Mental Health, Psychiatric Drugs and Metabolism

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28th September 2015

Mental health disorders are predominantly treated with psychiatric medications, which are licensed psychoactive drugs. This document focuses primarily on psychiatric drug induced mood changing side effects in relation to metabolisation. Metabolism is defined as an ability of the body to break down medications. Individual inability to break down medications efficiently causes toxicity resulting in side effects. This enlightening information falls outside the remit of mental health mainstream literature. Although ‘side effects’ is common terminology, Adverse Drug Reactions (ADRs) is the more accurate term as it reflects drug induced toxicities and is referred to throughout this document. The term antipsychotic is definitively replaced by neuroleptic, which means literally to ‘seize the nerve’.1

Psychiatric Medications Adverse Drug Reactions

Many individuals treated with psychiatric medications experience severe ADRs, without any effective drug response.2 Whilst antidepressant and neuroleptic drugs can cause iatrogenic physical ADRs, it is not widely known that psychiatric medications can induce mood changing behavioural ADRs. SSRIs for depression can precipitate deepening depression,3 suicidal ideation,4 suicide,5 homicidal ideation,6 homicide, akathisia and agitation,7 mania and delirium,8 severe anxiety, bizarre thinking and reasoning9 psychosis,10 and hallucinations.11 Neuroleptics, used to treat psychosis, are linked with violence,12 suicidal and homicidal behaviour13 leading to completed suicide14 and homicide.15 These behavioural ADRs are toxic psychiatric disturbances.

So why do some individuals respond well to drugs and others not?

A major factor for varied drug responses is due to individuals’ differing genetic makeup,16 known as pharmacogenetics or drug metabolism. Although there are many metabolising systems in the body, the major metabolising systems for psychiatric medications are the CYP450 enzyme system, principally in the liver, and the serotonergic system. Both systems have an important role in the outcome of treatment, ADRs and efficacy.

Genotype Testing

CYP450, 5HTT-LPR and 5-HT receptor genotype testing can determine individual status for metabolizing psychiatric medications. Prescribers do not currently conduct genotype testing prior to treatment and take no account of whether or not individuals are able to efficiently metabolise medication.

Genotype testing of an individual prior to psychiatric medication treatment would enable assessment and prediction of potential neurotoxic behavioural ADRs in line with genotype status as depicted in the table above. The genotype test is a simple blood or swab test and in 2013 the standard cost of a test was £30. Retrospective genotyping for psychiatric drugs has demonstrated that there would have been a significant reduction in the financial outlay/cost based on the use of inappropriate medication and subsequent unnecessary healthcare costs.17
Genotype testing is used by pharmaceutical companies during medication trials (stages II - IV), to de-select individuals who are PMs and liable to suffer severe ADRs. This practice includes trials with psychiatric medication to show medication in its best light.

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APPENDIX

450CYP Enzyme System
75% of psychiatric\textsuperscript{18} including antidepressant and neuroleptic medications are metabolised through CYP2D6, which is one of the most variable metabolizing enzyme pathways known. Other pathways that metabolise antidepressants and neuroleptic drugs include CYP2C19, CYP2C9, CYP1A2, CYP 3A4 and CYP3A5.

Genetic variations, known as alleles, classify individuals as either being Poor Metaboliser (PM), Intermediate Metaboliser (IM), Extensive Metaboliser (EM) or Ultra Metaboliser (UM) genotypes.\textsuperscript{19} PMs have two non-functional alleles and IMs have one non-functional allele plus one diminished allele or two diminished alleles or two partially active alleles.\textsuperscript{20} UMs have more than two active gene copies on the same allele, or increased expression of a single allele.\textsuperscript{7} EMs have one or at the most two functional alleles with ‘normal’ activity.\textsuperscript{20}

Genetic variability affects psychiatric medication outcomes. PMs and IMs incur neurotoxicities leading to violent acts, as do UMs with prodrug use. EM individuals are likely to have a therapeutic response without neurotoxic ADRs.

EMs determine the window of opportunity for a drug therapeutic level and sets the recommended drug dosage. This is important, as drug companies do not specify drug dosage for UMs, IMs and PMs, which explains why these individuals do not respond well to standard drug doses.

| Table 1. General Population Frequency of CYP450 Genotypes: |
|-------------|----------|----------|----------|--------|--------|
| Gene       | PM       | IM       | PM & IM  | EM     | UM     |
| CYP 2D6    | 10%      | 35%      | 45%      | 48%    | 7%     |
| CYP 2C19   | 3-21%    | 24-36%   | 27% - 57%| ~60%   | N/A    |
| CYP 2C9    | 4%       | 38%      | 42%      | 14-44% | 30%    |

Ref 21

| Table 2. Population Frequency for Poor Metabolisers of CYP450 2D6, 2C19 and 2C9 Pathways |
|-------------|----------|----------|----------|
| 2D6 PM      | 2C19 PM  | 2C9 PM   |
| 5 - 10% of Caucasians\textsuperscript{22} | 2-6% of Caucasians\textsuperscript{23} | 35% of Caucasians\textsuperscript{24} |
| 41% Pacific Islanders\textsuperscript{22} | 41% Asians\textsuperscript{22} | 42% Croatsians\textsuperscript{25} |
| 6.3% Africans\textsuperscript{26} | 10-20% Africans\textsuperscript{27} | 0.5-4% Africans & Asian\textsuperscript{28} |
| 14.5% African American \textsuperscript{26} | Up to 90% Melanesians\textsuperscript{29} | 15-20% Japanese\textsuperscript{27} |
Combined PM and IM frequency via CYP450 2D6:  
26% Caucasians  50% Africans  
40-50% African-Americans

Statistically, **Black Minority and Ethnic (BME) populations** have greater difficulty metabolising psychiatric medications compared with White and Asian population, due to the higher frequency of lower metabolism at CYP 2D6. BME groups are four times more likely to experience psychosis than Caucasians, with *African* Caribbean people three to five times more likely than any other group, of being diagnosed with schizophrenia and admitted to hospital.

**Serotonergic**  
Antidepressants and neuroleptics are regulated through the serotonergic system. The serotonin system consists of the Serotonin Transporter Gene and serotonin receptors (5-HT). As with the CYP450 system, the serotonergic system has genetic variations that affect outcomes.

**Serotonin Transporter Gene and Antidepressants**  
Genetic variations in the promoter region of the Serotonin Transporter Gene (5HTT-LPR) are coded as L/L (2 long alleles), L/S (a long and a short allele) or S/S (2 short alleles). Those individuals with the L/L code have a ‘normal’ gene activity and respond well to antidepressant medications. In contrast individuals with the short allele have slower gene activity, resulting in a reduction of serotonin transmission. Both L/S and S/S individuals treated with antidepressants have poor outcomes, and a ‘powerfully predicted non response’. Emerging antidepressant ADRs are inevitable for individuals with the short allele.

Individuals coded with (S/S) and (S/L) genotype:  
Caucasians S/S (39%)  Caucasians S/L (52%)  East Asians S/S (49–74%)
Native Americans S/S (42%)  African Americans S/S (7–17%)  
Goldman  Goldman  Goldman

Individuals coded with L/L genotype:  
Caucasians (29–43%)  African Americans (45–56%)
Native American (10–14%)  East Asian samples (1–13%)

**Serotonin Receptors**  
There are 14 types of 5-HT receptors that can be targeted by antidepressants and neuroleptics. However the 5-HT 2A serotonin receptor variant, in particular, is associated with individual poor response and increased risk of ADRs when treated with antidepressant selective serotonin reuptake inhibitors. This same receptor variant has been linked to poor response from some individuals having neuroleptic treatment.
Table 3. The Link between Genotype Status and Psychiatric Disturbances for CYP450, 5HTT-LPR and 5-HT Allele Variants when treated with Antidepressant Medications

<table>
<thead>
<tr>
<th>NEUROTOXIC BEHAVIOURAL ADRs</th>
<th>CYP450 AND SEROTONERGIC GENETIC VARIANTS</th>
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| Akathisia/agitation/ restlessness | CYP450 2D6 and 2C19 non-functional alleles\(^7\)  
CYP450 2D6 and 2C9 diminished function alleles\(^7\)  
CYP450 2C19 ultra rapid multiple allele duplications\(^7\)  
CYP2C9 non-functional alleles\(^46\)  
5-HTT-LPR short allele\(^47, 48\)  
5-HTR2A receptor variant\(^44\) |
| Suicide/suicide risk | CYP450 2D6, 2C19 and 2C9 non-functional and diminished function alleles\(^7, 46\)  
CYP450 2D6 ultra rapid multiple allele duplications\(^7\)  
5-HT1AC receptor variant\(^49\) |
| Homicide/attempted homicide | CYP450 2D6 and 2C19 non-functional\(^7\)  
CYP450 2D6 and 2C9 diminished function alleles\(^7\)  
CYP450 2C19 ultra rapid multiple allele duplications\(^7\) |
| Insomnia | 5-HTTLPR short allele\(^47\) |
| Mania/delirium | CYP450 2D6 and 2C19 non-functional alleles\(^7\)  
CYP450 2D6 and 2C9 diminished function alleles\(^7\)  
CYP450 2C19 ultra rapid multiple allele duplications\(^7\)  
5-HTTLPR short allele\(^48, 50\) |
| Serotonin Syndrome | CYP450 2D6 IM\(^51\) |
| Psychosis | CYP2D6 non-functional and diminished allele\(^46\) |
| Delusions | CYP2D6 diminished allele\(^46\) |
| Dysphoria | CYP2D6 non-functional allele and diminished function allele\(^46\) |
| Hallucinations | CYP2D6 non-functional allele and diminished function allele\(^46\) |

Antidepressants linked with Psychiatric Disturbances and Genetic Variations

- Fluoxetine
- Escitalopram
- Paroxetine
- Citalopram
- Sertraline
- Venlafaxine
Discussion
Neurotoxic behavioural ADRs are not understood in psychiatry. When individuals do not respond therapeutically to psychiatric medication or show neuropsychiatric disturbances, the practice in mental health is to increase the dose and/or polypharmacy. This practice is futile as further medications increase neurotoxicities. Individuals are theoretically being overdosed, albeit unwittingly by prescribers. Prescribing of psychiatric medications is done on a trial and error basis. Individual suffering is immense. This needs to change.

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