

Impact of Genomic Medicine on the Future of Neuropsychopharmacology

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Editorial

Neuropsychopharmacology is a historical discipline devoted to the development, characterization, and clinical assessment of drugs for the treatment of brain disorders. From a pathogenic perspective, central nervous system (CNS) disorders can be classified into 6 major categories: (i) Neurodevelopmental disorders (i.e., mental retardation, attention deficit hyperactivity disorder, autism), (ii) Mental disorders (i.e., schizophrenia/psychosis, depression, anxiety), (iii) Age-related neurodegenerative disorders (i.e., motor-neuron disease, demyelinating disorder, Alzheimer's disease, Parkinson's disease, Huntington's disease), (iv) Cerebrovascular disorders (i.e., migraine, stroke), (v) Neurotoxic disorders (i.e., drug addiction, alcoholism), and (vi) Other complex disorders (i.e., epilepsy). The different forms of CNS disorders pose several challenges to our society and the scientific community: (i) They represent an epidemiological problem, and a socio-economic, psychological and family burden; (ii) Most of them have an obscure/complex pathogenesis; (iii) Their diagnosis is not easy and lacks specific biomarkers; and (iv) Their treatment is difficult and inefficient. In terms of economic burden, approximately 10-20% of direct costs are associated with pharmacological treatment, with a gradual increase in parallel with the severity of the disease [1-3].

The International Classification of Drugs differentiates 13 categories of CNS drugs: (i) General Anesthetics (10 FDA-approved drugs); (ii) Analgesics and Antipyretics (nonsteroidal anti-inflammatory agents, 35; opiate agonists, 21; opiate partial agonists, 4; miscellaneous analgesics and antipyretics, 7); (iii) Opiate Antagonists (3 drugs); (iv) Anticonvulsants (barbiturates, 4; benzodiazepines, 4; hydantoins, 3; succinimides, 2; miscellaneous anticonvulsants, 17); (v) Psychotherapeutic agents (antidepressants: monoamine oxidase inhibitors, 6; selective serotonin- and norepinephrine-reuptake inhibitors, 4; selective serotonin-reuptake inhibitors, 6; serotonin modulators, 2; tricyclics and other norepinephrine-reuptake inhibitors, 12; miscellaneous antidepressants, 5; antipsychotics: atypical antipsychotics, 10; butyrophenones, 3; phenothiazines, 9; thioxanthenes, 3; miscellaneous antipsychotics, 4); (vi) Anorexigenic agents and respiratory and cerebral stimulants (amphetamines, 6; miscellaneous anorexigenic agents and respiratory and cerebral stimulants, 13); (vii) Anxiolytics, sedatives, and hypnotics (barbiturates, 6; benzodiazepines, 19; miscellaneous anxiolytics, sedatives, and hypnotics, 14); (viii) Antimanic agents (6 drugs); (ix) Antimigraine agents (selective serotonin agonists, 7; Miscellaneous antimigraine agents, 9); (x) Antiparkinsonian agents (adamantanes, 1; anticholinergic agents, 5; catechol-O-methyltransferase (COMT) inhibitors, 2; dopamine precursors, 3; dopamine receptor agonists, 8; monoamine oxidase B inhibitors, 2); (xi) Anti-dementia agents (cholinesterase inhibitors, 4; nootropics, 2; neuroprotective agents, 2; vasoactive agents, 4; immunotrophins, 2; anti-atherogenic compounds, 2; other anti-dementia drugs, 1); (xii) Fibromyalgia agents (3 drugs); (xiii) Miscellaneous CNS agents (9 drugs) [4]. Most of these drugs are "neuro-repressive" or symptomatic, but not anti-pathogenic for brain disorders. The existence of effective neuroprotective agents to stimulate brain maturity in childhood or prevent neurodegeneration in old age are missing among over 300 FDA-approved CNS drugs. In

the case of mental disorders, conventional drugs have been developed on the basis of old, doubtful (restrictive) pathogenic hypotheses associated with neurotransmitter dysfunction (i.e., dopamine in schizophrenia; noradrenaline and serotonin in depression; GABA in anxiety; acetylcholine in Alzheimer's disease, etc.). However, recent knowledge on the pathogenesis of most CNS disorders indicates that all these brain pathologies are complex disorders in which multiple defects distributed across the human genome might be involved, in conjunction with diverse environmental factors and epigenetic phenomena [3,5-8]. In this context, genomic medicine (genomics, transcriptomics, proteomics, metabolomics) will revolutionize medical practice in terms of etiology, diagnosis and treatment, including (i) the understanding of causative factors and pathogenesis of CNS disorders, (ii) the characterization of specific biomarkers for an early diagnosis and/or identification of predictive risks for potential prevention; and (iii) the personalization of treatments by means of pharmacogenomics and pharmacoeugenomics protocols [3,8-10].

The optimization of CNS therapeutics requires the establishment of new postulates regarding (i) the costs of medicines, (ii) the assessment of protocols for multifactorial treatment in chronic disorders, (iii) the implementation of novel therapeutics addressing causative factors, and (iv) the setting-up of pharmacogenomic strategies for drug development and personalized treatments [3,5]. Pharmacogenomics account for 30-90% variability in pharmacokinetics and pharmacodynamics; however, pharmacogenetics alone does not predict all phenotypic variations in drug response. Individual differences in drug response are associated with genetic and epigenetic variability and disease determinants [8,9]. The efficacy and safety of CNS drugs and other medications are closely associated with the efficiency of the pharmacogenetic process; and the gene clusters involved in the pharmacogenetic network (pathogenic, mechanistic, metabolic, transporter, pleiotropic genes) are also under the influence of epigenetic changes which may determine the therapeutic outcome [3,8-10]. 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, aldehyde dehydrogenases, aldo-keto reductases, amine oxidases, carbonyl reductases, cytidine

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deaminase, cytochrome P450 family monooxygenases, cytochrome b5 reductase, dihydroprimidine dehydrogenase, esterases, epoxidases, flavin-containing monooxygenases, glutathione reductase/peroxidases, short-chain dehydrogenases/reductases, superoxide dismutases, and xanthine dehydrogenase; and (b) Phase II reaction enzymes: amino acid transferases, dehydrogenases, esterases, glucuronosyl transferases, glutathione transferases, methyl transferases, N-acetyl transferases, thioltransferase, and sulfotransferases; (iv) Genes associated with drug transporters: ABC genes, especially *ABCB1* (ATP-binding cassette, subfamily B, member 1; P-glycoprotein-1, P-gp1; Multidrug Resistance 1, MDR1), *ABCC1*, *ABCG2* (White1), genes of the solute carrier superfamily (*SLC*) and solute carrier organic (*SLCO*) transporter family, responsible for the transport of multiple endogenous and exogenous compounds, including folate, urea, monoamines, amino acids, nucleotides, fatty acids, neurotransmitters (*SLC6A2*, noradrenaline transporter; *SLC6A3*, dopamine transporter; *SLC6A4*, serotonin transporter), glutamate, and others; and (v) Pleiotropic genes involved in multifaceted cascades and metabolic reactions [3,10]. Epigenetics is the molecular phenomenon by which phenotypic changes are transmitted from one generation to another with no apparent alterations in structural DNA. Classical epigenetic mechanisms, including DNA methylation, histone modifications, and microRNAs (miRNAs) regulation, are among the major regulatory elements that control metabolic pathways at the molecular level. These epigenetic modifications regulate gene expression transcriptionally, and miRNAs suppress gene expression post-transcriptionally [11,12]. Distinctly methylated genes identified in different human populations suggest an influence of DNA methylation on phenotype differences, such as susceptibility to certain diseases and pathogens, and response to drugs and xenobiotic agents. DNA methylation contributes to natural human variation [13,14]. Epigenetics has emerged in recent years as one of the most important biological mechanisms linking exposures during the course of life to long-term health. Epigenetic status is influenced by a range of environmental exposures and different modalities of pharmacological intervention. Epigenetic status is also influenced by genotype, and genetic variation in genes encoding a plethora of enzymes and proteins. Epigenetic modifications are reversible and can potentially be targeted by pharmacological and dietary interventions [8,12,15-17]. 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 affect cytochrome P450 enzyme expression, major transporter function, and nuclear receptor interactions [4,18-20]. The redundancy and promiscuity of this complex system regulating drug effects and toxicity is a scientific challenge of paramount importance for the pharmaceutical industry and the medical community in the coming years [21].

With regard to the future of pharmacogenomics as a practical discipline to efficiently optimize CNS therapeutics, 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 pharmacogenomics outcomes must become a clinical routine (without genetic testing there is no pharmacogenetics); (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 incorporated into the patient information leaflet and the pharmaceutical

vade mecum; and (vi) New guidelines for daily praxis, such as that of the first World Guide for Drug Use and Pharmacogenomics [4], will facilitate the understanding of the relationship between drugs and genes (and vice versa) to make drug prescription a real personalized procedure. By knowing the pharmacogenomics profiles of patients who require treatments with CNS drugs of current use, it might be possible to obtain some of the following benefits related to efficacy and safety issues: (i) to identify candidate patients with the ideal genomic profile to receive a particular drug; (ii) to adapt the dose in over 90% of the cases according to the condition of CYP-related extensive (EM), intermediate (IM), poor (PM) or ultra-rapid metabolizer (UM) (diminishing the occurrence of direct side-effects in 30-50% of the cases); (iii) to reduce drug interactions by 30-50% (avoiding the administration of inhibitors or inducers able to modify the normal enzymatic activity on a particular substrate); (iv) to enhance efficacy; and (v) to eliminate unnecessary costs (>30% of pharmaceutical direct costs) derived from the consequences of an inappropriate drug selection and the overmedication administered to mitigate ADRs [1].

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