A Look at Psychiatric Pharmacogenomics in Practice

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Developed in partnership between ASHP and the American Pharmacists Association (APhA).
Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Learning Objectives

• Compare Clinical Pharmacogenomics Implementation Consortium (CPIC) guideline recommendations with interpretation results from a commercial laboratory.

• Given the results of pharmacogenetic (PGx) testing, provide patient-specific recommendations for antidepressant and antipsychotic use.

• Interpret pharmacogenomic results and recommend appropriate therapy for geriatric patients with depression.
Session Outline

• Overview of PGx resources
  – CPIC
  – PharmGKB

• Introduction to commercial PGx panel tests
  – General concepts
  – Complexities
  – Examples

• Case studies
Question for the Audience

Which of the following events has occurred in your practice within the past year?

a. I recommended ordering a PGx test to assist with prescribing psychiatric medications
b. A patient came in seeking advice about PGx test results
c. Both A and B
d. I am not currently in practice
CPIC and PharmGKB

• CPIC creates guidelines for gene-drug pairs using standard terms
  – Guidelines do not state WHEN to test
  – Cpicpgx.org

• PharmGKB is a more inclusive resource:
  – Drug metabolism pathways, links to guidelines, and research summaries for gene-drug pairs still in early investigation stages
  – Pharmgkb.org
Which of the following metabolizing enzyme phenotypes is least common?

a. Ultrarapid CYP2C19 metabolizers
b. Poor CYP2C19 metabolizers
c. Ultrarapid CYP2D6 metabolizers
d. Poor CYP2D6 metabolizers
Psychiatric PGx Implementation: Overview

- **CYP2D6**
  - Poor metabolizers: ~1-10% of patients
  - Ultrarapid metabolizers: ~1-20% of patients

- **CYP2C19**
  - Poor metabolizers: ~2-15% of patients
  - Ultrarapid metabolizers: ~2-5% of patients

PharmGKB. Accessed 10/15/18.
### Example: CPIC Guideline for Sertraline and CYP2C19

#### Table 3b Dosing recommendations for sertraline based on CYP2C19 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implication</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 Ultrapid metabolizer</td>
<td>Increased metabolism when compared to extensive metabolizers.</td>
<td>Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.</td>
<td>Optional</td>
</tr>
<tr>
<td>CYP2C19 Extensive metabolizer</td>
<td>Normal metabolism</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2C19 Intermediate metabolizer</td>
<td>Reduced metabolism when compared to extensive metabolizers.</td>
<td>Initiate therapy with recommended starting dose.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2C19 Poor metabolizer</td>
<td>Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.</td>
<td>Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.</td>
<td>Optional</td>
</tr>
</tbody>
</table>

*Rating scheme described in Supplemental Materials.*

Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy. Per the FDA warning, citalopram 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation. FDA product labeling additionally cautions that citalopram dosing should be limited to 20 mg/day in patients with hepatic impairment, those taking a CYP2C19 inhibitor, and patients greater than 60 years of age.

Percent dose adjustments corresponding to percent difference in oral clearances have been calculated/estimated by Stingl et al. (1).

---


<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CYP2D6 ultrarapid metabolizer</th>
<th>CYP2D6 normal metabolizer</th>
<th>CYP2D6 intermediate metabolizer</th>
<th>CYP2D6 poor metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultrapid or rapid</td>
<td>Avoid amitriptyline use (^a)</td>
<td>Consider alternative drug</td>
<td>Avoid amitriptyline use (^a)</td>
<td>Avoid amitriptyline use</td>
</tr>
<tr>
<td></td>
<td>Classification of recommendation (^b): Optional</td>
<td>not metabolized by CYP2C19(^c)</td>
<td>Classification of recommendation (^b): Optional</td>
<td>Classification of recommendation (^b): Optional</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Avoid amitriptyline use. If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers) (^d) Classification of recommendation (^c): Strong</td>
<td>Consider a 25% reduction of recommended starting dose (^e) Classification of recommendation (^d): Strong</td>
<td>Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose (^e) Classification of recommendation (^d): Strong</td>
<td></td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>Avoid amitriptyline use (^a)</td>
<td>Classification of recommendation (^b): Optional</td>
<td>Consider a 25% reduction of recommended starting dose (^e) Classification of recommendation (^d): Strong</td>
<td>Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose (^e) Classification of recommendation (^d): Strong</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizer</td>
<td>Avoid amitriptyline use (^a)</td>
<td>Classification of recommendation (^b): Optional</td>
<td>Avoid amitriptyline use (^a)</td>
<td>Avoid amitriptyline use (^a)</td>
</tr>
</tbody>
</table>

\(^a\) Dosing recommendations only apply to higher initial doses of TCAs for treatment of conditions such as depression. See other considerations for dosing recommendations for conditions where lower initial doses are used, such as neuropathic pain. \(^b\) The dosing recommendations are based on studies focusing on amitriptyline. Because tricyclic antidepressants have comparable pharmacokinetic properties, it may be reasonable to apply these guidelines to other tertiary amines including clomipramine, doxepin, imipramine, and trimipramine (the classification of this recommendation is optional). \(^c\) If amitriptyline is warranted, utilize therapeutic drug monitoring \(^h\) to guide dose adjustment. \(^d\) The rating scheme for the recommendation classification is described in Supplementary Data. See CYP2D6 and CYP2C19 combined dosing recommendations for explanation of classification of recommendations for this table. TCAs without major CYP2D6 metabolism include the secondary amines nortriptyline and desipramine. \(^e\) Utilizing therapeutic drug monitoring if a tricyclic is prescribed to a patient with CYP2D6 ultrarapid, intermediate, or poor metabolism in combination with CYP2C19 ultrarapid, intermediate, or poor metabolism is strongly recommended. \(^f\) Dose to observed clinical response with symptom improvement and minimal (if any) side effects. Patients may receive an initial low dose of TCAs, which is then increased over several days to the recommended steady-state dose. The starting dose in this guideline refers to the recommended steady-state dose.

**Example: PharmGKB Input**

Annotation of CPIC Guideline for sertraline and CYP2C19

Specify a genotype for specific annotations

Pick alleles for CYP2C19

Alleles not present in the above pull-down menus have no CPIC recommendation.

Summary

The CPIC Dosing Guideline for the selective serotonin reuptake inhibitor sertraline recommends to consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19 for CYP2C19 poor metabolizers.

Based on a CPIC dosing guideline

PharmGKB. Accessed 10/15/18. [https://www.pharmgkb.org/chemical/PA451333/guideline/PA166127639](https://www.pharmgkb.org/chemical/PA451333/guideline/PA166127639)

Shared under the Creative Commons Attribution-ShareAlike 4.0 International License: [https://www.pharmgkb.org/page/dataUsagePolicy](https://www.pharmgkb.org/page/dataUsagePolicy)
Panel Testing in Psychiatry: Introduction

- Studies supporting PGx panel testing in psychiatry have increased
  - Panel testing: genotyping for multiple variants across several genes

- Tests are expensive, and reimbursement is variable
Psychiatric PGx Panel Testing: Complications in Result Interpretation

• The tested variants are inconsistent across labs

• Results may be translated by “binning” (i.e. grouping) medications into categories based on proprietary algorithms that are often variations of:
  – *Use as directed/no gene-drug interaction*
  – *Moderate gene-drug interaction*
  – *Major gene-drug interaction*
Common Elements of PGx Test Reports

• Patient, prescriber, and lab information

• Genotype and phenotype
  – For CYP450 genes, phenotype nomenclature may use terms standardized by CPIC

• Interpretation of results: where “binning” may be used
Commercial Testing Labs

- The Community Pharmacists Pharmacogenetics Network (CPPN) provides a list of PGx labs: [http://rxpgx.com/rxpgx-labs](http://rxpgx.com/rxpgx-labs)

- The following example reports were selected to demonstrate different approaches for PGx panel result interpretation, and are not endorsements for the associated companies
## Example Test Report 1: Result Interpretation

### Antidepressant

<table>
<thead>
<tr>
<th>Major gene-drug interaction</th>
<th>Moderate gene-drug interaction</th>
<th>Minimal gene-drug interaction</th>
<th>Limited genetic impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline (Elavil®)</td>
<td>Duloxetine (Cymbalta®)</td>
<td>Bupropion (Wellbutrin®)</td>
<td>Desvenlafaxine (Pristiq®)</td>
</tr>
<tr>
<td>Citalopram (Celexa®)</td>
<td>Selegiline (Eldepryl®, Emsam®)</td>
<td>Desipramine (Norpramin®)</td>
<td>Milnacipran (Savella®)</td>
</tr>
<tr>
<td>Clomipramine (Anafranil®)</td>
<td>Sertraline (Zoloft®)</td>
<td>Fluoxetine (Prozac®, Sarafem®)</td>
<td></td>
</tr>
<tr>
<td>Doxepin (Silenor®)</td>
<td></td>
<td>Fluvoxamine (Luvox®)</td>
<td></td>
</tr>
<tr>
<td>Escitalopram (Lexapro®)</td>
<td></td>
<td>Levomilnacipran (Fetzima®)</td>
<td></td>
</tr>
<tr>
<td>Imipramine (Tofranil®)</td>
<td></td>
<td>Mirtazapine (Remeron®)</td>
<td></td>
</tr>
<tr>
<td>Trimipramine</td>
<td></td>
<td>Nefazodone</td>
<td></td>
</tr>
</tbody>
</table>

OneOme. 2018 Used with permission.

# Example Test Report 1: Genotype and Phenotype Results

## Gene and phenotype summary

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype summary / Metabolic status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>*1A/*1F</td>
<td>Rapid: Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolite(s) may lack efficacy.</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>*1/*5</td>
<td>Intermediate to Normal: Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*3</td>
<td>Intermediate: Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.</td>
</tr>
</tbody>
</table>

### ANTIDEPRESSANTS

**USE AS DIRECTED**

- desvenlafaxine (Pristiq®)
- levomilnacipran (Fetzima®)
- vilazodone (Viibryd®)

**MODERATE GENE-DRUG INTERACTION**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>trazodone (Desyrel®)</td>
<td>1</td>
</tr>
<tr>
<td>venlafaxine (Effexor®)</td>
<td>1</td>
</tr>
<tr>
<td>selegiline (Emsam®)</td>
<td>2</td>
</tr>
<tr>
<td>fluoxetine (Prozac®)</td>
<td>1,4</td>
</tr>
<tr>
<td>citalopram (Celexa®)</td>
<td>3,4</td>
</tr>
<tr>
<td>escitalopram (Lexapro®)</td>
<td>3,4</td>
</tr>
<tr>
<td>sertraline (Zoloft®)</td>
<td>3,4</td>
</tr>
</tbody>
</table>

**SIGNIFICANT GENE-DRUG INTERACTION**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>bupropion (Wellbutrin®)</td>
<td>1,6</td>
</tr>
<tr>
<td>mirtazapine (Remeron®)</td>
<td>1,6</td>
</tr>
<tr>
<td>amitriptyline (Elavil®)</td>
<td>3,8</td>
</tr>
<tr>
<td>clomipramine (Anafranil®)</td>
<td>1,6,8</td>
</tr>
<tr>
<td>desipramine (Norpramin®)</td>
<td>1,6,8</td>
</tr>
<tr>
<td>doxepin (Sinequan®)</td>
<td>1,6,8</td>
</tr>
<tr>
<td>duloxetine (Cymbalta®)</td>
<td>1,6,8</td>
</tr>
<tr>
<td>imipramine (Tofranil®)</td>
<td>1,6,8</td>
</tr>
<tr>
<td>nortriptyline (Pamelor®)</td>
<td>1,6,8</td>
</tr>
<tr>
<td>vortioxetine (Trintellix®)</td>
<td>1,6,8</td>
</tr>
<tr>
<td>fluvoxamine (Luvox®)</td>
<td>1,4,6,8</td>
</tr>
<tr>
<td>paroxetine (Paxil®)</td>
<td>1,4,6,8</td>
</tr>
</tbody>
</table>

AssureRx Health. Used with permission.  
PATIENT GENOTYPES AND PHENOTYPES

PHARMACOKINETIC GENES

CYP1A2

*1/*1

Extensive (Normal) Metabolizer

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CYP2B6

*1/*6

Intermediate Metabolizer

CYP2B6*1 allele enzyme activity: Normal
CYP2B6*6 allele enzyme activity: Reduced

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.

CYP2D6

*4/*4 (Duplication)

Poor Metabolizer

CYP2D6*4 allele enzyme activity: None
CYP2D6*4 allele enzyme activity: None

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.

A duplication of the gene CYP2D6 has been detected in this patient. While current genotyping techniques allow for the detection of this duplication, in the case of heterozygosity, such techniques do not allow for the identification of the allele that has been duplicated. This duplication, depending on the allele duplicated, can result in increased expression of CYP2D6.

AssureRx Health. Used with permission.
<table>
<thead>
<tr>
<th>GENE RESULT</th>
<th>THERAPEUTIC IMPLICATIONS</th>
<th>INTERACTION</th>
<th>CLINICAL IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin Transporter (SLC6A4)</td>
<td>SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake</td>
<td>Use caution with SSRIs</td>
<td>Therapeutic options: SNRIs or non-SSRI antidepressants may be used if clinically indicated</td>
</tr>
<tr>
<td>S/S [Higher risk of non-response]</td>
<td>- SSRIs act by blocking this transporter to produce a therapeutic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Higher risk of poor response, slow response or intolerance to SSRIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Potential for increased cortisol release in response to stress in S/S, L(G)/S or L(G)/L(G) patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Therapeutic options such as SNRIs or other non-SSRI antidepressants may be used if clinically indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium Channel (CACNA1C)</td>
<td>CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain</td>
<td>Therapeutic options: atypical antipsychotics, mood stabilizers and/or omega-3 fatty acids may be used if clinically indicated</td>
<td></td>
</tr>
<tr>
<td>A/A [Increased risk of altered neuronal signaling]</td>
<td>- Altered calcium signaling may be clinically associated with impairment of mood or cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin Receptor 2C (5HT2C)</td>
<td>5HT2C is a receptor involved in the regulation of satiety</td>
<td>Use caution with atypical antipsychotics</td>
<td>Therapeutic options: metformin, lorcaserin or other anti-obesity interventions may be used if clinically indicated</td>
</tr>
<tr>
<td>C/C [Weight gain risk]</td>
<td>- Atypical antipsychotics act by blocking this receptor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Patients with the C/C genotype have risk of weight gain with atypical antipsychotics, however, this is the most common genotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Metformin, lorcaserin or other anti-obesity interventions may be beneficial to mitigate weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanocortin 4 Receptor (MC4R)</td>
<td>MC4R is a receptor that plays a central role in the control of food intake</td>
<td>Use caution with atypical antipsychotics</td>
<td>Therapeutic Options: metformin, lorcaserin or other anti-obesity interventions may be used if clinically indicated</td>
</tr>
<tr>
<td>A/A [High weight gain risk]</td>
<td>- Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Metformin, lorcaserin or other anti-obesity interventions may be beneficial to mitigate weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- High risk: Clozapine; Olanzapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Medium risk: Aripiprazole; Iloperidone; Paliperidone; Quetiapine; Risperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Lower risk: Asenapine; Brexpiprazole; Cariprazine; Lurasidone; Ziprasidone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Genomind. 2018. Used with permission.  
Panel Comparison: Bousman et al

• Compared CYP2D6 and CYP2C19 allele coverage and result reporting among 20 psychiatric panel tests

• None of the labs reported the same combination of star alleles, although all covered “major” variants

• All of the labs reported the *1 allele as the result when a variant wasn’t detected

Question for the Audience

Is testing for more star alleles always better?

a. Yes
b. No
c. I’m not sure
d. It depends
CYP2D6 Example for Audience Question

- CPIC guidelines lists >100 different CYP2D6 star alleles and their known functional impact
- The *4 “no function” allele frequency varies: ~ 2.5-18.2%
- Some star alleles are rare (<1%) across groups, and some have an uncertain impact on function

Recap of Introduction

- PharmGKB and CPIC are useful resources for PGx result interpretation
- The genetic variants tested and results interpretation and reporting vary among commercial lab PGx panel tests
- Currently, the clearest evidence for using PGx to assist with psychiatric medication decisions is for CYP2C19 and CYP2D6 extreme metabolizers and select SSRIs and TCAs
Practice Cases
Case Study 1

MM is a 19-year-old female who began experiencing symptoms of depression and social anxiety at college. She is hoping to start treatment because her mood has been significantly depressed for more than 6 months. During her intake interview, she shares that during the past semester she also had difficulty falling asleep and decreased appetite, resulting in a 5-lb weight loss. Current BMI is 19 kg/m². The provider and MM agree to start an antidepressant and therapy. Her mom is insisting upon genetic testing.

The team agrees, and the results include:
## Case 1, Continued

<table>
<thead>
<tr>
<th>Minimal gene-drug interaction</th>
<th>Moderate gene-drug interaction</th>
<th>Major gene-drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvenlafaxine</td>
<td>TCAs</td>
<td>Fluvoxamine Paroxetine</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escitalopram</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>*1/*1</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*9/*11</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*1</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>S/S</td>
<td>Potential reduced response to SSRIs</td>
</tr>
</tbody>
</table>
Serotonin Transporter (SLC6A4 Long and Short Alleles)

Escitalopram
- Increased response in L/L and S/L carriers when compared to S/S carriers

Citalopram
- Increased response and decreased risk of adverse events for L/L carriers when compared to S/S carriers
- L/S carriers may have decreased response compared to L/L carriers

PharmGKB. Accessed 10/15/18.
# Serotonin Transporter (SLC6A4 Long and Short Alleles)

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>VARIANT</th>
<th>GENE</th>
<th>MOLECULE</th>
<th>TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read Now</td>
<td>Level 2A</td>
<td>SLC6A4 HTTLPR long form (L allele), SLC6A4 HTTLPR short form (S allele)</td>
<td>SLC6A4</td>
<td>escitalopram</td>
</tr>
<tr>
<td>Read Now</td>
<td>Level 2A</td>
<td>SLC6A4 HTTLPR long form (L allele), SLC6A4 HTTLPR short form (S allele)</td>
<td>SLC6A4</td>
<td>citalopram</td>
</tr>
</tbody>
</table>

Group Discussion, Case 1

The team decides to initiate treatment with desvenlafaxine, but the patient experiences intolerable nausea and wants to switch to another antidepressant. Given the previous information, which of the following medications would you recommend?

- a. Citalopram
- b. Escitalopram
- c. Mirtazapine
- d. Venlafaxine
Case 1 Wrap Up

- Genotype is informative

- *SLC6A4 S/S* carrier status modified binning for SSRIs

- Ultimately, it will always be important to consider other patient factors, like difficulty sleeping and weight loss
Case Study 2

RM is a 55-year-old female with a 20-year history of depression and anxiety. She presents to your clinic stating “my medications aren’t working anymore” and describes worsening symptoms of low mood, amotivation, frequent crying spells, and hypersomnia. RM says these symptoms had been controlled for about the past year on a combination of sertraline 200 mg daily, bupropion XL 150 mg daily, and aripiprazole 2.5 mg daily. However, 2 months ago she experienced a significant increase in symptoms with no appreciable trigger event. RM states she is very “good” about taking her medications.
Case 2, Continued

• Medical History:
  – Hypertension
  – Obesity: BMI 34 mg/kg²
  – Nonsmoker

• Labs (1 month ago):
  – A1c: 6%
  – Fasting blood sugar: 110 mg/dL

The decision was made to order pharmacogenetic testing, results include:

• Medication list
  – Trazodone 100 mg at bedtime
  – Lisinopril 10 mg daily
  – Sertraline 200 mg daily
  – Bupropion XL 150 mg daily
  – Aripiprazole 2.5 mg daily
### Case 2, Continued

<table>
<thead>
<tr>
<th>Minimal gene-drug interaction</th>
<th>Moderate gene-drug interaction</th>
<th>Major gene-drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SSRIs</td>
<td>Mirtazapine</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Duloxetine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>All TCAs</td>
<td></td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gene</strong></th>
<th><strong>Genotype</strong></th>
<th><strong>Phenotype</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>-163C&gt;A - A/A</td>
<td>Ultrarapid metabolizer</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*1/*1</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*1</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>L/L</td>
<td>Anticipated normal response to SSRIs</td>
</tr>
</tbody>
</table>
Case 2, Continued

• The patient is upset that many of the medications she tried were in the “green” category, but they still did not work for her. Provide a response to the patient by working with a neighbor.
Clinical Pearl Related to Case 2

- **CYP1A2 *1F variant**: homozygous in 23-50% of individuals
- Appears to be most important in the presence of **inducers**

- Which of the following induce CYP1A2?
  a. Smoking cigarettes
  b. Aripiprazole
  c. Sertraline
  d. Grapes

[dbSNP.](https://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=762551)
Case 2 Wrap Up

• PGx testing probably will not explain the history of response or tolerability to all medications in an individual, and testing is not capable of predicting future response for medications

• CYP1A2 ultrarapid metabolizers are not uncommon, so it is important to understand the potential impact of enzyme inducers in patients with this phenotype
Case Study 3

GR is a 72-year-old male who arrives at the clinic with his wife. Over the last 2 years, his wife has noticed that GR has had difficulty focusing on tasks, falling asleep, and enjoying activities he previously used to, like golfing and fishing. His wife says that he is increasingly withdrawn, and with the exception of visits to see their children and grandchildren, he prefers to stay home. GR is most bothered by his inability to focus and his insomnia. He will consider medications but refuses any type of cognitive therapy.
Case 3, Continued

• Medical History
  – Stent placement for a ST-segment elevation myocardial infarction 5 years ago
  – GERD
  – Hypertension
  – Type 2 diabetes mellitus

• Medications
  – Aspirin
  – Ticagrelor
  – Metformin
  – Metoprolol succinate
  – Valsartan
  – Omeprazole

• Labs
  – The patient’s wife notes that at this time, GR had his “genes tested” and ended up on ticagrelor instead of clopidogrel
Case 3, Continued

Considering the following table, what CYP2C19 phenotype(s) describes the patient based on his wife’s “gene testing” comment?

a. Ultrarapid metabolizer  
b. Intermediate metabolizer  
c. Normal metabolizer  
d. Poor metabolizer
### Case 3, Continued

Table 2: Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients

<table>
<thead>
<tr>
<th>Phenotype (genotype)</th>
<th>Implications for clopidogrel</th>
<th>Therapeutic recommendations</th>
<th>Classification of recommendations³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)</td>
<td>Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation⁴</td>
<td>Clopidogrel: label-recommended dosage and administration</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer (*1/*2, *1/*3, *2/*17)</td>
<td>Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor metabolizer (*2/*2, *2/*3, *3/*3)</td>
<td>Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Strong</td>
</tr>
</tbody>
</table>

³See Supplementary Materials and Methods (Strength of Therapeutic Recommendations) online. ⁴The CYP2C19*17 allele may be associated with increased bleeding risks (ref. 15). ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.
Case 3, Continued

Pick alleles for CYP2C19

*2 ▼ *3 ▼

Alleles not present in the above pull-down menus have no CPIC recommendation.

**Implications**
Greatly reduced metabolism when compared to normal metabolizers.
Higher plasma concentrations may increase the probability of side effects

**Metabolizer Status**
Poor Metabolizer

Case 3, Continued

Pick alleles for CYP2C19

*2 △ *3 △

Alleles not present in the above pull-down menus have no CPIC recommendation.

Phenotype (Genotype)
An individual carrying two no function alleles

Recommendations
Consider a 50% reduction of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19

Case 3, Continued

- His PCP’s office sends over GR’s lab results and the CYP2C19 genotype is *2/*3

- Use PharmGKB.com resources on the previous slide to identify the correct starting doses for escitalopram for this patient:
  a. 2.5 mg daily
  b. 5 mg daily
  c. 10 mg daily
  d. 15 mg daily
Case 3, Continued

GR was placed on mirtazapine, which has improved his insomnia and some symptoms of low mood, but 4 months later he is still struggling with difficulty concentrating. The team believes it is closely linked to residual symptoms of depression. They want to start adjunctive use of bupropion.
Case 3, Continued

How would adjunctive bupropion impact concomitant CYP2D6 substrate concentrations if GR was:

- **Scenario 1**: A normal metabolizer of CYP2D6
  
  a. CYP2D6 substrate serum concentration would increase markedly
  b. CYP2D6 substrate serum concentration would decrease markedly
  c. CYP2D6 substrate serum concentrations would not change significantly
  d. CYP2D6 substrate serum concentration would be unpredictable
Case 3, Continued

How would adjunctive bupropion impact concomitant CYP2D6 substrate concentrations if GR was:

• **Scenario 2**: A poor metabolizer of CYP2D6
  
a. CYP2D6 substrate serum concentration would increase markedly  
b. CYP2D6 substrate serum concentration would decrease markedly  
c. CYP2D6 substrate serum concentrations would not change significantly  
d. CYP2D6 substrate serum concentration would be unpredictable
Case 3 Wrap Up

• PharmGKB: can “plug in” a genotype to obtain guideline interpretations for several antidepressants with CYP2D6 or CYP2C19 results

• Drug interactions will impact apparent metabolizing phenotype
KEY TAKEAWAYS

1) **KEY TAKEAWAY**
Available PGx test panels can vary in the specific genes examined, the different variants included in the testing panel, and the interpretation of the results.

2) **KEY TAKEAWAY**
It is important that pharmacists understand the level of evidence associated with drug-gene pairs in test results to provide thoughtful treatment recommendations.

3) **KEY TAKEAWAY**
Thank you for your time!

What questions do you have for us?
References


