gender, illnesses) factors, in addition to genetic ones<sup>1</sup>. This global vision of patient health requires TDM, as this reflects the influence of environmental and personal factors involved in metabolism, as well as the transport of drugs and the measurement of active metabolites 103. The combination of CYP genotyping and TDM may find its way into clinical practice in the near future in order to improve the safety and efficacy of some psychiatric drugs <sup>103</sup>. In this respect, a group of European psychiatrists has published the most comprehensive TDM guidelines in psychiatry 58. To be clinically useful in the future, pharmacogenetic testing may need to include epigenetic factors, pharmacokinetics and pharmacodynamics, therapeutic windows, idiosyncratic and dose-related ADRs, and should be used in association with TDM and other phenotyping tests 103.

The lack of agreement on regulatory issues by agencies in charge in USA and some European countries has left a vacuum for companies to take advantage of by marketing non-validated pharmacogenetic tests with no, or very limited, data on clinical validity and utility <sup>113</sup>. We propose that genetic testing for 1) CY-P1A2, CYP2B6, CYP3A4 or CYP3A5; 2) brain neurotransmitters and/or transporter genes; and 3) diagnosing schizophrenia, depression or bipolar disorder should not be ordered by clinicians since there is no data supporting their clinical validity and utility <sup>114</sup>.

## Conclusions

This article has summarized the current evidence regarding the role of CYP genetic variants in pharmacokinetics and clinical response to the most commonly used psychotropic drugs. The implications of CYP genotyping techniques in psychiatry have been critically reviewed. As there have been limited validated findings from well-controlled studies that could orient clinicians in the use of CYP genotyping in clinical work, the present paper is focused on the available evidence-based medicine data, interpreting this in a clinical light.

CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 genetic polymorphisms and their contributions to the metabolism of psychotropic drugs were thoroughly reviewed. CYP1A2, CYP2B6 and CYP3A4 genotyping may be of interest in an academic context, but have limited clinical usefulness at present. CYP2C9 can be used for clinical testing but does not currently have a place in psychiatry. CY-P2D6 and CY2C19 genotyping are the most important kinds of CYP genotyping for psychiatrists. Recommendations from practice guidelines describing CYP2D6 and CY2C19 genotyping for dosing several psychiatric drugs were reviewed in detail (Tab. II).

TCAs have a narrow therapeutic window and pose substantial risk of ADRs, including potentially fatal dose-related arrhythmias. Therefore, ADRs are much more likely to occur in CYP2D6 and CYP2C19 PMs, but may be more likely for severe cases of major depression. As a result, expertise in TCA-related genotyping and TDM may be a "niche" skill that psychiatrists need to master in order to dose TCA safely. Practice guidelines recommend prescribing an antidepressant other than venlafaxine or using TDM in CYP2D6 PMs, as well as increasing doses by a factor of 1.5 in CYP2D6 UMs<sup>46</sup>. Practice guidelines also recommend TDM and increasing doses by a factor of 1.5 in CYP2C19 UM patients receiving citalopram or escitalopram; the dose should be halved in CYP2C19 PMs taking sertraline<sup>46</sup>. Individuals who do not have CYP2C19 or CYP2D6 (PMs for both isoenzymes) will have problems metabolizing TCAs and most, but not all, of the newer antidepressants.

The dose of aripiprazole, haloperidol, risperidone, or zuclopenthixol should be reduced by 50% in PMs or an alternative drug used. In UMs on the other hand, clinicians should use TDM or prescribe an alternative drug <sup>46</sup>. The respective long-acting aripiprazole dose in CYP2D6 PMs and CYP2D6 PMs taking CY-P3A4 inhibitors should be 75 and 50% of the average

dose <sup>97</sup>. The US prescribing information recommends CYP2D6 genotyping for prescribing pimozide doses > 4 mg/day since CYP2D6 PMs should not take doses > 4 mg/day <sup>90</sup> (Tab. II).

When the evidence is limited, there is need to use the available pharmacological mechanistic information to personalize treatment in psychiatry, for example by combining CYP genotyping with TDM<sup>103</sup>.

#### **Conflict of interest**

In the past few years, Dr. Spina has participated in speakers/ advisory boards and lectures supported by Arcapharma, Astra-Zeneca, Bristol-Myers, Eli Lilly & Co, Janssen Pharmaceuticals, Lundbeck and Pfizer. He is not a shareholder in any pharmaceutical company. Dr. de Leon personally develops his presentations for lecturing, has never lectured using any pharmaceutical or pharmacogenetic company presentations, and has never been a consultant for pharmacogenetic or pharmaceutical companies. In the past, Dr. de Leon received researcher-initiated grants from Eli Lilly (one ended in 2003 and the other, as co-investigator, ended in 2007); from Roche Molecular Systems, Inc. (ended in 2007); and, in a collaboration with Genomas, Inc., from the NIH Small Business Innovation Research program (ended in 2010). He has been on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003). Roche Molecular Systems supported one of his educational presentations, which was published in a peer-reviewed journal (2005). His lectures were supported once by Sandoz (1997), twice by Lundbeck (1999 and 1999), twice by Pfizer (2001 and 2001), three times by Eli Lilly (2003, 2006, and 2006), twice by Janssen (2000 and 2006), once by Bristol-Myers Squibb (2006), and seven times by Roche Molecular Systems, Inc. (once in 2005 and six times in 2006).

## Take home messages for psychiatric care

- Genetic polymorphisms of cytochrome P450 (CYP) enzymes play an important role in the pharmacokinetics of many drugs used in psychiatry, in particular antidepressants and antipsychotics
- The influence of CYP variants on pharmacokinetic parameters of psychotropic drugs has not been associated so far with consistent results on a clinical level, that is, in terms of therapeutic effect and adverse events
- Genotyping for allelic variants of CYP2D6 and CYP2C19 can be used to personalize dosing for some antidepressants (i.e., tricyclic antidepressants and venlafaxine) and antipsychotics (i.e., aripiprazole) in certain clinical situations such as non-response or severe adverse effects, but not on a routine basis
- Knowledge of CYP2D6 and CYP2C19 genotype should be integrated with therapeutic drug monitoring, so thus allowing identification of individuals with extreme rates of drug metabolism including poor or ultrarapid metabolizers
- At present, genotyping for CYP1A2, CYP2B6, CYP2C9 and CYP3A4 may be of interest only on a scientific level, but has no clinical utility in psychiatry

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