

Pharmacogenetics and personalized medicine

Michael Adams Conroy's Tragedy ^[1]

In October 2000 Fortune magazine published a story of a boy who died because personalized medicine was not available. Young child born to abusive mother adopted to age 3 with signs of obsessive compulsive disorder prescribed Prozac® [Fluoxetine] to control his emotional outbursts. The child died suddenly and TOX test showed massive overdose of Prozac®. The death of nine-year-old Michael Adams-Conroy didn't seem at first time like a signal event in medicine.... While recuperating from what seemed to be flu, Michael went into a prolonged grand mal seizure and died. His grieving parents Jayne and Neil soon got another shock an autopsy showed a massive overdose of Prozac in Michael's blood and tissues raising the specter of a murder charge against them..... Adoptive parents investigated for homicide and their other two children put into protective custody. Michael's Prozac level were accumulating after every dose little drug was being cleared from his system ..

He was poor metabolizer of drug through his CYP450 2D6 genotype which convert Prozac and many other drugs to form lead to their excretion. Based on this evidence the homicide investigations was closed. Hazardous metabolic deficiencies like Michael's are far more common than many doctors realize. Current concepts in drug therapy often attempt drug Treatment of large patient populations as groups, Irrespective of the potential for individual, genetically Based differences in drug response It is well recognized that most medications exhibit wide inter-patient variability in their efficacy and toxicity .

What is Pharmacogenetics?

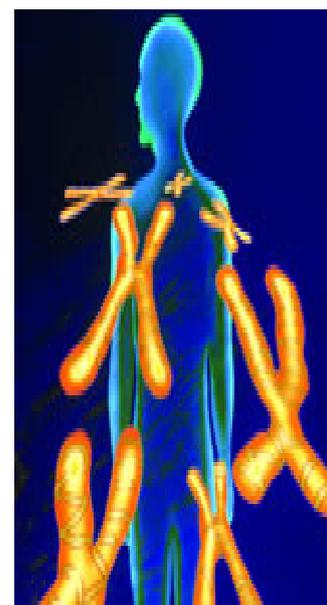
is the study of how the genetic variations affect drug response in individual patients. The traditional pharmacogenetic approach relies on studying sequence variations in candidate genes that probably affect drug response. Pharmacogenetics may help focus effective therapy on smaller patient subpopulations which although demonstrating the same disease phenotype are characterized by distinct genetic profiles.

Special points of interest:

- What is Pharmacogenetics.
- What is Genetic polymorphism.

Inside this issue:

- Pharmacogenetics and personalized medicine .
- St.John's words



Advances in molecular toxicology have shown that diversity of drug metabolizing enzymes becomes extremely important to consider the drug toxicity. For an increasing number of such enzymes, allelic variants with different catalytic activities from those of the wild-type form have been identified. As the toxicological aspects of genetic polymorphism, idiosyncratic toxicity of drugs and chemicals has been reported. [2] In this meeting, Fluoxetine (Prozac®) induced toxicity will be described [3].

What is Genetic polymorphism?

The occurrence in a population or among populations of several phenotypic forms associated with mutant alleles of one gene or homologs of one chromosome. The major polymorphically expressed P450 enzyme is CYP2D6. Based on the ability of the drug metabolizing enzymes, four phenotypic subpopulations of metabolizers exist. CYP2D6 acts on 25% of drugs including the SSRI, TCA, Beta blockers, opioids, Quinidine, Phenformin, Halopridol, cyclobenzaprine, cimetidine, Tamoxifen, Loratidine, Propafenone [3].

Approximately 10% of the population has a slow acting form of this enzyme and 7% a super-fast acting form. 35% are carriers of non-functional CYP2D6 allele, especially elevating the risks of adverse drug reactions when these individuals are taking multiple drugs.

Numerous genes in particular those encoding drug metabolizing enzymes, drug transporters and drug targets, have been identified to play a role in drug response and toxicity.

All of this will lead to novel approaches in drug discovery, individualized dosing of medications, and new insights into disease susceptibility and prevention. Due to the importance of pharmacogenetics, the great potential application of pharmacogenetics in future medicine and drug development, along with the vital role of pharmacists in healthcare, pharmacy students must be educated with suitable knowledge in pharmacogenetics [2].

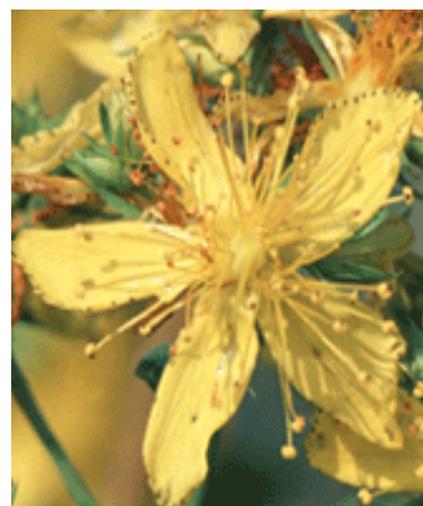
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1. FORTUNE Magazine October 30, 2000, By David Stipp .
2. SHUFENG ZHOU. [Teaching of clinical pharmacogenetics for pharmacy student at national university of Singapore.] pharmacy education, September/ December 2005; 5(3/4): 253-240.
3. Werner Kalow Pharmacogenetics and personalized medicine. Blackwell science fundamental and clinical pharmacology 16(2002)337-324.

St. John's wort

St. John's wort is a plant with yellow flowers whose medicinal uses were first recorded in ancient Greece. The name St. John's wort apparently refers to John the Baptist, as the plant blooms around the time of the feast of St. John the Baptist in late June.

Common Names—St. John's wort, hypericum, Klamath weed, goat weed
Latin Name—*Hypericum perforatum*.



St. John's wort uses :

- for the treatment of mild to moderately severe depressive disorders.
- to treat mental disorders and nerve pain.
- used as a sedative and a treatment for malaria, as well as a balm for wounds, burns, and insect bites.
- Hyperforin, a major constituent, has also been found to have antibacterial properties; in ultrapurified form a concentration of 0.1 mg/ml kills methicillin-resistant *Staphylococcus aureus*.
- It may decrease alcohol intake. The constituent hyperforin (found in the plant) appears to be responsible for decreasing alcohol consumption.

Clinical studies of St John's wort preparations have mainly focused on the efficacy of the herb in clinical depression. Several studies and meta-analyses have found it to be effective in the treatment of mild to moderate depression, with fewer side effects than many conventional antidepressants. Other studies, including a major National Institutes of Health (NIH) study that focused on participants with major depression, have shown no improvements. In Europe, St. John's wort is widely prescribed for depression.

St. John's wort products are sold as :

- Capsules ,tablets ,Teas ,Liquid extracts .

Pharmacology

The mechanism by which St John's wort exert its action as antidepressant is believed to involve inhibition of serotonin (5-HT) reuptake this action is due to hyperforin and hypericin . that hyperforin is the major constituent responsible for antidepressant activity, and it has been shown to inhibit the uptake of 5-HT, dopamine, noradrenaline, GABA and glutamate.

Adverse effects

- The most common adverse effects reported are gastrointestinal symptoms, dizziness, confusion, tiredness and sedation.
- trigger mania in bipolar patients.
- rarely cause photosensitivity .

Drug interactions**• Pharmacokinetic interactions**

St John's wort has been shown to cause multiple drug interactions mainly through induction of the cytochrome P450 enzyme. This results in the increased metabolism of those drugs, resulting in decreased concentration and clinical effect. The principal constituent thought to be responsible is hyperforin .

Class	Drugs
antiretrovirals	non-nucleoside reverse transcriptase inhibitors, protease inhibitors
benzodiazepines	alprazolam , midazolam
hormonal contraception	Contraceptives St John's wort may reduce the effectiveness of oral contraceptives by up to 50%.
immunosuppressants	calcineurin inhibitors , ciclosporin , tacrolimus
others	digoxin , methadone , omeprazole , phenobarbital , theophylline , warfarin , levodopa , suboxone .

Pharmacodynamic interactions

St John's wort may also contribute to [serotonin syndrome](#) in combination with other drugs which may elevate [5-HT](#) (serotonin) levels in the [central nervous system](#) (CNS).

Drugs which may contribute to

Class	Drugs
antidepressants	MAOIs , TCAs , SSRIs , mirtazapine , venlafaxine
opioids	tramadol , pethidine
CNS stimulants	phentermine , diethylpropion , amphetamines , sibutramine
5-HT₁ agonists	triptans
illicit drugs	methylenedioxyamphetamine (MDMA), lysergic acid diethylamide (LSD), cocaine
others	selegiline , tryptophan , buspirone , lithium , linezolid , dextromethorphan , 5-HTP .

References:

- 1- National Center for Complementary and Alternative Medicine. *St. John's Wort and the Treatment of Depression*. [National Center for Complementary and Alternative Medicine Web site](#). Accessed June 29, 2007.
- 2- Hypericum Depression Trial Study Group. [Effect of Hypericum perforatum \(St. John's wort\) in major depressive disorder: a randomized controlled trial](#). *Journal of the American Medical Association*. 2002;287(14):1807–1814.

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