Pharmacokinetics of Oral Second-Generation Antipsychotics

Jose de Leon, MD

(12-11-15)

Learning Objectives

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

1) Appreciate the relevance of absorption for some second-generation antipsychotics.
2) Appreciate the relevance of renal elimination for some second-generation antipsychotics.
3) Summarize 3 major second-generation antipsychotic drug-drug interaction profiles:
   (a) clozapine and olanzapine (CYP1A2)
   (b) cariprazine, lurasidone and quetiapine (CYP3A44)
   (c) aripiprazole, brexpiprazole, iloperidone and risperidone (CYP2D6/3A4).
4) Be aware that ziprasidone, asenapine, amisulpride and paliperidone have different profiles.

Abbreviations

- ADR: adverse drug reaction
- AED: antiepileptic drug
- AGNP: Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (German TDM expert group)
- BBB: blood-brain barrier
- C/D ratio: concentration/dose (C/D) ratio.
- Cr Cl: creatinine clearance
- CRP: C-reactive protein
- CYP: cytochrome P450
- DDI: drug-drug interaction
- EM: extensive metabolizer (normal activity)
- FMO: flavin-containing monooxigenase
- P-gp: P-glycoprotein
- PM: poor metabolizer (no activity)
- SGAP: second-generation antipsychotic
- TDM: therapeutic drug monitoring
- UM: ultrarapid metabolizer (↑ activity)
- VPA: valproic acid

SGAP abbreviations

- AMI: amisulpride (not approved in the USA)
- ARI: aripiprazole
- ASE: asenapine
- BRE: brexpiprazole (marketed in the USA in 2015)
- CAR: cariprazine (marketed in the USA in 2015)
- CLO: clozapine
- ILO: iloperidone
- LUR: lurasidone
- OLA: olanzapine
- PAL: paliperidone (or 9-hydroxyrisperidone)
- QUE: quetiapine
- RIS: risperidone
- ZIP: ziprasidone

New SGAPs Marketed in 2015

- Please write these two new names several times until you have learned them:

  - BRE: brexpiprazole
  - CAR: cariprazine

- You may also want to write the commercial names of these drugs, as used in your country, to learn them.

Dosing Table: Examples of Correction Factors

- RIS correction factor for carbamazepine = 2
- RIS correction factor for paroxetine = 0.5

- If in your typical RIS patient you use 4 mg/d:
  - In a carbamazepine patient, you should use 8 mg/d (4 mg/d x 2 = 8 mg/d).
  - In a paroxetine patient, you should use 2 mg/d (4 mg/d x 0.5 = 2 mg/d).

Correction Factors are PROVISIONAL

- The correction factors will need to be updated as the literature gets better.
  Published correction factors for 2 SGAPs, when co-prescribing potent inducers, have been updated from an article published in 2015 http://www.ncbi.nlm.nih.gov/pubmed/25745819
  The new correction factor for:
  - clozapine: 1.5-2 x
  - olanzapine: 2-3 x
- The best way to avoid using "imperfect" correction factors is to use TDM (blood levels) to individualize your patient's dose. The case presentation lectures explain how to do this using the concept of concentration/dose (C/D) ratio.

Warning

This is an extraordinarily long presentation (>200 slides):

1) You may need to read it more than once until you have become familiar with key aspects. If it looks too complicated, skip the TDM section during the first reading.
2) More importantly, you need to practice every day and review the pharmacokinetics of drugs when any of your patients are receiving polypharmacy, including SGAPs.
2) Most important to remember is that SGAPs (except asenapine) rarely influence other drug metabolism, but they can be influenced by inducers and inhibitors. See the "Do Not Forget" Section and pay attention to the red print.
3) Data is limited on the effects of inflammation/ infection on CYP3A4 drugs. Dr. de Leon prefers to worry about DDIs than see ADRs. Use CRP to detect inflammation.

Lecture Content

1. SGAP Absorption

2. SGAP Renal Elimination

3. Metabolism

4. Hepatic Impairment

5. Pregnancy
6. Effects on Other Drug Metabolism
7. Do Not Forget

Lecture Content

1. SGAP Absorption

1. Absorption

1.1. Absorption: Sublingual

1.2. Absorption: Not Crushed

1.3. Absorption: Food

1.1. SGA Sublingual Absorption

1.1. Absorption: Sublingual

- ASE:
  - Oral: Major effects of first-pass metabolism
  - Sublingual administration
  - Drinking or eating within 10 min of intake will ↓ absorption.
  - The patient should not swallow the tablets.

1.2. SGA Absorption: Not Crushed

1.2. Absorption: Not Crushed

- Any extended-release formulation:
  - PAL
  - QUE extended-release

1.3. SGA Absorption: Food

1.3. Absorption: Food

- SGAPs that NEED to be administered with food:
  - ZIP
  - LUR

- SGAP that SHOULD NOT be administered with food (no more than a light snack):
  - QUE extended-release.

2. SGAP Renal Elimination

2. Renal Elimination

2.1. Renal Elimination: Percentage

2.2. Renal Insufficiency

2.1. SGAP Renal Elimination: Percentage

2.1. Renal Elimination: Percentage

	% Unchanged	% Changed
AMI[1]	22-25	
ARI[2]	<1	24-25
ASE[3]	Not described	50
BRE[3]	<1	25
CAR[3]	1	20
CLO[2]	0.5	48.5
ILO[2]	<1	57-58
LUR[3]	Not described	9
OLA[2]	7	50
PAL[2]	60	20
QUE[2]	<0.5	72.5
RIS[2]	5	65 (includes active metabolite)
ZIP[2]	<1	19-20

[1] http://www.ncbi.nlm.nih.gov/pubmed/15521794
[2] http://www.ncbi.nlm.nih.gov/pubmed/20540690
[3] US prescribing information

2.2. SGAP Renal Elimination: Renal Insufficiency

2.1. Renal Insufficiency: Dose Correction

- AMI: □ Cr Cl 30-60 ml/min: 1/2 dose
  □ Cr Cl 10-30 ml/min: 1/3 dose
- BRE: Cr Cl<60 ml/min maximum recommended dose:
  □ 2 mg/d for major depressive disorder
  □ 3 mg/d for schizophrenia
- CAR: □ Cr Cl≥ 30 ml/min: no dose change
  □ Cr Cl< 30 ml/min: not recommended
- CLO: no studies are available
- LUR: □ Cr Cl 50-10 ml/min: dose ≤ 40 mg/d
- PAL: □ normal : ≤ 12 mg/day
  □ Cr Cl 80-50 ml/min: ≤ 6 mg/day
  □ Cr Cl 50-10 ml/min: ≤ 3 mg/day
  □ Cr Cl <10 ml/min: not recommended
- RIS: □ initial dose: 0.5 mg twice a day
  □ dose increases: ≤ 0.5 mg twice a day
  □ for doses > 3 mg/day wait ≥1 week for further ↑
- Other SGAPs would not need dose correction.

3. SGAP Metabolism

3. Metabolism

3.1. Enzymes
3.2. TDM
3.3. CLO & OLA Profile
3.4. QUE, LUR and CAR Profile
3.5. ARI, ILO, RIS & BRE Profile
3.6. ZIP Metabolism
3.7. ASE Metabolism
3.8. PAL & AMI Renal Elimination

3.1. SGAP Enzymes

3.1. Enzymes

3.1.1 Three Major DDI Profiles

3.1.2. SGAPs and Infections

3.1.3. SGAPs and AEDs

3.1.1. SGAPs: Three Major Profiles

3.1. Enzymes

- Three major DDI profiles:
  - CYP1A2 APs: CLO and OLA
  - CYP3A4 APs: QUE, LUR & CAR
  - CYP2D6/3A4 APs: ARI, ILO, RIS & BRE
- Other APs:
  - ZIP: Aldehyde oxidase (CYP3A4)
  - ASE: Most important UGT1A4
  - PAL & AMI: Renal excretion

3.1.1. SGAPs: Three Major DDI Profiles

	CLO OLA	QUE LUR	RIS ARI ILO
CYP	1A2	3A4	2D6/3A
GENETIC PM/UMs	Rare <1%	Rare <1%	7% PMs* 1.5%UMs*
ENVIRONMENTAL PM/UMS			
Drug inhibitors	=PM	=PM	=PM
Infection/inflammation	=PM	Probably	Probably
Drug inducers	=UM	=UM	=UM
Smoking	=UM	No effects	No effects

*Prevalences in US population

3.1.2. SGAPs and Infections

3.1.2. SGAPs and Infections

- AIDS or TB meds: high DDI risk (See article tables http://www.ncbi.nlm.nih.gov/pubmed/15883149).
- QUE, LUR, CAR, ARI, BRE, ILO & RIS: Use alternatives to ketoconazole or erythromycin.
- CLO & OLA: Use alternatives to ciprofloxacin http://www.ncbi.nlm.nih.gov/pubmed/15883149
- CLO & OLA: Pneumonias, serious upper respiratory infections and appendicitis release cytokines (CYP1A2 inhibitors). They may also be CYP3A4 inhibitors (QUE, LUR, CAR, ARI, BRE, ILO & RIS). Use ↑ CRP, as inflammation sign http://www.ncbi.nlm.nih.gov/pubmed/26032842

3.1.3. SGAPs and AEDs

3.1.4. SGAPs and AEDs

http://www.ncbi.nlm.nih.gov/pubmed/25745819

- Carbamazepine, phenytoin & phenobarbital are major inducers and induce most APs.
  - Possible small effects on AMI & ZIP
  - ASE: not well studied
  - 1.5-2 x dose: CLO
  - 2 x dose: ARI, ILO, RIS
  - 2-3 x dose: OLA
  - 3 x dose: PAL
  - ≥5 x dose: LUR & QUE (avoid)

3.1.4. SGAPs and AEDs

http://www.ncbi.nlm.nih.gov/pubmed/25745819

- Lamotrigine: DDIs are unlikely to be important. OLA may be an exception (UGT inhibition).

  http://www.ncbi.nlm.nih.gov/pubmed/18555573

  It is a possibly a mild QUE inducer.
- Oxcarbazepine, topiramate and valproate are mild inducers. Inductive effects:
  - can be obscured by their inhibitory properties,
  - may only be present in high doses, and
  - require even longer than potent AED inducers (sometimes months) to reach maximum effects or disappear.

3.1.4. SGAPs and AEDs

- Oxcarbazepine (≥ 1200 mg/d) and topiramate (≥ 400 mg/d) may be inducers of CLO, OLA, QUE, LUR, CAR, ARI, BRE, ILO & RIS. A recent case of quetiapine induction has been described: http://www.ncbi.nlm.nih.gov/pubmed/26469302
- Valproate in general has small effects on APs, but has not been well studied.
  - Inhibition: PAL
  - Mild induction: ARI
  - Induction/competitive inhibition: CLO & OLA
    Some patients may be very sensitive to induction.

http://www.ncbi.nlm.nih.gov/pubmed/25745819

3.2. SGAP TDM

3.2. SGAP TDM

Remember, you need at least 5 half-lives of a drug (and any active metabolite) to reach steady state and be able to draw blood for TDM.

3.2. SGAP TDM

- The AGNP consensus guideline was updated in 2011 http://www.ncbi.nlm.nih.gov/pubmed/22053351 and recommends SGAP TDM as follows:
  - Strongly: AMI, CLO & OLA
  - Recommended: ARI, PAL, QUE, RIS & ZIP
  - Useful: ILO & LUR
  - Potentially useful: ASE

3.2.1. Therapeutic Reference Ranges

3.2.1. Therapeutic Reference Ranges

- The AGNP defines Therapeutic Reference Ranges = ranges of medication concentrations:
  - a lower limit below which a drug-induced therapeutic response is relatively unlikely to occur and
  - an upper limit above which tolerability decreases or above which it is relatively unlikely that therapeutic improvement may still be enhanced.

3.2.1. Therapeutic Reference Ranges

- 8 SGAs with reasonable information:
  - AMI: 100-320 ng/mL
  - ARI: 150-500 ng/mL
  - CLO: 350-600 ng/mL
  - OLA: 20-80 ng/mL
  - PAL: 20-60 ng/mL
  - QUE: 100-500 ng/mL
  - RIS: 20-60 ng/mL
  - ZIP: 50-200 ng/mL

3.2.2. Therapeutic Window

3.2.2. Therapeutic Window

- To find the therapeutic window or index:
  Divide upper limit by lower limit.
  - Imipramine: 100-300 ng/ml
    You divide 300/100=3

3.2.2. Therapeutic Window

What is the therapeutic window/index for AMI?

3.2.2. Therapeutic Window

What is the therapeutic window/index for AMI?

320/100=3.2

3.2.2. Therapeutic Window

What is the therapeutic window/index for ARI?

3.2.2. Therapeutic Window

What is the therapeutic window/index for ARI?

500/150=3.3

3.2.2. Therapeutic Window

What is the therapeutic window/index for CLO?

3.2.2. Therapeutic Window

What is the therapeutic window/index for CLO?

600/350=1.7

3.2.2. Therapeutic Window

What is the therapeutic window/index for OLA?

3.2.2. Therapeutic Window

What is the therapeutic window/index for OLA?

80/20=4

3.2.2. Therapeutic Window

What is the therapeutic window/index for PAL?

3.2.2. Therapeutic Window

What is the therapeutic window/index for PAL?

60/20=3

3.2.2. Therapeutic Window

What is the therapeutic window/index for QUE?

3.2.2. Therapeutic Window

What is the therapeutic window/index for QUE?

500/100=5

3.2.2. Therapeutic Window

What is the therapeutic window/index for RIS?

3.2.2. Therapeutic Window

What is the therapeutic window/index for RIS?

60/20=3

3.2.2. Therapeutic Window

What is the therapeutic window/index for ZIP?

3.2.2. Therapeutic Window

What is the therapeutic window/index for ZIP?

200/50=4

3.2.2. Therapeutic Window

- Drug therapeutic window/index:
  - narrow ≤ 3
  - wide > 3

3.2.2. Therapeutic Window

What are the SGAPs with a narrow therapeutic window/index?

3.2.2. Therapeutic Window

- SGAPs with narrow therapeutic windows/indexes:
  - CLO = 1.7
  - PAL & RIS = 3

Narrow therapeutic window SGAPs tend to be more toxic.

3.2.2. Therapeutic Window

What are the SGAPs with a wide therapeutic window/index?

3.2.2. Therapeutic Window

- SGAPs with wide therapeutic windows/indexes:
  - QUE = 5
  - OLA & ZIP = 4
  - ARI = 3.3
  - AMI = 3.2

3.3. CYP1A2 Profiles of CLO (other CYPs) and OLA (also UGT1A4)

3.3.1. CLO

3.3.1. CLO

3.3.1.1. Metabolism

3.3.1.2. DDIs

3.3.1.3. TDM

3.3.1.1. CLO Metabolism

3.3.1.1. CLO Metabolism

- The main pathway to norclozapine (or desmethylclozapine) is CYP1A2.
  - Others involved:
    - CYP2C19
    - CYP3A4
    - CYP2D6
- The secondary pathway to clozapine-N-oxide is reversible and mainly mediated by FMO.
- Another pathway: UGT

3.3.1.2. CLO DDIs

3.3.1.2. CLO DDIs

3.3.1.2.1. Inducers

3.3.1.2.2. Inhibitors

3.3.1.2.3. VPA

3.3.1.2.1. Inducers on CLO

3.3.1.2.1. Inducers on CLO

DDI	Corr F	Action
Rifampicin[1]		Avoid
AED potent inducers (phenytoin & phenobarbital)[2]	1.5-2	TDM
AED mild inducers[3]		TDM
Smoking	1.5	TDM
Omeprazole[4]		TDM

[1]Very potent inducer

[2]Carbamazepine is not recommended due to the risk of causing agranulocytosis.

[3]High-dose topiramate (≥400 mg/d) and oxcarbazepine (≥1200 mg/d) may be mild inducers.

[4]Use other proton pump inhibitors, such as rabeprazole, which may lack inductive properties

3.3.1.2.2. Inhibitors on CLO

3.3.1.2.2.2. Inhibitors on CLO

DDI	Corr F	Action
Fluvoxamine	0.1-0.2	TDM: risky
Fluoxetine/paroxetine	No need	TDM if ADR
TCA		Risky[1]
Caffeine	0.5	Stable use[2]
Ciprofloxacin	0.5	Avoid[3]
Oral contraceptives		TDM
Inflammation[4]	0.5	TDM

[1]Only use if you are familiar with clozapine and TCA TDMs.

[2]Recommend that the patient who uses caffeine consume consistent amounts.

[3]Use other fluroquinolones, including gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin and trovafloxacin.

[4]Any systemic inflammation or any serious infection including pneumonias, upper respiratory infections with fever, or appendicitis.

3.3.1.2.3. VPA on CLO

3.3.1.2.3. VPA on CLO

- Most articles report that VPA has no effects on CLO metabolism, but Dr. de Leon has:
  - seen rare cases of potent induction
  - replicated in studies the finding that VPA may be a mild inducer
  - seen studies in which VPA is a mild inhibitor. Moreover, VPA is associated with ↑ clozapine myocarditis risk due to rapid titration.

3.3.1.3. CLO TDM

3.3.1.3. CLO TDM

- For efficacy: focus only on clozapine
  - Therapeutic reference range: 350-600 ng/mL
  - Narrow therapeutic window: 1.7
- Focus on total concentrations: (clozapine + norclozapine)
  - if worried about ADRs
  - if you are a pharmacologist interested in metabolism and DDIs

3.3.1.3. CLO TDM

- Dr. de Leon uses clozapine C/D ratio to personalize dosing: http://www.ncbi.nlm.nih.gov/pubmed/25200585
  - Normal range is 0.6-1.2 in the USA
    - 0.6 is normal for a ♂ smoker
    - 1.2 is normal for a ♀ non-smoker
  - Based on pharmacokinetic predictions, the normal range is 1.2-2.4 in East Asians and CYP2C19 PMs
    - 1.2 is normal for a ♂ smoker
    - 2.4 is normal for a ♀ non-smoker

See 5 Clozapine Case presentations.

3.3.2. OLA

3.3.2. OLA

3.3.2.1. Metabolism

3.3.2.2. DDIs

3.3.2.3. TDM

3.3.2.1. OLA Metabolism

3.3.2.1. OLA Metabolism

- Main pathway: CYP1A2
- Second pathway: UGT1A4
- Other less important pathways:
  - FMO
  - CYP2D6

3.3.2.2. OLA DDIs

3.3.2.2. OLA DDIs

3.3.2.2.1. Inducers

3.3.2.2.2. Inhibitors

3.3.2.2.3. Others

3.3.2.2.1. Inducers on OLA

3.3.2.2.1. Inducers on OLA

DDI	Corr F	Action
Rifampicin[1]		Avoid
AED potent inducers[2]	2-3	TDM
AED mild inducers[3]		TDM
Smoking	1.5	TDM
Omeprazole[4]		TDM

[1]Very potent inducer

[2]Carbamazepine, phenytoin and phenobarbital

[3]High-dose topiramate (≥400 mg/d) and oxcarbazepine (≥1200 mg/d) may be mild inducers.

[4]Use other proton pump inhibitors, such as rabeprazole, which may lack inductive properties.

3.3.2.2.2. Inhibitors on OLA

3.3.2.2. Inhibitors on OLA

DDI	Corr F	Action
Fluvoxamine	0.3-0.5	TDM
Fluoxetine/paroxetine	No need	TDM if ADR
TCA		Risky[1]
Caffeine	0.5	Stable use[2]
Ciprofloxacin	0.5	Avoid[3]
Inflammation[4]	0.5	TDM

[1]Only use if you are familiar with olanzapine and TCA TDMs.

[2]Recommend that the patient who uses caffeine consume consistent amounts.

[3]Use other fluroquinolones, including gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin and trovafloxacin.

[4]Any systemic inflammation or any serious infection including pneumonias, upper respiratory infections with fever, or appendicitis.

3.3.2.2.3. Other Drugs on OLA

3.3.1.2. VPA on OLA

- Based on a prospective study,

http://www.ncbi.nlm.nih.gov/pubmed/19865002

Dr. de Leon has no doubt that:

- VPA is a mild inducer, and
- VPA can behave as a competitive inhibitor with greater effects on greater VPA concentrations.

In most cases, this should not be clinically relevant, but Dr. de Leon recommends OLA TDM to be safe.

3.3.1.2. Lamotrigine on OLA

- Some limited information:
  - Lamotrigine is a mild inhibitor. In most cases, this should not be clinically relevant.

3.3.2.3. OLA TDM

3.3.2.3. OLA TDM

- Therapeutic reference range: 20-80 ng/mL
- Wide therapeutic window: 4
  This has consequences when compared with CLO:
  - OLA DDIs with inhibitors are much less risky, and
  - OLA correction factors are similar but are less crucial, and
  - OLA TDM is not as essential.

3.4. CYP3A4 SGAPs:

QUE

LUR

CAR

3.4. CYP3A4 SGAPs

3.4.1. Metabolism

3.3.2. DDIs

3.4.3. TDM

3.4.4. Very Slow CAR titration

3.4.1. CYP3A4 SGAPs: Metabolism

3.4.1. CYP3A4 SGAPs: Metabolism

- QUE: mainly CYP3A4
  - Norquetiapine may contribute to QUE antidepressant properties, but currently this is only a hypothesis.
- LUR: mainly CYP3A4
  - ID-14823 appears to be an active metabolite.
- CAR: mainly CYP3A4 (CYP2D6 minor)

  Two active metabolites:
  - didesmethyl-CAR: most important
  - desmethyl-CAR.

3.4.2. CYP3A4 SGAPs: DDIs

Most data is from QUE, but LUR & CAR appear to have a similar profile.

3.4.1. CYP3A4 SGAPs DDIs: CAR

- CAR prescribing information

  http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4b5f7c65-aa2d-452a-b3db-bc85c06ff12f

  On CYP3A4:
  - Inducers: no recommendation; Dr. de Leon prefers to use QUE recommendation for CAR.
  - Inhibitors: 0.5 correction factor; Dr. de Leon prefers to use QUE recommendation for CAR, too.

3.4. CYP3A4 SGAP DDIs

3.4.2.1. Inducers

3.4.2.2. Inhibitors

3.4.2.3. Other Drugs on QUE

3.4.2.1. Inducers on QUE, LUR and CAR

3.4.2.1. Inducers on QUE, LUR & CAR

DDI	Corr F	Action
Rifampicin[1]		Avoid
AED potent inducers[2]		Avoid
AED mild inducers[3]		Avoid[4]
Other mild inducers[5]		Avoid[4]

[1]Very potent inducer

[2]Carbamazepine, phenytoin and phenobarbital. Correction factor is too high (>5)

[3]High-dose topiramate (≥400 mg/d) and oxcarbazepine (≥1200 mg/d) may be mild inducers. Others are clobazam, eslicarbazepine, felbamate and rufinamide.

[4]It is better to avoid but do not combine unless you are familiar with TDM.

[5]St. John's wort or some corticosteroids (e.g., dexamethasone or prednisone)

3.4.2.2. Inhibitors on QUE, LUR and CAR

3.4.2.2. Inhibitors on QUE, LUR & CAR

DDI	Corr F	Action
Ketoconazole		Avoid[1]
Erythromycin (& clarithromycin)		Avoid[1]
Grapefruit juice		Avoid[1]
Diltiazem		Avoid[1]
Fluoxetine/fluvoxamine[2]		Not studied
Inflammation[3]		Be careful

[1]All of these are powerful CYP3A4 inhibitors. It is better to avoid them.

[2]Fluoxetine and fluvoxamine are mild/moderate CYP3A4 inhibitors. Be careful, as they are not well studied.

[3]Any systemic inflammation or any serious infection including pneumonias, upper respiratory infections with fever, or appendicitis.

3.4.2.3. Other Drugs on QUE

3.4..2.3. Other Drugs on QUE

- Limited TDM studies indicate:
  - Lamotrigine may be a mild inducer.
  - VPA may be a mild inhibitor.

  In most cases, this should not be clinically relevant since QUE is a wide therapeutic window drug.

3.4.3. CYP3A4 SGAP TDM

3.4.3. CYP3A4 SGAP TDM

3.4.3.1. QUE TDM

3.4.3.2. LUR TDM

3.4.3.3. CAR TDM

3.4.3.1. QUE TDM

3.4.3.1. QUE TDM

- Therapeutic reference range: 100-500 ng/mL
- Wide therapeutic window: 5
  QUE DDIs with inhibitors are not likely to be clinically relevant.

3.4.3.1. QUE TDM: Warning

- QUE has a very short half-life, with peak concentrations almost 10 times higher than in the trough.
- QUE TDM is complicated to interpret since:
  - variations in administration (2 versus 3 times/day) and
  - time to last drug intake may have relevant effects on trough concentrations.

3.4.3.2. LUR TDM

3.4.3.2. LUR TDM

- Information is very limited. Suggested therapeutic reference range: 40-120 ng/mL

3.4.3.3. CAR TDM

3.4.3.3. CAR TDM

- Limited TDM data is available from the company.
  Total CAR plasma concentrations:
  - 70 % didesmethyl-CAR
  - 20% CAR
  - 10 % desmethyl-CAR

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4b5f7c65-aa2d-452a-b3db-bc85c06ff12f

3.4.3.3. CAR TDM

- A minimum of 5 half-lives are needed to reach steady state. Half-lives are:
  - CAR = 3-5 days
  - desmethylCAR= 3-5 days
  - didesmethylCAR= 2-3 weeks

http://www.ncbi.nlm.nih.gov/pubmed/23966785

3.4.3.3. CAR TDM

Let's assume that in the future you want to do CAR TDM.

How long do you need to wait to draw TDM after a CAR dose change?

3.4.3.3. CAR TDM

Let's assume that in the future you want to do CAR TDM.

How long do you need to wait to draw TDM after a CAR dose change?

Up to 15 weeks (5 x 3 weeks)

3.4.4. Very Slow CAR Titration

3.4.4. Very Slow CAR Titration

Half-life also applies to dosing too. How long do you need to wait to make another dose change before the first dose has its full effects?

3.4.4. Very Slow CAR Titration

Half-life also applies to dosing too.

How long do you need to wait to make another dose change before the first dose has its full effects?

10-15 weeks (5 x 2 weeks – 5 x 3 weeks),

or 2.5 – 4 months.

CAR is different than other SGAPs.

3.4.4. Very Slow CAR Titration (Prescribing Information)

	Dose (mg/day)	
	Starting	Recommended
Schizophrenia	1.5	1.5-6
Bipolar mania	1.5	3-6 .

3.5. CYP2D6/3A4 Profiles:

ARI

BRE

ILO

RIS

3.5. CYP2D6/3A4 APs

- RIS:
  - Dr. de Leon has considerable experience.
- ARI & BRE:
  - good company studies
  - offering clear recommendations
- ILO:
  - only company studies
  - no independent studies

3.5. CYP2D6/3A4 APs

- To simplify,
  the same recommendations for correction factors are used for 4 SGAPs: ARI, BRE, ILO and RIS.

3.5. CYP2D6/CYP3A4 SGAPs

3.5.1. Metabolism

3.5.2. CYP2D6 Genetics

3.5.3. DDIs

3.5.4. TDM

3.5.5. Very Slow Titrations

3.5.1. CYP2D6/3A4 SGAPs: Metabolism

3.5.1. CYP2D6/3A4 SGAPs: Metabolism

- Most articles state that, for ARI, BRE, ILO & RIS:
  - CYP2D6 is major enzyme, and
  - CYP3A4 is secondary.
- Dr. de Leon believes that, in patients taking potent CYP3A4 inducers, CYP3A4 becomes the most important metabolic enzyme.
- CYP2D6 PMs do not have CYP2D6. They use CYP3A4 to metabolize ARI, BRE, ILO & RIS.

3.5.1. CYP2D6/3A4 SGAPs: Metabolism

- Active metabolites:
  - ARI: dehydroaripiprazole
    Its clinical relevance is unclear.
  - BRE: none
  - ILO:
    - P88 (It does not cross the BBB.)
    - P95
  - RIS: 9-hydroxyrisperidone (PAL)
    - According to the marketer they are equally active. http://www.ncbi.nlm.nih.gov/pubmed/20118446
    - Dr. de Leon believes RIS is more active and more toxic in the brain. 9-hydroxyrisperidone may cross the BBB more poorly (>P-gp affinity).

3.5.2. CYP2D6/3A4 SGAPs: CYP2D6 Genetics

(presentation on “Pharmacogenetic Testing in Psychiatry” provides details on CYP2D6 genotyping)

3.5.2. CYP2D6/3A4 SGAPs: CYP2D6 Genetics

- CYP2D6 PMs: □ 7% of Caucasians
  □ 1-3% of other races

  Dr. de Leon recommends a correction factor of 0.5 (half of dosage) for ARI, ILO & RIS.

  In his study CYP2D6 PM status explained 16% of RIS ADRs and 9% of RIS discontinuations http://www.ncbi.nlm.nih.gov/pubmed/15669884

- Long-acting ARI prescribing information: CYP2D6 PMs should receive 75% of the average dose.

3.5.2. CYP2D6/3A4 APs: Genetics

- CYP2D6 UMs:
  - 1% of Caucasians (7% in southern Europe)
  - 1.5% of Caucasians in the USA
  - 2% of African-Americans in the USA
  - >25% in North Africa and the Middle East

The use of higher doses has not been studied. Using TDM of CYP2D6 UMs taking ARI, BRE, ILO or RIS may be a good idea.

3.5.3. CYP2D6/3A4 SGAPs: DDIs

3.5.3 CYP2D6/3A4 SGAP DDIs

3.5.3.1. Inducers

3.5.3.2. Inhibitors

3.5.3.3. Others

3.5.3.1. Inducers on ARI, BRE, ILO and RIS

3.5.3.1. Inducers on ARI, BRE, ILO & RIS

DDI	Corr F	Action
Rifampicin[1]		Avoid
AED potent inducers[2]	2	TDM
AED mild inducers[3]		TDM
Other mild inducers[4]		TDM

[1]Very potent inducer

[2]Carbamazepine, phenytoin and phenobarbital

[3]High-dose topiramate (≥400 mg/d) and oxcarbazepine (≥1200 mg/d) may be mild inducers. Others are clobazam, eslicarbazepine, felbamate and rufinamide.

[4]St. John's wort or some corticosteroids (e.g., dexamethasone or prednisone)

3.5.3.2. Inhibitors on ARI, BRE, ILO & RIS

3.5.3.2. Inhibitors on ARI, BRE, ILO & RIS

DDI	Corr F	Action
Powerful CYP3A inhibitors[1]		Avoid
CYP2D6/3A4 inhibition[2]	0.25	TDM
Paroxetine[3]	0.5	TDM
Bupropion/duloxetine/TCAs[4]		TDM
Fluvoxamine/high-dose sertraline[5]		TDM
Inflammation[6]		Be careful

[1]Ketoconazole, erythromycin, clarithromycin, grapefruit juice and diltiazem are powerful CYP3A4 inhibitors.

[2]Both CYPs are inhibited: 1) fluoxetine is a powerful CYP2D6 inhibitor and a mild/moderate CYP3A4 inhibitor; or
2) CYP2D6 PM plus any kind of CYP3A4 inhibitor

[2]Paroxetine is a powerful CYP2D6 inhibitor.

[3]Moderate CYP2D6 inhibitors that are not well studied

[4]Mild CYP2D6 inhibitors that are not well studied

[5]Any systemic inflammation or any serious infection including pneumonias, upper respiratory infections with fever, or appendicitis.

3.5.3.3. Other DDIs on ARI

3.5.3.3. Other DDIs on ARI

- A prospective study by the company indicated:
  - VPA may be a mild inhibitor.
    Dose correction factor: 0.75

3.5.4. CYP2D6/3A4 SGAPs: TDM

3.5.4 CYP2D6/3A4 SGAP TDM

3.5.4.1. ARI TDM

3.5.4.2. BRE TDM

3.5.4.3. ILO TDM

3.5.4.4. RIS TDM

3.5.4.1. ARI TDM

3.5.4.1. ARI TDM

- Therapeutic reference range: 150-500 ng/mL
- Wide therapeutic window: 3.3
- The clinical relevance of dehydroaripiprazole is currently unclear.
- VERY IMPORTANT: ARI has a very long half-life: 60-80 hours, which is around 3 days (80 hours=3.3 days).
  Wait at least 2 weeks after ARI dose change to draw TDM. It may be safer to wait 3 weeks.

3.5.4.2. BRE TDM

3.5.4.2. BRE TDM

- TDM data from the company is limited.
  Total BRE plasma concentrations:
  - 48% DM-3411: inactive

    http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2d301358-6291-4ec1-bd87-37b4ad9bd850

- Half-lives:
  - BRE: 91 hours (3.8 days)
  - DM-3411: 86 hours

3.5.4.3. ILO TDM

3.5.4.3. ILO TDM

- Limited data. Suggested therapeutic reference range: 5-10 ng/mL

3.5.4.4. RIS TDM

3.5.4.4. RIS TDM

- Therapeutic reference range:
  20-60 ng/mL
  It includes 9-hydroxyrisperidone.
- Narrow therapeutic window: 3

3.5.4.4. RIS TDM

- Dr. de Leon uses RIS TDM to personalize dosing.

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

  - RIS/9-hydroxyrisperidone ratio:
    a CYP2D6 activity index
  - Total C/D ratio is an index of RIS clearance
    (the ability to eliminate RIS from body).
    It is calculated by adding concentrations
    of RIS + 9-hydroxyrisperidone and dividing
    by RIS daily dose.

See the two risperidone case presentations.

3.5.4.4 RIS TDM

3.5.4.4.1. RIS/9-hydroxyrisperidone Ratio

3.5.4.4.2. Total C/D Ratio

3.5.4.4.1. RIS/9-hydroxyrisperidone Ratio

3.5.4.4. RIS TDM

- RIS/9-hydroxyrisperidone ratio
  The lowest, the highest CYP2D6 activity
  - <1: Normal
  - >1
    - CYP2D6 PM, or
    - Taking a CYP2D6 inhibitor, or
    - Not drawn at steady state.
      You need to collect in the early morning before taking medications and 1 week after from RIS dose changes (with no changes in inducer or inhibitor doses).

3.5.4.4.2. Total C/D Ratio

3.5.4.4.2. RIS TDM: Total C/D Ratio

Labs	USA[1]	Some in Europe[2]
Normal	7	10
range	>3.5 to <14	>5 to <20
Reduced	<3.5	<5
CYP3A4 inducers		
Not taking RIS		
Increased	>14	>20
CYP inhibitors		
CYP26 PM		
Renal insufficiency		

[1]In Dr. de Leon's experience, USA clinical and research labs had normal C/D ratio=7. Not sure it is true for all USA labs.

[2]In Dr. de Leon's experience, Italian and Spanish research labs had normal C/D ratio=9-10. Not sure it is true for all European labs. Differences are explained by calibration differences.

3.5.5. Very Slow Titration

3.5.5. Very Slow Titrations

3.5.5.1. ARI Slow Titration

3.5.5.2. BRE Slow Titration

3.5.5.3. All Partial D_2 Agonists: Slow Titration

3.5.5.1. ARI Slow Titration

3.5.5.1. ARI Slow Titration

How long do you need to wait to make another dose change before the first ARI dose has its full effects?

3.5.5.1. ARI Slow Titration

How long do you need to wait to make another dose change before the first ARI dose has its full effects?

Up to 16 days (5 x 3.3 days),
or >2 weeks.
ARI is different than other SGAPs.

3.5.5.2. BRE Slow Titration

3.5.5.2. BRE Slow Titration

How long do you need to wait to make another dose change before the first BRE dose has its full effects?

3.5.5.2. BRE Slow Titration

How long do you need to wait to make another dose change before the first BRE dose has its full effects?

Up to 19 days (5 x 3.8 days),
or almost 3 weeks.
BRE is different than other SGAPs.

3.5.5.2. BRE Slow Titration (Prescribing Information)

	Dose (mg/day)		
	Starting	Recommended	Maximum
S	1	2-4	4
MDD	0.5-1	2	3

S: schizophrenia
MDD: major depressive disorder
Prescribing information recommends that dosage increases should occur at weekly intervals.

3.5.5.3. Partial D_2 Agonists: Slow Titration

3.5.5.3. Partial D_2 Agonists: Slow Titration

- SGA partial D_2 agonists: long half-lives. After you ↑ the dose, it will take a long time to see full effects and reach steady state.

	Days	Week	Month
ARI	up to 16	>2	<1
BRE	up to 19	>2	<1
CAR	70-105	10-15	2.5-4

If you ↑ doses earlier, you may end up with doses higher than needed. These drugs do not appear to be good drugs to manage acute situations. On the other hand, CAR efficacy and ADRs will last for months after discontinuation.

3.6. ZIP

3.6. ZIP

3.6.1. ZIP Metabolism

3.6.2. ZIP DDIs

3.6.3. ZIP TDM

3.6.1. ZIP Metabolism

3.6.1. ZIP Metabolism

- Main enzyme: aldehyde oxidase, which is a cytoplasmic enzyme. It is an unusual way to metabolize drugs.
- Less important: CYP3A4

3.6.2. ZIP DDIs

3.6.2. ZIP DDIs

- CYP3A inducers:
  - Mild effects compared to QUE.
  - Carbamazepine: 1.33 x ZIP dose.
    (calculated using prescribing information)
- CYP3A inhibitors:
  - Mild effects compared to QUE.
  - Ketoconazole: 0.70 x ZIP dose.
    (calculated using prescribing information)

3.6.2. ZIP DDIs

- US ZIP daily dose range: 40-160.
- ZIP is the least sensitive of the USA SGAs to potent inducers. If you add a potent inducer, you may not need to ↑ ZIP dose. If you want to be completely sure for correcting inducer effects, consider using the high range of recommended ZIP daily dose.
- You can ignore powerful CYP3A4 inhibitors (consider using the low range of recommended ZIP daily dose).

3.6.3. ZIP TDM

3.6.3. ZIP TDM

- Therapeutic reference range: 50-200 ng/mL
- Wide therapeutic window: 4
  ZIP DDIs with inhibitors may not be likely to be clinically relevant.

3.6.3. ZIP TDM : Warning

- ZIP has a very short half-life, with peak concentrations that are much higher than trough concentrations.

- ZIP TDM is complicated to interpret since:
  - time to last drug intake may have relevant effects on trough concentrations.

3.7. ASE

3.7. ASE

3.7.1. ASE Metabolism
3.7.2. ASE DDIs
3.7.3. ASE TDM

3.7.1. ASE Metabolism

3.7.1. ASE Metabolism

- According to *in vitro* studies quoted in the prescribing information, ASE is a substrate for:
  - UGT1A4
  - CYP1A2
  - CYP3A4 and CYP2D6, to a lesser extent
- ASE is a weak inhibitor of CYP2D6.
- ASE is not an inducer of
  - CYP1A2 or
  - CYP3A4

3.7.2. ASE DDIs

3.7.2. ASE DDIs

- The US Prescribing Information for ASE recommends these doses:
  - 5-10 mg twice a day, or
  - 10-20 mg/day.

http://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=ASENAPINE+MALEATE

3.7.2. ASE DDIs

- The US Prescribing Information for ASE describes DDI studies with:
  - fluvoxamine
  - carbamazepine
  - valproate
  - smoking

They were not conducted with doses and durations relevant for clinical practice.

http://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=ASENAPINE+MALEATE

3.7.2. ASE DDIs

- In prior versions of this presentation, Dr. de Leon described these DDI studies conducted by the company. His residents appeared somewhat confused and unclear about the practical implications.
- In this version of this presentation, Dr. de Leon is providing "rough" recommendations based on limited experience and literature.

3.7.2. ASE DDIs

3.7.2.1. Inducers on ASE

3.7.2.2. Inhibitors on ASE

3.7.2.3. ASE: a CYP2D6 Inhibitor

3.7.2.1. Inducers on ASE

3.7.2.1. Inducers on ASE: Provisional Suggestions

DDI	Action
Rifampicin[1]	Avoid
AED potent inducers[2]	Avoid
AED mild inducers[3]	Consider 20 mg/day
Smoking	Consider 20 mg/day
Omeprazole[4]	Avoid

[1]Very potent inducer

[2]Carbamazepine, phenytoin and phenobarbital

[3]High-dose topiramate (≥400 mg/d) and oxcarbazepine (≥1200 mg/d) may be mild inducers. Others are clobazam, eslicarbazepine, felbamate and rufinamide.

[4]Use other proton pump inhibitors, such as rabeprazole, which may lack inductive properties.

3.7.2.2. Inhibitors on ASE

3.7.2.2. Inhibitors on ASE: Provisional Suggestions

DDI	Actions	Corr Factor
Fluvoxamine		0.5-0.75
Caffeine	Stable use[1]	
Ciprofloxacin	Avoid[2]	
VPA	Be careful: consider ↓ dose	
Inflammation[3]	Consider ↓ dose	

[1]Recommend that the patient who uses caffeine consume consistent amounts.

[2]Use other fluroquinolones, including gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin and trovafloxacin.

[3]Any systemic inflammation or any serious infection including pneumonias, upper respiratory infections with fever, or appendicitis.

3.7.2.3. ASE: a CYP2D6 Inhibitor

3.7.2.3. ASE: a CYP2D6 Inhibitor

- Do not use with antidepressants dependent on CYP2D6:
  - TCAs
  - fluoxetine or paroxetine
  - venlafaxine
  - vortioxetine

If you decide to co-prescribe, consider:

  - using TDM for antidepressants, and/or
  - lowering the antidepressant dose.

3.7.2.3. ASE: a CYP2D6 Inhibitor

- There is no reason to co-prescribe ASE with an SGA dependent on CYP2D6:
  - ARI, BRE, ILO or RIS

If you decide to co-prescribe, consider:

- using TDM for ARI, ILO or RIS
  and/or
- ↓ dose of ARI, BRE, ILO or RIS

3.7.3. ASE TDM

3.7.3. ASE TDM

- Information is very limited. Suggested therapeutic reference range: 2-5 ng/mL

3.8. SGA Renally Excreted

3.8. SGA Renally Excreted

3.8.1. AMI

3.8.2. PAL

3.8.1. AMI

3.8.1. AMI

3.8.1.1. Metabolism

3.8.1.2. DDIs

3.8.1.3. TDM

3.8.1.1. AMI Metabolism

3. 8.1.1. AMI Metabolism

- Our understanding is very limited.
- A 2006 review http://www.ncbi.nlm.nih.gov/pubmed/15521794 states:
  - goes through minimal metabolism to 2 inactive metabolites
  - 22-25% of the oral dose is eliminated unchanged in urine.
- A 2001 review adds: http://www.ncbi.nlm.nih.gov/pubmed/11735643 2 main metabolites are produced by:
  - oxidation
  - de-ethylation

3.8.1.2. AMI DDIs

3.8.1.2. AMI DDI

- Australian prescribing information:
  - "*In vitro* studies using human liver microsomes and cryopreserved human hepatocytes did not show evidence of significant amisulpride metabolism."
  - "Based on these results, it is unlikely that drug interactions involving amisulpride would occur due to inhibition or induction of cytochrome P450–mediated metabolism."

http://www.sanofi.com.au/products/aus_pi_solian.pdf

3.8.1.2. AMI DDI

- In summary:
  - It is unclear how AMI is metabolized.
  - There is no data to support the concept that CYP inducers and inhibitors influence AMI metabolism.
  - There are no AMI clinical DDI studies in which CYP inducers or inhibitors were added.
  - Until more data is available, it appears reasonable to classify AMI as a SGA preferentially eliminated by the kidney.

3.8.1.3. AMI TDM

3.8.1.3. AMI TDM

- Therapeutic reference range: 100-320 ng/mL
- Wide therapeutic window: 3.2

3.8.2. PAL

3.8.2. PAL

3.8.2.1. Metabolism

3.8.2.2. DDIs

3.8.2.3. TDM

3.8.2.1. PAL Metabolism

3.8.2.1. PAL Metabolism

3.8.2.1.1. Prescribing Information

3.8.2.1.2. Company Studies

3.8.2.1.3. Dr. de Leon's Prediction

3.8.2.1.1. PAL Metabolism: Prescribing Information

http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7b8e5b26-b9e4-4704-921b-3c3c0d159916

3. 8.2.1.1. PAL Metabolism: Prescribing Information

- Not a substrate of CYP1A2,
  CYP2A6,
  CYP2C9, and
  CYP2C19,

  so that an interaction with inhibitors or inducers of these isozymes is unlikely.
- CYP2D6 and CYP3A4
  - *In vitro* studies: they may be **minimally** involved in paliperidone metabolism
  - *In vivo* studies do not show decreased elimination by them and they contribute to only a **small fraction** of total body clearance.

3.8.2.1.2. PAL Metabolism: Company Studies

3.8.1.2. PAL Metabolism: Company Study

http://www.ncbi.nlm.nih.gov/pubmed/20540690

- Using isotopes:

PERCENTAGE OF ELIMINATION

Renal		Fecal	Unrecovered
Unchanged	Changed		
60	20	11	9

- According to this study, at least 20% of PAL is metabolized in the average patient.

Is 20% **"a small fraction of total body clearance"**?

3.8.1.2. PAL Metabolism: Company Study

- Using a carbamazepine study by the company, http://onlinelibrary.wiley.com/doi/10.1002/cpdd.122/abstract
  Dr. de Leon calculated a correction factor of 1.37.
  The company appeared to design the study to get negative results:
  - using a low dose of carbamazepine (400 mg/day), and
  - not reaching maximum induction and not reaching steady state (3 weeks).

3.8.2.1.3. PAL Metabolism: Dr. de Leon's Prediction

3. 8.1.3. PAL Metabolism: Dr. de Leon's Prediction

- In a 2010 article http://www.ncbi.nlm.nih.gov/pubmed/20118446 Dr. de Leon hypothesized, "Moreover, even if CYP3A plays a small role in 9-OHR metabolism under normal conditions, CYP3A can play a much more important role in induction."
- A 2013 study http://www.ncbi.nlm.nih.gov/pubmed/24052066 verified that carbamazepine dramatically ↑ PAL clearance (correction factor=3). This is compatible with CYP3A4 becoming a major metabolic enzyme for PAL metabolism during induction.

3.8.2.2. PAL DDIs

3.8.2.2. PAL DDIs

3.8.2.2.1. Inducers on PAL

3.8.2.2.2. CYP Inhibitors on PAL

3.8.2.2.3. VPA on PAL

3.8.2.2.1. Inducers on PAL

3.8.2.2.1. Inducers on PAL

DDI	Corr F	Action
Rifampicin[1]		TDM[2]
AED potent inducers[3]	3	TDM
AED mild inducers[4]		TDM[2]
Other mild inducers[5]		TDM[2]

[1]Very potent inducer

[2]Do not co-prescribe unless you have access to TDM.

[3]Carbamazepine, phenytoin and phenobarbital.

[4]High-dose topiramate (≥400 mg/d) and oxcarbazepine (≥1200 mg/d) may be mild inducers. Others are clobazam, eslicarbazepine, felbamate and rufinamide.

[5]St. John's wort or some corticosteroids (e.g., dexamethasone or prednisone)

3.8.2.2.2. CYP Inhibitors on PAL

3.8.2.2.2. CYP Inhibitors on PAL

- Using a paroxetine study by the company, http://www.ncbi.nlm.nih.gov/pubmed/19585395

  Dr. de Leon calculated a correction factor of 0.84.

  The company appeared to design the study to get negative results:
  - using single doses of PAL (3 mg), and
  - using low doses of an inhibitor (20 mg).

3.8.2.2.2. CYP Inhibitors on PAL

- There is no information indicating that CYP2D6 or CYP3A4 inhibitors may decrease PAL metabolism to the point of requiring modifying PAL doses.

- DDI studies by independent investigators are needed.

3.8.2.2.3. VPA on PAL

3.8.2.2.3. VPA on PAL

- Using a VPA study by the company, http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7b8e5b26-b9e4-4704-921b-3c3c0d159916

  Dr. de Leon calculated a correction factor of 0.50.

  The company appeared to design the study to get negative results:

  - using a single dose of PAL (12 mg), and
  - using a low VPA dose (1000 mg).

- The inhibitory mechanism is not well understood: P-gp inhibition is suggested.

3.8.2.3. PAL TDM

3.8.2.3. PAL TDM

- Therapeutic reference range: 20-60 ng/mL
- Narrow therapeutic window: 3

4. Hepatic Impairment

4. Hepatic Impairment

4.1. Severity
4.2. Dose Correction
4.3. Use Not Recommended

4.1. Hepatic Impairment: Severity

4.1. Hepatic Impairment: Severity

http://www.ncbi.nlm.nih.gov/pubmed/18293281

- Child-Pugh scale for
  - cirrhosis prognosis, and
  - drug clearance studies.
- Modified version:
  - serum bilirubin,
  - serum albumin,
  - ascites,
  - encephalopathy, and
  - prothrombin time.
- Each measure is scored 1-3, with 3 indicating the most severe impairment
- Grades:
  - A (5-6 points),
  - B (7 to 9 points), or
  - C (10 to 15 points).

4.2. Hepatic Impairment: Dose Correction

4.2. Hepatic Impairment: Dose Correction

- According to the Prescribing Information there is **no need for dose correction** in patients with hepatic impairment, for patients on:

  - AMI: for hepatic insufficiency
  - ARI: for mild, moderate and severe impairment
  - ASE: for mild and moderate impairment
    is not recommended for severe impairment
  - CAR: for mild and moderate impairment
    is not recommended for severe impairment
  - OLA: for mild and moderate impairment
  - PAL: for mild and moderate impairment
  - ZIP: for mild, moderate and severe impairment

4.2. Hepatic Impairment: Dose Correction

- BRE: moderate to severe impairment:
  Maximum recommended dose:
  - 2 mg/d for major depressive disorder
  - 3 mg/d for schizophrenia
- LUR: dose ≤ 40 mg/d in moderate to severe impairment.
- QUE:
  - Initial dose: 25 mg daily.
  - Titrate slowly.
  - Once dose ≥ 200 mg/d, one can switch to the equivalent dose of extended release.
- RIS:
  - initial dose: 0.5 mg twice a day
  - dose increases: ≤ 0.5 mg twice a day
  - for doses > 3 mg/: wait ≥1 week for further increases.

4.3. Hepatic Impairment: Use Not Recommended

4.3. Hepatic Impairment: Use Not Recommended

- CLO & ILO:
  - Studies were not completed.
  - Their use is not recommended.

5. Pregnancy

5. Pregnancy

- There are no SGAP pharmacokinetic studies occurring during pregnancy.
- Pregnancy influences some metabolic enzymes: http://www.ncbi.nlm.nih.gov/pubmed/17696806
  - ↓ activity: CYP1A2 and CYP2C19
  - ↑ activity: CYP2B6, CYP2C9, CYP2D6, CYP3A4 and UGT1A4.

5. Pregnancy

- Pregnancy should be expected to
  - ↓ metabolism (and ↑ plasma concentrations):
    - CLO & OLA
  - ↑ metabolism (and ↓ plasma concentrations):
    - CYP3A4 SGAPs: QUE, LUR & CAR
    - CYP2D6/3A4 SGAPs: ARI, ILO, RIS & BRE

6. Effects on Other Drug Metabolism

6. Effects of SGAPs on the Metabolism of Other Drugs

- No SGAP is an inducer.
- Clinically relevant inhibition:
  - ASE is a CYP2D6 inhibitor
  - Other SGAPs are not CYP inhibitors
- In special circumstances, any SGAP can behave as an inhibitor:
  - It is called competitive inhibition.
  - It may occur in very peculiar patient-related circumstances with polytherapy and compromised drug metabolism. Adding an SGA may be the straw that breaks the camel's back.

7. Do Not Forget

7. Do Not Forget

- The effects of other drugs on SGAPs:
  - CYP1A2 (CLO & OLA)
    - Inducers: smoking & AEDs
    - Inhibitors: fluvoxamine
  - CYP3A4 (QUE, LUR & CAR)
    - Very sensitive to inducers: AEDs
    - CYP3A4 Inhibitors
  - CYP2D6/3A4 (ARI, BRE, ILO, & RIS)
    - CYP2D6 PM: 0.5 x dose
    - Inducers AEDs: 2 x dose
    - CYP2D6 inhibitors: some antidepressants
  - ZIP & AMI: little effects of DDIs
  - PAL: AED inducers require 3 x dose
  - UGT1A4 & CYP1A2 (ASE): not well studied

7. Do Not Forget

- The effects of SGAPs on other drugs:
  - No SGAP is an inducer.
  - ASE is an CYP2D6 inhibitor.
  - On rare occasions, SGAPs can behave as competitive inhibitors.

References for SGAP Pharmacokinetics

1) 2005 article http://www.ncbi.nlm.nih.gov/pubmed/15883149 has DDI information on ARI, CLO, OLA, QUE, RIS & ZIP.
2) 2009 article http://www.ncbi.nlm.nih.gov/pubmed/19865002 has information on valproate DDI with CLO & OLA.
3) 2010 article http://www.ncbi.nlm.nih.gov/pubmed/20118446 has information on PAL and RIS.
4) 2012 article http://www.ncbi.nlm.nih.gov/pubmed/22332980 focuses on DDIs between SGAPs and AEDs.
5) 2014 article http://www.ncbi.nlm.nih.gov/pubmed/24494611 focuses on DDIs between SGAPs and antidepressants.
6) 2015 articles http://www.ncbi.nlm.nih.gov/pubmed/257458190 on the effect of inducer psychiatric drugs, including SGAPs.

References for SGAPs

1) 2006 article http://www.ncbi.nlm.nih.gov/pubmed/16040229 has a guideline for CLO.
2) 2008 article http://www.ncbi.nlm.nih.gov/pubmed/18448784 has information on RIS pharmacodynamics/kinetics (part I).
3) 2008 article http://www.ncbi.nlm.nih.gov/pubmed/18621942 has information on RIS pharmacodynamics/kinetics (part II).
4) 2009 article http://www.ncbi.nlm.nih.gov/pubmed/15883149 has guidelines for ARI, OLA, PAL, QUE, RIS & ZIP.

Questions

-Please review the 10 questions in the Word document titled “Questions on the Presentation: Pharmacokinetics of Oral Second-Generation Antipsychotics”.

-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 do not answer all the questions correctly, please review the Power Point presentation once again to reinforce the pharmacological concepts.

Thank you

Answers

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