Pharmacogenetics and Mental Health.

Schizophrenia Depression & Cannabis

Medication Implications
Introduction

Over 50% of the population who are prescribed common medications such as anti-malarials, acne treatment, contraceptive pills, painkillers, cardiac drugs, antibiotics and antidepressants, may experience severe mood changes and hallucinations.

Many doctors fail to realise that these are psychological Adverse Drug Reactions (ADR’s) resulting from patients’ in-born inability to break down medications efficiently.

Due to doctors’ lack of pharmacogenetic knowledge, patients who experience psychological ADR’s are likely to be referred to the mental health services and attain a diagnosis of severe and enduring mental health illness.
Schizophrenia

“The number of people who will be diagnosed as having schizophrenia in a year is about one in 4,000. So about 1.5 million people will be diagnosed with schizophrenia this year, worldwide.” ²

“… the lifetime morbid risk (the likelihood that a particular individual will develop schizophrenia in their lifetime) is 7.2 per 1,000.” ³ i.e. approx. 1%.

“Schizophrenia affects 0.8% of the UK population, usually starts in early adult life and leads to persistent disability in most cases.” ⁴

A percentage of this population will have been taking medications that cause psychological ADR’s that mimic schizophrenia symptomology.

The misdiagnosed condition will inevitably incur use of antipsychotic medication in accordance with NICE guidance. ⁵
Antipsychotic Medications

Most Antipsychotic medications are metabolised through CYP 2D6 and CYP 2C19 pathways.

See Appendix 1

The prevalence of the population who are Poor Metabolisers (PM) and Intermediate Metabolisers (IM), i.e. patients with either no metabolising ability or reduced metabolising ability via these pathways are very varied.

See Appendix 3

Poor or Intermediate Metaboliser patients are likely to experience inevitable ADR’s from antipsychotics. Due to experiencing mind changing psychological ADR’s patients will receive little or no therapeutic benefit.
Schizophrenia - Statistics & Facts.

It is generally accepted that there are:
250,000  Schizophrenia patients in the UK
242,000  Schizophrenia patients treated with neuroleptics (97%)

It is known that approximately:
72,000 - 30% do reasonably well, socialise, continue working etc
   - 5% no longer need neuroleptics
72,000 - 30% relapse repetitively, unable to work, and do poorly
72,000 - 30% do very poorly being contained in secure units /hospitals

Overall: In 60% the outcome is poor.
Schizophrenia - Implications of Metaboliser Status

- How many schizophrenia patients are likely to be Poor or Intermediate Metabolisers?

- Are 60% of patients doing poorly because they are having problems with schizophrenia medications that are metabolised through CYP 2D6 & 2C19 pathways?
Schizophrenia
Poor Outcomes and Metaboliser Status

The premise is that in the UK the high proportion of schizophrenia people who do poorly is likely to be due to having in-born pharmacogenetic PM and IM variations.

The % of schizophrenia patients doing poorly would be expected to exceed the % PM’s and IM’s in the population in general because:

- Schizophrenia patients are likely to have been ‘pre-selected’ to have Poor or Intermediate Metaboliser status. i.e. a number will have symptoms mimicking schizophrenia due to medication psychological ADR’s or street drugs.
Cannabis and Schizophrenia

Cannabis is metabolised through **CYP 2C9** and **PM’s** or **IM’s** for this pathway will not be able to metabolise cannabis efficiently.

Paranoia and hallucinations/psychosis are likely to be a street drug ADR and provides a plausible explanation for “up to up to 25 per cent of new cases of schizophrenia in the UK may be due to cannabis use.”

Cases of cannabis-induced schizophrenia are likely to be highest from the Caucasian and Croatian populations, due to the high rate of **PM’s** and **IM’s** for the **CYP 2C9** pathway.

See Appendix 4
Depression and Antidepressant Medications

The majority of antidepressant medications are broken down by CYP450 2D6 and 2C19 pathways.

See Appendix 2

Poor and Intermediate Metabolisers are vulnerable individuals when prescribed antidepressant medications and are likely to have serious mental changes due to their in-born inability to metabolise antidepressants medications efficiently.
Antidepressants
Poor Outcomes and Metaboliser Status

Outcomes for depression will potentially follow a similar pattern to outcomes for schizophrenia, after treatment with SSRI medication:

1/3 are likely to do well, retain employment and speak favourably about SSRIs.

2/3 are likely to deteriorate psychologically due to ADR mania, psychosis, suicidal ideation and/or attempted suicide, with referrals to mental health services.

Prescribing of further psychiatric medications that are metabolised through the same CYP450 2D6 and 2C19 pathways will incur additional psychological Adverse Drug Reactions.
Pharmacogenetics and Mental ILL Health

The incidence of Suicide, Suicidality, Bipolar and Schizophrenia are likely to be connected with Poor and Intermediate Metabolisers.

GP’s need to be vigilant about medications that cause mind altering changes and psychotic reactions which could incur a label of schizophrenia.
In both depression and schizophrenia, the likelihood of the population who do not have a beneficial psychological effect, where the outcomes are poor, will be due to…

People who are Poor and Intermediate Metabolisers for antidepressant and antipsychotic medications.
Pharmacogenetic Screening

Genotype testing determines the in-born ability of people to metabolise medications and can be accessed by doctors or by lay people.

When patients have little or no metabolising abilities doctors are able to adjust medication dose to protect patients from the build up of toxicities that cause ADR’s.

Different medications use different metabolising systems, so genotype testing is specific to medications used.

“The hope is that this might allow prescriptions to be tailored to an individual’s genotype and, in principle, reduce drug safety problems and improve the effectiveness of treatments.”

9
General Physical Conditions and Pharmacogentic Screening

Leukaemia, Inflammatory Bowel Disease, Rheumatoid Arthritis, dermatological conditions and following organ transplantation are treated with immunosuppressants medications such as the Thiopurines including Azathioprine.\textsuperscript{10,11}

TPMT \textit{genotype testing} is used by two-thirds of NHS hospital consultants for guideline prescribing purposes, prior to Azathioprine treatment.\textsuperscript{11}

Prior to Warfarin treatment, NHS doctors have accessed the Roche AmpliChip \textit{CYP450 genotype test}.\textsuperscript{12} (Lab 21, 2007, personal communication).

In both examples, for \textbf{PM/IM} patients, the standard medication dose would constitute an overdose. Personalising or adjusting medication dose to the genetic profile prevents emergency hospital admissions due to ADR’s. e.g. Azathioprine: blood, liver and kidney toxicities\textsuperscript{13} and Warfarin: internal haemorrhage\textsuperscript{14} all reactions being potentially fatal.

Patient safety is considered important by NHS doctors in these conditions and the \textbf{“one size fits all”} does not apply.\textsuperscript{9}
Mental Health Conditions and Pharmacogenetic Screening

Research has identified antipsychotic physical ADR’s, i.e. Parkinsonism\textsuperscript{15} & \textsuperscript{16} and Tardive Dyskinesia in connection with schizophrenia CYP 2D6 PM status. \textsuperscript{17}

Tardive Dyskinesia is connected with poor clinical outcomes \textsuperscript{18} & \textsuperscript{19} indicating the under researched and neglected psychological ADR is connected with PM/IM for CYP 2D6 and CYP 2C19 pathways.

Whilst research from the United States, Canada, England, Germany, Spain and Sweden is favourable towards genotype profiling prior to antipsychotic and antidepressant medication prescribing \textsuperscript{6} & \textsuperscript{20} the NHS does not access genotype testing for mental health.
Schizophrenia and Depression Medications

Antipsychotic medications disrupt the brain’s normal functions and have a vast range of physical $^{21}$ and psychological $^{7}$ ADR’s that include shortened life span, dementia, life threatening conditions, Super Sensitivity Psychosis (SSP), i.e. recurrent psychosis and akathesia which is associated with suicide.

Antidepressants have both short and long term ADR’s which can cause physical and psychological ill health. These include Parkinson’s disease, psychosis and suicide.$^{22}$

When many mental health patients undergo legalised sectioning and have no option but to take psychiatric medications, enduring psychiatric ADR medication toxicities is tantamount to torture.
Genotyping is of Paramount Importance in the use of Psychiatric Medications

Patient safety is just as important in mental health as it is in physical conditions.

Doctors and psychiatrists need to implement the Roche AmpliChip CYP450 genotype test\textsuperscript{12}, prior to prescribing antidepressant and antipsychotic medications, similar to the genotyping practice of dermatologists, gastroenterologists and rheumatologists.

Personalising the dose to fit patients with CYP 2D6 and 2C19 PM/IM status would go a long way towards removing trial and error prescribing\textsuperscript{23} and minimise antidepressant and antipsychotic ADR’s.

Emergency hospital admissions resulting from mania, suicidal ideation and SSP would be averted.
Cost of Pharmacogenetic Screening

The cost of a genotype test for clinical research purposes at universities is approximately £30.

The Doctors Laboratory (TDL) used to provide the Roche AmpliChip *CYP2D6/2C19* testing facility to the NHS at a cost of £300, including any administration fees and platform costs (TDL, April 2008, personal communication). ²⁴

Whatever the initial cost - this is a once only cost and needs to be weighed up with the life long financial burden to the UK Government and the cost of humanity for those who are PM’s and IM’s.
Depression and Schizophrenia Hypothesis

Depression and schizophrenia are thought to be chemical imbalances; this concept is merely a hypothesis as there is no proof.\textsuperscript{25} & \textsuperscript{26}

Despite the hypothesis, psychiatric medication still has a dominant role in treatment.

For schizophrenia to be known as a ‘disease’ is misleading.

There are many cases where ‘schizophrenia’ successful recovery has been achieved without the antipsychotic medications and many more cases that show antipsychotics impede recovery.\textsuperscript{27}
Appendix 1

Examples of Antipsychotic medications metabolised through CYP2D6 and CYP2C19.

<table>
<thead>
<tr>
<th>CYP 2D6</th>
<th>CYP 2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>acuphase - clopixol</td>
<td>acuphase</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>clozapine</td>
</tr>
<tr>
<td>clozapine</td>
<td></td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>perphenazine</td>
</tr>
<tr>
<td>fluphenazine - modecate</td>
<td>phenothiazines -</td>
</tr>
<tr>
<td>haloperidol</td>
<td>trifluoperazine/stelazine</td>
</tr>
<tr>
<td>olanzapine</td>
<td>quetiapine-seroquel</td>
</tr>
<tr>
<td></td>
<td>risperidone</td>
</tr>
<tr>
<td></td>
<td>thioridazine – melleral,</td>
</tr>
<tr>
<td></td>
<td>zuclopenthixol</td>
</tr>
</tbody>
</table>

Ref 28 & 29

Many drugs go through multiple pathways. Those using 2D6 and 2C19 as a minor or less potent pathway are shown in blue.
Appendix 2

Examples of Antidepressant medications metabolised through CYP2D6 and CYP2C19.

<table>
<thead>
<tr>
<th>CYP 2D6</th>
<th>CYP 2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>bupropion</td>
<td>citalopram</td>
</tr>
<tr>
<td><strong>citalopram</strong></td>
<td>clomipramine</td>
</tr>
<tr>
<td>clomipramine</td>
<td>escitalopram</td>
</tr>
<tr>
<td>desipramine</td>
<td>fluoxetine (Prozac)</td>
</tr>
<tr>
<td>doxepin</td>
<td>imipramine</td>
</tr>
<tr>
<td>duloxetine (Cymbalta)</td>
<td>moclobemide</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>sertraline</td>
</tr>
<tr>
<td></td>
<td>trimipramine</td>
</tr>
</tbody>
</table>

Ref 28 & 29
Many drugs go through multiple pathways. Those using 2D6 and 2C19 as a minor or less potent pathway are shown in blue.
Appendix 3

Prevalence of Poor and Intermediate Metabolisers for Antipsychotics and Antidepressants.

<table>
<thead>
<tr>
<th>Gene</th>
<th>PM</th>
<th>IM</th>
<th>PM &amp; IM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 2D6</td>
<td>10%</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>CYP 2C19</td>
<td>3-21%</td>
<td>24-36%</td>
<td>27% to 57%</td>
</tr>
<tr>
<td>CYP 2C9</td>
<td>4%</td>
<td>38%</td>
<td>42%</td>
</tr>
</tbody>
</table>

Ref 30
Appendix 4

Population Frequency of Poor Metabolisers via CYP 2C9 pathway for Cannabis users:

Poor Metabolisers for CYP 2C9:
35% of Caucasians
42% Croatsians
0.5-4% Africans and Asians
>2% African Americans
References:


(6) Arehart-Treichel J. Gene Testing Could Help Predict Drug Responses
News http://pn.psychiatryonline.org/content/40/10/33.1.full

(7) Clarke, C. and Evans, J. Antipsychotic Psychological Adverse Reactions
March 2011
http://www.neuroleptic-awareness.co.uk/PMHIS/?Professional_Mental_Health_Information_Series:Antipsychotic_Adverse_Reactions

(8) Matthew Hickman, Peter Vickerman, John Macleod, James Kirkbride, Peter B.
Jones. Cannabis and schizophrenia: model projections of the impact of the rise in

(9) A, Smart et al Tailored Medicine: Whom will it Fit? The Ethics of Patient and
Disease Stratification. Bioethics Volume 18 Number 4 2004
© Blackwell Publishing Ltd. 2004, 9600 Garsington Road, Oxford OX4 2DQ, UK
(10) Ballantyne, A. and Waters, R. “A Pill Just for You” Reader’s Digest UK July 2005


(14) Robert S. Epstein, MD, et al, *Warfarin Genotyping Reduces Hospitalization Rates Results From the MM-WES (Medco-Mayo Warfarin Effectiveness Study) J Am Coll Cardiol, 2010; 55:2804-2812, (Published online 30 March 2010). © 2010 by the American College of Cardiology Foundation [http://content.onlinejacc.org/cgi/content/abstract/j.jacc.2010.03.009v1](http://content.onlinejacc.org/cgi/content/abstract/j.jacc.2010.03.009v1)


(21) Clarke, C. and Evans, J. Antipsychotic Physical Adverse Reactions. March 2011 [http://www.neuroleptic-awareness.co.uk/PMHIS/?Professional_Mental_Health_Information_Series:Antipsychotic_Adverse_Reactions](http://www.neuroleptic-awareness.co.uk/PMHIS/?Professional_Mental_Health_Information_Series:Antipsychotic_Adverse_Reactions)

(22) Clarke, C. and Evans, J. Antidepressant Adverse Reactions. February 2011 [http://www.neuroleptic-awareness.co.uk/PMHIS/?Professional_Mental_Health_Information_Series:Antidepressants_Adverse_Reactions](http://www.neuroleptic-awareness.co.uk/PMHIS/?Professional_Mental_Health_Information_Series:Antidepressants_Adverse_Reactions)
(23) Carol Isaacson Barash, *Ethical Issues in Pharmacogenetics*  
ActionBioscience.org original article  
[http://www.actionbioscience.org/genomic/barash.html#primer](http://www.actionbioscience.org/genomic/barash.html#primer)

‘The clinical effectiveness and cost effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation.’


(26) Kendler, Kenneth Ed Psychological Med. – “We have hunted for big simple neurochemical explanations for psychiatric disorders and have not found them.” Kenneth Kendler, *Psychological Medicine,* 2005.
(27) Clarke, C. and Evans, J. Successful Non-Neuroleptic Treatments for "Schizophrenia" January 2011
http://www.neuroleptic-awareness.co.uk/PMHIS/?Professional_Mental_Health_Information_Series:Schizophrenia

(28) Cytochrome P450 2D6 Genotyping http://www.healthanddna.com/healthcare-professional/p450-2d6-genotyping.html and CYP450 Drug Interaction Table, Division of Clinical Pharmacology, Indiana University School of Medicine
http://medicine.iupui.edu/clinpharm/ddis/table.asp

(29) Cytochrome P450 2C19 Genotyping http://www.healthanddna.com/healthcare-professional/p450-2c19-genotyping.html and CYP450 Drug Interaction Table, Division of Clinical Pharmacology, Indiana University School of Medicine
http://medicine.iupui.edu/clinpharm/ddis/table.asp
(30) Population Frequency of Cytochrome p450 (CYP) genotypes
http://www.healthanddna.com/healthcare-professional/pharmacogenetics.html

Contributors:

Catherine Clarke SRN, SCM, MSSCH, MBChA
Jan Evans MCSP. Grad Dip Phys

July 2011