

# Pharmacodynamics of Antidepressants

Jose de Leon, MD  
(11-13-15)

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

# Learning Objectives

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

- 1) Appreciate the relevance of pharmacodynamics for antidepressant efficacy.
- 2) Appreciate the relevance of pharmacodynamics for antidepressant safety.
- 3) Summarize frequent adverse drug reactions (ADRs) including a) sleepiness/ insomnia, b) weight changes, c) withdrawal symptoms, d) sexual ADRs, and e) gastro-intestinal ADRs.
- 4) Remember that, on rare occasions, antidepressants can kill your patients by contributing to arrhythmias, serotonin syndrome or hemorrhages.

# 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 pharmacodynamics of drugs when any of your patients are taking antidepressants in the context of polypharmacy.
- 2) Our understanding of brain pharmacodynamics is limited; therefore, there are many disagreements in the literature. In the process of summarizing, Dr. de Leon had to make arbitrary decisions with which other authors may not agree.
- 3) As Dr. de Leon is not an expert in this area, for the “Do Not Forget” Section, he selected a recent review on frequent ADRs in primary care.

# Abbreviations

- ADH: antidiuretic hormone
- ADHD: attention deficit-hyperactivity disorder
- ADR: adverse drug reaction
- DDI: drug-drug interaction
- GI: gastro-intestinal
- HERG: ether-a-go-go-related gene
- OCD: obsessive-compulsive disorder
- SIADH: syndrome of inappropriate ADH secretion

## Neurotransmission

- 5HT: serotonin
- $\alpha$ : alpha adrenergic
- H: histamine
- M: muscarinic
- MT: melatonin
- norepinephrine=noradrenaline. Not abbreviated.

# Abbreviations for Antidepressants

- Antidepressants that are not included:
  - MAOIs: monoamine oxidase inhibitors
  - nefazadone
- This presentation focuses on:
  - TCAs: tricyclic antidepressants, and
  - newer compounds:
    - SNRIs: serotonin-norepinephrine inhibitors
    - SSRIs: selective serotonin reuptake inhibitors
    - Others: the rest

# Lecture Content

- 1. Efficacy**
- 2. Safety**
- 3. Pharmacokinetics:  
Facilitator of  
Pharmacodynamics**
- 4. “Do Not Forget” Section**

# Lecture Content on Efficacy

## 1. Efficacy

1.1. Depression

1.2. OCD

1.3. Anxiety

1.4. Pain

1.5. Weight Loss

1.6. Smoking Cessation

1.7. ADHD

1.8. Insomnia

1.9. Cataplexy

1.10. Some Types of Urinary Incontinence

1.11. Menopausal Vasomotor Symptoms

# Lecture Content on Safety

**2.1. Brain**

**2.2. Periphery (with/without brain)**



# Lecture Content on Safety: Brain Mechanisms

## 2.1. Brain

2.1.1. Weight Gain

2.1.2. ↓ Seizure Threshold

2.1.3. ↓ Dopaminergic Activity

2.1.4. Psychotic Exacerbation

2.1.5. Insomnia

2.1.6. Sedation

2.1.7. Memory Impairment

# Lecture Content on Safety: Periphery Mechanisms

- 2.2.1. Nausea and Vomiting
- 2.2.2. Tachycardia and/or Hypertension
- 2.2.3. Orthostatic Hypotension
- 2.2.4. Diarrhea
- 2.2.5. Sexual ADRs
- 2.2.6. Hyperlipidemia
- 2.2.7. Anticholinergic Symptoms
- 2.2.8. Urinary Symptoms
- 2.2.9. Mydriasis
- 2.2.10. Hyperhydrosis
- 2.2.11. Osteoporosis
- 2.2.12. Discontinuation/Withdrawal Syndrome
- 2.2.13. Risk for Bleeding
- 2.2.14. Serotonin Syndrome
- 2.2.15. Arrhythmias
- 2.2.16. Neutropenia
- 2.2.17. Hyponatremia
- 2.2.18. Liver Injury

# 1. Pharmacodynamics of Antidepressant Efficacy

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1.1. Depression

1.2. OCD

1.3. Anxiety

1.4. Pain

1.5. Weight Loss

1.6. Smoking Cessation

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1.10. Some Types of Urinary Incontinence

1.11. Menopausal Vasomotor Symptoms

# 1.1. Depression

# 1.1. Depression

## ■ Textbooks

- usually report that the majority of antidepressants act by inhibiting the reuptake of transporters,
- but they also usually acknowledge that this is not a definitively proven theory, since the chronology of reuptake inhibition does not match the chronology of antidepressant response.

## ■ Even less agreement is found concerning the mechanism of action of:

- mirtazapine, or
- trazadone.

# 1.1. Mechanism of Action: Transporters

- Inhibitors of noradrenaline and serotonin transporters:
  - Desvenlafaxine, duloxetine and venlafaxine
  - Levomilnacipran and milnacipran (not in the USA)
  - TCAs
- Selective inhibitors of the serotonin transporter: SSRIs
- Selective inhibitors of the serotonin transporter and serotonin receptor antagonists
  - Vilazodone: partial agonism of the 5-HT<sub>1A</sub> receptor.
  - Vortioxetine: ● antagonist: 5-HT<sub>3A</sub> and 5-HT<sub>7</sub>
    - partial agonist: 5-HT<sub>1B</sub>
    - agonist: 5-HT<sub>1A</sub>
- Inhibitor of noradrenaline and dopamine transporters:
  - Bupropion
- Selective inhibitor of noradrenaline transporter: Reboxetine (not in the USA)

# 1.1. Mechanism of Action: Others

- Trazadone:
  - 5-HT<sub>2</sub> antagonist, and
  - m-CPP (its major metabolite): 5-HT<sub>2C</sub> agonist
- Mirtazapine:
  - $\alpha_2$  adrenergic receptor antagonist and/or
  - 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> antagonist
- Agomelatine (not in the USA):
  - Melatonergic analogue (MT<sub>1</sub>/MT<sub>2</sub> agonist) and
  - 5-HT<sub>2C</sub> antagonist



# 1.2. OCD

## 1.2. OCD

- Inhibition of the serotonin transporter:
  - SSRIs: first line
    - Approved in USA: ● fluoxetine
    - fluvoxamine
    - paroxetine
    - sertraline
  - Clomipramine
- SNRIs (off-label):
  - Desvenlafaxine
  - Duloxetine
  - Venlafaxine

# 1.3. Anxiety

## 1.3. Anxiety

- It is usually assumed the mechanism is the same as for depression.
- Specificity for specific disorders is doubtful, but only some drugs have been studied for approval.

## 1.3.1. Generalized Anxiety Disorder

- Approved in the USA:
  - Duloxetine
  - Escitalopram
  - Paroxetine
  - Venlafaxine

## 1.3.2. Social Anxiety

- Approved in the USA:
  - Paroxetine
  - Sertraline
  - Venlafaxine

## 1.3.3. Panic Disorder

- Approved in the USA:
  - Paroxetine
  - Sertraline
  - Venlafaxine
- TCAs: effective but off-label

# 1.3.3. Panic Disorder

## ■ Second-generation antidepressant meta-analysis:

<http://www.ncbi.nlm.nih.gov/pubmed/23111544>

□ superior to placebo for panic symptoms:

citalopram>sertraline>paroxetine>fluoxetine>venlafaxine

□ superior to placebo for overall anxiety symptoms:

paroxetine>fluoxetine>fluvoxamine>citalopram>venlafaxine  
>mirtazapine

□ lower drop-outs than placebo:

>venlafaxine>fluoxetine>sertraline>paroxetine>citalopram>  
mirtazapine

□ not different from placebo in drop-outs:

fluvoxamine and reboxetine



# 1.4. Pain

## 1.4. Pain

- Inhibition of the noradrenalin transporter: appears more important.
- TCAs: frequently used (off-label)
- Approved in the USA for fibromyalgia:
  - Duloxetine
  - Milnacipran
- Duloxetine is also approved in the USA for:
  - Diabetic peripheral neuropathy
  - Chronic musculoskeletal pain

# **1.5. Migraine Prophylaxis**

## 1.5. Migraine Prophylaxis

- Mechanism of action: unknown.
- Off-label in the USA:
  - TCAs: amitriptyline (better studied)
  - Venlafaxine: less data

# 1.6. Weight Loss

## 1.6. Weight Loss

### ■ Bupropion:

inhibition of dopamine transporter

□ Off-label in the USA

□ In combination with naltrexone, it is approved in the USA for obesity.

### ■ Fluoxetine: some weight loss,

according to meta-analysis:

limited to the acute phase of treatment.

<http://www.ncbi.nlm.nih.gov/pubmed/21062615>

# 1.7. Smoking Cessation

## 1.7. Smoking Cessation

- Bupropion:  
inhibition of dopamine transporter



# 1.8. ADHD

## 1.8. ADHD

### ■ Bupropion:

- Inhibition of noradrenergic and dopamine transporters
- Off-label in the USA
- Superior to placebo in adults

<http://www.ncbi.nlm.nih.gov/pubmed/22176279>

### ■ Other antidepressants: very limited data

# 1.9. Insomnia

## 1.9. Insomnia

- Antagonism of brain  $H_1$  receptors  
(daily sedation can be a problem)  
All drugs are off-label in the USA:
  - Amitriptyline
  - Mirtazapine
  - Trazadone
- Agonism of brain  $MT_2$  receptors
  - Agomelatine (not approved in the USA)

# 1.10. Cataplexy

## 1.10. Cataplexy

- Suppression of REM sleep:  
Off-label in the USA:
  - TCAs
  - Venlafaxine

# **1.11. Some Types of Urinary Incontinence**

# 1.11. Some Types of Urinary Incontinence

- Noradrenergic mechanisms are important.
- Stress urinary incontinence:
  - Duloxetine: off-label in the USA
- Nocturnal enuresis in children:
  - Imipramine



# **1.12. Menopausal Vasomotor Symptoms**

# 1.12. Menopausal Vasomotor Symptoms

- Including:
  - Hot flashes
  - Night sweats
- Off-label in the USA
  - SNRIs
  - SSRIs

# **2. Pharmacodynamics of Antidepressant Safety**

## **2. Pharmacodynamics of Antidepressant Safety**

**2.1. Brain**

**2.2. Periphery (with/without brain)**

# **2.1. Brain Pharmacodynamics of Antidepressant Safety**

## **2.1. Brain Pharmacodynamics of Antidepressant Safety**

2.1.1. Weight Gain

2.1.2. ↓ Seizure Threshold

2.1.3. ↓ Dopaminergic activity

2.1.4. Psychotic Exacerbation

2.1.5. Insomnia

2.1.6. Sedation

2.1.7. Memory Impairment

## **2.1.1. Weight Gain**

## 2.1.1. Weight Gain

- Mechanism: ↑ appetite
  - TCAs: H<sub>1</sub> & M antagonists
    - Amitriptyline (worst)
  - Mirtazapine: H<sub>1</sub> & 5HT<sub>2C</sub> antagonist
  - Paroxetine: H<sub>1</sub> antagonist
- Agomelatine: 5HT<sub>2C</sub> antagonist
  - Not enough long-term data
  - Case reports: associated with weight gain



**2.1.2.**

**↓ Seizure Threshold**

## 2.1.2. ↓ Seizure Threshold

- Unknown mechanism
- Versus placebo: <http://www.ncbi.nlm.nih.gov/pubmed/17223086>
  - Worse: ● Bupropion
    - TCAs
  - Better: other newer compounds
- Fluoxetine:
  - Anti-seizure activity: animal models
  - Seizures: according to case reports

**2.1.3.**

**↓ Dopaminergic Activity**

## 2.1.3. ↓ Dopaminergic Activity

- Mechanism not well understood.
- ↓ Dopaminergic activity manifests as:
  - Akathisia (rare): SSRIs
  - Other extrapyramidal symptoms (rare): all antidepressants
  - Hyperprolactinemia (rare): probably all antidepressants

## **2.1.4. Psychotic Exacerbations**

## 2.1.4. Psychotic Exacerbations

- Rare and manifest as:
  - New psychotic episodes
  - Psychotic exacerbations
- Described in connection with:
  - Bupropion: inhibition of dopamine transporter
  - TCAs: unknown mechanism

## **2.1.5. Insomnia**

## 2.1.5. Insomnia

- In all new antidepressants except agomelatine.
- Mechanisms:
  - Stimulation 5HT<sub>2</sub>: SSRIs
  - Blockade noradrenaline transporter:
    - Bupropion
    - Reboxetine
    - SNRIs
  - ↑ Noradrenergic activity: high doses of mirtazapine.



## **2.1.6. Sedation**

## 2.1.6. Sedation

- Antidepressants used to treat insomnia can cause sedation.
- Mechanism:
  - $H_1$  antagonism:
    - TCAs
    - Mirtazapine
    - Trazadone
  - $MT_2$ : agonism
    - Agomelatine (not in the USA)

## **2.1.7. Memory Impairment**

## 2.1.7. Memory Impairment

- Mechanism: blockade of brain M receptors
- Blockade of  $M_1$  and  $M_2$  receptors has been associated with impaired learning and memory in animal studies.
- Potent compounds in high doses or in vulnerable patients (demented) can cause confusion/delirium.

## 2.1.7. Muscarinic Blockade

- High potency:
  - Amitriptyline
  - Clomipramine
  - Protriptyline
- Moderate potency:
  - Doxepin
  - Imipramine
  - Nortriptyline
  - Trimipramine
- Low potency (relevant only in high doses):
  - Amoxapine
  - Desimipramine
  - Maprotiline
  - Mirtazapine
  - Paroxetine

## 2.1.7. Muscarinic Blockade: Unclear

- Anti-muscarinic activity is seen in some studies, but not in others:
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Sertraline
  - Trazadone

# **2.2. Peripheral Pharmacodynamics of Antidepressant Safety**

## **2.2. Peripheral Pharmacodynamics of Antidepressant Safety**

- 2.2.1. Nausea and Vomiting
- 2.2.2. Tachycardia and/or Hypertension
- 2.2.3. Orthostatic Hypotension
- 2.2.4. Diarrhea
- 2.2.5. Sexual ADRs
- 2.2.6. Hyperlipidemia
- 2.2.7. Anticholinergic Symptoms
- 2.2.8. Urinary Symptoms
- 2.2.9. Mydriasis
- 2.2.10. Hyperhidrosis
- 2.2.11. Osteoporosis
- 2.2.12. Discontinuation/Withdrawal Syndrome
- 2.2.13. Risk for Bleeding
- 2.2.14. Serotonin Syndrome
- 2.2.15. Arrhythmias
- 2.2.16. Neutropenia
- 2.2.17. Hyponatremia
- 2.2.18. Liver Injury



## **2.2.1. Nausea and Vomiting**

## 2.2.1. Nausea and Vomiting

- Mechanism:
  - inhibition of serotonin transporter.
- Common in newer antidepressants;
  - most frequent cause of discontinuation in the first 30 days

## 2.2.1. Nausea and Vomiting

- Probably worse:
  - Desvenlafaxine
  - Duloxetine
  - Venlafaxine
- Probably intermediate:
  - SSRIs
  - Vilazodone
  - Vortioxetine
- Probably lower risk:
  - Levomilnacipran
  - Milnacipran

## 2.2.1. Nausea and Vomiting

■ Be aware:

- mirtazapine, and

- TCAs

may help with some nausea and have been used for “psychogenic vomiting”.

# **2.2.2. Tachycardia and/or Hypertension**

## 2.2.2. Tachycardia and/or Hypertension

- Probable mechanism:

  - inhibition of noradrenalin transporter

- Rare in RCTs.

  - TCAs are associated with hypertension in pharmacoepidemiology studies.

- Review on hypertension:

  - <http://www.ncbi.nlm.nih.gov/pubmed/18652794>

  - Venlafaxine: definitively associated

  - Desvenlafaxine and milnacipran:  
also associated

  - Duloxetine: be cautious in hypertensive patients.

## **2.2.3. Orthostatic Hypotension**

## 2.2.3. Orthostatic Hypotension

- Mechanism: blockade  $\alpha_1$
- Tolerance is important and can be avoided by titration.
- Definitively associated with:
  - TCAs
  - Trazadone
- Mirtazapine:
  - Very low  $\alpha_1$  affinity
  - Rarely associated with syncope
- Venlafaxine:
  - No  $\alpha_1$  affinity
  - Associated with orthostatic changes in geriatric patients



## **2.2.4. Diarrhea**

## 2.2.4. Diarrhea

- Mechanism: unknown
- Definitely more frequent with:
  - Sertraline
- Others:
  - Vilazodone
  - Vortioxetine

## **2.2.5. Sexual ADRs**

## 2.2.5. Sexual ADRs

- Serotonergic mechanisms:
  - Stimulation of 5TH<sub>2</sub> and 5TH<sub>3</sub>
  - Effect of serotonin on nitric oxide production
- ♀:
  - ↓ Libido
  - Others
- ♂:
  - Erectile dysfunction
  - Problems with orgasm
  - ↓ Libido

## 2.2.5. Sexual ADRs

- Frequent:
  - SNRIs
  - SSRIs
  - TCAs
- > Placebo:
  - Vilazodone
  - Vortioxetine
- Very low risk:
  - Agomelatine
  - Reboxetine
- No different than placebo:
  - Bupropion
  - Mirtazapine

## 2.2.5. Sexual ADRs: Priapism

- It is rare but does occur with trazadone.
- Blockade  $\alpha_1$  (&  $\alpha_2$ ) in periphery

## **2.2.6. Hyperlipidemia**

## 2.2.6. Hyperlipidemia:

- Indirect: Weight-mediated
- Direct in lipid metabolism:
  - Mirtazapine



## **2.2.7. Anticholinergic Symptoms**

## 2.2.7. Anticholinergic Symptoms

- Antimuscarinic symptoms
- Blockade of peripheral M receptors
- Symptoms:
  - Tachycardia: M<sub>2</sub> heart
  - Constipation: M<sub>3</sub> colon
  - Dry mouth: M<sub>1</sub> and M<sub>3</sub> salivary glands
  - Urinary retention: M<sub>3</sub> detrusor muscle in bladder
  - Blurred vision: M<sub>3</sub> eye

## 2.2.7. Muscarinic Blockade

- High potency:
  - Amitriptyline
  - Clomipramine
  - Protriptyline
- Moderate potency:
  - Doxepin
  - Imipramine
  - Nortriptyline
  - Trimipramine
- Low potency (relevant only in high doses):
  - Amoxapine
  - Desimipramine
  - Maprotiline
  - Mirtazapine
  - Paroxetine

## 2.2.7. Muscarinic Blockade: Unclear

- In some studies anti-muscarinic activity but not in others:
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Sertraline
  - Trazadone
  
- Reboxetine:
  - Can cause:
    - Dry mouth
    - Constipation
    - Urinary retention, on rare occasions
  - It is believed affinity for muscarinic receptors is too low.
  - No anti-muscarinic metabolites have been identified.
  - These symptoms may occur through noradrenergic mechanisms.

## 2.2.7. Risk for Heat Stroke

- Potent anti-muscarinic TCAs: ↓ sweating
- Rare but potentially lethal (elderly)
- Other risk factors:
  - Polypharmacy (additive effects):
    - Antipsychotic: temperature regulation
    - Topiramate/zonisamide: ↓ sweating by inhibition of carbonic anhydrase
  - After heat exposure:
    - High temperatures in summer, or
    - Intense exercise

## 2.2.8. Urinary Symptoms

## 2.2.8. Urinary Symptoms

- Symptoms:
  - Dysuria
  - Urinary retention
  - Sensation of incomplete bladder emptying
- Mechanisms: noradrenergic
- Antidepressants:
  - SNRIs
  - Reboxetine

## 2.2.9. Mydriasis



## 2.2.9. Midriasis

- Risk for patients with uncontrolled narrow-angle glaucoma
- Mechanisms: inhibition of noradrenergic transporter
- Antidepressants:
  - SNRIs
  - Reboxetine
  - TCAs

## **2.2.10. Hyperhidrosis**

## 2.2.10. Hyperhidrosis

### ■ Frequency:

- Uncommon in all antidepressants
- Common (5-14%) in SSRIs or SNRIs, according to a recent article

<http://www.ncbi.nlm.nih.gov/pubmed/23638448>

### ■ Mechanisms:

- Peripheral noradrenergic
- Central serotonergic

### ■ Treatment:

- Terazosin:  $\alpha_1$  blocker (be careful with orthostatic hypotension)

<http://www.ncbi.nlm.nih.gov/pubmed/23638448>

## **2.2.11. Osteoporosis**

## 2.2.11. Osteoporosis

- After many years of treatment:
  - Not well-studied
  - Associated with SSRIs in pharmacoepidemiological studies
- Mechanisms:
  - Serotonergic mechanisms in bone tissue

## **2.2.12. Discontinuation/ Withdrawal Syndrome**

## **2.2.12. Discontinuation/Withdrawal Syndromes**

**2.2.12.1. Newer Compounds**

**2.2.12.2. TCAs: Cholinergic  
Rebound**

## **2.2.12.1. Discontinuation**

**Syndrome: Newer Compounds**



## 2.2.12.1. Discontinuation Syndrome: Newer Compounds

### ■ Frequency:

- High: paroxetine and venlafaxine
- Intermediate: others
- Very rare if it exists: fluoxetine  
due to long half-life

### ■ Absent:

- Agomelatine
- Reboxetine

## 2.2.12.1. Discontinuation Syndrome: Newer Compounds

- Mechanisms: not well-understood
- Most frequent:
  - Acute headaches
  - Dizziness
  - Nausea
- Others:
  - Lethargy and sleep disturbances
  - Psychological symptoms:
    - Anxiety
    - Agitation
    - Irritability
    - Poor concentration

## 2.2.12.1. Withdrawal Syndrome: Newer Compounds

- The literature is confusing.
- Chouinard & Chouinard proposed a new classification with diagnostic criteria.

<http://www.ncbi.nlm.nih.gov/pubmed/25721565>

After SSRI or SNRI withdrawal:

- New withdrawal symptoms
- Rebound withdrawal
- Persistent post-withdrawal disorder

# 2.2.12.2. TCAs: Cholinergic Rebound

## 2.2.12.2. Cholinergic Rebound: TCAs

- Mechanisms:
  - Sudden discontinuation of TCAs
  - Cholinergic rebound due to lack of muscarinic blockade
- Symptoms:
  - Nausea/vomiting
  - Diarrhea
  - Diaphoresis
  - Restlessness
  - Insomnia
- They respond to anticholinergic drugs.

## **2.2.13. Risk for Bleeding**

## 2.2.13. Risk for Bleeding; SSRIs

- Rare but potentially lethal
- It can happen with SSRIs without any other risk <http://www.ncbi.nlm.nih.gov/pubmed/22424167>
- Typically in combination:
  - Drugs with hemorrhagic risk
  - Surgery
  - Delivery

## 2.2.13. Risk for Bleeding

### ■ Main mechanism:

- Serotonin depletion at platelets due to inhibition of serotonin transporter

### ■ Other mechanisms:

<http://www.ncbi.nlm.nih.gov/pubmed/21190637>

- ↑ Gastric acid secretion: for upper gastrointestinal bleeding
- ↓ Ischemic heart disease
  - ↓ Platelet reactivity
  - ↓ Endothelial reactivity
  - Inflammatory markers



## **2.2.14. Serotonin Syndrome**

## 2.2.14. Serotonin Syndrome

- Rare but potentially lethal.
- Mechanism: ↑ serotonin activity
  - Central nervous system, and
  - Periphery
- Usually combinations of serotonergic drugs

## 2.2.14. Serotonin Syndrome

### ■ Main symptoms that warrant the diagnosis

- 1) Spontaneous clonus,
  - 2) Inducible clonus with agitation or diaphoresis,
  - 3) Ocular clonus with agitation or diaphoresis, or
  - 4) Tremor and hyperreflexia.
- Hypertonia,  $T > 38^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ )  
and ocular or inducible clonus

<http://www.ncbi.nlm.nih.gov/pubmed/20433130> pdf available at PubMed.

### ■ Ocular clonus: slow, continuous, horizontal eye movements

## **2.2.15. Arrhythmias**

## 2.2.15. Arrhythmias

2.2.15.1. Arrhythmias by TCAs

2.2.15.2. Torsades de Pointes

2.2.15.3. Risks for Brugada Syndrome

**2.2.15.1.**

**Arrhythmias  
due to TCAs**

## 2.2.15.1. Arrhythmias due to TCAs

- Blockade of heart sodium repolarizing channels
- Manifests in:
  - QRS widening
  - QTc prolongation
  - Ventricular arrhythmias
- Dose-related:
  - High serum concentrations
  - An overdose can be lethal.
- Narrow therapeutic window

**2.2.15.2.**

**Torsades de Pointes**



## 2.2.15.2. Torsades de Pointes

- Blockade of heart potassium repolarizing channels which are encoded by the human ether-a-go-go-related gene (HERG).
- Torsades de Pointes has been described for:
  - Citalopram
  - Fluoxetine
  - Sertraline. <http://www.ncbi.nlm.nih.gov/pubmed/25114780>

## 2.2.15.2. Torsades de Pointes

- Most cases of drug-induced torsades de pointes occur in the context of substantial prolongation of the QTc interval, typically ( $>500$  msec), but QTc alone is a relatively poor predictor of arrhythmic risk in any individual patient.
- Citalopram US prescribing information recommends against doses  $> 40$  mg/day.

## 2.2.15.2. Torsades de Pointes

- The literature on clinical cases of torsades de pointes is very complex.
  - Cases frequently include polypharmacy and DDIs with:
    - A pharmacodynamic component: multiple drugs with HERG channel inhibitory properties and sometimes
    - A pharmacokinetic component: an inhibitor ↑ concentrations of one or several of the drugs
  - Other risk factors

## 2.2.15.2. Torsades de Pointes

- Other risk factors:
  - Geriatric age
  - Female gender
  - Bradycardia
  - Hypokalemia
  - Hypomagnesemia
- Be careful when prescribing SSRIs in patients with risk factors.
- Be extremely careful when prescribing SSRI-antipsychotic combinations in patients with risk factors.

**2.2.15.3.**

**Brugada Syndrome**

## 2.2.15.3. Brugada Syndrome

- Genetic channelopathy at heart repolarizing channels, either:
  - Sodium
  - Potassium
  - Calcium
- Characterized by:
  - High incidence of ventricular fibrillation and
  - Specific ECG pattern:
    - Pseudo right bundle branch block and
    - Persistent ST elevation in  $V_1$  to  $V_3$ .

## 2.2.15.3. Brugada Syndrome

- It is preferable to avoid:
  - Fluoxetine
  - Fluvoxamine
  - Paroxetine

<http://www.brugadadrugs.org/advisory-board/>

## **2.2.16. Neutropenia**



## 2.2.16. Neutropenia

- Mechanism: unknown
- Described with mirtazapine on rare occasions

## **2.2.17. Hyponatremia**

## 2.2.17. Risk for Hyponatremia

- Rare cases have been described with all antidepressants, usually in geriatric patients, particularly females.
- Mechanism:
  - SIADH and/or  $\uparrow$  ADH sensitivity
  - It is not understood how antidepressants can cause it.

## **2.2.18. Liver Injury**

## **2.2.18. Liver Injury**

**2.2.18.1. ↑ Liver Enzymes**

**2.2.18.2. Life-Threatening  
Liver Injury**

**2.2.18.1.**

**↑ Liver Enzymes**

## 2.2.18.1. ↑ Liver Enzymes

- Mechanism: unknown
- Agomelatine:
  - Up to 5% in 50 mg/day
- Other antidepressants:
  - Rare

**2.2.18.2.**

**Life-Threatening  
Liver Injury**



## 2.2.18.2. Life-Threatening Liver Injury

### ■ Mechanism:

- Immuno-allergy or
- Toxicity from metabolites

### ■ Risk: <http://www.ncbi.nlm.nih.gov/pubmed/24362450>

- Agomelatine>
- Bupropion, duloxetine, TCAs>
- Others>
- Lowest: citalopram, escitalopram, fluoxetine and paroxetine

**3. Pharmacokinetics  
Facilitates  
Pharmacodynamics**

### 3. Pharmacokinetics Facilitates Pharmacodynamics

- Pharmacokinetics facilitates pharmacodynamics.
- Efficacy:
  - Sufficient drug concentration may be needed.
  - Once there is sufficient drug concentration, pharmacodynamics determines efficacy.
- Safety:
  - ADRs are dose-related: sufficient concentration at the action site may be needed.  
Pharmacokinetics plays a facilitator role.
  - When ADRs are not dose-related: small concentrations at the action site may be enough.  
Pharmacokinetics may not be relevant.

### 3. Pharmacokinetics Facilitates Pharmacodynamics

- Pharmacodynamics probably determines specific ADRs in a patient when concentrations at the site of action are sufficient for “toxicity”.  
Too-high drug concentrations (pharmacokinetics):  
contribute to poor safety in general.
- Pharmacodynamic factors probably determine
  - Whether ADRs develop or not
  - Which ADRs

# 4. The “Do Not Forget” Section

## 4. The “Do Not Forget” Section

- This is a very long and complex presentation:
  - Efficacy: list 11 possible reasons for prescription
  - Safety brain mechanisms: list 7 ADRs
  - Safety periphery mechanisms: list 18 ADRs
- Dr. de Leon is not an expert in this area but decided to select for the “Do Not Forget Section”:
  - Common ADRs of antidepressants commonly prescribed in the USA
  - Possible lethal ADRs
  - Reflections on TCAs

## 4. The “Do Not Forget” Section

- 4.1. Common ADRs of Antidepressants Commonly Prescribed in the USA
- 4.2. Possible Lethal ADRs
- 4.3. Reflections on TCAs

# **4.1. Common ADRs of Antidepressants Commonly Prescribed in the USA**



## 4.1. Common ADRs

- A recent US antidepressant trial in primary care:
  - included a “Depression Medication Choice” aid, and
  - studied 11 antidepressants:

- citalopram
- escitalopram
- fluoxetine
- paroxetine
- sertraline
- amitriptyline or nortriptyline as TCAs
- desvenlafaxine
- duloxetine
- venlafaxine
- bupropion
- mirtazapine

<http://www.ncbi.nlm.nih.gov/pubmed/26414670>

## 4.1. Common ADRs

- Provide ratings on 6 issues with “+s” or “-s”:

- Sleep
- Weight changes
- Stopping approaches
- Sexual issues
- Costs
- Keep in mind GI ADRs and other issues.

The take home patient leaflets are provided in supplemental material <http://archinte.jamanetwork.com/article.aspx?articleid=2443367> and are summarized in the next slides.

- The “Depression Medication Choice” aid appears to Dr. de Leon to be an updated reasonable summary of the most frequent antidepressants used in the USA. Experts may disagree on some of the details on ADRs.

## **4.1. Common ADRs**

(Depression Medication Choice Aid)

4.1.1. Sleep

4.1.2. Weight Change

4.1.3. Stopping Approach

4.1.4. Sexual Issues

4.1.5. GI ADRs

4.1.6. Other Issues

## **4.1.1. Sleep**

### **(Depression Medication Choice Aid)**

## 4.1.1. Sleep (Depression Medication Choice Aid)

### ■ Insomnia/sleepiness:

□ Insomnia: ++: ● bupropion

□ Sleepiness: ++: ● mirtazapine  
● TCAs

## **4.1.2. Weight Change (Depression Medication Choice Aid)**

## 4.1.2. Weight Change (Depression Medication Choice Aid)

### ■ Weight:

- Gain: ++++: ● escitalopram
  - paroxetine
  - mirtazapine
  - TCAs
- +++ : ● citalopram
- ++ : ● duloxetine
  - venlafaxine
- + : ● sertraline
- Loss: - : ● duloxetine
- : ● bupropion

## **4.1.3. Stopping Approach (Depression Medication Choice Aid)**



### 4.1.3. Stopping Approach (Depression Medication Choice Aid)

#### ■ Quitting will make you sick:

+++:

- paroxetine (sickness if you skip)

- venlafaxine (sickness if you skip)

+:

- citalopram

- escitalopram

- fluvoxamine

- sertraline

- desvenlafaxine (some risk of sickness if you skip)

- duloxetine (some risk of sickness if you skip)

- bupropion

- mirtazapine

- TCAs

#### ■ No risk:

- fluoxetine

## **4.1.4. Sexual Issues**

### **(Depression Medication Choice Aid)**

#### 4.1.4. Sexual Issues (Depression Medication Choice Aid)

##### ■ Libido:

- Less: ---: ● paroxetine
- : ● TCAs
- : ● citalopram
- escitalopram
- fluoxetine
- fluvoxamine
- sertraline
- desvenlafaxine
- duloxetine
- venlafaxine
- mirtazapine
- More: ++: ● bupropion

**4.1.5. GI ADRs**  
**(Depression Medication Choice Aid)**

#### 4.1.5. GI ADRs (Depression Medication Choice Aid)

- Fluvoxamine: more likely to cause constipation, diarrhea or nausea
- Sertraline: more likely to cause diarrhea
- Venlafaxine: more likely to cause nausea/vomiting
- TCAs: more likely to cause constipation, diarrhea or nausea

## **4.1.6. Other Issues**

### **(Depression Medication Choice Aid)**

#### 4.1.6. Other Issues (Depression Medication Choice Aid)

- Citalopram: risk of QTc prolongation
- Fluoxetine: DDIs (inhibit other drugs)
- Fluvoxamine: no US approval for depression
- Paroxetine: risk of teratogenicity
- Desvenlafaxine: hypertension issues
- Duloxetine: hypertension issues  
can help ease pain
- Venlafaxine: hypertension and cardiac issues
- Bupropion: higher risk of seizure
- Mirtazapine: starts to work more quickly
- TCAs: can help ease pain  
not a good choice for the elderly

## **4.2. Possible Lethal ADRs**



## 4.2. Possible Lethal ADRs

- Dr. de Leon has reviewed >600 deaths at Kentucky state mental health facilities since 2002:
  - Antipsychotics occasionally cause deaths.
  - Mood stabilizers occasionally cause deaths.
  - Antidepressants have not caused deaths.

There was not clear case of overdose only by TCAs but TCAs are rarely prescribed.
- Antidepressants can contribute to deaths through:
  - Arrhythmias
  - Serotonin syndrome
  - Hemorrhages

## **4.3. Reflections on TCAs**

### 4.3. Reflections on TCAs

- TCAs are rarely used as antidepressants by non-psychiatrists.
  - Thus, TCA expertise may be a “niche” skill that psychiatrists need to master.  
If you use TCAs, you need expertise on:
    - ADRs: many are dose-related, including risk for arrhythmias
    - TCA pharmacokinetics, including:
      - CYP2D6 and CYP2C19 genotyping
      - TDM
- See “Antidepressant Pharmacokinetics”.

# References for Antidepressant Pharmacodynamics

- 1) 2014 article <http://www.ncbi.nlm.nih.gov/pubmed/25196459> with pdf [http://uknowledge.uky.edu/psychiatry\\_facpub/40/](http://uknowledge.uky.edu/psychiatry_facpub/40/) has the best figures for all antidepressant pharmacodynamics and focuses on AED DDIs.
- 2) 2014 article <http://www.ncbi.nlm.nih.gov/pubmed/24494611> with pdf [http://uknowledge.uky.edu/psychiatry\\_facpub/42/](http://uknowledge.uky.edu/psychiatry_facpub/42/) focuses on DDIs between second-generation antidepressants and second-generation antipsychotics.

# Questions

- Please review the 10 questions in the pdf titled “Questions on the Presentation: Pharmacodynamics 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. D

4. A

5. C

6. A

7. D

8. D

9. D

10. A