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Pre-prescription testing in psychiatry: an overview

Abstract

Drug therapy 'tailored' towards an individual based on his/her genetic profile is becoming increasingly popular in the era of personalised medicine. Pre-prescription testing which enables this, exploits the link between a relevant set of genetic variants and drug metabolism profile to maximise drug efficacy and lower the risk of adverse drug reactions. Since the conception over 50 years ago that drug response might be linked to underlying genetic makeup, the science around this field has evolved rapidly across a wide range of drugs including antipsychotics. Over 80% of both typical and atypical antipsychotics are known to be metabolised by phase-I drug metabolising enzymes such as cytochrome P450 (CYP450) family of genes which harbour extensive genetic variations. This has encouraged variant testing in these genes among patients with neuropsychiatric disorders. A confluence of accelerated variant discovery and next generation sequencing offers a fast and cost-effective approach. However, genomic literacy among the end users, i.e., the psychiatrists, patients, and their primary caregivers remains low, posing a major hindrance in the realisation of this pharmacogenetic goal. A well-oiled, multi-disciplinary machinery comprising of researchers, psychiatrists, and genetic counsellors would be the key for optimal dissemination of this intervention. This review presents a broad conceptual background of pharmacogenetics/pharmacogenomics, its potential in psychiatry in particular, together with clinical evidence, and the accompanying challenges for its effective implementation in clinical settings.

Keywords: Pharmacogenetics. Pharmacogenomics. Neuropsychiatric disorders. Antipsychotic drugs. Clinical practice.

Anirban Mukhopadhyay[1], Chandra Bhushan Rai[2], Smita N Deshpande[3], BK Thelma[4]

[1]Department of Genetics, University of Delhi South Campus, New Delhi-110021, India, [2]Department of Psychiatry, Centre of Excellence in Mental Health, Atal Bihari Vajpayee Institute of Medical Sciences & Dr. Ram Manohar Lohia Hospital, New Delhi-110001, India, [3]Department of Psychiatry, Employees' State Insurance Corporation (ESIC) Medical College, Faridabad, Haryana-121012, India,[4]Department of Genetics, University of Delhi South Campus, New Delhi-110021, India

Correspondence: Smita N Deshpande, Department of Psychiatry, Employees' State Insurance Corporation (ESIC) Medical College, NH-3, KL Mehta Road, Behind BK Hospital, New Industrial Town, Faridabad, Haryana-121012, India. smitadeshp@gmail.com

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INTRODUCTION

The diploid human genome is comprised of ~6.2Mb of nucleic acid sequences packaged discretely into 46 chromosomes - 22 pairs of autosomes and a pair of sex chromosomes (XX in females and XY in males) within the nucleus of each somatic cell and is known as the nuclear genome. Conversely, the haploid genome (~3.1Mb) resides in the germ cells namely the eggs and the sperms. There also exists another much smaller (~16.5Kb) and independent deoxyribonucleic acid (DNA) molecule within the mitochondria referred to as the mitochondrial genome. The language of DNA is made up of four letters or chemical bases - adenine (A), cytosine (C), guanine (G), and thymine (T), functionally organised into nucleotides. Long stretches of sequences in each DNA molecule are generated by the permutation and combination of these letters; with only approximately two per cent of the stretches carrying information for ~21,000 protein coding genes,[1] while the function of the rest of the genome, termed non-coding is largely unclear.[2] Single changes at any of these four bases (termed base substitutions) throughout the diploid genome are abundant, resulting in the much advertised ~0.1% dissimilarity between any two individuals except monozygotic twins. These differences can increase six-fold, even if just one other among a few more, class of variants namely insertions or deletions of one to two bases (termed indels) of at one or more locations in the genome is considered.[3]

As the scientific community accrued more knowledge about genetics, a parallel advancement was also taking place in the field of computer science and the subsequent convergence of these two in the Human Genome Project (HGP) would eventually lead to a genetic boom that enables us today to discuss a wide range of topics under the broad umbrella of the human genome. To better understand the blueprint that builds a person - HGP - an international collaborative effort between 1990-2003 coordinated by the National Institutes of Health and the United States (US) Department of Energy was initiated. The project married several fields, from genetics through molecular biology to bioinformatics and computer science to achieve the big transformation to genomics, for realising one single dream of deciphering the entire DNA code, literally 50 years after the discovery of the DNA double helix, ushering in its wake an exciting era of consortium-based science.[4] The project greatly aided in estimating the number of protein coding genes to a more accurate ballpark of ~20,000, compared to the much earlier estimate of 100,000

genes, but the role of a majority of these genes remains a mystery. Furthermore, these coding genes comprise a mere two per cent of the total genome, and the rest are broadly termed as non-coding and functionally referred to as junk, essentially due to our limited analysis of this difficult to tread genomic regions and consequently limited understanding. Thus, the major outcome of this project encompassing cloning, mapping, and sequencing of the human genome was the insightful capturing of the large number of variations/alternate spellings/spelling mistakes present throughout the coding and non-coding genome vocabulary. With major advances in development of *in silico* analysis tools combined with experimental approaches, uncovering the constituents of this ~98% non-protein coding DNA and their likely regulatory roles in gene expression by either direct alteration or through altered secondary structures of DNA, is gaining importance in genetics of health and disease.

Yet, in a very definitive way, HGP was the final brick that laid a robust groundwork for all subsequent genome research in both monogenic diseases as well as the more common complex psychiatric, cardiovascular, lifestyle disorders, etc., be it at the DNA, ribonucleic acid (RNA), protein or metabolite levels.[5] A slowly evolving, long-term handle that the results of HGP would end up providing would be in understanding the causality of diseases (or gross phenotypic changes) using the presence/absence of the 'spelling mistakes' between affected and unaffected individuals. Unlike monogenic disorders where the presence of one single 'spelling mistake' (termed mutation) pushed the individual towards a disease state, the genetic landscape in complex disorders has been very intriguing with multiple 'spelling mistakes' in multiple genes with an additive effect together with non-genetic or environmental attributes.[6] However, it soon became apparent that this phenomenon of specific variations in the genome segregating with a particular phenotype consistently held true and occurred more than just by chance. The largest group of such single letter spelling errors termed as single nucleotide polymorphisms (SNPs) distributed throughout the genome, began to be viewed as markers, since they could potentially be used to differentiate and/or predict a wide range of clinically/functionally/evolutionarily more relevant manifestations across individuals. Utility of this approach spans across a range of genotype-phenotype correlation studies including healthy/primary disease phenotype or drug response/non-response or efficacy/toxicity/adverse drug reactions or cognitive differences between two defined groups or several other assessable traits. Knowledge of such abundant genetic variation in the genome which emanated from HGP, opened up a range of post-omics era activities, which include functional genomics, pharmacogenomics, computational genomics, evolutionary genomics, and more on the sequence/structural front and transcriptomics, proteomics, metabolomics, etc. at the functional (expression) level.[7] Restricting the study of these markers or genetic variations within a set of candidate genes or genome-wide, with reference to a given drug response/efficacy/toxicity in a given disease phenotype comprises pharmacogenetics or pharmacogenomics respectively (often interchangeably used) of that drug. This article presents an overview of this branch of omics, which has a considerable potential for clinical use.

WHAT IS PHARMACOGENETICS?

The term pharmacogenetics coined in 1959 by Friedrich Vogel was initially used to describe the phenotypic variation seen in drug metabolism and response[8] between individuals. One of the classical examples of differential drug response - efficacy or toxicity is chloroquin for malaria. SNPs from several independent genes believed to be responsible for the metabolism, transport, uptake, degradation, etc. broadly constituting the pharmacokinetic and pharmacodynamic pathways began to be tested for their association with drug response. The field remained stagnant until the 1980s when a combinatorial effect of the development of human gene cloning and advanced genome analysis methods, moved it from a candidate gene analysis to a genome-wide approach. This was envisaged to provide a better understanding of the underlying genetic basis of this patient-to-patient variation in drug response and thereby, hopefully translatable for individual specific or personalised treatment regimen.

Drug response, like the primary disease itself is also a complex phenotype - governed by both genetic determinants and a host of non-genetic contributors.[9] However, unlike unclear genetic aetiology of complex polygenic disorders, basic pharmacological knowledge of drug metabolism and downstream steps in the biology of drug response offer more promise of clinical utility. In the conventional and popular candidate gene-based association analysis, also known as hypothesis testing, genes involved in i) drug metabolism (pharmacokinetics), ii) transport, uptake and degradation (pharmacodynamics), and iii) adverse drug reactions (ADRs) such as hypersensitivity, toxicity, etc. form the core of pharmacogenetics. On the other hand, genome-wide association studies (GWASs) and next generation sequencing (NGS) emerging as hypothesis free approaches are expected to uncover additional genetic determinants of drug response phenotype (similar to studies on genetics of complex disorders).[10] Despite this changing paradigm, phase I and II drug metabolising enzymes (DMEs) and genes encoding them remain the largest group of players in the pharmacogenetics of a broad range of drugs,[11] with transporters, receptors, etc. at the target cells/tissues playing a major role at the next level (pharmacodynamics) in the drug response/non-response cascade. This approach also holds true for ADRs, another phenotype in drug response assessment, though additional factors such as increased serum concentration of drugs due to poor drug metabolism, off target effects, little understood gene-gene interactions, etc. may also contribute to this phenotype. Selection of candidate genes based on pharmacological/biochemical/genetic evidence for the representative disease phenotype/endophenotype in a hypothesis testing approach as has been previously explained.[10] Using the same principle, the concept of a gene being a likely drug target in the dopaminergic pathway for example, in the candidate gene strategy in pharmacogenetics, has been schematically presented in Figure 1. Pharmacogenetics of antipsychotic drugs being the theme in this article, the subsequent sections have been largely limited to genetic players from both pharmacokinetic (largely metabolisers) and pharmacodynamic (transporters or pre- or post-synaptic receptors from or at the site of action etc.) pathways as relevant for this group of drugs.

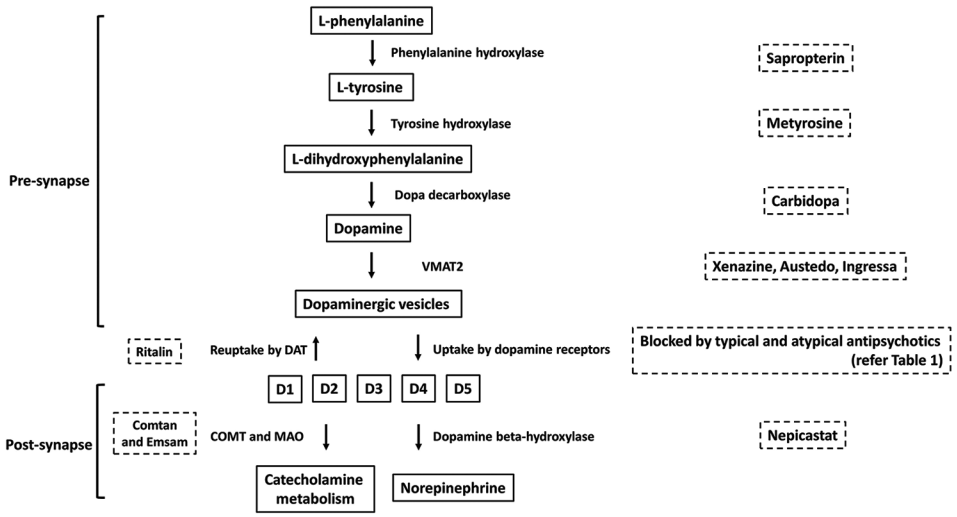


Figure 1: A representative schema of commercial drugs (staggered boxes) that block the enzymes encoded by genes in the dopaminergic pathway.

PHARMACOGENETICS IN PSYCHIATRY

Neuropsychiatric disorders are one of the few and early examples of pharmacogenetic testing prior to treatment decisions, though not routinely practiced nationally or internationally. A large majority of the antipsychotic drugs - both typical and atypical are metabolised by one single family of cytochrome P450 (CYP450) genes (phase I DMEs), while flavin monooxygenases, uridine 5'-diphospho (UDP)- glucuronosyltransferase (UGTs), glutathione transferases (GSTs), sulfotransferases (SULTs), and *N*-acetyltransferases (NATs) (phase II) contribute to a lesser extent (Figure 2).[12] Like the adenosine triphosphate (ATP) binding cassette subfamily B (ABCB) group of genes (multi-drug resistance [MDR]), these genes are believed to be under natural selection implying a higher extent of genetic variation within them and population specific patterns.[13] For example, *CYP2D6* is known to have over 130 SNPs along with copy number variations (CNVs)[14] which determine the poor/intermediate/ultra-rapid metaboliser status of an individual. The lack of this hepatic enzyme is seen in approximately seven to ten per cent of Caucasians as compared to approximately two per cent in Asians and people of African-American descent.[15]

Genes in pharmacokinetics

Genes coding for DMEs comprise the central core of pharmacokinetic players for the antipsychotic drugs. DMEs are broadly placed into two major groups termed phase I and phase II. Over 80% of the antipsychotic drugs are metabolised by CYP450 family (CYP1, 2, and 3) of enzymes which are the most important group of DMEs. Of note, of the ~50 CYP450 members, only six are responsible for metabolising approximately 75-90% of all antipsychotics.[16] *CYP3A4* and *CYP2D6* are responsible for metabolism of ~50% and 30% of the commonly prescribed antipsychotics and antidepressants respectively while *CYP1A2*, *CYP2C*, *CYP2C19*, and *CYP2E1* contribute to a lesser extent. Of note, extensive inter-individual variation/heterogeneity has been documented in the drug metabolism profiles. Based on the extent of metabolism determined by their enzyme activity measurements, individuals are categorised into distinct groups, namely poor metabolisers (PM), ultra-rapid metabolisers (UM), and intermediate metabolisers (IM). On the other hand, the phase II DMEs are comprised of genes which code for products involved in conjugation reactions with different chemical species such as sulphates and methyl groups. One class of enzymes that are involved in this phase are the popular NATs. Individuals are grouped as rapid or slow acetylators depending on the acetylation efficiency. For this group, in one case study, the differential metabolism due to NAT polymorphisms was observed in tuberculosis patients, treated with isoniazid which is primarily metabolised by *N*-acetylation.[17] Variants in the gene encoding the enzyme would determine whether a person would be a rapid acetylator and would end up clearing out the drug efficiently, or a slow acetylator, which would lead to an increase in elevated serum concentration of the drug. This would then furnish pre-emptive strategies to prescribe the drug in lower doses. However, without the genetic knowledge and/or pre-prescription testing, it may manifest in adverse neurological side effects due to an accumulation of the unmetabolised drug. In addition to the commonly investigated SNPs in both phase I and phase II genes, CNVs (another class of variants) in these candidates also determine their metabolic profile and consequently the drug response phenotype. Depending on the presence of different variants and their variable frequencies, inter- and intra-population specific patterns are also commonly observed in drug response profiles.[18]

Genes in pharmacodynamics

Genetic variants when present in genes that function like drug targets can also alter how the small signalling molecules and metabolites interact with their intended targets.[19] Such target genes, which influence the pharmacodynamic component of drug response, are generally specific cell surface receptors, ion channels, transporters, proteins, etc. These pharmacodynamic determinants are also favourite candidates in the pre-prescription testing toolkit and their

broad grouping is shown in Table 1.[20-22] In the case of typical antipsychotics, it has been shown that there are associations between variants in *DRD2*, *DRD3*, *DRD4, COMT*, *SLC6A3*, *ANKS1B*, *CNTNAP5,* and *AKT1*, with response outcomes.[23] Of note, variants in serotonin receptor genes like *HTR1A* and *HTR2A* as well as serotonin transporter gene *SLC6A4* have shown significant associations with outcome responses in the case of atypical antipsychotics.[24]

Adverse drug reactions

Tardive dyskinesia (TD) is the late onset of abnormal, rhythmic, and involuntary movements affecting the face, mouth, trunk, and limbs in a small subset of patients on antipsychotic medication. Antipsychotics are the main agents known to be involved in the pathophysiology of TD with the prevalence being 32.4% with typical antipsychotics and 13.1% with atypical antipsychotics,[25] and more recently reported with ~25.3% prevalence among psychiatric patients on antipsychotic treatment[26] and notably with no difference between those treated with either typical or atypical antipsychotics.[27,28] Evidence, though often lacking, replicability and reproducibility has suggested a genetic predisposition to TD with variants in *DRD2, DRD3, MnSOD, CYP2D6, GRIN2A, GRIN2B* genes implicated in the pathophysiology.[29-33] A recent Russian GWAS found orofacial type of TD to be associated with the 3p22.2, 8q21.13, and 13q14.2 genetic loci and limbo-truncal type of TD to be associated with a locus on chromosome 3p13.[34] Other GWASs have suggested putative susceptibility of TD to *GLI2*, *HSPG2*, and *DPP6*.[35-39] In the largest GWAS to date consisting of 280 TD samples and 1126 non-TD samples, *GSE1, TNFRSF1B*, *EPB41L2*, and *CALCOCO1* were suggested to confer susceptibility to TD.[40]

Depending on the pathophysiology, once TD has been diagnosed, management often involves prescription of certain medications. A phase III trial cleared and now commercialised drug, deutetrabenazine is regularly used in clinical settings to manage TD. However, it is established that CYP2D6 plays a major role in deutetrabenazine metabolism and therefore, a daily dosage of 36 mg/day should not be exceeded for known CYP2D6 metabolisers. These findings show how pharmacogenetics may be involved in both the onset as well as management of an ADR.

Similar evidences are present for other genes and antipsychotics as well. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) candidate gene study which aimed to provide important information about the effectiveness of current treatments in primary care and specialty settings in real world patients - SNPs in genes like *5-HTT, 5-HTR2A*, various CYP genes, *FKBP5, BDNF*, and a

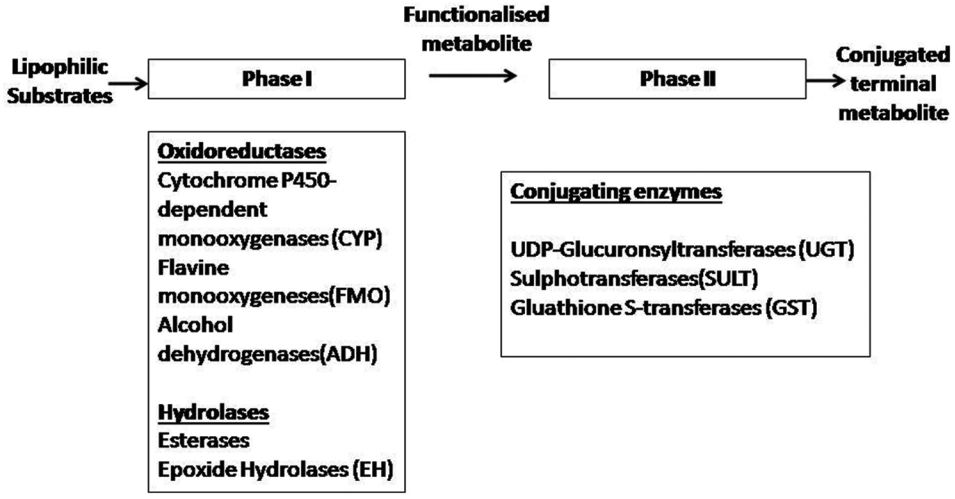


Figure 2: The phase concept of drug metabolism with the role of phase I and phase II DMEs (Reproduced from Oesch *et al.*).[12]

Table 1: CYP enzymes involved in the metabolism of different classes of antipsychotic drugs

CYP enzymes	Atypical antipsychotics	Typical antipsychotics	Other psychiatric drugs such as anti-depressants and SSNRIs
CYP1A2	Clozapine, Olanzapine	Chlorpromazine, Perphenazine	Duloxetine, Mirtazapine, Clomipramine
CYP2C9			Valproic acid
CYP2C19			Amitryptiline, Diazepam, Moclobemide, Clomipramine, Citalopram
CYP2D6	Risperidone, Sertindole, Aripiprazol, Olanzapine	Haloperidol, Fluphenazine, Zuclopentixol	
CYP3A4	Ziprasidone, Quetiapine		Sertindole, Aripiprazole, Carbamazepine

CYP: Cytochromes P450, SSNRIs: Selective serotonin/norepinephrine reuptake inhibitors

(Referenced from De Leon *et al*.,[20] Zanger *et al*.,[21] Brouwers *et al*.[22])

few genes of the phosphodiesterase family were found to be significantly associated with response to citalopram.

Besides this, contemporary approaches including GWASs which aim at a hypothesis free identification of genetic determinants associated with a phenotype have been performed and several genes/loci have been identified for antipsychotic drugs. Some of these developments are briefly described below.

In a drug response GWAS, significant associations of *PAPLN*, *UBE3C*, *BMP7*, *RORA* with citalopram response was reported.[41-43] In another GWAS which aimed to look at treatment responses to mood stabilisers, association of *GRIA2, SDC2*, and *ODZ4* with lithium which is used as an anti-suicidal was observed.[44] Previous candidate gene based studies, from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[32,45-47] and recent GWASs[48-52] to uncover association of genes with efficacy, antipsychotic induced Parkinsonism, extra pyramidal side effects of antipsychotics have also identified several loci with suggestive associations but only 4p15, 11q24 loci, and *ZNF202* showed significant associations. The drug treatments included olanzapine, quetiapine, risperidone, ziprasidone, perphenazine. *CYP2D6* variants have also been shown to significantly correlate with serum levels of antidepressants such as paroxetine, venlafaxine and notriptyline. On similar lines, individuals with *CYP2D6* duplication were found to be ultra-metabolisers of nortriptyline whereas those harbouring two non-functional copies of the gene had elevated plasma levels of poorly metabolised tricyclic antidepressants.[24] Encouragingly, similar observations have been made for pharmacogenetics in other medical fields such as oncology, cardiology, and infectious diseases.

Of all the time-tested genes and their variants for clinical use in different disorders, and several tests done in house in different hospital research labs, appendix A[53] lists the ones that are the most commonly considered.

WHAT PHARMACOGENETICS OFFERS

Over the past decades, new classes of antidepressants, antipsychotics, and mood stabilisers have been developed which are believed to be more efficacious and safer without ADRs. Despite this, our ability to address mental illnesses has remained sub-optimal. In the STAR*D study, only 37% patients with non-psychotic major depression achieved remission and 16.3% dropped treatment completely because of drug intolerance.[54] A much worse discontinuation rate of 74% was seen in the CATIE study, which aimed to treat schizophrenia patients with a variety of antipsychotics, to mimic realistic clinical practice.[55] In the case of patients with bipolar disorders, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial where antidepressants and mood stabilisers were used, 75% symptom relapse was observed on follow-up.[56] These figures are indeed humbling and therefore the promise of pre-prescription testing and personalised medication schedule offers much hope amongst clinicians, affected individuals, and the scientific community at large.

With advancements in our understanding of the genome and genomic medicine, it is expected that newer markers will be discovered and a comprehensive set of these in the arsenal will encourage a robust shift of the medical community from the current 'hit and trial' therapy to a more personalised treatment strategy. The expected benefits of these newer approaches are being viewed as manifold - from reduction in the statistics of non-response or adverse reactions to speedy precision treatment, which will impact positively the overall physical, emotional, and economic burden which is the present hallmark of neuropsychiatric diseases.

LIMITATIONS IN TRANSLATION

With large consortia and deep sequencing-based discovery genomics projects, the concept of biomarkers for drug response prediction and precision medicine in not only neuropsychiatric diseases, but also most of the common complex traits/disorders is surely being showcased as a paradigm with promise. However, the ground reality seems to suggest otherwise. A vast number of biomarkers have been discovered, yet, majority of these have not moved beyond mere identification. An important factor which has emerged as a splinter over and over again is the lack of replication of these biomarkers across inter- and intra-population studies. Such observations are not uncommon in genetic studies due to inherent genetic heterogeneity between individuals or due to an underpowered study altogether. Furthermore, not all of the genetic variants identified as "associated" with a given drug response are from the protein coding regions (exons) or are protein sequence disturbing variants. Functional characterisation of non-coding variants being a challenge, genotype-phenotype correlations, a pre-requisite for translational medicine/diagnostics are inadequate.

As mentioned previously, like in the primary disease wherein non-genetic factors play an important role in disease aetiology they also contribute in the drug response phenotype. These include factors such as diet, comorbidities, age, weight, drug non-compliance, co-prescribed drug interactions, etc., limiting the identification of reliable biomarkers. All of these factors with the long-drawn, extensive and expensive course of biomarker discovery have dampened the success of effective pre-prescription testing in the clinically heterogeneous neuropsychiatric disorders. Nevertheless, a few biomarkers discovered to date, such as *CYP2D6* and *CYP2C19* are in different phases of clinical trials. In brief, translation of genetic findings to practice of precision medicine is still unrealised. In 2018, in a systemic review, 40 pharmacogenomics tests had been translated from candidate gene studies on depression, among which 11 had been investigated using both randomised as well as non-randomised control trials. But, in the clinical setting, translation remained poor due to lack of experimental validation or poor evidence of effectiveness and cost/utility of these tests.[57]

THE WAY FORWARD

Based on a 2017 study,[58] even though 84.3% of the total participants (practising psychiatrists) agreed that pharmacogenetic (PGx) testing was important in their current medical practice, 65.7% had never recommended or ordered

a test in the preceding one year. Approximately 40% ascribed this to lack of clarity and education on the basic principles of PGx. 91.7% of the 18.6% clinicians who had sought PGx testing for their patients found it useful.

In the same survey, clinicians attested to have a sound knowledge on classical genetics (78.6%) and pharmacology and drug metabolism (85.8%) while knowledge about PGx and interpretation of results of a PGx test was lower at 61.5% and 51.4% respectively. Even though, education on other parameters for clinical practice was acquired from the formal medical school training, almost 30% of them admitted that they were not sensitised to interpreting PGx results.

Both lack of knowledge of drugs for which PGx testing was possible (41.4%) and using test results to adjust drug dosage (37.2%) were expressed as major gaps/deficits among clinicians. 67.1% said they would be able to better utilise PGx testing for effective drug therapy if they had better knowledge of drug metabolism, while 40% agreed they needed institutional support to apply this knowledge in their daily practice.

In most surveys conducted till date, clinicians voiced that having a thorough knowledge in PGx and being able to interpret test results would help them adopt this test regularly in their daily practice which would greatly improve patient management.[59] Therefore, thorough professional/special training programmes need to be set in place to address this knowledge gap along with proper dissemination of the training material. In addition, guidelines/policies for PGx would also be essential.

As mentioned before, treatment response in general is individual specific and depends on a complex architecture with multiple genes and patient history embedded in its fabric. Therefore, it is extremely hard to carry out appropriately designed studies with sufficient power to develop drug response prediction algorithms. The largest studies have also been plagued with small sizes and inappropriate periods of follow-up. To address this, compilation and creation of combinatorial datasets as well as carrying out meta-analyses are the encouraged strategies. Yet again, a thorough implementation of this approach is beleaguered by genetic heterogeneity amongst patient populations, different study designs, and differences in individual responses. Developing algorithms that account for these multiple levels of heterogeneity and training a model on already available data in existing datasets with known outcomes to produce a robust deep learning neural network seems to be a way forward. This model can then theoretically predict outcomes such as personalised drug response, ADR probability, and even identify novel pharmacogenetic variants leading to their pathway mapping, depending on the quality of the datasets it was trained on. Thus, similar to artificial intelligence/machine learning (AI/ML) methods now popular for complex trait prediction, automated system of patient evaluation and PGx for precision medicine seem to emerge as preliminary tools. However, experimental validation of these predictions will have to be done and that is where going back to the laboratory work bench would be inevitable.

Finally, the beauty of pharmacogenetics/pharmacogenomics lies in its multidisciplinary approach to a layered and complex problem, encouraging a well-oiled amalgamation of clinicians, bioinformaticians, and geneticists. A proper network where these cogs can interact freely, discuss and collaborate at every level may lay the foundation for a holistic implementation of pharmacogenomics from the bench to the bedside.

Conclusions

Both psychotropic drugs and medical genomics have come a long way over the past three decades. On one hand, side effects of antipsychotics, antidepressants, and mood stabilisers in the market have been addressed significantly and on the other, documentation of the common or rare genetic variants in well phenotyped patient samples is commonplace. Commendable efforts to link the genetic variants to differential drug response and/or ADRs have been made but mostly in Caucasian populations enabling PGx to some extent in a routine psychiatric clinical setting. However, newer paradigms or tools, well designed moderate to large pharmacogenomic studies in transethnic settings and development of newer therapeutics in psychiatry would be essential to enhance psychiatric patient care and enable 100% rehabilitation, currently only a dream in psychiatric healthcare.

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APPENDIX

Appendix A: A list of commercialised medicines for which pharmacogenetic testing is currently available

Medicine	Gene(s)
Warfarin: a blood thinner	*CYP2C9, VKORC1*
Plavix, a blood thinner	*CYP2C19*
Antidepressants, epilepsy medicines	*CYP2D6, CYPD6, CYP2C9, CYP1A2, SLC6A4, HTR2A/C*
Tamoxifen, a treatment for breast cancer	*CYP2D6*
Antipsychotics	*DRD3, CYP2D6, CYP2C19, CYP1A2*
Treatments for attention deficit disorder	*DRD4*
Carbamazepine, a treatment for epilepsy	*HLA-B*1502*
Abacavir, a treatment for human immunodeficiency virus (HIV)	*HLA-B*5701*
Opioids	*OPRM1*
Statins, medicines that treat high cholesterol	*SLCO1B1*
Treatments for childhood leukemia and certain autoimmune disorders	*TPMT*

(Reproduced from https://medlineplus.gov/lab-tests/pharmacogenetic-tests/)[53]