Pharmacogenetics: A Resource for Efficient Management of Psychiatric Disorders

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PA581: Clinical Year Seminar

April 8, 2022

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Objectives

1. Identify the current research surrounding pharmacogenetic testing as it pertains to psychiatric management.
2. Evaluate the efficacy and ability of pharmacogenetic testing to minimize polypharmacy.
3. Evaluate the efficacy and ability of pharmacogenetic testing to minimize adverse drug reactions.
4. Offer guidance for integration of pharmacogenetic testing into clinical practice.

Key Words

Pharmacogenetic testing

Pharmacogenomics

Polymorphism

Adverse drug reaction

Polypharmacy

Introduction

One out of every five adults in the United States lives with a mental health disorder. These disorders are defined as "any mental illness" (AMI), meaning the individual experiences no, mild, or moderate impairment, or a "serious mental illness" (SMI), meaning the individual's daily functioning is severely impaired. There is no doubt of the global burden brought on by these conditions, as over one trillion dollars worth of productivity was lost in the year 2020 due to major depressive disorder (MDD) and generalized anxiety disorder (GAD) alone. When considering the burden brought to the individual, those suffering from a mental health disorder are more likely to be hospitalized, experience unemployment or develop cardiovascular or metabolic disorders when compared to those without mental illness.[1]

While mental health treatment has progressed, with 46.2 percent of AMI patients and 64.5 percent of SMI patients receiving treatment in the year 2020, the uncertainty of how to define and achieve successful treatment still remains.[1] Treatment is not always methodical and requires patients to gauge their personal experience with each medication. Even though first line options are recommended, there are associations with various adverse drug reactions and no way to know how an individual will respond to any medication until they try it. Additionally, the definition of successful treatment remains subjective and determined by the provider, causing any statistics to be vaguely-defined and inconsistent. Another complexity of this uncertainty is whether or not providers will use polypharmacy, defined as the use of more than one drug, in their treatments. Polypharmacy use has increased over the last couple of decades and has shown promise, especially in treating more than one comorbid illness, unremitting symptoms, and adverse effects like extrapyramidal symptoms (EPS) associated with antipsychotics.[2] Despite its promise, the problem still remains that the correct combinations of drugs will vary between

patients and adverse effects become harder to pin down. They may even compound as medications are added. There are also a limited number of research studies evaluating the efficacy, side effects and long term implications of polypharmacy.[2] With all of this uncertainty and lack of quantitative research, it is clear that if providers can obtain insight into how their patients will react to various drugs, in the short term and long term, then treatment will become much faster, more effective, and generally more efficient.

A potential resolution lies in the knowledge that at least 95 percent of the population carries one or more genetic variations that are contradictory with at least one medication.[3] Enzyme analysis groups patients into either poor or extensive metabolizers of certain drugs based on pharmacokinetic (PK) or pharmacodynamic (PD) panels.[4] PK panels offer information on the individual's metabolism, while PD panels offer information on the potential efficacy, or adverse effect profiles of the drug.[4] Since current clinical practice only routinely utilizes this information for drugs involved in chemotherapy or immunosuppression, there is a general lack of accepted pharmacogenetic-guided treatment algorithms.[5] Therefore, the specific aims of this paper are to identify the current research surrounding pharmacogenetic testing as it pertains to psychiatric management, specifically its efficacy and ability to minimize polypharmacy and adverse drug reactions, with the hopes of offering guidance for integration into clinical practice.

Methods

Search Strategy

A detailed literature search was performed in October 2021 using several databases, including Pubmed, ScienceDirect, PsychINFO, PsychARTICLES, ClinicalKey, and Health Source. Search parameters for "publication date from 2016-2021" and "adult subjects" and "full text" and "clinical research study" were implemented.

Inclusion and Exclusion Criteria

Articles were excluded based on the following criteria: 1. Studies involving nonhuman subjects; 2. Studies in which pharmacogenetic testing was not performed on subjects; 3. Studies in which participants were not diagnosed with mental health disorders; 4. Opinion articles. The remaining articles were analyzed for their experimental design, findings and limitations as they pertained to the specific aims of this paper.

Study Selection

The remaining research articles were diverse in their experiment design. While some utilized a prospective or retrospective analytic approach, others varied in length of treatment ranging from eight weeks to ten years. Likewise, a mixture of open label, single blind, and double blind experiment designs were found. Every design included participants diagnosed with MDD, while a quarter included those with GAD. Otherwise, only one article contained individuals diagnosed with obsessive compulsive disorder (OCD) and another contained those with Post Traumatic Stress Disorder (PTSD) or Bipolar Disorder (BD). Despite the differences in design, most articles investigating the efficacy of pharmacogenetic analysis for psychiatric management made use of similar variables, measures and targets.

With respect to the variables utilized, the routinely investigated PK and PD variants were associated with the following genes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, SLC6A4, COMT, HTR2A, MTHFR.[6] Cytochrome P450 (CYP), Serotonin (SLC/HTR), Catecholamine (COMT), and Homocysteine (MTHFR) enzymes are responsible for the metabolism of foreign substances in the human body. These genes are of particular interest due to established research that certain polymorphisms alter the metabolism of psychotropic

medications. For instance, polymorphisms of the CYP3A4 and CYP2C19 genes have been found to correlate with longer half-lives of benzodiazepines.[7]

Experimental designs that monitored treatment response to medications utilized patient assessment tools included HAM-D, HAM-A, QIDS, PHQ-9, GAD-7, NPQ, SDC and Y-BOSC. Otherwise, measures directly correlated to the study's goals including grading of the seriousness of adverse drug reactions (ADR) and hospitalizations.

The goal of every research article was to utilize gene analysis to classify patients as either responders, nonresponders, or refractory to certain psychiatric medications. For prospective studies, authors compared genetic suggestions of predicted efficacies and ADR profiles of the "next intended treatment" as documented by the provider. For those that were retrospective, efficacy and ADR profiles were predicted via genetic analysis then compared with the patient's clinical outcomes. For studies that initiated or changed a patient's psychiatric medication on the basis of genetic analysis, progression was monitored by the previously mentioned assessment tools.

Results

The authors of the above mentioned articles found an overwhelming amount of data that supports the use of pharmacogenetic analysis for efficient treatment of MDD. Every paper's analysis found that pharmacogenetic-guided treatment (PGx) greatly improved response and remission rates for patients with depression when compared to the standard of care or control groups. One particular study found that PGx more than doubled the remission rate for patients with depression.[8] Even more significant increases in response rates were seen when compared to control groups for individuals suffering specifically from severe or treatment-resistant depression.[6] Another interesting finding of several articles was that when switched to a

"genetically suitable" medication, the ADR reported by patients with MDD, if present at all, were much more tolerable and less apparent than those reported by the control groups.[9]

Significant improvements were also seen in all the articles that utilized PGx for GAD. When compared to control groups containing those who received "treatment as usual", those receiving PGx improved in all outcome measures and assessment tools.[10] In addition to symptom remission, PGx patients also reported higher levels of treatment satisfaction when asked to rate their provider's competency.[11]

Less promising findings were found by articles investigating PGx for patients with OCD, PTSD, or BD. For the one study that included patients with OCD, there were no significant changes in treatment responses when compared to control groups from the analyzed genetic polymorphisms.[12] The single study that included patients with PTSD and BD found that only patients with PTSD showed potential benefits of PGx. Of those with a positive response, the improvement was not considered statistically significant.[13] Despite these discouraging findings, clinicians in this study reported feeling more confident utilizing PGx than their usual treatment regimens, especially for patients with polymorphisms that generate warnings for higher risks of ADRs.

Articles with specific focus on ADR analysis between PGx and control groups also showed a significant amount of promising data. Prospective studies, such as the one by Ramsey et al. indicated that in approximately 20 percent of individuals, the next intended treatment, as documented by providers, had a significant interaction potential and approximately 45 percent had a moderate interaction potential.[14] Articles with a retrospective analysis found that upwards of 85 percent of participants were already taking psychiatric medications with the potential for a genetic interaction.[15,16] For studies that initiated or changed a patient's psychiatric medication on

the basis of PGx, it was found that only 28 percent reported ADR when compared to 53 percent of those in the control groups.[15] Another potential benefit found from PGx-guided ADR studies is that pharmacists and providers reported significantly high levels of "decision support," as they felt more comfortable being able to anticipate ADR.[17]

Discussion

As outlined above, the major development from these research studies was the validation that PGx greatly improved response and remission rates and decreased the overall severity of ADR in patients with MDD and GAD. This evidence indicates that PGx can successfully be used for initial drug and dosing selection in addition to the prediction of potential side effects that patients might experience. The benefit of these genetically-guided treatment algorithms is that they offer a "mechanical instead of merely descriptive information of effectiveness".[18] Therefore, instead of providers basing their first or next intended treatment on biased experiences, such as personal preference or previous patient success, they are able to make an informed and scientific decision.

These findings suggest that if utilized properly by the clinician, patients will be put on the best psychiatric medication for them, with limited side effects, eliminating the need for polypharmacy or multiple trials of medication. A benefit of genetic analysis is that a patient's polymorphisms are constant over their lifetime. PGx results will not change over the course of someone's life and will not be influenced by exogenous factors such as fluctuations in hormone levels or simultaneous drug administration. Theoretically, a patient's condition could be adequately treated with one medication for their entire life. A case report by Stäuble et al. documents the use of PGx in a 38 year old male with a 16 year history of treatment-resistant MDD. At the time of hospital admission, the patient was experiencing acoustic and visual

hallucinations related to subtherapeutic serum levels of bupropion, despite being prescribed a high dosage. PGx revealed that the patient was a carrier of the CYP2B6*6 allele, which is related to reduced bupropion metabolism and subsequent decreased levels of the active metabolite. This patient was successfully transitioned to Trazodone, a genetically suitable medication, to treat his condition.[19] This case study highlights the benefit of preemptive pharmacogenetic testing to prevent prolonged suffering due to inadequate drug or dosing selections.

Despite these promising findings, there were several limitations from the research found that needs to be addressed in further investigations. First, there were very limited research studies that investigated the use of PGx in conditions other than MDD and GAD. Because of such overwhelming evidence supporting PGx in these conditions, evidence needs to be collected whether or not this is applicable in conditions such as BD, OCD, PTSD, etc. Second, the current research focuses on patients over the age of 18. Again, with such promising results for adults with MDD and GAD, further research should be conducted that evaluates the efficacy of PGx on children and the elderly. PGx would be especially beneficial in children and adolescents, because if they can be started on the proper medications, these would theoretically be effective for their entire life. This should spare them the time and suffering associated with multiple failed medication attempts. The elderly would also benefit as they tend to suffer significantly more than other populations from ADR and polypharmacy. If their psychiatric medications could be effectively reduced to one or two prescriptions, then adverse outcomes, such as hospitalizations, could be avoided. Likewise, a known prolife of potential genetic-based ADR could be beneficial to other healthcare professionals when evaluating potentially confounding symptoms. Third, none of the studies mention the potential of PGx psychiatric medications to be affected by

tolerance. Longevity studies need to be completed that assess if these medications, or their dosages, are any less effective as time progresses.

Other considerations include the barriers that revolve around integrating this resource into current medical practice. The cost alone to perform and analyze this testing can be a large hurdle for most patients, given that insurance companies do not completely cover this type of testing. For instance, Genesight, a company offering comprehensive psychotropic reports based on pharmacogenetics, costs patients an average of $330 out of pocket. This does not include the cost of the patient to be seen by a provider capable of analyzing the results or to pick up their prescriptions. Additionally, even if prices were reasonable enough to be accessible to most patients, there lies the question of whether providers would even be willing to incorporate it into practice. In an investigation by Vest et al. [20], one provider is quoted saying:

> There's a comfort level we have, we have a usual repertoire and beyond that there's also, some of it [medications] maybe that we don't use as often, but we do have a comfort level with. And there were some that we would never use. If I remember correctly, I think that the ones that were maybe most recommended were things that I would never consider using. And I use one, something that was sort of in the middle row that seemed like it would be helpful. So I think it does help, at least gives us food for thought … there still are some things that we would probably never feel that comfortable prescribing.

Another practitioner is quoted with the following:

> The fact that psychiatry is touched by so many different components of a human person … So we're looking at the genes as if they are the sixth unmovable set of dictates that kind of tells you what is going to happen to a person. And yet then, we have the nun study that they've got 97-year-old nuns with the APOE gene and have never demonstrated any symptoms of Alzheimer's … So hanging all of our hats

on these hooks may not be where it's at in terms of fixing the problem of psychiatry not making people better. But I'm hoping that it can give us one more tool to use wisely and judiciously.

A general consensus found in this research is that while providers are appreciative of the scientific advancements and recommendations for prescribing guidelines brought by PGx, there is a certain level of comfort that they are not willing to part with. However, an argument can be made that anecdotally relying on the "safety" of one drug, as witnessed via the administration to another patient, is even more dangerous than administering an unfamiliar drug with a known side effect profile for the patient.

Even if one overlooks the barriers of cost and comfortability, healthcare providers must, at the end of the day, be the ones to address and treat their overall patient. This includes taking into account their comorbidities and social determinants of health. For instance, it would most likely be a waste of resources to incorporate PGx into the treatment plan for a teenage patient with no comorbidities, presenting at an initial appointment with a chief complaint of anxiety. However, a patient presenting with comorbidities such as cancer or congestive heart failure, who is most likely on a laundry list of medications, would benefit from the use of PGx, especially for treatment-resistant psychiatric disorders. Not only would this limit their psychiatric medications to a few prescriptions, but it would provide less opportunity for drug-drug interactions and ADR. Likewise, it could spare the patient time and money that can be put towards the treatment of other medical conditions. Similarly, PGx could best be utilized in patients that strongly fear common ADR of antipsychotics, such as decreased sex drive. Whether they struggle with the condition already, or have a great concern for developing it, stratifying their risk of developing it could put both the patient and provider's mind at ease. We can find this to be a great resource in helping those struggling with substance abuse or addiction, as they can aim to avoid the more

addictive medications, such as benzodiazepines, in favor of an alternative class that is more genetically suitable for them.

Conclusion

Research reveals an overwhelming amount of evidence suggesting how beneficial pharmacogenetic-guided treatment can be for MDD and GAD. From this information, providers can obtain insight into how their patients will react to various drugs in the short and long term. This holds the potential to personalize future prescribing and treatment techniques while delivering faster and more effective relief to patients. Therefore, this suggests that, if implemented, a general decline would be seen in ADR and the necessity for polypharmacy. While this evidence exists, there are many boundaries that exist before widespread use of pharmacogenomics is incorporated into regular clinical practice.

With reference to the Physician Assistant Competencies, there are several key ways in which the incorporation of pharmacogenomic-guided treatment upholds the standards of practice. For example, the competency of medical knowledge would indicate that providers are aware of pharmacogenetic testing and its potential benefits. Even if the provider decides not to incorporate it into their practice, they should make the patient aware of this technology and be able to educate them on its use. The competency of interpersonal skills would indicate that the provider reaches out to other professionals, such as genetic researchers and pharmacists, to interpret and implement the findings of these analyses. The competency of patient-centered care would indicate that the provider puts the patient's best interests and wishes first. Therefore, an argument can be made that if a patient is stable on their current psychiatric treatment plan, there would be no need to utilize PGx, even if readily available, as changes in their current management could cause unnecessary stress. On the other hand, if a provider utilized PGx, they

should still recommend treatment additives such as talk therapy, counseling, meditation, or other means that could improve the patient's condition and overall quality of life. The competency of practice-based learning would indicate that the provider incorporates new technology into their work while being mindful of the patient's financial situation. As a relationship was recognized between increased health care costs and trials of unsuccessful medications, efficient and effective treatment could lower the overall burden on the patient.[21] While PGx currently costs around $330, this one time expense could greatly outweigh a lifetime of medical and psychiatric consultations and treatments. Finally, the competency of systems-based practice indicates that providers recognize the social determinants of health, among which is genetics. While not a modifiable factor, our unique genetic makeup holds the key to a more personalized approach to medicine. If unlocked, this technology could save patients time, money, and unnecessary suffering.

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