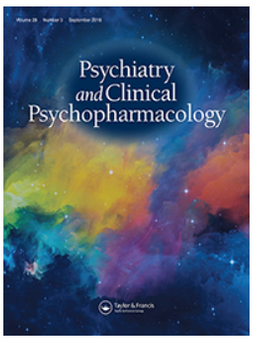

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EDITORIAL

Psychiatric pharmacogenomics in the age of neuroscience: promises and challenges

Simplicity is the ultimate form of sophistication.
– Leonardo da Vinci

Most psychiatric disorders including major depressive disorder (MDD), anxiety disorders, bipolar disorder, obsessive-compulsive disorder (OCD), schizophrenia, autism, and attention-deficit/ hyperactivity disorder (ADHD) are known to be genetically sophisticated disorders. The polygenic architecture of these psychiatric disorders has been determined by the aggregate effect of common genetic variants through various combinations of interacting factors such as numerous single nucleotide polymorphisms (SNPs), copy number variations (CNVs), and rearrangements at chromosomal level [1]. Candidate-gene studies and genome-wide approaches can disentangle complex genetic architecture and offer insight into the neurobiological underpinnings of psychiatric disorders and their proper management.

Pharmacogenomics (PGx) refers to the study of how genetic variation influences response to drug treatments in terms of efficacy (*efficacy pharmacogenomics*) or tolerability (*safety pharmacogenomics*). Currently available PGx testing can be divided into two primary categories: metabolic enzymes (cytochrome P450 enzyme system also referred to as *pharmacokinetics*); and genes that effect neuronal function (dopamine transporter and receptor genes frequently referred to as *pharmacodynamics*). Recent evidence indicates that genetic factors play a critical role (42–50%) in determining the differences in both response and adverse effects of antidepressants and this evidence serves as the foundation of *precision medicine*. The benefits are obvious as it would allow psychiatrists to tailor medications to their patients in such a way that maximizes their efficacy and tolerability, thus fulfilling the goals of *personalized medicine*. In addition; by elucidating the pathways by which drugs act to treat psychiatric disorders or provoke unwanted adverse effects, pharmacogenomics may inform the rational development of new treatments that are ever more safe and efficacious. Precision medicine, a novel approach to disease prevention and treatment, is based on an appreciation of the heterogeneity of disease entities and individual differences in genetic make-up. Psychiatric pharmacogenomics, a gene-based method to improve precision in psychotropic medication prescribing, analyzes polymorphisms in pharmacokinetics and pharmacodynamics of genes that affect the metabolism of and response to antidepressant and antipsychotic medications [2]. This approach is designed to assist clinicians in selecting medications for individual patients based on objective, evidence-based genomic information with the goal of improving clinical outcomes and predicting those drugs that may lead to failed medication trials and poor prognoses [3]. This allows clinicians to optimize the choice of which medications to prescribe and also how to dose them for maximum efficacy and minimal adverse effects.

Psychiatric pharmacogenomics is in its infancy due to the fact that there are currently few validated and clinically useful gene-response associations that can be used to reliably guide psychotropic medication choice. Reasons that psychiatry may be lagging behind other specialties such as oncology include the heterogeneity of psychiatric disorders (general syndromes rather than distinct pathophysiologically based disorders), the lack of biomarkers for specific illnesses, and the difficulty in defining and standardizing clinical outcomes [4]. Although numerous biomarkers have been associated with psychiatric disorders such as genes for BDNF (brain-derived neurotrophic factor), COMT, DRD1, DRD2, DISC1, GABABR1 (γ-aminobutyric acid B receptor 1), 5HTR1A, and genes for myelination, glutaminergic and GABAergic neurotransmission, oxidative stress, signal transduction, response to the environment, cell survival and proliferation, and cell shrinkage and apoptosis, no genetic biomarker has yet been shown to be useful in prospectively identifying any specific psychiatric disorders [5]. Genetic predisposition in psychiatry is thinly distributed over thousands of loci, each loci contributing a small effect, with considerable overlap of brain systems and shared common genetic factors. In addition, epigenetic and other factors that alter DNA structure and conformation would determine whether susceptibility genes are expressed or suppressed, further complicating studies of the relationship between genotype and phenotype. Environmental

factors (age, gender, diet, alcohol use, hormonal status, general health etc.) and comedication are usually more important factors than inherited determinants of drug metabolism and response [6]. Antidepressants are reported to be among the most prescribed class of drugs, only behind antihyperlipidemics and analgesics. Although antipsychotic medications account for a smaller number of prescriptions dispensed, they still comprise a substantial market share, in terms of dollars spent [7]. Antidepressant use has increased over the past decade but only half of those taking them will respond and about 55% will experience at least one bothersome adverse effect [8]. In the largest and longest evaluation of antidepressants, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, it took more than 50 weeks and at least four trials to obtain a cumulative remission rate of 67% [9]. Current pharmacological strategies include swifter dose escalation and medication changes as well as augmentation strategies. Information about whether the patient is likely to benefit or suffer intolerable adverse effects in relation to dosing strategies is not available to the clinician, so finding the most effective and best-tolerated pharmacotherapy relies on the clinician's application of a stepwise strategy that is largely guided by educated guessing and the process of elimination rather than by personalized prognostic data. In clinical practice, this approach often leads to patient attrition, prolonged suffering, and other adverse sequelae. An emerging and promising strategy is to utilize a person's pharmacokinetic and pharmacodynamic genetic profile to guide personalized psychopharmacological therapy decisions.

Several combinatorial pharmacogenetic test products, such as Amplichip (developed by Roche, Basel, Switzerland), GeneSight (developed by AssureRx, a subsidiary of Myriad Genetics, Inc.), GeneCept (marketed by Genomind, King of Prussia, Pa.), CNSDose (marketed by Alpha Genomix Laboratories, Lawrenceville, Ga.), Neuropharmagen (developed by AB-Biotics SA, Barcelona, Spain) have undergone clinical trial testing in randomized controlled trials [10]. These studies used a variety of meta-analytic, prospective, and retrospective designs, with or without blinding of participants or clinicians assessing symptom severity outcomes, notable methodological weaknesses, such as the lack of control groups, lack of blinding, small sample sizes, and potential conflicts of interest among investigators. Commercially available genetic tests that claim to guide psychotropic prescribing and offer patients information primarily about how their specific genetic profile might affect their metabolism of psychotropic drugs. Although the presentation of the results differs, in general, patients are presented with a list of psychotropic drugs grouped into different categories that correspond to different prescription recommendations: *use as normally prescribed*, *use with caution*, or *use with extreme caution*. The companies' recommendations are based on an integrated analysis of multiple genetic variants thought to affect the functioning of enzymes involved in metabolizing psychotropic drugs. The patients are then classified as *poor*, *intermediate*, *extensive*, or *ultrarapid metabolizers* for each drug, and corresponding prescription recommendations are offered. Practically speaking, what these results suggest is that patients who are slower metabolizers of a given medication are more likely to benefit from lower doses of that medication to avoid toxicity, and, conversely, more rapid metabolizers may require higher doses to achieve desired therapeutic effect.

Promising findings toward potential opportunities for genetic testing have been reported in the literature. For example, Cheung et al. reported that in a Han Chinese population, HLA-B*15:02 is moderately to strongly predictive of development of severe skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis induced by carbamazepine, phenytoin, or lamotrigine [11]. These are life-threatening complications that appear to occur randomly in clinical settings, so identification of risk alleles can literally be lifesaving. When pharmacogenomically avoidable events are reported, such as the death of a child exposed to fluoxetine, with CYP2D6 poor metabolism, it is important that clinicians act on the available evidence. De Leon suggests that the approach of psychiatric pharmacologic treatment should change: clinicians need to personalize their pharmacologic interventions as much as possible, but the field needs to also consider subdividing psychiatric syndromes into groups that may be more homogeneous based on treatment responses [12]. Perhaps the most progress has been made in identifying genetic variants that are associated with adverse effects of psychotropic medications (in contrast to those that try to predict therapeutic efficacy). This may be because the presence of a side effect is more easily defined and quantified than clinical efficacy. In addition, clinicians feel compelled to first reduce adverse medication reactions before addressing targeted symptoms. Saito et al. compared a group of Japanese individuals with schizophrenia who developed clozapine-induced granulocytosis/granulocytopenia (CIAG). CIAG with a control group of Japanese individuals who were exposed to clozapine but did not develop CIAG. With the use of an iterative series of increasingly specific genetic scans to identify variants that distinguished the two groups, they found that the presence of the genetic variant HLA-B*59:01 was associated with a tenfold increased risk of CIAG [13]. The study by Saito et al. is representative of the dynamic, rapidly evolving nature of pharmacogenomics and illustrates its dramatic potential to transform clinical care in psychiatry. If there is a clear report of significant side effects, such as an unusual increase in irritability, lethargy, activation, or other

unexpected physiologic signs (i.e. marked changes in blood pressure, pulse), pharmacogenomic testing should be strongly considered. In an open study of 900 patients treated with venlafaxine who were both genotyped and phenotyped for CYP2D6, 4% were genotypically *poor metabolizers*, while 27% were phenotypically *poor metabolizers*, suggesting that 23% of patients with other genotypes had converted to a poor metabolizer phenotype as a result of concomitant medications [14]. Polymorphisms in the 5HT2C receptor gene have been linked to variability in metabolic side effects, more specifically, antipsychotic drug-induced weight gain. The Food and Drug Administration (FDA) now recommends that all patients of Asian descent be tested for a specific variant of the HLA-B gene before initiating therapy to avoid carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. While this is a valuable, and potentially lifesaving, discovery, it is clearly only a first, small step toward a broader application of pharmacogenomics in psychiatry.

Genetic variation of the hepatic CYP450 gene family confers differential metabolic capacity among individuals, which can dramatically affect the pharmacokinetic profile of common concurrently administered psychoactive medications and affect individual patient response to some antidepressants. In fact, incorporation of pharmacogenomic information into clinical practice has already begun in the form of FDA labelling associated with several newer antidepressants. The FDA listed over 100 medications with pharmacogenomics biomarkers in drug labelling and 26 of these are psychotropic medications [15]. Some companies base their advice on diagnostic, demographic, and symptom information obtained by the clinician in addition to pharmacogenomic testing results. When that occurs, it cannot be clear whether the pharmacogenomic testing results made a substantial contribution. In fact, no study used a proper comparison, such as free, readily available published protocols for the treatment of MDD (eg, STAR*D and the Texas Medication Algorithm Project, both available online) [9,16]. Therein lies a key issue: to be valuable, pharmacogenomic testing should outperform good care. It should not be an expensive alternative for attending to standard protocols. One thing is already clear from pharmacogenomics in psychiatry: Tests do not select drugs. Prescribers do. That is, it is highly unlikely that any single test will ever dictate which drugs to prescribe or not to prescribe in most cases. There is no known single gene for any major psychiatric disorder nor for any drug response to a psychiatric disorder, nor is one ever likely to be found, since genes do not code for psychiatric disorders, nor for psychiatric symptoms, nor for drug responses to psychiatric symptoms. Instead, genes code for proteins and epigenetic factors that regulate the efficiency of information processing in brain circuits, and that can be increasingly visualized with neuroimaging techniques. Rather than looking for a single gene that regulates drug response, psychiatric research is instead currently attempting to link treatment response to a portfolio of genes that regulate brain circuitries that are the substrates of various psychiatric symptoms. Such a portfolio of biomarkers will hopefully show which drugs will be somewhat more likely to work or to cause an adverse effect in a given patient. Right now, however, it is not clear that the available pharmacogenomic tests add substantial value proportionate to their cost for selection of first-line treatments of mental disorders. For selection of a first-line therapy, current treatment guidelines alone may be most cost-effective. If there is a place for current pharmacogenomic testing, it may be in the selection of drugs for patients who are treatment-resistant or treatment-intolerant to trials of evidence based therapies, particularly when these test results are augmented with therapeutic drug-level monitoring combined with classical approaches to selecting treatments. If that is the case, this would mean combining the classical approach of empiric case-based evidence from use of drugs that have a pharmacologic rationale for an individual patient, including a specific patient's unique information (personal symptom profile, prior clinical response or nonresponse to other agents, particular side effects experienced, family history, and preferences), with information from genotyping (both pharmacokinetic and pharmacodynamic markers; phenotyping therapeutic drug levels; and obtaining results from various epigenetic, proteomic, and neuroimaging biomarkers as well).

Despite notable progress over the past decade, the promise of pharmacogenetics in psychiatry has not yet been fully realized yet. The major obstacle to translating the promise into reality is that we still do not have a clear understanding of how genetic factors influence treatment response to psychotropic medications. The studies carried out to date suggest a number of intriguing hypotheses that merit further studies, but they do not point to any definitive associations that can be used with confidence to predict how a patient will respond to a particular treatment. The difficulty with the pharmacogenomic associations thus far reported is the lack of consistent findings. For every positive association, there are typically several negative studies that cast doubt on the positive finding. As a result, it is difficult to draw firm conclusions about the clinical relevance of any genes that may be implicated. There are several reasons for the difficulty. First, treatment responses to psychotropic medications are complex phenotypes. They may be as complex as the disorders for which they are used to treat. Psychotropic medications may act on a number of different molecular pathways to exert their therapeutic effect, and in turn they may be acted on by a number of different molecular pathways in the process of their

absorption, distribution, and elimination. Consequently, multiple variants in distinct and converging genetic pathways may independently and interactively contribute to a particular drug response. In addition, multiple environmental factors may further contribute to variability in the response. Demographic factors, diet, substance abuse, smoking, concomitant treatments and comorbidities may all affect the actions of psychotropic drugs. It has been shown that smoking induces CYP450 activity and promotes the metabolism of substrate drugs, while SSRI's are known to inhibit CYP450 activity and may disrupt the metabolism of other concomitant medications. Therefore, treatment responses may be the sum of a number of impinging genetic and environmental factors, making it difficult to identify any one factor in isolation and to construct more complete models of the determinants of drug response. Second, it is particularly challenging to conduct appropriately designed pharmacogenetic studies that can illuminate the complex architecture of treatment responses. The studies carried out to date have had rather small sample sizes and short periods of follow-up. Even the largest studies that have been reported are significantly underpowered to detect genes with effect sizes likely involved in treatment responses. To address this issue, efforts have been made to combine data across studies in meta or mega analyses. Finally, to complicate matters, within each study, patients often take multiple medications and have erratic patterns of adherence. As a result, the responses to any one drug during follow-up may be hopelessly masked. A clear demonstration of a genotype/blood level relationship in a single dose or 8-week study may not correlate with chronic treatment, in which compensatory changes in secondary metabolic pathways and drug transporters, up- or downregulation of genes, saturation pharmacokinetics and other factors may modify the impact of oxidative enzyme polymorphisms on final drug level. With chronic treatment, some psychotropic drug metabolites form complexes with P450 enzymes that alter or even reverse the acute effect on metabolism. Long-term changes in P450 enzymes also occur in the brain, not only on the substrate drug, but on neurotransmitters and neurosteroids metabolized by the same enzymes on which the medication may act. Another complicating factor is that the disorder, as well as medications used to treat it, can alter the relationship between pharmacologic genotype and phenotype. For example, many proinflammatory cytokines and acute-phase proteins that are associated with mood and anxiety disorders act on transcription or posttranslational protein modification to downregulate some CYP450 genes and upregulate others. At the same time, suppression of cytokines by antidepressants can alter gene expression in directions that antagonize improvement of depression. Finally, pharmacogenomic tests, may distract from careful history taking (especially in differential diagnosis of schizoaffective disorder from other psychotic disorders) and assessment of drug effects and interactions and cannot replace knowing and following the principles of the large literature on appropriate serial drug choice. Another potential risk is loss of genetic privacy. Although privacy concerns are not unique to pharmacogenetic testing, it has been argued that genetic data is perceived as being higher quality and more definitive than other laboratory data, suggesting special protections are necessary.

Conclusions

Given the potential to improve patient treatment outcomes, even a modest increase in remission rates of depression or reduction of adverse event risk would significantly reduce the growing disease burden of depression at the population level. Clinical psychiatrists are encouraged to consider the evidence base of these tools in the context of their practice and their diverse patient needs. By personalizing treatments to psychotropic medications, pharmacogenomic testing holds great promise to dramatically improve care in psychiatry. Pharmacogenomic test results orients the advanced prescriber's thinking along a neurobiological perspective in order to select treatments that are biologically plausible, rather than just utilizing intuition, habit, or trial and error. This appears to have the potential to improve drug selection and treatment cost-effectiveness. That approach is not to take a classical trial-and-error approach to selecting treatments, but instead to put the results of pharmacogenomic testing into the decision-making formula by pursuing a genetically informed, neurobiologically empowered, data-oriented, novel, and rational approach to selecting a treatment or combination that is already showing signs of yielding better symptomatic outcomes, better dosing, and reduced cost of treatment. In order to advance, the field of psychiatric pharmacogenetics needs to develop clear phenotypic definitions, robust outcome measures, and comprehensive molecular analysis of biomaterials. Only a paradigm shift can bring a fundamental change in psychiatric practice, allowing to disentangle the intricacies of psychiatric disorders. Until adequately powered studies that address gene number and expression and that control for confounding factors that affect outcome such as comorbidity, polypharmacy, environmental exposure, age, gender, ethnicity, substance use, and treatment adherence emerge, psychotropic medication prescribing would still remain a careful art of trial and error.

Declaration of interest

S.K., M.C.: The authors reported no conflicts of interest related to this article.

Disclosure Statement

No potential conflict of interest was reported by the authors.

References

[1] Schreiber M, Dorschner M, Tsuang D. Next-generation sequencing in schizophrenia and other neuropsychiatric disorders. Am J Med Genet B Neuropsychiatr Genet. 2013;162:671–678.

[2] Kung S, Xiaofan L. The clinical use of pharmacogenomic testing in treatment-resistant depression. Prim Psychiatry. 2010;17:46–51.

[3] Hall-Flavin DK, Winner JG, Allen JD, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012;2:e172.

[4] Dubovsky SL. The limitations of genetic testing in psychiatry. Psychother Psychosom. 2016;85(3):129–135.

[5] Li JZ. Circadian rhythms and mood: opportunities for multi-level analyses in genomics and neuroscience. Bioessays. 2013;36:305–315.

[6] Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138(1):103–141.

[7] IMS Institute for Healthcare Informatics. Medicines use and spending in the US: a review of 2015 and outlook to 2020. Parsippany, NJ, USA; 2016.

[8] Papakostas GI. Tolerability of modern antidepressants. J Clin Psychiatry. 2008;69(Suppl E1):8–13.

[9] Gaynes BN, Warden D, Trivedi MH, et al. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv. 2009;60(11):1439–1445.

[10] Zeier Z, Carpenter LL, Kalin NH, et al. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. Am J Psychiatry. 2018 Apr 25:appiajp201817111282.

[11] Cheung YK, Cheng SH, Chan EJ, et al. HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. Epilepsia. 2013;54(7):1307–1314.

[12] de Leon J. Focusing on drug versus disease mechanisms and on clinical subgrouping to advance personalised medicine in psychiatry. Acta Neuropsychiatr. 2014;26(6):327–333.

[13] Saito T, Ikeda M, Mushiroda T, et al. Pharmacogenomic study of clozapine-induced agranulocytosis/granulocytopenia in a Japanese population. Biol Psychiatry. 2016;80:636–642.

[14] Preskorn SH, Kane CP, Lobello K, et al. Cytochrome P450 2D6 phenoconversion is common in patients being treated for depression: implications for personalized medicine. J Clin Psychiatry. 2013;74:614–621.

[15] US Food and Drug Administration. Drugs: table of pharmacogenomic biomarkers in drug labeling. Available at: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm.

[16] Crismon ML, Trivedi M, Pigott TA, et al. The texas medication algorithm project: report of the texas consensus conference panel on medication treatment of major depressive disorder. J Clin Psychiatry. 1999;60:142–156.

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