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Pharmacogenomics in Psychiatry: From Therapeutic Drug Monitoring to Genomic Medicine

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Pharmacogenomics in psychiatry – from TDM to genomic medicine

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INTRODUCTION

Psychiatry is increasingly combining new pharmacogenomic findings with therapeutic drug monitoring (TDM) to improve the safety and efficacy of pharmacotherapy. However, distinction should be made between «nice to know» and «need to know» pharmacogenomic data, as many results are statistically significant in meta-analyses but are not clinically relevant due to their low effect sizes. Some examples will illustrate this integration.

PERSONALIZED PRESCRIPTION

Personalized prescription can be expressed as personalizing dosing and/or drug selection and should include genetic as well as environmental (e.g. co-medications, herbal medicines, smoking, foods, beverages) and personal (e.g. age, gender, ethnicity, illnesses) variables (1).

PHARMACOKINETIC PATHWAY-RELATED GENES FOR PERSONALIZED DOSING

Among genes involved in pharmacokinetics, the members of the cytochrome P450 (CYP) family display large interindividual and interethnic variability in activity. Thus, the FDA table of pharmacogenetic markers in drug labels (http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm) contains approximately 120 drugs (29 used in psychiatry), most of them CYP2D6-dependent drugs.

CYP2D6 is important for the metabolism of many drugs, including antidepressants and antipsychotics, and its activity varies significantly between poor, intermediate, extensive and ultrarapid metabolizers (PMs, IMs, EMs and UMs). PM status can be rather reliably predicted in Caucasians based on genotyping 5 to 10 single nucleotide polymorphisms (SNPs)

covering 95-99% of the PM alleles, while the UM status is only partly captured by genotyping. However, the frequencies of different alleles vary importantly according to ethnicity, thus increasing the number of alleles needed to predict CYP2D6 status in mixed populations. CYP2D6 genotyping was extensively studied during phase 1 and 2 studies of atomoxetine, a drug approved for attention-deficit/hyperactivity disorder. In randomized clinical trials (RCTs), CYP2D6 PMs had significantly higher response rates than CYP2D6 EMs, with a 10-fold higher mean plasma concentration measured in the former group. Although having no impact on discontinuation due to adverse drug reactions (ADRs), higher prevalence of several ADRs (e.g., decreased appetite, insomnia, sedation, tremor or itching) were noted in PMs with, for example, a 3-fold difference in depression prevalence between PMs and EMs (6% and 2%, respectively). Despite recommendations for dose-adjustment in CYP2D6 PMs or with co-prescription of potent CYP2D6 inhibitors, the drug label does not require CYP2D6 genotyping; new studies are needed to establish whether CYP2D6 UMs need higher than maximal recommended doses.

CYP2B6 is also highly polymorphic but under strong regulation by ligand-activated nuclear receptors, in contrast to CYP2D6, and may be involved in the metabolism of more drugs than initially thought. Methadone, an opioid agonist used for maintenance treatment in opioid addiction, can prolong the QT interval with risk for ventricular tachyarrythmia and Torsades de Pointes. Methadone is a chiral mixture of (R)-methadone, the major agonist on opioid receptors, and (S)-methadone, a weak agonist but more potent blocker of the cardiac hERG channel responsible for QT interval prolongation. Methadone is mainly metabolized by CYP2B6 and CYP3A4, while (S)-methadone is metabolized preferentially by CYP2B6. Compared to CYP2B6 EMs, slow metabolizers had longer QTc intervals (odds ratio, OR=6.3; p=0.003) during methadone treatment (2). *CYP2B6* genotyping cannot substitute for the electrocardiogram to predict cardiac arrhythmias and sudden death in methadone patients since diminished CYP2B6 activity is associated with a large number of *CYP2B6* SNPs and haplotypes (several of them with yet unknown functions), and since pharmacodynamic

related-pathway genes in the heart and other factors (e.g. electrolyte disturbances) may be important, too.

CYP1A2 is involved in particular in the metabolism of clozapine, an atypical antipsychotic. Clozapine appears to be a more promising drug for personalizing dosing since TDM reviews have definitively established that efficacy is associated with plasma clozapine concentration > 350 ng/ml (3). Rare cases of genetic CYP1A2 variants have been associated with very low or high clozapine metabolic activity but currently CYP1A2 genotyping is not informative in most patients. Studies have also shown that CYP1A2 activity is also controlled by other (non CYP1A2) genetic factors, including the P450 oxydo-reductase and the nuclear receptor genes. However, genotyping of those additional genes adds little in predicting CYP1A2 variability, possibly due in part to the environmental influence on CYP1A2 activity (for example decreased by inhibitors such as oral contraceptives that may contribute to lower female activity and increased by inducers such as smoking). Thus, phenotyping tests (*in vivo* measurement of the activity using a probe substance such as caffeine) or TDM are more appropriate for personalized dosing of clozapine or of other CYP1A2-dependent drugs.

The CYP3A subfamily, crucial for the metabolism of approximately half of all marketed drugs, is comprised of CYP3A4, CYP3A5 and CYP3A7, which have overlapping substrate specificities. Inducers and inhibitors have major influence on CYP3A activity and genotyping is not clinically relevant unless the drug is preferentially metabolized by CYP3A5 (to our knowledge there are no example in psychiatry).

In summary, for personalized dosing, genotyping of pharmacokinetic pathway-related genes can be most informative in addition to TDM, particularly at the beginning of the pharmacological treatment, to modify dosing. However, TDM remains essential, as it combines the influence of environmental and personal factors involved in metabolism and transport of drugs and allows the measurement of active metabolites.

PHARMACODYNAMIC PATHWAY-RELATED GENES FOR PERSONALIZED DRUG SELECTION

Genetic testing of pharmacodynamic factors is presently more promising for preventing rare idiosyncratic ADRs rather than to predict response to treatment. Carbamazepine, an anticonvulsant and a mood-stabilizing drug, can cause the Stevens–Johnson syndrome (SJS)-toxic epidermal necrolysis (TEN). According to the FDA labeling of carbamazepine, these reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian population but the risk is highly increased in patients of Asian ancestry. In this population, the HLA-B*1502 allele has been identified as a predictor of SJS–TEN (OR=1357, $p=1.6*10^{-41}$). FDA carbamazepine drug labeling requires that Asian ancestry patients should be screened for the presence of HLA-B*1502 prior to initiating treatment. Patients carrying this allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk. A prospective screening in Taiwan of HLA-B*1502 before carbamazepine prescription in 4877 patients provided the proof of concept. No SJS-TEN case was observed in the HLA-B*1502 negative patients whereas 10 cases were expected based on historical incidence without screening (4). The HLA-A*3101 allele has been proposed as a clinically relevant marker to predict hypersensitivity reactions to carbamazepine in Caucasians and Japanese, but has low sensitivity. Another variant of HLA (HLA-DQB1) has been associated with clozapine-induced agranulocytosis (OR=16.9, $p<0.001$) and could be useful to identify patients with an exceptionally high risk, but due to the low test sensitivity, it cannot yet replace white blood cell monitoring (5).

Studies have looked for pharmacodynamic pathway-related genes associated with weight gain and metabolic ADRs during antipsychotic treatment, one of the most concerning issues in psychiatry. Some candidate genes, (e.g. the fat mass and obesity-associated gene [FTO], the melanocortin-4 receptor [MC4R] and the CREB-regulated transcription coactivator 1 [CRTC1]) have been associated with important body mass index variations. There is less

information on genes associated with antipsychotic induced-diabetes mellitus and hyperlipidemia. The practical clinical value of these promising pharmacogenomic variations remains to be determined.

NUMBER NEEDED TO GENOTYPE (NNG)

By analogy to the “number needed to treat”, one can define the NNG. For carbamazepine prescription in patients of Asian origin, considering an incidence of 0.25% of SJS-TEN and a sensitivity of 98.3% for the HLAB*1502 allele, the NNG would be 407 (100/(0.25x0.983)) i.e., 407 patients must be screened to prevent a case of SJS-TEN. Even with the present cost of genotyping for this allele (around $100-200), the cost-benefit ratio is in favor of the test considering this ADR severity. For clozapine, with an incidence of 1.3% of agranulocytosis and a sensitivity of 21.5% for the HLA-DQB1, the NNG would be 358 (100/(1.3x0.215)). Although the value is similar to carbamazepine, the cost-benefit evaluation for HLA-DQB1 genotyping must take into account that it does not replace the mandatory hematological monitoring which decreases the interest in this test at the current price. Concerning pharmacokinetic pathway-related genes, dose recommendations according to CYP genotypes have been published for several psychotropic drugs. However, due to the very low sensitivity of the tests, very high NNG would be calculated. This can explain, in conjunction with the low specificity of the tests, why genotyping of pharmacokinetic pathway-related genes such as CYP isoforms are presently mostly done in psychiatry on a retrospective basis to understand unusual drug responses.

PERSPECTIVES

The large prospective RCTs needed to establish the classical proof of concept as well as the cost-benefit ratio of pharmacogenomics in psychiatry will not happen due to very high costs and lack of funding mechanism. However, very rapid technological advances and the

subsequent sharply diminishing costs of genetic analysis (presently <$1000 reagent costs for whole genome sequencing, <$100 for approximately 500,000 SNPs) already dramatically reduce the cost-benefit ratio (and will reduce it even further in the future) and favor pharmacogenomic testing. Proof of concept studies with comparisons to historical data (4) are more likely to be used in the future to demonstrate the validity of pharmacogenomics in specific contexts. However, to be clinically useful, pharmacogenomics (including epigenetic factors) will still need to be incorporated, as a piece of a complex puzzle, into a comprehensive pharmacological knowledge of the drug which includes pharmacokinetics and pharmacodynamics, therapeutic window, idiosyncratic and dose-related ADRs and is used in association with TDM and other phenotyping tests (Figures 1 and 2).

CONFLICT OF INTEREST/DISCLOSURE

No commercial organizations had any role in the writing of this paper for publication.

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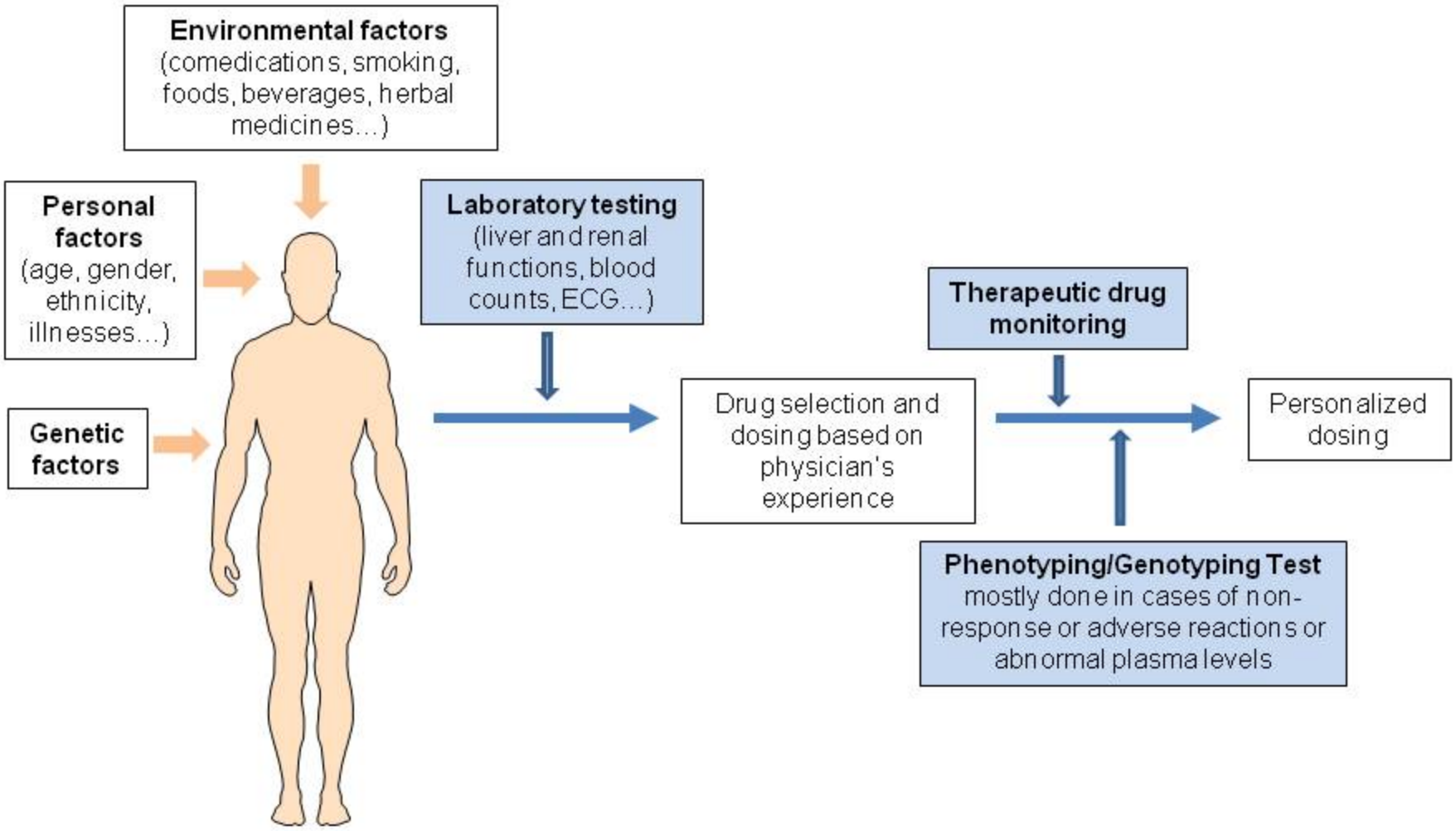
FIGURE LEGENDS

Figure 1. Patient care in the present: drug selection and dosing based on physician's choice. ECG, electrocardiogram; TDM, therapeutic drug monitoring.

Figure 2. Patient care in the immediate future: personalized drug selection and dosing with comprehensive genotyping. ECG, electrocardiogram; PD, pharmacodynamics; PK, pharmacokinetics; TDM, therapeutic drug monitoring.

Patient care in the present



Patient care in the immediate future