Psychiatric Pharmacogenomics: Introduction and Applications

Stephanie Ebner, Ph.D.
Medical Science Liaison
Disclosure

• Relevant Financial Relationships:
  – Employed as a Medical Science Liaison with Assurex Health
Current Medication Decision Factors

- Adherence
- Adverse Effects
- Patient Experience
- Illness
- Family History
- Cost

Medication Selection
Challenges in Clinical Practice

LACK OF RESPONSE

~50% of patients with depression do not respond to their first treatment\(^1\)

SIDE EFFECTS

In clinical studies, up to 30% of patients discontinued treatment due to intolerable side effects\(^2,3\)

NONADHERENCE

Up to 70% of patients receiving prescriptions for antidepressant drugs are nonadherent, with side effects being the most common reason\(^4,5\)

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

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Current Standard of Care

Current Prescribing Practice is Highly Empiric

“Trial and Error” standard of care prescribing leads to:

- Repeated drug trials with limited efficacy
- Increasing rates of side effects
- 70% non-compliance
- High rates of polypharmacy

Sequenced Treatment Alternatives to Relieve Depression

<table>
<thead>
<tr>
<th>Drug Trial</th>
<th>Treatment Response</th>
<th>Treatment Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49%</td>
<td>16%</td>
</tr>
<tr>
<td>2</td>
<td>29%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>17%</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>16%</td>
<td>34%</td>
</tr>
</tbody>
</table>

Three Patients

Patient 1
- Venlafaxine XR 75 mg qd
- No SE
- Full remission

Patient 2
- Venlafaxine XR 150 mg qd
- Severe SE: GI, fatigue, sexual
- No response

Patient 3
- Venlafaxine XR 300 mg qd
- No SE
- No response

Images used in this presentation are from a stock photography source and do not reflect the quoted individuals.
Current Medication Decision Factors

- Patient Experience
- Adverse Effects
- Adherence
- Illness
- Family History
- Cost

Medication Selection
Implications for Family History

CYP2B6 alleles

*1 normal activity
*6 reduced activity
*4 increased activity
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
Personalized Medication Selection Factors

- Adherence
- Illness
- Family History
- Cost
- Adverse Effects
- Patient Experience

Pharmacogenomics

Personalized Medication Selection
Genes and Alleles

- A gene is a sequence of DNA that codes for a protein.
- An “allele” is the term that refers to the different versions of a gene.
- In most cases, we randomly inherit one copy of each gene from each parent.
- The combination of alleles (genotype) that we receive creates a certain physical presentation (phenotype).

Figure 2.6b
© 2012 W. H. Freeman and Company
Pharmacodynamics and Pharmacokinetics

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.
Drug Metabolism

• The CYP450 system is a family of about 57 enzymes responsible for drug metabolism, primarily in the liver.

• The UGT system is made up of 3 known groups of UGT genes – UGT1, UGT2, and UGT3, each of which includes multiple genes

• Multiple enzymes may be involved in the metabolism of a given drug.

Importance of CYP and UGT enzymes in metabolizing commonly prescribed neuropsychiatric medications
CYP2D6

- A highly variable gene with 17 common, clinically relevant polymorphisms.
- Located at a site on chromosome 22.
- Duplications can occur.
CYP2D6 Expression & Phenotype

*1/*5 Genotype

Intermediate Metabolizer Phenotype

CYP2D6 Gene

*1 Normal

*5 Deletion

CYP2D6 Enzyme

*1 Normal

*5 Deletion
CYP2D6 Expression & Phenotype

*5/*5 Genotype

CYP2D6 Gene

*5 Deletion

Chromosome 22

Poor Metabolizer Phenotype

CYP2D6 Enzyme

*5 Deletion

*5 Deletion
CYP2D6 Expression & Phenotype

Chromosome 22

CYP2D6 Gene

*1 Duplication

CYP2D6 Gene

*1 Normal

*1/*1 w/dup Genotype

Ultrarapid Metabolizer Phenotype

*1 Duplication

CYP2D6 Enzyme

*1 Normal
How Genetics Can Affect Medication Blood Levels

CYP2D6 Phenotype Frequency*

- Ultrarapid Metabolizer: 7%
- Extensive (Normal) Metabolizer: 56%
- Intermediate Metabolizer: 23%
- Poor Metabolizer: 14%

*Phenotype frequency is based on internal Assurex Health data of over 100,000 tested patients.
CYP2D6 and Nortriptyline

CYP2D6 and Nortriptyline

Number of functional CYP2D6 genes

Plasma concentration/25 mg dose (nmol/L)

Hours

Metabolic Pathway of Amitriptyline

Three Patients

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CYP2D6 EM

CYP2D6 PM

CYP2D6 UM
Pharmacodynamics and Pharmacokinetics

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.

Excretion
Pharmacodynamic Pharmacogenomics – SLC6A4

Serotonin Transporter (SLC6A4)

- 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
Pharmacodynamic Pharmacogenomics - HLA

Human Leukocyte Antigen (HLA)

• Helps regulate the immune system and recognize foreign substances such as viral and bacterial peptides¹

Genetics

• Located on chromosome 6; highly polymorphic¹
• HLA-A*3101 and HLA-B*1502 alleles have been associated with severe cutaneous adverse drug reactions (cADRs), including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
• Oxcarbazepine and carbamazepine are two medications most commonly associated with cADRs²,³

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA-A*3101</th>
<th>HLA-B*1502</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine (Trileptal®)³</td>
<td>-</td>
<td>√</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol®)²</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

Meta-analysis of 20 studies found certain HLA alleles significantly overrepresented in patients showing CBZ-induced cADRs⁠¹

- HLA-A*3101 (OR 7.75)
- HLA-B*1502 (OR 19.33)

<table>
<thead>
<tr>
<th>Subcategorized by severity of cADRs</th>
<th>HLA-A*3101 (OR)</th>
<th>HLA-B*1502 (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJS/TEN</td>
<td>5.65</td>
<td>80.70</td>
</tr>
<tr>
<td>Less severe cADRs</td>
<td>8.58</td>
<td>NS for predictive value</td>
</tr>
</tbody>
</table>

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# Prevalence of HLA-A*3101 and HLA-B*1502

<table>
<thead>
<tr>
<th>HLA-A*3101</th>
<th>Prevalence</th>
<th>HLA-B*1502</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese, Native American</td>
<td>&gt; 15%</td>
<td>Hong Kong, Thailand, Malaysia, parts of Philippines</td>
</tr>
<tr>
<td>Han Chinese, Korean, European, Latin America</td>
<td>~10%</td>
<td>Taiwan</td>
</tr>
<tr>
<td>African American, Indian, Thai, Taiwanese, Chinese (Hong Kong)</td>
<td>~4%</td>
<td>North China</td>
</tr>
<tr>
<td></td>
<td>2%-4%</td>
<td>South Asia, including India</td>
</tr>
<tr>
<td></td>
<td>&lt;1%</td>
<td>Japan, Korea</td>
</tr>
<tr>
<td></td>
<td>Largely Absent</td>
<td>Individuals not of Asian origin (Caucasians, African Americans, Hispanics, Native Americans)</td>
</tr>
</tbody>
</table>

_Tegretol [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014._
The FDA and the HLA genes

HLA-B*1502

FDA has added a black box warning to the carbamazepine package insert, stating that carbamazepine should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks\(^1\).

The FDA-approved package insert for oxcarbazepine also warns against the use of oxcarbazepine in patients positive for HLA-B*1502\(^2\).

HLA-A*3101

The carbamazepine package insert discourages the use of carbamazepine in HLA-A*3101 positive patients\(^1\).

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### The FDA and Pharmacogenomics

The Food and Drug Administration (FDA) includes pharmacogenomic language in the package inserts of many commonly prescribed psychiatric medications:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Instructions</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>
</tr>
<tr>
<td>Citalopram</td>
<td>“The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers.”</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>“The use of thioridazine in patients known to have reduced activity of P450 2D6 are contraindicated.”</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>“The maximum recommended dose of BRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers.”</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>“Patients testing positive for the HLA-B*1502 allele should not be treated with Tegretol unless the benefit clearly outweighs the risk.”</td>
</tr>
</tbody>
</table>

The contents of this page have not been endorsed by the FDA.
Psychiatric Pharmacogenomics: Clinical Studies
<table>
<thead>
<tr>
<th>Psychiatric Pharmacogenomic Testing Companies</th>
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<tbody>
<tr>
<td>• Access Genetics</td>
</tr>
<tr>
<td>• AGI</td>
</tr>
<tr>
<td>• AI Bio Tech</td>
</tr>
<tr>
<td>• AltheaDx</td>
</tr>
<tr>
<td>• Assurex Health</td>
</tr>
<tr>
<td>• CompanionDx</td>
</tr>
<tr>
<td>• DNA Stat</td>
</tr>
<tr>
<td>• ENSr Medical</td>
</tr>
<tr>
<td>• Genelex</td>
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<td>• GENETWORx</td>
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<td>• Genomas</td>
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<tr>
<td>• Genomind</td>
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<tr>
<td>• Genotox</td>
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<tr>
<td>• Infiniti Labs</td>
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<tr>
<td>• Iverson Genetics</td>
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<td>• Millennium Labs</td>
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<td>• MonogramBio</td>
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<tr>
<td>• Natural Molecular</td>
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<tr>
<td>• NeuroPharmagen</td>
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<tr>
<td>• OneOme</td>
</tr>
<tr>
<td>• Pathway Genomics</td>
</tr>
<tr>
<td>• ProoveBiosciences</td>
</tr>
<tr>
<td>• Vantari Genetics</td>
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Evaluation of a Pharmacogenomic Test

Clinical Validity
- Is the test predictive of patient outcome?

Clinical Utility
- Does the test help guide a healthcare provider toward a more effective and/or tolerable medication?

Economic Utility
- Does the test reduce healthcare expenditures?
<table>
<thead>
<tr>
<th>Clinical Validity</th>
<th>Clinical Utility</th>
<th>Economic Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall-Flavin, et al. 2013</td>
<td></td>
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</tbody>
</table>
Clinical Validity: Individual Gene Phenotyping

Traditional gene phenotyping fails to identify patients with differential response to medications.

Combinatorial Pharmacogenomics identifies patients who are least likely to respond to their treatment regimen, allowing clinicians to prescribe more suitable medications.

Combinatorial pharmacogenomics identifies patients who are least likely to respond to their treatment regimen, allowing clinicians to prescribe more suitable medications.


- 12 Week, prospective double blind randomized trial comparing outcomes of genetically guided versus unguided treatment.

- Genetically guided group was 2.52 times more likely to remit from depression than unguided group.

- Unguided group was 1.13 times more likely to have medication tolerability problems requiring either dose reduction or cessation.

- Naturalistic, unblinded, prospective analysis of psychiatric patients and clinicians who utilized the pharmacogenomic report

- 87% showed improvement

- Patients reported significant decreases in depression, anxiety, and medication side effects, and increases in quality of life

Treatment guided by the pharmacogenomic report resulted in up to a **four fold** greater improvement in symptoms.
Treatment guided by the pharmacogenomic report resulted in up to two fold greater improvement in symptoms.
Prevalence of Patients Taking Medications that are Not Genetically Optimal

Thirty percent of the patients in a typical psychiatric practice are taking medications that are not genetically optimal, unbeknownst to their treating clinician.


This was a retrospective chart review of 96 adults diagnosed with a depressive or anxiety disorder. All subjects were treated with one or more psychotropic medications from CPGx panel. Medical records were analyzed for healthcare utilization during a one year period from April 2010 to April 2011.

Increased healthcare utilization among subjects taking “red category” resulted in more than $5,100 greater spending than green or yellow category subjects.

This was a prospective case-control study of pharmacy data from 2,168 CPGx-guided patients vs. 10,880 propensity matched controls. The study enrolled patients who failed at least one CPGx panel medication and were currently taking another CPGx panel medication. Six months of pre-test data was compared to 12 months of post-test data.

In addition to cost savings, patients treated using CPGx test experienced significant increases in adherence and significant reductions in polypharmacy.

Total medication cost of patients on congruent medication was $2,774 lower than for patients whose clinicians did not follow report recommendations.