Pharmacogenomics in psychiatry and neurology: Bridging research and clinical practice

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ABSTRACT

The incorporation of pharmacogenomic information in clinical decisions is expected to lead to improved patient care and decreased health care costs. It is not always clear how and when to obtain pharmacogenomic information, due to a lack of guidelines on how to use this information. This article discusses some of the major groups which aim to address these barriers and several important drug-gene pairs relevant to the fields of neurology and psychiatry.

KEYWORDS

pharmacogenomics, Pharmacogenomics Research Network, genetics

Although medications confer benefit to patients with psychiatric and neurologic illnesses, their use is not without risks, some of which can be severe or life-threatening, and may result in non-adherence. Thus, proper drug selection and dosing to avoid over- and under-treatment are vital. Nonetheless, most clinical practice guidelines and recommendations do not differentiate among therapeutic disease targets nor provide a therapeutic window to avoid side effects for a preponderance of neuropsychiatric medications. A plethora of literature, as well as prescription drug labeling, support the commonly encountered experience that some patients are at greater risk for therapeutic failure or adverse reactions. However, it is not well established who faces these risks or how they can be reduced or managed. For fear of side effects, dosing is often initiated with a "start low, go slow" approach. This approach may prolong the time to symptom control and increase morbidity. Yet due to inability to predict responders and patients who will suffer adverse reactions, this remains standard practice in many settings. Pharmacogenomics represents one area that may address some unanswered questions about who might respond, who might experience toxicity, and why that is. The potential contribution of pharmacogenomics to clinical practice is a guided departure from the current treatment approaches and personalized medication regimens for patients with psychiatric and neurologic illnesses.

GOALS FOR THE APPLICATION OF PHARMACOGENOMICS (PGX) IN CLINICAL PRACTICE

Incorporating pharmacogenomic information in clinical decisions is expected to impact many factors, ultimately resulting in improved patient care and decreased health care costs. Specifically, guided medication therapy (drug selection and dosing) can impact

- Time to response to medication
- Length of stay (and associated costs)
- Medication cost
- Occurrence of side effects
- Management of side effects, including addition of other medications
- Future changes to medication regimen
- Drug-drug interactions

BARRIERS TO THE ADOPTION OF PHARMACOGENOMICS IN CLINICAL PRACTICE

While the above outcomes are clearly optimal for patients and clinicians, how and when to obtain and use pharmacogenomic information is not always clear. At present, there is an overall slow rate of incorporation of pharmacogenomics in clinical practice. This is, in part, due to a lack of guidelines on how and when to use genetic test results to select and adjust medications. Ideally, this guidance will come from freely accessible guidelines that are peer-reviewed, updated, and evidence-based.

Scientists and clinicians are historically taught that the gold standard for study design is the double-blind, randomized, placebo-controlled trial. Generally, these designs lend themselves well to medication interventions.

One barrier to the acceptance of pharmacogenomic study results may be the perception of the strength of evidence, owing to the design. Russ Altman, MD, PhD, a leader in clinical bioinformatics and pharmacogenomics, called attention to this obstacle in his 2011 commentary, '"Noninferiority" is sufficient for initial implementation.'[1] Several widely accepted and common clinical practices are not supported by gold standard studies, and Dr. Altman suggests that if incorporation of pharmacogenomics in practice is not inferior to current prescribing practices, it is reasonable to implement its use. A closely related issue, also a focus in the commentary, is clinicians' requisite for cost-benefit studies prior to adopting pharmacogenomics in clinical practice. Since the advent of pharmacogenomic testing, many commercially available tests have become available, and cost of genotyping has consistently decreased to the current rates in the hundreds of dollars, depending on the number of genes tested. Further, test results are not likely to prompt additional costly follow-up tests. Taken together, these barriers may not be sufficient to preclude the use of pharmacogenomics in clinical practice. "…There are many clinically useful applications of pharmacogenomics that may never require or merit large trials to prove utility, and can reasonably be tried in an instrumented setting."[1]

Many health care providers do not utilize pharmacogenomic test results on a daily basis. Consequently, there may not be a constant awareness of or motivation to search for existing test results for every patient. Routine integration of the test results is also not commonplace, hence awareness of existing results may not be adequate to guide medication decisions. Pharmacogenomic information must be available and usable in electronic medical records. Integrating the information with the system, such that during prescriber order entry, informational prompts or notifications appear, would facilitate utility during clinical decision-making.

Comparative effective research has served as an arena for the study of clinical pharmacogenomics, featured in the large warfarin study led by Medco and Mayo, which demonstrated reduced hospitalization rates utilizing genetic testing and made media headlines in 2010.[2] This highlights the importance of systematic collection and documentation of clinical data and calls clinicians to help strengthen the data available for evaluation of practice. Regular evaluation of the results of clinical interventions will allow clinicians and researchers to recognize successes and failures. This knowledge can then guide use of pharmacogenomics in medication selection and dosing.

MAJOR GROUPS IN PHARMACOGENOMICS RESEARCH AND BRINGING PHARMACOGENOMICS TO CLINICAL PRACTICE

The **Pharmacogenomics Knowledge Base (PharmGKB)** is a research tool, and is publicly accessible via the Internet. It was developed with funding from the National Institutes of Health (NIH) and is part of the Pharmacogenomics Research Network (PGRN). The aim of PharmGKB database is to assist researchers in the understanding the contribution of genetic variations to drug reactions. The mission is to collect, encode, and disseminate knowledge about the impact of human genetic variations on drug response. PharmGKB curates primary genotype and phenotype data, annotates gene variants and gene-drug-disease relationships via literature review, summarizes important PGx genes and drug pathways, and enables consortia examining important questions in pharmacogenomics (http://www.pharmgkb.org/home/pharmgkb_mission_statement.jsp). The database is a repository for genetic and clinical data from pharmacogenomics research studies. The PharmGKB welcomes data submissions; information on submitting data may be found at http://www.pharmgkb.org/home/overview.jsp.

The **Pharmacogenomics Research Network (PGRN)** is supported by the National Institutes of Health, U.S. Department of Health and Human Services, with a vision "to lead discovery and advance translation in genomics, in order to enable safer and more effective drug therapies." The major indicators of success are well-matched to the needs of clinicians:

- Discovery of novel insights into mechanisms relating genomic variation to differences in drug responses
- Demonstration of the use and utility of genomic information to improve outcomes for drug therapies
- Incorporation of genomic data to predict and personalize medicine use into routine clinical practice

The PGRN (http://www.pharmgkb.org/network/pgrn_mission_statement.jsp) and PharmGKB missions complement each other to advance the application of pharmacogenomic knowledge, through research, data-sharing, collaboration, and dissemination. The PGRN mission is to

- Implement studies in basic, translational, and clinical science to advance the scientific vision

- Develop novel experimental methods and tools to solve pharmacogenomic problems
- Share data and, where feasible, biological samples in collaborations
- Foster cross-disciplinary teams for discovery and dissemination of new information
- Build effective partnerships and alliances with key stakeholders outside the PGRN
- Engage related disciplines to advance the application of pharmacogenomic knowledge
- Work together to make the network become more than the sum of the parts

Recognizing the knowledge gap and unmet clinical needs, the **Clinical Pharmacogenetics Implementation Consortium (CPIC)** formed in 2009, with goals of addressing these barriers and providing guidelines to translate scientific knowledge of pharmacogenomics into clinical practice. The CPIC is part of the PGRN and PharmGKB and also includes pharmacogenomics and laboratory medicine experts. CPIC members will develop, disseminate, review, and update summaries and recommendations for implementing pharmacogenomic tests and actionable practices.

The CPIC conducted surveys in 2009 and 2010 to help prioritize content of guidelines translating pharmacogenomic information to actions in the clinical setting for specific medications. Results from the American Society for Clinical Pharmacology and

Table 1. Important Drug-Gene Pairs Relevant to Neurology and Psychiatry

Drug	Gene	Protein	Significance
Warfarin	***CYP2C9***	Drug metabolizing enzyme, CYP2C9, metabolizes ***S***-warfarin	Common genetic variants in CYP2C9 and VKORC1, with known nongenetic factors, account for ~50% warfarin dose variability
Warfarin	***VKORC1***	Site of action (warfarin inhibits) vitamin K-epoxide reductase complex	
Carbamazepine	***HLA-B***	Immune system human leukocyte antigen; major histocompatibility complex, class I, B	Variant allele (**HLA-B*1502)** increases risk for Stevens-Johnson syndrome and toxic epidermal necrolysis
Codeine	***CYP2D6***	Drug metabolizing enzyme, CYP2D6, bioactivates codeine to morphine	Genetic variants may decrease CYP2D6 activity, resulting in little to no analgesia; variants may increase CYP2D6 activity, increasing risk of morphine toxicity
Phenytoin	***HLA-B***	Immune system human leukocyte antigen; major histocompatibility complex, class I, B	Variant allele (**HLA-B*1502)** increases risk for Stevens-Johnson syndrome and toxic epidermal necrolysis
Fluoxetine	***CYP2D6***	Drug metabolizing enzyme, CYP2D6, metabolizes ***S***-fluoxetine	Genetic variants may decrease CYP2D6 activity, resulting higher ***S***-fluoxetine and lower ***S***-norfluoxetine concentrations; variants may increase CYP2D6 activity, resulting in lower fluoxetine and norfluoxetine concentrations
Imipramine	***CYP2D6***	Drug metabolizing enzyme, CYP2D6, hydroxylates imipramine	Genetic variants may decrease or increase CYP2D6 activity, resulting in higher or lower imipramine concentrations
Desipramine	***CYP2D6***	Drug metabolizing enzyme, CYP2D6, hydroxylates desipramine	Genetic variants may decrease or increase CYP2D6 activity, resulting in higher or lower desipramine concentrations
Nortriptyline	***CYP2D6***	Drug metabolizing enzyme, CYP2D6, metabolizes nortriptyline	Genetic variants may decrease CYP2D6 activity, resulting in higher nortriptyline concentrations, some recommendations* advise dose reduction; variants may increase CYP2D6 activity, resulting in lower nortriptyline concentrations, some recommendations* advise alternate drug
Valproic acid	***OTC***	Ornithine transcarbamylase, catalyzes second step of urea cycle	Valproic acid is contraindicated in patients with urea cycle disorders (UCD), as patients can experience fatal hyperammonemic encephalopathy. UCD results from mutations in one of several genes, including ***OTC***, ***CPS1***.
Valproic acid	***CPS1***	Carbamoyl-phosphate synthetase 1, rate-limiting enzyme that catalyzes first step of hepatic urea cycle	

* The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group

Therapeutics survey depicted the 29 highest ranked drug-gene pairs, with warfarin, (CYP2C9 and VKORC1) at the top of the list. Approximately 1/3 of the 29 highest-ranked drug gene pairs are relevant to neurology and psychiatry. The highest ranked of these was carbamazepine and HLA-B, followed by codeine and CYP2D6, phenytoin and HLA-B, fluoxetine and CYP2D6, imipramine and CYP2D6, desipramine and CYP2D6, nortriptyline and CYP2D6, valproic acid and OTC, and valproic acid and CPS1.[3] Table 1 further details these drug-gene pairs.

The CPIC prioritized tests already used in clinical settings and the drug-gene pairs identified in the surveys. The guidelines help clinicians utilize genetic rest results in drug therapy; they are not designed to guide clinicians with respect to whether or not to order a test. Each guideline follows a standard format and system for grading evidence and assigning strength for recommendations. Guidelines published to date include thiopurines and TPMT;[4] clopidogrel and CYP2C19;[5] warfarin, CYP2C9, and VKORC1;[6] and codeine and CYP2D6.[7] An international selective serotonin reuptake inhibitor (SSRI) pharmacogenomics consortium has also been established to work on guidelines.

Anyone with clinical interests in pharmacogenetics is eligible for membership, and CPIC welcomes new members to assist with clinical implementation of pharmacogenomics. Information on how to join the consortium may be found at http://www.pharmgkb.org/contributors/consortia/cpic_profile.jsp.

MORE ABOUT PHARMGKB (WWW.PHARMGKB.ORG)

- Take a tour of PharmGKB! See the overview at http://www.pharmgkb.org/tutorial/PharmGKB_tutorial_2011.pdf
- View a comprehensive resource for pharmacogenomics (drug dosing guidelines, drug labels with PGX information, clinical interpretation of genetic tests and variants associated with medication response) at: http://www.pharmgkb.org/tutorial/PharmGKB_tutorial_2011_clinicalPGx.pdf
- Learn more about PGx research (annotation of genetic variants associated with drug response; summaries for top genes and drugs; drug-centered pathways; relationship among drugs, genes and diseases; haplotype mapping tables) at: http://www.pharmgkb.org/tutorial/PharmGKB_tutorial_2011_PGxResearch.pdf

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