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COMMENTARY

Pharmacists as facilitators of pharmacogenomic guidance for antidepressant drug selection and dosing

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INTRODUCTION

Many patients require trials of different antidepressants to find a suitable treatment for depression and anxiety disorders. Pharmacogenomic (PGx) testing may provide opportunities to improve drug selection or dosing. How and when to obtain this information and integrate it into clinical care remains a challenge. A recent randomized controlled trial of PGx to guide antidepressant treatment by integrating community pharmacists provides an opportunity to reflect on current challenges and interprofessional opportunities to improve patient care.

Finding effective and tolerable medications for individuals with depression or anxiety is a challenge. These conditions are quite common, but despite a number of approved antidepressants, remission to initial treatments is achieved by only approximately one-third of patients.[1] Sequential strategies for switching or augmentation may be helpful for some patients, but the journey may be long. Determining effectiveness in the outpatient setting may take 4–8 weeks per medication. Depending on illness severity, the need to trial multiple medications in a sequential fashion may result in many months of direct and indirect costs related to illness, and inadequate treatment may increase the risk for suicide.

PGx has long been regarded as a seemingly logical and enticing approach to improve the precision with which we choose and dose antidepressants.[2] PGx tests have been available for over 10 years,[3] yet we as a mental health field have struggled to incorporate this element of precision medicine into clinical practice. Other therapeutic disciplines (e.g., oncology), however, now have "-omic" technologies integrated into the standard of care. Higher level challenges to integrating PGx into clinical care for mental health include (1) how best to test and quantify clinical impact, and (2) how to effectively incorporate PGx into clinical care in a structured and evidence-based fashion. Papastergiou et al. conducted a randomized controlled trial of PGx guidance for antidepressants versus standard care in a community pharmacy setting. They identified greater improvements in symptom and disability measures over time in those receiving pharmacist recommendations that incorporated PGx results versus those that did not have PGx information. The study design, approach, and results offer an opportunity to gain further insights into the aforementioned barriers as we expand our evidence base for PGx facilitate care in mental health.

HOW CAN WE BEST TEST AND QUANTIFY THE IMPACT OF PGX FOR ANTIDEPRESSANTS?

On the surface, using PGx as additional information to assist with pharmacological treatment decisions seems like it should be relatively straightforward. However, as one descends into

the weeds, numerous complexities become apparent. Despite efforts from guideline and regulatory groups to provide evidence evaluations of drugs and genes, there are discrepancies in guidance across clinically available PGx tests.[4] A search of the National Center for Biotechnology Information Genetic Test Registry reveals over 30 PGx tests applicable to drugs used in mental health. Across tests, a range of pharmacokinetic and in some cases pharmacodynamic genes are included. Genes referenced in regulatory information and guidelines for antidepressants currently include those that encode drug metabolizing enzymes, such as those examined in the present study.[5] Contributions of pharmacodynamic genes to antidepressant outcomes are plausible, although clarifications are needed regarding how they should be considered in drug selection or dosing. Does this variability across PGx tests necessitate the formal evaluation of each in a clinical trial? Some may argue yes, although an important consideration is how the results of a test are intended to be used. If the intent is to explicitly direct pharmacotherapy with a test result, then perhaps formal evaluation is needed. On the other hand, there are common PGx elements across most tests that include the genetic markers evaluated in guidelines and regulatory information. Furthermore, most clinicians agree that PGx test results cannot be and should not be interpreted in isolation. Thus, perhaps there are better ways to study the clinical impact of PGx tests and the dissemination of patient-specific recommendations to providers.

Related to this is the concept of the integrity or validity of PGx as an "intervention" tested in a clinical trial. Testing the efficacy or effectiveness of PGx guidance is easier and more "clinical trial friendly" if a provider follows discrete results with drugs categorized in simple ways based on perceived severities of interacting genetic factors. However, this approach may be at the expense of patient-specific information that provides important real-world context about other factors important for pharmacotherapy choices beyond genetics. Contextualizing PGx information or drug-gene results, however, introduces opportunities for variance based on differences in available clinical information, as well as background knowledge of the clinician applying PGx results. This context-specific variability may be perceived to lessen the integrity of PGx as an intervention in a trial. In this regard, the integration of pharmacists into a PGx assessment and recommendation process holds some opportunities and promise, albeit not without challenges.

Pharmacists and community pharmacies have patient medication information as well as ancillary clinical information (or means to obtain it) to facilitate a meaningful assessment or perhaps serve as an initial review of PGx information considering current and prior therapies. In most cases, however, this is not at the level of information available to a clinic or prescriber. The investigators of the present study note an important limitation of their pharmacists not having antidepressant exposure histories for participants. This is information prescribers consider when selecting subsequent treatments, and thus should be considered by pharmacists making recommendations. Training programs to educate clinicians on the scientific fundamentals of PGx and how to consider results based on existing evidence, resources, and clinical context are becoming more accessible and a welcome integration into the methods of Papastergiou et al. Additional future opportunities abound in the convergence of PGx-specific training and the application of standardized Comprehensive Medication Management (CMM) evaluations that have been determined to be viable interventions on their own.[6] Furthermore, community pharmacy environments that promote communication with patients through CMM or related interactions also present opportunities for more detailed pre- and post-PGx test patient counseling and education beyond what may be feasible in a prescriber's office. This presents a path forward to building our evidence base, while not overlooking the value of clinical context and other important patient-specific factors.

Assessing and collecting relevant outcome measures is an essential aspect of testing and quantifying the impact of an intervention. In the present study, the authors collected commonly used and validated self-report measures of depression and anxiety symptoms along with a measure of treatment satisfaction. Additional clinician-rated scales for measuring outcomes would have been desirable but come with additional logistical challenges and time burden for participants and providers. With tolerability issues known to drive early discontinuations of antidepressants, the assessment of side-effects is important. In this regard, the SATMED-Q used in the present study provides very general assessments of satisfaction and side effects and is perhaps a missed opportunity to collect more detailed tolerability information.

HOW CAN WE EFFECTIVELY INCORPORATE PGX INTO CLINICAL CARE IN A STRUCTURED AND EVIDENCE-BASED FASHION?

The optimal entry point of PGx into clinical care in mental health is also an area in need of clarification. Direct prescriber and clinic involvement are ideal, although complicated by common logistical challenges, including limited time to spend with prescribers. This is particularly notable in primary care where many treatments for depression and anxiety are initiated. From an outpatient perspective, community pharmacies present accessible options to patients, provided that the pharmacists have the capacity and training to perform PGx evaluations. Pharmacists are well-positioned to effectively communicate test results and recommendations with prescribers, clinics, and patients. Even

the most user-friendly PGx test reports or results require time to review and a thoughtful consideration of other current and past therapies and clinical factors. Although there may not be one best entry point, community pharmacies offer viable options provided that communication with prescribers and clinics is established and that there is agreement on the preferred methods to convey results and recommendations. That said, anyone who has visited or worked in different community pharmacy settings knows that opportunities for pharmacist communication with patients and prescribers may vary based on a variety of factors. Thus, translating "well-positioned" to "realized" potential for facilitating PGx in this environment necessitates positive and open communications among pharmacists, patients, and prescribers. PGx aside, the present study identified improvements in medication satisfaction over time regardless of intervention arm. As participant eligibility was in part based on expressing some degree of dissatisfaction with current treatment, these findings indicate that more direct community pharmacist involvement in antidepressant management may be generally helpful to patients with depression or anxiety.

A related challenge to the integration of PGx into clinical care is when best to obtain testing for a patient. At the very beginning of therapy, after multiple options have already been exhausted, or at some point in between? Conceptually, it seems favorable to have PGx information earlier in treatment to avoid unnecessary medication journeys. Genetic variation in genes related to drug metabolism as studied in Papastergiou et al. produce a clinical impact on antidepressants similar to drug interactions or altered liver function. Interactions and altered liver function are factors we have long accepted as clinically meaningful and important considerations before beginning treatment without requiring clinical trials. This logic has not directly translated to the use or study of PGx tests. Most PGx trials to date have entry criteria involving inadequate response or intolerability to at least one prior antidepressant. Although reasonable, this criterion results in a range of prior treatment experiences making it difficult to pinpoint whether obtaining a test earlier or later in illness is better. The present study included individuals with depression or anxiety who may have been newly starting treatment as well as those switched from a prior antidepressant. Studying participants meeting the entry criteria for this trial revealed favorable and clinically meaningful improvements in both depressive and anxiety symptoms for those receiving PGx guidance, which is encouraging. Moving forward, examining the relative benefit of testing earlier versus later in the course of illness will be beneficial to the field. This may involve both a direct examination of outcomes within a study as well as follow-up analyses to identify realized or missed opportunities over time.

THE PATH FORWARD

The utility of PGx to optimize antidepressant therapies has been previously described with a dichotomy of both enthusiasm[2] and skepticism.[7] As noted earlier, PGx information allows clinicians to identify genetic factors with impact comparable to drug interactions and altered liver function that may be important to consider prior to antidepressant selection and dosing.[8,9] Yet, the testing resources available to clinicians for PGx are more expensive, variable in content, and often include result reports that are more complicated than a simple liver function test or drug interaction assessment tool. This has contributed to a demand for prospective trials to evaluate the benefit of PGx for applications in mental health. Rigorous evaluation of an intervention or clinical application is a good thing, but the ways in which PGx must be considered clinically presents challenges in trial design as well as the translation evidence-based principles to clinical application. The present study offers some unique elements of design and clinical application that begin to address some of these challenges. However, it is not without its limitations. As previously mentioned, the lack of antidepressant histories and more detailed drug tolerability measures are notable. Additionally, whereas the PGx training for pharmacists represents a step toward improving consistency in evaluating test results, opportunities to further standardize integration with medication evaluations still exist. Furthermore, in the context of primary care and community pharmacy, PGx tests like the one used in this study have the potential for much broader application beyond antidepressants. Evaluating and quantifying this broader impact is essential to maximizing the impact of PGx. Despite these limitations, the integration of pharmacists into a clinical trial evaluation of PGx for antidepressant guidance presents opportunities to address challenges previously noted with prior studies. This also represents an opportunity to demonstrate how interprofessional collaboration in the community may be a viable path toward evidence-based application of PGx.

CONFLICT OF INTEREST

The author declared no competing interests for this work.

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