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Benefits of and Barriers to Pharmacogenomics-Guided Treatment for Major Depressive Disorder

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Introduction

Antidepressants have reduced the symptom burden for many MDD patients, but drug-related side effects and treatment resistance continue to present major challenges(1).

Pharmacogenomics represents one approach to enhance antidepressant efficacy and avoid adverse reactions, but concerns remain with regard to the overall “value equation”, and several barriers must be overcome to achieve the full potential of MDD pharmacogenomics.

Background

Pharmacogenetics, as every reader of “Clinical Pharmacology and Therapeutics” knows, involves the study of the role of inheritance in individual variation in drug response phenotypes (2). Over the past decade, pharmacogenetics has evolved scientifically from a focus on individual candidate genes, most often genes encoding drug metabolizing enzymes and drug transporters, proteins that influence drug pharmacokinetics (PK), to become pharmacogenomics (PGx) —with the ability to scan agnostically across the entire genome to identify genes associated with drug response and, as mentioned subsequently, it is now becoming pharmacogenomics, merging genomic data with other “omics” information (e.g. metabolomics)(3). Psychiatry has been an early adopter of PGx in an effort to optimize and individualize drug therapy, especially the therapy of MDD. Since there are very few biologically-based biomarkers for MDD drug response, the application of genomic markers to help optimize antidepressant therapy represents an attempt to bring greater precision to the pharmacotherapy of individual patients than that provided by depending on information

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Supplementary Materials File Names

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provided by clinical trials that inform with regard to the response of the “average” MDD patient. . Finally, PGx is rapidly moving into an era when genomic data for a panel of pharmacogenes for every patient will be stored preemptively in the electronic health record (EHR). That information can be made available to the physician at the point care as the prescription is written—joined with clinical decision support tools. If psychiatry, like all of medicine, is moving toward that type of situation, the list of challenges and barriers to MDD PGx will have to include issues discussed subsequently under the heading of “**Implementation**”.

Functional variation in pharmacogenes that encode drug metabolizing enzymes and drug transporters is common. For example, in a pilot study of randomly selected Mayo Clinic Biobank subjects, 1002 of the 1013 subjects included in the study (99%) had an actionable variant in at least one of the top five of the 84 pharmacogenes that had been sequenced—*CYP2D6*, *CYP2C9*, *CYP2C19*, *SLOC1B1* and *VCORC1*. Most of those subjects had actionable variants in more than one of the five genes (4). With regard to antidepressants, 79% of these subjects had a “non-normal” metabolizer phenotype for *CYP2D6*, an enzyme that metabolizes many antidepressants (i.e. fluoxetine, paroxetine, nortriptyline and desipramine), followed by 60% for *CYP2C19*, the major metabolic enzyme for citalopram and escitalopram, and 36% for *CYP2C9*, an enzyme that metabolizes amitriptyline and fluoxetine. Since pharmacogene functional variants with known clinical utility are common, a series of questions immediately arises. The first relates to the nature of the data in support of the clinical utility of MDD PGx and, if there is evidence of clinical utility, how can we provide that information to the prescribing physician in an easily understood and usable form at the point of care so it can be used in the treatment of MDD patients without disrupting the clinical workflow?

Clinical Utility, Safety, Adherence, Efficacy and Pharmacoeconomics

PGx testing is already having an impact on clinical practice, primarily with regard to drug safety and avoiding toxicity. As shown graphically in Figure 1, psychotropics are a class of drugs with a high proportion of FDA approved PGx information incorporated in their labels —although those labels do not yet suggest that genotyping be performed prior to the initiation of therapy (2). Often this information has focused on *CYP2D6* and *CYP2C19* poor metabolizer phenotypes and risk for QTc prolongation.

PGx Implementation

Preceding paragraphs have described potential benefits of PGx testing in terms of adherence, efficacy and decreased incidence of adverse drug reactions when PGx is used to help guide antidepressant therapy. If that is the case, then how—in a practical sense—are we to implement this aspect of clinical genomics without disrupting the clinical workflow for psychiatrists or other healthcare team members? Many academic medical centers and healthcare systems are already testing various approaches to PGx implementation. The most common involves use of the electronic health record (EHR) to deliver alerts at the point of care when drugs are prescribed for which PGx information might prove useful. For example, at the Mayo Clinic, 19 of these drug-gene pair alerts are currently firing, six involving

antidepressant drugs, for all 1.4 million individual patients who are seen at Mayo each year. However, these alerts are “reactive,” they require that the physician consider ordering a genotype test. That approach is only a temporary solution, and eventually the process will probably involve placing DNA sequence-based pharmacogene panel information in the EHR preemptively(5). The selection of genes to include is usually an internal peer-reviewed process based on guidelines developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC), a joint effort of the NIH-supported PharmGKB and the Pharmacogenomics Research Network (PGRN), as well as guidelines from the Dutch Pharmacogenetics Working Group. Once a set of alerts has been established, a significant institutional educational effort directed at physicians, pharmacists, nurses and patients has to be developed. Of particular importance is the development of user friendly clinical decision support tools to assist physicians and other members of the healthcare team in the interpretation of PGx test results.

Future Considerations

In spite of its potential positive impact on clinical outcomes, incorporating PGx testing into clinical practice is and will be challenging. Physicians have to believe that PGx testing will be of benefit to their patients, and the evidence base supporting PGx testing in mood disorder populations will have to be better developed, with larger studies conducted by disinterested groups. Ideally, those studies will include patients with bipolar disease. Furthermore, there are currently no published studies on PGx-guided treatment in adolescent mood disorders where the theoretical benefit might be great given the concern that exists with regard to emergent suicidal ideation during therapy with these drugs in adolescents. Finally, most of the published literature has focused on single gene variants, mostly for genes involved in PK. Future studies will move the focus to multiple genes, with a much greater emphasis on PD. Those studies will also increasingly utilize a pharmaco-omics strategy, as demonstrated by a recent study in which metabolomics was used to inform genomics, resulting in the identification of two novel genes, *TSPAN5* and *ERICH3*, that were top signals related to SSRI treatment response in patients with MDD (3). In summary, the benefits of PGx-guided antidepressant therapy are still emerging and center on drug safety, side effect burden, treatment adherence and response rates. A great deal of future work will be needed to address both scientific and logistic barriers to the implementation of this aspect of clinical genomics, genomic science that has the potential to truly individualize the drug therapy of MDD.

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Conflict of Interest:

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Abbreviations:

MDD	Major Depressive Disorder
PGx	Pharmacogenomics
SSRI	Selective Serotonin Reuptake Inhibitor
FDA	Food and Drug Administration

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Figure 1. Food and Drug Administration Pharmacogenomic Biomarkers for noncancer therapeutic agents by disease category. Numbers represent the number of drugs included in that category.