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Psychiatric Pharmacogenomics: The Evidence Base

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"The young and exciting field of psychiatric pharmacogenomics is providing a third pillar of understanding to aid in our competent and informed prescribing of drugs, joining the more well-established pillars of pharmacokinetics and pharmacodynamics."

FROM THE EDITOR

Research in the field of pharmacogenomics has grown exponentially over the past 2 decades, resulting in a vast literature exploring the impact of gene variations on medications' pharmacokinetics and pharmacodynamics. In tandem with this growth, there has been an increase of interest in using pharmacogenomic testing (PGx) to inform prescribing decisions and to help recognize and address the role of genetics in medication management. It has been proposed that addressing genetic variations in patients by individualizing prescribing can maximize treatment benefit and reduce undesirable outcomes. However, this proliferation of resources and options can be confusing and, without proper science, can lead clinicians down incorrect and even dangerous paths.

The 3 pillars of knowledge for rational medication prescribing are pharmacokinetics, pharmacodynamics, and pharmacogenomics. One of the greatest pioneers in psychiatric pharmacogenomics was David A. Mrazek, MD, during his tenure at the Mayo Clinic College of Medicine and Science in Rochester, Minnesota. Mrazek authored a textbook[1] and a comprehensive manuscript[2] laying the foundation for this young field. In view of new research and calls for action, this piece will share updates to further help readers make sense of the array of available information.

Looking to the Experts

Anticipating the need to vet gene/drug interactions with evidence-based clinical applicability, 2 objective organizations were created and they continue to curate this data:

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides a continuously updated open-access online database to document the degree of evidence for all drugs that have been studied.

The International Society of Psychiatric Genetics (ISPG) focuses only on psychiatric medications.

In 2009, the Pharmacogenomics Global Research Network and PharmGKB, which has been managed at Stanford University in California since 2001 and is financially supported by the National Institutes of Health/National Human Genome Research Institute/National Institute of Child Health and Human Development, joined in the development of CPIC. The mission of CPIC is to evaluate all evidence-based, peer-reviewed publications and maintain an open-access database to inform clinicians about gene/drug practice guidelines for all classes of drugs.

This is an important distinction from the role of the ISPG because a gene may be "actionable" for a specific nonpsychiatric drug with adequate published clinical data but not for all drugs that interface with that gene, including psychiatric drugs. A current example of this is the determination by CPIC that the drug efavirenz has an "actionable" prescribing modification based on a patient's genotype at cytochrome P450 2B6 (*CYP2B6*), but there are no clinically relevant data as to how—or whether—the *CYP2B6* genotype will impact the prescribing of bupropion, which is primarily metabolized by *CYP2B6*.

CPIC was created to guide the clinical interpretation and implications of specific drug-gene combinations and how existing pharmacogenetic information should be used. CPIC guidelines are published to help clinicians better understand how to consider PGx information when it is available to optimize drug therapy, not to advise which medications should be evaluated or when pharmacogenetic testing should be obtained.

A significant advance in psychiatric pharmacogenomics occurred in 2015 when CPIC published a comprehensive guideline summarizing the evidence base for clinical decision-making when prescribing selective serotonin reuptake inhibitors affected by the genotypes of *CYP2D6* and *CYP2C19*.[3] The following year, CPIC published additional guidelines for *CYP2D6* and *CYP2C19* genotypes and dosing of tricyclic antidepressants.[4]

The second organization, ISPG, also maintains an active and evidence-based website, which it updates as new information is established. Its most recent genetic testing statement for psychiatric disorders includes the following[5]:

"We recommend [human leukocyte antigen] *HLA-A* and *HLA-B* testing prior to use of carbamazepine and oxcarbazepine, in alignment with regulatory agencies and expert groups."

"Genetic information for *CYP2C19* and *CYP2D6* would likely be most beneficial for individuals who have experienced an inadequate response or adverse reaction to a previous antidepressant or antipsychotic trial."

Additionally, the US Food and Drug Administration (FDA) recognized that caution is needed when considering DNA variations and antidepressant use. They noted, "The FDA is aware that health care providers have made changes to patients' medication based on genetic test results that claim to provide information on the personalized dosage or treatment regimens for some antidepressant medications, which could potentially lead to patient harm."[6] Subsequent to this warning in 2018, the FDA created a regularly updated Table of Pharmacogenetic Associations.[7]

Significantly, all 3 of these databases—CPIC, ISPG, and FDA—concluded that, at the present time, evidence-based clinical research on psychiatric medications supports the use of PGx testing for only 5 genes at: 3 cytochrome P450 genes (*CYP2D6*, *CYP2C19*, and *CYP2C9*) and 2 HLA genes (*HLA-B**15:02 and *HLA-A**31:01) (**Table 1**).

Importantly, a group of experts assembled by the ISPG performed a comprehensive review of all available data on pharmacogenomic testing in psychiatry, published in 2021, which reached the same conclusions.[8]

The practicing clinician can order testing for any of these 5 evidence-based genes individually from most laboratories. If the labs do not perform the test themselves, they can send it out for processing, with a usual quick turnaround for the results. The resulting report will vary depending on the gene requested. For cytochrome P450 metabolic enzyme genes, the result is typically reported by defining the presumptive phenotype of predicted enzyme activity based on the genotype of the 2 alleles of that gene for the patient (**Table 2**).

The predicted enzyme activity is listed as one of 4 types of metabolic activity: ultrarapid, normal (previously called "extensive"[9]), intermediate, and poor. *HLA* reports will list the allele as present or absent.

CYP2D6

Approximately 60 human *CYP450* metabolic enzymes have been identified. Of these, 6 are responsible for 90% of human drug oxidation: *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1*, and *CYP3A4*. Not coincidentally, the 2 enzymes that are most studied have the highest number of alleles, which results in more potential phenotypes along the functional spectrum of poor metabolism to ultrarapid metabolism—*CYP2D6* with more than 100 alleles differentiated to date, and *CYP2C19* with more than 30. These 2 *CYP450* enzymes play an important role in the metabolism of many common psychiatric drugs (Table 1).

It has been hypothesized that the large number of alleles for the *CYP2D6* gene is a result of evolutionary pressure on this detoxifying enzyme as humans migrated to novel geographic environments that contained different dietary nutrients. A mutation in the *CYP2D6* gene that creates a new allele providing greater efficiency in metabolizing and detoxifying new food products would be preserved; hence, the high degree of genetic polymorphism of the *CYP2D6* gene may align with the migratory patterns of our ancestors. There is well-established ethnic variability of the *CYP2D6* enzyme, with 10% of Caucasian individuals and 2% of Asian individuals being genotypic poor metabolizers. One percent of the US population consists of genotypic ultrarapid metabolizers, with the highest incidence occurring in individuals of Middle Eastern or North African descent.

HLAs

HLAs are a large family of genes that code for proteins making up the major histocompatibility complex, an important human immune defense system. The *HLA* is a significant component of the protein complex on the surface of cells that assist the immune system in the identification of self from "foreign invader" by inserting small peptides from inside the cell to the cell's surface, where they can be monitored by the immune system. As an example, the *HLA-B* gene has polymorphic alleles that code for proteins with differing quaternary structures. There are occasional alleles whose protein product will combine with a specific drug, flagging the resulting complex as "foreign invader" and leading to an aggressive immune response that can be lethal to the patient.

Under most circumstances, if the allele for the *HLA* is present, the associated drug should not be prescribed for that patient. These results are pharmacodynamic in nature, and the presence of a specific *HLA* allele often is significantly increased in specific ethnicities. The most dramatic established example of this pharmacogenomic test in psychiatry is that a clinician should almost never prescribe carbamazepine to an individual who tested present for the *HLA-B**15:02 allele. This allele occurs 10 to 50 times more commonly in patients of Asian descent than in other populations.[10] As a result of this significant life-threatening risk, the FDA issued a boxed warning for carbamazepine advising that at-risk populations should be screened for the presence of *HLA-B**15:02 before initiating carbamazepine, and those who have this allele should not receive the drug unless the prescriber determines the benefit robustly outweighs this risk.[11] The exposure of a patient with the *HLA-B**15:02 allele to carbamazepine can result in a severe cutaneous reaction, including Stevens-Johnson syndrome and toxic epidermal necrolysis. Other drugs that share this risk include oxcarbazepine, phenytoin/fosphenytoin,[12] and lamotrigine.

The second *HLA* that has crossed the threshold to clinically actionable data is *HLA-A**31:01, specifically for carbamazepine. Prescribing carbamazepine in the presence of this allele significantly increases the risk of developing a syndrome named Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). The onset of DRESS usually occurs between 2 and 8 weeks after starting carbamazepine.

Its symptoms can include increased eosinophils, a rash, fever, facial edema, enlarged lymph nodes, and possible damage to the kidneys or liver. In patients prescribed carbamazepine who have the *HLA-A**31:01 allele, the odds ratio for developing DRESS in all populations is 13.2. This odds ratio is increased to 57.6 in European populations and to 23 in Chinese populations.[13]

Pharmacogenomic Panels

During the past decade, specialty labs have offered psychiatric panels to look at gene arrays to guide medical providers about what drug to use for a particular psychiatric disorder based on the totality of the results of all genes in the panel. Most often these labs describe their use of proprietary algorithms that their expert scientists developed to assemble their recommendations. Curiously, many of these panels contain a significant number of genes that have not reached the actionable threshold as established by CPIC, ISGP, and the FDA.

Additionally, expert consensus publications and editorials from thought leaders in psychiatry published since 2016 have consistently concluded that psychiatric pharmacogenomic panels (ie, combinatorial pharmacogenetic tests) are not currently evidence-based, and clinical decisions should not be based on their reports.[14-21] Common genes that are not evidence-based but are included in many of these pharmacogenomic panels include *DRD2, UGT2B15, HTR2A, HTR2C, SLC6A4, MTHFR, COMT, CYP1A2, CYP3A4,* and *CYP2B6*. Publications exist concluding that some of these gene panels have somewhat better patient outcomes in comparison with "treatment as usual," but these studies are almost entirely funded by the pharmacogenomic labs that manufacture and market these panels.[22,23]

The Unknown

Every major scientific and medical advance is often accompanied by a brief euphoric feeling that we have finally opened a door to exponential progress in our attempt to understand our role on this planet, in this galaxy, and in this universe. In fact, the progress we have made in all the sciences over the past 200 years is quite remarkable. At age 62 years, I have settled on what I believe to be an optimistic as well as realistic understanding of what we know in each moment moving forward in time. It is encapsulated by the phrase "the more we learn, the less we know."

The field of pharmacogenomics has progressed at a truly remarkable rate. The resulting advances in diagnoses and treatments in hematology and oncology are dramatic and highly consequential. We in psychiatry are beginning to bear the fruits of pharmacogenomic research. And, with the wise and evidence-based guidance from CPIC and ISPG, we are slowly building a portfolio of evidence-based drug-gene interactions that continue to raise the quality of care for our patients. However, the initial euphoria and excitement in psychiatric pharmacogenomics resulted in a frenzy of research that prematurely evolved into a mythology that many genes of interest have reached the scientific understanding for clinical utilization in our patients; that is far from the case. More disturbing, some clinicians routinely implement information reported from companies that market combinatorial pharmacogenomic testing/psychiatric pharmacogenomic gene panels whose results are determined by proprietary algorithms with no peer review and choose which antidepressant or antipsychotic to use based on these results.

CPIC and ISPG should be applauded for retaining the true scientific method in determining which genes have crossed the threshold of clinical applicability for our patients based on the quality and reproducibility of the associated pharmacogenomic research. Additionally, all the data vetted are available freely and with open access.

Furthermore, we have much to learn in the young field of genetics before we can confidently determine the functional phenotype of a specific gene in our patient because of a wide range of processes that alter the genotype that pharmacogenomic testing provides. Epigenetic modifications on a gene's promoter sequence can dramatically affect the amount of gene product that is produced. Epigenetic modifications on histones surrounding the chromosome can increase or decrease access to a gene and determine the amount of gene product transcribed.[24,25]

Concluding Thoughts

The young and exciting field of psychiatric pharmacogenomics is providing a third pillar of understanding to aid in our competent and informed prescribing of drugs, joining the more well-established pillars of pharmacokinetics and pharmacodynamics. On a positive note, more than 30,000 research articles related to pharmacogenomics have been published since the first rough draft of the human genome was published in 2003. The challenge for clinicians is utilizing the small subset of information that has been vetted and objectively concluded to be evidence-based to aid in clinical decision-making. This article has been an attempt to summarize the state of pharmacogenomic applications in clinical psychiatry at the present time.

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