Pharmacokinetics of Antidepressants

Jose de Leon, MD

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Learning Objectives

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

1) Appreciate the relevance of absorption, renal and hepatic impairment for some antidepressants.
3) Summarize major metabolic pathways of:
   (a) tricyclic antidepressants,
   (b) selective serotonin reuptake inhibitors,
   (c) selective noradrenergic reuptake inhibitors, and
   (d) others.
4) Be aware that antidepressants can be involved in clinically-relevant drug-drug interactions since:
   (a) some antidepressants are inhibitors, and
   (b) inducers, inhibitors and pregnancy can influence their metabolism.

Warning

This is an extraordinarily long presentation:

1) You may need to read it more than once until you have become familiar with key aspects. More importantly, you need to practice every day and review the pharmacokinetics of drugs when any of your patients are taking antidepressants in the context of polypharmacy.
3) The most important concept to remember is that some antidepressants are clinically significant inhibitors of the metabolism of some other drugs. See the "Do Not Forget" Section. See important facts in red.
4) The section on CYP genotyping is very complex if you are not familiar with these concepts. If you want to understand it better, please review the lecture titled, "Pharmacogenetic Testing in Psychiatry".

Abbreviations

- ADR: adverse drug reaction
- AED: antiepileptic drug
- C: concentration
- C/D ratio: concentration-to-dose ratio
- CYP: cytochrome P450
- CYP2C: CYP2C8, CYP2C9 & CYP2C19
- D: dose
- DDI: drug-drug interaction
- GFR: glomerular filtration rate
- nor=desmethyl when describing metabolites. norclomipramine=desmethylclomipramine
- TDM: therapeutic drug monitoring
- UGT: uridine diphosphate glucuronosyltransferase

Abbreviations of Included Antidepressants

This presentation focuses on:

- TCAs: tricyclic antidepressants
  Only 5 TCAs are described.
- SNRIs: serotonin-norepinephrine inhibitors
- SSRIs: selective serotonin reuptake inhibitors
- The rest are included in “Others.”

Antidepressants That Are Not Included

- MAOIs: monoamine oxidase inhibitors
- nefazadone

Described Antidepressants Not Marketed in the US

- agomelatine
- milnacipran
- reboxetine

Signs Used for Dosing and to Correct for DDIs

- Arrows:
  - ↑: increase D.
  - ↓: decrease D.
- Correction factor; use this number to multiply by the average daily D to correct for DDIs.

Inducers > 1 (e.g., x 2 D, multiply D by 2)
Inhibitors < 1 (e.g., 0.5 D, multiply D by 0.5)

- Potent AED inducers are:
  - carbamazepine
  - phenytoin
  - phenobarbital

Examples of a Correction Factor

- The risperidone correction factor for
  - carbamazepine = 2 x D
  - paroxetine = 0.5 x D
- If you use 4 mg/day of risperidone in a typical patient,
  - In a carbamazepine patient, you should use 8 mg/day risperidone (2 x 4 mg/day = 8 mg/day).
  - In a paroxetine patient, you should use 2 mg/day risperidone (0.5 x 4 mg/day = 2 mg/day).

Lecture Content

0. CYP Terminology

1. Absorption

2. Renal Elimination

3. Metabolism

4. Hepatic Impairment

5. Pregnancy
6. Do Not Forget

Lecture Content

0. CYP Terminology (only for the brave of heart)

0. CYP Terminology

0.1. Definitions
0.2. CYP2D6
0.3. CYP2C19

0.1. CYP Definitions

0.1 CYP Definitions

0.1.1. Phenotype
0.1.2. Allele *1
0.1.3. Two Alleles for a Phenotype

0.1.1. Phenotype

0.1.1. 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

0.1.1. Phenotype

- Phenotype abbreviations:
  - UM: ultrarapid metabolizer (↑ activity),
  - EM: extensive metabolizer (normal activity),
  - IM: intermediate metabolizer (low activity),
  - PM: poor metabolizer (no activity).

0.1.1. Phenotype

- Unfortunately, this terminology 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.
- 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.

0.1.2. Allele *1

0.1.2. 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 that laboratory tests is found. Think carefully about this before moving to the next slide.

0.1.2. Allele *1

- Imagine two hypothetical labs:
  - One lab only tests for *2 and *3. This lab will find many *1s.
  - One 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 *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 matter of fact, they are not.

0.1.2. 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.

0.1.3. Two Alleles for a Phenotype

0.1.3. 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)

0.2. CYP2D6 Terminology

0.2. CYP2D6 Terminology

0.2.1. CYP2D6 Phenotypes
0.2.2. CYP2D6 Alleles
0.2.3. CYP2D6 Phenotypes and Alleles
0.2.4. CYP2D6 Phenotypes and Race
0.2.5. CYP2D6 Genotyping Practical Rules

0.2.1. CYP2D6 Terminology

0.2.1. CYP2D6 Terminology

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

Phenotype	N active copies
Ultrarapid metabolizer (UM)	≥3
Extensive metabolizer (EM)	1 to <3
Intermediate metabolizer (IM)	0 to <1
Poor metabolizer (PM)	0

Used by Some Labs

Phenotype	N active copies
Ultrarapid metabolizer (UM)	≥3
Extensive metabolizer (EM)	>1 to <3
Intermediate metabolizer (IM)	≤1
Poor metabolizer (PM)	0

0.2.2. CYP2D6 Alleles

0.2.2. The Most Important 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.

0.2.3. CYP2D6 Phenotypes and Alleles

0.2.3. CYP2D6 Phenotypes and Alleles

Alleles	Phenotype
*1xn/*1 or *2xn/*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)
any combination *3,*4,*5 or *6: *3/*3, *3/4, *3/5, *3/6, *4/*4, *4/5, *4/6, *5/*5, *5/*6 & *6/*6	PM

0.2.4. CYP2D6 Phenotypes and Race

0.2.4. CYP2D6: Phenotype and Race

- CYP2D6 PMs (no CYP2D6):
  - Caucasians: approximately 7%
  - Other races: 1-3 (<5%)
- CYP2D6 IMs (with low activity):
  - East Asians: 2-3%
    - *10/*10: activity of 0.05 (vs. 2 in *1/*1)
  - Africans (*17): 2-3%
    - *17/*17: low CYP2D6 activity for many drugs
- CYP2D6 UMs (≥ 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%

0.2.5. Practical Rules for CYP2D6 Genotyping

0.2.5. 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.

0.3. CYP2C19 Terminology

0.3. CYP2C19 Terminology

0.3.1. CYP2C19 Phenotypes
0.3.2. CYP2C19 Alleles
0.3.3. CYP2C19 Phenotypes and Alleles
0.3.4. CYP2C19 Phenotypes and Race
0.3.5. Practical Rules for CYP2C19 Genotyping

0.3.1. CYP2C19 Phenotypes

0.3.1. CYP2C19 Phenotypes

Terminology Preferred by Dr. de Leon

Phenotype	N active copies
Ultrarapid metabolizer (UM)	↑ expression
Extensive metabolizer (EM)	1 or 2
Poor metabolizer (PM)	0[c]

Terminology Used by Some Labs

Phenotype	N active copies
Ultrarapid metabolizer (UM)	↑ expression
Extensive metabolizer (EM)	2
Intermediate metabolizer (IM)	1
Poor metabolizer (PM)	0[c]

0.3.2. CYP2C19 Alleles

0.3.2. 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.

0.3.3. CYP2C19 Phenotypes and Alleles

0.3.3. CYP2C19 Phenotypes and Alleles

Alleles	Activity	Phenotype
*17/*17	↑ ↑ expression	UM
*1/*17	↑ expression	UM some labs
*1/*1	normal	EM some labs
*1/*2 or *1/*3	lower	EM some labs IM some labs
*2 /*2 or*3/*3 or *2/*2	no	PM

0.3.4. CYP2C19 Phenotypes and Race

0.3.4. CYP2C19: Phenotype and Race

- CYP2C19 PMs:
  - East Asians: 25 %
  - Other races: <5%

- CYP2C19 UMs:

  *17: associated with ↑ expression

  Clinical relevance not well established.
  - Frequency 1-5% *17/*17
  - Higher frequency with only one *17

0.3.5. Practical Rules for CYP2C19 Genotyping

0.3.5. 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: probably reliable but the literature does not agree on clinical relevance.

Antidepressant Pharmacokinetics

1. Absorption
2. Renal Elimination
3. Metabolism
4. Hepatic Impairment
5. Pregnancy

1. Antidepressant Absorption

1. Absorption

1.1. Absorption: Food

1.1. Absorption: Food

- An antidepressant that NEEDs to be administered with food:
  - vilazodone

2. Antidepressants: Renal Elimination

2. Antidepressants: Renal Elimination

2.1. No Good Reviews on Renal Elimination

2.2. Chronic Kidney Disease

2.3. Recent Drugs

2.1. Renal Elimination: Antidepressant

2.1. Antidepressants: Renal Elimination

- No good comparative reviews.

- Some antidepressants are mainly eliminated by the kidney:
  - desvenlafaxine,
  - levomilnacipran, and
  - milnacipran.

  These 3 antidepressant are not good antidepressants for patients with renal impairment.

2.2. Chronic Kidney Disease

2.2. Chronic Kidney Disease

2012 recommendations by European Renal Best Practice:

Based on a summary of 28 studies for 24 antidepressants:

- ↓ dose for:
  - TCAs:
    - clomipramine
  - SNRIs:
    - desvenlafaxine:
    - venlafaxine:
- Others:
    - bupropion:
    - milnacipran
    - reboxetine
    - selegiline (MAOI)
    - tianeptine (not marketed in the US)

http://www.ncbi.nlm.nih.gov/pubmed/22859791

2.2. Chronic Kidney Disease

Bautovich et al., 2014 (comprehensive literature review):
http://www.ncbi.nlm.nih.gov/pubmed/24658294

- ↑ risk for ADRs on all antidepressants

- Recommendations on drugs to avoid:
  - duloxetine: GFR< 30 ml/min: contraindicated
    GFR> 30 ml/min: start a low D
    ↑ D slowly

- Recommendations on drugs to use (next slide)

2.2. Chronic Kidney Disease

- Recommended antidepressants: http://www.ncbi.nlm.nih.gov/pubmed/24658294
  - Evidence available suggests they are usually safe but may require additional monitoring and dose ↓:
    - citalopram: use with caution when GFR < 10ml/min
    - fluoxetine: GFR < 20ml/min: ↓ dose or alternate days
  - Evidence available can be used but greater caution is needed):
    - amitriptyline: start low and increase slowly
      TDM may be useful
    - mirtazapine: GFR = 10-50 ml/min: dose as usual
      GFR < 10 ml/min: start low dose and increase slowly
    - paroxetine: GFR < 30 ml/min: start 10-20 mg/day and increase slowly
    - sertraline: no dose adjustment required
    - venlafaxine: GFR < 30 ml/min: avoid slow-release formulation

2.3. Renal Impairment: Recent Drugs

2.3. Renal Impairment: Recent Drugs

- Vilazadone: no need for D correction even in end-stage renal disease

  http://www.ncbi.nlm.nih.gov/pubmed/25474324

- Vortioxetine: no need for D correction in mild-to-moderate renal impairment

  http://www.ncbi.nlm.nih.gov/pubmed/25650679

3. Antidepressant Metabolism

3. Metabolism

3.1. TCAs

3.2. SSRIs

3.3. SNRIs

3.4. Others

3.1. TCAs

3.1. TCAs

- 3.1.1. Metabolic Enzymes
- 3.1.2. CYP Genotyping
- 3.1.3. TDM
- 3.1.4. DDIs

3.1.1. TCAs: Metabolic Enzymes

3.1.1. TCAs: Metabolic Enzymes

- Chemical classification:
  - Tertiary amines:

    Compounds (and active metabolite):
    - amitriptyline (nortriptyline)
    - clomipramine (nordesmethylclomipramine)
    - imipramine (desipramine)
  - Secondary amines:

    Compounds:
    - nortriptyline
    - desipramine

    Less ADRs than tertiary amines

3.1.1. TCAs: Metabolic Enzymes

- Tertiary amines:
  - Desmethylation: CYP2C19 (CYP1A2, CYP2C9 and CYP3A4)
  - Hydroxylation of active metabolite: CYP2D6
- Secondary amines: Hydroxylation: CYP2D6

3.1.1. TCAs: Metabolic Enzymes

- Dr. de Leon's reminder: this is in normal circumstances:
  - Tertiary amines: CYP2C19 and CYP2D6
  - Secondary amines: CYP2D6

- Not well-studied under induction:
  - It is possible that CYP3A4 may become more important

- Not well-studied under inhibition:
  - If you inhibit CYP2C19 and/or CYP2D6, other CYPs may become more important

3.1.2. TCAs: CYP Genotyping

3.1.2. TCAs: CYP Genotyping

- Hicks et al., 2014 : http://www.ncbi.nlm.nih.gov/pubmed/23486447
  - CYP2D6 PMs: avoid TCAs or ↓ dose by 50% and use TDM for dosing
  - CYP2D6 UMs: avoid TCAs
  - CYP2C19 PMs: amitriptyline: ↓ dose by 50% and use TDM for dosing
  - CYP2C19 UMs: amitriptyline: select another antidepressant not metabolized by CYP2C19
  - CYP2C19 PM/UMs: recommendations for amitriptyline probably apply to clomipramine and imipramine

3.1.3. TCAs: TDM

3.1.3. 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 getting steady-state trough TDM,
  the C/D ratio indicates CYP2D6 activity:
  - <0.5: Patient is: • CYP2D6 UM, or
    • non-compliant
  - 0.5-1.5: Patient is CYP2D6 EM
  - >1.5: Patient is: • CYP2D6 PM, or
    • taking a potent CYP2D6 inhibitor.
- Additional reminders by Dr. de Leon:
  - Inducers may provide low C/D ratios.
  - CYP2C19 PMs may provide high C/D ratios in tertiary amines.

3.1.3. 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

3.1.4. TCA DDIs

3.1.4. TCA DDIs

3.1.4.1. Effects of Other Drugs on TCAs

3.1.4.2. Effects of TCAs on Other Drugs

3.1.4.1. Effects of Other Drugs on TCAs

3.1.4.1. DDIs: Effects of Other Drugs on TCAs

- Inhibitors on TCAs: use TDM
  - Potent CYP2D6 inhibitors:
    - fluoxetine
    - paroxetine
  - Moderate CYP2D6 inhibitors:
    - bupropion
    - duloxetine
  - Mild CYP2D6 inhibitors:
    - fluvoxamine
    - sertraline (dose-related)
  - CYP2C19 inhibitors:
    - fluvoxamine: potent
    - fluoxetine: weak to moderate
- AED inducers on TCAs: correction factor: x 2 (1.4-2.5) D. Use TDM

3.1.4.2. Effects of TCAs on Other Drugs

3.1.4.2. DDIs: Effects of TCAs on Other Drugs

- TCAs are CYP inhibitors:
  - Tertiary amines: moderate CYP2C19 inhibitors
  - Tertiary and secondary amines: weak CYP2D6 inhibitors

3.2. SSRIs

3.2. SSRIs

- 3.2.1. Citalopram
- 3.2.2. Escitalopram
- 3.2.3. Fluoxetine
- 3.2.3. Fluvoxamine
- 3.2.4. Paroxetine
- 3.2.5. Sertraline

3.2.1. Citalopram

3.2.1. Citalopram

- The most important metabolic enzyme: CYP2C19
  - Others: CYP3A4 and CYP2D6
- CYP2C19 genotyping

  http://www.ncbi.nlm.nih.gov/pubmed/25974703
  - 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
- DDI with inhibitors: be careful
  - CYP2C19 inhibitors: • fluvoxamine
    • omeprazole
- DDI with inducers: not relevant?

  (correction factor 1.3 x D)
- Effect of citalopram on other drugs: weak CYP2D6 inhibitor

  In most circumstances it is not clinically relevant

3.2.2. Escitalopram

3.2.2. Escitalopram

- The most important metabolic enzyme: CYP2C19
  - Others: CYP3A4 and CYP2D6
- CYP2C19 genotyping http://www.ncbi.nlm.nih.gov/pubmed/25974703
  - 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
- DDI with inhibitors: probably not relevant
  - CYP2C19 inhibitors: • fluvoxamine
    • omeprazole
- DDI with inducers: not studied
- Effect of escitalopram on other drugs: weak CYP2D6 inhibitor
  In most circumstances this is not clinically relevant

3.2.3. Fluoxetine

3.2.3. Fluoxetine

- The most important metabolic enzyme: CYP2D6
  - Others: CYP2C9, CYP2C19 and CYP3A4
- Active metabolite: norfluoxetine (steady state: • usually 2-3 months
  . • up to 6 months)
- Non-linear kinetics: inhibits its own metabolism
- CYP2D6 genotyping http://www.ncbi.nlm.nih.gov/pubmed/25974703
  - 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
- DDI with inhibitors: probably not relevant
- DDI with inducers: probably not relevant
- Effect of fluoxetine on other drugs:
  - potent inhibitor: CYP2D6
  - moderate inhibitor: CYP2C9
  - weak to moderate inhibitor: CYP2C19 and CYP3A4
  - weak: CYP1A2

Norfluoxetine remains for months and is more important for inhibition

3.2.4. Fluvoxamine

3.2.4. Fluvoxamine

- The most important metabolic enzymes: CYP1A2 and CYP2D6
- CYP2D6 genotyping http://www.ncbi.nlm.nih.gov/pubmed/25974703
  - PMs: ● select an agent not dependent on CYP2D6, or
    ● correct by 0.50 x initial D and titrate accordingly
  - UMs: no data
- DDI with inhibitors: probably not relevant
- DDI with inducers: probably not relevant
- Effects of fluvoxamine on other drugs:
  - potent inhibitor: CYP1A2 and CYP2C19
  - moderate inhibitor: CYP2C9 and CYP3A4
  - weak inhibitor: CYP2D6

3.2.5. Paroxetine

3.2.4. Paroxetine

- The most important metabolic enzyme: CYP2D6
  - Other: CYP3A4
- Non-linear kinetics: inhibits its own metabolism
- CYP2D6 genotyping http://www.ncbi.nlm.nih.gov/pubmed/25974703
  - 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.
- DDI with inhibitors: probably not relevant
- DDI with inducers: not relevant?
  (correction factor 1.3 x D)
- Effects of paroxetine on other drugs:
  - potent inhibitor: CYP2D6
  - weak inhibitor: CYP1A2, CYP2C9, CYP2C19 and CYP3A4

3.2.6. Sertraline

3.2.5. Sertraline

- The most important metabolic enzyme: CYP2B6 or CYP2C19
  - Others: CYP2C9, CYP2D6, CYP3A4
- CYP2C19 genotyping http://www.ncbi.nlm.nih.gov/pubmed/25974703
  - 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 patient does not respond consider an agent not dependent on CYP2C19
- DDI with inhibitors: probably not relevant
- DDI with inducers: correction factor 5 x D
- Sertraline on other drugs:
  - weak to moderate inhibitor (dose-related): CYP2D6
  - weak inhibitor: CYP1A2, CYP2C9, CYP2C19 and CYP3A4

3.3. SNRIs

3.3. SNRIs

3.3.1. Desvenlafaxine
3.3.2. Duloxetine
3.3.3. Levomilnacipran
3.3.3. Milnacipran
3.3.4. Venlafaxine

3.3.1. Desvenlafaxine

3.3.1. Desvenlafaxine

- Elimination:
  - Most important: renal
  - Other: UGTs and CYP3A4
- DDI with inhibitors: probably not important
- DDI with inducers: not studied
- Effect of desvenlafaxine on other drugs: rarely relevant

3.3.2. Duloxetine

3.3.2. Duloxetine

- The most important metabolic enzyme: CYP1A2
  - Other: CYP2D6
- DDI with inhibitors:
  - CYP1A2 inhibitors: consider↓ D
    - fluvoxamine
    - ciprofloxacin
- DDI with inducers:
  - AED potent inducers: not studied
  - smoking: not studied
- Effect of duloxetine on other drugs:
  - moderate CYP2D6 inhibitor

3.3.3. Levomilnacipran

3.3.3. Levomilnacipran

- Elimination:
  - Most important: renal
  - Others: UGTs and CYP3A4
- DDI with inhibitors: probably not important
- DDI with inducers: not studied
- Effect of levomilnacipran on other drugs: rarely relevant

3.3.4. Milnacipran

3.3.4. Milnacipran

- Elimination:
  - Most important: renal (50%)
  - Others: CYP3A4 (20%) and UGTs (30%)
- Metabolites:
  - most metabolites are inactive
  - hydroxylated metabolite (F2782): active but unlikely to be relevant (accounts <1% dose)

http://www.ncbi.nlm.nih.gov/pubmed/16122284

- DDI with inhibitors: probably not important
- DDI with inducers: not relevant? (correction factor 1.3 x D)
- Effect of milnacipran on other drugs:
  - mild CYP3A4 inhibitor

3.3.5. Venlafaxine

3.3.4. Venlafaxine

- Most important metabolic enzyme: CYP2D6
  - Other: CYP3A4
- Active metabolite: desvenlafaxine
- TDM: http://www.ncbi.nlm.nih.gov/pubmed/23541126

  O-desmethylvenlafaxine/venlafaxine C ratio

  < 1 indicates a CYP2D6 PM who may respond more poorly.
- CYP2D6 genotyping: http://www.ncbi.nlm.nih.gov/pubmed/21412232
  - PMs : select another antidepressant or use TDM
  - UMs : correction factor x 1.5 D
- DDI with inhibitors: not well studied: consider TDM or ↓ D
  - Potent CYP2D6 inhibitors: fluoxetine and paroxetine
  - Moderate CYP2D6 inhibitors: bupropion and duloxetine
  - Weak CYP2D6 inhibitors: fluvoxamine and sertraline
- DDI with inducers: not studied
- Effect of venlafaxine on other drugs: in most circumstances is not clinically relevant, but, venlafaxine can inhibit its own metabolism (CYP2D6 competitive inhibition).

3.4. Other Antidepressants

3.4. Other Antidepressants

3.4.1. Agomelatine
3.4.2. Bupropion
3.4.3. Mirtazapine
3.4.4. Reboxetine
3.4.5. Trazadone
3.4.6. Vilazadone
3.4.7. Vortioxetine

3.4.1. Agomelatine

3.4.1. Agomelatine

- Most important metabolic enzyme: CYP1A2
  - Other: CYP2C9
- DDI with inhibitors: be very careful
  - Potent CYP1A2 inhibitors:
    - fluvoxamine
    - ciprofloxacin
  - Other CYP1A2 inhibitors:
    - estrogens
    - infections
- DDI with inducers:
  - AED potent inducers
  - smoking
  - omeprazole
- Effect of agomelatine on other drugs: rarely relevant

3.4.2. Bupropion

3.4.2. Bupropion

- Most important metabolic enzyme: CYP2B6
- Active metabolites:
  - hydroxybupropion
  - threohydrobupropion
  - erythrohydrobupropion
- DDI with inhibitors:
  - CYP2B6 inhibitors:
    - clopidogrel
    - ticlopidine
- DDI with inducers: AED potent inducers
  do not co-prescribe
  correction factor: x 10 D
- Effects of bupropion: moderate CYP2D6 inhibitor

3.4.3. Mirtazapine

3.4.3. Mirtazapine

- Metabolic enzymes:
  - Most important: CYP2D6 and CYP3A4
  - Others: CYP1A2 and UGTs
- DDI with inhibitors: probably not important
- DDI with inducers: AED potent inducers
  correction factor: x 2-3 D
- Effect of mirtazapine on other drugs: rarely relevant

3.4.4. Reboxetine

3.4.4. Reboxetine

- Metabolic enzyme: CYP3A4
- DDI with inhibitors:
  - ketoconazole and erythromycin
  - grapefruit juice
- DDI with inducers:
  - St John's wort
  - AED potent inducers: not studied

    Quetiapine is metabolized by CYP3A4 and has a correction factor: >5 x D.
- Effect of reboxetine on other drugs: rarely relevant

3.4.5. Trazadone

3.4.5. Trazadone

- Metabolic enzyme: CYP3A4
- Active metabolite metabolized by CYP2D6: m-CPP (M-chlorophenylpiperazine):
- DDI with inhibitors:
  - ketoconazole and erythromycin
  - grapefruit juice
- DDI with inducers:
  - St John's wort
  - AED potent inducers: not studied
- Effect of trazadone on other drugs: rarely relevant

3.4.6. Vilazodone

3.4.6. Vilazodone

- The most important enzyme: CYP3A4
  - Others: CY2PC9, CYP2D6 and carboxylesterase
- DDI with inhibitors: http://www.ncbi.nlm.nih.gov/pubmed/25236915
  - ketoconazole: not more than 20 mg/day
  - erythromycin and grapefruit juice
- DDI with inducers: AED potent inducers:
  - Poor study (carbamazepine 400 mg/day for 19 days)
    They recommend maximum Ds up to 80 mg/day.
    Correction factor: 2 x D
  - Dr. de Leon's opinion: higher Ds may be needed:
    Quetiapine is metabolized by CYP3A4
    and has a correction factor: > 5 x D.
- Effects of vilazodone: CYP2C8 inhibitor (unclear clinical relevance)
  (in vitro: moderate inhibitor of CYP2D6 and CYP2C19)

3.4.7. Vortioxetine

3.4.7. Vortioxetine

- The most important enzyme: CYP2D6
  - Others: CYP2A6, CYP2B6, CYP2C, CYP2D6
- CYP2D6 PM: correction factor x 0.5 D
- DDI with inhibitors:
  - Potent CYP2D6 inhibitors: x 0.5 D
    - fluoxetine and paroxetine
  - Moderate CYP2D6 inhibitors:
    - bupropion
    - duloxetine
  - Mild CYP2D6 inhibitors:
    - fluvoxamine
    - sertraline(dose-related)
- DDI with AED inducers: x 3 D http://www.ncbi.nlm.nih.gov/pubmed/24165478
- Effect of vortioxetine on other drugs: rarely relevant

4. Hepatic Impairment

4. Hepatic Impairment

4.1. Severity
4.2. Antidepressants

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)
  - C (10 to 15 points)

4.2. Hepatic Impairment: Antidepressants

4.2. Hepatic Impairment: Antidepressants

4.2.1. Lack of Studies
4.2.2. Contraindications
4.2.3. Dose Corrections
4.2.4. Recent Drugs

4.2.1. Hepatic Impairment: Lack of Studies

- Studies are very limited.
- Few articles address this issue:
  - One review on DDIs: contraindications

    http://www.ncbi.nlm.nih.gov/pubmed/25196459
  - One review on pharmacokinetics during hepatic impairment: dose corrections

    http://www.ncbi.nlm.nih.gov/pubmed/25248846

4.2.2. Hepatic Impairment: Contraindications

- Absolute contraindications: agomelatine
- Relative contraindications:
  On rare occasions, other antidepressants have been associated with life-threatening hepatotoxicity:
  - bupropion,
  - duloxetine,
  - TCAs, and
  - trazadone.

  Avoid them on patients with:
  - history of liver injury, or
  - ↑ liver enzymes.

  http://www.ncbi.nlm.nih.gov/pubmed/25196459

4.2. Hepatic Impairment: Dose Correction

- Lower maximum doses: http://www.ncbi.nlm.nih.gov/pubmed/25248846
  - TCAs:
    - amitriptyline: 100 mg/day
    - desipramine: 150 mg/day
    - imipramine: 150 mg/day
    - nortriptyline: 150 mg/day
  - SSRIs:
    - citalopram: 20 mg/day
    - escitalopram: 10 mg/day
    - fluoxetine: 40 mg/day
    - fluvoxamine: 150 mg/day
    - paroxetine: 40 mg/day
    - sertraline: 100 mg/day
  - SNRIs:
    - desvenlafaxine: 100 mg/day
    - duloxetine: 20 mg/day
    - venlafaxine: 100 mg/day
  - Others:
    - bupropion: 150 mg/day
    - mirtazapine: 30 mg/day
    - trazadone 400 mg/day

4.2.4. Hepatic Impairment: Recent Drugs

- Vilazodone: no need for D correction

  http://www.ncbi.nlm.nih.gov/pubmed/25474324

- Vortioxetine: no need for D correction
  in mild-to-moderate hepatic impairment

  http://www.ncbi.nlm.nih.gov/pubmed/24165478

5. Pregnancy

5. 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 (probably).

5. Pregnancy

- Few antidepressant pharmacokinetic studies have been conducted during pregnancy.
- After 20 weeks ↑ D for:
  - TCAs:
    - clomipramine
    - imipramine
    - nortriptyline

    (Use TDM and ↓ D after delivery.)
  - SSRIs:
    - citalopram
    - fluoxetine
    - fluvoxamine
    - paroxetine
    - sertraline

http://www.ncbi.nlm.nih.gov/pubmed/24525634

6. Do Not Forget

6. Do Not Forget

6.1. Some Antidepressants are Inhibitors

6.2. Other Drugs May Influence Antidepressants

6.1. Some Antidepressants are Inhibitors

6.1. Some Antidepressants are Inhibitors

- Fluoxetine and fluvoxamine inhibit several CYPs. Norfluoxetine stays for months after discontinuation
- Some antidepressants are CYP2D6 inhibitors, so be very careful when adding them to TCAs:
  - Potent CYP2D6 inhibitors: • fluoxetine
    • paroxetine
  - Moderate CYP2D6 inhibitors: • bupropion
    • duloxetine
  - Mild CYP2D6 inhibitors: • fluvoxamine
    • sertraline (dose-related)
  - Rarely relevant CYP2D6 inhibitors: • citalopram
    • escitalopram
    • venlafaxine
- CYP2C19 inhibitors: • fluvoxamine: potent
  • fluoxetine: weak to moderate

6.2. Other Drugs May Influence Antidepressants

6.2. Other Drugs May Influence Antidepressants

- Pregnancy: review slide.
- AED inducers may eliminate antidepressant efficacy:
  - Do not prescribe bupropion.
  - Not well studied but likely to have major effects on:
    - reboxetine
    - sertraline
    - trazadone
    - vilazadone
  - Use antidepressant TDM and/or ↑ D (≥2-3 x) see slides:
    - mirtazapine
    - TCAs
    - vortioxetine

References for Antidepressant Pharmacokinetics

1) 2015 article http://www.ncbi.nlm.nih.gov/pubmed/257458190 with pdf http://uknowledge.uky.edu/psychiatry_facpub/37/ is the most updated on induction by AEDs.

2) 2014 article http://www.ncbi.nlm.nih.gov/pubmed/25196459 with pdf http://uknowledge.uky.edu/psychiatry_facpub/40/ has the best tables for all antidepressant pharmacokinetics and focuses on AED DDIs.

3) 2014 article http://www.ncbi.nlm.nih.gov/pubmed/24494611 with pdf http://uknowledge.uky.edu/psychiatry_facpub/42/ focuses on DDI between second-generation antidepressants and second-generation antipsychotics.

4) Spina's 2008 article on SSRI DDIs http://www.ncbi.nlm.nih.gov/pubmed/18691982

5) Spina's 2012 article on DDI of newer second-generation antidepressants http://www.ncbi.nlm.nih.gov/pubmed/22171584

Questions

-Please review the 10 questions in the pdf titled “Questions on the Presentation Pharmacokinetics of Antidepressants”.

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