Risperidone Case 2: Genetics 1-15-16

Bork (a resident) et al.

J Clin Psychiatry 1999;60:469-76

http://www.ncbi.nlm.nih.gov/pubmed/10453802

Jose de Leon, MD

Educational Objectives

At the conclusion of this presentation, the participant should be able to:

1. Consider pharmacological principles in all patients.
2. Appreciate the potential for genetic influences on risperidone metabolism.
3. Show familiarity with how to correct risperidone dosing according to genetic variations.

Abbreviations

- 9-OHR: 9-hydroxyrisperidone (Marketed as paliperidone)
- C: concentration (ng/mL)
- D: dose (mg/day)
- C/D: concentration/dose ratio.

  It is an index of drug clearance.

  For R: Total C = R C+ 9-OHR C (both active)

  $$\text{C/D ratio} = \frac{\text{R C + 9-OHR C}}{\text{R D}}$$

- P-gp: p-glycoprotein
- R: risperidone
- R/9-OHR ratio = $\frac{\text{R C}}{\text{9-OHR C}}$
- RCT: randomized controlled trial
- TDM: therapeutic drug monitoring (blood levels)

CYP2D6 Terminology

- 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

CYP2D6 Terminology Preferred by Dr. de Leon

Phenotype	Number of active alleles
Ultrarapid metabolizer (UM)	≥3
Extensive metabolizer (EM)	1 to <3
Intermediate metabolizer (IM)	0 to <1
Poor metabolizer (PM)	0

http://www.ncbi.nlm.nih.gov/pubmed/19169185

Dr. de Leon has only one normal active allele. He considers himself a CYP2D6 EM.

See the presentation “Pharmacogenetic Testing in Psychiatry” for more details.

CYP2D6 Terminology: According to Some Pharmacogenetic Companies

Phenotype	Number of active alleles
Ultrarapid metabolizer (UM)	≥3
Extensive metabolizer (EM)	>1 to <3
Intermediate metabolizer (IM)	0 to 1
Poor metabolizer (PM)	0

Dr. de Leon has only one normal active allele. He is a CYP2D6 IM for some pharmacogenetic companies providing CYP2D6 genotyping.

Statistical Definitions

- **Median:**
  - Wikipedia: “numerical value separating the higher half of a sample” http://en.wikipedia.org/wiki/Median
  - Easier definition for physicians: 50th percentile (P50).

    Half the values are above and half are below.

    It is a better average measure than the mean when you have only a few values or an asymmetric distribution.
- **25th Percentile (P25):**
  - ¾ values are above and ¼ below.
- **75th Percentile (P75):**
  - ¼ values are above and ¾ below.

2.0.
Risperidone
Case 2

Risperidone Case 2

2.1. Case Description
2.2. R TDM Review in 1996

2.3. Case Interpretation

2.4. R Pharmacokinetics

2.5. Points to Remember

Risperidone Case 2

2.1. Case Description
2.2. R TDM Review in 1996
- 2.2.1. R/9-OHR Ratio
- 2.2.2. C/D Ratio

2.3. Case Interpretation
- 2.3.1. First TDM
- 2.3.2. Second TDM
- 2.3.3. Outcome

2.4. R Pharmacokinetics
- 2.4.1. CYP2D6 PMs
- 2.4.2. R's Manufacturer and CYP2D6
- 2.4.3. CYP2D6 and R Metabolism
- 2.4.4. R TDM and CYP2D6: Dr. de Leon's Studies

2.5. Points to Remember

2.1. Case Description

2.1. Risperidone Case 2: Case

- 45-year-old Caucasian ♀
- Non-smoker
- Diagnosis of schizophrenia and severe tardive dyskinesia.
- Medication stable for months
  - Risperidone 6 mg/day

2.2. R TDM Review in 1996
(This is when Dr. de Leon treated this patient)

2.2. R TDM Review in 1996

2.2.1. R/9-OHR Ratio in 1996
2.2.2. C/D Ratio in 1996

2.2.1. R/9-OHR Ratio in 1996

2.1.1. Risperidone Case 1: R/9-OHR Ratio

- In 1996, Ereshefsky described the R/9-OHR ratio:

http://www.ncbi.nlm.nih.gov/pubmed/8941167

  - an index of CYP2D6 activity
  - >1: CYP2D6 PM or taking a CYP2D6 inhibitor

2.1.2. R C/D Ratio in 1996

2.1.2. Risperidone Case 2: C/D Ratio

- Concentration-to-dose ratio (C/D) provides an estimation of the medication clearance once steady state has been reached.
- In R this will be calculated by dividing the total concentration (C) (R + 9-OHR) by the R dose (D).

2.2.2. Risperidone Case 2: C/D Ratio

- In the manufacturer's RCTs, Dr. de Leon found an average C/D ratio = 7.

2.2.2. Risperidone Case 2: C/D Ratio

- Many years after 1996:
  this C/D ratio =7 was found to be correct in Dr. de Leon's studies.

  http://www.ncbi.nlm.nih.gov/pubmed/17541883
- In Dr. de Leon's experience, some labs in Europe appear to provide higher C/D ratios, close to 10 (probably explained by differences in calibration of the chromatography system).

2.3. Case Interpretation

2.3. Case Interpretation

2.3.1. First TDM
2.3.2. Second TDM
2.3.3. Outcome

2.3.1. First TDM

2.3.1. Case 2: First TDM
R TDM on 6 mg/day

	R C ng/ml	9-OHR C ng/ml	Total ng/ml	R/9-OHR ratio	C/D ratio
Expected	8	34	42	0.25	7
Found	79	17	96	4.3	16

2.3.1. Case 2: First TDM

So, how did you interpret this R TDM?

2.3.1. Case 2: First TDM

So, how did you interpret this R TDM?

You have 2 ratios:

R/9-OHR ratio=4.3

and C/D ratio=16.

2.3.1. First TDM

2.3.1.1. First R/9-OHR
2.3.1.2. First R C/D Ratio

2.3.1.1. First R/9-OHR Ratio

2.3.1.1. First R/9OHR Ratio

So, what can you say about a R/9-OHR ratio=4.3?

2.3.1.1. First R/9OHR Ratio

So, what can you say about a R/9-OHR ratio=4.3?

R/9-OHR ratio >1 suggests a CYP2D6 PM, in the absence of CYP2D6 inhibitors.

2.3.1.2. First R C/D Ratio

2.3.1.2. First R C/D Ratio

So, what can you say about a R C/D ratio =16?

2.3.1.2. First R C/D Ratio

So, what can you say about a R C/D ratio =16?

A R C/D ratio >14 (14 is 2 x normal value of 7) suggests poor elimination of R from the body.

2.3.1.2. First R C/D Ratio

So, what is the R D that corresponds total C=96 ng/ml?

2.3.1.2. First R C/D Ratio

So, what is the R D that corresponds total C=96 ng/ml?

C=96 D=x and C/D ratio =7, 96/x=7 or x=96/7=13.7. It corresponds to D=14 mg/day.

2.3.1.2. First R C/D Ratio

So, what are your conclusions?

2.3.1.2. First R C/D Ratio

So, what are your conclusions?

Possibly a CYP2D6 PM:

1) abnormally high C/D ratio =16 and

2) D=6 mg/day but TDM suggests D=14.

2.3.1.2. First R C/D Ratio

What would you do?

2.3.1.2. First R C/D Ratio

What would you do?

Dr. de Leon

↓ D to 2 mg/day.

2.3.2. Second TDM

2.3.2. Case 2: Second TDM
R TDM on 2 mg/day

	R ng/ml	9-OHR ng/ml	Total ng/ml	R/9-OHR ratio	C/D ratio
Expected	<5	11	<16	<0.45	<8
Found	27	8	35	3.4	17.5

2.3.2. Case 2: First and Second TDM

Dose mg/day	R ng/ml	9-OHR ng/ml	Total ng/ml	R/9-OHR ratio	C/D ratio
6	79	17	96	4.3	16
2	27	8	35	3.4	17.5

2.3.2. Case 2: Second TDM

So, how did you interpret this R TDM?

2.3.2. Case 2: Second TDM

So, how did you interpret this R TDM?

You have 2 ratios:

R/9-OHR ratio =3.4

C/D ratio =17.5.

2.3.2. Second TDM

2.3.2.1. Second R/9-OHR
2.3.2.2. Second R C/D Ratio

2.3.2.1. Second R/9-OHR Ratio

2.3.2.1. Second R/9-OHR Ratio

So, what can you say about R/9-OHR=3.4?

2.3.2.1. Second R/9OHR Ratio

So, what can you say about R/9-OHR=3.4?

Second time R/9-OHR>1; no CYP2D6 inhibitors. The patient is a CYP2D6 PM.

2.3.2.2. Second R C/D Ratio

2.3.2.2. Second R C/D Ratio

So, what can you say about a C/D ratio =17.5?

2.3.2.2. Second R C/D Ratio

So, what can you say about a C/D ratio =17.5?

A C/D ratio >14 (14 is 2 x normal value of 7) suggests poor elimination of R from the body.

2.3.2.2. Second R C/D Ratio

So, what is the D that corresponds to total R C=35 ng/ml?

2.3.2.2. Second R C/D Ratio

So, what is the D that corresponds to total R C=35 ng/ml?

C=35 D=x and C/D=7

35/x=7; x=35/7=5.

It corresponds to D=5 mg/day.

2.3.2.2. Second R C/D Ratio

So, what are your conclusions?

2.3.2.2. Second R C/D Ratio

So, what are your conclusions?

The patient is a CYP2D6 PM:

1) abnormally high C/D=17.5, and

2) D=2 mg/day,

but TDM suggests D=5.

2.3.3. Outcome

2.3.3. Outcome

- The patient was tested to determine CYP2D6 genotype.
  - Two abnormal alleles = CYP2D6 PM (CYP2D6*4/*4)

    See the presentation “Pharmacogenetic Testing in Psychiatry” for more details.
- Treatment: The patient was switched to olanzapine (not dependent on CYP2D6 for its metabolism).
- She improved and was discharged.

2.4. R Pharmacokinetics

2.4. R Pharmacokinetics

2.4.1. CYP2D6 PMs
2.4.2. R's Manufacturer and CYP2D6
2.4.3. CYP2D6 and R Metabolism:
Dr. de Leon's Hypothesis
2.4.4. R TDM and CYP2D6:
Dr. de Leon's Studies

2.4.1. CYP2D6 PMs

2.4.1. CYP2D6 PMs

- CYP2D6 PMs have no CYP2D6 activity (no enzyme or inactive enzyme).

- Prevalence is influenced by race or ethnicity.
  - Caucasians: approximately 7%
  - Other races: 1-3 (<5%)

2.4.1. CYP2D6 PMs

	Cau	EastAsian	AA	MidE
CYP2D6				
PM	7	<1	1-2	2
UM	1.5	<1	2	10-29
Other	80-94	10-25 (*10)	96-97 (*17)	69-88
		IMs Frequent		

Cau: Caucasians; AA:African Americans; MidE: Middle Easterners.

For more details, see the presentation “Pharmacogenetic Testing in Psychiatry”.

2.4.2. R’s Manufacturer and CYP2D6

2.4.2. CYP2D6: Information Provided by the Manufacturer in 1996

- R is metabolized to 9-OHR by CYP2D6.
- CYP2D6 EMs: little serum R and much 9-OHR. CYP2D6 PMs: much serum R and little 9-OHR. Same total serum moiety (R+9-OHR)(Fact A).
- Pharmacodynamic studies in rats suggest that R and 9-OHR may be equipotent (Fact B).
- Based on Facts A and B: Huang et al. (*Clin Pharmacol Ther* 1993;54:257-68) proposed that “the polymorphic nature of risperidone kinetics is of no clinical consequence”.

http://www.ncbi.nlm.nih.gov/pubmed/7690693

2.4.3. CYP2D6: Prescribing Information

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7e117c7e-02fc-4343-92a1-230061dfc5e0

- "Although EMs have lower risperidone and higher 9-hydroxyrisperidone concentrations than PMs, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in EMs and PMs."
- "The therapeutic benefits and adverse effects of risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of PMs given RISPERDAL® do not suggest important differences between PMs and EMs."
- Literal quotations (except abbreviations EMs & PMs) Quinidine is a powerful CYP2D6 inhibitor.

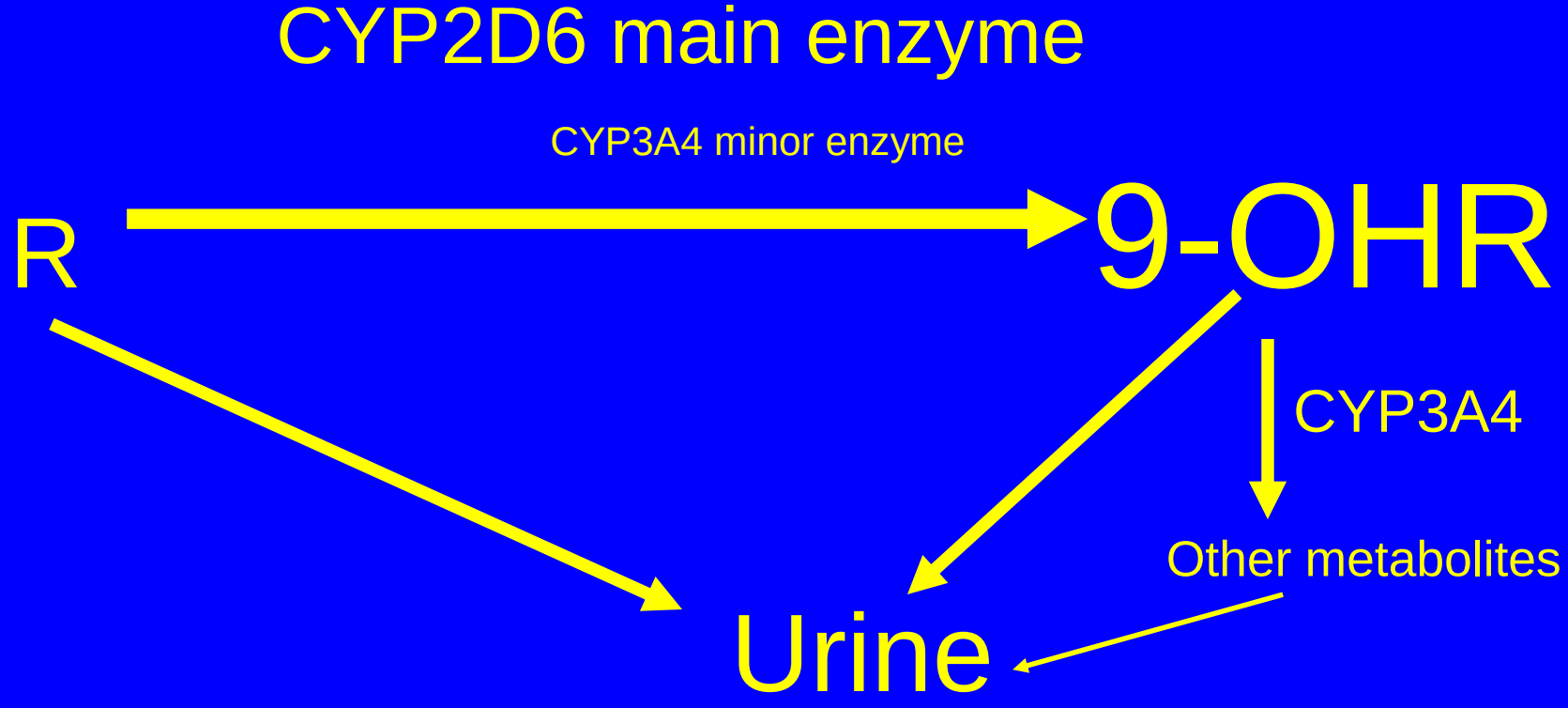
2.4.3. CYP2D6 and R Metabolism: Dr. de Leon's Hypothesis

2.4.3. CYP2D6 and R Metabolism: Dr. de Leon's Hypothesis

2.4.3.1. R Metabolism: Patients with CYP2D6
2.4.3.2. R Metabolism: CYP2D6 PMs
2.4.3.3. R Brain Penetrance

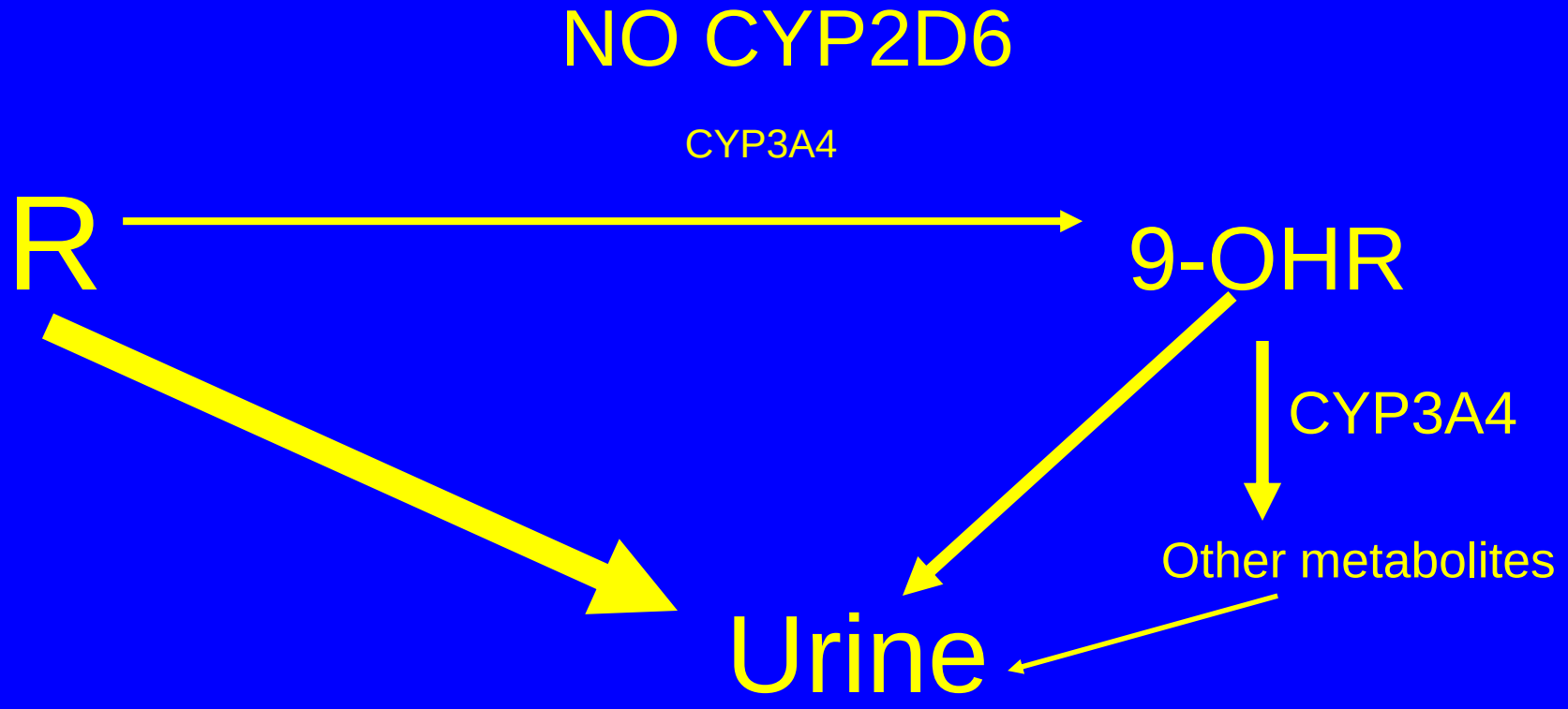
2.4.3.1. R Metabolism: Patients with CYP2D6 (Dr. de Leon's Hypothesis)

2.4.3.1. R Metabolism: Patients with CYP2D6



2.4.3.2. R Metabolism: CYP2D6 PMs (Dr. de Leon's Hypothesis)

2.4.3.2. CYP2D6 and R: CYP2D6 PMs



2.4.3.3. R Brain Penetrance (Dr. de Leon's Hypothesis)

2.4.3.3. R Brain Penetrance

- P-glycoprotein (P-gp) is a transporter, it:
  - has affinity for CYP3A substrates
  - works closely with CYP3A to avoid substrate absorption in the intestine
  - has stronger effects on 9-OHR than on R at the blood-brain barrier:
    Less 9-OHR than R crosses this barrier

http://www.ncbi.nlm.nih.gov/pubmed/15683552

- If you have an interest in learning more about P-gp, see the presentation “Induction by Antiepileptic Drugs: An Update for Clinicians.”

2.4.3.3. R Brain Penetrance

- Dr. de Leon's hypothesis is that
  - serum R is more toxic than serum 9-OHR, since more R reaches the brain.
  - P-gp rejects more 9-OHR than R at the blood-brain barrier.

http://www.ncbi.nlm.nih.gov/pubmed/20118446

- The next 3 slides represent that graphically:
  - First: CYP2D6 IM: serum R/9-OHR=1
  - Second: CYP2D6 EM: serum R/9-OHR=0.2
  - Third: CYP2D6 PM: serum R/9-OHR=2.5

2.4.3.3. R Brain Penetrance Dr. de Leon's Hypothesis

2.4.3.3.1. R Brain Penetrance in a CYP2D6 IM
2.4.3.3.2. R Brain Penetrance in a CYP2D6 EM
2.4.3.3.3. R Brain Penetrance in a CYP2D6 PM

2.4.3.3.1. R Brain Penetrance in a CYP2D6 IM (Dr. de Leon's Hypothesis)

2.4.3.3.1. R Brain Penetrance in a CYP2D6 IM

Brain R 9-OHR

Blood R 9-OHR

Serum R/9-OHR=1 (same serum R and 9-OHR Cs)

2.4.3.3.2. R Brain Penetrance in a CYP2D6 EM (Dr. de Leon's Hypothesis)

2.4.3.3.1. R Brain Penetrance in a CYP2D6 EM

Brain R 9-OHR

Blood R 9-OHR

Serum R/9-OHR=0.2 (serum RC<9-OHR C)

2.4.3.3.3. R Brain Penetrance in a CYP2D6 PM (Dr. de Leon's Hypothesis)

2.4.3.3.1. R Brain Penetrance in a CYP2D6 PM

Brain R 9-OHR

Blood R 9-OHR

Serum R/9-OHR=2.5 (serum R C>9-OHR C)

2.4.4. R TDM and CYP2D6: Dr. de Leon's Studies

2.4.4. R TDM and CYP2D6: Dr. de Leon's Studies

2.4.4.1. R/9-OHR Ratio: Patients Not Taking Inhibitors

2.4.4.2. R/9-OHR Ratio: Lack of Inhibitors vs. Inhibitors

2.4.4.1. R/9-OHR Ratio: Patients Not Taking Inhibitors

2.4.4.1. R/9-OHR Ratio: No Inhibitors http://www.ncbi.nlm.nih.gov/pubmed/18621942

	N	Active alleles	R/9-OHR Median	P25	P75
UM	7	3	0.03	0.02	0.06
EM	3	2.4	0.05	0.02	0.10
EM	69	2.0	0.06	0.03	0.14
EM	40	1.4	0.08	0.04	0.18
EM	7	1.2	0.08	0.06	0.27
EM	60	1.0	0.14	0.07	0.28
IM	5	0.8	0.24	0.17	2.0
IM	4	0.6	0.45	0.15	0.61
IM	11	0.4	0.94	0.35	1.3
PM	14	0	2.5	1.8	4.1

N: sample size; Active alleles: refers to activity (“3” is a UM with an activity of 3 and 3 active alleles,; “0.4” is a IM with little activity).
P25: 25th percentile; P75: 75th percentile.

2.4.4.1. R/9-OHR ratio: No Inhibitors http://www.ncbi.nlm.nih.gov/pubmed/18621942

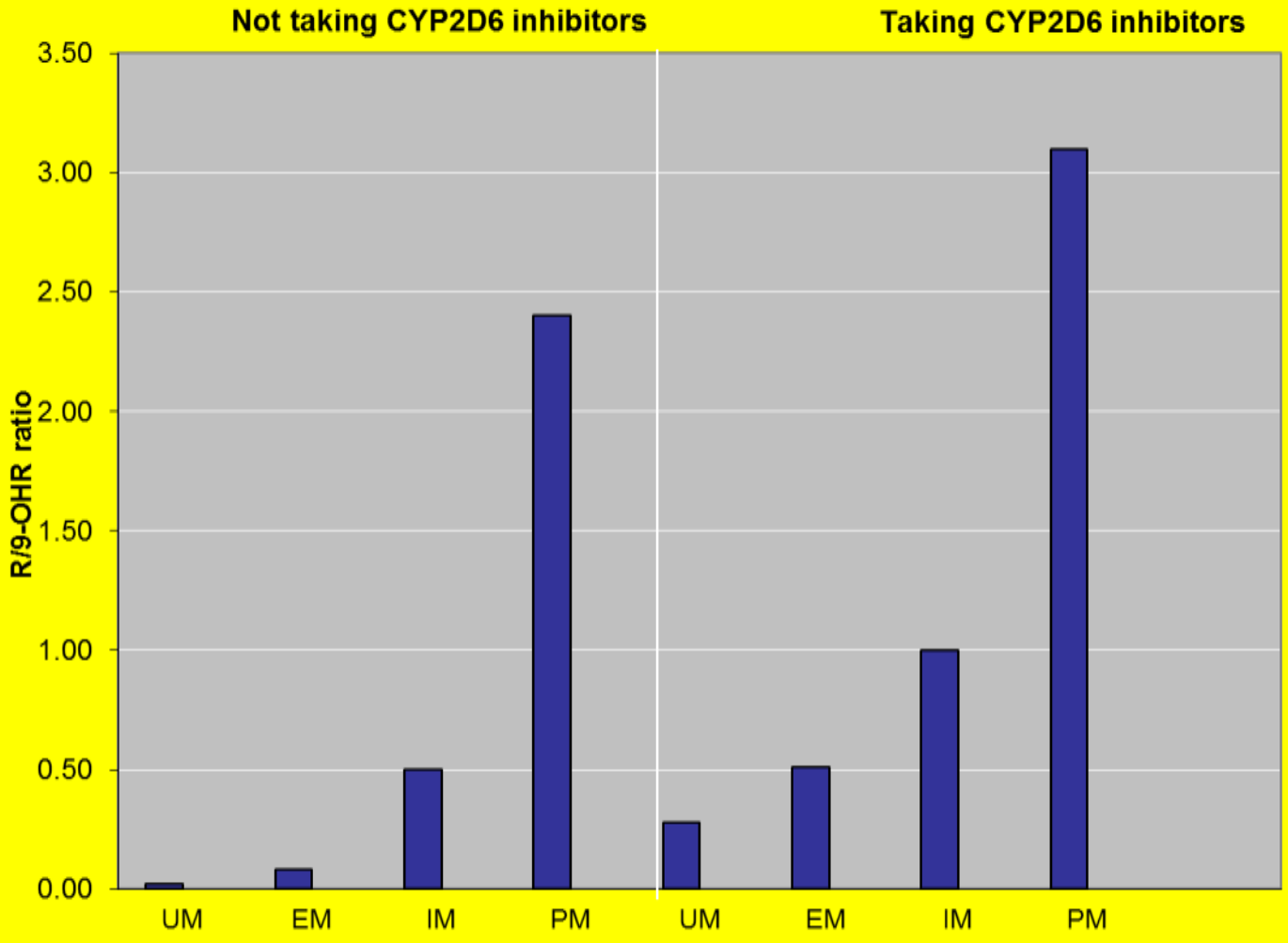
The most important information for this case:
CYP2D6 PMs have R/9-OHR>1 with a median=2.5

	N	Allele activity	R/9-OHR Median	P25	P75
PM	14	0	2.5	1.8	4.1

N: sample size; Alleles: refers to activity ("0" reflects that PM have no CYP2D6 activity).
P25: 25th percentile; P75: 75th percentile.

2.4.4.2. R/9-OHR Ratio: Lack of Inhibitors vs. Inhibitors

2.4.4.2. R/9-OHR Ratio: Lack of Inhibitors vs. Inhibitors



2.4.4.2. R/9-OHR Ratio: Lack of Inhibitors vs. Inhibitors

- The most important information in the prior slide:
  - CYP2D6 PMs: R/9-OHR ratio changes little

	from no inhibitors	to inhibitor
median	around 2.5	around 3

  - CYP2D6 IMs: R/9-OHR ratio changes a lot

	from no inhibitors	to inhibitor
median	0.5	1.0

  - CYP2D6 EMs: R/9-OHR ratio changes but not clear clinical relevance

	from no inhibitors	to inhibitor
median	around 0.2	0.5

  - CYP2D6 UMs: R/9-OHR ratio changes but not clear clinical relevance

	from no inhibitors	to inhibitor
median	<0.1	around 0.3

2.4.4.2. R/9-OHR Ratio: Lack of Inhibitors vs. Inhibitors

- CYP2D6 Inhibitors:
  - Adding: ↑ R/9-OHR ratio
    ↓ CYP2D6 activity
  - Discontinuing: ↓ R/9-OHR ratio
    ↑ CYP2D6 activity

2.4.4.2. R/9-OHR Ratio: Lack of Inhibitors vs. Inhibitors

Inhibitors	CYP2D6	CYP3A4
Fluoxetine	Potent	Weak-moderate
Paroxetine	Potent	
Bupropion	Moderate	
Duloxetine	Moderate	
Sertraline	Weak-moderate (dose-related)	
Fluvoxamine	Weak	Moderate
Citalopram	Not relevant*	
Escitalopram	Not relevant*	

*Probably are such weak inhibitors that they are not clinically relevant.

See the presentation on “Antidepressant Pharmacokinetics”.

2.4.4.2. R/9-OHR Ratio: Lack of Inhibitors vs. Inhibitors

- Dr. de Leon has almost no experience with CYP2D6 IMs with very limited activity (*10/*10) (frequent in East Asians). He suspects that they should be very sensitive to CYP2D6 inhibitors (see prior slide) and after taking them may behave as CYP2D6 PMs.

2.5. Points to Remember

2.5. Points to Remember

- CYP2D6 PMs:
  - have problems eliminating R (high C/D ratio) with high serum R C.
  - according to Dr. de Leon's hypothesis, have a more toxic serum profile (R C>9-OHR C).
    - R is more active (toxic) than 9-OHR
    - because R penetrates the BBB better.
  - Dr. de Leon recommends lower Ds (half).

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

- These ideas are supported by very limited studies

http://www.ncbi.nlm.nih.gov/pubmed/15669884

and ignored by the majority of articles and textbooks.

Questions

- Please review the 10 questions in the pdf entitled “Questions on the Presentation: Risperidone Case 2”.
- You will find the answers on the last slide after the “Thank you slide”. No peeking until you have answered all the questions.
- If you did not answer all the questions correctly, please review the PowerPoint presentation again to reinforce the pharmacological concepts.

Thank you

Answers

1. B
2. A
3. A
4. A
5. D
6. C
7. D
8. D
9. D
10. C