Personalized prescribing: a new medical model for clinical implementation of psychotropic drugs

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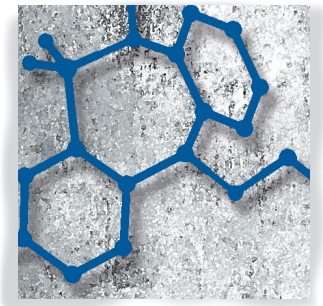

*The use of pharmacogenetic tests was already being proposed in psychiatry in the early 2000s because genetic factors were known to influence drug pharmacokinetics and pharmacodynamics. However, sufficient levels of evidence to justify routine use have been achieved for only a few tests (eg, major histocompatibility complex, class I, B, allele 1502 [HLA-B*1502] for carbamazepine in epilepsy and bipolar disorders); many findings are too preliminary or, when replicated, of low clinical relevance because of a small effect size. Although drug selection and dose adaptation according to cytochrome P450 genotypes are sound, a large number of patients need to be genotyped in order to prevent one case of severe side effect and/or nonresponse. The decrease in cost for genetic analysis shifts the cost:benefit ratio toward increasing use of pharmacogenetic tests. However, they have to be combined with careful clinical evaluations and other tools (eg, therapeutic drug monitoring and phenotyping) to contribute to the general aim of providing the best care for psychiatric patients.*

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Introduction

Psychiatric illnesses are associated with a high prevalence of therapeutic failure, drug-associated side effects, and recurrent conditions. In psychiatry, as in other diseases, there is a high interindividual variability in drug responses for efficacy, tolerability, and safety, which is determined by patient factors such as illnesses, sex, age, ethnicity, and genetic variability, and by environmental factors, including concomitant medication, smoking, and/or diet.[1,2] This variability in drug response is affected by variability in pharmacokinetics, ie, drug disposition (absorption, distribution, metabolism and excretion [ADME]), leading to a variability in plasma concentration of the active drug, but also by variability in pharmacodynamics, ie, the interaction of the drug with its target site (such as enzymes, receptors, and transporters).[1] Personalized prescribing can be expressed as personalized dosing and/or drug selection, taking into account genetic, as well as environmental and personal, variables.[3] This review discusses the present and future use of pharmacogenetics in psychiatry, which, combined with careful clinical evaluations and other tools such as

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Selected abbreviations and acronyms

CYP	*cytochrome P450*
EM	*extensive metabolizer*
GWAS	*genome-wide association study*
HLA	*human leukocyte antigen*
HLA-B	*major histocompatibility complex, class I, B*
IM	*intermediate metabolizer*
PM	*poor metabolizer*
SJS	*Stevens-Johnson syndrome*
SSRI	*selective serotonin reuptake inhibitor*
TCA	*tricyclic antidepressants*
TDM	*therapeutic drug monitoring*
TEN	*toxic epidermal necrolysis*
UM	*ultrarapid metabolizer*

therapeutic drug monitoring (TDM) and phenotyping, can help provide the best care for psychiatric patients. This review is based on arbitrarily selected pharmacogenetic studies. The topic of TDM is covered in detail by a consensus article[4] and is not discussed here. Whereas our review has a stronger focus on the clinical applications and usefulness of pharmacogenetics tests, the article by Eum et al in this issue (p 323) provides a much more detailed elaboration of currently commercially available tests.

Pharmacokinetics genes

Among pharmacokinetics proteins, the members of the cytochrome P450 (CYP) family display large interindividual and interethnic variability in activity, controlling the metabolism of many psychotropic drugs. More than 50 CYP enzymes have been identified in humans, but more than 90% of all drugs are metabolized by only a few of them—CYP1A2, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5. The US Food and Drug Administration (FDA) table of pharmacogenetic markers in drug labels[5] contains more than 135 drugs, a fifth used in psychiatry, most of them CYP2D6-dependent drugs.

Various CYP2D6-activity phenotypes exist, including poor, intermediate, extensive, and ultrarapid metabolizers (PMs, IMs, EMs, and UMs), with PMs having no functional alleles, IMs being heterozygous for an active and an inactive allele or having two alleles with reduced activity, EMs being wild-type with two active alleles, and UMs having an amplification of functional alleles (3 to 13 copies).[6,7] The PM status can be genotyped, with 5 to 10 single-nucleotide polymorphisms (SNPs) accounting for 95% to 99% of the variability. However, more than 100 variants and subvariants have been described for *CYP2D6*,[8] with a strong influence by geographic and ethnic factors, which should be taken into account.

Some studies showed that CYP2D6 might influence the metabolism of endogenous compounds, such as the ligand for the cannabinoid receptor anandamide,[9] or the production of serotonin,[10] with a higher platelet serotonin concentration in UMs than in EMs and PMs.[11] It has been suggested that this could lead to variations in personality, neurocognitive function, and vulnerability to psychopathology, including suicidality.[12,13] Indeed, a high occurrence of the CYP2D6 UM phenotype has been found in suicide cases[14-16]; this association could be due to failure of treatment with drugs metabolized by CYP2D6 but also to the metabolism of endogenous substrates. However, CYP2D6 is not a useful predictor of psychiatric symptoms and/or disorders.

On the other hand, many studies have shown a strong influence of CYP2D6 activity on the pharmacokinetics of psychotropic drugs. These include drugs for attention-deficit/hyperactivity disorder (eg, atomoxetine); antidepressants, such as tricyclics (TCAs) or tetracyclics (TeCAs) that are serotonin and/or norepinephrine reuptake inhibitors (eg, amitriptyline, clomipramine, desipramine, doxepine, imipramine, maprotiline, nortriptyline, or trimipramine), selective serotonin reuptake inhibitors (SSRIs; eg, citalopram, escitalopram, fluoxetine, fluvoxamine, or paroxetine), and serotonin-norepinephrine reuptake inhibitors (SNRI; eg, duloxetine or venlafaxine); other antidepressants (eg, mianserin or mirtazapine); and antipsychotics (eg, aripiprazole, haloperidol, levomepromazine, perphenazine, risperidone, thioridazine, or zuclopentixol).[6,17] Of note, the activity of CYP2D6 and other CYP isoforms can be blocked; several compounds, including some of the abovementioned drugs, are strong CYP2D6 inhibitors (eg, levomepromazine, paroxetine, and fluoxetine) and can potentially transform the phenotype from CYP2D6 EM to PM.[2] On the other hand, CYP2D6 activity cannot be induced in contrast to other CYP isoforms (one Website listing drugs with their CYP-mediated metabolism, as well as important metabolic interactions, can be found in ref 18).

Optimal therapeutic ranges for drug concentrations in plasma have been demonstrated for TCAs, such as

amitriptyline, clomipramine, doxepin, imipramine, and trimipramine,[4] with UMs at increased risk of therapeutic failure and PMs at increased risk of toxicity (in particular, for cardiac and anticholinergic effects). A higher risk of side effects has been observed in patients with at least one nonfunctional *CYP2D6* allele than in those with two functional alleles.[7] The first genotype-based dose recommendations for antidepressants, including amitriptyline, were proposed by Kirchheiner et al in 2001.[19] More recently, the Pharmacogenetics Working Group from the Royal Dutch Association for the Advancement of Pharmacy developed guidelines.[20] Also, the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health's Pharmacogenomics Research Network developed a detailed guideline—updated periodically[21]—for CYP2D6 and CYP2C19 genotypes and dosing of TCAs.[7] For example, in the treatment of depression with amitriptyline, the CPIC recommends consideration of an alternative drug for CYP2D6 UMs and PMs.

Personal dosing in psychiatry according to CYP genotype is best adapted for TCAs.[7] However, in psychiatry, the impact of such a strategy is limited since the prescription of TCAs has greatly decreased since the introduction of newer antidepressants (TCAs being mainly used nowadays at lower doses for pain management). Personalized prescribing according to CYP2D6 genotype has been proposed for more recent antidepressants, such as SSRIs (eg, paroxetine, fluoxetine), which are first-line treatments for depression, but also for other psychiatric conditions, such as anxiety, panic, and obsessive-compulsive disorders.[17] Therapeutic ranges have also been proposed for these newer antidepressants[4]; however, as they have wider margins of safety in terms of overdose, as well as lower risks for side effects, the specificity and sensitivity are decreased for CYP genotyping tests in regard to prevention of side effects and/or increasing therapeutic response. Drug choice and/or dose adaptations made on the basis of *CYP2D6* genotype have also been proposed for other antidepressants, such as SNRIs (eg, venlafaxine), and for typical (eg, perphenazine, thioridazine) and atypical antipsychotics (eg, risperidone, aripiprazole).[17,20] Of note, several studies found a higher prevalence of psychotropic drug–induced side effects associated with CYP activity, in particular with CYP2D6 PM status[22-28]; however, most studies investigating an association between CYP2D6 phenotype and/or genotype and treatment response had negative results,[29-31] though some had positive results.[32]

CYP2C19 is also highly polymorphic with more than 30 described variants, and allele frequencies are strongly influenced by ethnicity. Similarly, PMs, IMs, EMs, and UMs have been described; the UM phenotype might arise from enhanced gene transcription resulting from the *17 allele, possibly increasing metabolism of antidepressants, such as citalopram and escitalopram.[33] In addition, because the QT-inducing potential associated with these two drugs is higher than with other SSRIs, the CYP2C19 PM phenotype could be a risk factor in treatment with escitalopram.[34] Higher amitriptyline and lower nortriptyline plasma concentrations were measured in CYP2C19 PMs and IMs than in EMs. Personalized prescribing of SSRIs according to *CYP2C19* genotype has also been proposed.[35] The CPIC also made recommendations for amitriptyline dosing for combined CYP2D6 and CYP2C19 phenotypes; however, as clinical evidence for an additive effect of CYP2D6 and CYP2C19 in tricyclic dosing is sparse, the recommendations are classified as optional.

CYP2B6 metabolizes a fewer number of compounds, which include methadone and bupropion among psychotropic drugs. Its activity is also highly variable between individuals and within individuals because of genetic and environmental factors.[36] *CYP2B6* is highly polymorphic, with variants associated with multiple mechanisms (transcriptional regulation, splicing, messenger RNA and protein expression, and catalytic activity).[36] The simultaneous combinations of many variants producing multiple haplotypes, in addition to the large ethnic influence on *CYP2B6* polymorphism, complicates its analysis and the interpretation of results. Methadone, a mu-opioid agonist used in pain treatment and for opioid-dependent patients, can prolong the QT interval and carries a risk for ventricular tachyarrhythmia and Torsades de pointes. Methadone is marketed as a 50%/50% mixture of (*R*)- and (*S*)-methadone, with few countries (eg, Germany, Austria, and Switzerland) currently having the pure (*R*)-enantiomer also available. (*R*)-methadone is the active form on opioid receptors, whereas (*S*)-methadone blocks more potently the human ether-à-gogo–related gene (hERG) voltage-gated potassium channel, which is responsible for QT-interval prolongation.[37] (*S*)-methadone is metabolized preferentially by CYP2B6, with multiple genetic polymorphisms helping to explain extreme (*S*)-methadone plasma lev-

els.[38] CYP2B6 slow metabolizers have longer corrected QT (QTc) intervals during methadone treatment, and slow CYP2B6 metabolism significantly increases the risk for a borderline or prolonged QTc interval (odds ratio, 6.3).[37] In addition, the replacement of (*R,S*)-methadone by a half dose of (*R*)-methadone significantly decreases the QTc interval in opioid-dependent patients treated with methadone.[39] Prescription of (*R*)-methadone instead of the racemate, therefore, decreases (but does not abolish) methadone cardiotoxicity and should also decrease the influence of CYP2B6-decreased metabolism. However, for a number of reasons, *CYP2B6* genotyping cannot substitute for an electrocardiogram in the prediction of cardiac arrhythmias and sudden death in methadone patients. Firstly, diminished CYP2B6 activity is associated with many variants and haplotypes (several with yet unknown functions). Secondly, the presence of several pharmacodynamic heart genes and multiple other risk factors (eg, electrolyte disturbances, pharmaceutical or illicit drugs prolonging the QT interval and/or inhibiting methadone metabolism) may confound the conclusions.

CYP1A2 is particularly involved in the metabolism of clozapine or olanzapine—two atypical antipsychotics—and of duloxetine, an SNRI. Clozapine appears to be more promising than other drugs for personalized dosing because several studies have demonstrated an optimal plasma concentration for this drug; furthermore, high plasma levels are associated with a higher risk of convulsions.[4] Some genetic CYP1A2 variants have been associated with low or high clozapine metabolic activity,[40,41] but these alleles are either rare or have low predictive value. Therefore, *CYP1A2* genotyping is currently of little help for most patients. CYP1A2 activity is also controlled by other (non-CYP1A2) genetic factors, including the P450 oxidoreductase and nuclear factors—such as constitutive androstane receptor (*CAR*), retinoid X receptor α (*RXRa*), pregnane X receptor (*PXR*), and vitamin D receptor (*VDR*)—which are involved in the regulation of constitutive and/or inducible CYP1A2 activity.[42-44] Genotyping of those additional genes adds little to predicting CYP1A2 variability, possibly due to the influences of other genes and to the environmental influence on CYP1A2 activity. Thus, phenotyping tests (in vivo measurement of the activity using a probe substance, such as caffeine[45]) or TDM are more appropriate for personalized dosing of clozapine or of other CYP1A2-dependent drugs.

Because of its abundance in the intestine and liver, CYP3A—a term that in adults reflects the collective activity of CYP3A4, CYP3A5, and CYP3A7—is responsible for the metabolism of more than 50% of marketed drugs. There is a large overlap of activity between CYP isoforms, potentially reducing the influence of *CYP3A* genetic heterogeneity on the pharmacokinetics of CYP3A-dependent drugs as a deficiency of one isoform may be partially compensated for by the activity of others. Although rare cases have been described of CYP3A PMs in which there is the simultaneous occurrence of mutations in different isoforms leading to very low or no CYP3A activity, genotyping is of little clinical relevance[46] unless the drug is preferentially metabolized by CYP3A5 (there is no known example in psychiatry). As is the case for CYP1A2, estimation of CYP3A activity is best measured by phenotyping tests, eg, performed with a very low oral dose of midazolam,[45,47] such a test also integrating the modification of CYP3A activity by environmental factors.

Other pharmacokinetic genes are not discussed in the present review, in particular *ABCB1*, which encodes for the permeability P-glycoprotein. Although *ABCB1* has been investigated in many studies for its influence on pharmacokinetics and on the response to psychotropic drugs, mixed results have been published and evidence is lacking for the clinical use of *ABCB1* genotyping in psychiatry.[48,49] This gene is discussed in more detail in the companion article by Eum et al in this issue.

In summary, pharmacokinetic genotyping can be useful in drug selection and/or for guiding dosing modifications with the aim to personalize dosing. This is especially important for TCAs, which have a well-defined therapeutic window; nowadays, however, this class of drug is seldom prescribed for depression. Even if the impact of such tests is less important for other drugs, such a strategy is based on a sound and legitimate objective to reduce the interindividual variability in drug pharmacokinetics and the risks associated with extreme phenotypes. CYP genotyping appears more useful at the start of treatment than later on; after long-term treatment, the drug best adapted to a particular patient would possibly already have been selected through trial and error, and the drug dose already adapted according to effect.[7] However, some CYP isoform activity (eg, CYP1A2 or CYP3A) is poorly predicted by gene analysis and must be determined by phenotyping. Thus,

pharmacogenetic tests would not replace, but rather complement, other clinical tools, such as TDM, the latter combining the influence of environmental (eg, diet and/or taking of comedications that induce or inhibit activity), genetic (eg, CYP variants), and personal factors (eg, age, sex, weight, and illness) involved in metabolism and transport of drugs. Last but not least, TDM allows the measurement of active metabolites.[1]

Pharmacodynamic genes for personalized drug selection

Genetic testing of pharmacodynamic factors is presently more promising for preventing rare idiosyncratic adverse drug reactions than for predicting treatment response. Some recent findings linking pharmacogenetic factors with therapeutic response are interesting but need to be replicated.

Response to treatment and pharmacodynamic factors

Because of the common mechanism of many antidepressants—the inhibition of the reuptake of serotonin by the serotonin transporter—polymorphisms in the serotonin-transporter-linked polymorphic region (5-HTTLPR) of the serotonin transporter gene (*SLC6A4*) have been extensively studied. In particular, the long (l)-allele is associated with a twofold higher expression than the short (s)-allele. Despite some discrepant results, a meta-analysis of 33 studies confirmed the association between the (l)-allele and response to SSRIs and remission in whites, with sex, age, and age at onset of depression modulating the association.[50] However, the clinical impact of *SLC6A4* genotyping is modest, with a low odds ratio value (around 1.5), and therefore of little clinical help for predicting response. Other genes—including serotonin receptors (5-hydroxytryptamine receptors 1A and 2A [*HTR1A*, *HTR2A*]); tryptophan hydroxylase (*TPH1*), involved in serotonin biosynthesis; serotonin transporter gene functional intron 2 (*STin2*), influencing serotonin transporter expression; and brain-derived neurotrophic factor (*BDNF*), probably involved in antidepressant action—may also modestly modulate antidepressant response.[51] The hypothalamic-pituitary-adrenal (HPA) axis has been implicated in antidepressant response; polymorphisms in the FK506 binding protein 5 (*FKBP5*), which regulates glucocorticoid receptor sensitivity has been associated with rapid response to antidepressant treatment.[52] However, this study was followed by others that in some cases supported these findings and in others did not.[53]

Because dopamine is involved in the neurotransmitter pathology of schizophrenia and because of the antagonist (all antipsychotics) or mixed agonist (aripiprazole) activity of antipsychotics on the dopamine D_2 receptor, dopamine receptor and transporter genes have also been investigated. Polymorphisms in the D_2 receptor, in particular the -141Ins/Del polymorphism located in the promoter region, were associated with treatment response (lower response for Del allele) in a meta-analysis, but with a modest effect.[54] Other significant, but modest, associations were also found with other catecholamine systems, as well as glutamate and γ-aminobutyric acid (GABA) systems, although none of them could be considered clinically discriminant.[55]

Although topiramate, an antiepileptic drug, has no official indication for the treatment of alcoholism, it reduces drinking and heavy drinking in individuals with alcohol dependence. Topiramate has multiple pharmacologic effects, including the facilitation of GABAergic function and antagonism of glutamate activity at the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid class of glutamate receptor (AMPA) and at kainate receptors, particularly for those containing GluK1 and GluK2 subunits (encoded by *GRIK1* and *GRIK2*, respectively). The efficacy of topiramate for reducing heavy drinking was recently found to be significantly greater than placebo only in *GRIK1* rs2832407 C-allele homozygotes.[56] If these results are replicated, it would allow identification of heavy drinkers who would probably respond well to topiramate. This is important because there are only a few drugs available for alcoholism treatment, and they have limited success.

A meta-analysis of three genome-wide association study (GWAS) analyses (GENDEP [GENome-based therapeutic drugs for DEPression], MARS [Munich Antidepressant Response Signatures], and STAR*D [Sequenced Treatment Alternatives to Relieve Depression]), examining the association with antidepressant drug response in 2256 individuals of Northern European descent with major depressive disorders, failed to identify reliable predictors of antidepressant treatment.[57] A recent GWAS was performed for lithium response in bipolar 1 disorder with 294 patients of Han Chinese descent and replicated in two smaller groups.[58] Variations in the gene encoding glutamate decarboxyl-

ase–like protein 1 (*GADL1*) were found to be associated with response to lithium with an extraordinarily highly significant *P* value ($P=10^{-37}$). The mechanism by which GADL1 would influence response is unknown, but its involvement in the biosynthesis of GABA is discussed. This finding has to be confirmed in Chinese patients, and other mutations have to be found in Caucasian and black African subjects (there is a low frequency of the variant of interest in these two populations). Interestingly, a recent study pointed to a variant located in a methylated DNA immunoprecipitation sequencing (MeDIP-seq) site in the brain that may have exome-wide significance for treatment remission in depressed Mexican-Americans treated with fluoxetine; this finding suggests that this variant may be involved in epigenetic regulation of neuronal gene expression.[59] This study emphasizes the need for pharmacogenetic studies to include epigenetic factors.

Adverse events and pharmacodynamic factors

Concerning antipsychotics, dopamine receptor and transporter genes have also been investigated for associations between genetic polymorphisms and antipsychotic-induced side effects, eg, hyperprolactinemia, extrapyramidal symptoms, and weight gain. Some results were inconsistent, whereas others were significant in meta-analyses only and were of low effect size as they needed a high number of patients to reach statistical significance. The discrepant results and/or the weak significant associations observed could be due, in part, to the proportions of classical (higher risk of hyperprolactinemia and extrapyramidal symptoms) and atypical antipsychotics (higher risks of weight gain) differing between studies; thus, the described associations are of weak or modest predictive value.[55] For antidepressants, genetic variations in serotoninergic mediators (eg, serotonin transporter and receptors), as well as in intracellular signal transduction pathways, have also been extensively studied.[60] The results, when replicated, appear to be more related to tolerance and side effects than to the antidepressant response. Evidence and effect sizes that are sufficient to allow clinical applications are lacking.

A large number of psychotropic drugs, including many antipsychotics (eg, clozapine or olanzapine), some mood stabilizers (eg, valproate), and some antidepressants (eg, mirtazapine), have been associated with substantial weight gain and/or other metabolic dysfunctions (eg, obesity, hyperlipidemia, hypertension, and/or diabetes). Drug-induced weight gain and other metabolic symptoms are of major clinical consequence as they contribute heavily to a marked decrease in life expectancy, with the natural mortality rate in psychiatric patients being 1.5- to 2-fold higher than in the general population, mainly due to a twofold higher prevalence of cardiovascular risk factors.[61-63] Pharmacogenetics of psychotropic-induced weight gain has been extensively studied through hypothesis-driven candidate gene approaches. The polymorphisms that were the most studied and for which results were best replicated were in dopamine and serotonin receptors.[64] Additionally, other genes implicated in leptin-melanocortin pathways (eg, leptin [*LEP*], leptin receptor [*LEPR*], melanocortin 4 receptor [*MC4R*], and neuropeptide Y [*NPY*]), the endocannabinoid system (cannabinoid receptor type 1 [*CNR1*]), or genes involved in fatty acid and cholesterol production (scavenger receptor class B type I [*SCARB1*], insulin-induced gene 2 [*INSIG2*]) showed an association with weight gain among psychiatric cohorts treated with antipsychotics.[65] Recently, research conducted in our department showed other candidate genes coding for enzymes involved in metabolic pathways (phosphoenolpyruvate carboxykinase 1 [PCK1], 11β-hydroxysteroid dehydrogenase [11βHSDW1]), for receptors (melanin concentrating hormone receptor 2 [MCHR2]), and for transcriptional coactivators (CREB-regulated transcriptional coactivator 1 [CRTC1]) involved in energy balance, appetite regulation, and glucose homeostasis.[66-69] There is less information on genes associated with antipsychotic-induced diabetes mellitus and hyperlipidemia. A recent GWAS (N=189) identified no associations with antipsychotic-induced weight gain at the genome-wide threshold, but trends for some variants were observed, variants that should be investigated further.[70] The occurrence of metabolic effects can be best predicted by a combination of clinical factors (eg, age and baseline body mass index) with multiple genetic factors, possibly aggregated in genetic risk scores.[71] However, the value of such combinations in clinical practice remains to be determined.

Presently, the drug in psychiatry with probably the most compelling evidence in support of pharmacogenetic testing is carbamazepine, an anticonvulsant and a mood-stabilizer drug. It can cause Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) reac-

tions, which occur in about 1 to 6 per 10 000 new users in the white population, but the risk is strongly increased in Asian patients. In Asians, major histocompatibility complex, class I, B, allele 1502 (HLAB*1502 allele) is a predictor of SJS-TEN, with an extraordinarily high odds ratio (odds ratio, 1357, P=1.6*10^{-41}).[72] The FDA requires that Asian patients be screened for the presence of HLA-B*1502 before initiating carbamazepine treatment. Because this allele is also present in patients with non-Asian ancestry, and because Asian ancestry can neither be deduced from the family name nor from the physical appearance, the extension of these analyses in all patients has been advocated.[73] Patients carrying this allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk. In a prospective screening for HLA-B*1502 before prescription of carbamazepine in 4877 Asian patients, no SJS-TEN case was observed in the HLA-B*1502-negative patients, whereas 10 cases were expected, based on historical incidence, without screening.[74] The HLA-A*3101 allele has been proposed as a clinically relevant marker to predict hypersensitivity reactions to carbamazepine in whites and Japanese, but has low sensitivity. The positive predictive value and negative predictive value for a HLA-B*1502 screening test in Asians is 1.8% (7.7% in Han only) and 100%, respectively, with 461 patients needing to be tested to prevent one case of SJS-TEN,[73] which is a favorable cost:benefit ratio considering the present cost of genotyping and the severity of the syndrome. The low positive predictive value (referring to the proportion of patients who test positive for HLA-B*1502 and who then develop SJS-TEN) means that many carriers would not suffer from SJS-TEN, which is theoretically not a major concern because other pharmacological alternatives are available. However, the high negative predictive value (referring to the proportion of patients who test negative for HLA-B*1502 and who do not develop SJS-TEN) is valuable when making a decision to select carbamazepine. Lamotrigine, an antiepileptic drug also used for the treatment of depression in bipolar disorders, can also cause TEN. Although lamotrigine-induced TEN has also been associated with variants of the human leukocyte antigen (HLA) system, there are presently insufficient data to justify HLA genetic testing for lamotrigine treatment.[5]

Clozapine is considered the most efficient antipsychotic in resistant schizophrenia.[75] Because of the risk of agranulocytosis, it is licensed for use only in schizophrenic patients whose illness has not responded adequately to standard treatment. Other variants of HLA (eg, *HLA-DQB1* and *HLA-B*) have been associated with clozapine-induced agranulocytosis and could be useful in identifying patients at high risk.[76,77] However, considering a positive genetic test, if an individual carried either risk factor, the sensitivity and specificity of the test would be 0.36 and 0.89, with more than half of cases not carrying the two risk factors.[77] Theoretically, a genetic test for clozapine needs a high positive predictive value because patients must not be denied a treatment while there are no, or only few, alternatives. In addition, a high negative predictive value is needed to propose pharmacogenetic tests as an alternative to white blood cell monitoring. The usefulness of pharmacogenetic tests for clozapine must therefore be reassessed in the future, with the discovery of other genetic risks, and possibly also protection factors, increasing the negative and positive predictive value.

Perspectives

The use of pharmacogenetics in psychiatry is already challenging because of factors associated with the complexity of psychiatric illness, a high prevalence of comorbidites, difficulties in classification, and overlapping phenotypes. In addition, there are no valid and reliable diagnostic and prognostic biological markers, in contrast with other diseases (eg, blood glucose levels for type 2 diabetes).[78] Finally, psychiatric diseases are polygenic (a recent GWAS study identified 128 independent associations from 108 defined loci with schizophrenia[79]).

Concerning pharmacokinetic genes, dose recommendations according to CYP genotypes have been published for several psychotropic drugs. However, due to the low sensitivity of the tests, a very high number of patients must be genotyped to prevent one case of severe side effect and/or nonresponse. This can explain, in conjunction with the low specificity of the tests and the present cost of genetic analysis, why genotyping of pharmacokinetic factors such as CYP isoforms is presently mostly done in psychiatry on a retrospective basis to understand unusual drug responses. In addition, the activity of specific isoforms (ie, activity of CYP1A2 and CYP3A) cannot be reliably used because of the multigenic and environmental influences. However, drug selection and dose recommendations made on the ba-

sis of CYP activity (determined by genotyping and/or phenotyping) remains a legitimate objective. Concerning pharmacodynamic genes, there is presently only one for which there is strong evidence in favor of proposing testing on a routine basis (*HLA-B*1502* for carbamazepine). New pharmacogenetic factors using SNP analysis will be discovered in the future, but the influence of other sources of variability—including genetic factors (eg, copy number variants and microRNA), as well as epigenetic factors (eg, histone deacetylation and gene methylation)—must be taken into account.[57-80] Because of the very rapid technological advances and the sharply diminishing costs of genetic analysis, pharmacogenomic testing is increasingly used nowadays. However, the substantial differences in the levels of evidence between markers, combined with the low sensitivity and/or specificity for the large majority of them, has to be taken into account. Pharmacogenetic tests are not magic bullets and to be clinically useful they need to be incorporated into a comprehensive pharmacological knowledge of the drug, which includes its pharmacokinetics and pharmacodynamics, its therapeutic window, and its idiosyncratic and dose-related adverse drug reactions. Only when combined with careful clinical evaluation—with the help of other tools, such as TDM and/or phenotyping tests—can pharmacogenetics contribute to the general aim of providing the best care for psychiatric patients. ❑

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Prescripción personalizada: un nuevo modelo médico para el uso clínico de los psicofármacos

*Dada la influencia de los factores genéticos en la farmacocinética y farmacodinámica de los medicamentos, el amplio empleo de pruebas farmacogenéticas en psiquiatría ya ha sido propuesta desde los comienzos de los años 2000. Sin embargo, sólo unas pocas pruebas (ej. HLA-B*1502 para la carbamazepina en epilepsia o trastornos bipolares) han alcanzado niveles de evidencia para justificar su uso rutinario, mientras que muchos hallazgos son demasiado preliminares o, cuando se han replicado, son de baja relevancia clínica debido a la reducida magnitud del efecto. Si bien la selección del fármaco y el ajuste de dosis de acuerdo con los genotipos de los citocromos P 450 están justificados, un gran número de pacientes necesitan ser genotipados para prevenir un caso de efecto secundario grave y/o de no respuesta. La disminución de los costos de los análisis genéticos modifica la relación costo-beneficio a favor de un aumento del empleo de las pruebas farmacogenéticas. Sin embargo, ellas tienen que combinarse con evaluaciones clínicas cuidadosas y otras herramientas (ej. monitoreo de drogas terapéuticas, fenotipado) para contribuir al objetivo general de proporcionar la mejor atención para los pacientes psiquiátricos.*

Prescription personnalisée : un nouveau modèle médical pour la mise en place des psychotropes

*Les facteurs génétiques influant sur la pharmacocinétique et la pharmacodynamique des médicaments, l'utilisation de tests pharmacogénétiques a déjà été proposée en psychiatrie dès le début des années 2000. Cependant, seuls quelques tests bénéficient de niveaux de preuve suffisants pour justifier leur utilisation en routine (par exemple, complexe majeur d'histocompatibilité, classe I, B, allèle 1502 [HLA-B*1502] pour la carbamazépine dans l'épilepsie et les troubles bipolaires) ; de nombreux résultats, lorsqu'ils sont reproduits, sont trop préliminaires ou n'ont finalement qu'une pertinence clinique limitée en raison de la faible ampleur de leur effet. Le choix des médicaments et l'adaptation posologique selon les génotypes des cytochromes P450 sont des démarches sensées mais il faut génotyper un grand nombre de patients pour prévenir un cas d'effet indésirable sévère et/ou d'absence de réponse. La diminution des coûts de l'analyse génétique a orienté le rapport coût/bénéfice vers une plus large utilisation des tests pharmacogénétiques. Ils doivent néanmoins être associés à un examen clinique soigneux et à d'autres moyens (par exemple, suivi thérapeutique des médicaments et phénotypage) afin d'apporter les meilleurs soins aux patients psychiatriques.*

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