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Pharmacogenetics: A reality or misplaced optimism?

Accessible summary

- Evidence from research relating to the way genes affect medication effectiveness and side effects is reviewed.
- Currently, there is strong evidence suggesting that drug response varies across individuals and this is particularly so across racial and ethnic lines. These differences are genetically determined
- There is hope that in future; an individual's genetic information can be used to help to decide which drug is effective for which person and at what dose before treatment.

Abstract

The paper aims to review current evidence that support the application of genetic information in the management and use of psychotropic medication. Although the importance of an individual's genetic makeup in the metabolism of drugs has been known for at least 50 years, it is only recently that such information is finding clinical application. A literature review of recent studies suggests that there are clear variations in the way people respond to psychotropic medication. These variations can be seen across racial and ethnic lines and, are genetically determined. The hope is that, in future we will be able use genetic information to predict which patient will benefit from which drug and at what dose. In other fields of healthcare such as anticoagulant therapy, the application of pharmacogenetics is now established in routine clinical care. Several psychiatric pharmacogenetic tests are currently available, including tests for the determination of metabolic status, risk of agranulocytosis and metabolic syndrome, and selection of beneficial medications. Since nurses are the centrepiece of mental health care, these advances are likely to alter significantly future mental health nurse education and practice.

Introduction

The role of psychotropic medication in the treatment and recovery of people with mental health problems is well recognised in spite of other treatment modalities. Moreover it has been demonstrated that service users place a high importance on the use of medication to aid recovery (Piat *et al.* 2009). Despite this recognition, debate still exists as to their effectiveness for a number of reasons. From a safety perspective, psychotropic medication and antipsychotics in particular presents a considerable risk both in terms of the way they interact

with each other and overdose. In addition, there is an alarming abuse of inappropriate psychotropic drug consumption worldwide with the use of polypharmacy being a typical example (Barnes and Paton 2011). The modest efficacy profile and substantial safety risk of psychotropic medication poses considerable challenges for mental health care. In mental health nursing, it has been argued that nurses lack adequate knowledge of psychopharmacology and this has resulted in nurses giving suboptimal advice to service users. (Latter *et al.* 2000; Kaas *et al.* 2000; Jordan *et al.* 1999; Skingsley *et al.* 2006). Inadequate knowledge almost always leads to suboptimal care of patients and this is clearly demonstrated in Latter *et al.* (2000) study. In their study, the investigators found that nurses' contribution to medication education for patients was frequently limited to giving simple information i.e. giving the name of medication, purpose, colour of tablet and the number of times, it is to be taken. In many respects, this inadequate knowledge is due to the shift away from a biological to a social science model of nursing care which has resulted in a reduction in pharmacological knowledge and this has had important ramifications for nurses at pre and post registration level (Cooper *et al.* 2008). In particular there is evidence to suggest this inadequate understanding of pharmacology has negatively and significantly impacted on nurse prescribing training where pharmacology is a critical component of the course (Meade *et al.* 2009). In mental health nursing, this problem assumes a greater importance due to the recent growth in medication options and the increasing complexity of pharmacological decision making process. This is particularly critical especially for mental health nurse prescribers where inadequate understanding of psychopharmacology has been reported (Skingsley *et al.* 2006).

In recognition of the above, the NMC have developed the Essential Skills Cluster (ESC) in which Medicines Management is one such skill. As from September 2008 it has been a mandatory requirement that all student nurses demonstrate competency in medicines management at the point of registration. Specifically, ESC 36 states that, "*People can trust the newly registered graduate nurse to ensure safe and effective practice in medicines management through **comprehensive knowledge of medicines their actions, risks and benefits***". This stand is clearly underpinned by the reality that in many mental health settings, it is the mental health nurse who is responsible for administering medication. It is also the mental health nurse who should be alert to adverse medication reaction and take steps to minimize side effects. Moreover, it is the mental health nurse who is responsible for co-

coordinating treatment modalities and integrates drug treatments with a variety of essential treatments in a way that is safe and acceptable to the patient.

Patient's response to medication and safety is likely to be dramatically altered by the integration of genetic information during the treatment process. These advances have the potential to alter significantly the way in which mental health nurses practice or deliver care.

This article reviews the progress made in research toward understanding how genetic factors influence psychotropic drug responses. As in any new field of research, there are challenges that lie ahead in translating the research findings into clinical practices that yield tangible benefits for patients with mental health problems. This review begins by discussing the importance of pharmacogenetics in healthcare before explaining the relationship between genetic variation and drug response. The link between antipsychotics, antidepressants, mood stabilisers and genetic variation will be reviewed and finally, the clinical implication of pharmacogenetics will be discussed.

The importance of pharmacogenetics

Pharmacogenetics is the science dedicated to the identification of genes influencing response to medication. It had a clear breakthrough in the 1950s with the discovery that the antihypertensive drug debrisoquine showed inheritable patterns of metabolism. Since then, pharmacogenetic research has expanded to cover most fields in medicine, acquiring special importance in complex diseases, including psychiatric illnesses (Arranz and Kapur 2008). As previously acknowledged, the effectiveness of current psychotropic drugs in clinical practice is suboptimal and they are effective in only a proportion of patients or produce partial response in other patients. Additionally, they are usually associated with adverse side effects that impact negatively on adherence and quality of life. More importantly, most of these drugs were not developed based on an understanding of the pathophysiology of the illnesses being treated and this has important ramifications in the treatment response and recovery of patients.

Pharmacogenetics research has established that drug response varies across racial and ethnic lines. For example, current evidence among other findings suggests that Chinese people can be treated with antipsychotic doses that are significantly lower than their Caucasian counterparts (Lin et al., 1988). This variable response to psychotropic medication has been attributed to the way genes influence individual metabolism of drugs. There is growing

optimism that pharmacogenetics will ultimately provide the right drug to the right person for the right illness in the right dose. To better understand the role of genetic factors we need to review the link between genes, enzymes and metabolism of drugs.

How does genetic variation affect drug response?

Drugs given to a patient usually enter the blood circulation after absorption into the blood stream. From the blood stream, the drug is distributed throughout the body including the brain and then broken down (metabolised) mostly in the liver before it is eliminated from the body mostly through the kidneys. The rate at which the drug is broken down by the liver affects its concentration in the blood circulation. A slow rate of metabolism results in higher concentration of the drug in the blood circulation. A higher concentration of the drug in the blood typically leads to heightened adverse side effects. A fast rate of metabolism, on the other hand, leads to low concentration of the drug in blood making it less effective. So, what affects the rate of metabolism of a drug? The answer is enzymes.

Enzymes are proteins found in both animals and plants, which act as organic catalysts. They help chemical reactions such as drug metabolism to proceed quickly and efficiently. Whether a drug has a pharmacological (beneficial) or toxicological (harmful) effect largely depends on its metabolism and therefore on enzymes. The enzymes responsible for controlling drug metabolism are found mostly in the liver and are called Cytochrome P450 enzymes. The production of CYP enzyme is controlled by genes (one gene-one enzyme) and genetic mutation give rise to different versions of a CYP enzyme. This variation is called pharmacogenetic polymorphism (literally, 'many forms') and is more pronounced across racial groups. This pharmacogenetic polymorphism partly explains why medicine response varies across people, especially across racial groups.

Pharmacogenetic polymorphism divides the population into at least three types of responders. The first group is those people with a gene variant (allele) that is not working or missing. These people are called poor metabolisers. Poor metabolisers biotransform medicines more slowly than average, resulting in higher concentration of the drug in the blood circulation. In practice poor metabolisers require lower doses of the drug to achieve a therapeutic effect and they are prone to adverse side effects. In other words, poor metabolism is seen in people who have the genetic inability to metabolise a drug efficiently. For example, 33 percent of African Americans and 37 percent of Asians are slow metabolisers of several antipsychotic

medications and antidepressants (Lin et al., 1997). The second group is those with an allele that is functioning normally, and they are called extensive metabolisers. Extensive metabolisers are able to biotransform a medicine at a normal and expected rate and therefore in practice, require the recommended dose of the drug. The third group have an allele that is very fast at metabolising a drug and they are called ultra-extensive metabolisers. These people biotransform a drug at a much higher rate than most people, and in practice will need a higher medicine dose to achieve therapeutic effect. In Physical Medicine for example, tamoxifen is known to be less effective in non white patients because non white patients tend to be ultra extensive metabolisers of this drug. With respect to psychotropic medication, there is evidence suggesting different types of psychotropic medication are metabolised differently in different people including racial groups.

[B] Antipsychotics

It is well known that there is wide variability in clinical response and adverse side effects tolerability of antipsychotic medications in individuals. Typical antipsychotics like haloperidol are effective in about 70% of the patients in predominantly alleviating positive symptoms like delusions and hallucinations (Wilffert *et al.* 2005). They are also limited in their use because they induce adverse side effects and are less effective in treating negative symptoms. On the other hand, atypical antipsychotics usually treat both positive and negative symptoms but patients show heterogeneity in their response to treatment. This variation is supported by promising evidence from epidemiological and pharmacogenetics studies that suggest a strong link between drug response and genetics (Foster *et al.* 2010). Since the middle of 1990s, hundreds of studies of pharmacogenetics of antipsychotic drugs have been published, making it a rapidly growing research area. Twin and family studies suggest that response to antipsychotics medication is a heritable trait. Studies of single pairs of monozygotic twins observed similar response to treatment with antipsychotics (Mata *et al.* 2001; Vojvoda *et al.* 1996) and have similar levels of drug induced weight gain (Wehmeier *et al.* 2005). Studies of siblings and first-degree relatives have demonstrated similar levels of treatment-induced tardive dyskinesia (TD), movement disorders, and response to medications. There is also preliminary evidence to suggest that the side-effect profiles of second-generation antipsychotic medications and their propensity to cause weight gain, glucose and lipid abnormalities as well as tardive dyskinesia is related to genetic factors (Patsopoulos *et al.* 2005). Such knowledge has clinical application that will ultimately drive choices of antipsychotic medication based on the likelihood of clinical response and

development of side effects in light of a particular patient's genetic profile. This is particularly so in different ethnic and racial groups, where clear differences in antipsychotic response have been consistently noted (Wolinsky 2011; Burroughs *et al.* 2002). For example, an early study found that when given comparable doses of medication, Chinese patients with schizophrenia and Chinese normal volunteers showed plasma haloperidol concentrations that were approximately 50% greater than their Caucasian counterparts (Lin *et al.* 1988). At the same time, the study showed a greater prolactin response to haloperidol in Chinese than Caucasians. Recent studies (Subramaniam *et al.* 2007) have supported earlier findings. In a study that examined metabolic disturbances in different ethnic groups Subramaniam *et al.* (2007) found that there were no ethnic differences in the mean plasma clozapine concentration between Asian and Caucasian despite Asians being prescribed lower doses of clozapine. However, Caucasian patients suffered more metabolic disorders than Asian patients. In the UK, clozapine is used much less among African-Caribbean patients than other ethnic minorities (Mallinger and Lamberti 2006). Lower normal ranges for white blood cell counts in these patients (benign ethnic neutropenia) may partly explain this discrepancy that has also been observed in Middle-Eastern ethnic groups. Ashkenazi Jews also appear to have an increased susceptibility to clozapine-induced agranulocytosis (Whiskey and Taylor 2007). The cross ethnic variation to antipsychotic is now supported by a recent meta-analysis that has found that the gene variant Gly9 is associated with a significantly higher risk of developing tardive dyskinesia in people of Chinese origin than Caucasians (Bakker *et al.* 2006). This provides a clear example of the potential clinical application of pharmacogenetic information, especially when combined with relevant environmental and clinical information. In many respects, the relationship between a person's genetic and how they respond to antipsychotics mirrors the relationship between genetics and antidepressants.

Antidepressants

In the ground breaking and recently completed Sequenced Treatment Alternative to Relieve Depression (STAR*D) study, in which patients with major depression were followed for up to 6 years, only 37% achieved remission on first line therapy and a further 16% withdrew after suffering adverse drug effects (Zandi and Judy 2010). Up to 60% of depressed patients did not respond completely to antidepressants and up to 30% did not respond at all. It is estimated that genetic factors accounted for as much as 50% of antidepressant response (Crisafulli *et al.* 2011). Clearly, antidepressants do not work as well for everyone and this is true for psychotropic medication in general. With respect to Serotonin Reuptake Inhibitors

(SSRI), although they have quickly gained popularity and are the most widely used antidepressants, they like any other psychotropics, are only effective in a subset of patients and are associated with certain adverse side effects such as weight gain and sexual dysfunction. One serotonin allele that has been identified as a “target gene” is the serotonin transporter gene (SLC6A4) which has alleles that have been shown to influence clinical response in Caucasians treated with SSRIs (Zandi and Judy 2010). In general, huge differences in the way antidepressant drugs are metabolised in different individuals have been consistently shown across many types of antidepressants.

In terms of race and ethnicity, there are key differences across ethnic groups in the way people respond to antidepressants. Recently, two meta-analyses of pharmacogenetic studies of antidepressants have reported associations between some serotonin gene variants and treatment response (Serretti *et al.* 2007). In their meta analysis of 15 studies, Serretti *et al.* (2007) found that one serotonin allele was associated with better treatment response and better remission rates. In the second meta-analysis of, 9 studies found, that the same gene variant was also associated with reduced side effects profile in patients (Kato and Serretti 2010). In addition, it is known that CYP2D6 enzyme that is abundant in the liver and is involved in the metabolism of many psychotropic medications including antidepressants is associated with a tendency to develop toxic reactions. Therefore, individuals who use the CYP2D6 to metabolise psychotropics are likely to develop extrapyramidal side effects and weight gain (Arranz and Kapur 2008). The distribution of CYP2D6 allele varies geographically, with up to 10% of Caucasians and up to 2% of Asians using this gene variant to metabolise psychotropics. Similar cross ethnic variation has been observed with other CYP enzymes and some candidate-genes have already been identified, showing promising results (Monnin *et al.* 2009).

With respect to tricyclic antidepressants for example, early studies have reported that Caucasians appear to have lower plasma levels of tricyclic antidepressants and attain plasma peaks later when compared with Asians from the Indian subcontinent (Rudorfer *et al.* 1984). These differences have been attributed to a greater incidence of slower pharmacokinetics among Asians compared with Caucasians. Mood stabilisers like all psychotropic drugs are influenced by genetics in their metabolism.

Mood stabilisers

Carbamazepine is a widely used drug for the treatment of epilepsy and is a mood stabiliser. In rare cases, carbamazepine causes life threatening hypersensitivity reactions, including Stevens– Johnson syndrome. The risk of these events is estimated to be up to six per 10,000 new users in countries with mainly Caucasian populations and the risk multiplies tenfold in Asian populations (Lim *et al.* 2008; Farkas 2007). A striking genetic association with carbamazepine was detected in a sample of Han Chinese in Taiwan, where a gene variant (HLA-B*1502) was present (Lim *et al.* 2008). In this sample, 100% of people who suffered carbamazepine-induced Stevens Johnson Syndrome, had this gene variant compared to only 3% who had other gene variants (Chung *et al.* 2004).. These findings were replicated in subsequent series across Asia (Mehta *et al.* 2009; Hung *et al.* 2006; Lochareonkul *et al.* 2008) but not in Caucasians (Lonjou *et al.* 2006). Based on these studies some regulatory bodies including the European Medicines Agency and the US Food and Drug Administration recommend HLA genetic testing in at-risk populations such as Chinese prior to initiating carbamazepine therapy (Ferraldeschi and Newman 2011).

Implications of pharmacogenetics in mental health practice

The main clinical application of pharmacogenetics is to be able to predict which patient will benefit from which drug based on genetic information. The clinical utility of this science is evolving and this should facilitate delivery of individually tailored treatment to maximize treatment response and minimise adverse drug induced side effects. Clearly, this is in line with the Recovery Approach principles. In the area of antipsychotic drug treatment, research from the past two decades has provided converging evidence that several genetic polymorphisms are capable of predicting treatment response or adverse drug-induced effects. These findings have been replicated in a number of studies, in various ethnic groups and different medications (Zhang and Malhotra, 2011). Since most of the variation comes in the form of inactivation or reduction in activity in the enzymes, the result is higher amounts of medication in the blood, triggering untoward side effects. This awareness should lead to more cautious prescribing practices, which usually mean starting patients at lower doses in the beginning of treatment. Unfortunately, just the opposite is true for some ethnic minority groups. The combination of slow metabolism and overmedication of antipsychotic drugs in people of African or Chinese descent can yield very uncomfortable extrapyramidal side effects. (Sussman *et al.* 1987) have asserted that these are the kinds of experiences likely to contribute to the mistrust of mental health services reported by some ethnic minority groups. Greater awareness of the role of pharmacogenetics is expected to improve treatment

effectiveness in psychiatry. However, a number of issues need to be resolved before pharmacogenetic findings can be meaningfully applied to clinical practice and this is clearly evidenced by the licensing of Isosorbide Dinitrate and Hydralazine hcl(BiDil).

In the USA, the Food and Drug Administration (FDA)'s approved BiDil, as the first drug to be licensed for a specific ethnic population, namely self-identified blacks. However, BiDil remains mired in controversy over race-based medicine. This controversy has played out mainly in the USA but has important implications worldwide for the future of personalised medicine. There is compelling evidence of BiDil's efficacy (Sengun et al., 2008). No other drug combination has been shown, under similar circumstances, to have such a large survival advantage, and improvement in time to first hospitalization and quality of life in African Americans with heart failure (Seguin *et al.* 2008). However, the problematic nature of racial classification has generated heated debate as to the clinical utility of pharmacogenetics (Duster 2007). Physical traits commonly associated with "racial groups" such as skin colour, facial features are superficial to the response to drugs and therefore race is an imprecise proxy measure of these genetic differences (Burroughs *et al.* 2002). The picture is further complicated by the well-documented contribution of environmental, clinical, and demographic factors, which are difficult to study.

In reality, race and ethnicity should be considered along with cultural and environmental factors such as age gender, diet, smoking, family influence, climate and pollutants to name a few. These factors may operate independently or interactively. However, in spite of the role of environmental and cultural factors in drug response and tolerability, it is still generally accepted that genetic factors are the major biological determinants of drug response and responsible for many differences in pharmacological activity among patients. They may account for 60–90% of drug variability in drug disposition and pharmacodynamics and for this reason, the clinical utility of pharmacogenetics is obvious (Cacabelos and Martinez-Bouza 2010). Prescribers can obtain genetic information along with all other factors that help to predict the individual drug response before the start of treatment and use this information to select the most appropriate drug for the patient. Ideally, a combination of genetic and non genetic information should be used for the selection of appropriate treatment, but genetic testing can be useful on its own as a pre-treatment test. In this regard, there is a growing trend towards moving away from the concept of "one drug fits all" to a rather more individualized and personalized medicine. The goal is to define the appropriate drug dose that maximizes

efficacy and minimizes toxicity in each individual patient. A good example of this is the role of the enzyme CYP2C9 genotyping in patients receiving oral anticoagulants.

In spite of its inherent challenges, chronic oral anticoagulation with warfarin is difficult to maintain within the therapeutic range and requires frequent monitoring and dose adjustments. This is due to genetically derived variation in metabolism of warfarin. Recent studies suggest that the pharmacogenomics-guided dosing algorithm can accurately predict warfarin dosage and might reduce adverse events (Ferraldeschi and Newman 2011). Therefore, incorporating pharmacogenetic testing or biomarker measurements into treatment algorithms has the potential to speed up recovery by shortening or eliminating current lengthy and at times ineffective trial and error approach. It is without doubt one of the most promising aspects of modern healthcare practice.

In the future, this targeted approach (Wolinsky 2011) may become informative for prescribers choosing a psychotropic medication for an individual patient with mental health problems. This view is supported by a recent study by (Serretti 2011) that evaluated the benefit of pharmacogenetics in antidepressant treatment in a group of 100,000 patients with a current episode of major depressive disorder receiving citalopram or bupropion. The authors found that, genetic test use was associated with an increase in antidepressant response and better tolerability although the cost to benefit ratio was very high. However, a recent Danish study found no difference in cost between one psychiatric treatment centre that recommended genetic testing and another that did not (Herbild *et al.* 2011). In spite of these optimistic findings, other investigators have expressed caution before adopting routine genetic testing in clinical practice at this stage. Fleeman *et al.* (2011) have carried out a systematic review of 47 studies that examined the role of Cytochrome enzyme to consider whether testing for CYP450 polymorphisms in adults on antipsychotic treatment predicts and leads to improvements in clinical outcomes. Currently, the evidence supporting the role of CYP2D6 polymorphisms in antipsychotic efficacy is inconclusive, although there is an association between CYP2D6 genotype and extrapyramidal adverse effects. The authors conclude that evidence supporting the clinical validity and utility of CYP2D6 testing in patients being prescribed antipsychotics is lacking, and thus, routine pharmacogenetic testing prior to antipsychotic prescription cannot be supported at present (Fleeman *et al.* 2011).

Conclusion

Technological advances have changed the nature of pharmacogenetic research and this has enormous implications on the future of healthcare in a general and that of mental health in particular. There is hope that drug treatment in future will be individualised, helping to minimize side-effects and identify patients sensitive or resistant to specific treatments. This is because in the last few decades, research has uncovered significant differences among people in the metabolism, clinical effectiveness, and side-effect profiles of many clinically important drugs including psychotropic medication (Barroughs et al., 2002). The full impact of these changes will take many years to unfold but genetic fingerprinting using DNA arrays is already practical. Ultimately, such approaches could drive choices of psychotropic medication based on the likelihood of clinical response and development of side effects in light of a particular patient's genetic profile. In the future, this targeted approach (personalized medicine) along with the influence of the public in agitating for better healthcare will have a profound effect on the ways mental health nurses deliver care that is orientated towards the Recovery Approach.

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