Risperidone Case 1: Drug-Drug Interactions 1-14-16

de Leon & Bork (a resident)

J Clin Psychiatry 1997;58:450-1

Jose de Leon, MD

Educational Objectives

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

1. Consider pharmacological principles in the context of polypharmacy.

2. Appreciate the potential for risperidone drug-drug interaction.

3. Show familiarity with how to correct for drug-drug interactions.

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)

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

- R: risperidone
- R/9-OHR ratio = $\dfrac{R\ C}{9\text{-}OHR\ C}$

- 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."

CYP2D6 Terminology Preferred by Dr. de Leon

Phenotype	N active copies
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	N active copies
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.

1.0

Risperidone

Case 1

Relevance for Dr. de Leon

- This case convinced Dr. de Leon that R pharmacokinetics was important for clinical practice.
- This was his first article on R pharmacokinetics. Currently he has > 10 articles in that area.
- Two have been quoted > 100 times in literature:
  - de Leon J, Susce MT, Pan RM, Fairchild M, Koch WH, Wedlund PJ. The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation. J Clin Psychiatry. 2005 Jan;66(1):15-27. PubMed PMID: 15669884. http://www.ncbi.nlm.nih.gov/pubmed/15669884
  - Bork JA, Rogers T, Wedlund PJ, de Leon J. A pilot study on risperidone metabolism: the role of cytochromes P450 2D6 and 3A. J Clin Psychiatry. 1999 Jul;60(7):469-76. PubMed PMID: 10453802. http://www.ncbi.nlm.nih.gov/pubmed/10453802
- ISI provides quotations from each article on their "Web of Science" page. It is not free.

  http://thomsonreuters.com/en/products-services/scholarly-scientific-research/scholarly-search-and-discovery/web-of-science.html
- ResearchGate provides quotations from each article. It is free but requires signing in. https://www.researchgate.net/

Risperidone Case 1

1.1. Case Description
1.2. R TDM in 1996

1.3. Outcome

1.4. Case Interpretation
1.5. Update on R TDM

1.6. Conclusion of the Case

Risperidone Case 1

1.1. Case Description
1.2. R TDM in 1996
 1.2.1. R/9-OHR Ratio
 1.2.2. C/D Ratio
1.3. Outcome
 1.3.1. TDM After First Medication Change
 1.3.2. Second Medication Change
1.4. Case Interpretation
1.5. Update on R TDM
 1.5.1. Gene Effects: CYP2D6
 1.5.2. Environmental Effects
  1.5.2.1. Inducers
  1.5.2.2. Inhibitors
1.6. Conclusion of the Case

1.1. Case Description

1.1. Risperidone Case 1: Description

- 22-year-old Caucasian ♂
- Non-smoker
- Diagnosis of schizophrenia
- Medication stable for months
  - R D: 4 mg/day
  - Carbamazepine D: 600 mg/day
- Dr. de Leon had a discussion with a resident on how to verify non-response to R.

So, what is the first step in verifying that the patient is not really responding to R?

So, what is the first step in verifying that the patient is not really responding to R?

Being sure that the R D is sufficient.

So, how do you know that the patient is getting enough R?

So, how do you know that the patient is getting enough R?

Measure R in blood (TDM).

1.2. R TDM in 1996

1.2. R TDM in 1996

1.2.1. R/9-OHR ratio in 1996
1.2.2. C/D ratio in 1996

1.2. Risperidone Case 1: TDM in 1996 R 4 mg/day and Carbamazepine

	R	9-OHR	Total
Found	<5	10	<15

Carbamazepine C: 7.9 mcg/l

So, in 1996 how did Dr. de Leon know how to interpret R TDM?

So, in 1996 how did Dr. de Leon know how to interpret R TDM?

He looked at PubMed.

1.2. Risperidone Case 1: TDM in 1996

■ Ereshefsky in 1996 reviewed the pharmacokinetics of available second-generation antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/8941167

■ He had participated in the R North American RCTs and had access to TDM data.

1.2. Risperidone Case 1: TDM in 1996

■ Ereshefsky described the R/9-OHR ratio:

  □ Index of CYP2D6 activity

  □ >1:CYP2D6 PM or
       taking CYP2D6 inhibitors

1.2.1. R/9-OHR in 1996

1.2.1. Risperidone Case 1: R/9-OHR
R 4 mg/d and Carbamazepine

	R	9-OHR	Total C	R/9-OHR
Found	<5	10	<15	<0.5

1.2.1. Risperidone Case 1: R/9-OHR

What can you say about R/9-OHR<0.5?

What can you say about R/9-OHR<0.5?

The patient was NOT a CYP2D6 PM.

1.2.1. Risperidone Case 1: R/9-OHR

- Ereshefsky provided Dr. de Leon a poster presented as an abstract at the American Psychiatric Association meeting.

- Anderson CB, True JE, Ereshefsky L, et al: Risperidone dose, plasma levels and response, in New Research Program and Abstracts, presented at Annual Meeting, American Psychiatric Association, San Francisco, CA, May 1993 (NR 217; p 113).

1.2.1. Risperidone Case 1: R 4 mg/day and Carbamazepine

	D	Total C
Found	4	<15
Expected*	2	14
	6	42

*North American R RCT

What can you say about
total R C <15
for R D=4 mg/day?

1.2.1. Risperidone Case 1: R/9-OHR

What can you say about
total R C <15
for R D=4 mg/day?

It is too low.
It corresponds to D <2 mg/d.

1.2.1. Risperidone Case 1: R/9-OHR

Is there a better way
to describe this relationship?

Is there a better way
to describe this relationship?

Yes.
The C/D ratio.

1.2.2. R C/D Ratio in 1996

1.2.2. Risperidone Case 1: C/D Ratio

- The C/D ratio provides an estimation of the medication clearance once steady state has been reached.
- In R this is calculated by dividing the total C (R + 9-OHR) by R D.

1.2.2. Risperidone Case 1: C/D Ratio

- According to the poster from the manufacturers:
  - D=10 mg/day
  - Total C=72.8 ng/ml.
  - Thus, the C/D ratio is 72.8/10=7.28.
- As a matter of fact, all doses studied (2, 4, 10 and 16 mg/day) provided a C/D ratio very close to 7.

1.2.2. Risperidone Case 1: C/D Ratio

- The R North American RCT TDM was never published beyond that poster.
- Dr. de Leon published graphs based on the data in one of his review articles.

http://www.ncbi.nlm.nih.gov/pubmed/18621942

1.2.2. Risperidone Case 1: C/D Ratio
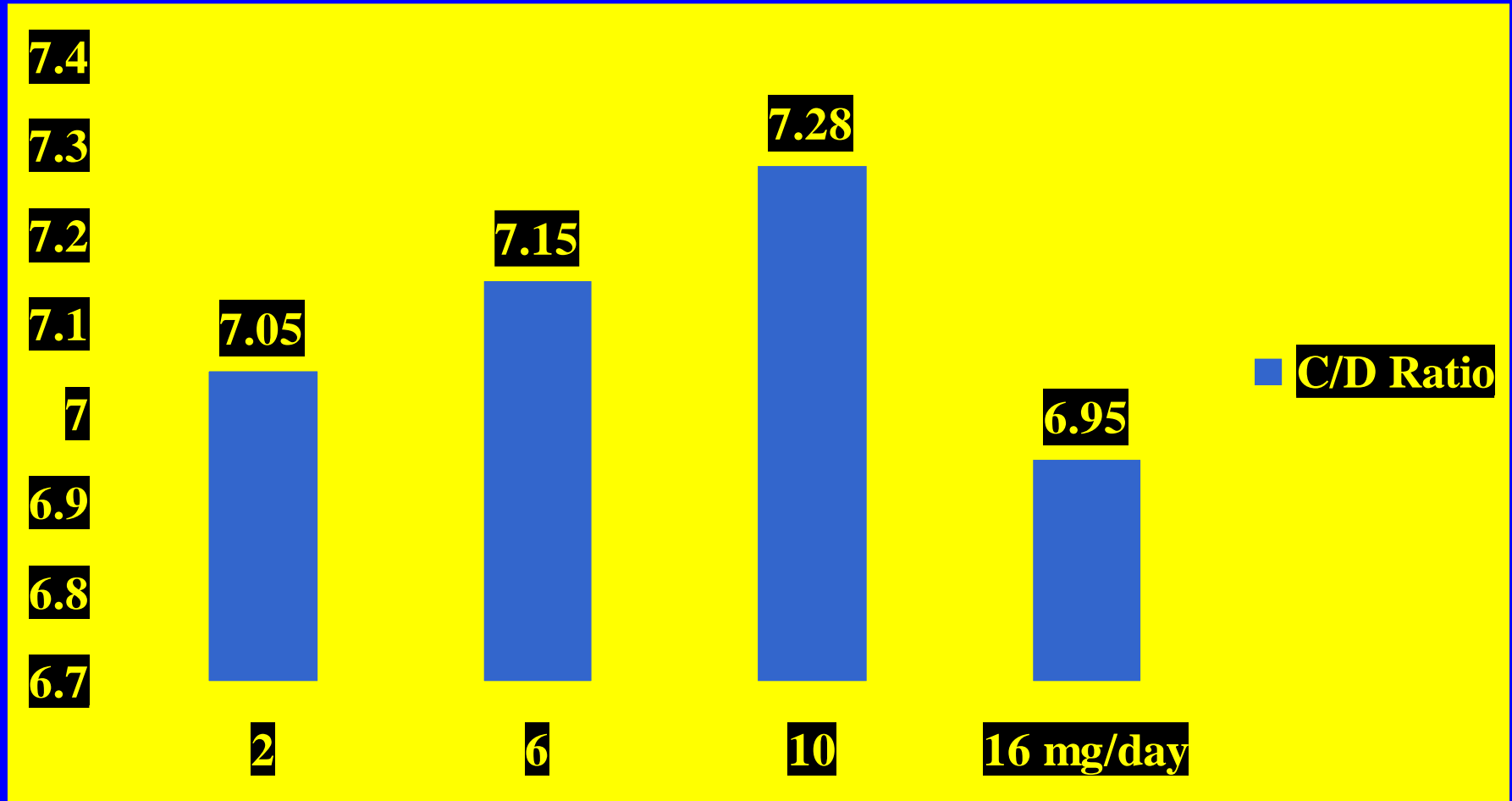
1.2.2. Risperidone Case 1: C/D Ratio

- The C/D ratio =7 is used to calculate the expected C in this patient.
- Later, a 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.

1.2.2. Risperidone Case 1: C/D Ratio

- The best way of representing the C/D relationship is in a graph.
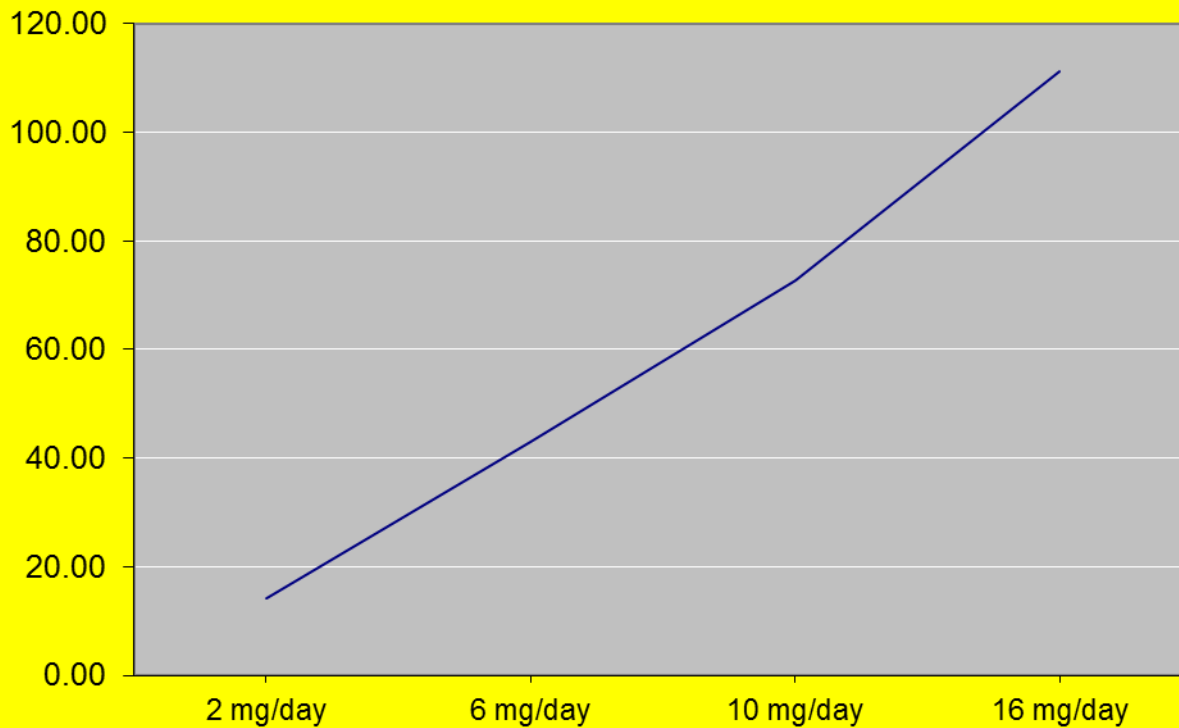
1.2.2 Risperidone Case 1: C/D Ratio

So, what does this graph showing C and D tell you about R TDM?

So, what does this graph showing C and D tell you about R TDM?

R follows linear kinetics.

So, what are the consequences of following linear kinetics?

1.2.2. Risperidone Case 1: C/D Ratio

■ Consequences:
  □ There is a linear relationship between R D and R C.
  □ If the R D ↑ by 2 x, the C ↑ by 2 x.

So, what is the D that corresponds to total R C <15 ng/ml?

So, what is the D that corresponds to
total R C <15 ng/ml?

CD ratio =7, 15/x=7
x<2 mg/day.

So, how do you interpret this C?

So, how do you interpret this C?

R D=4 mg/day
but TDM suggests
D=1-2 mg/day.

Is a R D=1-2 mg/day enough?

Is a R
D=1-2 mg/day
enough?

Probably not.

1.2.2. Risperidone Case 1: C/D Ratio

What would you do?

What would you do?

Dr. de Leon doubled the R D.

1.3. Outcome

1.3. Outcome

1.3.1. TDM After First Change
1.3.2. Second Medication Change

1.3.1. TDM After First Change

1.3.1. Risperidone Case 1: Follow-up R 8 mg/d and Carbamazepine

	R	9-OHR	Total	C/D	R/9-OHR
Expected	10	46	56	7.0	0.2
Found	<5	19	24	<3.7	<0.3

Carbamazepine C: 7.8 mcg/l

So, what is the D that corresponds to a total R C =24 ng/ml?

So, what is the D that corresponds to a total R C =24 ng/ml?

CD ratio =7, 24/x=7 x<4 mg/day.

So, how do you interpret this C?

So, how do you interpret this C?

R D=8 mg/day
but TDM suggests
D=3-4 mg/day.

1.3.1. Risperidone Case 1: Change 1

- In 1996, according to information provided by the manufacturer, R was metabolized by CYP2D6.

- In 1996, Ereshefsky found that:

  - Carbamazepine ↑ metabolism of some antipsychotics.

  - Carbamazepine is not likely to influence R.

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

The patient had two low R Cs, based on the D. Is there any other explanation besides carbamazepine?

The patient had two low R Cs, based on the D. Is there any other explanation besides carbamazepine?

The patient was a CYP2D6 UM.

1.3.1. Risperidone Case 1: Change 1

- But this patient was a CYP2D6 EM. He had two normal alleles (*1/*1).

1.3.2. Second Medication Change

What would you do next?

What would you do next?

Dr. de Leon stopped carbamazepine.

1.3.2. Risperidone Case 1: Follow-up TDM on 8 mg/day. No carbamazepine

	R	9-OHR	TotalC/D	R/9-OHR
Expected	10	46	56 7.0	0.2
Found	<5	49	<54 <6.8	<0.1

He developed akathisia.

So, what is the D that corresponds to a total R C < 54 ng/ml?

So, what is the D that corresponds to a total R C < 54 ng/ml?

CD ratio =7, 54/x=7
X=7-8 mg/day.

So, how do you interpret this C?

So, how do you interpret this C?

**R D=8 mg/day
but TDM suggests
D=7-8 mg/day.**

What can you conclude?

What can you conclude?

After stopping carbamazepine, he metabolized R normally.

1.4. Case Interpretation

1.4. Case Interpretation

1.4.1. Interpretation
1.4.2. Relevance

1.4.1. Interpretation

1.4.1. Risperidone Case 1: Interpretation

- Drs. de Leon & Bork proposed:
  - Carbamazepine ↓ R C 2-fold.
  - CYP3A is involved in R metabolism.

  http://www.ncbi.nlm.nih.gov/pubmed/9375597

1.4.1. Risperidone Case 1: Interpretation

- In 1999, R was verified to be metabolized by CYP3A4:
  - In vitro study http://www.ncbi.nlm.nih.gov/pubmed/10048600 and
  - A larger clinical sample (Bork et al.): CYP3A inducers and inhibitors influence R TDM.
    http://www.ncbi.nlm.nih.gov/pubmed/10453802

1.4.2. Relevance

Is the carbamazepine effect on R clinically relevant?

Is the carbamazepine effect on R clinically relevant?

Yes.
Ask the R manufacturer.

- R manufacturers developed a RCT to try to prove R is effective as an adjunct treatment for mania.
- R or placebo was added to:
  - lithium,
  - valproate, or
  - carbamazepine.

1.4.2. Risperidone Case 1: Relevance

■ The RCT was published in 2003.

http://www.ncbi.nlm.nih.gov/pubmed/12562742

■ R added to lithium or valproate was effective.

■ R added to carbamazepine was no different from placebo.

What was the R manufacturer's mistake?

What was the R manufacturer's mistake? **The R dose in the carbamazepine patients was not corrected to compensate for induction.**

How can you correct for inducer effects on R metabolism?

How can you correct for inducer effects on R metabolism?

You need to double R D.

1.4.2. Risperidone Case 1: Relevance

■ To demonstrate R efficacy in carbamazepine patients, this study needed to use a R pill with twice the potency in these patients.

■ In a better-designed RCT, to make carbamazepine effective, each pill should have:

☐ 1 mg of R for use in patients with lithium or valproate

☐ 2 mg of R for use in patients with carbamazepine

☐ 0 mg of R for use in patients with placebo

- Carbamazepine effects appeared to ↓ the average total C by two times across all subjects.
- According to Dr. de Leon's study, it happens in CYP2D6 PMs and in patients taking powerful inhibitors (fluoxetine or paroxetine). See the next section. Remember: normal total C/D ratio=7.

1.5. Update on R TDM:

Using a Published Figure
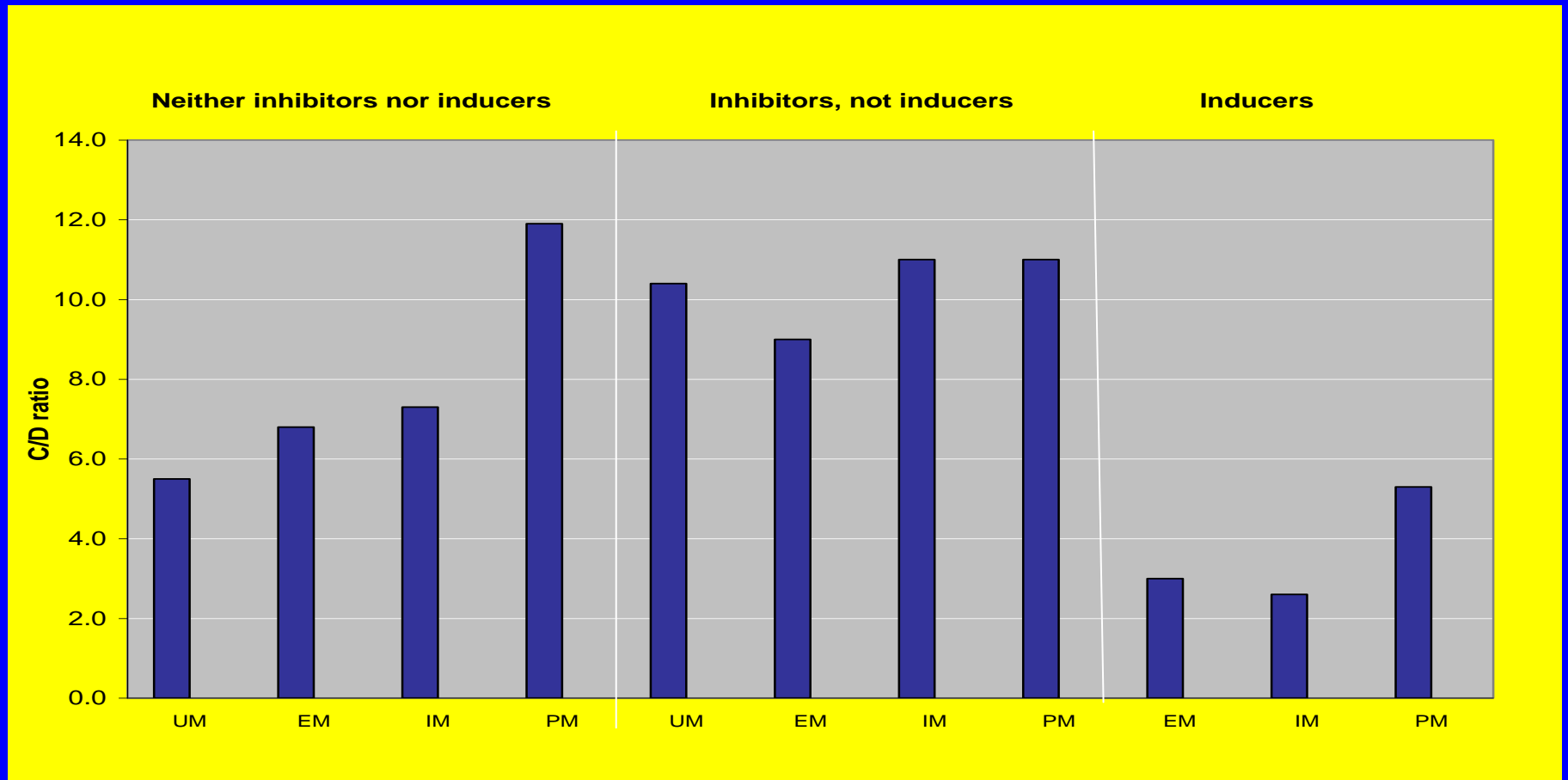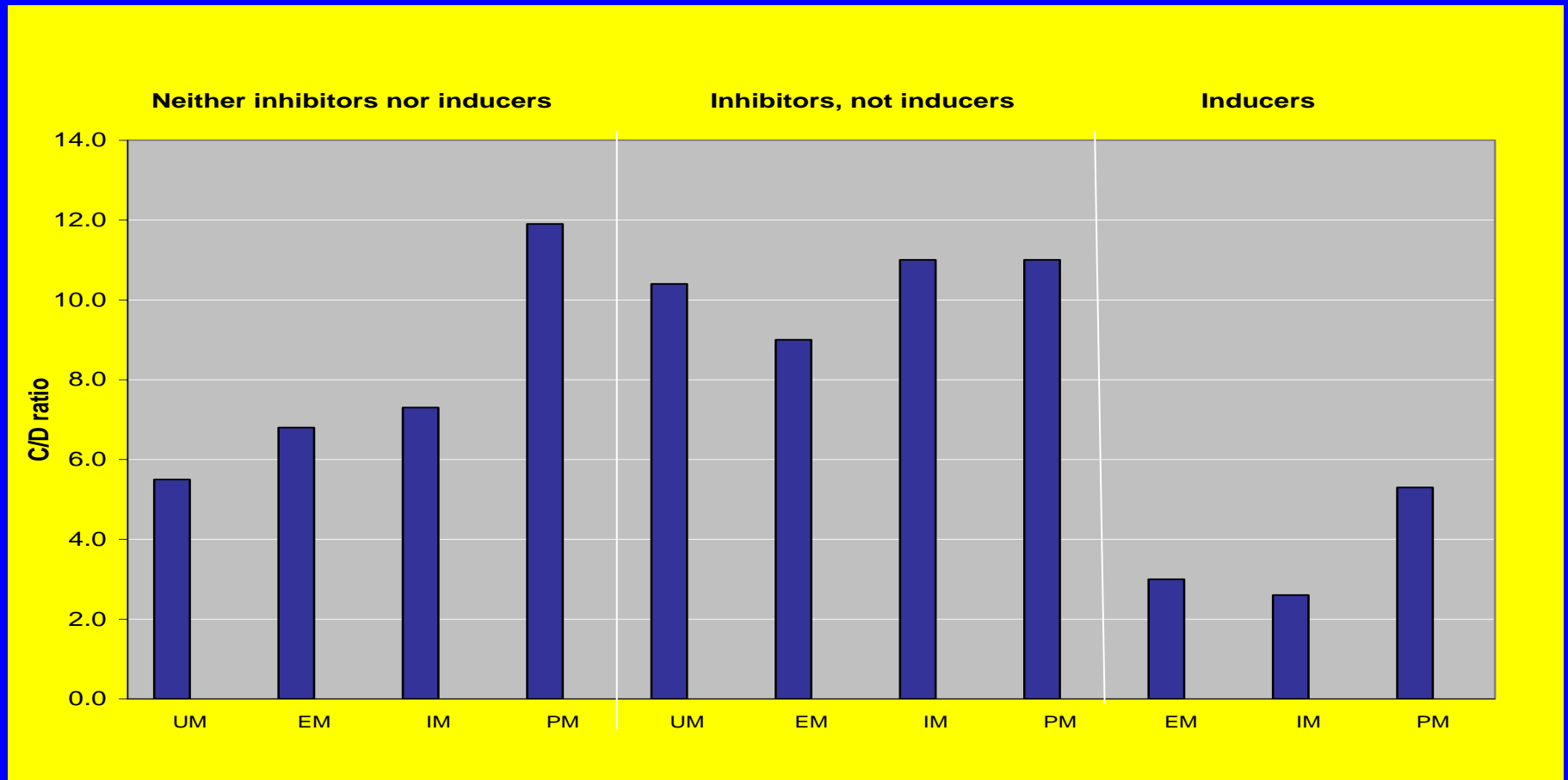
1.5. Risperidone Case 1: R TDM

■ The figure has 3 panels:
- □ Left panel: (bars 1-4)
- □ Middle panel: (bars 5-8)
- □ Right panel: (bars 9-11).

1.5. Risperidone Case 1: R TDM

Left panel: bars 1-4   Middle panel: bars 5-8   Right panel: bars 9-11

1.5. Update on R TDM

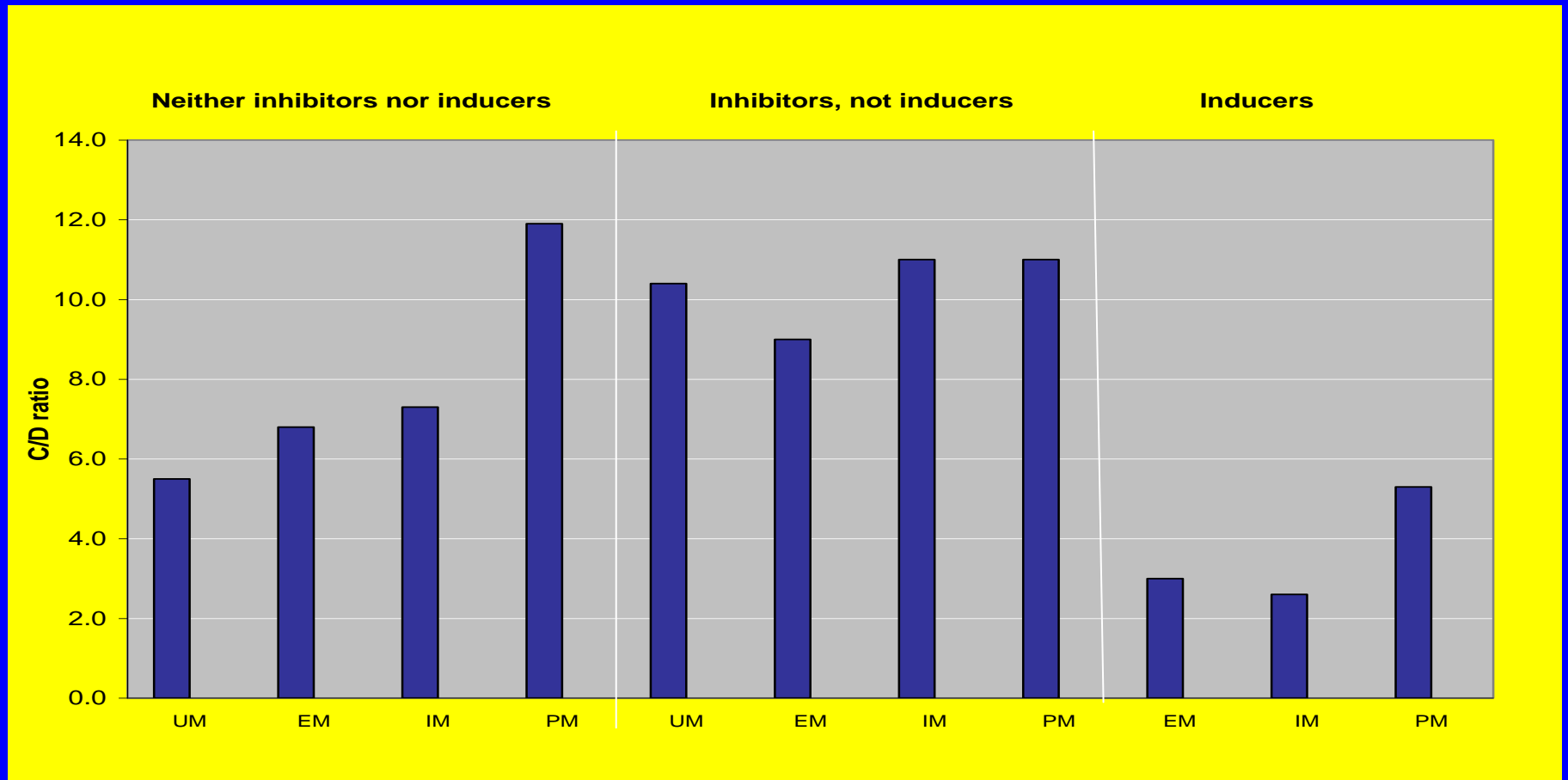1.5.1. Gene: CYP2D6
1.5.2. Environment
     1.5.2.1. Inducers
     1.5.2.2. Inhibitors

1.5.1. R TDM: CYP2D6

1.5.1. Risperidone Case 1: R TDM & CYP2D6

Focus on left panel: bars 1-4   Middle panel: bars 5-8   Right panel: bars 9-11

■ Left panel (bars 1-3)
  □ UMs: C/D ratio <6.0 (bar 1)
  □ EMs: C/D ratio around 7.0 (bar 2)
  □ IMs: C/D ratio around 7.0 (bar 3)
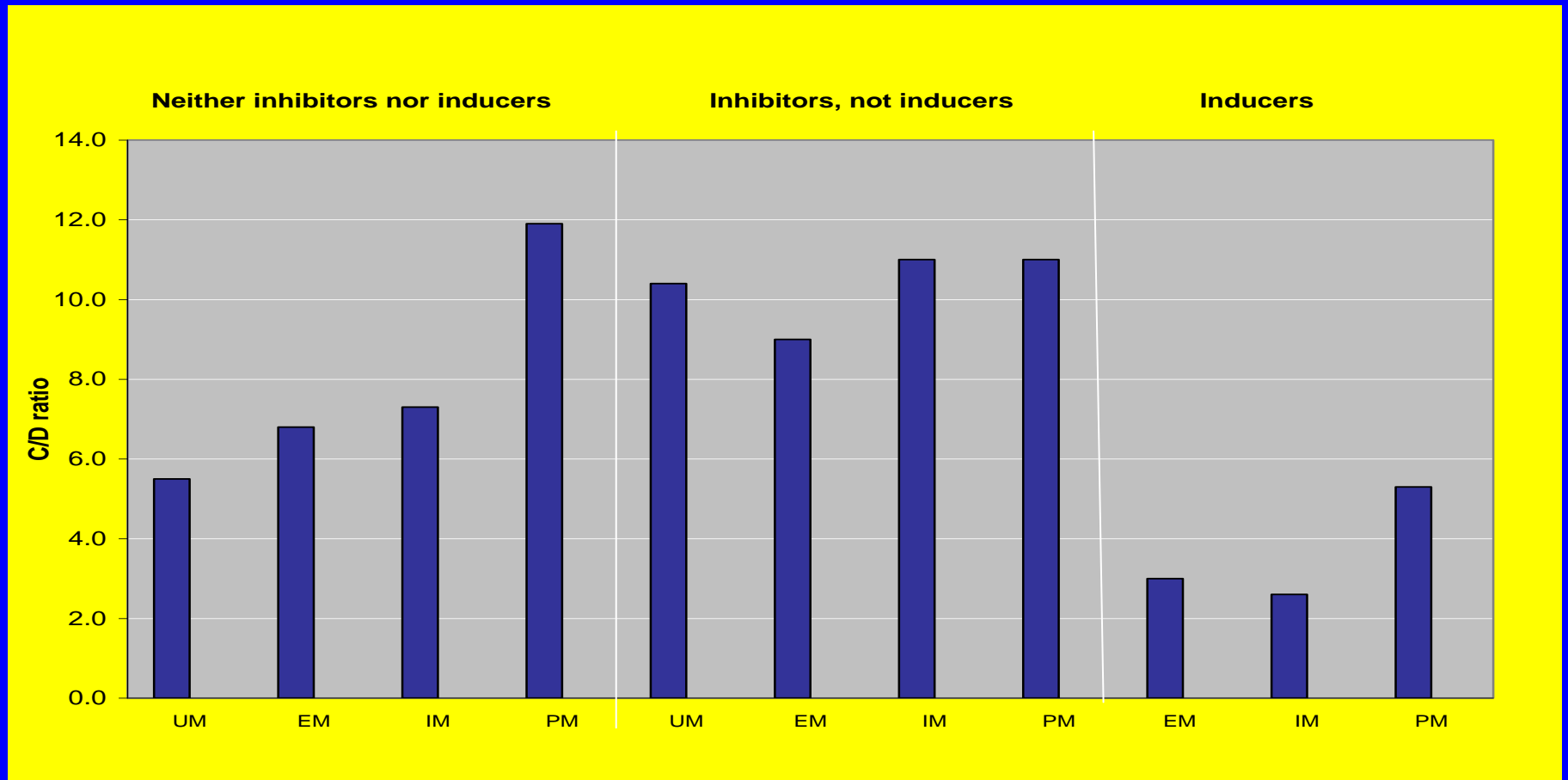   All of these are normal (around 7)
■ Left panel (bar 4)
  □ PMs: C/D ratio =12.0 (bar 4)
    Too high.

1.5.1. Risperidone Case 1: R TDM & CYP2D6

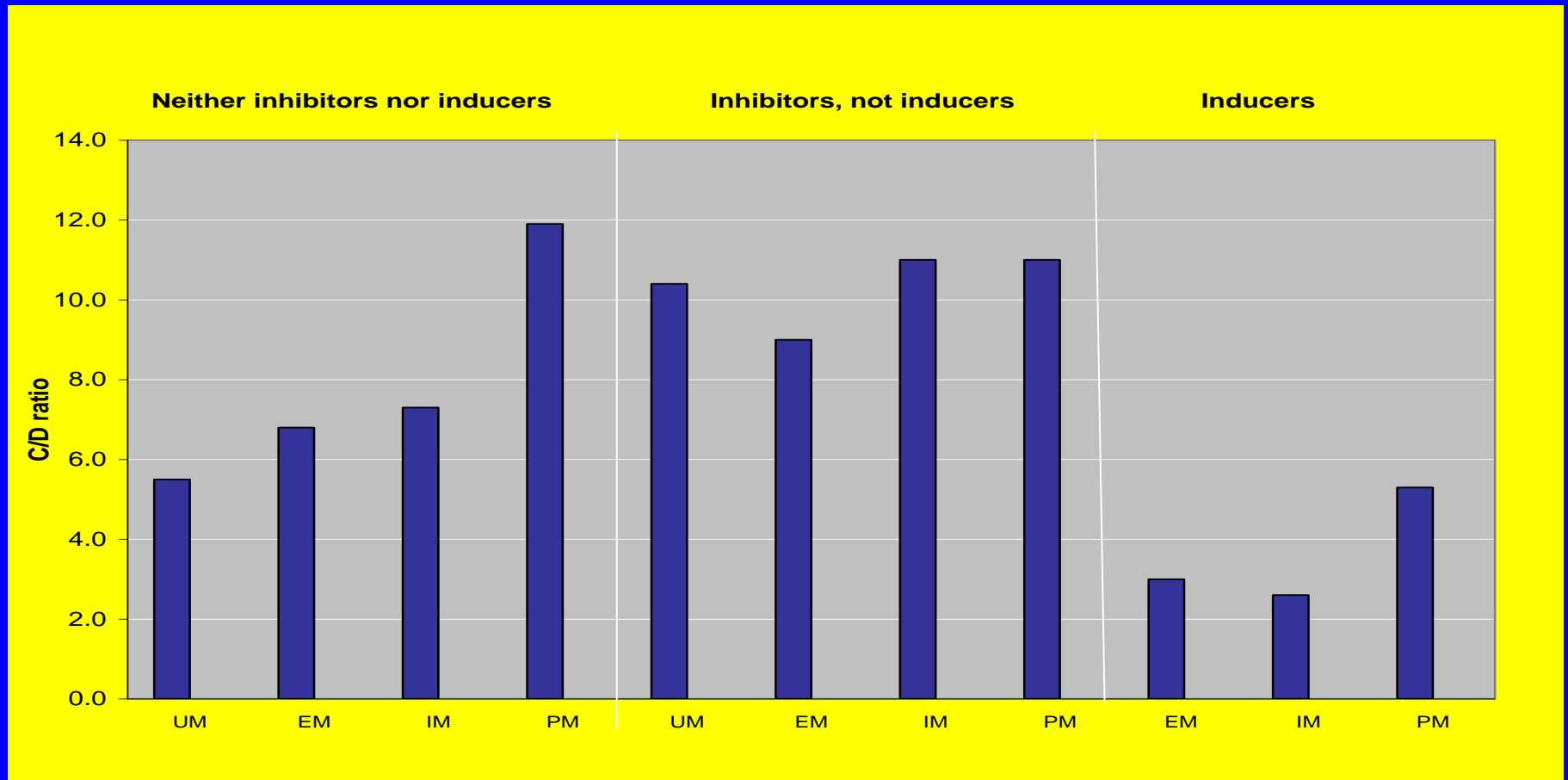Focus on left panel: bars 1-4   Middle panel: bars 5-8   Right panel: bars 9-11

- CYP2D6 PMs do not have active
  CYP2D6 enzyme and
  they metabolize R poorly.
  Figure: C/D ratio =12.0 (bar 4)
  This is almost twice the normal ratio.

1.5.2. R TDM: Environment

1.5.2.1. R TDM: Inducers

1.5.2.1. Risperidone Case 1: TDM & Inducers

http://www.ncbi.nlm.nih.gov/pubmed/17541883

Left panel: bars 1-4   Middle panel: bars 5-8   Focus on right panel: bars 9-11
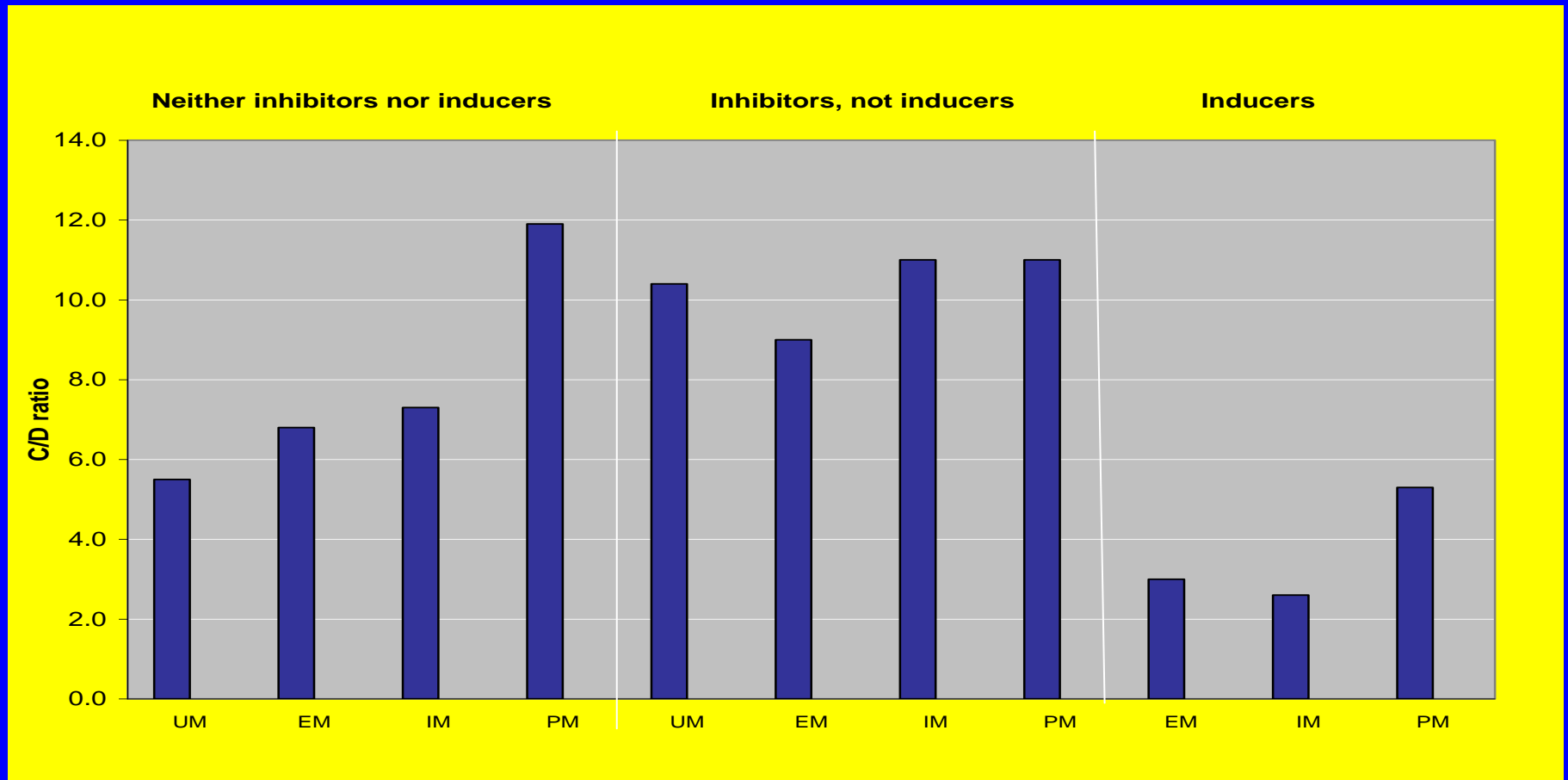
- Right panel (bars 9-10)
  - UMs: None taking inducers
  - EMs: C/D ratio around 3.0 (bar 9)
  - IMs: C/D ratio around 3.0 (bar 10)
  These are half of normal (7).
- Right panel (bar 11)
  - PMs: C/D ratio <6.0 (bar 11)
  Lower than normal.

1.5.2.1. Risperidone Case 1: TDM & Inducers

Left panel: bars 1-4   Middle panel: bars 5-8   Focus on right panel: bars 9-11

- Adding carbamazepine is <u>approximately</u> equivalent to ↓ R dose by two times.
- Discontinuing carbamazepine is <u>approximately</u> equivalent to ↑ R dose by two times.

■ Smoking is NOT an inducer of R metabolism.

■ Polycyclic aromatic hydrocarbon compounds on smoke induce:

☐ CYP1A2 (olanzapine, clozapine and probably some phenothiazines).

☐ Some glucuronidation enzymes (haloperidol and possibly olanzapine and some phenothiazines).

■ Carbamazepine (and other inducers) appear to have very powerful effects and have greater effects on R metabolism than not having CYP2D6 (PMs).

1.5.2.1. Risperidone Case 1: TDM & Inducers

■ When marketing R, the R manufacturer proposed that R and 9-OHR are equally potent.

■ Later, when marketing paliperidone, R manufacturer data suggests that R may be more potent than paliperidone (9-OHR). The R manufacturer recommends paliperidone Ds that are 2 x higher than R Ds.http://www.ncbi.nlm.nih.gov/pubmed/20118446
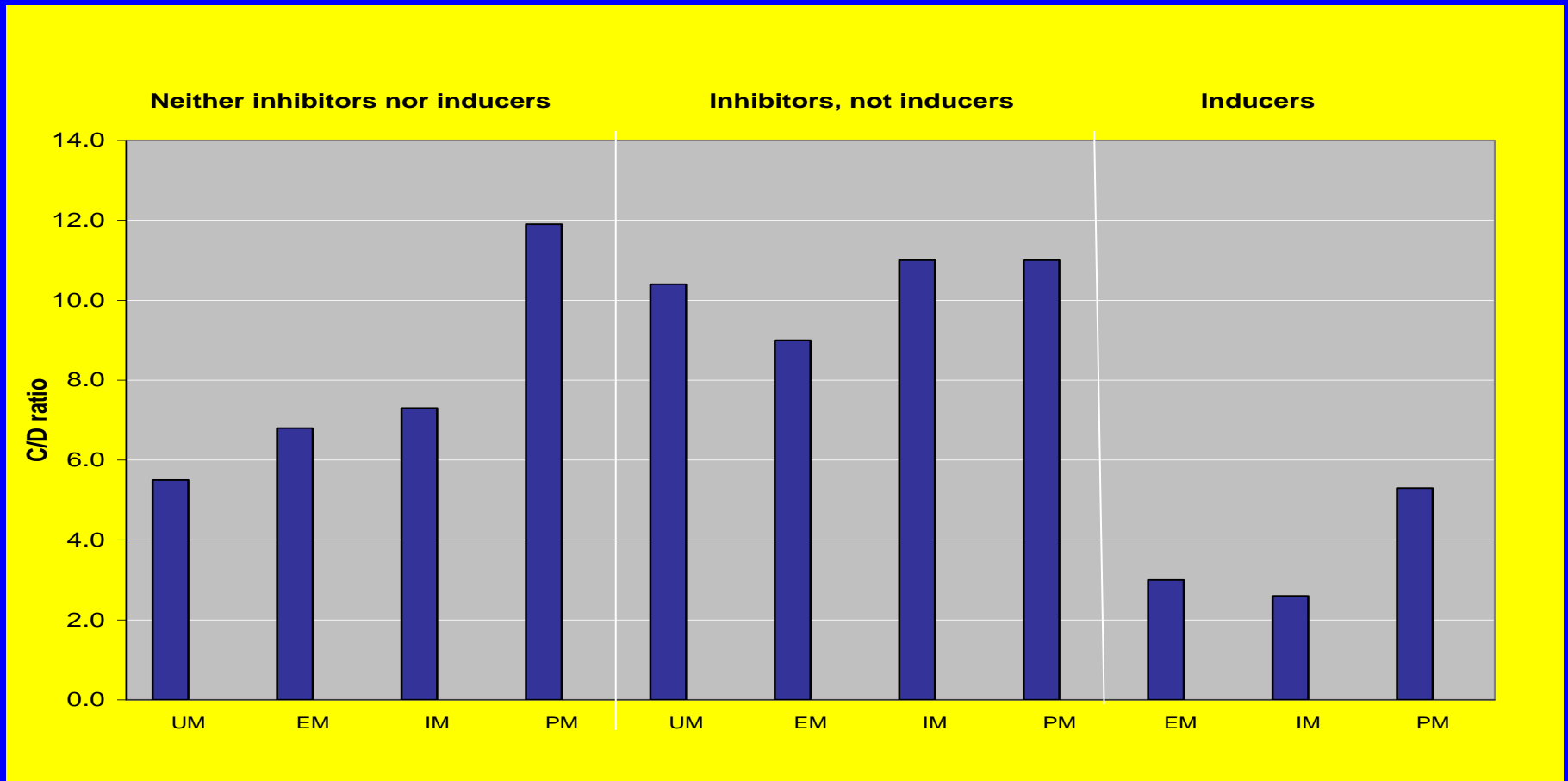
■ If Dr. de Leon is correct and
R is more potent than 9-OHR
(see Risperidone Case 2 Genetics),
it will be difficult to predict the
outcomes for:
☐ carbamazepine + CYP2D6 PM
☐ carbamazepine + paroxetine
Paroxetine can inhibit CYP2D6
completely.

1.5.2.2. R TDM: Inhibitors

1.5.2.2. Risperidone Case 1: TDM & Inhibitors

Left panel: bars 1-4   Focus on middle panel: Right panel: bars 9-11
bars 5-8

■ R patients taking powerful inhibitors
may have complete inhibition of
CYP2D6 and in some cases
CYP3A4 inhibition.
They may metabolize R poorly.

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 "Antidepressant Pharmacokinetics".

1.5.2.2. Risperidone Case 1: TDM & Inhibitors
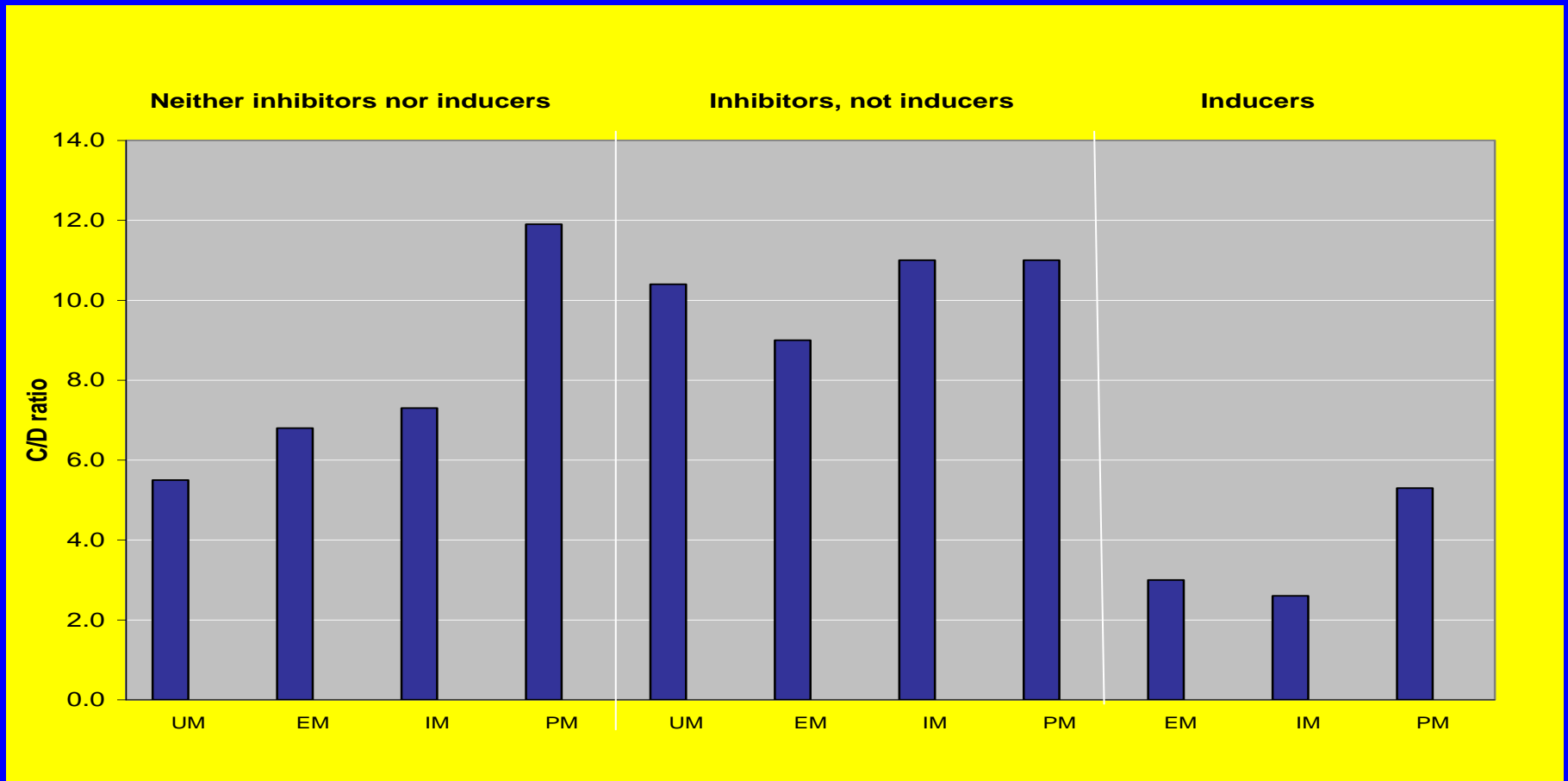
Left panel: bars 1-4   Focus on middle panel: Right panel: bars 9-11
bars 5-8

■ Middle panel (bars 5-8)

☐ UMs: C/D ratio around 10.0 (bar 5)

☐ EMs: C/D ratio around 9.0 (bar 6)

☐ IMs: C/D ratio around 11.0 (bar 7)

☐ PMs: C/D ratio around 11.0 (bar 8)
PMs (bar 4) and
PM+ inhibitors (bar 8) look similar.
You cannot inhibit CYP2D6 if you
do not have it.
You can inhibit CYP3A4.

1.6. Conclusion of Case

1.6. Risperidone Case 1: Conclusion

■ The patient was able to tolerate
  R D=8 mg/day + carbamazepine.

■ The patient was unable to tolerate
  R D=8 mg/day
  without carbamazepine.
  He developed akathisia.

■ He was switched to clozapine.
  He eventually was discharged.

Questions

- Please review the 10 questions in the pdf entitled "Questions on the Presentation: Risperidone Case 1".
- 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. D

5. D

6. D

7. D

8. C

9. B

10. A