Neuroleptic Awareness
Part 7

Pharmacogenetics

Introduction

Pharmacogenetics is the study of individual inherited variations influence on medication response in relation to how drugs are metabolised or broken down in the body.

Knowledge of pharmacogenetics is important for all doctors and people who take medications as it provides the basis for understanding the reason why some patients experience a beneficial response with minimal side effects, in contrast with others who get severe side effects and no therapeutic effect.

Introduction cont…

Although pharmacogenetics is used by pharmaceutical industries in drug trials, the science is generally unknown to doctors because of the lack of education at British Medical Schools.

Additionally lack of awareness is exacerbated by industries failure to incorporate pharmacogenetics into their public data i.e. the Summary of Product Characteristics (SmPC) and the Patient information Leaflets (PILs). SmPCs include medication side effect information and form the basis for the British National Formulary used by doctors. PILs have to be supplied with all UK medicinal products whether dispensed by the pharmacist or bought over the counter.
http://www.lirg.org.uk/lir/pdf/article80a.pdf

Pathway Variations

Medications are metabolised through many different pathways in the body and brain and therapeutic response and severity of side effects is determined by genetic variations.

75% of **psychotropic** medications including neuroleptics are metabolised through **CYP450 2D6,** a highly variable enzyme pathway found mainly in the liver.
"Gene Testing Could Help Predict Drug Responses" Arehart-Treichel J.(2005).
http://pnhw.psychiatryonline.org/content/40/10/33.1.full

Variations for the **CYP450** pathways include poor, intermediate, extensive and ultra fast genetic metabolisers.

Poor and Intermediate Metabolisers

Poor or slow Metabolisers (PMs), are inefficient metabolisers, have no metabolising activity and ***will not have a therapeutic response when neuroleptic drugs are metabolised through CYP450 pathways.***

When there is no metabolising activity, drug toxicities build up in the body and the increasing toxicity (poisoning) results in side effects or adverse reactions.

Intermediate Metabolisers (IMs) are able to metabolise drugs but at about a **50%** rate; side effects will occur, but not to the level of severity as in **PMs**.

Extensive and Ultra Metabolisers

Extensive Metabolisers (EMs) are efficient metabolisers, medications are mostly therapeutic and patients do not usually experience side effects.

Ultra Metabolisers (UMs) are inefficient metabolisers because medications either pass too quickly through the body having little effect or in the case of pro-drugs, e.g. Invega, toxic levels of the active metabolite build up rapidly.

When the dose is raised for **UMs** the medication is either effective or toxic depending on the type of drug used.

Neuroleptics and Pharmacogenetic Implications

When patients are prescribed neuroleptics and do not experience a therapeutic response, the lack of pharmacogenetic explanation results in psychiatrists raising the dose. Even though this would be within the suggested range according to the British National Formulary (**BNF)**, if patients are **PMs**, **IMs** and **UMs** (for prodrugs), no amount of neuroleptics will achieve the expected beneficial response.

Further more increasing the dose escalates toxicities, resulting in psychological side effects, which replicate symptoms of 'schizophrenia'; a spiralling circle ensues with psychiatrists increasing the dose in an attempt to control positive symptoms, that in turn exacerbates psychological and physical side effects.

Read the science:
"Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response." *Kircheiner J. et al. (2004)*
http://www.nature.com/mp/journal/v9/n5/full/4001494a.html

Implications for Schizophrenia & Bipolar Disorder

In the UK Schizophrenia affects around 1in100 therefore 600,000 people, *http://www.socialanxietyselfhelp.com/blog/2011/02/mental-health-in-the-uk/* and bipolar disorder in the UK, affects approx. 700,000 people. *www.bipolar-lives.com/bipolar-disorder-statistics.html*

Both schizophrenia and bipolar disorder are 'treated' with neuroleptics.

In schizophrenia it is known that approximately:

30% do reasonably well on neuroleptics.
30% relapse repetitively (revolving door)
30% do very poorly and are chronic sufferers

Overall: **60% of these 'treated' numbers do poorly**

Outcomes for Schizophrenia & Bipolar Disorder

The same **30%** outcome measures apply to all 'treated' with neuroleptics.

Number of patients in UK	Schizophrenia 600,000	Bipolar Disorder 700,000	Total 1,300,000
30% reasonably well with medication	180,000	210,000	390,000
30% repetitively relapsing with meds.	180,000	210,000	390,000
30% chronic sufferers with medication	180,000	210,000	390,000
Overall 60% with poor outcomes on meds.	360,000	420,000	**780,000**

Overall 60% - 780,000 - do poorly.

Ethnicity and Metaboliser Status

Poor and Intermediate Metabolisers for CYP450 2D6:

7-14% Caucasians - Poor Metabolisers

35% Caucasians - Intermediate Metabolisers

20-26% Europeans - Poor Metabolisers

40-50% Asians, Pacific Islanders, Africans (BME) - Poor Metabolisers.

http://www.healthanddna.com/healthcare-professional/p450-2d6-genotyping.html

Ultra Metabolisers for CYP450 2D6:

29% Ethiopians

21% Saudi Arabians

Benny K. Abraham et al (2001) http://medind.nic.in/ibi/t01/i3/ibit01i3p147.pdf

7% Caucasians

Linda S. W. Steijns et al (1998) http://www.clinchem.org/content/44/5/914.long

CYP 2D6 metabolises the majority of neuroleptics.

Ethnicity and Metaboliser Status

Poor and Intermediate Metabolisers for CYP450 2C19

10-20% Africans - Poor Metabolisers
24-36% Africans - Intermediate Metabolisers
5% Africans - Ultra Metabolisers
2-6% Caucasians - Poor Metabolisers
13-19% Asians - Poor Metabolisers
15-20% Japanese - Poor Metabolisers
http://www.healthanddna.com/healthcare-professional/p450-2c19-genotyping.html

CYP 2C19 is also relevant in metabolism of neuroleptics.

Combinations of Genetic Status

Multiple inefficient metabolising pathways can also have an effect on drug toxicity clearance:

26% of Europeans are a combination of **PMs** and **IMs** via **CYP450 2D6** pathway.

40% - 50% of Black and Minority Ethnic people are **PMs** and **IMs** via **CYP450 2D6** pathway.

Frequency of Various Genotypes in General Population

Frequency of Poor and Intermediate Metabolisers:

45% via **CYP450 2D6**
27% - 57% via **CYP450 2C19**
42% via **CYP450 2C9** pathways.

Frequency of Ultra Metabolisers:

7% via **CYP450 2D6**
30% via **CYP450 2C19**

http://www.healthanddna.com/healthcare-professional/pharmacogenetics.html

Schizophrenia and Genetic Metabolism

It is fair to suggest that 50% to 70%, i.e. approx 60% diagnosed with 'schizophrenia' are Poor, Intermediate or Ultra Metabolisers.

This correlates with the 60% who do poorly.
i.e. the same 60% who are Poor, Intermediate or Ultra Metabolisers.

30% correlates with those 30% who do *very* poorly and are likely Poor Metabolisers of psychotropic drugs.

Other Variable Neuroleptic Metabolising Systems

Other genetic variations that affect how patients process and react to neuroleptic drugs include:

CYP450 1A2 clozapine, olanzapine, haloperidol
Source: http://www.healthanddna.com/healthcare-professional/p450-1a2-genotyping.html

P-glycoproteins (P-gp's)
Source: Jun-Shen Wang et al (2006) http://www.springerlink.com/content/n346826657236753

U-glucuronisil transferases. (UGT's)
Source: Guillemette, C. (2003) http://www.nature.com/tpj/journal/v3/n3/full/6500171a.html

Catechol-O-methyltransferase (COMT) enzyme
Serotonin Transporter Gene (SERT)
Source: Jian-Ping Zhang et al (2011) http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057913/

All these genetic metabolising *variations* may incur inevitable side effects from neuroleptic medications.

Metaboliser Status and Side Effects

Patients prescribed neuroleptics who are Poor Metabolisers or Ultra Metabolisers for prodrugs, will develop side effects such as Tardive Dyskinesia, Extra Pyramidal Symptoms (Parkinsonism), Neuroleptic Malignant Syndrome and suicide.

Neuroleptic Physical Side effects:

Tardive Dyskinesia

Source: Nikoloff, D. et al (2002) http://www.nature.com/tpj/journal/v2/n6/full/6500138a.html

Extra Pyramidal Symptoms (EPS)

Source: Scordo, MG. et al (2000) http://www.ncbi.nlm.nih.gov/pubmed/11214775

Neuroleptic Malignant Syndrome.

Source: Ochi S. et al (2011) http://www.ncbi.nlm.nih.gov/pubmed/21749835

Neuroleptic Psychological Side Effects:

Suicide

Sources: Koski A et al (2006) http://www.ncbi.nlm.nih.gov/pubmed/16024198
Zackrisson AL et al (2010) http://www.ncbi.nlm.nih.gov/pubmed/19907421

Metaboliser Status and Side Effects

Akathisia **Homicide** **Violence** **Suicide**

CYP450 2D6 Poor and **Ultra Metabolisers** are associated with antidepressant medication induced suicide, violence and homicide in relation with serotonin toxicity/akathisia. *Source: Lucire Y. (2011)* *http://www.nt.gov.au/lant/parliamentary-business/committees/ctc/youth-suicides/Submissions/Sub%20No.%2016,%20Dr%20Yolande%20Lucire,%20Part%204,%20Sept%2030%20Sept%202011.pdf*

It is known that akathisia can develop very rapidly after initiating or increasing neuroleptic medication and treatment with neuroleptic drugs is acknowledged by the DSM IV to exacerbate the condition.

American Psychiatric Association. Schizophrenia and other psychotic disorders and Mood Disorders. *Diagnostic and statistical manualof mental disorders* (*DSM IV*), 4th ed. Washington DC: APA; 1994:273–391.

Most atypical neuroleptics are metabolised through the same **CYP450 2D6** pathway as antidepressants, therefore it is certainly possible **CYP450 2D6** variants will also be associated with homicide, violence, akathisia and suicide.

Non-Psychiatric Medications and Genetic Metaboliser Status

Dextromethorphan, a common ingredient in several prescriptions and over-the-counter cough preparations, has been associated with suicidality in a non-psychiatric patient, whose genetic status was **CYP450 Poor Metaboliser.**

Source: Matin et al (2008) http://www.ncbi.nlm.nih.gov/pubmed/17719518

Non-psychiatric tramadol and simvastatin medications are associated with akathisia in a patient who had multiple **CYP450** variants.

Suicidality and akathisia ameliorated on medication withdrawal, indicating that the behavioural effects were iatrogenic due to drug interaction with **CYP450** variants.

Metaboliser Status and Psychosis

It is difficult to locate a metaboliser reference source relating **Poor, Intermediate** or **Ultra Metaboliser** genotypes with neuroleptics and **Super Sensitivity Psychosis** i.e. spiralling toxic psychosis.

This is likely due to the industries' trial design, inadequate reporting and subsequent lack of side effect data, that limits research in the public domain.

However one non-psychiatric case study does depict a drug induced psychosis in a **Poor Metaboliser** resulting from a cough syrup containing Dextromethorphan.
Source: Matin et al (2008) *http://www.ncbi.nlm.nih.gov/pubmed/17719518*

Pharmaceutical Clinical Drug Trials

Pharmaceutical companies regularly use prospective genotyping tests in clinical trials, i.e. ‘genostratification’ to exclude **Poor** and **Intermediate Metabolisers** from the trials, thereby withholding sensitive psychological side effect information from public view.

It would not be in drug companies financial interests to admit to undesirable behavioural effects which would occur in **Poor, Intermediate** or **Ultra Metabolisers**.

Drug trial phases 2-5 exclude all **Poor Metabolisers** so the Summary of Product Characteristics excludes the most severe side effects, so as not to impede sales.

Drugs are marketed as a ‘one size fits all’ panacea with dose levels tailored to cater for **Extensive Metabolisers**.

Treatment Resistance

"Treatment resistance in schizophrenia is relatively common, in that between a fifth and a third of service users show a disappointing response to adequate trials of antipsychotic medication."
Source: NICE Guideline for Schizophrenia 6.5.1

When patients are unable to metabolise neuroleptics efficiently, it is inevitable they will ***show a disappointing response***; the worsening of psychotic symptoms is due to neuroleptic toxicities, often mistaken for signs of "disease".

Treatment "resistance" is due to common variations in patients' **CYP450** liver enzyme metabolising system.

When **70%** of non-responders are excluded from drug trials, this clearly accounts for the **60%** who do poorly in 'schizophrenia'.
Source: Benijts T. *http://cemo.fr/files/cemo_2004_n-4.pdf?phpMyAdmin=bd9gq8GpdTmKeSfqZo8kMOjYoBb*

Genotyping Test

A genotyping test is done with a simple mouth swab or blood test and can be obtained privately from: **www.genelex.com**

This service is available for both professionals and the public. For patients a referral from a doctor is not necessary, as self referrals are accepted.

The results are quick and sent to the recipient. A full follow up service is provided.

General Medicine and Genotyping

In general medicine genotype testing is being increasingly applied within the NHS prior to medication treatment for Leukaemia, Inflammatory Bowel Disease, Rheumatoid Arthritis, dermatological conditions, cancer and immunosuppressants following organ transplants.

In identifying patients' genetic status in connection with a specific medication, there are many benefits; it cuts down on financial costs, as trial and error prescribing is eliminated, potential emergency hospital admissions resulting from dangerous toxic adverse reactions are avoided. Patient safety is ensured by the genotype test when physical conditions necessitate treatment with toxic medications.

Mental Health and Genotyping

In mental health, genotype testing does not take place, despite the benefits when applied in general medicine.

DH acknowledges the ***'differences in drug handling across migrant, national and ethnic groups'***, thus implying their pharmacogenetic knowledge of inherited genetic variations in metabolising status impacting upon drug response in association with efficacy and toxicities. *Source: NICE Guidelines 5.3.1*

NICE has concluded pharmacogenetics would have to be cost effective and latterly has disowned responsibility for pursuing the genotyping test in mental health.

Personalised Medicines

One of the goals of pharmacogenetics from the pharmaceutical industry is to develop drugs that are tailored to the individual so they will give the maximum beneficial pharmacological effect with minimal side effects or toxicity.

This idealistic situation is aeons of time away due to the multiple complexities of metabolism with the known metabolism enzymes let alone those, which are yet to be discovered. An exact medication dose to fit an exact genotype is currently not realistic.

Personalised Medicines

What is realistic and practical is to use the available pharmacogenetic information in the interest of patient safety. When patients are genotyped before taking neuroleptics, the genetic status in **Poor, Intermediate** or **Ultra Metaboliser,** can inform clinicians' prescribing decisions as to the type of neuroleptic used and whether it is appropriate to keep the dose low.

Source: Jose de Leon (2006)
http://www.primarypsychiatry.com/aspx/articledetail.aspx?articleid=1698

Psychological side effects that often mimic a psychiatric diagnosis would be reduced and would go a long way to prevent patient dependency on the mental health system and facilitate progressive recovery. This action would also have a follow on beneficial effect for carers, nurses and doctors.

Government Funded Research

Whilst postponing further research on mental health and genotyping, the UK Government continues to allocate £millions on research projects for mental health.

These include:-
Trialling more psychiatric drugs for 'schizophrenia'; this research would incur similar psychological and physical health side effects with the associated heavy financial costs if the genotype test is not used prior to prescribing.

Cash incentives for neuroleptic adherence; when side effects described as ***"quite bad"*** to ***"intolerable"***, and excessive morbidity and mortality rates are acknowledged by the Government in NICE; these neuroleptic conditions are subsequently denied as having any relevance to patients.

SEE: http://www.hta.ac.uk/project/1929.asp AND: http://www.hta.ac.uk/project/1855.asp

Government Funded Research

The UK government funded Medical Research Council was granted £400,000 taxpayers money to find a gene responsible for 'schizophrenia'.
Source: *http://www.fbs.leeds.ac.uk/research/bulletin/index.php?id=1164*

Despite intensive research carried out over the past century, and more recently spectacular advances in molecular biology, no single gene variation has been found.

It would be fortuitous for the UK government to re-assess their mental health financial budget including expensive research projects and balance the cost of these figures with the minimal cost of genotyping approximately £30. Appropriate psychotropic prescribing in relation with genotyping would have a follow on impact in reducing the financial costs of long-term community care, hospital short and long-term care, Disability Living and Severe Disablement Allowances.

Financial Conflict of Interests

The government depends largely on the pharmaceutical industry for revenue income.

See: **The Influence of the Pharmaceutical Industry, Fourth Report of Session 2004–05 House of Commons Health Committee**

http://www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf

In UK, up to an estimated one and a half million patients are prescribed neuroleptic drugs for 'schizophrenia' and 'bi-polar'; countless others with alzheimers, autism and the elderly are also prescribed neuroleptics. All these vulnerable people support the UK economy.

It follows therefore; the Government may have a financial conflict of interests if the genotyping test is used prior to neuroleptic prescribing, because many patients would be inefficient metabolisers, and so would be unsuitable for neuroleptic treatment. The consequence would therefore be a significant loss to the government.

Patient Centred Health Services

Over the last decade, the provision of treatment from National and Local policies has focused upon services being person or patient centred i.e. New Ways of Working Psychiatrists (2005) and The National Mental Workforce Strategy (2004) which states: "To ensure services represent the needs of patients and preferences of the population they serve".

To day the goal posts have shifted so patients are geared up to the group norm.

The DH suppression of pharmacogenetic scientific literature and knowledge has played a dominant role in this shift as without the genotyping test there is no safe patient centred care in relation with medication treatment within mental health.

Patient Centred Health Services

The DH ensures all psychiatric treatment provision is confined within boundaries of national professional, legal and local codes of ethical practice.
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4087169

However when the DH does not address the following issues:

The conflicting evidence for the assumed beneficial use of psychotropic drugs.
Source: Murray TL (2006) http://psychrights.org/articles/OtherSideOfPsychopharmacology.pdf

"…after 50 years of neuroleptic drugs, are we able to answer the following simple question(s): Are neuroleptics effective in treating schizophrenia?"
Source: Stip E. (2002) http://www.ncbi.nlm.nih.gov/pubmed/12052571

No valid diagnostic tests exist to determine a disease process for the great majority of psychiatric diagnoses found in the DSM IV.
Source: Murray TL (2006) http://psychrights.org/articles/OtherSideOfPsychopharmacology.pdf

Authentic patient centred care is further negated.

Conclusion

Pharmacogenetics such as the **Genotyping Test** can help to predict the occurrence of specific physical neuroleptic side effects i.e. Tardive Dyskinesia, EPS and Neuroleptic Malignant Syndrome. Psychological side effects such as psychosis, suicide, homicide and violence are potentially linked with inefficient metabolisers.

There are moral and ethical issues concerning the NHS/DH who are perceived by many to be 100% trustworthy.

The difficulty for patients, carers and many professionals in acquiring pharmacogenetic information is that this knowledge is not available in NHS/ DH mainstream literature. Consequently taking prescribed medications without knowledge of genetic metabolising status is just as dangerous as *not* testing for ABO group prior to blood transfusion.

Source: Lucire Y. (2011) http://www.nt.gov.au/lant/parliamentary-business/committees/ctc/youth-suicides/Submissions/Sub%20No.%2016,%20Dr%20Yolande%20Lucire,%20Part%204,%20Sept%2030%20Sept%202011.pdf

Conclusion

When many patients are legally sectioned and forced to take neuroleptic drugs they are not able to metabolise efficiently, it is the equivalent of being legally forced to take an over dose, even at low doses.

The NHS/DH has been responsible in suppressing knowledge about pharmacogenetics in relation with side effects. Such action is negligent and unethical to all patients, particularly mental health patients who are potentially subjected to legal sectioning. When patients' trust is betrayed, trust in the NHS /DH plummets abysmally.

Useful websites and papers:

Super CYP Database: A comprehensive database on Cytochrome P450 enzymes including a tool for analysis of CYP-drug interactions. Preissner S., et al.
Nucleic Acids Res 38(Database issue): D237-43. (2010)
http://bioinformatics.charite.de/supercyp/

Psychotropic Medication and Cytochromes, Pharmacological Iatrogenesis
http://www.lucire.com.au/documents/Cytochromes-paradigmatic.aspx

Pharmacogenetics and Antipsychotics: Therapeutic Efficacy and Side Effects Prediction
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057913/

Includes metaboliser type graph
http://www.prozactruth.com/drtphysician.htm

Genelex Resources: Pharmacogenetics
http://www.healthanddna.com/dna-learning/resources-pharmacogenetics.html

Cytochrome P450 Enzymes and Psychopharmacology
http://www.acnp.org/g4/GN401000086/CH085.html

The Role of Pharmacogenomics in Clinical Trials
Tom Benijts, Ph.D., Scientific Business Development Manager,
LabCorpClinical Trials
http://cemo.fr/files/cemo_2004_n-4.pdf?phpMyAdmin=bd9gq8GpdTmKeSfqZo8kMOjYoBb

New tool: Genotyping makes prescribing safer, more effective.
2D6 enzyme variations identify patients at risk for an unexpected response
David A. Mrazek, MD The Journal of Family Practice Vol. 3, No. 9 / September 2004
http://www.jfponline.com/Pages.asp?AID=799

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