Clinical Implementation of Psychiatric Pharmacogenomic Testing

David A. Mrazek, M.D., F.R.C.Psych.
Mayo Clinic

Characterizing and Displaying Genetic Variants for Clinical Action
December 2, 2011

Relationships of Potential Interest

I am a full time employee of the Mayo Clinic

The Mayo Clinic has a small equity interest in a company which is named AssureRx Health.

AssureRx has licensed intellectual property from the Mayo Clinic and I am one of the inventors of this intellectual property.

AssureRx Health has built a web-based electronic interface to support pharmacogenomic decision making in clinical practice.

My Objectives

- To review how pharmacogenomic testing is currently being used in clinical practice at the Mayo Clinic

- To discuss how “clinical utility” should be assessed when practicing individualized medicine

The Implementation of Psychiatric Pharmacogenomic Testing at Mayo

- CYP2D6 clinical genotyping initiated in February 2003 and results were included in the EMR.
- Mayo Medical Laboratories began offering CYP2D6, CYP2C19, and CYP2C9 genotyping in April 2004.
- Pharmacogenomic testing became regularly used in the psychiatric practice by 2006.
- Introduction of the algorithmic panel report with subsequent initiation of a series of clinical utility studies in 2009.

Consider a CYP 450 Profile. A 43 Year Old Caucasian woman is being considered for an SSRI. Should this variant be routinely used?

Definitely Yes	3%
Probably Yes	13%
Probably Not	38%
Definitely Not	16%
Don’t Know or No Opinion	31%

Consider a CYP 450 Profile. A 43 Year Old Caucasian woman is being considered for an SSRI. Should this variant be routinely used?

Related Questions:

1. What is CYP 450 Profile?
2. Why is this woman receiving an SSRI?
3. What variant is being considered?
4. What does “routinely” mean?

What gene variants are included in a typical algorithmic genotyping profile to guide the selection and dosing of antidepressants and antipsychotic medications?

CYP2D6	12 variants and indels
CYP2C19	5 variants
CYP2C9	3 variants
CYP1A2	6 variants
SLC6A4	3 variants and indels
HTR2A	3 variants
HTR2C	1 variant

An important concept is that many variants are included in clinical algorithms

Is knowing that a Patient has Impaired CYP 2D6 Metabolic Capacity Actionable?

This is a very different question than :

Are the results of a pharmacogenomic algorithm designed to provide physician guidance on the selection and dosing of antidepressant medication actionable?

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

GENOMIC MEDICINE

Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D., *Editors*

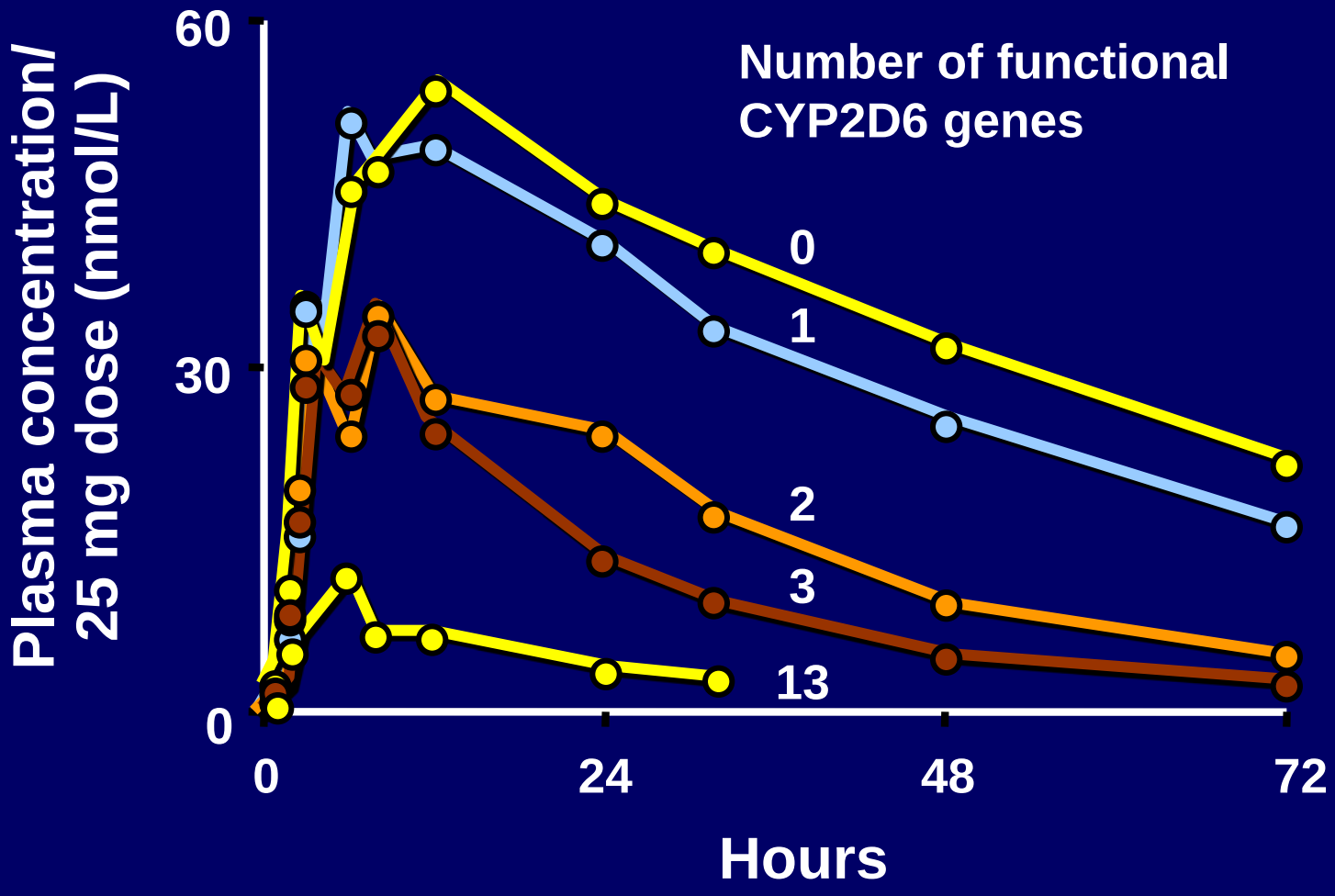
Inheritance and Drug Response

Richard Weinshilboum, M.D.

THE PROMISE OF PHARMACOGENETICS, THE STUDY OF THE ROLE OF INheritance in the individual variation in drug response, lies in its potential to identify the right drug and dose for each patient. Even though individual differences in drug response can result from the effects of age, sex, disease, or drug interactions, genetic factors also influence both the efficacy of a drug and the likelihood of an adverse reaction.[1-3] This article briefly reviews concepts that underlie the emerging fields of pharmacogenetics and pharmacogenomics, with an emphasis on the pharmacogenetics of drug metabolism. Although only a few examples will be provided to illustrate concepts and to demonstrate the potential contribution of pharmacogenetics to medical practice, it is now clear that virtually every pathway of drug metabolism will eventually be found to have genetic variation. The accompanying article by Evans and McLeod[4] expands on many of the themes introduced here.

From the Departments of Molecular Pharmacology and Experimental Therapeutics and Medicine, Mayo Medical School, Mayo Clinic, and Mayo Foundation, Rochester, Minn. Address reprint requests to Dr. Weinshilboum at the Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Medical School–Mayo Clinic–Mayo Foundation, Rochester, MN 55905, or at weinshilboum.richard@mayo.edu.

Nortriptyline Pharmacogenetics



ORIGINAL ARTICLE

A Fatal Doxepin Poisoning Associated With a Defective *CYP2D6* Genotype

Anna Koski, PhD, Ilkka Ojanperä, PhD, Johanna Sistonen, MSc, Erkki Vuori, MD, PhD, and Antti Sajantila, MD, PhD

Abstract: It has been suggested that the polymorphism of the *CYP2D6* gene can contribute to occurrence of fatal adverse effects. We therefore investigated postmortem toxicology cases of fatal drug poisonings related to CYP2D6 substrates, with the manner of death denoted as accidental or undetermined. *CYP2D6* genotypes were determined in 11 consecutive cases with samples available for DNA analysis. A case of fatal doxepin poisoning with an undetermined manner of death was found to coincide with a completely nonfunctional *CYP2D6* genotype (*3/*4), indicating a total absence of CYP2D6 enzyme and suggesting a poor metabolizer phenotype.

The doxepin concentration was 2.4 mg/L, the concentration of nordoxepin 2.9 mg/L, and the doxepin/nordoxepin ratio 0.83, the lowest found among the 35 nordoxepin-positive postmortem cases analyzed during the same year. No alcohols or other drugs were detected in the case. The CYP2C19 genotype was determined as that of an extensive metabolizer.

The high *N*-desmethylmetabolite concentration is not consistent with acute intoxication. It is therefore probable that the defective genotype has contributed to the death, possibly involving repeated high dosage of doxepin. Our case strongly emphasizes that a pharmacogenetic analysis in postmortem forensic setting may reveal new insight to the cause or manner of death.

Key Words: doxepin, fatal intoxication, pharmacogenetics, CYP2D6

(*Am J Forensic Med Pathol* 2007;28: 259–261)

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Volume 10, Number 1, 2000
Mary Ann Liebert, Inc.
Pp. 27–34

Case Report

Fluoxetine-Related Death in a Child with Cytochrome P-450 2D6 Genetic Deficiency

FLOYD R. SALLEE, M.D., Ph.D.,[1] C. LINDSAY DEVANE, Pharm.D.,[2] and ROBERT E. FERRELL, Ph.D.[3]

ABSTRACT

The clinical course of a 9-year-old diagnosed with attention-deficit hyperactivity disorder, obsessive-compulsive disorder, and Tourette's disorder and treated with a combination of methylphenidate, clonidine, and fluoxetine is described. The patient experienced over a 10-month period, signs and symptoms suggestive of metabolic toxicity marked by bouts of gastrointestinal distress, low-grade fever, incoordination, and disorientation. Generalized seizures were observed, and the patient lapsed into status epilepticus followed by cardiac arrest and subsequently expired. At autopsy, blood, brain, and other tissue concentrations of fluoxetine and norfluoxetine were several-fold higher than expected based on literature reports for overdose situations. The medical examiner's report indicated death caused by fluoxetine toxicity. As the child's adoptive parents controlled medication access, they were investigated by social welfare agencies. Further genetic testing of autopsy tissue revealed the presence of a gene defect at the cytochrome P450 *CYP2D* locus, which results in poor metabolism of fluoxetine. As a result of this and other evidence, the investigation of the adoptive parents was terminated. This is the first report of a fluoxetine-related death in a child with a confirmed genetic polymorphism of the *CYP2D6* gene that results in impaired drug metabolism. Issues relevant to child and adolescent psychopharmacology arising from this case are discussed.

INTRODUCTION

THE USE OF PSYCHOTROPIC MEDICATIONS in children and adolescents is frequently accompanied by an uncertainty of predictable pharmacologic effects. This is partly due to a relative lack of data from controlled clinical trials supporting safety, tolerability, and efficacy in these age groups. In recent years, the field of child psychopharmacology has been shaken by the realization that such practices might be haz-

[1]Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio.
[2]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina.
[3]Department of Human Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania.

Is knowing that a Patient has severely impaired CYP2D6 Metabolic Capacity Actionable?

- Would you give this patient Prozac, Paxil, or Effexor?
- Would you give this patient Norpramin or Tofranil?
- Would you give this patient Haldol or Risperidol?
- Would you give this patient Strattera?
- Would you give this patient codeine?

- Would you give this patient Celexa, Lexapro, or Luvox?
- Would you give this patient Cymbalta or Pristiq?
- Would you give this patient Zyprexa or Geodon?
- Would you give this patient Concerta?

A Pharmacogenomic Report with Decreased Metabolic Capacity

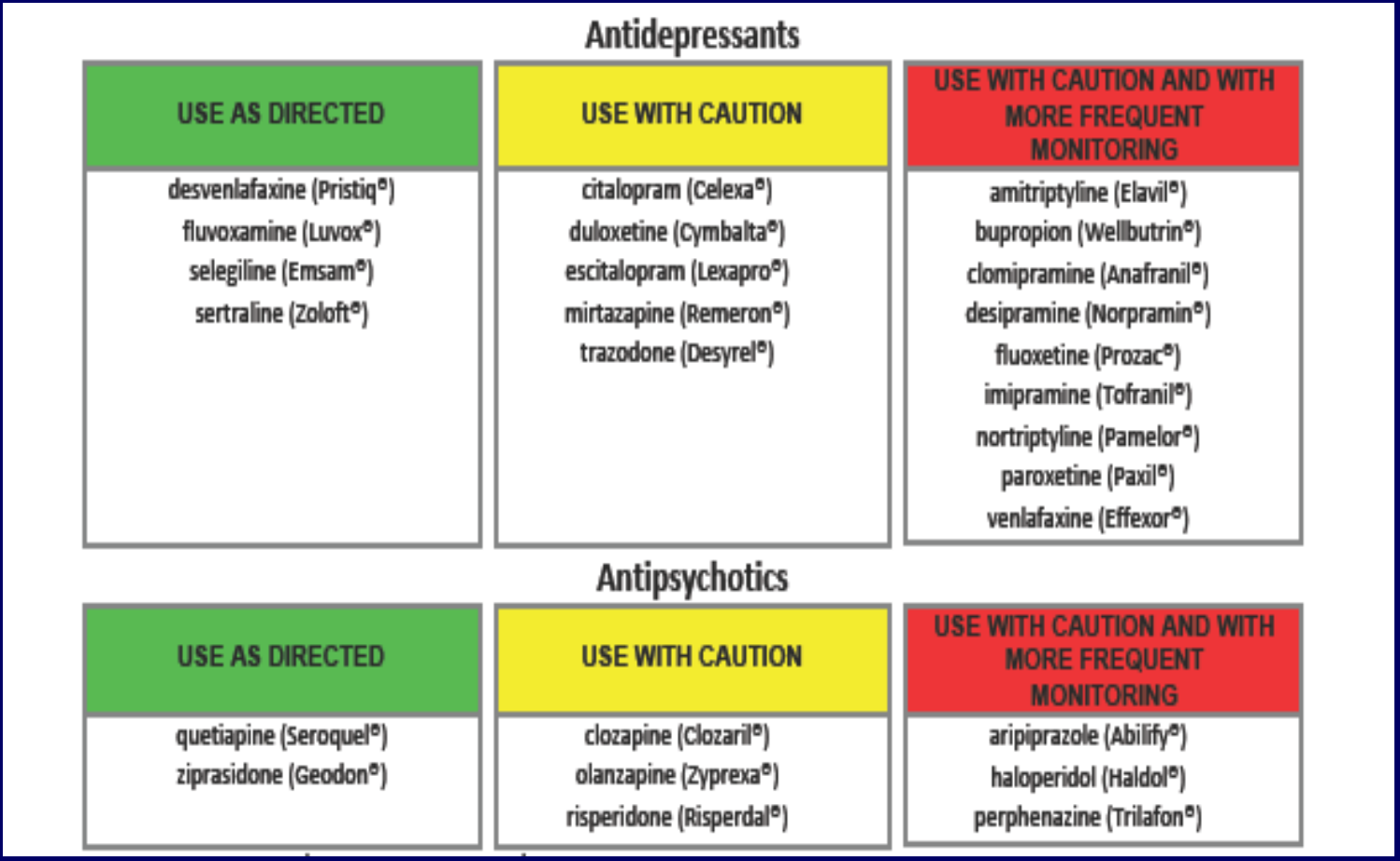
Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®)	amitriptyline (Elavil®)	
duloxetine (Cymbalta®)	bupropion (Wellbutrin®)	
fluvoxamine (Luvox®)	citalopram (Celexa®)	
mirtazapine (Remeron®)	clomipramine (Anafranil®)	
selegiline (Emsam®)	desipramine (Norpramin®)	
	escitalopram (Lexapro®)	
	fluoxetine (Prozac®)	
	imipramine (Tofranil®)	
	nortriptyline (Pamelor®)	
	paroxetine (Paxil®)	
	sertraline (Zoloft®)	
	trazodone (Desyrel®)	
	venlafaxine (Effexor®)	

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
clozapine (Clozaril®)	aripiprazole (Abilify®)	
olanzapine (Zyprexa®)	haloperidol (Haldol®)	
quetiapine (Seroquel®)	perphenazine (Trilafon®)	
ziprasidone (Geodon®)	risperidone (Risperdal®)	

A pharmacogenomic report illustrating impaired 2D6 and 2C19 metabolism



Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
desvenlafaxine (Pristiq®)	citalopram (Celexa®)	amitriptyline (Elavil®)
fluvoxamine (Luvox®)	duloxetine (Cymbalta®)	bupropion (Wellbutrin®)
selegiline (Emsam®)	escitalopram (Lexapro®)	clomipramine (Anafranil®)
sertraline (Zoloft®)	mirtazapine (Remeron®)	desipramine (Norpramin®)
	trazodone (Desyrel®)	fluoxetine (Prozac®)
		imipramine (Tofranil®)
		nortriptyline (Pamelor®)
		paroxetine (Paxil®)
		venlafaxine (Effexor®)

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH CAUTION AND WITH MORE FREQUENT MONITORING
quetiapine (Seroquel®)	clozapine (Clozaril®)	aripiprazole (Abilify®)
ziprasidone (Geodon®)	olanzapine (Zyprexa®)	haloperidol (Haldol®)
	risperidone (Risperdal®)	perphenazine (Trilafon®)

COMMENTARY

Facilitating Clinical Implementation of Pharmacogenomics

David A. Mrazek, MD, FRCPsych

Caryn Lerman, PhD

JAMA, July 20, 2011—Vol 306, No. 3

What level of evidence is needed for wider clinical adoption?

- In the past, the standard of a prospective randomized clinical trial (RCT) has been the necessary condition to justify adoption.

- However, the nature of the questions being addressed in testing many relatively uncommon variants raise the issue of whether pragmatic clinical trials (PCT) in “real world” settings should be considered as an alternative to RCTs.

What types of studies should be considered to evaluate clinical utility? (as opposed to concerns for safety)

- Retrospective studies of clinical practice
- Prospective studies in “real world” practice settings (i.e. pragmatic clinical trials}

A Retrospective Study the Psychiatric Consultation Practice at the Mayo Clinic

- Reviewed the care of 2390 patients from 2006-2010
- 19% of the consultation practice patients were tested
- 58% of the more seriously treatment resistant patients were provided pharmacogenomic testing

Rundell et al, 2011 Translational Psychiatry

Two Prospective PCT Outpatient Studies

- Hamm Clinic in St. Paul
  - Proof of Principe (n=60)
  - 31.2% reduction in depressive symptoms with testing versus 7.2% reduction without testing ($p < .02$)
- Mayo Health System in La Crosse, Wisconsin
  - Replication Study (n = 200)
  - 44.8% reduction in depressive symptoms with testing versus 26.4% reduction without testing ($p < .001$)

Hall-Flavin et al, under review

Conclusion: Decision support algorithmic reports will accelerate the implementation of clinical testing

- Initial laboratory reports that only reported genotypes and predicted phenotypes were assessed by clinicians as not being very helpful.
- Recognition of the need to develop a clinical algorithm led to the creation of a new approach to reporting results.
- An improved strategy of reporting has proven to be to “sort” the available psychotropic medications into categories that clinicians perceive to be useful.

Questions and Comments

Carbamazepine and Steven Johnson Syndrome: An example of rapid adoption in psychiatry

- Asian patients were shown to have a higher risk of skin reactions if they had an HLA-B *1502 allele.

- On December 12, 2007, the FDA issued a warning stating that in at risk patients of Asian ancestry genotyping was necessary prior to prescribing carbamazepine.

Antiepileptic Black Box Warning

Serious Dermatologic Reactions and HLA-B*1502 Allele

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with antiepileptics. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with antiepileptics. Patients testing positive for the allele should not be treated with antiepileptics unless the benefit clearly outweighs the risk.

Mayo Clinic Response

- A new laboratory test was available within one month
- Physician education was not addressed using an institution-wide strategy
- An electronic prompt in the medication ordering software is still not in place