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Original article

A NARRATIVE REVIEW OF ADVANCES IN PHARMACOGENETICS AND PERSONALIZED MEDICINE IN PSYCHIATRY.

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Abstract.

The variable effectiveness and side effects demonstrated in patients who receive psychotropic drugs show that there is a need for developing personalized medicines in psychiatry. Pharmacogenetics significantly impacts the pharmacokinetics and pharmacodynamics of psychotropic drugs. In the course of this review, the role of metabolism and receptor expression in the efficacy and adverse events of psychiatric drugs is discussed. Exogenous factors that affect the therapy are discussed. Further, key challenges in the application of pharmacogenomics to personalized medicine in psychiatry are discussed, along with their potential solutions. It is concluded that therapeutic drug monitoring along with pharmacogenetic testing in clinical practice can help devise personalized tailored treatment plans which can improve the mental health and quality of life of an individual and maintain a high benefit-to-risk ratio.

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1. INTRODUCTION.

Precision medicines are now a favorable mode of treatment over conventional medicines reason being they offer more target-specific benefits and reduce the number of side effects. The drug discovery era in which drugs target the mass population which benefitted both the masses and the pharmaceutical industry has come to a halt [1]. Here in this era, the drugs that target a specific population who have the same comorbidities, same genetic makeup, and the same set of clinical manifestation is on the rise. The demand for precision medicine is rare owing to the small population it targets but the advantages it has over conventional medicines are significant [2, 3].

Precision targets a small group of population having closely related diagnoses and genetic makeup. Genetic makeup plays an important role in the administration, absorption, target activity, metabolism, and elimination [2]. Especially when it comes to psychotropic drugs they have varied metabolism depending upon the cytochrome P enzyme possessed by an individual. Cytochrome P is responsible for the metabolism and elimination of psychotropic drugs [3, 4]. Metabolism and elimination has profound effect on the efficiency of the drug, and the time it gets in the body to interact with the receptors [4]. Apart from the metabolism, the expression of the target receptors also depends on the genetics of the individual which in turn affects the efficacy of the drug.

Psychotropic drugs usually have associated adverse drug reactions which decrease the patient's compatibility [4-6]. The adverse drug reactions

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are of different magnitude and differ in terms of occurrence which can be correlated to the genetic makeup. Patients with psychiatry disorder have the same set of clinical manifestations but the magnitude of symptoms varies significantly which implies that the pathophysiology of the psychiatric disorder may be different which can again depend on the genetics of the patients [5, 6]. All the above factors discussed emphasize the importance of pharmacogenetics in psychiatry medicine.

1.1. Metabolism of the psychotropic drugs and genetics.

Endogenous factors: The cytochrome P, which is responsible for the metabolism of the drugs, has different polymorphs. Depending on which genetic allele is present in an individual they code for a particular polymorph of cytochrome P. Different polymorphs are responsible for metabolism of the different drugs, when a particular drug is received by different ethnic populations they have different metabolism, and thus show varying response towards same drugs.

It has been observed that a particular ethnic population is more prone to one or more severe side effects compared to a particular drug. The adverse drug reactions cannot be generalized for all the population. For instance, Steven Johnson syndrome associated with carbamazepine is more popular in the Asian population than in any other ethnic population.

Certain genetic disorder which affects the mental health of an individual such as autism and Down syndrome have genetic makeup completely different from normal individuals so there will be a significant difference in the reaction of the body towards the particular drug. The ethnic population and genetic disorder are the contributing factors to different genetic makeup which can affect the psychotropic action of the drugs given for psychiatric disorders. The genetic makeup varies in ethnic populations because they are exposed to distinct climatic conditions, toxins, food, as well as social environment. Some genetic alle- les which are responsible for the synthesis of cytochrome P polymorphs vary greatly leading to inter-individual variability in pharmacokinetics of the drug. Personalized medication dedicated to a specific group of individuals having the same genetic makeup can reduce the metabolic variability among the individual and make the pharmacokinetics of the drug predictable.

Exogenous factors: Co-administration of another drug that either inhibits or induces the activity of certain cytochrome P polymorphs affects the metabolism of a particular psychotropic drug. Also, certain drugs are autoinducers, meaning they induce their metabolism, and some drugs in- hibit their metabolism, meaning they are autoinhibitors. Certain drugs have phytoconstituents that induce or inhibit their metabolism. Comorbidities existing along with psychiatric disorders have a similar role in the pharmacokinetics of the drug.

These are exogenous factors some of which are preventable such as a certain group of foods that can be avoided when one is taking psychotropic medication but most of the comorbidities and drug-drug interaction cannot be simply eliminated when considering the pharmacokinetics of the drug, Several studies have been conducted to identify drug-drug interaction that can be harmful, but an individual's pathophysiology when two diseases coexist can be different leading to different reactions toward the same drugs administered [6-8].

1.2. How do psychotropic drugs act differently on each individual?

The pharmacodynamics of psychotropic drugs make the drug act differently in an individual. Receptors that interact with the drug are expressed based on the genetic makeup of an individual, and similarly, transporters that help the drug reach the site of action are also influenced by the genet- ics of an individual. Some individuals have exaggerated responses to the same drug, whereas other individuals do not show significant responses to the same drug [9].

Generally, physicians rely on posology calculations for determining the dosage of an individual [10]. This dose can be too low or too high for an individual who has not been exposed to any psychotropic drugs, depending on the expression of

the receptors and the metabolism of the drug in the body. Side effects that occur in an individual due to antipsychotics vary greatly. Side effects such as weight gain and dyskinesia are common, yet their magnitude differs [10]. Depending on whether an individual is a fast metabolizer of the drug or a slow metabolizer, the side effect occurs. In some people, the side effects can lead to dele- terious cardiovascular problems that are either irreversible or possibly harm the patient more than the benefits achieved due to its antipsychotic activity.

1.3. Role of personalized medicines.

Therapeutic drug monitoring is the method by which physicians can assess the safety and efficacy of the drug in an individual [11]. Although this can help in adjusting the dose, understanding efficacy and patient compliance are of equal importance. If the side effects, such as weight gain, can discourage patients from taking the therapy, Nevertheless, certain contraindications are obvious and should be avoided at any cost such as teratogenic drugs during pregnancy. However certain side effects, which might appear harmless when compared to the benefits, can affect patient's compliance. Especially in neuropsychiatry, the psychology of the patient can severely affect their compliance. So it is necessary to calculate the individualized benefit-to-risk ratio.

Pharmacogenetics testing aids in understanding how well the drug is tolerated in the body. Physicians can predict the magnitude of side effects from their understanding of pharmacogenetics. It is not just limited to side effects; the therapeutic action of the drug and its efficacy can also be predicted. A personalized medicine will have a high benefit-to-risk ratio. A review of pharmacokinetics and pharmacodynamics in a group of patients with similar pharmacogenetics can accurately provide physicians with all the knowledge required for developing a personalized treatment plan [12].

Genetics do play a substantial role, but the metabolism and efficacy of the drug are severely affected by exogenous and environmental factors as well [13]. Exposure to toxins, smoking, food habits, drug-drug interaction, and sociocultural habits can cause substantial changes in the pharmacokinetics and pharmacodynamics of the drugs and thus along with genetics a thorough examination of the history is also required to develop a personalized medication plan.

2. CHALLENGES.

2.1. Clinical trial

There are various clinical trials carried out but in most of the cases, they are restricted to a specific population, more precisely to a specific gene pool belonging to the same ethnicity. Inter-individual variability is rarely a consideration in conducting clinical trials. Most of the clinical trial findings show that a particular adverse event is rare and the population experiencing such an adverse event is negligible. However, when a larger population is considered such occurrence of adverse events can be observed in a significant number of participants [10-14].

Collecting the data of such a narrow group of individuals and testing them for the safety, tolerability, and efficacy of a particular drug becomes tedious and expensive. To overcome such challenges, the institute conducting clinical trials should collect genetic data from the participants and record it for further study while maintain- ing the confidentiality of the data. A large pool of such data can be resourceful for further reviews and studies by clinicians. This can be an economical yet effective way of developing studies without conducting trials [13].

2.2. Clinical practice.

Most physicians are not convinced about the role of genetics in psychiatry medicines. The pharmacogenetic testing before the treatment can be expensive and lead to rejection of the ther- apy from the patients. pharmacogenetics testing only considers the alleles present for the poly- morphs of cytochrome P thus it can only predict the metabolism aspect and the duration the drug remains in the body to interact with the recep- tors. Pharmacogenetic testing does not consider

the role of exogenous factors in the pharmacokinetics and pharmacodynamics of a drug [14].

Traditionally therapeutic drug monitoring has played a significant role in deciding the treatment regimen. Therapeutic drug monitoring paired with pharmacogenetic testing can play a pivotal role in devising personalized genetically suitable psychotropic drug therapy for psychiatric disorders [15].

3. CONCLUSION.

The variable response to psychotropic drugs is due to genetic variations in the individual which affects the pharmacokinetics and pharmacodynamics of the drugs. Pharmacogenetic testing and pharmacogenetic identification of specific genotypes and their effects on the efficacy and safety of the drug can help devise personalized treatment plans for individuals. However, narrowing the genetic population and identifying the ideal treatment plan according to the range of clinical manifestations and symptoms shown by a patient in normal clinical practice remains a challenge. Pharmacogenetics, if applied to psychiatric drug therapy can significantly evolve patient compliance and treatments to a whole new level.

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5. CONFLICT OF INTEREST.

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