Pharmacogenetics and Mental Health.

Side Effects

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Introduction

It is recognised 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.** [1]

"As practitioners an aspect of our role is to understand the effects of medication on an individual." [2]

Mood and Behaviour Issues could be Side Effects

"Many drugs used for physical complaints can have an effect on our mood and behaviour." [3]

Medicines for indigestion, acne, pain, infections, cholesterol, and anaesthetics may cause side effects in the form of **serious mental changes**, and also withdrawal symptoms caused by antidepressants, tranquilisers and other psychiatric drugs. [3]

Long term treatment for perceived mental illness may be prevented if the psychiatric side effects are recognised in time. [3]

Suicidality Associated with Medication

Suicidal thoughts, suicidal ideation or parasuicide have all been reported by people resulting from taking the following medications:

SSRI & SNRI Antidepressants
Antipsychotics
Cortico-steroids
Acne medication
Proton Pump Inhibitors – Antacids
Contraceptive pills
Anti-malarial drugs
Pain killers
Cardiac drugs. [4]

Antidepressant Associated Suicidality

Antidepressant SSRIs can increase agitation in the early stages of treatment and during drug withdrawal. This condition is more aptly known as akathisia (inner restlessness/agitation) which is an SSRI adverse reaction and has the potential to lead to suicidality even in some healthy volunteers.[5]

"There is evidence for a small but significant increase in the presence of suicidal thoughts in the early stages of antidepressant treatment." [6, 7]

Suicide Associated with Psychiatric Drugs

In a study of 393 cases of suicide, all patients had been treated with psychiatric drugs within one year of their suicide.

- **63%** were treated with antidepressants.
- **77%** were treated with antidepressants and/or neuroleptics.
- **86%** were treated with any kind of psychiatric drug including tranquilizers/hypnotics, benzodiazepines or similar sleeping pills.[8]

This study indicates psychiatric drugs precipitated suicide and needs to be classified as an Adverse Drug Reaction.

Medications Associated with Hallucinations & Psychosis

"Hallucinations are one of the five most commonly reported serious **adverse drug reactions** to CSM (Committee on Safety of Medicines) West Midlands." [9]

"Hallucinations caused by drugs are commonly visual. They can be an isolated **adverse effect** but often occur as a part of drug-induced psychosis." [9]

Medication Induced Psychosis

"Of the best selling prescription drugs, 148 can cause depression, 133 hallucinations or psychoses…" [10]

See Appendix 1 for medications that have the potential for causing hallucinations.

Due to the absence of pharmacogenetic education at British Medical Schools, many doctors are unaware that adverse reactions result from a genetic inability to metabolise or breakdown medication.

Pharmacogenetics and Medication

"Pharmacogenetics is…the study of the genetic basis of drug response and is mainly concerned with the assessment of a drug's clinical efficacy and/or safety profile It is primarily focused on understanding how an individual's response to medication may be affected by their genetic make up (genotype)." [11]

Pharmacogenetics is the key to understanding and preventing side effects affecting mood and behaviour such as suicidal thoughts & psychosis.

Pharmacogenetics and Medication

The majority of medications are metabolised through genetically different liver enzymes of the **Cytochrome P450 system.** [12]

The enzyme **CYP450 2D6** metabolises a quarter of all prescription drugs, [13] and three quarters of all psychiatric medications. [14, 2]

General Medications include antacids, antihistamines, antiarrhythmics, antiemetics, beta blockers, chemotherapy drugs, anticholinergic drugs, dopamine agonists, corticosteroids, adrenergic drugs, (e.g. stimulants, propranolol, clonidine) thyroid hormones, cough syrup and opiate painkillers.

Psychiatric Medications include antipsychotics, both dopamine antagonists, and agonists such as abilify, and many antidepressants, such as SSRIs and SNRIs.

See Appendix 2

Pharmacogenetic Efficacy

The efficacy of the CYP450 pathways is determined by genetic variations in the metabolising pathways. Variations in functionality result in individuals who are ascribed as Ultrarapid, Extensive, Intermediate and/or Poor Metabolisers.

Extensive (EM) and **Ultrarapid Metabolisers (UM)** function at 100% and over 100% respectively. Providing a prodrug is not being used there is no accumulation of medication, the toxicities are minimal and side effects are minimal.

However, with prodrug use, where the drug achieves it's effect through an active metabolite after it is broken down, medication toxicities can build up quickly in Ultra rapid Metabolisers.

Pharmacogenetic Efficacy

Intermediate Metabolisers (IM)
Are able metabolise medication at a 50% rate. Because medication takes longer to clear from the body, side effects take longer to appear.

Poor Metabolisers (PM)
Have little or NO ability to metabolise medication. Consequently there are accumulations of high medication levels, with a corresponding increase of toxicity resulting in severe side effects. [15, 16]

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 17

As well as **CYP 2D6** pathway, many medications are metabolised through other CYP pathways i.e. **CYP 2C19** and **CYP 2C9**.

For medications that pass through the CYP 2D6 and CYP 2C19 pathways; patients who are PM and or IM will receive little or no therapeutic benefit from these medications. This situation is compounded by the inevitable side effects.[18]

Antidepressants: Side effects resulting from CYP2D6 variations.

Akathisia/agitation	CYP450 2D6 and 2C19 non-functional alleles[19] CYP450 2D6 and 2C9 diminished function alleles[19] CYP450 2C19*17 ultra rapid multiple allele duplications[19]
Suicide/suicide risk	CYP450 2D6, 2C19 and 2C9 non-functional and diminished function alleles.[19, 20] CYP450 2C19*17 ultra rapid multiple allele duplications[19]
Homicide/attempted homicide	CYP450 2D6 and 2C19 non-functional[19] CYP450 2D6 and 2C9 diminished function alleles[19] CYP450 2C19*17 ultra rapid multiple allele duplications[19]
Mania /delirium	CYP450 2D6 and 2C19 non-functional alleles[19] CYP450 2D6 and 2C9 diminished function alleles[19] CYP450 2C19*17 ultra rapid multiple allele duplications[19]

The Serotoninergic System

Many medications have serotonergic properties.

General medications include antimigraine agents; triptans (e.g., sumatriptan); anticonvulsants; antiparkinsonian agents; analgesics (e.g., meperidine, tramadol); OTC products (e.g., cough and cold medication containing dextromethorphan and the antibiotic linezolid.[21]

Psychiatric Medications include many serotonergic drugs including antidepressants (e.g., SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), buspirone, tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs) [21] and antipsychotics, dopamine antagonists and agonists such as abilify.

SSRI Antidepressants and the Serotonin Transporter Gene

Natural variations in the **Serotonin Transporter Gene** will result in a failure to achieve the expected beneficial response with SSRIs.

Deletion of **long alleles (L)** in the **Serotonin Transporter Gene Linked Promoter Region (5-HTTLPR)** is associated with a 'powerfully predicted non response' [22]

"S allele of 5HTT-LPR is associated with a poor outcome after treatment with selective serotonin reuptake inhibitors" [23]

42% Caucasians have the **short allele** frequency.[24]
57% Caucasians have long allele (L) frequency.
The genotypes are as follows: L/L – 32%, L/S 49% and S/S 19%.[25]

With SSRIs, over 50% of Caucasians are likely to experience mind altering side effects; this may be replicated with any other serotonergic medication.

Antidepressants: Side effects resulting from Serotonin Transporter Gene variations.

The **short allele (s)** variant is linked with emerging side effects[26] as follows:

Akathisia/agitation	Short allele variations [27]
Insomnia	Short allele variations [27]
Mania	Short allele variations [27, 28]
Delirium: including hallucinations and delusions [29]	Short allele variations [27, 29]

Antipsychotics and the Serotonin Transporter Gene

"Genetic variations in 5-HTT-LPR polymorphism have been also found to be associated with variations in antipsychotic drug response ." [30]

The 5-HTTLPR S allele was associated with a lower improvement in BPRS *(depression Rating)* scores and this effect was even stronger after pooling subjects with S or Lg containing alleles.[31]

"…. 5-HTTLPR was associated with the incidence of EPS in the schizophrenic patients treated with haloperidol." "The incidence rate of EPS patients with the S/S type (83.1%) was higher than those with the S/L type (62.2%) and L/L type (50.0%) (Table 3*)*. [32]

Other Variable Drug Metabolising Systems.

P-glycoproteins (P-gps)

U-glucuronisil transferases. (UGTs)

Both P-gp and UGT variations affect the outcome of medications.[33]

Incidence of Side Effects - US Experience:

"The GAO (United States Government Accountability Office) reports that 51% of new drugs have serious, undetected adverse effects at the time of approval." [33]

"ADRs are the fourth to sixth greatest killer in US with more than 100,000 deaths per year; and 2.2 million serious adverse reactions per year according to a 1998 Journal of the American Medical Association report. (JAMA 279:1200 1998) This study is a meta analysis of 39 research reports published from 1966 to 1996." [34]

Incidence of Side Effects - UK Experience:

Hospital admissions due to side effects increased by 76.8% from 1999 – 2009,[35] and in 2005 76,692 people were admitted to hospital suffering with side effects from medications.[36]

"ADRs have a major impact on public health. Our data suggest the number of ADR admissions has increased at a greater rate than the increase in total hospital admissions…" "Our findings should prompt policymakers to implement further measures to reduce ADR incidence and their associated in-hospital mortality…" [35]

The Cost of Increased Hospital Admissions:

"The projected annual cost of such admissions (related to an ADR) to the NHS is £466m" [37]

ADRs were responsible for 6.5% of all acute hospital admissions and at least 5,000 deaths per year.[36]

At what cost human suffering and mortality?

Metaboliser Status can Determine the Appropriateness of Medication.

"Knowledge of patient drug metabolising gene variants, found in ***more than half*** *of patients, can help determine the appropriateness and dosage of many of the most commonly prescribed drugs."* [17, 38]

The UK population receive medications on trust from our doctors with the expectation of doing them good and no harm. The population do not expect to be so severely affected by side effects to receive a mental health diagnosis.

However the potential of patients experiencing severe side effects either mental or physical remains uncontrolled.

With some patients side effects are a certainty.

Genotype Testing

Individual genotype testing provides knowledge of patients' individual CYP450 and 5-HTT-LPR drug metabolising status, reducing the unpredictability of patients experiencing Adverse Drug Reactions.

Pharmacogenetics offers a patient focus on Poor/Intermediate Metaboliser and/or an Intermediate /Poor Serotonin Transporter genotype, avoiding potentially dangerous medical practice.

Appendix 1

Medications that can cause Hallucinations & Psychosis

	Examples		***Examples***	
Medication	Brand Name	Generic Name	Brand Name	Generic Name
Neuroleptics	Aripiprazole Clopixol Clozaril Haldol Largactil Mellaril Navane	*Abilify* *Zuclopenthixol* *Clozapine* *Haloperidol* *Chlorpromazine* *Thioridazine* *Thiothixene*	Proxilin Risperdal Stelazine Sulpiride Zyprexa	*Fluphenazine Decanoate* *Risperidone* *Trifluoperazine* *Olanzapine*
Anti-Convulsants Mood Stabilisers	Depakote Dilantin Klonopin	*Divalproex Sodium* *Phenytoin* *Clonazepam*	Mysoline Tegretol Zarontin	*Primidone* *Carbamazepine* *Ethosuximide*

Causes of Psychosis (Cont)

Medication	Brand Name	Generic Name	Brand Name	Generic Name
Antimanic	Lithium Carbonate			
Anti depressants	Asendin Aventyl Desyrel Effexor Elavil Limbitrol Ludiomil Luvox	*Amoxapine* *Nortryptyline* *Trazodone* *Venlafaxine* *Amitriptyline* *Amitriptyline/ chlordiazepoxide* *Maprotiline* *Fluvoxamine*	Norpramin Paxil Prozac Sinequan Tofranil Triavil Wellbutrin Zoloft	*Desipramine* *Paroxetine* *Fluoxetine* *Doxepin* *Imipramine* *Amitriptyline/ Perphenazine* *Bupropion* *Sertraline*
Antidepressant &Anti Obsessional	Anafranil	*Clomipramine*		

Causes of Psychosis (Cont)

Medication	Brand Name	Generic Name	Brand Name	Generic Name
Minor Tranquillisers	Ativan Ambien BuSpar Halcion	*Lorazepam* *Zolpidem* *Buspirone* *Triazolam*	Noludar Placidyl Valium	*Methyprylon* *Ethchlorvynol* *Diazepam*
Anti-Parkinsons	Eldepryl Larodopa Parlodel	*Selegiline* *Levodopa* *Bromocriptine*	Permax Sinemet Ropinirole	*Pergolide* *Levodopa/carbidopa*
Pain killers/ narcotics	Arthopan Ascriptin Darvon Disalcid	*Choline-salicylate* *Buffered aspirin* *Asprin* *Propoxyphene* *Salsalate*	Indocin MS Contin Orudis Talwin Tramadol	*Indomethacin* *Morphine* *Ketoprofen* *Pentazocine* *Rybix*

Causes of Psychosis (Cont)

Medication	Brand Name	Generic Name	Brand Name	Generic Name
Steroids	Acthar Cortef Cortone	*Corticotropin* *Hydrocortisone* *Cortisone*	Decadron Metreton	*Dexamethasone* *Prednisolone*
Hypnotics	Imovane Ambien	*Zopiclone* *Zolpidem*		
Antibiotics	Floxin Zovirax Quinolones Clarithromycin	*Ofloxacin* *Acyclovir*		
Hypertensive medications	Aldomet Capoten Inderal	*Methlodopa* *Captopril* *Propanolol*	Sectral Tenormin	*Acebutolol* *Atenolol*

Causes of Psychosis (Cont)

Medication	Brand Name	Generic Name	Brand Name	Generic Name
Other Drugs	Lioresal Ritalin	*Baclofen* *Methlyphenidate*	Barbituates Atropine	
Nasal Decongestants	Sudafed	*Ephedrine* *Pseudoephedrine*		
Eye drugs	Betagan Timoptic	*Levobunolol* *Timolol*		
Asthma Drugs	Proventil	*Albuterol*		
Gastrointestinal drugs – Proton Pump Inhibitors	Tagamet Zoton Lansoprazole	*Cimetdine*		
Heart drugs	Lanoxin	*Digoxin*		

Ref: 9, 10

Appendix 2:

Super CYP Database

A Resource for CYP450 and drug metabolism information

Compiled by the Structural Bioinformatics Group at the Institute for Physiology in Berlin http://bioinformatics.charite.de/main/content/index.php, this database can be accessed through the internet at http://bioinformatics.charite.de/supercyp/ The information is compiled from papers published in journals and is provided for educational and research purposes.

This resource can be used to find out:

- which drugs are broken down through which CYP pathways
- information about the known different genetic variations of CYP enzymes
- comparisons of similar drugs for metabolism status
- interactions of drugs (anything where substrate, Inhibitor or Enhancer overlap indicates a drug interaction)

Appendix 2 cont… Super CYP Database

A Resource for CYP450 and drug metabolism information

Some of the language used is technical from bio-chemistry; the following table may help with some of the technical terms.

Everyday language	Bio-chemistry language	How it appears on the Super CYP database
A drug is **metabolised and broken down** by a particular CYP pathway	A drug is a **substrate** of a particular CYP enzyme/pathway	**S** is used for Substrate
A drug **reduces the ability** of a particular CYP pathway to do its job - the CYP pathway is slower and less efficient.	A drug is an **Inhibitor** of a particular CYP pathway.	**Inh** is used for Inhibitor
A drug **increases the ability** of a particular CYP pathway to do its job - the CYP pathway is faster and more efficient.	A drug is an **Inducer** of a particular CYP pathway	**Ind** is used for Inducer

Appendix 3: Pharmacogenetics and Medication

Examples of medications metabolised through **CYP2D6.**

Psychiatric drugs:	Fluoxetine	**Antacids:**	**Antihistamines:**	**Cough Medicine:**
amitriptyline	(Prozac)	Cimetidine *(Tagamet)*	chlorpheniramine	Dextromethorphan
aripiprazole	haloperidol	ranitidine *(Zantac)*	diphenhydramine	(*Benylin*)
atomoxetine	imipramine	**Anti arrhythmics:**	hydroxyzine	**Chemotherapy:**
benztropine	mirtazapine	amiodarone	loratadine *(Claritin)*	Tamoxifen
bupropion	nortripyline	encainide		doxorubicin
clozapine	olanzapine	mexiletine	**Beta Blockers:**	**Opiates:**
chlorpromazine	paroxetine	propafenone	alprenolol	codeine
citalopram	perphenazine	(*Rythmol*)	carveodilol	hydrocodone
clomipramine	quetiapine	**Anti emetics:**	metoprolol	oxycodone
desipramine	risperidone	Dolesetron	propranolol	tramadol
doxepin	sertraline	Metoclopramide	timolol	**Other:**
duloxetine	thioridazine	*(Reglan)*		tolterodine
fluvoxamine	venlafaxine	tropisetron		*(Detrol)*

Ref 39 Many drugs go via multiple pathways. Those that use 2D6 as a minor or less potent pathway are shown in blue.

Pharmacogenetics and Medication

A further percentage of psychiatric and general medications are metabolised through the also genetically variable liver enzyme **CYP450 2C19**.

Psychiatric drugs:	**Anticonvulsants:**	**Proton Pump Inhibitors:**
amitriptyline	mephenytoin	esomeprazole
citalopram	phenytoin	lansoprazole
clomipramine		omeprazole
clozapine	**Circulatory and Cardiac drugs:**	pantoprazole
diazepam	Cilostazol Clopidogrel	**Others:**
escitalopram	Propranolol	Carisoprodol, *Soma*
flunitrazapam	R-warfarin	Cyclophosphophamide
fluoxetine *(Prozac)*		ifosphosphamide
imipramine		nelfinavir
moclobemide		proguanil, *Malarone*
sertraline		Tolbutamide
trimipramine		Voriconazole

Ref 40 Many drugs go through multiple pathways. Those using 2C19 as a minor or less potent pathway are in blue.

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