The Use of Pharmacogenomics in Mental Health Medication Management

The study of how genes affect a person’s response to medication
Pharmacogenomics

The science that allows us to predict a response to drugs based on an individual’s genetic makeup
Pharmacogenomics and Mental Health Medications

- Pharmacogenomics explains why:
  - One patient has the anticipated response
  - One patient has adverse reactions
  - One patient has no clinical response to the same medication, at similar dosing.

- Pharmacogenomics and genetic testing:
  - Influences clinician decision-making
  - Increases treatment response
  - Increases patient compliance and costs
Personalized Medicine
How does this happen?
Key Terms

- **Pharmacokinetics**: how drugs are metabolized, what the body does to the drug.
- **Pharmacodynamics**: what the drug does to the body.
- **Gene**: the basic unit of hereditary function
- **Phenotype**: characteristic that is the result of gene expression (drug metabolism)

~Cytochrome P450 (CYP450) System~
What is the CYP450 System?

- A collection of enzyme that are responsible for the metabolism of medications.

- These enzyme genes help determine how much of the drug will be available for the body to use.

- The activity of these enzymes are genetically determined.

- These enzymes are highly concentrated in the liver and small intestines.

- 57 enzyme genes have been identified, over 100 subtypes
Drug Metabolism and CYP450

- Most drugs metabolize via CYP450 enzyme gene systems: CYP 3A4 (47%), CYP 2D6 (25%), CYP 1A2 (15%), CYP 2C9/19 (13%),
## CYP450 Enzymes and Psychotropic Medications

<table>
<thead>
<tr>
<th>CLASS</th>
<th>1A2</th>
<th>2B6</th>
<th>2C9/19</th>
<th>2D6</th>
<th>3A4</th>
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<tbody>
<tr>
<td>Antianxiety</td>
<td></td>
<td></td>
<td>Diazepam</td>
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<td>Alprazolam</td>
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<td>Clonazepam</td>
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<td>Diazepam</td>
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<td>Dementia</td>
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<td>Donepezil</td>
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<td>Galantapine</td>
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<td>Antidepressant</td>
<td>Amitriptyline</td>
<td>Bupropion</td>
<td>Amitriptyline</td>
<td>Paroxetine</td>
<td>Citalopram</td>
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<td></td>
<td>Duloxetine</td>
<td>Sertraline</td>
<td>Citalopram</td>
<td>Venlafaxine</td>
<td>Sertraline</td>
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<td>Fluvoxamine</td>
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<td>Fluoxetine</td>
<td>Mirtazapine</td>
<td>Mirtazapine</td>
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<td>Antipsychotic</td>
<td>Clozapine</td>
<td></td>
<td></td>
<td>Aripiprazole</td>
<td>Trazadone</td>
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<td></td>
<td>Haldoperidol</td>
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<td>Risperidone</td>
<td>Zolpidem</td>
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<td>Olanzapine</td>
<td></td>
<td></td>
<td>Iloperidone</td>
<td>Eszopiclone</td>
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<td>Hypnotic</td>
<td>Melatonin</td>
<td></td>
<td>Doxepin</td>
<td>Trazadone</td>
<td>Carbamazapine</td>
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<tr>
<td>Mood Stabilizer</td>
<td></td>
<td></td>
<td></td>
<td>Zolpidem</td>
<td></td>
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<tr>
<td>Stimulant</td>
<td></td>
<td></td>
<td></td>
<td>Modafinil</td>
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<tr>
<td>Other</td>
<td>Propranolol</td>
<td></td>
<td>Benztropine</td>
<td>Clonidine</td>
<td>Guanfacine</td>
</tr>
</tbody>
</table>
14 Genes involved in Psychotropic Medication Metabolism

- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2
- Catecholamine-O-methyltransferase gene
- Norepinephrine transporter gene
- Dopamine transporter gene
- Serotonin Transporter gene
- Serotonin 1A receptor gene
- Serotonin 2A receptor gene
- Serotonin 2C receptor gene
- D2 dopamine receptor gene
- D3 dopamine receptor gene
- D4 dopamine receptor gene
Genes and Metabolism

- Drug metabolism is determined by the pair of genes inherited from one’s parents.

- Play an important role in either the pharmacokinetic availability or pharmacodynamic effect of mental health medications.

- 4 inherited metabolism categories: extensive metabolizer, intermediate metabolizer, poor metabolizer, ultra-rapid metabolizer
Pharmacogenomics: Types of Metabolizers

- **Extensive Metabolizer**
  - Normal drug doses are metabolized at a normal rate

- **Intermediate Metabolizer**
  - Reduced rate of metabolism
  - Drug may not be tolerated
  - May required decreased dosage, slower titration
  - CYP2D6 variation: 7-12% of the population

- Variations in CYP450 2C19:
  - 30% European ancestry
  - 40% African American ancestry
  - 55% Asian ancestry
Pharmacogenomics: Types of Metabolizers—con’t

- Poor Metabolizers
  - Drug is not tolerated, potentially harmful
  - Slow rate of metabolism
  - Alternate treatment should be used
  - CYP2D6 variation: up to 35% of the population
    - Variations in CYP450 2C19
      - 2% European ancestry
      - 4% African American ancestry
      - Up to 20% Asian ancestry
Pharmacogenomics
Types of Metabolizers-con’t

- Ultra-rapid Metabolizers
  - Rapid metabolism with loss of therapeutic effect.
  - May require an increase dose
  - CYP2D6 variation: up to 29% of Asian population
Inducers and Inhibitors

- **Inducers**: drugs that *stimulate* CYP450 synthesis
  - If a drug is a CYP450 inducer of another drug...
  - the rate of drug metabolism is increased
  - = less drug bioavailability (less effect)

- **Inhibitors**: drugs that *reduce* CYP450 synthesis
  - If a drug is a CYP450 inhibitor of another drug...
  - The rate of drug metabolism is decreased
  - = more bioavailability (potential toxicity)
Important *inducers* to know:
- Steroids
- Anticonvulsant/Antiepileptics (AEDs)

Important *inhibitors* to know:
- Macrolide antibiotics
- Azole antifungals
- Antvirals
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Isoniazid (INH)
- $H_2$ blocker Cimetidine
- Grapefruit juice
- Cigarettes
Pharmacogenomic Testing

- Genetic profile is obtained
- Data analyzed and genotype is determined (ie. 2D6)
- Phenotype is assigned (ie. extensive metabolizer)
- Provider utilizes report to make medication decisions
  - Drug selection
  - Dosing
  - Drug to drug interactions
GeneSight® Psychotropic Results

Patient, Sample
DOB: 7/22/1984

Antidepressants

**USE AS DIRECTED**
- bupropion (Wellbutrin®)
- desvenlafaxine (Pristiq®)
- selegiline (Emsam®)
- vilazodone (Viibryd®)

**USE WITH CAUTION**
- amitriptyline (Elavil®) [2]
- citalopram (Celexa®) [3]
- clomipramine (Anafranil®) [2,7]
- doxepin (Sinequan®) [3]
- escitalopram (Lexapro®) [3]
- imipramine (Tofranil®) [3]
- sertraline (Zoloft®) [3]
- trazodone (Desyrel®) [2]

**USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING**
- desipramine (Norpramin®) [2]
- duloxetine (Cymbalta®) [2,7]
- fluoxetine (Prazac®) [2]
- fluvoxamine (Luvox®) [2,7]
- mirtazapine (Remeron®) [2,7]
- nortriptyline (Pamelor®) [2]
- paroxetine (Paxil®) [2,4,8]
- venlafaxine (Effexor®) [3]

Antipsychotics

**USE AS DIRECTED**
- fluphenazine (Prolixin®)
- lurasidone (Latuda®)
- paliperidone (Invega®)
- ziprasidone (Geodon®)

**USE WITH CAUTION**
- asenapine (Saphris®) [2,7]
- quetiapine (Seroquel®) [2]
- thiothixene (Navane®) [2,7]

**USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING**
- aripiprazole (Abilify®) [2]
- chlorpromazine (Thorazine®) [2,7]
- clozapine (Clozaril®) [2,7]
- haloperidol (Haldol®) [2]
- iloperidone (Fanapt®) [2]
- olanzapine (Zyprexa®) [2,7]
- perphenazine (Trilafon®) [2,7]
- risperidone (Risperdal®) [2]
- thioridazine (Mellaril®) [2,7]

[2]: Serum level may be too low, higher doses may be required.
[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[5]: Use of this drug may increase risk of side effects.
[7]: Serum level may be too low in smokers.

All psychotropic medications require clinical monitoring.
Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient’s individual needs and the characteristics of the drug prescribed.

Patient Genotypes and Phenotypes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Ultrarapid Metabolizer</td>
<td>*2A/*2A</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Intermediate Metabolizer</td>
<td>*1/*2</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Extensive Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Ultrarapid Metabolizer</td>
<td>-163C&gt;A - A/A</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>High Activity</td>
<td>L/L</td>
</tr>
<tr>
<td>HTR2A</td>
<td>Reduced Activity</td>
<td>G/G</td>
</tr>
</tbody>
</table>
### GeneSight® Psychotropic Results

**Patient Genotypes and Phenotypes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2D6</strong></td>
<td><strong>Poor Metabolizer</strong></td>
<td>*4/*4&lt;br&gt;This allele produces no enzyme activity.&lt;br&gt;This allele produces no enzyme activity.&lt;br&gt;This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.</td>
</tr>
<tr>
<td><strong>CYP2C19</strong></td>
<td><strong>Intermediate Metabolizer</strong></td>
<td>*1/*2&lt;br&gt;This allele produces normal enzyme activity.&lt;br&gt;This allele produces no enzyme activity.&lt;br&gt;This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.</td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
<td><strong>Intermediate Metabolizer</strong></td>
<td>*1/*2&lt;br&gt;This allele produces normal enzyme activity.&lt;br&gt;This allele produces reduced enzyme activity.&lt;br&gt;This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.</td>
</tr>
<tr>
<td><strong>CYP3A4</strong></td>
<td><strong>Extensive Metabolizer</strong></td>
<td>*1/*1&lt;br&gt;This allele produces normal enzyme activity.&lt;br&gt;This allele produces normal enzyme activity.&lt;br&gt;This genotype is most consistent with the extensive metabolizer (normal) phenotype.</td>
</tr>
</tbody>
</table>
# Personacene™ Patient Medication Report

<table>
<thead>
<tr>
<th>Gene*</th>
<th>Implications*</th>
<th>Therapeutic Recommendations*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3</strong></td>
<td>Poor Metabolizer of Methadone</td>
<td>May need lower dose than usual of Methadone.</td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>Normal Metabolizer of Clopidogrel</td>
<td>Start Clopidogrel at 300 mg (loading dose) and continue with 75 mg daily (maintenance dose). Avoid using Clopidogrel with omeprazole, a CYP2C19 inhibitor.</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Poor Metabolizer of Methadone</td>
<td>May need lower dose than usual of Methadone.</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Normal metabolizers are at no increased risk for adverse effects.</td>
<td>Follow label dosing and administration information. No change needed.</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>Normal metabolizers are at no increased risk for adverse effects.</td>
<td>Follow label dosing and administration information. No change needed.</td>
</tr>
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</table>

**Legend**

- **Use with increased caution and/or consider alternative therapy**
- **Use with caution**
- **Use as directed**


David G. Bostwick, M.D., M.B.A., NY COQ

This report does not take into consideration drug to drug interactions, drug sensitivity, patient history, and/or allergies. It is the responsibility of the physician to determine appropriate drug and dosing choices based on all available data.
Clinical genotype test result

- Translate variants into likely haplotypes
- Translate genotype into phenotype

Genotype
- e.g. CYP2D6 *1/*4

Phenotype
- e.g. CYP2D6 Intermediate Metabolizer

Priority determination

High Priority
- Report Drug-Gene/Drug-Drug Interactions
- Patient education
- Decision support at point of care

Routine Priority
- Report Drug-Gene/Drug-Drug Interactions
- Patient education

e.g. Alternative dosing may be required

e.g. Standard dosing practices apply
Medicine Today
Reactive, population-based, one-size-fits-all model of care

Personalized Medicine
Predictive, preventive, patient-centric model of care
References

Questions