Pharmacogenetic Opportunities in Depression and Pain Management
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University of Florida
College of Pharmacy

Objectives
• Describe pharmacogenetics and its potential to improve drug therapy
• Discuss data supporting genotype-guided prescribing of antidepressants and opiates
• List examples of pharmacogenetic implementation in clinical practice

2015 State of the Union: Precision Medicine Initiative

"...doctors have always tried to tailor their treatments as best they can to individuals. What if figuring out the right dose of medicine was as simple as taking our temperature?" -President Obama, January 20, 2015
Pharmacogenomics

- Hereditary basis for inter-individual differences in drug response.
- Goal to use genetic information to optimize drug therapy selection and dosing
  - Increase drug effectiveness
  - Minimize risk for adverse drug reactions

ASHP Statement on the Pharmacist’s Role in Clinical Pharmacogenomics

“ASHP believes that pharmacogenomic testing can improve medication-related outcomes across the continuum of care in all health-system practice settings....

“Pharmacists therefore have a fundamental responsibility to ensure that pharmacogenomic testing is performed when needed and that the results are used to optimize medication therapy.” AJHP 2015;72(7):579-81.

ASHP Foundation Pharmacy Forecast 2018 Strategic Recommendations for Practice Leaders

“Pharmacists must be precision medicine experts and leaders, understanding and applying next generation sequencing, emerging technologies, and targeted therapies to the care of their patients.” AJHP November 2017, sp180001; DOI: https://doi.org/10.2146/sp180001
Ways to Think about Drugs

• What the drug does to the body (aka – pharmacodynamics)
  – Beneficial effects (efficacy)
  – Adverse effects (toxicity)
• What the body does to the drug (aka – pharmacokinetics)
  – Determines how drug is eliminated from the body
  – Defines the dose required for a beneficial effect (or to avoid a toxic effect)

Genetics can influence all of these

Learning Assessment Question #1

Genotype can influence which of the following?
  a) Drug metabolism
  b) Drug transport
  c) Sensitivity to a drug
  d) All of the above

Answer: D. Genotype for drug metabolizing enzymes (e.g. CYP2D6 for codeine) and drug transporter proteins (e.g. SLCO1B1 for simvastatin) can affect pharmacokinetics, while genotype for drug target proteins (e.g. VKORC1 for warfarin) can influence pharmacodynamics.

Human Genome 101

• Composed of 4 nucleotides
  – Adenine
  – Thymine
  – Cytosine
  – Guanine
• Central dogma
  – One strand transcribed into RNA and translated to proteins
Single Nucleotide Polymorphism (SNP)

- **Synonymous SNP**
  - ACTGTA(G)
  - C to T
  - SNP

- **Nonsynonymous SNP**
  - ACTGTA(G)

Metabolism of Drugs

- **Active drug**
- **Prodrug (Inactive)**

- **Genetic variation:**
  - ↑ metabolism
  - ↓ metabolism
  - No metabolism

>150 Drugs with FDA-approved Genetic Labeling

- **Azathioprine**
- **Phenytoin**
- **Carbamazepine**
- **Clopidogrel**
- **Tramadol**
- **Voriconazole**
- **Omeprazole**
- **Aripiprazole**
- **Rasburicase**
- **Abacavir**
- **Thioridazine**
- **Ivacaftor**
- **Citalopram**
- **Codeine**
- **Captopril**
- **Candesartan**
- **Tramadol**
- **Irinotecan**
- **Tamoxifen**
- **Amitriptyline**
- **Irinotecan**
BOXED WARNING section of the FDA-approved carbamazepine label

WARNING
Serious dermatologic reactions with HLA-B*1502 allele

Patients from genetically at-risk populations should be screened for the allele before starting carbamazepine. Those testing positive should not be treated with the drug unless the benefit clearly outweighs the risk.

DOSAGE AND ADMINISTRATION section of the FDA-approved warfarin label

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
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<tbody>
<tr>
<td>-1639</td>
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</tr>
<tr>
<td>G/G</td>
<td>1/1</td>
</tr>
<tr>
<td>G/A</td>
<td>1/2</td>
</tr>
<tr>
<td>A/A</td>
<td>1/3</td>
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<td></td>
<td>2/2</td>
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<td>2/3</td>
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<table>
<thead>
<tr>
<th>Genes</th>
<th>Drug/Drug class</th>
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<tbody>
<tr>
<td>TPMT</td>
<td>Thiopurines</td>
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<tr>
<td>CYP2C19</td>
<td>Clopidogrel</td>
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<td>CYP2C9, VKORC1</td>
<td>Warfarin</td>
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<td>Codeine</td>
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<td>Abacavir</td>
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<td>Allopurinol</td>
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<tr>
<td>SLCO1B1</td>
<td>Simvastatin</td>
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<td>TCAs</td>
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<td>Fluoropyrimidines</td>
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<td>P-gp</td>
<td>Peginterferon alfa</td>
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<tr>
<td>CYP3A5</td>
<td>Tacrolimus</td>
</tr>
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<td>CYP2C19</td>
<td>Rasburicase</td>
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<tr>
<td>HLA-B</td>
<td>Metyrapone</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Select SSRIs</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Selective serotonin inhibitors</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Tienilic acid</td>
</tr>
</tbody>
</table>

CPIC
Clinical Pharmacogenetics Implementation Consortium

• Provides guidelines that enable the translation of genetic results into actionable prescribing decisions
• Designed to help clinicians understand HOW available genotype results should be used to optimize drug therapy, not WHETHER tests should be ordered

CYP2D6 Genotype and Opioid Metabolism

- Poor metabolizers (PMs)
  - 5-10%
  - 2 no function alleles
- Intermediate metabolizers (IMs)
  - 2-10%
  - Reduced fxn + no fun allele
CYP2D6 Genotype and Opioid Metabolism

- Poor metabolizers (PMs)
  - 5-10%
  - 2 no function alleles
- Intermediate metabolizers (IMs)
  - 2-10%
  - Reduced function allele
- Ultra-rapid metabolizers (UMs)
  - 1-2%
  - >2 fully functional alleles

Tramadol → O-desmethyltramadol
Hydrocodone → hydromorphone
Oxycodone → oxymorphone

Case Reports in CYP2D6 UMs

2 yo boy rx’d codeine/APAP s/p adenotonsillectomy died post-op day 2. Found to be a CYP2D6 UM and increased morphine concentrations.

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother
Lancet 2006;368:19-25.

Full-term breastfed male infant found dead on day 12, and blood concentrations of morphine were found to be in toxic range. Mother was taking codeine and had UM phenotype.

FDA Drug Safety Communication and Labeling Changes

Ultra-rapid Metabolism of Codeine – Life-Threatening Respiratory Depression in Children

Codeine contraindicated in children <12 years of age and in children <18 years of age following tonsillectomy and/or adenoidectomy.
Avoid codeine in adolescents 12-18 years of age who have other risk factors for respiratory depression.
**CPIC Guidelines**

CYP2D6 Genotype

- Ultra-rapid Metabolizer
- Normal Metabolizer
- Intermediate Metabolizer
- Poor Metabolizer

Avoid codeine because of toxicity risk.
Avoid tramadol.

Use codeine at recommended dose
Use codeine at recommended dose

Use alternative

**Learning Assessment Question #2**

A CYP2D6 poor metabolizer prescribed tramadol is at increased risk for which of the following?

- a. Respiratory depression
- b. Poor analgesic response
- c. Nausea and vomiting
- d. Rash

Answer: b. Tramadol is metabolized by CYP2D6 to a more potent metabolite with approximately 200-fold greater affinity for the opioid µ receptor. Poor metabolizers have less conversion to the more potent metabolite and less analgesic response.

**UF Health Personalized Medicine Program (PMP)**

Siegfried Schmidt, MD, PhD
Professor of Family Medicine
University of Florida
### Clinical Decision Support

**Best Practice Advisory – Ultrarapid Metabolizer**

**PROBLEM**
Codeine or tramadol use is NOT RECOMMENDED since this patient is predicted to be an ULTRA-RAPID METABOLIZER of these drugs based on CYP2D6 genotype.

**REASONS**
This patient’s CYP2D6 genotype is associated with production of excess amounts of active forms of codeine and tramadol, and increased risk of adverse events, including respiratory depression, or in rare cases, death.

**RECOMMENDATIONS**
Consider alternative analgesics such as non-opioid, hydromorphone, oxymorphone, or morphine that are not affected by CYP2D6 metabolism status. Hydrocodone and oxycodone are not good alternative because their metabolism is also affected by CYP2D6.

### Pragmatic Trial of CYP2D6 Guided Opioid Prescribing

**Patient with chronic pain on opioids**

**IMPLEMENTATION Clinics**
(n=4 clinics, 235 patients)

- Baseline
  - Collected genetic sample
- 1 week
  - Genotyped for CYP2D6
  - Assigned phenotype (genotype + inhibitors*)
  - Provided recommendation via consult note
- 3 months
  - Repeated pain assessment questionnaire
  - Offered genotyping to control group

**CONTROL Clinics**
(n=3, 135 patients)

*Strong/moderate inhibitors cause phenoconversion (PMID 24458010)

### Recommendations

**CYP2D6 Genotype + Drug Interactions***

- **Ultra-rapid Metabolizer**
  - Continue usual care
- **Normal Metabolizer**
  - Continue usual care
- **Intermediate Metabolizer**
  - Strong recommendation to avoid tramadol and codeine.
  - Moderate recommendation to avoid hydrocodone and oxycodone.
- **Poor Metabolizer**
  - Continue usual care

*Strong/moderate inhibitors cause phenoconversion (PMID 24458010)
CYP2D6 Phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype only</th>
<th>Genotype + drug interactions*</th>
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</thead>
<tbody>
<tr>
<td>PM</td>
<td>5%</td>
<td>19%</td>
</tr>
<tr>
<td>M</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>NM</td>
<td>86%</td>
<td>61%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Most common CYP2D6 inhibitors: duloxetine, bupropion, fluoxetine, paroxetine

Drug interactions “phenocverted” 28% of NMs to IM/PMs

Pragmatic Trial - Results

Change in composite pain intensity at 3 months for patients taking tramadol or codeine at baseline

23% of genotyped patients versus 0% of controls had a 30% reduction in pain intensity composite (p=0.04)

*p value by ANCOVA adjusted for baseline pain measure, age, sex, race, HTN, anxiety, other psych disorders

Clin Pharmacol Ther 2018;103(S1):S8

Pragmatic Trial - Summary and Next Steps

• Clinical implementation of CYP2D6-guided pain management is feasible
• Genotype-guided approach has potential to improve pain control
• Trial on-going in patients scheduled for arthroplasty surgery
  - Sample collected for genotyping during pre-operative visit
  - Primary outcome is feasibility of genotype-guided post-operative pain management
Rationale

- One in every four to five children and adolescents suffers from a mental illness, most often depression or anxiety disorder
- SSRIs most commonly prescribed antidepressant
  - Have substantial side effect burden
  - Take time to work
- PGx testing can make process easier

Metabolism of SSRIs

- Paroxetine
  - Fluvoxamine
  - CYP2D6
    - Genetic variation:
      - ↑ metabolism
      - ↓ metabolism
      - No metabolism
    - Less active metabolite
- Citalopram
  - Escitalopram
  - Sertraline
  - CYP2C19
    - Less active metabolite
**CYP2C19 Genotype/Phenotype**

<table>
<thead>
<tr>
<th>Allele</th>
<th>CYP2C19 Function</th>
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<tbody>
<tr>
<td>*1</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*3</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*17</td>
<td>Increased function</td>
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<table>
<thead>
<tr>
<th>Metabolizer Phenotype</th>
<th>Genotype</th>
<th>Prevalence (U.S.)</th>
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<tr>
<td>Poor (PM)</td>
<td>*2/*2, *2/*3, *3/*3</td>
<td>2-4%</td>
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<tr>
<td>Intermediate (IM)</td>
<td>*1/*2, *1/*3, *2/*17</td>
<td>20-30%</td>
</tr>
<tr>
<td>Normal (NM)</td>
<td>*1/*1</td>
<td>35-50%</td>
</tr>
<tr>
<td>Rapid (RM)</td>
<td>*1/*17</td>
<td>20-30%</td>
</tr>
<tr>
<td>Ultra-rapid (UM)</td>
<td>*17/*17</td>
<td>2-4%</td>
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**CPIC Guidelines**

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Paroxetine</th>
<th>Fluvoxamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>Consider 50% dose reduction or alternative drug</td>
<td>Consider 25-50% dose reduction or alternative drug</td>
</tr>
<tr>
<td>IM or UM</td>
<td>Initiative with usual dosing</td>
<td>Initiative with usual dosing</td>
</tr>
<tr>
<td>NM</td>
<td>Use alternative drug</td>
<td>Alternative drug</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYP2C19 Phenotype</th>
<th>Citalopram</th>
<th>Escitalopram</th>
<th>Sertraline</th>
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<tbody>
<tr>
<td>PM</td>
<td>Consider 50% dose reduction or alternative drug</td>
<td>Consider 50% dose reduction or alternative drug</td>
<td>Consider 50% dose reduction or alternative drug</td>
</tr>
<tr>
<td>IM or UM</td>
<td>Initiative with usual dosing</td>
<td>Initiative with usual dosing</td>
<td>Try sertraline; consider alternative if no response</td>
</tr>
<tr>
<td>NM</td>
<td>Consider alternative drug</td>
<td>Consider alternative drug</td>
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**Learning Assessment Question #3**

Data support initiation of escitalopram at a lower than usual dose for which of the following patient phenotypes?

a) CYP2D6 poor metabolizer  
b) CYP2C19 poor metabolizer  
c) CYP2D6 ultra-rapid metabolizer  
d) CYP2C19 ultra-rapid metabolizer

**Answer:** b. Escitalopram is metabolized by CYP2C19 to a less active metabolite. CYP2C19 poor metabolizers will have higher levels of escitalopram and are at increased risk for adverse effects with usual escitalopram doses.
Implementation of SSRI Pharmacogenetics

- Genotyping
  - CYP2D6 via Luminex platform
  - CYP2C19 via Genmark
  - Validated for buccal cell
- Genotype results available in ~7 days
- PGx pharmacist provide education and recommendations via case discussions

Lessons Learned with SSRI Pharmacogenetics

- Clinical implementation of genotyping to guide SSRI prescribing is feasible in the pediatric setting.
- Children strongly prefer noninvasive genetic sample collection.
- Prescribers and parents willing to wait to start/change therapy until genotype returned
- Clear guidance based on genotype result must be provided to the physician

Learning Assessment Question #4

Data support pharmacogenetic implementation for which of the follow gene-drug pairs?

a) CYP2D6-morphine
b) CYP2C19-duloxetine
c) CYP2C19-bupropion
d) CYP2D6-tramadol

Answer: d. Studies have consistently shown lower levels of the active tramadol metabolite and decreased analgesic effects in CYP2D6 poor metabolizers. Other data shown an increased for serious adverse effects with tramadol in CYP2D6 ultra-rapid metabolizers.
Summary

- Use of genetic information to guide decisions in about drug therapy will be increasingly common.
- CPIC Guidelines are available to assist with translation of genotype results into prescribing decisions.
- Data are beginning to emerge on the outcomes of implementation efforts, which should support further growth of the field.

https://ignite-genomics.org

Implementation Guides
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