Cacabelos R, J Psychiatr Depress Anxiety 2016, 2: 004
DOI: 10.24966/PDA-0150/100004

HSOA Journal of Psychiatry, Depression & Anxiety

Editorial

Trial-and-Error Versus Personalized Treatment in Depression: The Power of Pharmacogenomics

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Depression and mood-related disorders are complex clinical entities in which genomic, environmental and epigenetic factors are involved. It is estimated that 50% of patients with depression respond inappropriately to antidepressant treatment. This is mainly due to 3 reasons: (i) diagnostic inaccuracy, (ii) inadequate selection of treatment, and (iii) the patient's pharmacogenetic profile. Depression is a major problem of mental health in the community with a prevalence of 5-10% for females and 2-5% for males, and a lifetime risk of 10-25% in women and 5-12% in men. Although the epidemiological projections indicate that the prevalence of this psychiatric entity may increase in the future, some critical voices indicate that there is an over-diagnosis of depression and an excess of antidepressant treatment. Antidepressants are among the most prescribed drugs in the USA and the EU. The most important classes of antidepressants are selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors, and noradrenergic and serotonergic modulators [1]. The prescription of antidepressants is based on ideas proposed by the pharmaceutical industry, on data obtained from conventional clinical trials and on the daily clinical experience of psychiatrists, neglecting the genomic background of patients and their pharmacogenetic profile. Under arbitrary criteria, a high prevalence of inappropriate antidepressant use (under-use, abuse, non-optimal prescriptions) is somewhat frequent (50-80%) in the clinical setting.

Pharmacogenomics accounts for over 60-90% variability in the pharmacodynamics and pharmacokinetics of antidepressants. The genes involved in the pharmacogenomic response to drugs fall into five major categories: (i) genes associated with disease pathogenesis; (ii) genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers); (iii) genes associated with drug metabolism: (a) phase I reaction enzymes: Alcohol Dehydrogenases (ADH1-7), Aldehyde Dehydrogenases (ALDH1-9), Aldo-Keto Reductases (AKR1A-D), Amine Oxidases (MAOA, MAOB, SMOX), Carbonyl Reductases (CBR1-4), Cytidine Deaminase (CDA), Cytochrome P450 Family (CYP1-51, POR, TBXAS1), Cytochrome B5 Reductase (CYB5R3), Dihydroprimidinedehydrogenase (DPYD), Esterases (AADAC, CEL, CES1, CES1P1, CES2, CES3, CES5A, ESD, GZMA, GZMB, PON1, PON2, PON3, UCHL1, UCHL3), Epoxidases (EPHX1-2), Flavin-Containing Monooxygenases (FMO1-6), Glutathione Reductase/Peroxidases (GPX1-7, GSR), short-chain Dehydrogenases/Reductases (DHRS1-13, DHRSX, HSD11B1, HSD17B10, HSD17B11, HSD17B14), Superoxide Dismutases (SOD1-2), and Xanthine Dehydrogenase (XDH); and (b): phase II reaction enzymes: Amino Acid Transferases (AGXT, BAAT, CCBL1), Dehydrogenases (NQO1-2, XDH), Esterases (CES1-5), Glucuronosyl Transferases (UGT1-8), Glutathione Transferases (GSTA1-5, GSTK1, GSTM1-5, GSTO1-2, GSTP1, GSTT1-2, GSTZ1, GSTCD, MGST1-3, PTGES), Methyl Transferases (AS3MT, ASMT, COMT, GNMT, GAMT, HNMT, INMT, NNMT, PNMT, TPMT), N-Acetyl Transferases (ACSL1-4, ACSM1, ACSM2B, ACSM3, AANAT, GLYAT, NAA20, NAT1-2, SAT1), Thioltransferase (GLRX), and Sulfo transferases (CHST2-13, GAL3ST1, SULT1A1-3, SULT1B1, SULT1C1-4, SULT1E1, SULT2A1, SULT2B1, SULT4A1, SULT6B1, CHST1); (iv) genes associated with drug transporters: In humans there are 49 ABC transporter genes and the multidrug resistance associated proteins (MRP1/ABCC1, MRP2/ABCC2, MRP3/ABCC3, MRP4/ABCC4, MRP5/ABCC5, MRP6/ABCC6, MRP7/ABCC10, MRP8/ABCC11 and MRP9/ABCC12) which belong to the ABCC family integrated by 13 members. Other genes encoding transporter proteins are genes of the Solute Carrier Super family (SLC) and Solute Carrier Organic (SLCO) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, including folate (SLC19A1), urea (SLC14A1, SLC14A2), monoamines (SLC29A4, SLC22A3), amino acids (SLC1A5, SLC3A1, SLC7A3, SLC7A9, SLC38A1, SLC38A4, SLC38A5, SLC38A7, SLC43A2, SLC45A1), nucleotides (SLC29A2, SLC29A3), fatty acids (SLC27A1-6), neurotransmitters (SLC6A2 (Noradrenaline Transporter), SLC6A3 (Dopamine Transporter), SLC6A4 (Serotonin Transporter, SERT), SLC6A5, SLC6A6, SLC6A9, SLC6A11, SLC6A12, SLC6A14, SLC6A15, SLC6A16, SLC6A17, SLC6A18, SLC6A19), glutamate (SLC1A6, SLC1A7), and others); and (v) pleiotropic genes involved in multifaceted cascades and metabolic reactions [2,3].

Epigenetic aberrations (DNA methylation, histone modifications, microRNA dysregulation) can also affect the expression of genes involved in the pharmacogenetic cascade leading to abnormal processing of drugs with negative consequences on drug efficacy and safety [2]. Age-and sex-related epigenetic changes in metabolic and transporter genes may affect circadian rhythms, hormone secretion, brain function, and the metabolism of antidepressants [2]. Epigenetic regulation is responsible for the tissue-specific expression of genes involved in pharmacogenetic processes, and epigenetics plays a key role in the development of drug resistance. Epigenetic changes

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Citation: Cacabelos R (2016) Trial-and-Error versus Personalized Treatment in Depression: The Power of Pharmacogenomics. J Psychiatry Depress Anxiety 2: 004.

Received: March 01, 2016; **Accepted:** March 07, 2016; **Published:** March 21, 2016

affect cytochrome P450 enzyme expression, major transporter function, and nuclear receptor interactions. miRNAs target ABC transporters and are influential epigenetic regulators of drug metabolism, resistance and toxicity [4].

Over 90% of antidepressants are metabolized via CYP enzymes. About 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4 [1]. Among Caucasians, approximately one-quarter of the population is deficient in the enzymatic activity of the CYP2D6-CYP2C19-CYP2C9 cluster responsible for the metabolism of over 60% of current drugs [3]. Mutations in metabolic and transporter genes are responsible for toxicity and resistance to antidepressant drugs [1].

Recent studies indicate that the prescription of antidepressants by trial-and-error, neglecting the pharmacogenetic profile of the patients, is subject to an error rate of over 60% with the consequent problems in efficacy and safety [5].

Over 70% of the patients treated using the traditional criterion of trial-and-error are not taking the active ingredient most suited to their pharmacogenetic profile. The inclusion of pharmacogenetic information in the choice of drug and its dosage entails a significant, progressive reduction in depressive symptomatology, with an efficacy ratio of 80% and a faster remission of clinical symptoms (depressive phenotype) [6].

The development of new compounds or retesting of old drugs by using pharmacogenetic strategies encompasses a series of steps in a multidisciplinary fashion: (i) genetic screening (genotyping) of single genes to identify major gene targets; (ii) analysis of genetic variation to differentiate populations; (iii) structural and functional genomic analyses including genetic clusters and haplotypes; (iv) analysis of genotype-phenotype correlations to characterize major phenotypes as therapeutic targets associated with a particular gene or a cluster of genes involved in a metabolic pathway; and (v) implementation of basic and clinical pharmacogenomic procedures for drug development [7].

With regard to the future of pharmacogenomics as a practical discipline to efficiently optimize therapeutics in depression and other neuropsychiatric disorders, several issues should be addressed: (i) the education of physicians in medical genomics and pharmacogenomics is fundamental (less than 2% of the members of the medical community are familiar with genomic science); (ii) genomic screening of gene clusters involved in pharmacogenomic outcomes must become a clinical routine; (iii) each patient must be a carrier of a pharmacogenetic card indicating what kind of drugs he/she can take and which medications he/she should avoid; (iv) regulatory agencies should request pharmacogenetic data from the pharmaceutical industry when applying for drug approval; (v) pharmacogenetic data must be included in the patient information leaflet and the pharmaceutical vademecum; and (vi) new guidelines for daily praxis, such as that of the first World Guide for Drug Use and Pharmacogenomics [8], will facilitate the understanding of the relationship between drugs and genes (and vice versa) to make drug prescription a genuinely personalized procedure [1-3].

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