Pharmacogenetics in:
Primary Care

Bradley T. Wajda D.O.
<table>
<thead>
<tr>
<th>Challenges in Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LACK OF RESPONSE</strong></td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
</tr>
<tr>
<td><strong>NONADHERENCE</strong></td>
</tr>
</tbody>
</table>

These challenges can lead to symptomatic decline, the need to change medication, and frustration for both the patient and the clinician.
Pharmacogenomics Defined

Pharmacogenomics uses information about a person’s genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that particular person.

National Institutes of Health
National Human Genome Research Institute
Pharmacokinetics and Pharmacodynamics

Polymorphisms in pharmacodynamic (PD) genes can affect drug action at its target (e.g. receptor binding).

Polymorphisms in pharmacokinetic (PK) genes (e.g. CYP450) can affect drug blood levels.

Systemic Circulation

Excretion
Key Pharmacogenomic Genes

Pharmacodynamic (PD)
- OPRM1 (μ-opioid receptor)
- SLC6A4 (serotonin transporter)
- 5HTR2A (serotonin 2A receptor)
- ADRA2A (α-2A adrenergic receptor)
- COMT (catechol-o-methyltransferase)

Pharmacokinetic (PK)
- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2
- CYP2B6
- CYP3A4
- MTHFR (methyltetrahydrofolate reductase)
The CYP450 system is a family of about 57 enzymes responsible for drug metabolism, primarily in the liver. Multiple enzymes may be involved in the metabolism of a given drug.
CYP2D6 Expression & Phenotype

Chromosome 22

CYP2D6 Gene

*1 Normal

CYP2D6 Gene

*1 Normal

*1/*1 Genotype

CYP2D6 Enzyme

*1 Normal

Extensive Metabolizer Phenotype
CYP2D6 Expression & Phenotype

Chromosome 22

CYP2D6 Gene

*1 Normal

CYP2D6 Gene

*5 Deletion

*1/*5 Genotype

Intermediate Metabolizer Phenotype

*1 Normal

CYP2D6 Enzyme

*5 Deletion
CYP2D6 Expression & Phenotype

Chromosome 22

CYP2D6 Gene

*5 Deletion

CYP2D6 Gene

*5 Deletion

*5/*5 Genotype

CYP2D6 Enzyme

*5 Deletion

*5 Deletion

Poor Metabolizer Phenotype
CYP450 Metabolizer Phenotypes

- **Ultrarapid (UM)**: Rapid rate of metabolism
- **Extensive (EM)**: Normal metabolism
- **Intermediate (IM)**: Reduced rate of metabolism
- **Poor (PM)**: Slow rate of metabolism

CYP2D6 Phenotype Frequency:
- Ultrarapid (UM): 6%
- Extensive (EM): 35%
- Intermediate (IM): 46%
- Poor (PM): 13%
CYP2D6 and Nortriptyline

Plasma concentration/25 mg dose (nmol/L) vs. Number of functional CYP2D6 genes over time (Hours 0-72).

Clinical Outcomes

The La Crosse Study was a prospective, cohort study of 165 subjects with a primary diagnosis of a major depressive disorder. The study compared 8 weeks of treatment guided by PGT with unguided TAU.

**MEAN SYMPTOM IMPROVEMENT AT WEEK 8**

<table>
<thead>
<tr>
<th>Measure</th>
<th>PGT (n = 72)</th>
<th>TAU (n = 93)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIDS-C16</td>
<td>44.8%</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAM-D17</td>
<td>46.9%</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>40.1%</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Reduction in Score From Baseline (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment guided by PGT resulted in up to 100% greater improvement in symptoms

Clinical Outcomes

The Pine Rest Study was a blinded, randomized controlled trial of 49 subjects with a primary diagnosis of a major depressive disorder. The study compared 10 weeks of treatment guided by PGT with unguided TAU.

WEEK 8 MEAN IMPROVEMENT FROM BASELINE HAM-D17

<table>
<thead>
<tr>
<th>TAU</th>
<th>26.5%</th>
<th>9.1%</th>
<th>0.8%</th>
</tr>
</thead>
</table>

TAU patients who began the trial on red-category medications showed almost no improvement.

Clinical Outcomes

The Hamm Clinic Study was a prospective, cohort study of 44 adults with a primary diagnosis of a major depressive disorder.* The study compared 8 weeks of treatment guided by PGT with unguided treatment as usual (TAU).

**Mean Symptom Improvement at Week 8**

<table>
<thead>
<tr>
<th>Scale</th>
<th>PGT (n = 22)</th>
<th>TAU (n = 22)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>QIDS-C16</td>
<td>31.2%</td>
<td>7.2%</td>
<td>0.002</td>
</tr>
<tr>
<td>HAM-D17</td>
<td>30.8%</td>
<td>18.2%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Reduction in Score From Baseline (%)

*Treatment guided by PGT resulted in up to a 4-fold greater improvement in symptoms.*

The UHS Study was a retrospective chart review of 96 adults diagnosed with a depressive or anxiety disorder. All subjects were treated with at least one of the tested Psychotropic medications. Medical records were analyzed for healthcare utilization during a one year period from April 2010 to April 2011.

A meta-analysis of all the clinical studies demonstrated a statistically significant \( p = 0.004 \) improvement in the odds of clinical response in favor of PGT vs. TAU.

Patients are **2.3 times** more likely to respond when treatment is guided by PGT compared with TAU.
An extensive list of medications that the FDA has included pharmacogenetic references within the package inserts. These medications are categorized by Therapeutic Area(s), including:

- Anesthesiology
- Cardiology
- Dental
- Gastroenterology
- Gynecology
- Hematology
- Infectious Diseases
- Neurology
- Oncology
- Psychiatry
- Pulmonology
- Rheumatology
- Urology

The FDA also maintains “Drug Interactions and Labeling” giving an extensive list of “sensitive substrates”, strong to weak inhibitors, and strong to weak inducers arranged according to cytochrome P450 isoenzymes.
“Poor metabolizers of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of Strattera compared with EMs... Laboratory tests are available to identify CYP2D6 PMs... The higher blood levels in PMs lead to a higher rate of some adverse effects of Strattera.”

“In ...CYP2D6 PMs, Strattera should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.”
The FDA and Pharmacogenomics

The Food and Drug Administration (FDA) includes pharmacogenomic language in the package inserts:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Text</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>“The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose.”</td>
<td>CYP2D6 PM</td>
</tr>
<tr>
<td>Citalopram</td>
<td>“The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers.”</td>
<td>CYP2C19 PM</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>“The use of thioridazine in patients known to have reduced activity of P450 2D6 are contraindicated.”</td>
<td>CYP2D6 IM or PM</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>“The maximum recommended dose of BRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers.”</td>
<td>CYP2D6 PM</td>
</tr>
</tbody>
</table>
OPRM1 encodes the mu opioid receptor, the main target for many analgesic medications.

Patients who are carriers of the G allele for the A118G SNP show a reduced analgesic response with opioid medications such as morphine, codeine, and oxycodone.

In contrast to full μ-opioid agonist therapy (e.g. methadone), OPRM1 G-carriers show improved response to naltrexone in dependent patients compared to wild type. These findings support the use of OPRM1 to select patients for naltrexone therapy.

Despite showing reduced analgesic response, OPRM1 G-carriers have not been shown to be protected against respiratory depression.\textsuperscript{1} One study showed that, among patients with an acute drug overdose, G-carriers were 5.3 times more likely to experience cardiac or respiratory arrest.\textsuperscript{2} Other data has shown associations with OPRM1 G carriers and likelihood to become addicted to opiates.\textsuperscript{3}

CYP2D6 and Oxycodone

Oxymorphone [1,2,3] (40-fold higher affinity at μ opiate receptor; 14 times ‘more potent’ than oxycodone)

N-demethylation
CYP3A4 1,2,3
(80%)

N-demethylation
CYP2D6 1,2,3
(10%)

Oxycodone

Noroxymorphone [1,2,3]
(3 and 10-fold higher affinity at μ opiate receptor than oxycodone or noroxycodone, respectively), minimal activity

Glucuronidation

Noroxymorphone-3-glucuronide [3]

Noroxycodone [1,2,3] Minimal activity

CYP2D6 and Oxycodone

Codeine and CYP2D6

3.) FDA Label
CYP2D6 and Codeine

Median morphine AUC following a single 30 mg dose of codeine

<table>
<thead>
<tr>
<th>Type</th>
<th>AUC (µg h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>0.5</td>
</tr>
<tr>
<td>EM</td>
<td>11</td>
</tr>
<tr>
<td>UM</td>
<td>16</td>
</tr>
</tbody>
</table>

The FDA and Codeine

“Some people have genetic variations that make [CYP2D6] over-active, causing codeine to be converted to morphine faster and more completely than in other people. These ultra-rapid metabolizers are more likely to have higher than normal amounts of morphine in their blood after taking codeine. High levels of morphine can result in breathing difficulty, which may be fatal.”

“The only way to know if someone is an ultra-rapid metabolizer is to do a genetic test.”

http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm315467.htm
The FDA and Pharmacogenomics

The Food and Drug Administration (FDA) includes pharmacogenomic language in the package inserts of many of the medications in the PGT Psychotropic test:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Warning/Recommendation</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carisoprodol</td>
<td>“Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of SOMA to these patients.”</td>
<td>CYP2C19 PM</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>“Consider starting treatment at half the lowest recommended dose in poor metabolizers [of CYP2C9]. Consider using alternative management in JRA patients who are poor metabolizers.”</td>
<td>CYP2C9 PM</td>
</tr>
<tr>
<td>Codeine</td>
<td>“WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE: Respiratory depression and death have occurred in children who ... had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.”</td>
<td>CYP2D6 UM</td>
</tr>
</tbody>
</table>

The contents of this page have not been endorsed by the FDA and are the sole responsibility of Assurex Health.
The serotonin transporter is encoded by the SLC6A4 gene. It is responsible for reuptake of serotonin into the presynaptic neuron. Selective serotonin reuptake inhibitors (SSRIs) inhibit this process, allowing for more serotonin in the synaptic cleft.
The Serotonin Transporter

The SLC6A4 promoter has two main variants: short (S) and long (L).

The two variants are differentiated by a 44 base pair insertion/deletion.

The short allele results in lower transcription rates, providing less active sites for SSRIs.

The short allele is associated with lower rates of remission following SSRI treatment.
Clinical Implications of SLC6A4

Meta-analysis of published literature of the association of 5-HTTLPR with SSRI efficacy in depression - 1435 patients and 15 studies

- Patients with s/s variant had significantly lower remission rates (p<0.0001)
- Patients with s/s and s/l variants had significantly lower response rates (p=0.0002)
- Two other meta-analyses confirmed similar significant associations

---

Catechol-O-methyltransferase (COMT) breaks down both norepinephrine and dopamine in the synapse.

COMT gene has a polymorphism (Val158Met) that results in an amino acid change - methionine (met) for valine (val) at codon 158.

Met/Met homozygotes have 4-5x less COMT activity\(^1\)

Met/Met carriers showed a reduced rate of response to stimulant medications\(^2\)

---

ADHD Pharmacogenomics: ADRA2A

The alpha 2A adrenergic receptor is a receptor in the norepinephrine system.

A SNP in the promoter region (-1291G>C) of this gene has been shown to have an effect on response to methylphenidate and the alpha-2A agonists.

<table>
<thead>
<tr>
<th></th>
<th>Typical Response (G/G)</th>
<th>Typical Response (C/G)</th>
<th>Reduced Response (C/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>48%</td>
<td>11%</td>
<td>41%</td>
</tr>
</tbody>
</table>

The Noradrenergic Neuron

- Norepinephrine
- Adrenergic receptor

Diagram showing the distribution of response types with percentages.
**The Importance of Folate**

- Folate plays a critical role in the formation of SAMe, an important precursor to neurotransmitter synthesis.¹

- Folic acid (synthetic form) and dihydrofolate (dietary form) must be converted to L-methylfolate, the usable form, by methylenetetrahydrofolate reductase, an enzyme encoded by the MTHFR gene.²

---


The C677T SNP in the MTHFR gene confers reduced enzymatic activity.¹

Multiple studies have confirmed lower serum folate levels and higher homocysteine levels in individuals with the T/T or T/C genotype relative to the C/C genotype.²⁻⁴

---

MTHFR

Reduced methylfolate levels

MTHFR 677 T/T

Folate Intermediates

NORMAL methylfolate levels

MTHFR 677 C/C

INTERMEDIATE methylfolate levels

MTHFR 677 T/C

Reduced methylfolate levels

MTHFR 677 T/T
Clinical Implications of MTHFR

- Folate deficiency is treatable, with multiple options for folate supplementation:
  - Supplementation with l-methylfolate (5-MTHF), the active form of folate.
  - Several recent studies have shown that increasing the intake of folic acid to try and overcome the effect of reduced MTHFR activity has the potential to mask a Vitamin B12 deficiency. 

Look like a ROCK Star!