Pharmacogenomics in Psychiatric Disorders

Roxana-Georgiana Tauser[1]

[1] University of Medicine and Pharmacy "Grigore T. Popa" Iasi, Faculty of Pharmacy, Romania,
georgiana.tauser@gmail.com

Abstract: *The broad arsenal of psychotropic medications is characterised by significant interindividual variability in clinical response and adverse effects, stringent monitoring requirements, potential drug-drug interactions, difficult long-term adherence and high costs. Pharmacogenomics investigates the correlation between genetic polymorphisms and responsiveness to drugs and could provide a valuable guide to fulfill the promise of personalized therapy in the context of the genomic medicine era, by tailoring treatment based on the patient's specific genetic markers. The present paper overviews the current advances in the clinical applications of pharmacogenomics to individualized psychotropic therapy.*

Material and methods. The relevant recent pharmacogenomics literature is selected and analysed in order to illustrate the impact on the clinical outcomes and quality of life in psychiatric patients of the genetic variants in the neurotransmitter receptors (dopamine and serotonin), metabolic pathways of drugs (cytochrome CYP450 2D6 and 2C19) and the human leukocyte antigen system. The paper focuses on some of the major psychotropic drug classes, such as: antipsychotics, antidepressants and mood stabilizers. Validation of statistically significant pharmacogenomics relationships has enabled the development and market approval of some predictive tests which are already integrated into some psychotropic drugs label. Results and discussions. Predictive pharmacogenomics tests have changed the classical approach of prescription "trial-and error" and "one dose fits all patients" towards personalized therapy. In addition, in new therapeutic candidates' clinical development, pharmacogenomics practically guides the clinical studies design, by substantially reducing the failure rates, costs and exposure risks of non-responders patients to new drugs. Current translation barriers of predictive pharmacogenomic tests from bench to clinical practice are also discussed. Conclusion. The paper emphasizes the current progress and future prospects in the field of pharmacogenomics as a guide to personalized therapy of psychiatric disorders, by: a) pretreatment selection of the right drug, prescribed in its optimized dose, to the right patient, according to one's specific genetic biomarkers; b) by improved clinical trials design based on genetic stratification of patients' population into responders versus non-responders, especially in the costly phases III and IV.

Keywords: *pharmacogenomics; personalized therapy; antipsychotics; antidepressants; mood stabilisers.*

Pharmacogenomics: the promise of personalized psychotropic therapy

Clinical, demographic and genetic specific profiles could contribute in different ratios to significant interpatient variability noticed in both therapeutic efficacy and adverse drug reactions (ADR) (Moore, Hill & Panguluri, 2014; Tauser 2012). "Antipsychotic Trials of Intervention Effectiveness" (CATIE) estimates that over 70% of chronic schizophrenia patients stopped the antipsychotics because of sub-optimal efficacy or safety and treatment-resistant schizophrenia (TRS) affects ~30% of patients (Eum, Lee, & Bishop, 2016). Only 60%–70% TRS cases treated with clozapine, as the unique evidence-based treatment, are responsive (Lally et al., 2016). Moreover, both first (FGAs) and second generation antipsychotics (SGAs) can cause tardive diskinesia (TD) with a prevalence of 32.4%, and 13.1%, respectively (Zhang & Malhotra, 2011). In addition, "Systematic Treatment Enhancement Program for Bipolar Disorder" (STEPBD) trial proved that relapse ocurred to approximately 75% of patients during follow-up (Leucht et al., 2013). Furthermore, depression is expected to become the most costly psychiatric disorder in Europe (1% from gross domestic product) and the second one worldwide, as World Health Organisation estimates. "Sequenced Treatment Alternatives to Relieve Depression" (STAR*D) trial - the largest and longest evaluation of antidepressants – has proven that: only 37% of non-psychotic major depression cases reported remission to a selective serotonin reuptake inhibitor (SSRI) as first choice drug, and 16.3% of patients stopped the therapy because of poor tolerance; only 50% antidepressant-treated patients are responsive and about 55% experience at least one ADR; at least four antidepressant drugs by classical approach of prescription "trial-and error" and "one dose fits all patients", for more than 50 weeks, were necessary to obtain a cumulative remission rate of 67%; the antidepressant therapy was interrupted after 3 months in 42% of cases, and only 45% were compliant to longer treatment; a great variability (up to 40%) in pharmacokinetic plasmatic parameters is noticed for some antidepressants administered in the same standard therapeutic dose to different patients. Moreover, genetic polymorphisms could explain up to 42–50% of the differences in both positive clinical outcomes and ADR of antidepressants (Bousman et al., 2017; Tauser, 2012).

Personalized or precision medicine uses "genetic or other biomarker information to improve the safety, effectiveness and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment management approaches" (Lally et al.,

2016). *Pharmacogenetics* has mainly associated monogenic polymorphisms to the patients' variability in drugs' metabolism, with the potential to diminish the risk of ADR to the carriers (*i.e.*, persons who do not "average" respond). *Pharmacogenomics* investigates in an integrative approach the differences in genes' expression caused by the systemic interactions between medications and the whole genome, exploiting the acquisitions from genomics, proteomics, transcriptomics, metabolomics and epigenomics in the medical practice (Tauser, 2012). The two terms are still used interchangeably and will be here abbreviated by *PGx*. The present paper overviews the main correlations with clinical relevance between genetic polymorphisms in major metabolic pathways (cytochrome CYP450 2D6 and 2C19), targeted neurotransmitter receptors (dopamine DRD2, DRD3; serotonin 5HTR2A, 5HTR2C), catechol-*O*-methyltransferase (COMT), human leukocyte antigen system (HLA), and the efficacy and safety of the major psychotropic drug classes (*i.e.*: antipsychotics, antidepressants and mood stabilizers), emphasizing their predictive clinical implications.

Predictive pharmacokinetics PGx testing: *AmpliChip™ CYP450 Test*

The metabolizing phenotypes: extensive (EM), ultrarapid (UM), intermediate (IM) and poor (PM) metabolisers, related to key genetic mutations in CYP2D6 and CYP2C19 pathways, could be identified by Affymetrix microarray *AmpliChip™ CYP450 Test* (2005) - the first pharmacogenetic test approved by US Food and Drug Administration (FDA). The test is recommended for the pretreatment dose adjustements in non-responders or outliers (UM, PM, IM), so as to assure therapeutic efficacy and to minimise severe ADR. Despite its commercial availability, it costs over $600/test and requires about 14 days to perform, whilst delaying initiation of therapy associated with the clinical deterioration could be ethically inappropriate (Leucht et al., 2013; Tauser, 2012). Genotyping key alleles of CYP2D6 and CYP2C19 was approved by FDA only as informational test on labels of drugs mainly metabolized by these enzymes, for instance: CYP2D6 for atomoxetine, fluoxetine, paroxetine, amitriptyline, aripiprazole, risperidone. Based on the significant clinical correlations between CYP2D6 and CYP2C19 phenotype metaboliser and the drugs' efficacy and safety, Clinical Pharmacogenetics Implementation Consortium (CPIC) has developed dosing guidelines for some antipsychotics, SSRI and tricyclic antidepressants (Bousman et al.*,* 2017).

For instance, patients with PM phenotype (7-10% of Caucasian population), having null alleles CYP2D6*4, *3, *5 or *6, are susceptible to

43% increased risk of TD at standard doses of antipsychotics than EM (Zhang & Malhotra, 2011). Therefore, in the drug label for aripiprazole, brexpiprazole, iloperidone and pimozide, the personalization of doses for these PM patients means a reduction of the standard doses prescribed to normal metabolisers, carriers of wild-type, normally functional allele CYP2D6*1. On the contrary, UM patients (carriers of CYP2D6*Nxn multiple functional alleles) will require higher doses than those standard prescribed to "average"/ normal metabolisers (EM), so as to reach the expected therapeutic efficacy. The magnitude of influence is different in each medication that is a CYP2D6 substrate, with AUC increases ranging from 47% to 641% for the PMs. Halflife displayed an approximate twofold increase in PMs for aripiprazole, iloperidone, pimozide, and thioridazine, and a sevenfold increase for risperidone (Eum, Lee & Bishop, 2016). For instance, comparatively to EM, PM and IM metabolisers for CYP2D6 had an increased exposure to active moiety to risperidone and aripiprazole, by approximately 1.6-times and 1.4-times, respectively; therefore, daily doses of risperidone and aripiprazole administered to PM and IM should be diminished by 19%, and 15%, respectively (Jukić et al., 2018). The product labels for some antipsychotics (aripiprazole, brexpiprazole, iloperidone, pimozide) have already included pharmacogenetic testing recommendations, but specific guidelines of how best to interpret and apply this information are still lacking (Eum, Lee & Bishop, 2016; Leucht et al., 2013). Furthermore, FDA and CPIC state that fluvoxamine and paroxetine should be used cautiously in PM or IM metabolisers, suggesting a dose reduction by 50% for paroxetine and by 30% for fluvoxamine; as well as to patients with congenital long QT syndrome, or other conditions predisposing to higher fluoxetine exposure (liver failure, concomitant administration of CYP2D6 inhibitors or other highly protein-bound drugs) (Bousman et al. 2017, Hicks et al. 2015). Moreover, the practical advantage of CYP2C19 genotyping for personalization of escitalopram treatment is supported by the substantial impact of CYP2C19 metaboliser status on the serum concentrations: 3.3-fold higher for carriers of inactive allele CYP2C19Null/Null; significantly decreased in the carriers of gain-of-function allele (CYP2C19*17) by 10% recorded in IM group carriers of alleles CYP2C19*1/*17, and 20% in the UM group with CYP1C19*17/*17 genotype, comparatively to EM responders (CYP2C19*1/*1 carriers). In comparison to the wild-type CYP2C19*1/*1 carriers as EM phenotype, switches from escitalopram to another antidepressant within 1 year were 3.3, 1.6, and 3.0 times more frequent among the PM CYP2C19Null/Null, IM CYP2C19*1/*17, and UM CYP1C19*17/*17 groups, respectively (Jukić et al., 2019). FDA and CPIC

mention only for citalopram a maximum dose of 20 mg/day in adults (or 50% reduction) for PM group because of QT prolongation risk, or to consider another SSRI not catabolised by CYP2C19; minimal dose adjustments are warranted for IM CYP2C19 metabolisers treated by citalopram or escitalopram and no dose adjustment is recommended for UM (Hicks et al., 2015).

Pharmacodynamics PGx

The most relevant PGx markers associations to main psychiatric pharmacotherapeutics, replicated by different case-control studies, are illustrated in Table 1 (Eum, Lee & Bishop, 2016; Lally et al., 2016; Leucht et al., 2013, Rampino *et al.* 2019, Pardiñas et al., 2019; Philips et al., 2018; Tauser, 2012; Zhang & Malhotra, 2011).

Table 1. Main PGx correlations in main psychiatric pharmacotherapeutics

PGx biomarker	Clinical relevance to psychotropic drugs' responsivity
Dopamine receptor genes biomarkers	
-141C Ins/Ins DRD2	The predicted responsivity to antipsychotics is 54% higher for *Ins/Ins* carriers; *Del* allele carriers had poor response to clozapine and to chlorpromazine in Han Chinese, as well as higher latency to olanzapine's and risperidone's efficacy in first episode of schizophrenia
Taq1A SNP *DRD2*	*A1* carriers more responsive to antipsychotics, although *A2/A2* alleles correlated to greater response to therapy (smaller scores in PANSS[a] and BPRS[b]); higher risk of the TD as ADR for *A2/A2* genotype: one copy of the *A2* allele increased the risk of TD with 30%, and *A2/A2* genotype with 50%, respectively, relative to the *A1* allele
Ser9Gly SNP *DRD3*	Altered dopamine binding affinity; *Ser* allele was associated with better response to FGA, to clozapine; most recent trials with risperidone, aripiprazole and other SGA failed to prove substantial correlation; *Gly* allele predictive for higher risk of TD
Catechol-O-methyltransferase (COMT) gene	
Val108Met SNP	*Met/Met* genotype has 3-4 times lower enzyme activity and reduced prefrontal dopamine clearance as compared to *Val/Val* carriers; *Met/Met* carriers have reduced response to FGA, but better response to clozapine in cognitive symptoms; *Val/Val* carriers have diminished response of negative symptoms to olanzapine; *Val/Val* genotype predictive for 51% higher risk of TD

Serotonin receptor gene biomarkers	
A-1438G 5HTR2A	In *G/G* genotype, aripiprazole, olanzapine and clozapine were less effective, especially on negative symptoms; *G/G* genotype increased TD risk
T102C 5HTR2A	*C* allele carriers mainly non-responders to clozapine; and higher risk of TD: to 64% more than *T/T* homozygotes; *C/C* genotype: a significant association and better response to risperidone, especially for negative symptoms
His452Tyr 5HTR2A	*Tyr/Tyr* homozygotes or *Tyr* allele is significantly correlated to less responsivity to clozapine, than *His* allele
C759T 5HTR2C	*C/C* genotype: more than 2x higher risk for obesity (more than 7-10% weight gain) to SGA, especially clozapine, olanzapine and quetiapine
Serotonin transporter gene: repeat length polymorphism	
5-HTTLPR (insertion/deletion of a 44-bp in promoter region)	*long allele* carriers are 2x more responsive to therapy with symptoms remission after 1 month, and have reduced ADR risk, than those with *short/short* genotype; short allele is predictable for poor responsivity to risperidone and clozapine
5-HTTLPR	*long allele* carriers: better responsivity to citalopram, paroxetine, fluoxetine
HLA genes	
*HLA-B*1502* and *HLA-A*3101*	*Carbamazepine and oxcarbazepine- hipersensitivity:* SJS/TEN[c] FDA labels "Warning and precaution sections" and CPIC guidance: prescription should be avoided to: carbamazepine- or oxcarbazepine-naive and *HLA-B*1502* positive carriers, regardless of *HLA-A*3101* genotype
Haplotype: HLA-DQB1(126Q) and HLA-B (158T)	Higher risk of clozapine – induced agranulocytosis; *Recommended predictive pharmacogenetic tests in drug label –* „PGxPredict: Clozapine" testing, in parallel with white blood cell monitoring, in order to avoid prescription to patients with high granulocytosis risk and to improve safety

[a] Positive and Negative Syndrome Scale; [b] BPRS Brief Psychiatric Rating Scale;
[c] Stevens–Johnson syndrome/toxic epidermal necrolysis

The FDA labels for carbamazepine and oxcarbazepine have included a box in the "Warnings and precautions" section about the risk of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and maculopapular exanthema to patients testing positive for *HLA-B*1502* (estimated positive predictive value of 7.7% for carbamazepine, and 0.73% for oxcarbazepine), in order to avoid their prescription, unless the benefit clearly outweighs the risk, but then with more frequent clinical surveillance

and treatment discontinuation at the first cutaneous ADR. CPIC guidances point out to: avoid their prescription to carbamazepine- or oxcarbazepine-naive and *HLA-B*1502* carriers, as well as to carbamazepine-naive patients *HLA-B*1502* positive and regardless of *HLA-A*3101* genotype; to cautiously change to alternative drug (eslicarbazepine, lamotrigine) for carbamazepine-naive and *HLA-A*3101* positive patients; to cautiously prescribe carbamazepine to *HLA-A*3101* positive carriers previously treated for over 3 months in the absence of SJS/TEN, due to the usual latency development of these ADR within the first 4–28 days of therapy with regular dosing (Philips et al., 2018).

Published studies on pharmacogenetics of some mood stabilizers (lithium, valproate, lamotrigine and carbamazepine) refer only to the association with genetic mutations in key enzymes, whose pharmacological inhibition decreases free inositol, but the results are largely inconclusive among studies (Leucht et al., 2013).

Validation of statistically significant PGx relationships has enabled the development and market approval of some predictive tests which are already integrated into some psychotropic drugs label. For example, „PGxPredict: Clozapine" is a recommended predictive PGx test in clozapine label, based on *HLA-DQB1(126Q)* and *HLA-B(158T)* SNP (test's sensitivity is 21.5% and specificity 98.4%), whose implementation in parallel with white blood cell monitoring, could avoid clozapine administration to haplotype-positive carriers; however, its clinical utility is still controversial and requires further validations (due to low sensitivity; lack of consistent demonstration of agranulocytosis'dependency to the dose/ plasma concentrations) (Lally et al., 2016; Pardiñas et al., 2019). Predictive PGx tests have changed the classical approach of prescription "trial-and error" and "one dose fits all patients" towards personalized therapy. Although PGx testing in psychiatry is not yet a standard of practice, its increasing utilization (especially in the United States and Canada, PGx are 47% of all genetic tests recommended by 6% of psychiatrists, in 6 months) enables the precision-medicine approach in psychiatric disorders (Bousman et al., 2017; Eum, Lee & Bishop, 2016). However, PGx cost-effectiveness and improved health outcomes should be further demonstrated by replicated evidence in randomized clinical studies with high quality design and increased statistical significance and multiple predictive PGx biomarkers (Leucht et al., 2013; Rosenblat et al., 2017; Pardiñas et al., 2019).

Clinical trials design based on PGx

In new therapeutic candidates' clinical development, PGx practically guides the clinical studies design, by substantially reducing the failure rates, costs and exposure risks of non-responders patients to new drugs. Pipeline PGx means the convertion towards the *log* phase from the current *lag* one, reducing the attrition rate during the expensive late phase clinical development, through enrolment in the III-IV clinical studies only of the patients with highly predictable responsivity to treatment and avoiding the inclusion of patients with high ADR risk. Pharmacovigilance in the post-marketing phase guides the introduction of PGx biomarkers into approved drugs' labels, with further recommendations for dose optimization, warnings and contraindication, in order to exclude patients with genotype predictable for high non-responsivity or risk of severe ADR (Tauser, 2012).

PGx testing's clinical translation challenges

PGx testing should comprise genetic, demographic and clinical data to assist personalized therapy and should become cost-effective. PGx's translation from laboratory into clinical routine and individualized medicine should overcome the following hurdles: a) new global evidence for the clinical utility and validity of the PGx algorithms; b) requirements' harmonization regarding clinical studies design, population size, effect size, reproducibility; c) powerful statistical PGx correlations for diverse races; d) education of medical professionals and patients; e) bioethical and practical PGx consent guidelines; f) more sustainable legislation framework for the integration of PGx into medical practice; g) unifying standards for the multi-national networks concerning biorepository sharing; h) pharmacoeconomic aspects, including incentives for private companies (Jukić et al., 2019; Lally et al., 2016; Leucht et al., 2013; Rosenblat et al., 2017; Tauser, 2012; Zhang et al., 2011).

Conclusion

The current progress in the field of PGx encourages future personalised therapy of psychiatric disorders by: a) pretreatment selection of the right drug, prescribed in its optimized dose, to the right patient, *i.e.*, to responders group based on predictive PGx biomarkers identification; b) improved clinical trials design based on genetic stratification of patients' population into responders *versus* non-responders, by excluding those with genotype-predicted high risk of severe ADR, especially in the costly late phases.

References

Bousman, C. A., Forbes, M., Jayaram, M., Eyre, H., Reynolds, C.F., Berk, M., Hopwood M., & Ng, C. (2017). Antidepressant prescribing in the precision medicine era: a prescriber's primer on pharmacogenetic tools. *BMC Psychiatry, 17*(1), 60-74.

Eum, S., Lee, A. M., & Bishop, J. R. (2016). Pharmacogenetic tests for antipsychotic medications: clinical implications and considerations. *Dialogues in Clinical Neuroscience,18*(3), 323–337.

Hicks, J. K., Bishop, J. R., Sangkuhl, K., Müller, D. J., Ji, Y., Leckband, S. G., Leeder, J. S., Graham, R. L., Chiulli, D. L., LLerena, A., Skaar, T. C., Scott, S. A., Stingl, J. C., Klein, T. E., Caudle, K. E., Gaedigk, A., & Clinical Pharmacogenetics Implementation Consortium (2015). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clinical pharmacology and therapeutics, 98*(2), 127–134. https://doi.org/10.1002/cpt.147

Jukić, M. M., Haslemo, T., Molden, E., Ingelman-Sundberg, M. (2018). Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. *American Journal of Psychiatry, 175*(5), 463-470. https://doi.org/10.1176/appi.ajp.2017.17050550

Jukić, M. M., Smith, R. L., Haslemo, T., Molden, E., Ingelman-Sundberg, M. (2019). Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. The Lancet, 6(5), 418-426. https://doi.org/10.1016/S2215-0366(19)30088-4

Lally, J., Gaughran, F., Timms, P., & Curran, S.R. (2016). Treatment-resistant schizophrenia: current insights on the pharmacogenomics of antipsychotics. *Pharmacogenomics and personalized medicine, 9*, 117–129.

Leucht, S*.,* Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R. R., Geddes, J. R., Kissling, W., Stapf, M. P., Lässig, B., Salanti, G., & Davis J. M. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet, 14*(382), 951-962. https://doi.org/10.1016/S0140-6736(13)60733-3

Moore, T. R., Hill, A. M., & Panguluri, S. K. (2014). Pharmacogenomics in Psychiatry: Implications for Practice. *Recent Patents on Biotechnology, 8*, 152-161. https://doi.org/10.2174/1872208309666140904113615

Pardiñas, A. F., & Nalmpanti, M., Pocklington, A. J., Legge, S. E., Medway, C., King, A., Jansen, J., Helthuis, M., Zammit, S., MacCabe, J., Owen, M. J., O'Donovan, M. C., & Walters, J. T. R. (2019). Pharmacogenomic Variants and Drug Interactions Identified Through the Genetic Analysis of

Clozapine Metabolism. *American Journal of Psychiatry, 29*, 25-34. https://doi.org/10.1176/appi.ajp.2019.18050589

Phillips, E. J., Sukasem, C., Whirl-Carrillo, M., Müller, D. J., Dunnenberger, H. M., Chantratita, W., Goldspiel, B., Chen, Y. T., Carleton, B. C., George, A. L., Jr, Mushiroda, T., Klein, T., Gammal, R. S., & Pirmohamed, M. (2018). Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clinical pharmacology and therapeutics*, *103*(4), 574–581. https://doi.org/10.1002/cpt.1004

Rampino, A., Marakhovskaia, A., Soares-Silva, T., Torretta, S., Veneziani, F., & Beaulieu, J. M. (2019). Antipsychotic Drug Responsiveness and Dopamine Receptor Signaling; Old Players and New Prospects. *Frontiers in psychiatry*, *9*, 702. https://doi.org/10.3389/fpsyt.2018.00702

Rosenblat, J. D., Lee, Y., & McIntyre, R. S. (2017). Does Pharmacogenomic Testing Improve Clinical Outcomes for Major Depressive Disorder? A Systematic Review of Clinical Trials and Cost-Effectiveness Studies. *Journal of Clinical Psychiatry, 78*(6), 720-729. https://doi.org/10.4088/JCP.15r10583

Tauser, R. G. (2012). Pharmacogenetics: Matching the Right Foundation at Personalized Medicine in the Right Genomic Era. In Sanoudou, D. (Ed.), Clinical Applications of Pharmacogenetics (pp. 1-34). InTech Open Access. https://doi.org/10.5772/25824

Zhang, J. P. & Malhotra, A. K. (2011). Pharmacogenetics and antipsychotics: therapeutic efficacy and side effects prediction. *Expert opinion on drug metabolism & toxicology, 7*(1), 9–37.