

Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine



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Abstract

Antidepressants are commonly prescribed medications in the United States, and there is increasing interest in individualizing treatment selection for more than 20 US Food and Drug Administration–approved treatments for major depressive disorder. Providing greater precision to pharmacotherapeutic recommendations for individual patients beyond the large-scale clinical trials evidence base can potentially reduce adverse effect toxicity profiles and increase response rates and overall effectiveness. **It is increasingly recognized that genetic variation may contribute to this differential risk to benefit ratio and thus provides a unique opportunity to develop pharmacogenetic guidelines for psychiatry.** Key studies and concepts that review the rationale for cytochrome P450 2D6 (*CYP2D6*) and cytochrome P450 2C19 (*CYP2C19*) genetic testing can be delineated by serum levels, adverse events, and clinical outcome measures (eg, antidepressant response). In this article, we report the evidence that contributed to the implementation of pharmacokinetic pharmacogenetic guidelines for antidepressants primarily metabolized by *CYP2D6* and *CYP2C19*.

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In January 2015, President Barack Obama introduced the Precision Medicine Initiative with a mandate to promote more accurate diagnosis and personalized management of health and disease.^{1,2} Today, antidepressants are one of the most commonly prescribed medication classes in the United States, and there is increasing interest in individualizing treatment selection for more than 20 US Food and Drug Administration (FDA)–approved treatments for major depressive disorder. In a recent population-based drug prescription study of 142,377 Olmsted County, Minnesota, residents from the Rochester Epidemiology Project, antidepressants were identified as the second most commonly prescribed drug class (13%), with a peak prevalence rate of 26% in women aged 50 to 64 years.³ There is no question that selective serotonin reuptake inhibitors (SSRIs) have transformed the lives of patients with major depressive disorder, obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder, and chronic pain syndromes. It is clear that fluoxetine (Prozac) ushered in a new era

of prescription pharmacology and increased awareness of mental illness in general and depressive and anxiety disorders in particular.

Fluoxetine is FDA approved for major depressive disorder, OCD, bulimia nervosa, premenstrual dysphoric disorder, panic disorder, and bipolar disorder (in combination with olanzapine) and is the only drug FDA approved for major depression in children/adolescents aged 8 years or older. Paroxetine, or paroxetine controlled release, is FDA approved for major depressive disorder, OCD, panic disorder, social anxiety disorder, premenstrual dysphoric disorder, generalized anxiety disorder, and posttraumatic stress disorder. For fluoxetine and paroxetine, black box warnings have been issued for treatment-emergent suicidality, particularly in adolescents and young adults. Although SSRIs themselves are defined as a class, fluoxetine and paroxetine exhibit major structural, pharmacokinetic, and pharmacodynamic differences.⁴ Both are initially metabolized through cytochrome P450 (*CYP*) 2D6, which is subject to genetic variation and inhibition.



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These 2 drugs have been used in higher dosing strategies for treatment of OCD, and in fact, a 2010 meta-analysis revealed that higher dosing (fluoxetine at 60-80 mg, paroxetine at 60 mg), in comparison to lower dosing, had superior efficacy.⁵

The adverse effect toxicity profile of antidepressants and their effectiveness for major depression and anxiety disorders vary among patients, and it is increasingly recognized that genetic variation may contribute to this differential risk to benefit ratio.⁶⁻¹⁰ Thus, there is a unique opportunity to develop pharmacogenetic guidelines to bring precision medicine to psychiatry. Clinical examples of situations in which genomic variation has prompted regulatory drug label revision⁸ impacting clinical practice include carbamazepine and the *HLA-B*1502* variation associated with Stevens-Johnson syndrome in patients with ancestry across broad areas of Asia^{11,12} and tamoxifen-paroxetine/fluoxetine cotherapy given CYP2D6 poor metabolizer (PM) phenotype reducing metabolic conversion to chemotherapeutically active endoxifen.¹³ These examples highlight the potential merit of developing infrastructure to individualize medicine and identify the right drug for the right patient.¹⁴ This review illustrates key studies and concepts that contributed to the development of a pharmacokinetic pharmacogenetics prescription guide for antidepressants.

PHARMACOKINETIC VARIATION: A FOCUS ON CYP2D6 AND CYP2C19

There are approximately 105 and 35 major genetic allelic variants encoding for CYP2D6- and CYP2C19-metabolizing enzymes, respectively,¹⁵

and many of these allelic variations have been associated with specific enzyme activity (Table 1). These genetic variations have been categorized into 4 main metabolizer phenotypes (poor, intermediate, extensive [ie, normal], and ultrarapid).^{20,21} A PM phenotype has 2 inactive (2 null alleles) copies of the gene encoding for the enzyme. Poor metabolizers' inability to produce a functional enzyme leads to an increased drug plasma level with a potentially increased rate of adverse effects (ie, for medications with a dose-dependent increase in toxicity/intolerability). By the same mechanism, PMs have less enzyme activity to activate prodrugs (eg, codeine) to their active metabolite (eg, morphine), possibly affecting the drug efficacy.²² This is an area of increasing clinical investigation, specifically correlating clinical adverse effects directly to plasma levels associated with an increased risk of toxicity or decreased tolerability. The intermediate metabolizer phenotype is less likely to have clinical relevance in the context of adverse events or impact pharmacogenetic outcome measures. Extensive metabolizer (EM) phenotype is considered the wild type, in other words the normal phenotype. Ultrarapid metabolizers are exposed to fast metabolizing of medications and thus probably lower bioavailability and possibly efficacy. However, in some instances the phenotype prediction is not categorical, and thus a range of the possible phenotypes can be given (ie, poor to intermediate, intermediate to extensive, intermediate to ultrarapid, extensive to ultrarapid) (Table 2).

Fluoxetine, paroxetine, and venlafaxine are largely metabolized by CYP2D6. Citalopram and escitalopram are primarily metabolized by CYP2C19. In addition to a primary metabolic route that is subject to genetic variation, fluoxetine and paroxetine are also potent inhibitors of CYP2D6.²³ The combination of a genetic variation of non-PM plus concurrent fluoxetine- or paroxetine-associated inhibition treatment may in fact create an "iatrogenic poor phenotype," also referred to as "phenocopy" or "phenoconversion." CYP2D6 PMs, due to elevated blood levels, are at higher risk of toxicity with fluoxetine and paroxetine itself, or with other medications metabolized through CYP2D6 such as venlafaxine.²⁴

In 2006, several studies of fluoxetine and paroxetine were reviewed by Gardiner

TABLE 1. Predicted Enzyme Activity for CYP2D6 and CYP2C19 Alleles^a

| Predicted enzyme activity | CYP2D6 | CYP2C19 |
|-----------------------------|--|---|
| Increased activity | *2A ^b | *17 |
| Normal activity | *1, *35 | *1 |
| Decreased activity | *2, ^b *9, *10, *14B, *17, *29, *41 | *9 |
| No activity or null alleles | *3, *4, *5, *6, *7, *8, *11, *12, *13, *14A, *15, *36, *68 | *2, *3, *4, *5, *6, *7, *8, *10, *11 ^c |

^aPhenotyping was derived from the Human Cytochrome P450 (CYP) Allele Nomenclature Committee website¹⁶ and the PharmGKB website for the related Clinical Pharmacogenetics Implementation Consortium guidelines.¹⁷

^bCYP2D6*2A and CYP2D6*2 as described in Black et al.¹⁸

^cCYP2C19*11 is found in cis with the *2 variants; therefore, we have classified it a no activity or null allele.¹⁹

TABLE 2. Method for Prediction of Drug Metabolizer Phenotype for CYP2D6 and CYP2C19^{a,b}

| Predicted drug metabolizer phenotype | CYP2D6 | | CYP2C19 |
|--------------------------------------|---|--|--|
| | Without gene duplication | With gene duplication | |
| UM | Two increased activity alleles | Three normal and/or increased activity alleles | Two increased activity alleles |
| EM to UM | A combination of 1 normal activity allele with 1 increased activity allele | A combination of 2 normal activity alleles with 1 decreased activity allele | A combination of 1 normal activity allele with 1 increased activity allele |
| EM | Two normal activity alleles; a combination of 1 increased activity allele with 1 decreased activity allele | A combination of 2 normal activity alleles with 1 null allele; a combination of 1 normal activity allele with 2 decreased activity alleles | Two normal activity alleles |
| IM to UM | NA | A combination of an increased activity allele and a null allele but the duplicated allele cannot yet be determined | NA |
| IM to EM | A combination of 1 normal activity allele with 1 decreased activity allele; a combination of 1 increased activity allele with 1 null allele | One increased activity allele with 2 null alleles; 3 decreased activity alleles | A combination of 1 increased activity allele with 1 null allele; a combination of 1 normal activity allele and a decreased activity allele |
| IM | One normal activity allele with 1 null activity allele; 2 decreased activity alleles | One normal allele with 2 or more null alleles; 2 decreased activity alleles with 1 null allele | Two decreased activity alleles; a combination of 1 normal activity allele with a null allele |
| PM to IM | A combination of 1 decreased activity allele with 1 null allele | One decreased activity allele with 2 null alleles | A combination of 1 decreased activity allele with 1 null allele |
| PM | Only null alleles detected | | Two null alleles |

^aEM = extensive metabolizer; IM = intermediate metabolizer; PM = poor metabolizer; UM = ultrarapid metabolizer.
^bSee Table 1 for individual allele functions for these genes.

and Begg.²⁵ The fluoxetine pharmacokinetic studies reported the following: (1) single-dose fluoxetine at 20 mg had an area under the curve (AUC) that was 3.9-fold higher in PMs vs EMs, (2) single-dose fluoxetine at 60 mg had median AUCs for S- and R-fluoxetine that were 11.5- and 2.4-fold higher, respectively, in PMs vs EMs, and (3) the sum of racemic fluoxetine plus norfluoxetine trough concentrations after 23 days of fluoxetine at 20 mg were comparable between PMs and EMs. Taken together, the first 2 studies highlight CYP2D6 genotype and dose-related pharmacokinetic change in AUC, while the third study suggests that phenocopy (ie, drug inhibition) has the potential to change the phenotype from normal to poor outside of genotype. In a single-dose paroxetine pharmacokinetic study, the median AUC of a 30-mg dose was 7-fold higher in PMs vs EMs but declined to 1.7-fold with long-term use defined as 30 mg/d for 2 weeks. Similar concepts were reviewed by Preskorn,^{26,27} who reported that fluoxetine at a long-term dose of 20 mg/d converted an average of 43% of EMs to PMs.

In addition, fluoxetine at a long-term dose of 40 mg/d converted 95% of patients from EMs to PMs. On the other hand, paroxetine at a long-term dose of 20 mg/d converted an average of 70% of EMs to PMs. Fluoxetine and paroxetine can saturate and inhibit CYP2D6 metabolism in EMs, resulting in a nonlinear relationship between dose and serum concentration. This CYP2D6 inhibition mechanism, which results in autophenocopying, may explain the difference between single and long-term dosing. The time course of phenoconversion based on drug inhibition and its interaction with pharmacokinetic pharmacogenetic variation (ie, from ultrarapid metabolizer vs EM vs IM genotypes to PM phenotype) needs to be further studied.

Based on the reviewed studies, dose-dependent CYP2D6 inhibition and long-term use (2-3 weeks) of both paroxetine and fluoxetine at therapeutic doses contribute to phenoconversion of EM to PM.^{25,28} Pharmacokinetics data, however, do suggest secondary metabolism through other metabolic enzymes such CYP3A4, which is of

potential relevance.^{29,30} However, CYP3A4 and the other secondary pathways are currently less well studied and understood to a level of evidence for guideline development. The genotype of CYP2D6 is relevant in the short-term use of fluoxetine and paroxetine especially within the first few weeks, knowing that the drugs are metabolized by the saturable high-affinity CYP2D6 as well as other secondary enzymes with lower affinity.^{31,32} This factor may be relevant in the FDA black box warning that short-term treatment—emergent suicidal ideation and short-term antidepressant—induced mania both typically occur early in the course of treatment. The genotype was referenced as well in the FDA safety label change for fluoxetine for clinical situations that may prolong the QT interval.³³ In 2 published meta-analyses, higher SSRI dosing (including fluoxetine and paroxetine) in patients with OCD and major depressive disorder was associated with higher dropout rates due to adverse effects.^{5,34} Higher rates of adverse effects (eg, lower tolerability), which could be due to higher doses, particularly during the first few weeks of treatment, can lead to less treatment adherence and poorer outcomes.³⁵⁻⁴⁰ The higher dosing requirement of fluoxetine and paroxetine for OCD makes this potential risk of toxic blood levels even more clinically relevant.

PHARMACOGENETICS

Adverse Effect/Toxicity Profile

The evidence-based rationale for CYP2D6 (with or without CYP2D6 substrate inhibition) or CYP2C19 genetic testing can be delineated by serum levels, lower tolerability, serious adverse events (blood pressure changes, QT prolongation, seizures, and death), and pharmacogenetics-based primary outcome measures (eg, antidepressant response). In 49 patients treated with paroxetine and/or fluoxetine, Charlier et al⁴¹ found that the PM phenotype was associated with higher plasma concentrations of each drug in comparison to the EM phenotype. As reported previously by Alderman et al,⁴² a single-point pharmacokinetic study by Nichols et al⁴³ found that when treated with paroxetine, healthy controls had a 419% increase in the CYP2D6

substrate desipramine AUC and a 90% increase in peak plasma concentration in comparison to desipramine substrate alone. Sato et al⁴⁴ described a case of serotonin syndrome treated with paroxetine at 20 mg/d. The plasma concentration of paroxetine was substantially elevated (70 ng/mL; reference range, <23 ng/mL), which was attributed in part to the patient's CYP2D6 genotype of intermediate metabolizer. Finally, the FDA has recently issued safety labeling changes for fluoxetine, stating that the drug "should be used with caution in patients with congenital long QT syndrome; a previous history of QT prolongation; a family history of long QT syndrome or sudden cardiac death; and other conditions that predispose to QT prolongation and ventricular arrhythmia" and that such conditions include CYP2D6 PM and coadministration of CYP2D6 inhibitors.³³

In addition, CYP2D6 PMs taking venlafaxine have increased plasma levels of venlafaxine, which has been associated with higher rates of adverse effects including cardiotoxicity, nausea, vomiting, diarrhea, and hyponatremia.⁴⁵⁻⁴⁸ Shams et al⁴⁸ quantified the plasma *O*-desmethylvenlafaxine to venlafaxine ratio and reported a significantly higher rate of emerging adverse effects in the CYP2D6 PMs vs all other genotypes. Individuals with *O*-desmethylvenlafaxine to venlafaxine ratios of less than 0.3 were all identified as PMs (genotype *6/*4, *5/*4, or *6/*6) and had significantly more adverse effects (mainly gastrointestinal tract adverse events) in comparison with non-PMs.⁴⁸ There does not appear to be a PM genotype associated with fluoxetine- or paroxetine-induced hyponatremia.⁴⁹

The strongest evidence for adverse event and genomic variation associated with regulatory revision of drug labeling has been citalopram and QTc prolongation. Compared with placebo, citalopram has been associated with a dose-dependent QTc increase (20 mg, 8.5 ms; 60 mg, 18.5 ms). An initial FDA recommendation to not prescribe doses greater than 40 mg/d was revised to greater than 20 mg/d, with identification of CYP2C19 PM phenotype status contributing to this QTc prolongation risk.^{50,51} This recommendation applies to escitalopram (citalopram *S*-enantiomer) by extension.

Fatalities associated with genotyping are increasingly recognized in the forensic literature.

Jornil et al⁵² described a 34-year-old man with major depressive disorder who was taking venlafaxine at the time of death. They concluded that the cause of death was likely cardiac arrest due to a high blood concentration of venlafaxine (4.5 mg/kg) attributed to CYP2D6 PM phenotype, which was confirmed by genetic testing. Sallee et al⁵³ reported the case of a 9-year-old child with OCD and Tourette syndrome treated with a combination of methylphenidate, clonidine, and high-dose (80-100 mg/d) fluoxetine who had metabolic toxicity followed by seizures, status epilepticus, cardiac arrest, and death. Genetic testing of autopsy tissue revealed a CYP2D6 PM phenotype. In addition to the tragic death, the adoptive parents of the child were investigated by social services. Although long-term high-dose fluoxetine can produce an auto-phenocopy that further inhibits CYP2D6, the baseline PM phenotype based on genotype may have contributed in part to the fatality. These forensic cases will only increase in number⁵⁴⁻⁵⁶ with the growing use of antidepressants in younger patients and the expanding use of genetic testing.

Efficacy

Pharmacokinetic-related CYP2D6 outcome measures have been less systematically studied.^{57,58} In a study of 83 child and adolescent patients, the ratio of fluoxetine to S-norfluoxetine was inversely correlated with the number of active CYP2D6 alleles ($r=-0.450$; $P<.001$).⁵⁹ Interestingly, the CYP2D6 metabolite S-norfluoxetine is a potent SSRI and is also metabolized by CYP2D6.⁶⁰ In a prospective trial of 184 patients with OCD, the CYP2D6 non-EM phenotypes (poor, intermediate) were associated with a higher number of retrospectively identified treatment failures for presenting index episode ($P=.007$) and a nonsignificantly lower treatment response to a prospective trial of fluoxetine ($P=.056$).⁶¹ Multiple studies have reported an association between CYP2D6 ultrarapid phenotype and lower paroxetine plasma levels, which is particularly clinically relevant knowing that paroxetine metabolites are inactive; nonetheless, all these studies were limited by small sample size and inconclusive evidence.⁶²⁻⁶⁴

Gressier et al⁶⁵ conducted a prospective study of 87 white patients receiving antidepressants; CYP2D6 ultrarapid metabolizers

had a significantly lower response to antidepressants (>60% were taking fluoxetine or paroxetine) compared with composite poor/intermediate phenotype. Limited by small sample size, these data suggest a relationship between ultrarapid phenotype and treatment response; nevertheless, plasma level and dose-response for treatment outcome needs to be further investigated.

The strongest evidence to date of CYP2D6 pharmacokinetic variation and treatment response is venlafaxine.⁶⁶ In a review of 4 randomized, placebo-controlled studies ($n=464$ patients), the EM phenotype, in comparison to PM phenotype and placebo, was associated with a lower concentration of venlafaxine, a higher concentration of O-desmethylvenlafaxine, and a greater baseline to end point change in the Hamilton Rating Scale for Depression and overall 65% response and 41% remission rates.⁶⁶

The field is moving beyond single candidate gene analysis for adverse effect or treatment response and evaluating the impact of broader platform algorithm products that can allow rapid identification of multiple pharmacokinetic and/or pharmacodynamic genomic variation.⁶⁷ Preliminary data from a nonrandomized open-label 8-week prospective study of treatment-seeking patients with major depression revealed a significant reduction in depressive symptoms (both by the 17-item Hamilton Rating Scale for Depression and the Quick Inventory of Depressive Symptomatology – Clinician Rated [QIDS-C16]) with antidepressant pharmacogenetics-guided treatment selection ($n=22$ patients) vs unguided treatment as usual (22 patients).⁶⁸ This proof of concept study was replicated with a larger cohort (72 patients with antidepressant pharmacogenetics-guided treatment selection and 93 with unguided treatment as usual) and found statistically significant reductions in the Hamilton Rating Scale for Depression, QIDS-C16, and additional self-reported Patient Health Questionnaire (PHQ-9) and in the remission rate (QIDS-C16).⁶⁹

In comparison with genetic variation associated with adverse events or quantifiable biological processes (eg, rash, QTc prolongation), the evidence base for pharmacogenetics-based treatment recommendations is considerably smaller. Study designs have been limited by small sample size, overestimation of effect sizes,

and absence of comparative data and generalizability.⁷⁰ However, clinical trials are under way to further assess the clinical utility of pharmacogenetics testing, specifically for CYP2D6 and venlafaxine and nortriptyline.⁷¹

PHARMACOKINETIC PHARMACOGENETICS: CYP2D6/CYP2C19 GUIDELINE DEVELOPMENT

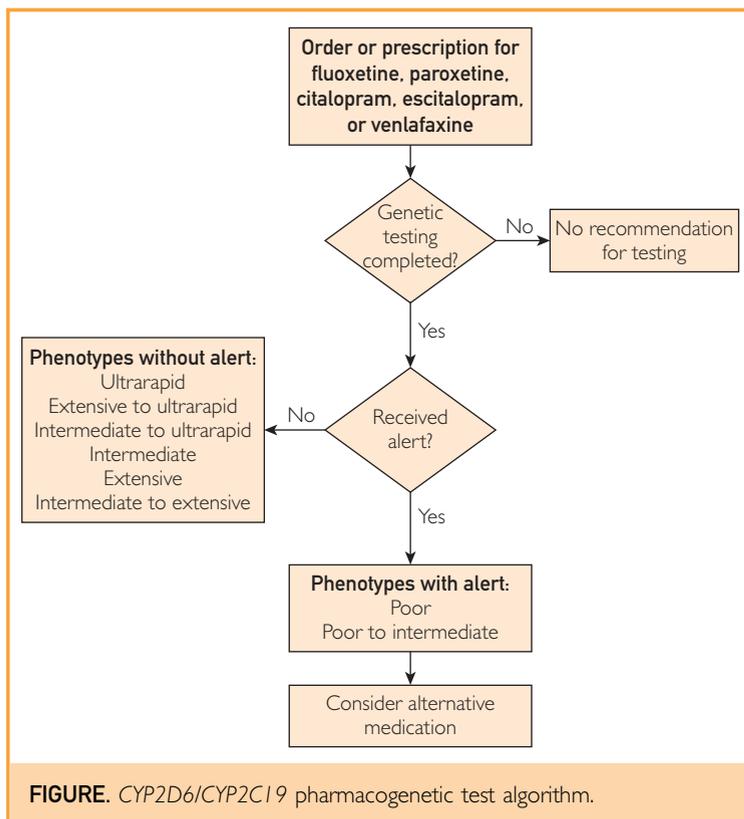
The Clinical Pharmacogenetics Implementation Consortium (CPIC) was established as a joint effort between PharmGKB and the Pharmacogenomics Research Network charged to review and develop peer-reviewed guidelines and while doing so address clinical translational barriers to implementation of pharmacogenomic tests into practice. Despite the growing evidence of the clinical importance of pharmacogenetics, its adoption into clinical practice has been hindered.⁷² This problem is attributed in part to the fact that health care professionals feel uncomfortable ordering/interpreting these tests, the lack of training in pharmacogenetics, and the continuously and rapidly emerging data in the field.^{73,74} The introduction of multidisciplinary pharmacogenetic education into the everyday

workflow of prescribers through electronic alerts at the time of prescribing has been suggested.⁷⁵

The CPIC has recently released guidelines for CYP2D6/CYP2C19 genotypes and dosing of SSRIs.²¹ Although these recommendations are broad in scope, our group at Mayo Clinic, through our Pharmacogenomics Task Force, has implemented decision support guidelines to provide clinicians with up-to-date information on a patient's genotype and subsequent recommendations. The decision support guidelines are linked to Web-based educational material (Ask Mayo Expert) to provide further information about specific genotypes, drugs, or decision support tools.⁷⁶ For example, when prescribing fluoxetine, paroxetine, or venlafaxine to a patient who is a known CYP2D6 poor or poor to intermediate metabolizer or prescribing citalopram or escitalopram to a patient who is a known CYP2C19 poor or poor to intermediate metabolizer, an alert will appear on the computerized physician order entry system. In the absence of clear FDA guidelines for dose adjustment, an alternative medication that is metabolized by another enzyme should be considered (Figure). Along with genetic variants, concurrent administration of specific medications can reduce CYP2D6 and CYP2C19 activity.⁷⁷

For PMS, we emphasize using an alternative medication rather than the option of reducing the dose (as suggested per CPIC guidelines²¹). Our rationale is that using an alternative medication is constructed on clinical applicability and ease—switching to an alternatively metabolized antidepressant vs careful monitoring of lowered-dose antidepressants. Furthermore, with the lack of clear evidence of clinically relevant differences in efficacy among the various SSRIs for treating depression,⁷⁸⁻⁸⁰ preventing possible adverse events by prescribing an alternative SSRI becomes more appropriate than lowering the dose of a potentially unsafe medication. Similarly, we have adopted a parallel guideline for fluoxetine and venlafaxine. We believe that the benefits of applying these recommendations outweigh the risks and that waiting for stronger evidence is not in the best interest of patients.

Medications with a narrow therapeutic index have been studied for specific therapeutic plasma levels (eg, lithium, 0.6-0.8 mmol/L; valproic acid, 50-100 mg/L; and nortriptyline,



70-170 ng/mL) or linear dose response (desipramine, 100-300 ng/mL).⁸¹⁻⁸⁴ In contrast to mood stabilizers and tricyclic antidepressants, there are limited data on plasma concentration and dose-response relationship for SSRI antidepressants⁸⁵⁻⁹⁸ with the exception of a recent meta-analysis revealing a significant association between SSRI dose and response.³⁴ There has been little systematic investigation of metabolism phenotype and plasma/serum level of antidepressant and any active metabolite. Therefore, because of the lack of evidence for a clear clinical association between ultrarapid metabolizers and low antidepressant plasma levels, we did not implement guidelines for ultrarapid metabolizer phenotypes. Finally, it is been reported that a minimum dose of each marketed SSRI produces 70% to 80% inhibition or occupancy of the serotonin transporter.^{99,100} More research is warranted to investigate any correlation between serotonin transporter occupancy and clinical response, plasma level (rather than the dose) needed to achieve this targeted occupancy, and any CYP genotype—guided dosing that can achieve this minimum plasma level to sufficiently occupy the serotonin transporter.¹⁰¹

The decision support guidelines we developed apply only to patients for whom the genotype is already known and is present in the electronic medical record. Clinicians are alerted only if a high-risk genotype for which action may be indicated on prescribing the involved drug is known. Currently, routine preemptive pharmacogenetic testing for antidepressant selection is not recommended for reasons that include lack of large-scale clinical trial data supporting its use, cost-effectiveness, and insurance coverage. This concept, however, will only increase in potential importance as the field matures. Nonetheless, it has been argued that preemptive genotyping may improve patient safety,¹⁰² and further research will clarify precision medicine's ability to increase the efficacy of individualized antidepressant treatment.¹⁴ The available genotyping data can be generated through multiple genotyping techniques that may vary by institution. At this point, we do not recommend any specific genotyping technique. However, similar to other clinical laboratory testing, genotyping techniques have different levels of accuracy, and genotyping errors remain. In addition, the

current knowledge about the variants in the CYP2D6 and CYP2C19 genes can be expanded further by adding epigenetic data. Currently available genetic testing can be reviewed through the Genetic Testing Registry.¹⁰³

Clinical genotyping for CYP2D6- and CYP2C19-metabolized medications is increasingly considered in clinical practice for treatment-resistant depression, when higher dosing for OCD is anticipated, if there is a known family history of CYP2D6/CYP2C19 PM phenotype, and in patients taking multiple drugs concurrently. Clear assessment of symptom misattribution (drug adverse effect vs somatic symptoms of depression/anxiety) is critical to manage patient expectations of the value of genotyping. Despite the pronounced potential of precision medicine, its adoption into clinical practice has been relatively slow, partially because of challenges in insurance coverage and reimbursement.^{104,105} When considering genomic and pharmacogenetic testing, insurers consider multiple factors in their medical coverage policies including the test cost-effectiveness, level of scientific evidence, availability of accepted guidelines, and clear clinical importance.¹⁰⁶⁻¹⁰⁸ One study evaluated the coverage policies of the major US insurance companies for genomic and pharmacogenetic testing and found that less than half of the reviewed tests were covered. The major reason for noncoverage was the lack of strong evidence of clinical utility, while the major reason for coverage was the inclusion of pharmacogenetic information in drugs labels.¹⁰⁹

To our knowledge, the proposed implementation of pharmacogenetic prescription guidelines has been structured according to the best existing empirical evidence. Although the evidence base for antidepressant pharmacogenetic outcomes is less robust than, for example, targeted cancer therapy,¹¹⁰⁻¹¹² it has been argued that waiting for such robust evidence might not be in the best interest of the patients and could deprive them of safer medications.¹¹³ However, genomic testing does not replace good psychiatric examination, and sound clinical judgment must be utilized alongside the recommendations based on genotyping testing.

CONCLUSION

With the continuous decrease in the cost of genetic testing, the willingness of insurance

companies to cover such tests, and the increase in published data providing more robust evidence of clinical importance, *CYP2D6/CYP2C19* genotyping might become, in the near future, a routine test before prescribing relevant antidepressants to all patients. Meanwhile, utilizing the current available evidence and trying to follow the most supported guidelines must be our provisional goal for more precise medical practice in psychiatry.

Abbreviations and Acronyms: **AUC** = area under the curve; **CPIC** = Clinical Pharmacogenetics Implementation Consortium; **CYP** = cytochrome P450; **EM** = extensive metabolizer; **FDA** = US Food and Drug Administration; **OCD** = obsessive-compulsive disorder; **PM** = poor metabolizer; **QIDS-C16** = Quick Inventory of Depressive Symptomatology — Clinician Rated; **SSRI** = selective serotonin reuptake inhibitor

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