



# Antidepressant Agents

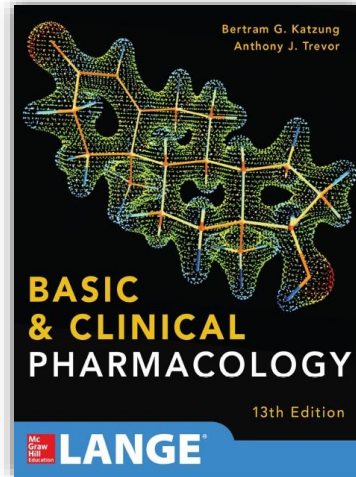
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# Basic & Clinical Pharmacology

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Chapter 30



## Outlines

### Antidepressant drugs

- Classification
- Pharmacokinetics
- Mechanism of pharmacological action
- Clinical indications
- Side effects
- Drug interactions



## Major Depression (MD)

- The diagnosis of depression still rests on the clinical interview
- Diagnosis requires presence of 5 of the following for at least 2 weeks:
  - Sad, depressed daily mood
  - Loss of interest in usual activities
  - Difficulties in sleeping
  - Poor appetite and weight loss
  - Loss of energy, great fatigue
  - Negative self-concept
  - Recurrent thoughts of suicide or death



## Major Depression (MD)

- Antidepressants are among the three most commonly prescribed classes of medications in the USA
- MD is associated with a variety of other problems
  - Disability
  - Chronic pain
  - Coronary artery disease
  - Patient's disease burden
  - High mortality rate



# Pathophysiology of MD

## The monoamine hypothesis

- Deficiency in the amount or function of cortical & limbic 5-HT, NE, DA
  - Reserpine treatment is associated with depression
  - Reduction in the 5-hydroxyindoleacetic acid in CSF
  - Diets free of tryptophan causes relapse of depression
  - All available antidepressants appear to have significant effects on the monoamine system

Limitation ???



# Pathophysiology of MD

## The Neurotrophic hypothesis

- Loss of neurotrophic support in CNS
  - Neurotrophic factors are critical in the regulation of neural plasticity and neurogenesis
  - Structural imaging has shown 5–10% loss of volume in the hippocampus in MD patients
  - Stress & pain are associated with a drop in BDNF levels
  - BDNF administration causes an antidepressant-like effect in animal models
  - All classes of antidepressants are associated with an increase in BDNF levels in CNS

# Pathophysiology of MD

## The Neuroendocrine hypothesis

- MD is known to be associated with a number of hormonal abnormalities
  - Both exogenous & endogenous glucocorticoids elevation cause mood symptoms and cognitive deficits
  - Thyroid dysregulation has also been reported in depressed
  - Sex hormones are also implicated in the pathophysiology of depression



## Antidepressant drugs

### 1. Selective serotonin reuptake inhibitors (SSRIs)

- One of the most commonly prescribed medications in medical practice
- Inhibition the activity of SERT
- Allosteric inhibitor
  - Fluoxetine
  - Sertraline
  - Citalopram
  - Paroxetine
  - Fluvoxamine
  - Escitalopram

# Antidepressant drugs

## 1. Selective serotonin reuptake inhibitors (SSRIs)

- SSRIs are highly lipophilic
- Fluoxetine has the longest half-life of all the SSRIs
- Fluoxetine & paroxetine are potent inhibitors of the CYP2D6 isoenzyme
- Fluvoxamine is an inhibitor of CYP3A4 isoenzyme



# Antidepressant drugs

## 2. Serotonin-norepinephrine reuptake inhibitors

### A. Serotonin-norepinephrine reuptake inhibitors

- Inhibit the activity of both SERT and NET
- SNRIs tends to be much greater for SERT than for NET

- |                  |                   |
|------------------|-------------------|
| ▪ Venlafaxine    | ▪ Milnacipran     |
| ▪ Desvenlafaxine | ▪ Levomilnacipran |
| ▪ Duloxetine     |                   |



## Antidepressant drugs

### 2. Serotonin-norepinephrine reuptake inhibitors

#### A. Serotonin-norepinephrine reuptake inhibitors

- Duloxetine & milnacipran is well absorbed
- Venlafaxine & desvenlafaxine have the lowest protein binding of all antidepressants (27–30%)
- Hepatic impairment significantly alters duloxetine levels unlike desvenlafaxine



## Antidepressant drugs

### 2. Serotonin-norepinephrine reuptake inhibitors

#### B. Tricyclic antidepressants (TCAs)

- Inhibit the activity of both SERT and NET
- There is difference in affinity for SERT & NET among TCAs
- TCAs have potent  $H_1$ ,  $\alpha$ -adrenergic, muscarinic, 5-HT<sub>2</sub> receptor blocking effects
  - Imipramine
  - Desipramine
  - Amitriptyline
  - Nortriptyline
  - Clomipramine
  - Trimipramine
  - Doxepin



## Antidepressant drugs

### 2. Serotonin–norepinephrine reuptake inhibitors

#### B. Tricyclic antidepressants (TCAs)

- Clomipramine has high affinity for SERT
  - Desipramine & nortriptyline have high affinity for NET
  - TCAs are well-absorbed and have long half-lives
  - Metabolism of TCAs consists of demethylation, hydroxylation, and glucuronide conjugation
  - TCAs are substrates of the CYP2D6 system
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## Antidepressant drugs

### 2. Serotonin–norepinephrine reuptake inhibitors

#### C. 5-HT<sub>2</sub> Receptor Modulators

- Potent 5-HT<sub>2</sub> antagonists
  - Trazodone is a potent sedative without tolerance or dependence
  - Trazodone has a weak  $\alpha$ -adrenergic and modest H<sub>1</sub> receptor blocking effects
- |             |              |
|-------------|--------------|
| ▪ Trazodone | ▪ Nefazodone |
|-------------|--------------|
- 

## Antidepressant drugs

### 2. Serotonin–norepinephrine reuptake inhibitors

#### C. 5-HT<sub>2</sub> Receptor Modulators

- Trazodone and nefazodone are rapidly absorbed
- They have limited bioavailability because of extensive metabolism
- Both trazodone and nefazodone have active metabolites that also exhibit 5-HT<sub>2</sub> antagonism
- Nefazodone is a potent inhibitor of the CYP3A4 system



## Antidepressant drugs

### 2. Serotonin–norepinephrine reuptake inhibitors

#### D. Tetracyclic and Unicyclic Antidepressants

- They have a complex pharmacology
- Use to treat MD which is unresponsive to other agents
- Special side effects

- |               |               |
|---------------|---------------|
| ▪ Bupropion   | ▪ Amoxapine   |
| ▪ Mirtazapine | ▪ Maprotiline |



# Antidepressant drugs

## 3. Monoamine Oxidase Inhibitors (MAOIs)

- The first modern class of antidepressants
  - The MAOIs are well absorbed from GI & have extensive first-pass effects
  - They have severe toxicity and potentially lethal food and drug interactions
  - Use to treat MD which is unresponsive to other agents
- |                          |                      |
|--------------------------|----------------------|
| ▪ <b>Phenelzine</b>      | ▪ <b>Moclobemide</b> |
| ▪ <b>Isocarboxazid</b>   |                      |
| ▪ <b>Tranylcypromine</b> |                      |



## Clinical Indications

### Depression

- Both acute and long-term treatment of MD
- The goal of acute treatment of MD is remission of all symptoms
- Acute episodes of MD lasts about 6–14 months untreated, but some episodes last 2 years or longer
- Cognitive behavioral therapy appear to be as effective as antidepressant treatment for mild to moderate forms of depression



## Clinical Indications

### Anxiety disorders

- GAD, PTSD, OCD, social anxiety disorder, panic disorder
- BZDs provide much more rapid relief of panic attack
- No risk of dependence and tolerance

### Pain disorders

- Neuropathic and other pain conditions (TCAs)
  - Chronic joint and muscle pain (Duloxetine)
  - Postherpetic neuralgia to chronic back pain (Desvenlafaxine)
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## Clinical Indications

### Premenstrual dysphoric disorder

- Prominent mood & physical symptoms during the late luteal phase of every cycle
- Anxiety, depressed mood, irritability, insomnia, fatigue, and a variety of other physical symptoms

### Smoking cessation

### Eating disorders

- Bulimia nervosa & anorexia nervosa
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# Clinical Indications

## Other uses for antidepressants

- TCAs uses in treatment of enuresis in children
- Duloxetine is approved in Europe for the treatment of urinary stress incontinence
- Desvenlafaxine uses in treatment of vasomotor symptom of perimenopause patients
- SSRIs use for premature ejaculation
- Bupropion uses to treat sexual adverse effects associated with SSRI use



# Side effects

## SSRIs

- GI side effects
  - Nausea, Diarrhea
  - Decrease after the first week
- Reduction of Libido, Delayed orgasm, Anorgasmia
  - 30-40% of Patients
- Headaches, Insomnia or Hypersomnia
- Weight Gain (particularly Paroxetine)
- Side effect are tolerable generally
- Discontinuation syndrome



## Side effects

### SNRIs

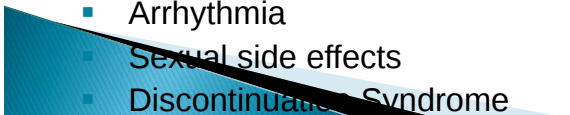
- Cardiovascular
  - increase in BP & HR
- CNS activation
  - Insomnia, anxiety, and agitation
- All SNRIs have discontinuation syndrome resembling that seen with SSRI



## Side effects

### TCAs

- Muscarinic blocking effects
  - Most common
  - Dry mouth, constipation, urinary retention, blurred vision, and confusion
  - Older patients are particularly sensitive
  - Amitriptyline & Imipramine > Desipramine & Nortriptyline
- H<sub>1</sub> blocking effects
  - Orthostatic Hypotension
- $\alpha$ -adrenergic blocking effects
  - Sedation, Weight Gain
- Arrhythmia
- Sexual side effects
- Discontinuation Syndrome



## Side effects

### MAOIs

- Orthostatic hypotension (most common)
- Weight gain
- Sexual side effects (higher than any antidepressant)
- Amphetamine-like effect
  - Activation, insomnia, and restlessness in some patients
- Anticholinergic Side Effects
- Discontinuation Syndrome



## Drug interactions

### SSRIs

- Paroxetine and fluoxetine are potent CYP2D6 inhibitors
- Fluvoxamine is a CYP3A4 inhibitor
- SSRIs have pharmacodynamic interactions with MAOIs to produce a serotonin syndrome



## Drug interactions

### SNRIs, TCAs

- Duloxetine is a moderate inhibitor of CYP2D6
  - SNRIs have pharmacodynamic interactions with MAOIs to produce a serotonin syndrome
  - Elevated TCA levels may occur when these used with CYP2D6 inhibitors
  - Additive anticholinergic or antihistamine effects when TCAs used with other agents with these properties
  - Antihypertensive drugs may exacerbate the orthostatic hypotension induced by TCAs
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## Drug interactions

### MAOIs

- Serotonergic agents including SSRIs, SNRIs, most TCAs, meperidine, tramadol
    - Serotonergic agent may result in a life-threatening serotonin syndrome
  - Tyramine in the diet or sympathomimetic drugs
    - Aged cheeses, beer, soy products, and dried sausages
    - Pseudoephedrine and phenylpropanolamine
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# Serotonin syndrome

- Caused by overstimulation of 5-HT receptors in the central gray nuclei & the medulla
- Symptoms range from mild to lethal
  - Cognitive (delirium, coma)
  - Autonomic (hypertension, tachycardia, diaphoreses)
  - Somatic (myoclonus, hyperreflexia, tremor)
- Serotonergic antidepressants should be discontinued at least 2 weeks before starting an MAOI
- MAOIs must be discontinued for at least 2 weeks before starting a serotonergic agent

