Antidepressant Awareness

Part 4

Pharmacogenetics

Introduction

Pharmacogenetics is the science of how drugs are broken down and used – i.e. metabolised in the body.

Knowledge of pharmacogenetics is important for all doctors and people who take medications, because both slow i.e. poor and ultra fast metabolisers are genetically inefficient in metabolising drugs.

Extensive Metabolisers

Extensive Metabolisers (EMs) represent the norm for metabolising capacity.

Individuals with Extensive Metaboliser genotype can take medications at standard dose levels without incurring severe adverse reactions or toxic effects.

Poor Metabolisers

Slow/Poor metabolisers, have no metabolising activity whatsoever and it is unlikely that they will ever have a therapeutic response to any medication.

Side effects and adverse reactions will be more severe, because of increasing toxicity in the body i.e. poisoning.

Ultra, Intermediate and Poor Metabolisers

Ultra Metabolisers are inefficient metabolisers as medications either pass too quickly through the body having little or no effect or in the case of pro-drugs, toxic levels of the active metabolite build up rapidly.

Prodrugs are inactive until they are broken down in the body and converted to their active drug form. http://en.wikipedia.org/wiki/Prodrug

Drug companies have a wide range of medication doses and whilst Extensive Metabolisers are catered for to achieve the expected beneficial response at the higher dose range; Ultra Metabolisers taking prodrugs, Intermediate and Poor Metabolisers are not catered for, as for them, the lower dose range is the equivalent of taking an overdose.

Psychotropic/Psychiatric Drugs

75% of all psychotropic drugs are metabolised through **CYP2D6** genetic enzyme pathway found mainly in the liver.

"Gene Testing Could Help Predict Drug Responses"
Arehart-Treichel J. Psychiatric News May 20, 2005
Volume 40 Number 10 Page 33.
http://pnhw.psychiatryonline.org/content/40/10/33.1.full

Antidepressant Metabolisers

Most antidepressants are metabolised through CYP2D6 which is a highly variable enzyme. When people take antidepressants, variations of this enzyme i.e. Poor and Intermediate Metabolisers, will experience adverse drug reactions from antidepressant medications.

Antidepressants and Poor Metabolisers

10% of Caucasians, 40-50% of Asians, Pacific Islanders, African and African Americans are **Poor Metabolisers** (people with no functional metabolising activity - otherwise known as slow metabolisers) for **CYP2D6.**

10-20% of Africans and 3-6% of Caucasians are **Poor Metabolisers** for **CYP2C19** which also metabolises some antidepressants.

Antidepressants and Intermediate Metabolisers

35% of Caucasians are **Intermediate Metabolisers** for **CYP2D6** - this group are able to metabolise drugs but at about 50% rate; **side effects build up slowly and appear later.**

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

Read the science:

"Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response."

Kircheiner J. et al. *Molecular Psychiatry* March 2004,9, p442-473.
http://www.nature.com/mp/journal/v9/n5/full/4001494a.html

When patients are Poor, Intermediate, Ultra and/or any combination of these three metaboliser genotypes for antidepressants i.e. have gene variations, they will not experience the expected beneficial response.

Because of the genetic susceptibility to adverse reactions, these patients have more potential to develop serotonin syndrome, mania or psychosis.

"Life-threatening serotonin syndrome in a patient with chronic heart failure and CYP2D6*1/*5." Sato A, et al. Mayo Clin Proc. 2004 Nov;79(11):1444-8. http://www.ncbi.nlm.nih.gov/pubmed/15544025

"…gene variants seem to influence human behaviour, liability to disorders and treatment response." "Pharmacogenetics of antidepressants" Crisafulli C, et al. Front Pharmacol. 2011;2:6. Epub 2011 Feb 16. http://www.ncbi.nlm.nih.gov/pubmed/21687501

Behavioural changes such as mania and psychosis can be induced by antidepressants in susceptible patients.

Antidepressant-associated mania and psychosis resulting in psychiatric admissions. Preda A., et al. J Clin Psychiatry. 2001Jan; 62(1):30-3. http://psychrights.org/research/Digest/AntiDepressants/DrJackson/Preda2001.pdf

Particular attention to the CYP2D6 and the CYP2C19 genetic status is needed to ascertain whether a patient will be able to tolerate antidepressants.

When people have CYP2D6 and CYP2C19 Poor and/or Intermediate Metaboliser genetic status, they would benefit by reducing the recommended antidepressant dose to avoid medication toxicities.

Read the science:

"CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards sub-population specific dosages."

Kircheiner J. et al. Acta Psychiatr Scand 2001 Dec; 104(3): 173-192.
http://www.ncbi.nlm.nih.gov/pubmed/11531654

SSRI Antidepressants and Serotonin Transporter Gene

42% Caucasians have the short allele variant on the Serotonin Transporter Gene Promoter
http://www.nature.com/npp/journal/v23/n5/full/1395540a.html#bib7

The short allele variant is linked with emerging side effects:
http://www.ncbi.nlm.nih.gov/pubmed/24558768

Akathisia, agitation, insomnia, mania and delirium are all associated with the short allele
http://www.biologicalpsychiatryjournal.com/article/S0006-3223%2803%2900424-4/abstract

Delirium symptoms include hallucinations & delusions
Genes, Memes, Culture, and Mental Illness: Toward an ...

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

"S allele of 5HTTLPR at the SLC6A4 locus is associated with a poor outcome after treatment with selective serotonin reuptake inhibitors"
http://archpsyc.jamanetwork.com/article.aspx?articleid=482088

Deletion of long alleles in the serotonin transporter gene (5-HTT) is associated with a 'powerfully predicted non response'
http://journals.lww.com/neuroreport/Abstract/2000/01170/Serotonin_transporter_gene_polymorphism_and.42.aspx

Other Variable Drug Metabolising Systems.

P-glycoproteins (P-gp's)

U-glucuronisil transferases. (UGT's)

Both P-gp and UGT variations affect the outcome of medications

See in: "Drug Interaction Principles for Medical Practice" Cozza, *Armstrong and Oesterheld.* ISBN-13: 9781585621118
Pub. January 2003

The genotyping test for genetic variations could be vital for the individual to prevent misdiagnosis from antidepressant iatrogenic mania, psychosis and suicide.

It is important patients are informed about the genotyping test prior to taking antidepressants so that they have an awareness of their potential unsuitability which would incur negative effects.

Otherwise taking psychotropic/psychiatric drugs is not unlike taking street drugs with their unpredictable effects, e.g. hallucinations.

Newton's third Law of motion states: " For every action there is an equal and opposite reaction"

With regard to Psychotropic/Psychiatric medication **Jackson's *First* Law of Biopsychiatry states:**

"For every action, there is an unequal and frequently unpredictable reaction."

Jackson, Grace E. MD, Appendix D, Transcript of
"What Doctors May Not Tell You About Psychiatric Drugs" Public Lecture,
Centre for Community Mental Health - UCE Birmingham June 2004

A Genotyping Test is Worthwhile for Patient Safety

However, currently in mental health genotyping for psychotropic drugs is perceived as not financially worthwhile by UK regulatory bodies and the UK Government.

When the genotyping test is available for NHS general medicine patients, this practice is showing discrimination towards patients in mental health.

Genotyping Test

A genotyping test can be done with a simple mouth swab.

- AmpliChip CYP450 Test (Roche) for genotyping was launched in Europe in 2004. The test is now CE marked and available for diagnostic use in the European Union.

- AmpiChip was passed by the FDA for use in USA in January 2005, EU and Japan in 2004 and Korea in 2007.

Genotyping can be obtained privately from:

Genelex (USA) 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.

Potential Outcome when Genotyping Test not used

To quote from a pilot study of 100 inpatients:

"the findings suggested that CYP 2D6 deficiency may be associated with more medication side-effects and subsequently with non-compliance and rehospitalisations."

"Pilot Study of the Cytochrome P-450 2D6 Genotype in a Psychiatric State Hospital."
Jose De Leon et al. Am J. Psychiatry 1998;155(9):1278-1280.
http://ajp.psychiatryonline.org/article.aspx?articleID=173007

Potential Outcome when Genotyping Test not used

"Fluoxetine (Prozac) - related death in a child with cytochrome P-450 2D6 genetic deficiency".
Sallee FR, et al J Child Adolesc Psychopharmacol. 2000 Spring; 10(1): 27-34.
http://www.ncbi.nlm.nih.gov/pubmed/10755579

The parents were investigated for murder and only after post mortem genotyping was carried out on the child, was the investigation dropped.

The test confirmed a variation in the CYP2D6 gene, which metabolises Prozac antidepressant.

Genotyping Is Not the End of the Story

In addition to genotyping there could be many other factors that impede a person from efficiently metabolising drugs.

Genotyping could be used just as inappropriately as over-prescribing of psychotropic/psychiatric drugs. e.g. If the SERT and CYP profile results come back as efficient metabolisers then experts, if not adequately trained in pharmacogenetics, may mistakenly believe severe side effects have nothing to do with medications.

Consequently this assumption could be interpreted as a manifestation of an underlying 'disease' rather than the toxic effects of medication.

It needs to be remembered there are other variations and diversities in your genome, which may effect how you process antidepressant drugs.

Every person is different,
One size does not fit all.

No one really knows how psychotropic drugs, or any other drugs, are processed in individuals.

The important thing is to be fully informed about likely side effects before taking any antidepressant drugs, and to think seriously about the alternatives and other options such as…

Psychological Therapies

Pharmacogenetic Education

It is important for doctors and pharmacists to be proficiently educated about pharmacogenetics in relation with antidepressant drugs.

This will enable mental health practitioners to be mindful that severe adverse reactions such as hallucinations, psychosis, suicidal ideation and mania may be antidepressant induced.

An awareness of pharmacogenetics for patients and professionals is empowering and contributes to safer drug use and a positive outcome.

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., Kroll K., Dunkel M., Goldsobel G., Kuzmann D., Senger S., Günther S., Winnenburg R., Schroeder M. and Preissner R.
Nucleic Acids Res 38(Database issue): D237-43. (2010)
http://bioinformatics.charite.de/supercyp/

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

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

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

Useful websites and papers:

Cytochrome P450 Enzymes and Psychopharmacology
Sheldon H. Preskorn, M.D. and Anne T. Harvey, Ph.D.
http://www.acnp.org/g4/GN401000086/CH085.html

Putting Pharmacogenetics into Practice
Michael M Hopkins et al
http://www.york.ac.uk/res/pgx/publications/nbt0406.pdf

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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