



# Should we be 'pushing meds'? The implications of pharmacogenomics

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## Should we be 'pushing meds'? The implications of pharmacogenomics

Medication continues to be the most widely prescribed treatment in the NHS for mental health problems. It has been known for many years that individuals differ in the way they respond to a given pharmaceutical therapy, and one reason for this lies in the genetic variation between individuals. This paper recognizes the impact that pharmacogenomics and pharmacogenetics are having in the field of mental health. Variants in genes that code for the drug metabolizing enzymes in the liver have been found to influence the way in which these enzymes handle psychotropic medication. Individuals can be classified as poor, moderate or extensive metabolizers when standard regimes are used, and this can lead to huge differences in therapeutic effect and toxicity. There are now genotyping tests available which provide information on the individual's ability to metabolize psychotropic medication. One author provides an account of the effects of medication on her son's physical and psychological well-being. Genotyping provided evidence for his poor metabolism of psychotropic medication, and his life is now changing as he is being very gradually weaned off this medication. This emerging field of work has implications for the way in which practitioners consider medication adherence.

**Keywords:** carer's narrative, genotyping, liver enzymes, medication adherence, pharmacogenetics, pharmacogenomics

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## Introduction

In 2005, the Healthcare Commission in the UK found that, on average 92% of mental health clients had taken medication in the previous year (Healthcare Commission 2007). At ward level, 91% take two or more medications for mental and physical health problems. Taking medication is not without risk, however, and it is clear that certain individuals have severe reactions to medication regimes. There is now an association between antipsychotic medication and the development of diabetes and cardiac disease in this client group (Lieberman 2004). It is also now recognized

that a given individual may not have sufficient enzymes in the liver to metabolize their medication effectively (Arehart-Treichel 2006).

While it is likely that many nurses are becoming aware of the metabolic syndrome link with medication, most are unlikely to know of the idiosyncratic nature of liver metabolism. This paper aims to inform psychiatric nurses as to the importance of the idiosyncratic nature of metabolism to individual experiences of medication.

In doing this, the paper is divided into two sections: the professional perspective discusses the implications from a clinical perspective while the carer perspective gives a

graphic account of a families experience with medication. In this division, there are areas of agreement, but also areas of potential conflict.

## Pharmacogenomics and pharmacogenetics

Pharmacogenomics and pharmacogenetics are often used synonymously. Though there are specific differences, the terms are frequently used interchangeably in literature. Pharmacogenomics is the name given to a broad-based pharmaceutical industry-led initiative, derived from the developments brought about by the Human Genome Project, the aim being to develop new therapeutic targets and interventions and also to investigate the constellation of genes that determine the toxicity and efficacy of specific medications (Williams-Jones & Corrigan 2003). Pharmacogenetics is the study of the genetic basis of drug response and is concerned with the assessment of a drug's clinical efficacy and safety profile. 'It is primarily focused on understanding how an individual's response to medication may be affected by their genetic make up (genotype)' (Martin & Morrison 2006). It is not routine practice to consider pharmacogenetics, and therefore, the failure of standard therapies is quite common (Moffat & Dawson 2001).

## Drug metabolism

As practitioners, an aspect of our role is to understand the effects of medication on an individual. It is now well recognized that individuals respond differently to medication and that, in addition to environmental factors, their genetic make-up can significantly alter the response to a drug, at times this can result in adverse drug reactions (ADR) (Kirk *et al.* 2006). Much metabolism is mediated through the hepatic and gut drug-metabolizing system known as the cytochrome P450 (CYP 450) enzyme system (Stahl 2000). One of the principal sites for drug action are enzymes, as proteins that act as catalysts enzymes are important in controlling the rate of chemical reactions in the body (Kelly 1995). Cytochrome P450 enzymes are concentrated in the liver (though also present in the tissues of other organs such as the kidney and lungs) and are of primary importance to the pharmacokinetics of psychotropic medication. In the 1970s, it was discovered that one liver enzyme-cytochrome P450 2D6 (CYP2D6) was important for metabolizing psychotropic drugs, and it is now known to be involved in breaking down 75% of all psychotropic medication (Arehart-Treichel 2006).

The varying levels of cytochrome P450 enzyme activity in individuals, determine the speed of metabolism of a drug, and therefore the plasma level, efficacy and adverse effects (Gillman 2006). Not all individuals have all the

same cytochrome P450 enzymes, and in these cases the enzyme is said to be polymorphic and an example of this is about 5–10% of Caucasians are poor metabolizers via the enzyme CYP2D6, which means they must metabolize drugs by alternative routes which may not be as efficient as CYP2D6 (Stahl 2000).

Besides the effect of the respective genotypes on the metabolizing capacity, the processes of CYP450 induction and inhibition may have a large effect on drug elimination and therefore influence their efficacy and toxicity (Bondy & Spellmann 2007). Enzyme inhibition generally involves competition with another drug for enzyme binding sites and enzyme induction increases the activity of the enzyme over time, because it induces the synthesis of more copies of the enzyme (Stahl 2000). Many individuals diagnosed with psychosis are on multidrug regimes and the potential for enzyme inhibitory reactions, and an increased rate of ADR is great (Bondy & Spellmann 2007).

## Genetic inheritance

The genetic characteristics of an individual influence the biochemical factors that affect the absorption and metabolism of medication. It is already recognized that certain populations metabolize medication differently, and there are ethnic differences in hepatic enzymes which influence the pharmacokinetics of drugs. For example, the incidence of poor metabolism of CYP 2C19 is much higher in some Asian subgroups (15% up to nearly 100%) than in Caucasians (3–6%) (Gillman 2006), while approximately 5–10% of Caucasians are poor metabolizers via the CYP enzyme 2D6 (Sharif 2003).

CYP 450 enzymes show large interindividual differences in activities owing to genetic variants. This can lead to individuals being distinguished as poor, intermediate, extensive or untrafast metabolizers (Bondy & Spellmann 2007).

There are few studies considering clinical relevance; however, De Leon (2005) has published results from such a study, the cytochrome P450 2D6 (CYP2D6) enzyme metabolizes risperidone, and 7% of whites and 1–2% of other races are CYP2D6 poor metabolizers. This study considered whether those individuals who were shown by genetic testing to be poor metabolizers of risperidone (with no CYP2D6 activity) had ADR (side effects) when taking risperidone and discontinued risperidone because of this. Though further study is required, initial findings suggested that the CYP2D6 poor metabolizer phenotype appears to be associated with adverse side effects and resulting discontinuation of risperidone.

The use of pharmacogenetics has consequences for the selection of therapeutic regimes, as drug absorption and

metabolism are influenced by the individual's genetic inheritance, importantly those enzymes involved in the metabolism of psychotropic medication. Variants in genes that code for the drug metabolizing enzymes in the liver are being found to influence the way that these enzymes handle psychotropic medication (Arehart-Treichel 2006).

### Impact of medication

All practitioners recognize that some of the service users they work with need very small amounts of medication before they become affected, others are prescribed large doses yet seem immune and a third group experience severe adverse effects with seemingly no therapeutic effects. If classified as a poor, moderate, extensive or ultra fast metaboliser when standard regimes are used, this can lead to huge differences in therapeutic effect and toxicity (Moffat & Dawson 2001). The science of pharmacogenetics begins to explain this and suggest solutions, where the prescribing of psychotropic medication would become a more precise process, as genetic tests are given to recognize which individuals are deficient in the cytochrome P450 enzymes and therefore 'poor metabolisers' of psychotropic medication (Gillman 2006).

### Testing

Diagnostic kits have been developed by pharmaceutical companies which analyse CYP2D6 and CYP2C19, two genes in the cytochrome P450 system that influence psychotropic drug metabolism. There are clear financial implications for treatment; though the initial test needs to be funded, they have to have the test once in a lifetime as genes do not change, testing patients for variants in the genes that code for CYP2D6 and CYP2C19 costs between \$200 and \$500 (Arehart-Treichel 2006). This is an important factor as, although the individual's ability to metabolize medication on a day-to-day basis will be affected by many factors such as age, gender, body mass, ingested food at time of medication and even nicotine levels, these are variables while the genetic marker is a persistent and major influence (Mann & Pons 2007). The work is emerging and there is as yet no detailed cost analysis. It is anticipated that if genotyping leads to increased adherence owing to decreased adverse effects, then there would be financial savings with decreased admissions and use of services. The greatest benefit would be in social capital as individuals regain their daily functioning, having previously been incapacitated by illness and adverse drug effects.

In Sweden, there is a recognition that genetic screening can determine which individuals are 'poor metabolisers' of psychotropic medication and treatment regimes can be tai-

lored to minimize the risk of potentially fatal side effects (Dahl & Sjoqvist 2000). Other healthcare specialties are also examining the implications of genetic screening with regard to medication efficacy, such as those concerned with epilepsy (Mann & Pons 2007) and Alzheimers (Poirier *et al.* 1995).

### Clinical implications

In the latest report in the UK from the National Confidential Inquiry into Suicide and Homicide by People with Mental Illness, clinicians identified factors which would have made the reported homicides less likely. The most cited factor was better compliance with treatment, and invariably medication was one of the main features of treatment (Appleby 2006). This suggests that clinicians believe that drug treatment is an essential factor when considering the level of risk an individual poses to both him/herself and society. The factor frequently disregarded in this equation is the evidence that a substantial proportion of patients with, e.g. psychosis, fail to make even an initial response to medication (they may be poor or ultrafast metabolizers) and many relapse in spite of ongoing drug treatment. However, the dominance of drug treatment continues to help create the impression that psychiatric conditions are easily treatable and drug treatment is effective for all (Moncrieff 2003).

Adherence therapy has emphasized an individualized, collaborative approach to medication compliance, ensuring that the service user is listened to, while working to achieve the lowest possible dose to ensure the lowest level of ADR. However, in a multisite randomized controlled trial, adherence therapy was no more effective than health education in improving quality of life for the service user (Gray *et al.* 2006), and so the effectiveness of this intervention, based on a collaborative approach between practitioners and service users, loses some credibility. This means that there is the potential for this systematic individualized approach to be sidelined. Yet, there are benefits for service users in taking medication. When attempting to reduce or come off medication, some service users found that they needed medication (Read 2005).

A further disquiet when administering medication is that adverse effects remain of concern and that concern is increasing as second generation antipsychotic medication, atypical antipsychotics, are linked to the potentially life-threatening syndrome referred to as the metabolic syndrome, which includes obesity, type 2 diabetes mellitus, hyperlipidaemia and diabetic ketoacidosis (Lieberman 2004, Usher *et al.* 2006).

It may seem logical to withdraw the patient from medication; however, this can have consequences. The discon-

tinuation of clozapine and possibly other antipsychotic drugs, in some individuals, may precipitate a rapid onset psychotic episode which is distinct from the underlying illness. That is, the withdrawal provokes a psychotic episode named supersensitivity psychosis (SSP) which can be very difficult to differentiate from the recognized psychosis (Moncrieff 2006).

At the beginning of drug treatment, any knowledge regarding the CYP 450 genotype may be helpful, as initiation with lower doses in poor metabolizers is liable to decrease the adverse effects and consequently increase adherence (Bondy & Spellmann 2007).

There is a current convincing argument suggesting that implementing evidence-based care when prescribing would require the selective use of antipsychotic medication based on two principles: no immediate administration of antipsychotic drugs for first-episode patients; every patient stabilized on antipsychotic drugs should be given the opportunity to gradually withdraw from them (Whitaker 2004).

While this discussion has been mainly centred around the physiological aspect of the patient, it must not be forgotten that there may be serious personal and social consequences from the effects of medication. These consequences are highlighted in the following case study, where a carer presents her perspective about the care of her son whose abnormal reactions to drugs were already evident in childhood.

### **A carer's perspective**

I am writing this as the carer of my son who has experienced psychosis and offer my perspective on the impact of pharmacogenomics in relation to my son's treatment. I cannot ignore my background in mental health nursing, and as I am not affiliated to any carer or professional mental health body on a salaried basis, I am able to write freely from my carer's subjective perspective. This flexibility with having no conflict of interests, enables me to introduce mental health research knowledge to support my opinions, but I do not intend this account to do more than express my own perspective.

My son is currently diagnosed with schizophrenia; however, in the light of his recent genotyping test that shows that he is a poor metabolizer for CYP450 2D6 and an intermediate metabolizer for CYP450 C19, I believe that the diagnosis is incorrect and a more accurate description would be 'Deficient Metaboliser – Iatrogenic Psychosis'. My first hand experience of the debilitating iatrogenic effects of his drug therapy illustrates the need for genotyping to become a more widely available course of action for people being prescribed psychotropic drugs.

### **Early experience**

My experience as a nurse has highlighted awareness of the many potential side effects and adverse reactions to all drugs. I am also aware that my son's adverse reaction to drugs can be traced back to his childhood. As a toddler, he became unconscious, following a standard dose of Calpol and Sudaphed, and years later, on emerging from a general anaesthetic, became uncharacteristically verbally aggressive. His reaction to being prescribed Prozac for depression was rather more serious, resulting in an acute psychotic episode which then became the focus for different treatment. Doubling the dose of Prozac in the preceding week appears to have triggered this initial psychosis.

### **Iatrogenic effects of polypharmacy**

At the time of diagnosis, no thought was given to his behaviour being an adverse reaction to the Prozac. In order to try and control the symptoms, a range of psychotropic drugs were prescribed and strong reactions would occur within a few days of starting an antipsychotic drug, regardless of whether it was typical or atypical. Both polypharmacy and dose increases worsened the degree of adverse reactions that he experienced.

Within the first few days of taking an atypical drug, extra pyramidal side effects (EPS) started, which was only minimally alleviated by Procyclidine. When prescribed Clozapine, which acts like Haloperidol at high levels (Suhara *et al.* 2002, Takano *et al.* 2006), my son developed a very fine body tremor, discernable by holding his wrist. At a medium dose of Clozapine, he salivated excessively, so much so that his pillow was wet through nightly. I was worried about the potential of him choking to death through his spittle. When one atypical drug was increased, I discovered the metal base of his hospital bed swimming in his excessive body perspiration. As Sulpiride was increased, he developed akathisia, which caused him to pace round and round our home, upstairs and downstairs, up the garden and back again for all his waking hours. The psychological impact was profound with an extreme inner restlessness that led him to say that he would rather commit suicide than to live the remainder of his life in torment. His moods changed between laughing 1 min and sobbing the next.

During the first year, as my son's condition spiralled downwards, I was disturbed to discover antipsychotics caused tardive dyskinesia (TD) and began to dread this appearing. So when he developed TD, I knew that this was connected with short-term memory loss and Alzheimer's disease and additionally the early appearance would indicate a 'poor outcome', which is illustrated by the long

periods on an acute ward and eventual admission to a secure unit. His involuntary movements have included puffing out of his cheeks, tongue protrusion and snaking, finger 'guitar' movements, swaying of his trunk and facial grimacing.

Later treatment included Acuphase which was combined with his base prescription of Risperidone, Diazepam and Haloperidol. This concoction induced signs and symptoms similar to neuroleptic malignant syndrome (NMS) (Pelonero *et al.* 1998) which fortunately did not develop to full blown NMS, as a nurse recognized that my son was deteriorating and one atypical dose was reduced. My son regressed emotionally and became delusional, and even refused an electrocardiograph to assess his cardiac function. The EPS was severe and distressing; his hands banged noisily on the table and because he salivated continuously, the skin on his lips came off from wiping them. His speech became so slurred that staff referred him for speech therapy, he was unable to walk and urinated on the floor. When he fell over, he needed assistance to stand up.

Watching my son's physical and emotional downslide was very traumatizing. On being discharged home from a secure unit, my son was like a robotic being with no motivation, apathy and indifference. He slept for 18 h 1 day, and apart from basic functions of self-care, such as eating and bathing, he had no will to read, watch television, listen to music, make a sandwich, converse with me or the rest of his family or even to leave the house on his own. His low level of concentration compounded his situation. His self-awareness was minimal, so when I took him for a walk I had to tell him to stop at the curb to wait for the traffic to pass by before crossing the road. The quality of his life was very low indeed.

### Professional concern

The Care Trust staff appeared to be aware at some level of my son's sensitivity to antipsychotics, for one psychiatrist embarked upon a section 3 (section 3 is part of the Mental Health Act which enables a person to be detained in hospital for a 6-month minimum period for treatment) prior to a course of Acuphase, which, according to a member of staff, was specifically embarked upon to act as a protection for clinical staff should this treatment lead to my son's death. I became distraught seeing him suffer and thought that my son was going to die.

Following the genotyping test, I now know that Acuphase, Haloperidol and Risperidone are metabolized through the CYP450 2D6 and Diazepam through CYP450 C19, the very pathways for which my son is deficient. Because of the build-up of antipsychotics within his body, he experienced repeated psychosis known as SSP

(Moncrieff 2006). The brain's natural adaptation to recompense the decreased dopamine in the dopaminergic synapses results in an increase of dopamine receptors and increased sensitivity and psychosis ensues. My son's medical notes clearly show this pattern. With each raised antipsychotic dose, he was initially emotionally sedated with a reduction of delusions and hallucinations. Over a period of 1 or 2 weeks, the psychotic symptomology would return with ever increasing intensity. In light of this knowledge, two psychiatrists agreed with my suggestion to withdraw the antipsychotics.

### Withdrawal

Withdrawal from antipsychotics was another nightmare experience. The speed of withdrawal proved crucial, as an abrupt withdrawal induced a neuroleptic discontinuation syndrome (Tranter & Healy 1998), alternatively known as tardive psychosis or rebound psychosis: a 'cold turkey' reaction affecting him physically and psychologically.

Following an agreement, my son commenced an antipsychotic drug-free period, though benzodiazepines were prescribed as necessary. Although the psychiatrist informed me that my son may become ill again, I did not know that it was virtually inevitable that he would experience a tardive psychosis because of the abrupt cessation of antipsychotics. After 6 days, my son started to experience hallucinations, which increased in severity, and his rapidly declining state distressed the nurses who were instructed only to give medication in an emergency. In the end, at the height of his terror, he had to take antipsychotics; he had no alternative.

Benzodiazepines, previously classified as minor tranquilisers, are recognized as causing dependency, and therefore it seems obvious that the stronger atypicals, and typicals, previously classified as major tranquillisers, will cause physical dependency. As my son fulfils the DSM-IV criteria for dependency, I think he is clearly dependent on antipsychotic drugs; this necessitates a very gradual withdrawal and even then with minimal reductions, he occasionally experiences physical withdrawal symptoms such as nausea, vomiting, heightened olfactory sensations, rebound insomnia, stomachache and mental alertness.

It would appear highly likely that the degree of antipsychotic dependency and ease of withdrawal correspond with the dysfunction of the metabolizing pathways. With each recurrence of SSP and tardive psychosis, my son within his delusional and hallucinatory experiences became increasingly physically and verbally aggressive, which was completely out of character with my knowledge of his previous behaviour. The excessive antipsychotic drugs in his system appeared to induce irrational anger – a charac-

teristic which appears to tally with reports that associate hostility and violence with high levels of antipsychotics (Herrera *et al.* 1998).

### Current situation

With a unique computational withdrawal programme for the antipsychotic drug of less than 5% per month, in cooperation with the outreach team, we have significantly reduced the risk of my son going 'cold turkey'. With my knowledge of Prouty's pre-therapy (Prouty *et al.* 2002), which enables me to make 'contact' with him on the rare occasions where his healthy functioning slips, my son continues to withdraw safely and securely at home.

Two and a half years after the start of the reduction programme, the chemical toxicity from the antipsychotic drug has been considerably reduced, and my son is changing in a very positive way. His healthy functioning, together with his self-awareness, is gradually increasing. He is able to go cycling and walking independently, and his concentration levels have improved, and he reads physics and chemistry research and plays games on the computer. He has started to initiate conversation and recently chose to have his hair cut for the first time in over 3 years. His emotions are returning, which is so important for him to be able to lead his life to his full potential.

### Professional implications

In the case study described, it is clear that genotyping provided scientific evidence for the young man's ADR and lack of therapeutic response; however, a careful individualized assessment, including both the service user and his carers, could also have provided this evidence. It is possible for genotyping to be considered 'the answer'; however, Williams-Jones & Corrigan (2003) rightly warn that pharmacogenomics is being driven by powerful actors in the biotechnology and pharmaceutical industries, various government departments and at times patient groups which will publicize their own agenda rather than having the individual's benefit as the sole agenda. However, this should not lead to the potential of genotyping being ignored.

There are implications for education, as Kirk *et al.* (2006) suggest that there is a need to support practitioners in becoming confident in applying genetics to their role; they cite the establishment of the NHS National Genetics Education and Development Centre, established in 2004, as being critical to this process. Matchar *et al.* (2006) recommend prospective studies of CYP450 genotyping in the treatment of non-psychotic depression with selective serotonin reuptake inhibitors to examine the utility of genotyp-

ing in routine practice. However, De Leon (2005) suggests that there are already enough results available which have implications for practitioners.

The potential of genotyping for medication is a real possibility in the future. As nurses are being trained to become medication prescribers as well as medication administrators, they need to be aware of the potential benefits offered and to keep abreast of ongoing developments and research.

### Discussion and conclusion

It would be easy to conclude that genotyping, although still in its infancy and not without process problems, can provide confidence in prescribing medication regimes, with the possibility that medication decisions are based on scientific evidence. However, the case study illustrates that evidence was there of over-prescribing, though it was not scientific but rather based on observation of the individual, his self-report and that of his carer's. From the beginning, the inability to metabolize the medication was apparent to any watchful eyes.

The problem for practitioners where a person does not have sufficient therapeutic effect from their medication is, what else to do, particularly when the individual is clearly distressed. Although a number of talking therapies are delivered with good effect in the treatment of mental health problems, their availability remains inconsistent and dependant on local priorities, expertise and resources (Brooker & Brabban 2005). Medication remains the main treatment offered; despite this, the basic process for the prescribing and administration of medication having changed little over the years, frequently nurses question whether they should be giving medication at all.

A scientist who carried out work on the CYP450 enzyme years ago stated:

Don't rely on tests, look at the patient and use tests to confirm a hypothesis when it might be useful. It is undoubtedly true that understanding the science behind variations in capacity to metabolise drugs, and the potential for drug interactions lends scientific credibility to the premise that every patient needs to be treated, assessed and monitored as an individual. One cannot throw in a cocktail of drugs without synergistic consequences, whether foreseeable or yet to be determined. (Dr S. Yates, 2007, pers. comm.)

A few years ago, practitioners working with pain developed the mantra 'pain is what the patient says it is'. In the case study, the evidence of lack of therapeutic effect and the presence of ADR was readily available, yet the medicating continued, perhaps the mantra could be 'side-effects are what the patient says they are.'

It is easy to recommend that training be given, yet guidelines are already in place (NICE 2002). In the UK, the Royal College of Psychiatrists take the issue very seriously and have produced a consensus statement on high-dose antipsychotic medication (RCP 2005). They note that up to a quarter of psychiatric inpatients are prescribed a high level of antipsychotic medication, though there is limited data on the prescribing of these drugs in the community. They state:

The results of the published trials of high-dose antipsychotic medication for treatment-resistant schizophrenia provide no evidence to support such a strategy. On the basis of current evidence, high dose prescribing, either with a single agent or combined antipsychotics, should only be used and then only for a time limited trial in treatment-resistant schizophrenia after all evidence-based approaches have been shown to be unsuccessful or inappropriate. (Royal College of Psychiatrists 2005, p. 6)

This paper is primarily about the use of genotyping to identify individuals unable to metabolize antipsychotic medication; however, there are implications for basic care, issues around listening to the service user and carer, then utilizing individualized therapies such as psychosocial approaches, solution-focused approaches, psychotherapy, problem solving and suchlike, wherever there is a delineated evidence base. The difficulty for any practitioner is when they have no other answer to the patient's distress than to medicate them. This needs to be done by the multidisciplinary team in collaboration with the service user and carer whenever possible, carried out thoughtfully, gradually and carefully following current guidelines, alongside the consideration that for some genotyping provide clear scientific evidence for reduction or discontinuation of psychotropic medication.

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