

**Pharmacogenetic Testing  
in  
Psychiatry**

**Jose de Leon, MD**

**(12-01-15)**

# Conflicts of Interest

(See more details on conflict of interest in the first presentation  
“Training Psychiatrists to Think like Pharmacologists”)

1. Dr. de Leon has had no direct relationship with commercial companies since 2007.
2. He has never been a consultant for any pharmacogenetics or pharmaceutical company.
3. He personally develops his presentations for lecturing and has never lectured using any pharmaceutical company presentations.
4. No commercial company had any role or influence in writing the article on which this presentation is based.
5. Dr. de Leon does not use the US tests designed to genotype simultaneously for many CYPs, serotonin receptors, serotonin transporters and other brain receptors.
6. Dr. de Leon occasionally recommends CYP2D6 and/or CYP2C19 genotyping for psychiatric patients.

# Controversial Ideas about Clozapine

- Be aware that other authors (and Dr. de Leon's old articles) did not consider CYP2C19 important in clozapine metabolism.
- In a Swiss study, 5 CYP2C19 PMs had impaired clozapine metabolism.

<http://www.ncbi.nlm.nih.gov/pubmed/19593168>

- Only time and independent replication will tell whether this hypothesis is wrong or not.

# Learning Objectives

After completing this presentation, the participant should be able to:

1. Appreciate the current relevance or lack of relevance of different CYPs in clinical practice in psychiatry.
2. Summarize two major relevant CYP genotypes which are relevant for clinical practice in psychiatry:
  - (a) CYP2D6
  - (b) CYP2C19
3. Be aware that genotyping HLA-B\*1502 in individuals with Asian ancestry is an FDA requirement before starting carbamazepine.

# Warning

This is an extraordinarily long presentation:

- 1) You may need to read it more than once to become familiar with key aspects.
- 2) The section on CYP genotyping is very complex if you are not familiar with these concepts. It is repeated in the lecture titled “Antidepressant Pharmacokinetics”.
- 3) If you have psychopharmacology expertise, you know that understanding FDA regulations is a key to understanding how new drugs are approved. It is impossible to explain why non-validated pharmacogenetic tests have been marketed in the US and Europe without understanding that currently it is a poorly regulated market. This is briefly explained in the introduction and conclusion sections but it may need to be expanded in future versions of this lecture.

# Abbreviations

- AED: antiepileptic drug
- C: concentration
- C/D ratio: concentration-to-dose ratio
- CLIA: clinical laboratory improvement amendments  
(rules regulating US clinical laboratories)
- CYP: cytochrome P450
- D: dose
- FDA: Food & Drug Administration
- HLA: human leukocyte antigen
- HERG: human ether-a-go-go-related gene (encodes potassium repolarizing channels associated with QTc prolongation)
- OD: odds ratio
- TCA: tricyclic antidepressant
- TDM: therapeutic drug monitoring
- SJS-TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis
- SSRI: selective serotonin reuptake inhibitor
- UGT: uridine diphosphate glucuronosyltransferase
- WBC: white blood count

# Pharmacogenetic Tests in Psychiatry

## 0. Introduction

## 1. CYP Genotyping

## 2. HLA Genotyping

## 3. Conclusions

# Pharmacogenetic Tests in Psychiatry

## 0. Introduction

### 0.1. Classification

0.1.1. Pharmacogenetic Tests for Disease Mechanisms

0.1.2. Pharmacogenetic Tests for Drug Mechanisms

### 0.2. Regulations for Marketing

## 1. CYP Genotyping

### 1.1. Not Ready for Clinical Use

1.1.1. CYP1A2

1.1.2. CYP2B6

1.1.3. CYP3A

### 1.2. Ready for Clinical Use

1.2.1. CYP2D6

1.2.2. CYP2C19

1.2.3. CYP2D6 and CYP2C19 Combined

## 2. HLA Genotyping

2.1. Not Ready for Clinical Use: Clozapine

2.2. Ready for Clinical Use: Carbamazepine and HLA-B\*15:02

## 3. Conclusions



# 0. Introduction

# Introduction

## 0.1. Classification

0.1.1. Pharmacogenetic Tests for Disease Mechanisms

0.1.2. Pharmacogenetic Tests for Drug Mechanisms

## 0.2. Regulations for Marketing

# 0.1. Classification

# 0.1. Classification of Pharmacogenetic Tests

- Two major overlapping traditions:
  - Pharmacological: focus on pharmacological mechanisms
  - Biomarkers: broader
    - normal biological processes: physiological mechanism
    - pathogenic processes (disease mechanism)
    - pharmacological response (pharmacological mechanism)
- Psychiatric journals talk about “personalizing treatment” or “biomarkers” or “pharmacogenetic testing”.  
They may be talking about testing for:
  - disease mechanisms, and/or
  - pharmacological mechanisms.

# 0.1. Classification

0.1.1. Pharmacogenetic Tests for Disease Mechanisms

0.1.2. Pharmacogenetic Tests for Drug Mechanisms

**0.1.1. Pharmacogenetic Tests  
for  
Disease Mechanisms**

## 0.1.1. Pharmacogenetic Tests for Disease Mechanisms

- Psychiatric disorders such as:
  - schizophrenia and
  - depressionare not diseases, in the medical sense, and are probably more like syndromes.
- Known biological markers overlap:
  - shared genes between schizophrenia and bipolar disorder
- There is no easy way of validating the tests.
- In the opinion of Dr. de Leon, pharmacogenetic tests focused on disease mechanisms are not ready for clinical practice. <http://www.ncbi.nlm.nih.gov/pubmed/25455256>

**0.1.2. Pharmacogenetic Tests  
for  
Drug Mechanisms**



## 0.1.2. Testing for Drug Mechanisms

- Pharmacological mechanisms:
  - Pharmacokinetic mechanisms:
    - The most important CYPs are reviewed. CYP2D6 and CYP2C19 guidelines have been published for TCAs and SSRIs.
    - Other: P-glycoprotein is not reviewed; it is not ready for clinical practice.
  - <http://www.ncbi.nlm.nih.gov/pubmed/26111722>
  - Pharmacodynamic mechanisms:
    - HLA: reviewed.
    - Other: Receptors/transporters are involved in neurotransmission. These genes are not ready for clinical practice.

## 0.1.2. Testing for Drug Mechanisms

- Pharmacogenetic tests for receptors/transporters involved in neurotransmission:
    - are marketed in the USA and Europe
    - there are no guidelines recommending them.
    - scientific information is limited:
      - no understanding of genotype/phenotype relationships
      - no understanding of how environmental and personal factors influence phenotype
      - frequently based on non-replicated studies.
- They will not be further discussed.

# **0.2. Regulations for Marketing**

## 0.2. Regulations for Marketing

- Regulations for pharmacogenetic testing:
  - US regulations are important since the US is the leader in the field.
  - Are not addressed in articles published in psychiatric journals.
  - Are briefly described in this presentation.
  - Are more thoroughly described in a 2009 article available in PubMed,

<http://www.ncbi.nlm.nih.gov/pubmed/18800072>

and are described with an update in a 2016 article. <http://www.ncbi.nlm.nih.gov/pubmed/26580456>

## 0.2. Regulations for Marketing

- Three properties are relevant for marketing:
  - Analytic validity: accurate and reliable measurement of the genotype
  - Clinical validity: the ability to detect or predict the associated disorder
  - Clinical utility: risks and benefit of test use
- US regulation is not well developed:
  - The Clinical Laboratory Improvement Amendments (CLIA) regulate quality standards for US clinical laboratories.
  - The FDA has been developing guidelines that include aspects of pharmacogenetic testing since 2005.

## 0.2. Regulations for Marketing

- A legal vacuum exists in the US:

<http://www.ncbi.nlm.nih.gov/pubmed/26580456>

- Only basic issues of analytic validity are regulated by CLIA.
- No regulatory agency has responsibility for clinical validity and utility.
- Non-validated tests are aggressively marketed.
- A 2014 FDA draft to regulate complex diagnostic tests was not well received by experts from clinical laboratories.

<http://www.ncbi.nlm.nih.gov/pubmed/26495591>

# 1. CYP Genotyping

# 1. CYP Genotyping

## 1. CYP Terminology

### 1.1. Not Ready for Clinical Use

1.1.1. CYP1A2

1.1.2. CYP2B6

1.1.3. CYP3A4

### 1.2. Ready for Clinical Use

1.2.1. CYP2D6

1.2.2. CYP2C19

1.2.3. CYP2D6 and CYP2C19 Combined



# **1.0. CYP Terminology (only for the brave of heart)**

# 1.0 CYP Terminology

1.0.1. Phenotype

1.0.2. Allele \*1

1.0.3. Two Alleles for a Phenotype

# 1.0.1. Phenotype

## 1.0.1. Phenotype

- Everyone has two alleles which determine his/her phenotype.

- Phenotype =

“The outward appearance of the individual. It is the product of interactions between genes, and between the GENOTYPE and the environment.”

<http://www.ncbi.nlm.nih.gov/mesh/?term=phenotype>

## 1.0.1. Phenotype

- CYP2D6 and CYP2C19 are polymorphic. Polymorphisms are usually defined as those genetic variations present in at least 1% of the population. Absence of CYP2D6 or CYP2C19 is present in >1% of the population.
- Unfortunately, terminology describing these polymorphisms is confusing. It means different things for CYP2D6 and CYP2C19 and different labs use it differently. Ordering tests without understanding CYP terminology may be wasting money.

## 1.0.1. Phenotype

### ■ Phenotype abbreviations:

- UM: ultrarapid metabolizer (↑ activity)
- EM: extensive metabolize (normal activity)
- IM: intermediate metabolizer (low activity)
- PM: poor metabolizer (no activity)

■ Please be aware that this terminology was originally applied to genetics but it is now broadly used. When an EM taking an inhibitor becomes a phenotypical PM this is called “phenoconversion”.

<http://www.ncbi.nlm.nih.gov/pubmed/25881716>

## 1.0.1. Phenotype

- UM status (↑ activity) can be caused:
  - on the basis of genetics, or
  - through phenoconversion:
    - by taking powerful inducers
    - pregnancy for some metabolic enzymes
- PM status (no activity) can be caused:
  - on the basis of genetics, or
  - through phenoconversion:
    - by taking powerful inhibitors
    - pregnancy for some metabolic enzymes
    - ↓ renal clearance in some drugs

# 1.0.2. Allele\*1



## 1.0.2. Allele\*1

- The most important concept to understand results from CYP genotyping. If you do not understand this, you will misinterpret any CYP genotyping that you order.
- Allele 1 or \*1:
  - is the normal (called “wild type”) allele.
  - is not determined by the lab. A laboratory will call an allele \*1 when none of the abnormal alleles for which that laboratory tests is found. Think carefully about this before moving to the next slide.

## 1.0.2. Allele\*1

- Imagine two hypothetical labs:
  - One lab only tests for \*2 and \*3. This lab will find many \*1s.
  - Another lab tests for \*2, \*3, \*4, \*5, \*6, \*7, \*8 and \*9. This lab will find considerably fewer \*1s.

This is a paradoxical situation: a poor lab will find many more allele\*1s and many more normal subjects than a good lab. Moreover, a clinician using a poor lab will think that many of the patients are normal when, as a matter of fact, they are not.

## 1.0.2. Allele\*1

■ This has very relevant clinical implications:

□ CYP2C19 is a very simple gene.

Most US labs doing CYP genotyping can be trusted for CYP2C19 genotyping.

□ CYP2D6 is a very complex gene.

Most US labs doing CYP genotyping

**CANNOT** be trusted for some aspects of CYP2D6 genotyping.

See the sections on practical rules for CYP2D6 and CYP2C19 genotyping for more details.

# 1.0.3. Two Alleles for a Phenotype

## 1.0.3. Two Alleles for a Phenotype

- A subject \*1/\*17: has an allele 1 and an allele 17.

The order is not important. \*1/\*17 = \*17/\*1

- Be very careful concerning the allele number:
  - It reflects the order in which it was discovered.
  - It has no relationship with activity level.
    - CYP2D6 \*17: typical of Africans
      - ↓ activity (or normal for risperidone).
    - CYP2C19 \*17: typical of Caucasians
      - ↑ activity (↑ expression)

# **1.1. CYPs: Not Ready for Clinical Use**

# 1.1. CYPs Not Ready for Clinical Use

## 1.1. Not Ready for Clinical Use

### 1.1.1. CYP1A2

#### 1.1.1.1. CYP1A2 Gene

#### 1.1.1.2. CYP1A2 and Psychiatric Drugs

### 1.1.2. CYP2B6

#### 1.1.2.1. CYP2B6 Gene

#### 1.1.2.2. CYP2B6 and Psychiatric Drugs

### 1.1.3. CYP3A

#### 1.1.3.1. CYP3A Genes

#### 1.1.3.2. CYP3A and Psychiatric Drugs

# 1.1.1. CYP1A2



# 1.1.1. CYP1A2

1.1.1.1. CYP1A2 Gene

1.1.1.2. CYP1A2 and Psychiatric Drugs

# 1.1.1.1. CYP1A2 Gene

## 1.1.1.1. CYP1A2 Gene

- Not ready for clinical practice.
  - Our understanding of the level of activity of different alleles is limited.

An allele with differences in sensitivity to induction has been described, but the results are not always replicated.
  - Very rare (<1%) cases of PMs or UMs have occasionally been published.

# 1.1.1.1. CYP1A2 Gene

## ■ Environmental influences:

### □ Inducers (moderate sensitivity: ++):

- Carbamazepine, phenytoin & phenobarbital
- Rifampicin
- Smoking (polycyclic aromatic hydrocarbons)

### □ Inhibitors:

- Fluvoxamine
- Ciprofloxacin
- Estrogens

## ■ Personal factors:

□ Females: lower activity

□ Pregnancy: ↓ activity

□ Severe infections/severe inflammations: ↓ activity  
possibly mediated by release of cytokines

# **1.1.1.2. CYP1A2 and Psychiatric Drugs**

## 1.1.1.2. CYP1A2 and Psychiatric Drugs

### ■ Antidepressants:

- Agomelatine: Most important enzyme.
- Duloxetine: CYP1A2 and CYP2D6 are most important.
- Fluvoxamine: Second CYP after CYP2D6.

### ■ Antipsychotics:

- Asenapine: UGT1A4 and CYP1A2 are the most important enzymes.
- Clozapine: Most important enzyme (CYP2C19?).
- Olanzapine: Most important enzyme, but UGT1A4 is relevant.

## 1.1.2. CYP2B6

## 1.1.2. CYP2B6

1.1.2.1. CYP2B6 Gene

1.1.2.2. CYP2B6 and Psychiatric Drugs



# **1.1.2.1. CYP2B6 Gene**

## 1.1.2.1. CY2B6 Gene

- Not ready for clinical practice.
  - Our understanding of the level of activity of different alleles is limited.
  - PM: appears to be present in Africans.  
(allele\*18 may have no activity)
  - Low activity: frequent in many populations.  
(allele\*6 in 15-60% of different populations).

# 1.1.2.1. CYP2B6 Gene

## ■ Environmental influences:

### □ Inducers (extremely sensitive ++++):

- Carbamazepine, phenytoin & phenobarbital
- Rifampicin
- Anti-retrovirals
- Cotrimazole
- Some Chinese herbs

### □ Inhibitors:

- Clopidogrel
- Ticlopidine

## ■ Personal factors:

- Pregnancy: ↑ activity (induction)

## **1.1.2.2. CYP2B6 and Psychiatric Drugs**

## 1.1.2.2. CYP2B6 and Psychiatric Drugs

### ■ Antidepressants:

- Bupropion
- Sertraline (and CYP2C19)

### ■ Substance abuse:

#### □ Methadone (chiral mixture):

- (R)-methadone: major opioid agonist  
metabolized by CYP2B6
- (S)-methadone: weaker opioid agonist  
potent blocker of HERG channels  
metabolized by CYP2B6 & CYP3A4

#### □ Others:

- Ketamine
- Ecstasy

# 1.1.3. CYP3A

## 1.1.3. CYP3A

1.1.3.1. CYP3A Genes

1.1.3.2. CYP3A and Psychiatric Drugs

# **1.1.3.1. CYP3A Genes**



## 1.1.3.1. CYP3A Genes

### ■ Three isoenzymes:

- CYP3A4: most important CYP: liver and gut
- CYP3A5: auxiliary if present;  
kidney may be relatively important
- CYP3A7: fetal age (absent in adults?)

### ■ Not ready for clinical practice.

- Our understanding of the level of activity of different alleles is limited.
- CYP3A4: no clear description of PMs or UMs  
(allele\*22: ↓ activity)
- CYP3A5: very confusing information  
(alleles\*3, \*6, and \*7: no or little activity)

# 1.1.3.1. CYP3A Genes

## ■ Environmental influences:

### □ Inducers (extremely sensitive ++++):

- Carbamazepine, phenytoin & phenobarbital
- Rifampicin
- Anti-retrovirals
- St. John's wort (mild inducer)
- Oxcarbazepine & topiramate (mild inducers)

### □ Inhibitors:

- Ketoconazole
- Erythromycin
- Grapefruit juice
- Diltiazem

## ■ Personal factors:

- First months of life: missing
- Pregnancy: ↑ activity (induction)
- Severe infections/severe inflammations: may ↓ activity  
possible mediated by cytokines

## **1.1.3.2. CYP3A and Psychiatric Drugs**

## 1.1.3.2. CYP3A and Psychiatric Drugs

- Important for many non-psychiatric drugs:
  - Immunosuppressants
  - Non-sedating antihistamines
  - Calcium channel blockers
  - Statins
  - Corticosteroids
  - Estrogens

## 1.1.3.2. CYP3A and Psychiatric Drugs

### ■ Antidepressants:

- Reboxetine, trazadone and vilazadone

### ■ Antipsychotics:

- Major metabolic pathway:

- Lurasidone and quetiapine

- Second after CYP2D6 (first if induced):

- Aripiprazole, iloperidone and risperidone

### ■ Benzodiazepines:

- Major metabolic pathway:

- Alprazolam, midazolam and triazolam

- Second after CYP2C19 (first pathway if induced):

- Clobazam and diazepam

### ■ Mood stabilizers:

- Carbamazepine (auto-induces its own metabolism)

# **1.2. CYPs Ready for Clinical Use**

# 1.2. CYPs Ready for Clinical Use

## 1.2. Ready for Clinical Use

### 1.2.1. CYP2D6

#### 1.2.1.1. CYP2D6 Gene

#### 1.2.1.2. CYP2D6 and Psychiatric Drugs

### 1.2.2. CYP2C19

#### 1.2.2.1. CYP2C19 Gene

#### 1.2.2.2. CYP2C19 and Psychiatric Drugs

### 1.2.3. CYP2D6 and CYP2C19 Combined

# 1.2.1. CYP2D6



# 1.2.1. CYP2D6

## 1.2.1.1. CYP2D6 Gene

1.2.1.1.1. CYP2D6 Phenotypes

1.2.1.1.2. CYP2D6 Alleles

1.2.1.1.3. CYP2D6 Phenotypes vs. Alleles

1.2.1.1.4. CYP2D6 Phenotypes vs. Race

1.2.1.1.5. Practical Rules for CYP2D6 Genotyping

## 1.2.1.2. CYP2D6 and Psychiatric Drugs

1.2.1.2.1. CYP2D6 and Antipsychotics

1.2.1.2.2. CYP2D6 and Antidepressants

1.2.1.2.3. CYP2D6 and Atomoxetine

# 1.1.2.1. CYP2D6 Gene

## 1.2.1.1. CYP2D6 Gene

1.2.1.1.1. CYP2D6 Phenotypes

1.2.1.1.2. CYP2D6 Alleles

1.2.1.1.3. CYP2D6 Phenotypes vs. Alleles

1.2.1.1.4. CYP2D6 Phenotypes vs. Race

1.2.1.1.5. Practical Rules for CYP2D6 Genotyping

# **1.1.2.1.1. CYP2D6 Phenotypes**

# 1.1.2.1.1. CYP2D6 Phenotypes

Preferred by Dr. de Leon <http://www.ncbi.nlm.nih.gov/pubmed/19169185>

<u>Phenotype</u>	<u>N active copies</u>
Ultrarapid metabolizer (UM)	$\geq 3$
Extensive metabolizer (EM)	1 to $< 3$
Intermediate metabolizer (IM)	0 to $< 1$
Poor metabolizer (PM)	0

Used by Some Labs

<u>Phenotype</u>	<u>N active copies</u>
Ultrarapid metabolizer (UM)	$\geq 3$
Extensive metabolizer (EM)	$> 1$ to $< 3$
Intermediate metabolizer (IM)	$\leq 1$
Poor metabolizer (PM)	0

## **1.1.2.1.2. CYP2D6 Alleles**

## 1.1.2.1.2. CYP2D6 Alleles

- CYP2D6\*1xn or \*2xn: increased number of copies. “x” refers to multiplication. It is usually double but can be more. Labs do not usually distinguish doubling (most frequent) from other forms of multiplication.
- CYP2D6\*1 (allele 1) is the normal allele. CYP2D6\*2 (allele 2) is usually considered a normal allele.
- CYP2D6\*17 (allele 17) is typical of Africans. It has low activity for many (but not all) CYP2D6 substrates.
- CYP2D6\*10 (allele 10) is typical of East Asians. It has very low activity for CYP2D6 substrates.
- CYP2D6\*3,\*4,\*5 and \*6 (alleles 3, 4, 5 and 6) are the most important null alleles with no activity.

# **1.1.2.1.3. CYP2D6 Phenotypes versus Alleles**



### 1.1.2.1.3. CYP2D6 Phenotypes versus Alleles

<u>Alleles</u>	<u>Phenotype</u>
*1 <sub>xn</sub> /*1 or *2 <sub>xn</sub> /*1	UM
*1/*1, *1/*2 or *2/*2	EM
*1/*3, *1/*4, *1/*5 & *1/*6 or *2/*3, *2/*4, *2/*5 & *2/*6	EM/IM
*10/*10	IM (very low activity)
any combination *3,*4,*5 or *6:	PM
*3/*3, *3/*4, *3/*5, *3/*6, *4/*4, *4/*5, *4/*6, *5/*5, *5/*6 & *6/*6	

---

# **1.1.2.1.4. CYP2D6 Phenotypes versus Race**

## 1.1.2.1.4. CYP2D6 Phenotypes versus Race

### ■ CYP2D6 PMs (no CYP2D6):

- Caucasians: approximately 7%
- Other races: 1-3 (<5%)

### ■ CYP2D6 IMs (with low activity):

- East Asians: 50%
  - \*10/\*10: activity of 0.05 (vs. 2 in \*1/\*1)
- Africans (\*17): 30%
  - \*17/\*17: low CYP2D6 activity for many drugs

### ■ CYP2D6 UMs ( $\geq 3$ copies of active alleles):

with 3: activity of 3.4 (vs. 2 in \*1/\*1) <http://www.ncbi.nlm.nih.gov/pubmed/21866098>

- North Africa: 40%
- Oceania: >20%
- Caucasians: 1-5%
- USA: 1-2%

# **1.1.2.1.5. Practical Rules for CYP2D6 Genotyping**

## 1.1.2.1.5. Practical Rules for CYP2D6 Genotyping

This reflects Dr. de Leon's experience with US labs:

- CYP2D6 PMs: Most labs are reliable.
- CYP2D6 IMs: Be careful
  - Is this a subject with low activity?
  - Is this a subject with at least \*1 allele and relatively normal activity?
- CYP2D6 EMs:
  - good labs: result is probably reliable.
  - poor labs: subject may be CYP2D6 IM or UM.
- CYP2D6 UMs:
  - good labs: result is probably reliable.
  - poor labs: may be missing CYP2D6 UMs or identifying as CYP2D6 UM subjects that are not CYP2D6 UMs.

# **1.2.1.2. CYP2D6 and Psychiatric Drugs**

## 1.2.1.2. CYP2D6 and Psychiatric Drugs

1.2.1.2.1. CYP2D6 and Antipsychotics

1.2.1.2.2. CYP2D6 and Antidepressants

1.2.1.2.3. CYP2D6 and Atomoxetine

# **1.1.2.2.1. CYP2D6 and Antipsychotics**



# 1.1.2.2.1. CYP2D6 and Antipsychotics

- Aripiprazole, haloperidol, risperidone or zuclopenthixol:
  - CYP2D6 PMs: ↓ D (x 0.5) or other antipsychotic
  - CYP2D6 UMs: be alert to ↓ C or other antipsychotic

Risperidone TDM: risperidone/9-hydroxyrisperidone ratio > 1 indicates CYP2D6 PM or taking CYP2D6 inhibitors  
(more information on risperidone TDM and personalizing dosing see <http://www.ncbi.nlm.nih.gov/pubmed/25200585> )

- Long-acting aripiprazole:
  - CYP2D6 PMs: ↓ D (x 0.75)
- Pimozide (in USA):
  - In adults D > 4mg/day. You need to genotype CYP2D6. CYP2D6 PMs cannot take > 4 mg/day

# **1.1.2.2.2. CYP2D6 and Antidepressants**

## **1.2.1.2.2. CYP2D6 and Antidepressants**

1.2.1.2.2.1. CYP2D6 and TCAs

1.2.1.2.2.2. CYP2D6 and SSRIs

1.2.1.2.2.3. CYP2D6 and Venlafaxine

# **1.1.2.2.2.1. CYP2D6 and TCAs**

## 1.1.2.2.2.1. CYP2D6 and TCAs

### ■ TCAs:

- CYP2D6 PMs: avoid

  - or ↓ D (x 0.5)

  - or use TDM for dosing

- CYP2D6 UMs: avoid

### ■ Dr. de Leon recommends using TDM whenever using TCAs in antidepressant doses. They are narrow therapeutic window drugs.

# 1.1.2.2.2. TCAs: TDM

- Preskorn: <http://www.ncbi.nlm.nih.gov/pubmed/8407856>

He uses the concentration/dose (C/D) ratio.

C: ng/ml. D: mg/day.

After reaching steady-state trough TDM, the C/D ratio indicates CYP2D6 activity:

- $<0.5$  = CYP2D6 UM or non-compliant
  - $0.5-1.5$  = CYP2D6 EM
  - $>1.5$  = CYP2D6 PM or taking potent CYP2D6 inhibitor
- Additional reminders by Dr. de Leon:
    - Inducers may provide low C/D ratios.
    - CYP2C19 PMs may register high C/D ratios in tertiary amines.

# 1.1.2.2.2. TCAs: TDM

■ Therapeutic ranges: <http://www.ncbi.nlm.nih.gov/pubmed/22053351>

□ amitriptyline + nortriptyline: 80-200 ng/mL

□ clomipramine + norclomipramine: 230-450 ng/mL

clomipramine: close to an SSRI

norclomipramine: close to a selective norepinephrine reuptake inhibitor

□ desipramine: 100-300 ng/mL

□ imipramine + desipramine: 175-300 ng/mL

□ nortriptyline: 70-170 ng/mL

■ They are narrow therapeutic window drugs:

□ To calculate that, divide upper range by lower range.

Nortriptyline:  $170/70=2.4$

Ratio  $\leq 3$ : narrow therapeutic window drugs

# 1.1.2.2.2. TCAs: TDM

<u>TCA</u>	<u>Lower</u>	<u>Upper</u>	<u>Ratio</u>
Amitriptyline totals	80	200	2.5 (=200/80)
Clomipramine totals	230	450	2.0 (=450/230)
Imipramine totals	175	300	2.5 (=300/175)
Desipramine	100	300	1.7 (=300/100)
<u>Nortriptyline</u>	<u>70</u>	<u>170</u>	<u>2.4 (=170/70)</u>

All TCAs had therapeutic window ratios  $\leq 3$ .

All TCAs are definitively narrow therapeutic window drugs.



## **1.1.2.2.2.2. CYP2D6 and SSRIs**

## 1.1.2.2.2.2. CYP2D6 and SSRIs

- Dr. de Leon is firmly convinced that CYP2D6 genotyping is important in the prescription of TCAs.
- Dr. de Leon has no experience in using CYP2D6 genotyping for SSRIs. They are complex pharmacokinetically:
  - Paroxetine and fluoxetine inhibit their own metabolism.
- The next slide provides dosing recommendations based on an excellent review:

<http://www.ncbi.nlm.nih.gov/pubmed/25974703>

## 1.1.2.2.2.2. CYP2D6 and SSRIs

### ■ Fluoxetine:

- PMs: ● Select an agent not dependent on CYP2D6, or  
● correct by 0.50 x initial D and titrate accordingly.
- UMs: Select another agent not dependent on CYP2D6.

### ■ Fluvoxamine:

- PMs: ● Select an agent not dependent on CYP2D6, or  
● correct by 0.50 x initial D and titrate accordingly.
- UMs: no data

### ■ Paroxetine:

- PMs: ● Select an agent not dependent on CYP2D6, or  
● correct by 0.50 x initial D and titrate accordingly.
- UMs: Select another agent not dependent on CYP2D6.

# **1.1.2.2.2.3. CYP2D6 and Venlafaxine**

# 1.1.2.2.2.3. CYP2D6 and Venlafaxine

## ■ Venlafaxine:

- CYP2D6 UMs:  $\uparrow D$  (x 1.5)
- CYP2D6 PMs: Select another drug or use TDM for dosing.

O-desmethylvenlafaxine/venlafaxine C ratio  $< 1$  (in the absence of CYP2D6 inhibitors) indicates a CYP2D6 PM who may respond more poorly.

# **1.1.2.2.3. CYP2D6 and Atomoxetine**

# 1.1.2.2.3. CYP2D6 and Atomoxetine

## ■ Atomoxetine:

- CYP2D6 UMs: be alert to ↓ efficacy or select another drug.

In a published editorial, Dr. de Leon indicated the need for studies using high doses and TDM for:

- CYP2D6 UMs and
- CYP2D6 EMs with 2 active alleles.

<http://www.jaacap.com/inpress>

## 1.2.2. CYP2C19



## 1.2.2. CYP2C19

### 1.2.2.1. CYP2C19 Gene

#### 1.2.2.1.1. CYP2C19 Phenotypes

#### 1.2.2.1.2. CYP2C19 Alleles

#### 1.2.2.1.3. CYP2C19 Phenotypes and Alleles

#### 1.2.2.1.4. CYP2C19 Phenotypes and Race

#### 1.2.2.1.5. Practical Rules for CYP2C19 Genotyping

### 1.2.2.2. CYP2C19 and Psychiatric Drugs

#### 1.2.2.2.1. CYP2C19 and Antidepressants

#### 1.2.2.2.2. CYP2C19 and Clozapine

## **1.2.2.1. CYP2C19 Gene**

## **1.2.2.1. CYP2C19 Gene**

1.2.2.2.1. CYP2C19 Phenotypes

1.2.2.2.2. CYP2C19 Alleles

1.2.2.2.3. CYP2C19 Phenotypes and Alleles

1.2.2.2.4. CYP2C19 Phenotypes and Race

1.2.2.2.5. Practical Rules for CYP2C19 Genotyping

# 1.2.2.1.1. CYP2C19 Phenotypes

## 1.2.2.1.1. CYP2C19 Phenotypes

Terminology Preferred by Dr. de Leon

<u>Phenotype</u>	<u>N active copies</u>
Ultrarapid metabolizer (UM)	↑ expression
Extensive metabolizer (EM)	1 or 2
Poor metabolizer (PM)	0 <sup>c</sup>

Terminology Used by Some Labs

<u>Phenotype</u>	<u>N active copies</u>
Ultrarapid metabolizer (UM)	↑ expression
Extensive metabolizer (EM)	2
Intermediate metabolizer (IM)	1
Poor metabolizer (PM)	0 <sup>c</sup>

## **1.2.2.1.2. CYP2C19 Alleles**

## 1.2.2.1.2. The Most Important CYP2C19 Alleles

- CYP2C19\*17 (allele 17): increased expression. There is no agreement about its clinical relevance.
- CYP2C19\*1 (allele 1) is the normal allele.
- CYP2C19\*2 and \*3 (alleles 2 and 3) are null alleles. Other more rare alleles are also null alleles.

# **1.2.2.1.3. CYP2C19**

## **Phenotypes and Alleles**



### 1.2.2.1.3. CYP2C19 Phenotypes and Alleles

<u>Alleles</u>	<u>Activity</u>	<u>Phenotype</u>
*17/*17	↑ ↑ expression	UM
*1/*17	↑ expression	UM in some labs
*1/*1	normal	EM in some labs
*1/*2 or *1/*3	lower	EM in some labs IM in some labs
*2/*2 or *3/*3 or *2/*2	none	PM

---

# **1.2.2.1.4. CYP2C19**

## **Phenotypes and Race**

## 1.2.2.1.4. CYP2C19: Phenotypes and Race

### ■ CYP2C19 PMs:

- East Asians: 25 %
- Other races: <5%

### ■ CYP2C19 UMs:

\*17: associated with ↑ expression

Its clinical relevance is not well established.

- The frequency is 1-5% for \*17/\*17.
- The frequency is higher with only one \*17.

# **1.2.2.1.5. Practical Rules for CYP2C19 Genotyping**

## 1.2.2.1.4. Practical Rules for CYP2C19 Genotyping

This reflects Dr. de Leon's experience with US labs:

- CYP2C19 PMs: Most labs are reliable.
- CYP2C19 IMs: Be careful.
  - Is this a subject with at least \*1 allele and relatively normal activity?
- CYP2C19 EMs: Most labs are probably reliable.
- CYP2C19 UMs:
  - Good labs are probably reliable, but the literature does not agree on its clinical relevance.

## **1.2.2.2. CYP2C19 and Psychiatric Drugs**

## 1.2.2.2. CYP2C19 and Psychiatric Drugs

1.2.2.2.1. CYP2C19 and Antidepressants

1.2.2.2.1. CYP2C19 and Clozapine

# **1.2.2.2.1. CYP2C19 and Antidepressants**



# 1.2.2.2.1. CYP2C19 and Antidepressants

1.2.2.2.1.1. CYP2C19 and TCAs

1.2.2.2.1.2. CYP2C19 and SSRIs

# **1.2.2.2.2.1. CYP2C19 and TCAs**

# 1.2.2.2.2.1. CYP2C19 and TCAs

## ■ TCAs:

- CYP2C19 PMs: avoid or ↓ D (x 0.5)  
or use TDM for dosing

## ■ Dr. de Leon recommends using TDM whenever using TCAs in antidepressant doses.

They are narrow therapeutic window drugs.

## 1.2.2.2.2. TCAs: TDM

- Dr. de Leon has no experience with CYP2C19 PMs on TCAs, but their pharmacological mechanism suggests that:  
After getting steady-state trough TDM in tertiary amine:  
amitriptyline, clomipramine or imipramine:  
You find C/D ratio > 1.5, think:
  - CYP2D6 PM or taking potent CYP2D6 inhibitor, or
  - CYP2C19 PM or taking potent CYP2C19 inhibitor.

## **1.2.2.2.2.2. CYP2C19 and SSRIs**

## 1.2.2.2.2.2. CYP2C19 and SSRIs

- Dr. de Leon is firmly convinced that CYP2C19 genotyping is important when TCAs are prescribed.
- Dr. de Leon has no experience in using CYP2C19 genotyping for SSRIs.
- The next slide provides dosing recommendations based on an excellent review.

<http://www.ncbi.nlm.nih.gov/pubmed/25974703>

# 1.2.2.2.2. CYP2C19 and SSRIs

## ■ Citalopram:

- PMs: ● select an agent not dependent on CYP2C19, or  
● correct by 0.50 x initial D and titrate accordingly
- UMs: select an agent not dependent on CYP2C19

## ■ Escitalopram:

- PMs: ● select an agent not dependent on CYP2C19, or  
● correct by 0.50 x initial D and titrate accordingly
- UMs: select an agent not dependent on CYP2C19

## ■ Sertraline

- PMs: ● select an agent not dependent on CYP2C19, or  
● correct by 0.50 x initial D and titrate accordingly
- UMs: start with recommended D, but if the patient does not respond, consider an agent not dependent on CYP2C19.

# **1.2.2.2.2. CYP2C19 and Clozapine**



## 1.2.2.2.2. CYP2C19 and Clozapine

- Better studies are needed for:
  - CYP2C19 PMs: may need half the usual clozapine D
  - East Asians: may need half the usual clozapine D. This may be explained by the high number of CYP2C19 PMs
- For more information on interpreting clozapine TDM and personalizing clozapine dosing, see:  
<http://www.ncbi.nlm.nih.gov/pubmed/25200585>

## **1.2.3. CYP2D6 and CYP2C19 Combined**

## 1.2.3. CYP2D6 and CYP2C19 Combined

- Very rare individuals (<1/1000) are double PMs:  
CYP2D6 and CYP2C19 PMs. <http://www.ncbi.nlm.nih.gov/pubmed/17008819>
- Most antidepressants are metabolized by:
  - CYP2D6 and/or
  - CYP2C19
- Double PMs may not be able to tolerate most antidepressants, but probably can take the following without problems:
  - bupropion (metabolized by CYP2B6)
  - mirtazapine (metabolized by multiple enzymes)
  - reboxetine (metabolized by CYP3A4)

## 1.2.3. CYP2D6 and CYP2C19 Combined

- The main message:

If a patient shows intolerance for many antidepressants, consider whether he/she may be a double (CYP2D6 and CYP2C19) PM.

- Your actions:

- carefully review all antidepressant trials, and
- consider CYP2D6 and CYP2C19 genotyping.

# 2. HLA Genotyping

## 2. HLA Genotyping

2.1. Not Ready for Clinical Use: Clozapine

2.2. Ready for Clinical Use: Carbamazepine and  
HLA-B\*1502

**2.1. HLA Genotyping:  
Not Ready for Clinical Use:  
Clozapine**

## 2.1. HLA Genotyping and Clozapine

- Clozapine can cause agranulocytosis.
- Individuals with HLA-DQB1 have increased risk (OR=16.9).
- Low sensitivity (true positive rate) = 22%.  
Many individuals who develop clozapine-induced agranulocytosis have other HLAs. Therefore, the FDA requires WBCs in order to start clozapine.



## 2.1. HLA Genotyping and Clozapine

- Clozapine and HLA-DQB (126 Q) genotyping:
    - Agranulocytosis incidence = 1.3%
    - Sensitivity = 21.5%
    - Number needed to genotype = 358  
 $358 = 100 / (1.3 \times 0.215)$
- This means that 358 patients need to be screened to prevent one agranulocytosis.
- As WBC needs to be done, the cost-benefit ratio is against genotyping.

**2.2. HLA Genotyping:  
Ready for Clinical Use:  
Carbamazepine and  
HLA-B\*15:02**

## 2.2. Carbamazepine and HLA-B\*15:02

- Carbamazepine can cause SJS-TEN.
- In Chinese individuals with HLA-B\*15:02 (OR=1357), the risk is almost 100%.  
Sensitivity (true positive rate) = 98.3%
- The FDA requires HLA genotyping before starting carbamazepine in an individual with Asian ancestry (↑ from India to China):
  - 10-15% in China, Indonesia, Malaysia, the Philippines, and Taiwan
  - 2-4% in India
  - <1% in Korea and Japan

## 2.2. Carbamazepine and HLA-B\*1502

- Carbamazepine and HLA-B\*15:02 genotyping in Chinese:
  - SJS-TEN incidence = 0.25%
  - HLA-B\*1502 sensitivity = 98.3%
  - Number needed to genotype = 407  
 $407 = 100 / (0.25 \times 0.983)$
- This means that 407 patients need to be screened to prevent one SJS-TEN.
- The cost of genotyping: \$100-200. The cost-benefit ratio is in favor of genotyping.

## 2.2. Carbamazepine and HLA-B\*15:02

- Europeans and Japanese:  
the HLA-A\*31:10 provides much lower sensitivity for predicting SJS-TEN.

## 2.2. Carbamazepine and HLA-B\*15:02

You see differences in HLA-B\*15:02 between Japanese and Chinese patients and wonder:  
Is Dr. de Leon trying to confuse you?

## 2.2. Carbamazepine and HLA-B\*15:02

You ask, “Dr. de Leon,  
Japanese and Chinese  
are close genetically  
with similar frequencies of  
CYP2C19 PMs.

How is it possible that they differ  
so much in HLA genes?”

## 2.2. Carbamazepine and HLA-B\*15:02

- The question is appropriate:  
Japanese and Chinese are closely related from the genetic point of view.
- The answer is complex:  
It appears that HLA genes are peculiar. In Asians, they may be inherited from another hominid group (Denisovans) who was living in Asia before humans arrived.

<http://www.ncbi.nlm.nih.gov/pubmed/21868630>



# 3. Conclusions

# 3. Conclusions

3.1. Conclusions from This Presentation

3.2. View on the Future Use of  
Pharmacogenetic Testing in Psychiatry

# **3.1. Conclusions from This Presentation**

## 3.1. Conclusions from This Presentation

- In some countries, including the US, pharmacogenetic tests are marketed for psychiatric patients. Many tests provide non-validated recommendations regarding using or avoiding drugs.
- Dr. de Leon does not recommend using genotyping results for the following in clinical practice:
  - CYP1A2, or CYP2B6 or CYP3A4 or CYP3A5,
  - neurotransmitter receptors/transporters, or
  - disease mechanisms.

## 3.1. Conclusions from This Presentation

- Dr. de Leon occasionally recommends genotyping for the following in clinical practice:
  - CYP2D6 or CYP2C19.
- If you use TCAs, become an expert in TDM and CYP2D6/CYP2C19 genotyping.
- If you use CYP2D6/CYP2C19 genotyping:
  - be familiar with complex terminology,
  - get to know the weaknesses and strengths of your CYP lab (select one), and
  - keep the published guidelines in an easily accessible place.

## 3.1. Conclusions of This Presentation

- Dr. de Leon rarely treats East Asians.  
If you want to start carbamazepine for them, you need to ask for their family country of origin and consider genotyping HLA-B\*15:02

## **3.2. View on the Future Use of Pharmacogenetic Testing in Psychiatry**

## 3.2. Future Pharmacogenetic Tests in Psychiatry

- This is a complex issue summarized with a:
  - theoretical reflection,
  - practical reflection on test approval, and
  - practical reflection on the use of approved tests.
- The issue is more thoroughly described in a 2009 article available in PubMed,

<http://www.ncbi.nlm.nih.gov/pubmed/18800072>

and is briefly updated in a 2016 article.

<http://www.ncbi.nlm.nih.gov/pubmed/26580456>



## **3.2. Future Pharmacogenetic Tests in Psychiatry**

3.2.1. Theoretical Reflection

3.2.2. Practical Reflection on Test Approval

3.2.3. Practical Reflection on the Use of Approved Tests

**3.2.1. Theoretical Reflection  
on  
Future Pharmacogenetic Tests  
in Psychiatry**

### 3.2.1. Future Pharmacogenetic Tests: Theoretical Reflection

- Pharmacogenetic tests should be integrated with:
  - environmental/personal factors
  - pharmacokinetics/pharmacodynamics
  - efficacy/safety (dose-related versus idiosyncratic ADRs), and
  - therapeutic window (consider TDM).

<http://www.ncbi.nlm.nih.gov/pubmed/24196844>

## **3.2.2. Practical Reflection on the Approval of Pharmacogenetic Tests in Psychiatry**

### 3.2.2. Future Pharmacogenetic Tests: Practical Reflection on Approval

- Dr. de Leon believes that US approval of pharmacogenetic tests requires:
  - understanding the pharmacological complexity of drug response,
  - modifying the oversight of non-FDA regulatory agencies,
  - clarifying the FDA's role, and
  - promoting innovative marketing.

<http://www.ncbi.nlm.nih.gov/pubmed/26580456>

### **3.2.3. Practical Reflection on the Use of Approved Pharmacogenetic Tests in Psychiatry**

### 3.2.3. Future Pharmacogenetic Tests: Practical Reflection on Use

- Dr. de Leon believes that the incorporation of pharmacogenetic tests into long-term clinical practice in psychiatry requires:
  - not jeopardizing pharmacogenetic testing by short-sighted marketing of non-validated tests,
  - educating prescribers about benefits,
  - educating patients about limitations, and
  - considering the differences between isolated testing and generalized testing incorporating big data.

# References on Practical Issues

1) Dr. de Leon's 2015 article

<http://www.ncbi.nlm.nih.gov/pubmed/25200585>

describes CYP genotyping and TDM in psychiatry.

2) Dr. de Leon's 2015 atomoxetine editorial focuses on CYP2D6 UMs <http://www.ncbi.nlm.nih.gov/pubmed/26088654>

3) A 2015 article <http://www.ncbi.nlm.nih.gov/pubmed/25974703>

describes a CYP genotyping guideline for SSRIs.

4) A 2013 article <http://www.ncbi.nlm.nih.gov/pubmed/23486447>

describes a CYP genotyping guideline for TCAs.



# References on Theoretical Issues

1) Dr. de Leon's 2009 article on biomarkers and US regulations for test approval.

pdf available <http://www.ncbi.nlm.nih.gov/pubmed/18800072>

2) Dr. de Leon's 2008 article described 5 pharmacogenetic tests in psychiatry available at that time.

<http://www.ncbi.nlm.nih.gov/pubmed/19059065>

3) Dr. de Leon's 2014 article described the integrated use of pharmacogenomics and TDM in psychiatry and HLA testing.

<http://www.ncbi.nlm.nih.gov/pubmed/24196844>

pdf of pre-published version [http://uknowledge.uky.edu/psychiatry\\_facpub/19/](http://uknowledge.uky.edu/psychiatry_facpub/19/)

4) Dr. de Leon's 2016 article titled "What is needed to incorporate clinical pharmacogenetic tests into the practice of psychopharmacotherapy?"

<http://www.ncbi.nlm.nih.gov/pubmed/26580456>

*Thank you*

# Answers

1. D

2. B

3. A

4. D

5. D

6. B

7. A

8. D

9. D

10. D