The Incorporation of Pharmacogenomics to Drug Development in Neuropsychiatric Disorders

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Introduction

The global pharmaceutical sales increased from $836 billion in 2014 to $967 billion in 2016 worldwide, from $369 billion to $446 billion in the USA, and from $179 billion to $201 billion in the EU [1]. In contrast, the number of new patents for drugs [2,3] and/or FDA drug approvals per year (20-40 drugs/year) remain stagnant or in regression [4]. Furthermore, the health/disease paradigm is changing, with

(i)   New pandemics in some geographic locations with potential dissemination to other regions.

(ii)   Expansion of chronic/degenerative disorders in developed countries in parallel with a decrease in infectious diseases in rich economies.

(iii)   An alarming increase of age-related disorders in both developed and developing countries.

(iv)   Inequalities in the distribution of health resources and health-care spending (44% in India; 43% in China; 12% in UK and USA).

(v)   Increase in the cost of health technologies.

(vi)   Conflict of interest associated with intellectual property of health products.

(vii)   Problems with the cost of medicines which are unaffordable in many developing countries [2,3,5].

Most of these issues demand an urgent revision by Governments, health-care providers, regulatory agencies, and the medical/scientific community. In terms of morbidity and mortality, cardiovascular disorders (25%), cancer (20-30%) and brain disorders (10-15%) are major problems of health, representing over 60-80% of mortality in developed countries. These medical conditions account for over 70% of health costs and about 80-90% of investments in drug development. However, most drugs on the market are not etiopathogenic, but symptomatic, with an efficacy rate below 40%. In this context, a conceptual reconsideration of drug development procedures and therapeutics is necessary to face the challenges that human health demands in the present century [6].

Over the past decades, important progress has been achieved in the field of pharmacogenomics [7,8]. However, pharmacogenetics is still in its infancy and its concept has evolved into a broader spectrum subsequent to the completion of the human genome project. Pharmacogenomics accounts for 30-90% variability in pharmacokinetics and Pharmacodynamics [9,10]; however, pharmacogenetics alone does not predict all phenotypic variations in drug response. Individual differences in drug response are associated with genetic and epigenetic variability (DNA methylation, histone/chromatin modifications, miRNA regulation) in pathogenic, mechanistic, metabolic, transporter, and pleiotropic genes involved in the pharmacogenomic cascade [11-14].

From a global health perspective, important issues to be addressed with regard to neuropsychiatric disorders (NPDs) and Neuropsychopharmocology are

(i)   Disease burden (DALYs: disability-adjusted life years; YLDs: years lived with disability; YLLs: years of life lost).

(ii)   The costs (direct, indirect) of disease.

(iii)   The impact that the identification of pre symptomatic biomarkers may have on disease burden in the future.

(iv)   More immediately, the effect that the implementation of pharmacogenetic procedures may have on drug efficacy and safety in NPDs.

NPDs (mental, neurological, substance use disorders) contribute approximately 10% of the global burden of disease. About 30% of all YLDs are assigned to NPDs, especially depression (11.8%), alcohol use disorders (3.3%), schizophrenia (2.8%), bipolar disorder (2.4%), and dementia (1.6%). The proportion of global disease burden increased from 7.3 to 10.4% between 1990 and 2010. There was a 41% increase in absolute DALYs caused by NPDs (from 182 to 258 million DALYs), together with an increase in excess deaths and suicides. Worldwide DALYs (%) of major NPDs include the following: 5.3% schizophrenia, 41.9% mood disorders, 2.2% conduct disorder, 2.3% anxiety disorders, 1.6% autism, 0.2% attention-deficit hyperactivity disorder,

0.4% intellectual disability, 8.7% migraine, 6.8% epilepsy, 4.4% dementia, 6.9% alcohol use disorders, 7.8% illicit drug use disorders, and suicide and self-harm (1.47% of Global Burden of Disease, GBD). NPDs are the leading cause of disease burden, responsible for 7.4% of global DALYs and 22.9% of global YLDs. Within NPDs, mental disorders account for 56.7% DALYs, followed by neurological disorders (28.6%) and substance use disorder (14.7%) [15].

A global cost of NPDs is projected to be about US$6 trillion by 2030. An estimated 8 million deaths annually are attributed to mental disorders. Approximately 127 million Europeans suffer brain disorders. The total annual cost of brain disorders in Europe is about €386 billion, with €135 billion in direct medical expenditures (€78 billion, inpatients; €45 billion, outpatients; €13 billion, pharmacological treatment), €179 billion in indirect costs (lost workdays, loss of productivity, permanent disability), and €72 billion in direct non-medical costs. Mental disorders represent €240 billion (62% of the total cost, excluding dementia), followed by neurological diseases (€84 billion, 22%) [16].

Depression is the third most important cause of disease burden worldwide, 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. According to the National Health and Nutrition Examination Survey, nearly 8% of persons aged ≥12 years (6% of males and 10% of females) report current depression (suicide deaths per 100,000 population: 13.0). Depression is the most common type of mental illness, affecting more than 26% of the U.S. population. It has been estimated that by the year 2020, depression will be the second leading cause of disability throughout the world, second only to ischemic heart disease [15]. The worldwide prevalence of schizophrenia ranges between 0.5% and 1%, with the first episode at 21 years of age in men and 27 years of age in women. Approximately one-third of the cases will attempt suicide and, eventually, about 1 out of 10 will take their own lives. Global costs for schizophrenia are estimated to be over $6 billion in the USA. Anxiety disorders (panic disorder, generalized anxiety disorder, post-traumatic stress disorder, phobias, and separation anxiety disorder) are the most common class of mental disorders present in the general population, with an estimated lifetime prevalence of 10-15%, and an annual cost of over $40 billion in the USA. Direct treatment costs for each mental disorder represent 1-2% of total national health care costs, and serious mental illness is associated with an annual loss of earnings totaling $193.2 billion [15].

Dementia (Alzheimer's disease, vascular dementia, mixed dementia) and Parkinson's disease are among the top 15 conditions with the highest increase in burden. Neurological disorders constitute 5.5% of YLDs (42.9 million YLDs), with migraine, epilepsy and dementia representing over 50% of neurological YLDs (2.9% of global YLDs) [15-17].

Approximately, 45-50 million people suffer dementia (75 million in 2030; 145 million in 2050; 7.7 million new cases/year).

The global economic cost for dementia is over US$604 billion, equivalent to 1% of the global gross domestic product. In terms of costs, Alzheimer's disease (AD) accounts for $226 billion/year in the USA and €160 billion/year in Europe (>50% are costs of informal care, and 10-20% are costs for pharmacological treatment). It is estimated that in the USA alone the direct cost of AD in people older than 65 years of age could be more than $1.1 trillion in 2050 (from 2015 to 2050, the estimated medical costs would be about $20.8 trillion). Strikingly, no new drugs have been developed for AD for the past 15 years [18]. Anti-AD drugs are not cost effective and less than 20% of patients can obtain a mild benefit with conventional drugs [19]. Pharmacogenomics of AD has demonstrated to be useful for prediction of therapeutic outcome and discrimination of responders vs non-responders [9,19-22].

Antidepressants were the third most common prescription drugs taken by Americans in the past decade. From 1988–1994 through 2005-2008, the rate of antidepressant use in the USA increased by nearly 400%. Eleven percent of Americans take antidepressant medication. Prescription of antidepressants varies widely between European countries despite no evidence of difference in the prevalence of affective disorders, and only 30-40% of depressed patients treated with medication achieve full remission [23,24].

Cost-effectiveness of interventions in NPDs ranges between US$100 and US$2,000 per healthy life year gained. However, drug effectiveness is lower than 30% in most NPDs [15].

Intervention priorities for NPDs, as proposed by commissioned authors of the World Bank [15] practically neglect genomic intervention either as prevention strategies or personalized treatments. However, it seems clear that multiple genomic defects, interacting with environmental factors and epigenetic phenomena, are at the basis of the pathogenic mechanisms underlying most NPDs [9,10,21,25]. Therefore, the elucidation of disease pathogenesis at molecular levels is a fundamental issue in order to identify suitable biomarkers for an early diagnosis or, even better, pre symptomatic markers for disease prevention [26]. Furthermore, 60-80% of psychotropic drugs are metabolized via CYP pathways; and only 20% of the Caucasian population are normal metabolizers for the tetragenic cluster integrated by the CYP2D6-2C9-2C19-3A4/5 genes, this indicating that, by trial and error, the possibility of prescribing the wrong medication to a particular patient, ignoring his/her pharmacogenetic profile, is over 70% [7,9]. In fact, over 60% of depressive patients are receiving an inappropriate medication according to their pharmacogenetic background [23,24], and community psychiatrists are more accurate in their psychotropic prescriptions when they know the CYP profile of their patients [27-29]. At the present time, pharmacogenetic testing is currently available for NPDs and a wide range of medical conditions. Tangible benefits to patients and reduced total health care costs have been observed. However, pharmacogenetic-guided therapy faces many barriers to full integration into clinical practice and

acceptance by stakeholders, whether practitioner, patient or payer [30-34].

In practical terms, biomarkers for early detection/intervention in NPDs might reduce disease burden by 5-15% during the first 5-year period of application; and disease-specific pharmacogenomic procedures would be able to help in (i) reducing acute side-effects by 20-30% and drug-related chronic toxicity by 25-40%, (ii) attenuating global DALYs by 5-10%, and (iii) developing anti-pathogenic drugs rather than conventional symptomatic compounds [7,9,10,21,26,35,36].It is likely that the change in mentality that requires the implantation of genomic medicine in NPDs will force some reluctant peers to assume that something is always better than nothing before reaching an unattainable perfection.

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