



Pharmacogenomic Approaches for the Use of Psychotropic Medications

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Lecture Objectives



- ▶ Explain the role of pharmacists in the field of pharmacogenomics and personalized medicine.
- ▶ Describe the utility of pharmacogenomics testing and the implications for pharmacy practice.
- ▶ Discuss the current status of pharmacogenomics testing to facilitate the selection of select psychotropic medications.
- ▶ Identify ways pharmacogenomics can be used to assist with treating psychiatric disorders.
- ▶ Discuss ways that pharmacists can be useful in incorporating pharmacogenomic principles in psychiatric practice.
- ▶ Apply medication management strategies for patients with mental illness through case discussions.


Opportunities for PG Testing in General

- ▶ Drug treatments for which efficacy responses are unpredictable.
- ▶ Drugs that cause serious adverse events resulting in patient harm.
- ▶ Serious and non-serious adverse drug events or complications that cause drug failure or substantially delay successful treatment of disease.
- ▶ Drug treatments that have marked efficacy in small subpopulations but dramatically less efficacy in larger populations with a given disease.



Background


- ▶ Diagnosis of psychiatric disorders is variable and subjective.
- ▶ Psychiatric disorders are inheritable.
- ▶ Adherence is challenging in psychiatric disorders.
- ▶ Treatment options for psychiatric disorders can cause medical and life-threatening side and adverse effects.



Why Consider Pharmacogenomics in Psychiatry?

Identify a "limitation" to using the following psychotropics:

- ▶ Antidepressants
- ▶ Antipsychotics
- ▶ Anxiolytics
- ▶ Anticonvulsants
- ▶ Mood Stabilizers
- ▶ Sedative Hypnotics



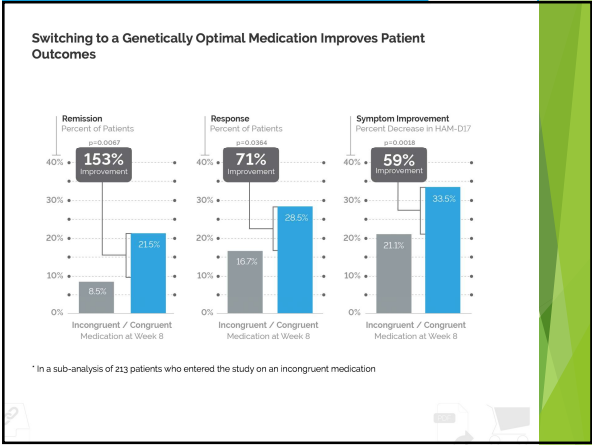
Knowledge Check

▶ How soon do the following classes of psychotropics take to start providing their therapeutic effects?

- ▶ Antidepressants
- ▶ Antipsychotics
- ▶ Mood stabilizers
- ▶ Benzodiazepines
- ▶ Sedative hypnotics
- ▶ Stimulants/Non-stimulants

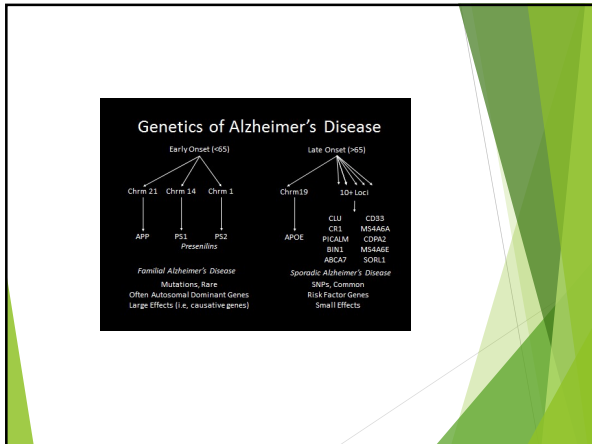
Scope of the Problem in Psychiatry

- ▶ Before a patient sees a psychiatrist, it is estimated that **2.9** psychotropic medications fail and it takes an average of **34 months** to identify the right medications.
- ▶ It is estimated that **30%** of patients receiving a psychotropic medication has significant gene-drug interactions. (Patient Medco Study)



Purpose of Pharmacogenetic Testing

- ▶ Disease Risk Prediction
 - ▶ i.e., APOE/Alzheimer's disease
- ▶ Drug Response Prediction




What is currently being done by pharmacists?

- ▶ Sequencing
- ▶ DNA Extraction
- ▶ Algorithms
- ▶ Interpretations
- ▶ Implementation
- ▶ Polymorphisms
- ▶ Bioinformatics
- ▶ Data security
- ▶ Monitoring
- ▶ Standardizing recommendations

Companies that Are Doing Pharmacogenetic Testing

- ▶ AssureRx
- ▶ Millenium Pharmaceuticals
- ▶ GenoMind
- ▶ PGXL Labs
- ▶ Roche Diagnostics (AmpliChip R CYP450)
- ▶ Illumina's VeraCode ADME core panel
- ▶ Affymetrix (DMET Plus Premier Pack)
- ▶ Genelex (YouScript®)
- ▶ Dynamic DNA

Mental Health Panel Medications List



Antidepressants		Anticonvulsants cont'd	
Brand Name	Generic Name	Brand Name	Generic Name
Wellbutrin, Zyban, Aplentin	Bupropion	Vimpat	Lacosamide
Vivitrol	Naltrexone	Zarontin	Ethosuximide
		Zonegran	Zonisamide


Anti-ADHD Agents		Antidementia Agents	
Brand Name	Generic Name	Brand Name	Generic Name
Adderall	Amphetamine	Aricept	Donepezil
Dexedrine	Dextroamphetamine	Namenda	Memantine
Focalin	Dexmethylphenidate	Razadyne	Galantamine
Intuniv	Guafacine		
Kapvay	Clonidine		
Ritalin	Methylphenidate		
Strattera	Atomoxetine		
Vyvanse	Lisdexamfetamine		

Antidepressants	
Brand Name	Generic Name
Amoxapine	Amoxapine
Anafanil	Clomipramine

Population Frequency of Cytochrome P450 (CYP) Genotypes


Gene	PM	IM	EM	RM & UM
CYP4502D6	10%	35%	48%	7%
CYP4502C9	2-4%	>35%	~60	N/A
CYP4502C19	2-20%	24-36%	14-44%	30%

CYP2C19 variability depends on ethnicity



Limits with Pharmacogenetic Testing

- ▶ High cost
- ▶ Long turn around time
- ▶ Sensitivity of tests



FDA-Approved Drugs with Pharmacogenomic Info in Their Labels

Psychotropic	Medication
Antidepressants	Citalopram, Clomipramine, Doxepin, Desipramine, Fluoxetine, Fluvoxamine, Imipramine, Nefazodone, Nortriptyline, Paroxetine, Protriptyline, Trimipramine, Venlafaxine
Antipsychotics	Aripiprazole, Clozapine, Iloperidone, Pimozide, Risperidone, Thioridazine
Anxiolytics/Sedative Hypnotics	Clobazam, Diazepam
Anticonvulsants	Carbamazepine, Valproic Acid
Miscellaneous	Atomoxetine, Modafanil

Pharmacogenomic Findings in Psychiatry- Depression/Anxiety

- ▶ Heritability is approximately 50%
- ▶ A low functioning variant of a promotor polymorphism has been identified for the gene coding for the serotonin transporter *HTTLPR* which is a target for the SSRIs.

HTTLPR may predict patients at risk for antidepressant-induced mania

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Genetic Test Interpretations

Alleles

- ▶ Functional alleles (CYP2D6*1 and *2)
- ▶ Reduced function alleles (CYP2D6*9, *10, and *41)
- ▶ Nonfunctional alleles (CYP2D6*3-*6)


Predicted functional status for 2D6 Alleles

- Functional alleles: 1
- Reduced Function alleles: 0.5
- Nonfunctional alleles: 0




Genetic Test Interpretation: Activity Scores

CYP2D6 Activity Score	Phenotype
0	Poor metabolizers
0.5	Intermediate metabolizers
1.0-2.0	Extensive metabolizers (normal)
>2.0	Ultrarapid metabolizers




Pharmacogenomic Findings in Bipolar Disorder

- ▶ Hereditary risks range from 10-20% if one parent is bipolar to <70% if both sides of the family have a strong pattern; identical twins don't always develop bipolar disorder




Pharmacogenomic Findings in Psychiatry- Bipolar Disorder

- ▶ Dr. Alexander Niculescu, III, (Indiana University School of Medicine) has identified 10 genes that are related to mood disorders.
- ▶ The genes implicated in Bipolar Disorder are found on chromosomes 4,6,12,13,15,16,21, and 22.




Pharmacogenomic Findings in Psychiatry- Lithium Response

- There is a linkage to a locus on chromosome 15q in lithium-responsive families with bipolar disorder
Mol. Psychiatry 6(5), 570-578 (2001)
- There is an association of the phospholipase C gene *PLCG1* to lithium-responsive families with bipolar disorder
Mol. Psychiatry 3(6), 534-538 (1998)
Psychiatr. Genet. 11(1), 41-43 (2001).




Pharmacogenomic Findings in Psychiatry-Bipolar Disorder

- ▶ The BDNF gene has been implicated in rapid cycling in Bipolar Disorder
- ▶ This gene inhibits GSK3beta
- ▶ GSKbeta is inhibited by lithium and valproic acid
 - ▶ *Hum Mol Genet. 2013 Jun 27. (Epub)*




Pharmacogenomic Findings in Psychiatry-Antipsychotics

- ▶ Clozaril
 - ▶ Allele at HLA-DQB1 locus associated with the risk of agranulocytosis
 - ▶ Sensitivity of the marker was 21%
 - ▶ *J Clin Psych* 2011;72:458-463




Pharmacogenomic Findings in Psychiatry-Antipsychotics

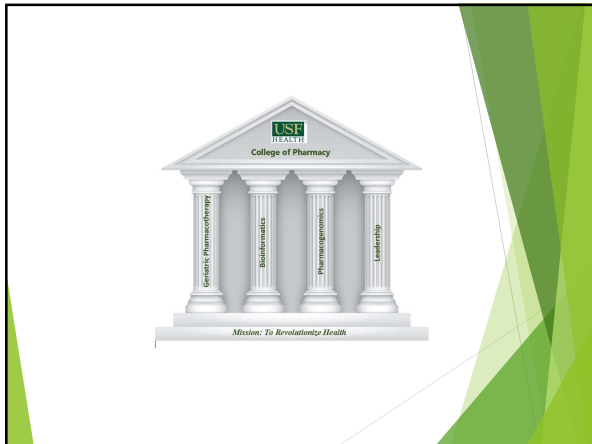
- ▶ Weight gain may be associated with polymorphisms on the 759 C or T alleles in the 5-HT_{2C} receptor gene (studies involving risperidone, chlorpromazine, and olanzapine)
 - ▶ *Lancet* 2002;359:2086-2087
 - ▶ *Pharmacogenet Genomics* 2005;15:195-200



Pharmacogenomic Findings in Psychiatry-Response to Antipsychotics

- ▶ DRD2 is associated with poor response to antipsychotic drugs, and also increases the liability of weight gain induced by antipsychotics
 - ▶ *Pharmacogenet Genomics* 2010;20:569-572





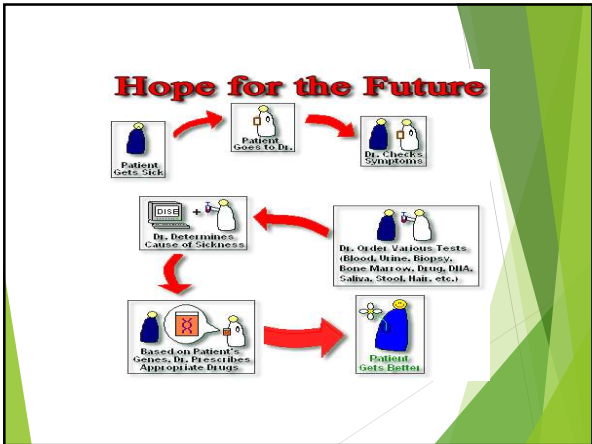




Case Studies for Genetics

Helpful Websites

- ▶ Visit: www.drugs.com
- ▶ www.pharmgkb.com



Applications

Learning Assessment Questions

1. Prediction of disease risk or _____ can currently be analyzed with pharmacogenomics testing.

- A. Side effects
- B. Drug response
- C. Drug interactions
- D. Dosing specifics

Learning Assessment Questions

2. Which of the following polymorphism may be associated with a patient not responding to lithium?

- A. Phospholipase C gene *PLCG1*
- B. MHFR
- C. GSKbeta
- D. HLA-DQB1

Learning Assessment Questions

3. Pharmacogenomic testing may be beneficial in determining patients at risk for _____ who receive clozapine.

- A. Hypersalivation
- B. Metabolic syndrome
- C. Seizures
- D. Agranulocytosis

Learning Assessment Questions

4. Pharmacogenomic testing may be beneficial in determining patients at risk for _____ who receive risperidone.

- A. Weight gain
- B. Sedation
- C. Akathisia
- D. EPS

Learning Assessment Questions

5. GSKbeta is inhibited by lithium and _____.

- A. Olanzapine
- B. Chlorpromazine
- C. Valproic Acid
- D. Clozapine

