SESSION C7

What's the Deal with Pharmacogenomics?
Kristen Allott, ND, MS, LAc

Session Description:

Pharmacogenomics and pharmacogenetics is a rising hot topic, again. Dr. Kristen Allott will focus on the practical use of genetic laboratory testing in a clinical psychiatric practice. Specifically, she will discuss MTHFR and cytochrome P450 testing.

Learning Objectives:
Following my presentation, participants will be able to:
1. Describe why MTHFR is significant in psychiatric conditions?
2. Discuss why folate should be prescribed with a B-complex vitamin.
3. Recognize why knowing cytochrome P450 helps you and patients.
What Is The Deal With Pharmacogenomics?

Pacific NW 37th Annual National Conference
Advanced Practice in Primary and Acute Care
October 9, 2014
Kristen Allott, ND, L.Ac.

Introduction

New Approach, Different Assumptions

× Can a physiological approach offer explanation and tools to mental health?
  Yes

× Are there physical markers that explain the symptoms of depression, anxiety, and bipolar?
  Yes

× How do we find the cause?
  We ask a lot of questions, to save money, time, & suffering.

Finding the Cause

Today’s Goals

1. What is pharmacogentics?
2. How is it useful in mental health conditions?
3. MTHFR
4. P450
5. How do we apply this?

Definitions

Pharmacogenetics

Pharmacogenomics
Pharmacogenomics Definitions

- A **genotype** is an individual’s collection of genes.
- **Alleles** are alternative forms of a gene that arise by mutation and are found at the same place on a chromosome.
- The expression of the genotype contributes to the individual's observable traits, called the **phenotype**.
- **Inducer**—a drug than simulates the expression of a gene
- **Inhibitor**—a drug that inhibits the function of an enzyme

**Methylenetetrahydrofolate Reductase (MTHFR) Deficiency**

In the general population:
- ×5-25% homozygous
- ×50% heterozygous


**MTHFR**

- ×24 polymorphisms
- ×2 alleles in the currently understudy
- C677T
  - Significant for schizophrenia and elevated homocysteine
- A1298C
  - needed to synthesis dopamine and serotonin and detoxification of ammonia

**Neurotransmitter Metabolism**

**MTHFR Deficiency: Signs and Symptoms**

- × Bipolar
- × Cognitive decline
- × Dementia
- × Depression
- × Schizophrenia
- × CVD
- × Diabetes
- × Migraine
- × Peripheral Neuropathy
- × Restless leg syndrome
The role of folic acid in 1-carbon metabolism and its potential mechanisms for cardiac protection

Folic Acid

Tetrahydrofolate (THF)

DNA methylation

Methionine

Homocysteine

Cystathionine

5,10-methylene THF

5-methyl THF

Antioxidant

Coupling of NOS

Cardioprotection

Endothelial function

Purine synthesis

aspartate amine

HCO₃⁻
glycine

formyl donor

formyl

glutamine amide

IMP

GMP

AMP

ATP

Neurotransmitter Metabolism

Tryptophan → 5-HTP → Serotonin → N-Acetyl Serotonin → Melatonin

Iron, BH4, Magnesium

Tryptophan Hydroxylase, Decarboxylase, Hydroxylase

Vit B6, Vit C

Copper, SAMe, Homocysteine

Methylation
**Individuals with Mental Health Diagnosis**

Odds Ratio for MTHFR:

- ×36% for unipolar depression
- ×44% for schizophrenia
- ×82% for bipolar

Gilbody (2007)

**Common Medications that Deplete Folic acid, B12, and B6**

- × Acid Suppressive Therapy - B12
- × Methotrexate Folic acid
- × Anticonvulsants-B6, Folic acid
- × Oral contraceptives - B-12, B6, Folic acid
- × Glucocorticoids-B12
- × B6- Folic acid
- × Metformin- B12
- × Folic acid- B12, B6

**Homocysteine and Depression**

- × Patients over 50 years old with high homocysteine concentrations (1.69 mg/L or 12 mmol/L) have an increased risk of about 70% of depression.

Almeida (2007)

**Laboratory Diagnosis**

- × Laboratory reference range for CVD is less than 12 mmol/L
- × Adjusted normal for mental health: less than 7 mmol/L

**Prescriptive for Elevated Homocysteine**

- × Deplin
  - 7.5 mg of L-methylfolate calcium (30 tablets for $93)
  - 15 mg of L-methylfolate calcium (30 tablets for $93)
- × Metanx (30 tablets for $40)
  - 3 mg of L-methylfolate calcium
  - 35 mg of Pyridoxal 5'-phosphate (B6)
  - 2 mg of methylcobalamin (B12)

**Supplement for Elevated Homocysteine**

Thorne: Methylguard Plus (180 Capsules for $36)

Dosage: 3 capsules/ day

Three Capsules Contain:

- × 90 mg Riboflavin 5'-Phosphate Sodium (B2)
- × 45 mg of Pyridoxal 5'-Phosphate (B6)
- × 3 mg of 5-Methyltetrahydrofolate (folate)
- × 3 mg of Methylcobalamin (B12)
- × 1,800 mg of Betaine Anhydrous (Trimethylglycine)
Cytochrome P450 Enzymes

The Liver is the Alchemist of the Body.

Drug Metabolism in the Liver

Phase 1 reactions
- Oxidation
  • CYP450
- Reduction
Phase 2 reaction
- Conjugation reaction
  • Glucoronidation
  • Sulfate
  • Glutathione
  • Glycine
  • Acetylation
  • Methylation

Types of Metabolizers

Poor (PM) - Has little to no functioning genes

Intermediate (IM) - Better than poor not as good as extensive (Less than normal amount of genes, usually one functioning gene)

Extensive (EM) (Normal) - Is normal functioning (2 normal functioning genes)

Ultra-rapid (UM) - Metabolizer because there is multiple copies of genes

Genetics Affect Drug Clearance
**Genetics Affect Drug Clearance**

Pro-Drugs

<table>
<thead>
<tr>
<th>Drug Response</th>
<th>Toxic level</th>
<th>Therapeutic level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UIM</td>
<td>EM</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>PM</td>
</tr>
</tbody>
</table>

**Drug Levels**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>4</td>
<td>5.4</td>
</tr>
<tr>
<td>5</td>
<td>6.5</td>
</tr>
<tr>
<td>6</td>
<td>7.6</td>
</tr>
<tr>
<td>7</td>
<td>8.7</td>
</tr>
<tr>
<td>8</td>
<td>9.8</td>
</tr>
<tr>
<td>9</td>
<td>10.9</td>
</tr>
<tr>
<td>10</td>
<td>11.0</td>
</tr>
</tbody>
</table>

**Metabolic enzymes identified in drug labels of FDA-approved drugs**


**Genetics Affect Drug Clearance**

Pro-Drugs

**Incidence of Genetic Variants Important to Drug Selection and Drug Dose**

<table>
<thead>
<tr>
<th>Gene</th>
<th>% of Extensive Metabolizers</th>
<th>% of Intermediate Metabolizers</th>
<th>% of Poor Metabolizers</th>
<th>% of Ultra-Rapid Metabolizers</th>
<th><strong>VARIANTS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>2D6</td>
<td>53%</td>
<td>35%</td>
<td>10%</td>
<td>2%</td>
<td>47%</td>
</tr>
<tr>
<td>2C9</td>
<td>36%</td>
<td>32%</td>
<td>6%</td>
<td>1%</td>
<td>64%</td>
</tr>
<tr>
<td>2C9</td>
<td>57%</td>
<td>40%</td>
<td>3%</td>
<td>NA</td>
<td>43%</td>
</tr>
<tr>
<td>2C19</td>
<td>87%</td>
<td>12%</td>
<td>1%</td>
<td>N/A</td>
<td>13%</td>
</tr>
<tr>
<td>2D6</td>
<td>25%</td>
<td>50%</td>
<td>25%</td>
<td>N/A</td>
<td>75%</td>
</tr>
</tbody>
</table>

**Genetic Variants impacting Patient Response to Medications**

1. Pharmacogeneic Knowledge Base Implementation: www.pharmgkb.org

**Incidence of Genetic Variants Important to Drug Selection and Drug Dose**

**CYC2D6 Poor Metabolizer (PM)**

10% of US Population

**CYC2D6 Intermediate Metabolizer (IM)**

35% of US Population

Common psychotropic medications which need a decrease in dose in IM and PM

- Fluoxetine (Prozac)*
- Paroxetine (Paxil)*
- Venlafaxine (Effexor)
- Burpropion (Wellbutrin)*
- Haloperidol (Haldol)
- Aripiprazole (Abilify)
- Risperidone (Risperdal)
- Buspirone (Buspar)

**CYC2D6 and Pro-Drugs for IM and PM**

Common pain medications that need an increased dose due to being a prodrug

- Tylenol 3 (coding is a prodrug)
- Oxycodone (oxyContin and Percocet)
- Hydrocodone (Vicodin, Lortab)
## Incidence of Genetic Variants Important to Drug Selection and Drug Dose

<table>
<thead>
<tr>
<th>Gene</th>
<th>% of Extensive Metabolizers</th>
<th>% of Intermediate Metabolizers</th>
<th>% of Poor Metabolizers</th>
<th>% of Ultra-Rapid Metabolizers</th>
<th>VARIANTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D6</td>
<td>53%</td>
<td>35%</td>
<td>10%</td>
<td>2%</td>
<td>47%</td>
</tr>
<tr>
<td>2C19</td>
<td>36%</td>
<td>32%</td>
<td>4%</td>
<td>28%</td>
<td>64%</td>
</tr>
<tr>
<td>2C9</td>
<td>57%</td>
<td>40%</td>
<td>3%</td>
<td>NA</td>
<td>43%</td>
</tr>
<tr>
<td>VKOR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;70%</td>
</tr>
<tr>
<td>3A4</td>
<td>87%</td>
<td>12%</td>
<td>1%</td>
<td>N/A</td>
<td>13%</td>
</tr>
<tr>
<td>3A5</td>
<td>1%</td>
<td>18%</td>
<td>81%</td>
<td>N/A</td>
<td>99%</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>25%</td>
<td>50%</td>
<td>25%</td>
<td>N/A</td>
<td>75%</td>
</tr>
</tbody>
</table>

Genetic Variants Impacting Patient Response to Medications

1. Pharmacogenetics Knowledge Base Implementation: [www.pharmgkb.org](http://www.pharmgkb.org)
Common Inhibitors of CYC2D6
- Bupropion (Wellbutrin®)
- Cinacalcet (Sensipar®)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac®)
- Goldenseal
- Paroxetine (Paxil®)
- Quinidine
- Terbinafine (Lamisil®)

CYC2D6 Ultra Metabolizer
28% of US Population
29% of N. African and Middle Eastern
Common psychotropic medications which need an increase in dose
- Fluoxetine (Prozac)*
- Paroxetine (Paxil)*
- Venlafaxine (Effexor)
- Bupropion (Wellbutrin)*
- Haloperidol (Haldol)
- Aripiprazole (Abilify)
- Risperidone (Risperdal)
- Buspirone (Buspar)

CYC2D6 Ultra Metabolizer
28% of US Population
29% of N. African and Middle Eastern
Common pain medications that need an increase dose due to being a prodrug
- Tylenol 3 (coding is a prodrug)
- Oxycodone (OxyContin and Percocet)
- Hydrocodone (Vicodin, Lortab)

Common Inhibitors of CYC2C19
- esomeprazole (Nexium®)
- fluvoxamine (Luvox®)
- voriconazole (Vfend®)
- fluconazole (Diflucan®)
- omeprazole (Protonix®)
- fluoxetine (Prozac®)
- ticlopidine (Ticlid®)

CYC2C19 Poor Metabolizer
4% of US Population
25% of East Asian
CYC2C19 Intermediate Metabolizer
32% of US Population
Common psychotropic medications which need a decrease in dose
- Fluoxetine (Prozac)*
- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Sertraline (Zoloft)
- Diazepam (Valium)
- Omeprazole (Prilosec, Protonix)*
- Esomeprazole (Nexium)*

Serotonin Syndrome

<table>
<thead>
<tr>
<th>Early Symptoms</th>
<th>Immediate Medical Attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Altered Mental Status</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>Muscle rigidity</td>
</tr>
<tr>
<td>Fatigue, drowsiness</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>Restlessness</td>
<td>High body temperature</td>
</tr>
<tr>
<td></td>
<td>fever</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td>Loss of consciousness and death</td>
</tr>
</tbody>
</table>

CYC2C19 Rapid and Ultra Metabolizer
2.3% of US Population
15% of Asian Population

Common psychotropic medications which need an increase in dose
- Fluoxetine (Prozac)*
- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Sertraline (Zoloft)
- Diazepam (Valium)
- Omeprazole (Prilosec, Protonix)*
- Esomeprazole (Nexium)*

Inducers of CYC2C19
- phenobarbital
- rifampin
- primidone (Mysoline®)
- St John’s Wort

Desipramine
• “The rate of metabolism of tricyclic antidepressants varies widely from individual to individual, chiefly on a genetically determined basis. Up to a 36-fold difference in plasma level may be noted among individuals taking the same oral dose of desipramine.”

Strattera
“Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs).”*

Seroquel
“SEROQUEL dose should be reduced to one sixth of original dose when co-medicated with a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone, etc.).”

“SEROQUEL dose should be increased up to 5 fold of the original dose when used in combination with a chronic treatment of a potent CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, avasimibe, St. John’s wort etc.).”

When To Consider Genetic Testing
• The patient has a history of multiple failed drug trials.
• The patient has a history of medication sensitivity and/or ADRs.
• The patient is on a complex medication regimen increasing the risk for ADRs.
• Plavix is being considered for anti-platelet therapy.
LabCorp Prices

**CYC2D6**
- CPT: 81226
- Price: $779

**CYC2C19**
- CPT 81225
- Price: $456

---

### Online Resources

- **Drugs@FDA:**
- **DailyMed:**
- **DrugBank:**
  - [http://www.drugbank.ca/](http://www.drugbank.ca/)
- **PharmGKB:**
  - [https://www.pharmgkb.org/index.jsp](https://www.pharmgkb.org/index.jsp)
  - Indiana University - [http://medicine.iupui.edu/clinpharm/ddis/](http://medicine.iupui.edu/clinpharm/ddis/)

---

### References