

Module: CNS  
Subject: Pharmacology  
Lecture: MBBS



# *Antidepressant Drugs-1*

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# *Mental Depression... What is it ?*



# *What is Mental Depression ?-Mood Disorder*

- **Unipolar Depression (Major Depression)**
  - Strong and enduring feelings of sadness, hopelessness, worthlessness, and inability to experience pleasure.
  - Relatively common.

Pleasure seeking = Hedonistic  
Inability to experience pleasure  
= **Anhedonia**



# *Disorders of Mood (Affective Disorders)*

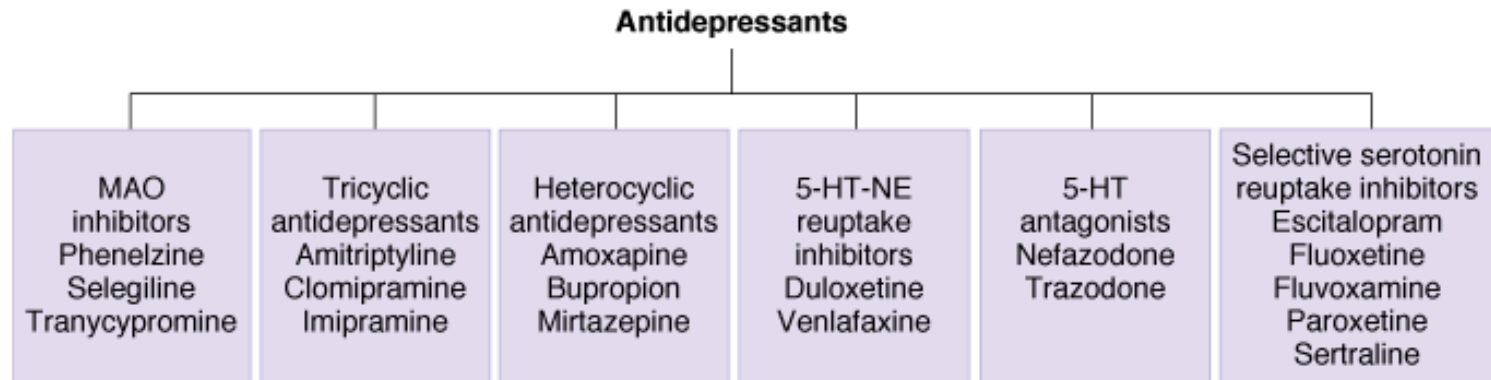
- Depression (unipolar depression)
- Mania
- Manic-depression (bipolar depression)

- 
- ```
graph LR; A[Depression (unipolar depression), Mania, Manic-depression (bipolar depression)] --> B[Reactive depression (75%), Endogenous depression (25%)];
```
- Reactive depression (75%)
  - Endogenous depression (25%)

What are the [possible mechanisms](#) of depression ?

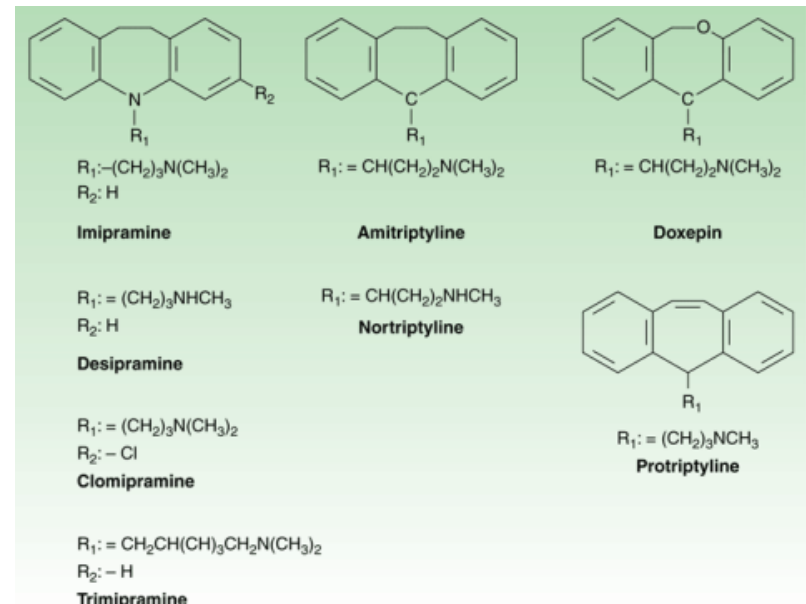
- Depression is associated with [insufficient central release of NE and 5-HT](#)
- Led to development of the Biogenic Amine Hypothesis

# Antidepressant Drugs-Classification



## ■ Tricyclic Agents

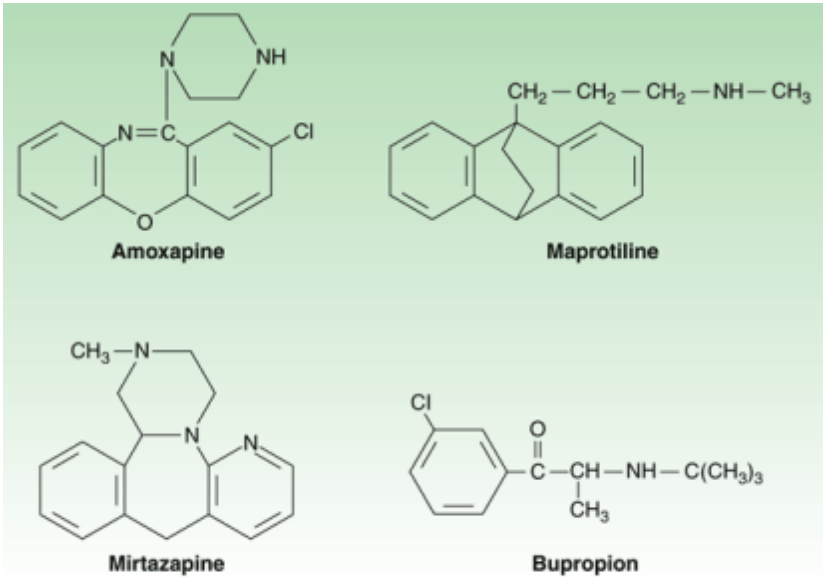
- Imipramine/Desipramine/  
Clomipramine/  
Amitriptyline/Nortriptyline/  
Protriptyline/Doxepin/  
Nordoxepin



Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th edition: www.accessmedicine.com

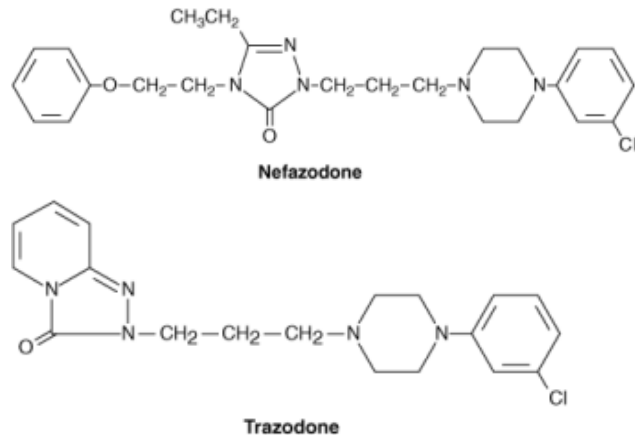
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# Antidepressant Drugs-Classification (contd.)



Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th edition: www.accessmedicine.com

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## ■ Heterocyclic Agents

### □ Unicyclic

#### ■ Bupropion

### □ Tetracyclic

#### ■ Amoxapine(N-desmethyl loxapine)/Maprotilene/ Mirtazapine

## ■ 5-HT<sub>2</sub> Antagonists

### □ Nefazodone/Trazodone

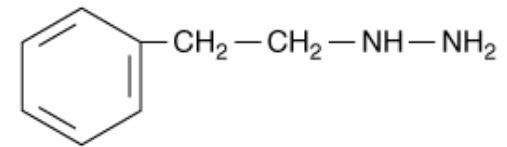
# *Antidepressant Drugs-Classification*

## *(contd.)*

### ■ Mono-Amine-Oxidase-A Isozyme Inhibitors (MAO-AI's)

#### □ Hydrazine group

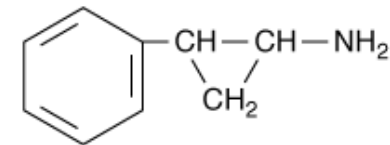
- Isocarboxazid/Phenelzine



Phenelzine

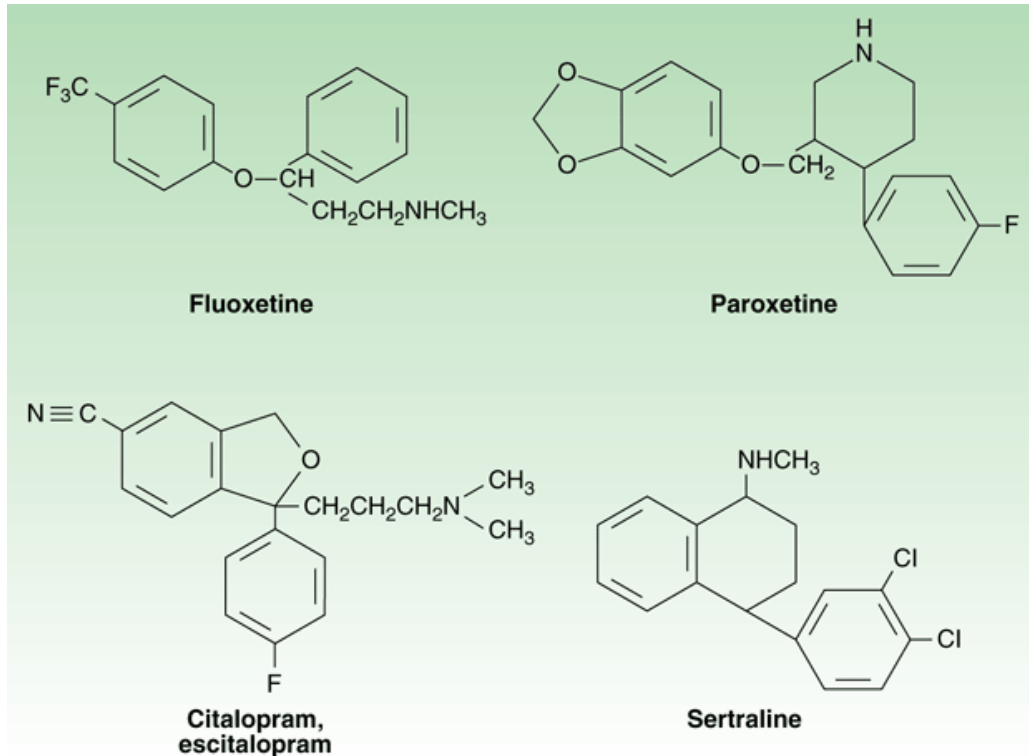
#### □ Nonhydrazine group

- Nialamide/Tranlycypromine/Clorgyline/Pargyline/  
Moclobemide/Brofaromine/Cimoxatone/Toloxatone



Tranlycypromine

# Selective Serotonin Reuptake Inhibitors (SSRI's)



## ■ Selective Serotonin Reuptake Inhibitors (SSRI's)

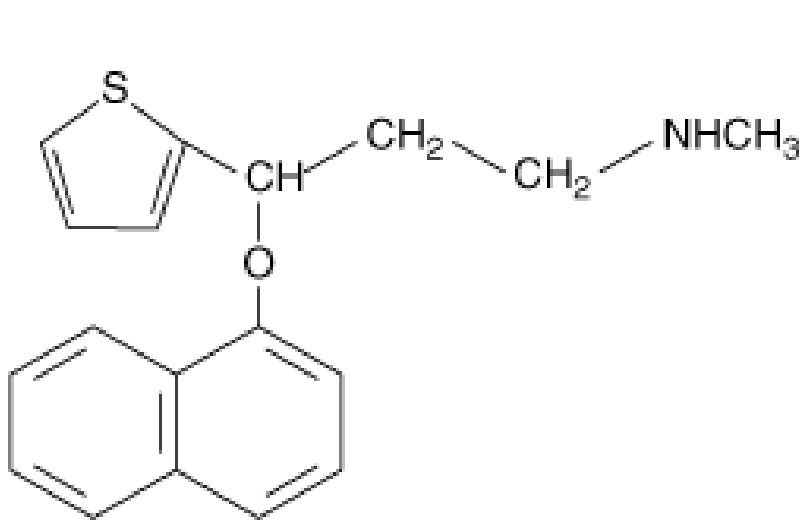
- Citalopram/  
Escitalopram/  
Fluoxetine/  
Paroxetine/  
Sertraline/  
Fluvoxamine

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition: [www.accessmedicine.com](http://www.accessmedicine.com)

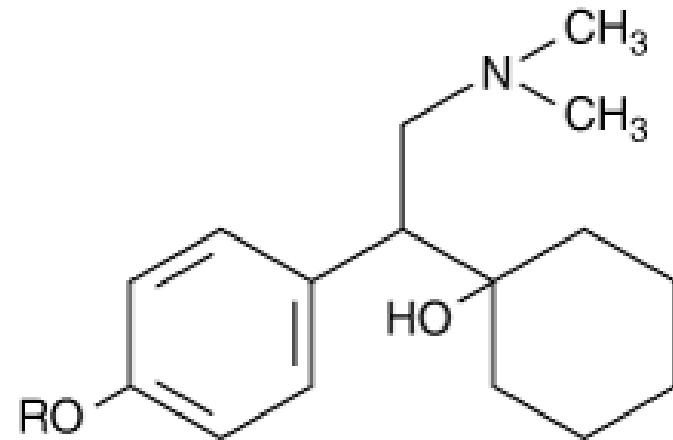
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# *Serotonin NE Reuptake Inhibitors (SNRI's)*



Duloxetine



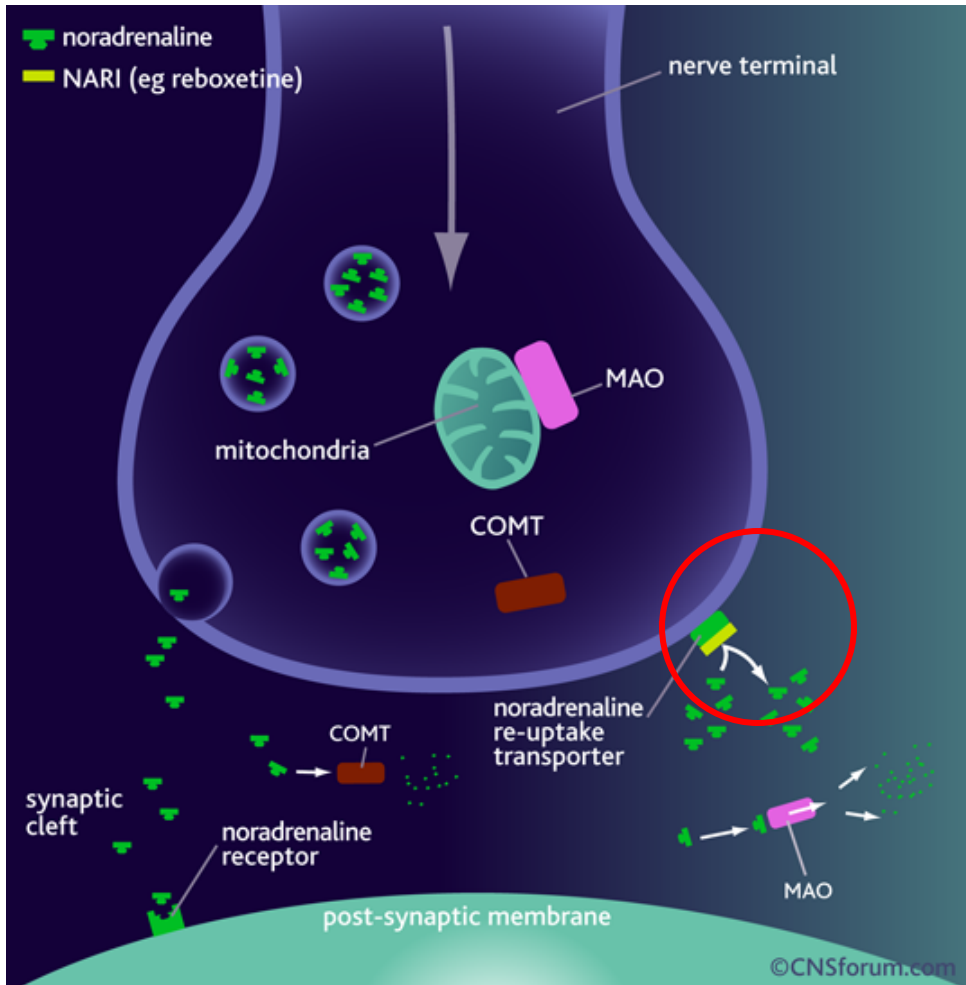
R = CH<sub>3</sub> : Venlafaxine

R = H : Desvenlafaxine

## ■ Serotonin Norepinephrine Reuptake Inhibitors (SNRI's)

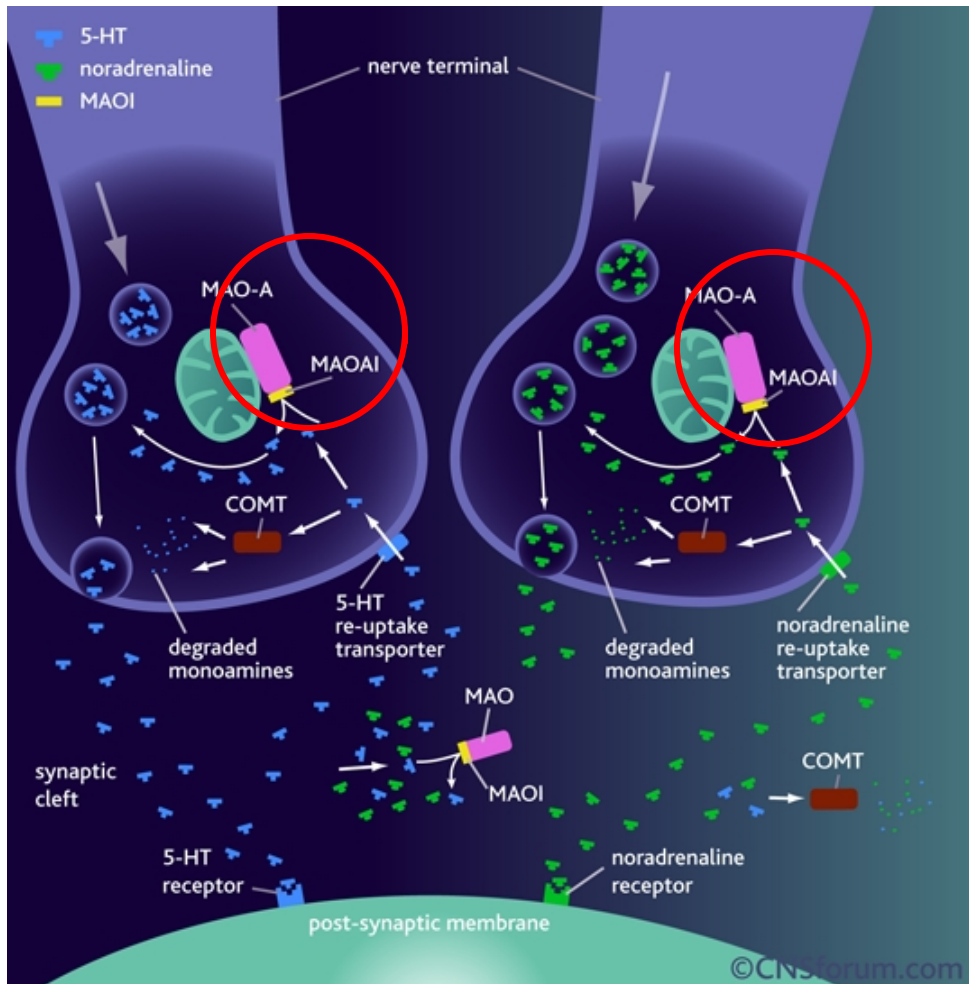
- Duloxetine
- Venlafaxine
- Desvenlafaxine

# Postulated Mode of Action of Tricyclic Antidepressant Drugs



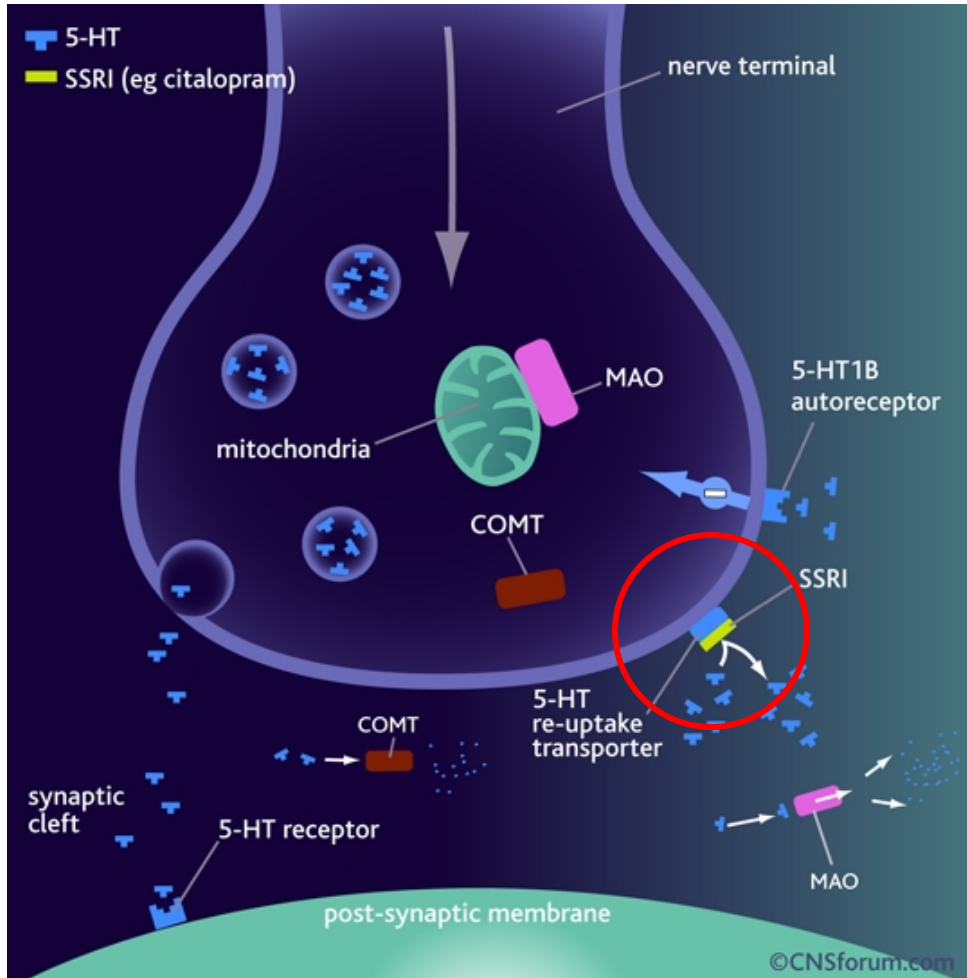
- TCA's → ↓ NE / ↓ 5-HT reuptake (↓ NET / ↓ SERT) → ↑ monoaminergic neurotransmission → Antidepressant action

# Postulated Mode of Action of MAO-A Inhibitor Drugs



- MAO-AI's → ↓ MAO-A isozyme → ↓ monoamine metabolism → ↑ monoaminergic neurotransmission → Antidepressant action

# SSRI's-Mechanism of Action



- SSRI's → selective  
↓ 5-HT reuptake  
(↓ SERT) →  
↑ monoaminergic  
(serotonergic)  
neurotransmission  
→ Antidepressant  
action

# *Tricyclic Antidepressants (TCA's)- Pharmacological Actions*

## ■ CNS Actions

- Mood elevation in depressed patients
- Latency period: 2-4 weeks
- Can cause EPS/Ataxia/Seizures/Coma

## ■ CVS Actions

- Orthostatic hypotension → ↑HR

## ■ ANS Actions

- Anticholinergic effects
- Most potent anticholinergic action (Amitriptyline)

# *Tricyclic Antidepressants (TCA's)- Pharmacokinetics*

## ■ Absorption

- Well absorbed orally

## ■ Distribution

- ↑ **Lipophilic** → ↑  $V_d$  → ↑  $T(1/2)$

## ■ Metabolism & Excretion

- Hepatic microsomal N-demethylation/  
oxidation/glucuronidation → **Renal Elimination**

# *Tricyclic Antidepressants(TCA's)- Therapeutic Uses*

- Severe endogenous depression (TCA's drug of choice)
- Nocturnal enuresis(Imipramine)
- Panic Disorder(Imipramine)
- **Obsessive-Compulsive Disorders(Clomipramine)**
- Chronic Neuropathic Pain(e.g., Trigeminal Neuralgia/Diabetic Neuropathy/Tabetic Neuropathy)
- Others(Eating Disorders(Bulimia)/Narcolepsy/School Phobia/ADHD)

# *Tricyclic Antidepressants(TCA's)-Adverse Effects*

- Excessive sedation/Lassitude/Fatigue/Confusion
- Sympathomimetic effects(Tachycardia/Agitation/Sweating/Insomnia)
- Anticholinergic('Atropine-like") effects
- Orthostatic hypotension/ECG abnormalities/Cardiomyopathies
- Tremor/Paresthesias/EPS



# *Tricyclic Antidepressants(TCA's)-Adverse Effects*

- Weight gain
- Overdosage(extremely hazardous): Remember 3C's
  - Agitation/Delirium/Neuromuscular irritability/Convulsions/Coma
  - Respiratory depression/Circulatory collapse
  - Hyperpyrexia
  - Cardiotoxicity(Cardiac conduction defects/Severe arrhythmias)

Module: CNS  
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# *Antidepressant Drugs-2*

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# *MAO-AI's-Pharmacological Actions*

## ■ CNS Actions

- Mood elevation
- Latency period: 2-3 weeks
- Tranylcypromine → Amphetamine-like → causes NE release in CNS → antidepressant action (48 h)
- MAOI's → ↓ REM sleep / ↓ Narcolepsy

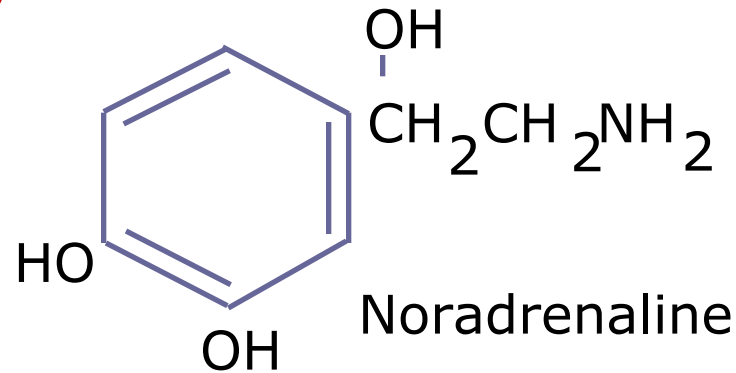
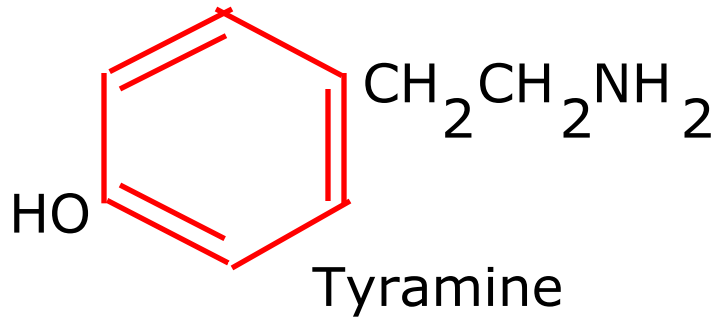
# *MAO-AI's-Pharmacological Actions*

## *(contd.)*

### ■ CVS Actions

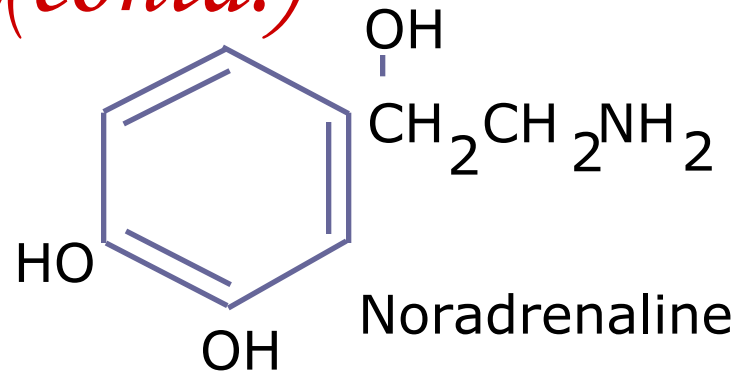
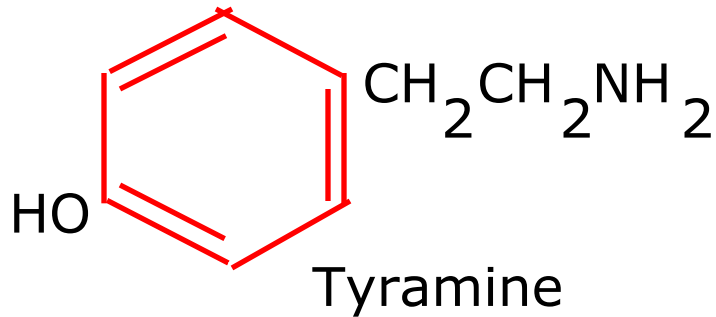
- Postural hypotension
- Beer/Cheese/Chicken Liver → ↑ Tyramine content / ↓ Tyramine metabolism → ↑↑ catecholamine release (nerve terminals) → **Hypertensive Crisis (Cheese Reaction)**

# *MAOI Interaction with Tyramine (‘Cheese Reaction’)*



- Tyramine is normally metabolized by MAO in gut and liver
- **If** unmetabolized, tyramine enters sympathetic nerve terminals where it displaces NE from vesicles into cytosol

# *MAOI Interaction with Tyramine (‘Cheese Reaction’)(contd.)*



- Because MAO in the nerve terminals is inhibited there is a massive ‘non-physiological’ release of NE from sympathetic nerve terminals which can lead to fatal hemorrhage
- Patients prescribed an MAOI are warned not to eat/drink certain substances (substances that contain tyramine etc.) e.g. beer, wine, cheese, marmite

# *MAO-AI's-Pharmacological Actions*

## *(contd.)*

### ■ Hepatic Actions

- Cause hepatotoxicity
- Interference with drug detoxification

# *MAO-AI's-Pharmacokinetics*

- MAO inhibitors are taken orally
- They are 'hit & run' drugs i.e., their effects greatly outlast their detectable presence in the body because they inhibit the enzyme irreversibly & termination of effect is dependent on synthesis of fresh enzyme(which takes weeks)
- The hydrazine group is acetylated(like INH) & the population is divided into slow & fast acetylators



# *MAO-AI's-Therapeutic Uses*

- Atypical Depression
  - Hyperanxiety/Hyperphagia/Hypersomnolence
- Panic Disorder

# *MAOI's-Adverse Effects & Drug Interactions*

## ■ Adverse Effects

- Headache/Drowsiness/Dry mouth/Weight gain/  
Orthostatic hypotension/Impotence/**Cheese Reaction**

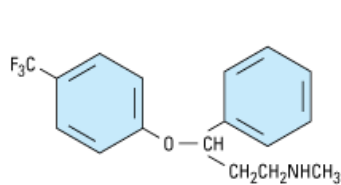
## ■ Drug Interactions

- MAOI's + SSRI's → **Serotonin Syndrome**(lethal)
- TCA's + CNS Depressants → ↑↑ CNS depression
- TCA's + MAOI's → Hyperpyrexia/Convulsions/ Coma

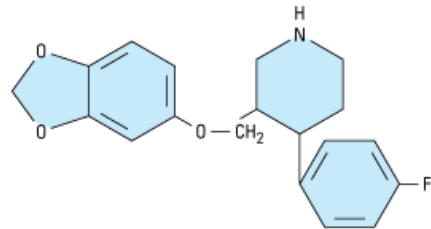
# *Selective Serotonin Reuptake Inhibitors (SSRI's)*



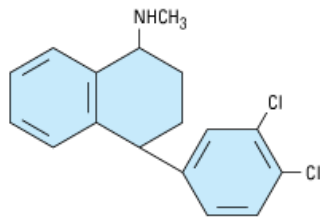
# Selective Serotonin Reuptake Inhibitors (SSRI's)



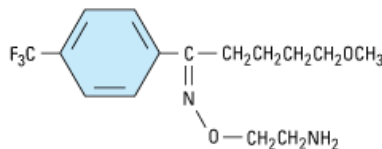
Fluoxetine



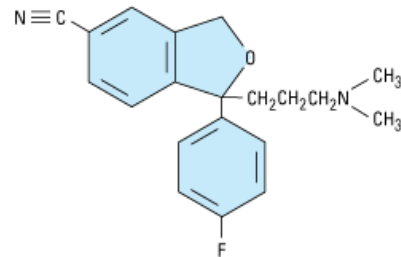
Paroxetine



Sertraline



Fluvoxamine



Citalopram

- Structurally distinct from the tricyclic molecules
- Have fewer adverse effects than the tricyclics and have become popular

# *Selective Serotonin Reuptake Inhibitors(SSRI's)-Pharmacokinetics*

## ■ Absorption

- Well-absorbed orally

## ■ Distribution

## ■ Metabolism

- Fluoxetine → Norfluoxetine

## ■ Excretion

- Renal elimination

- Elimination  $T(1/2)$  = 1-3 d(Fluoxetine)/  
7-15 d(Norfluoxetine)

# *Selective Serotonin Reuptake Inhibitors(SSRI's)-Therapeutic Uses*

- Endogenous Depression
- Obsessive-Compulsive Disorders
  - Fluoxetine/Clomipramine
- Panic Disorder

## *Case 7- Obsessive Compulsive Disorder(OCD)*

- A 33-year-old woman presents with a 7-year history of hand washing for 2-6 hours a day, as well as urges to check doors and stoves extensively before leaving her home.
- Her life is restricted, and her family members are upset about her behavior.
- How should she be evaluated and treated ?

[Jenike MA. Obsessive compulsive disorder. New Engl J Med 2004; 350: 259-265.]

# Case 7-Obsessive Compulsive Disorder(OCD)

**Table 1. DSM-IV Diagnostic Criteria for OCD.\***

Either obsessions or compulsions

Obsessions are defined by the following:

Recurrent and persistent thoughts, impulses, or images that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause marked anxiety or distress

Thoughts, impulses, or images that are not simply excessive worries about real-life problems

The effort by the affected person to ignore or suppress such thoughts, impulses, or images, or to neutralize them with some other thought or action

Recognition by the affected person that the obsessional thoughts, impulses, or images are a product of his or her own mind rather than imposed from without

Compulsions are defined by the following:

Repetitive activities (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession or according to rules that must be applied rigidly

Behavior or mental acts aimed at preventing or reducing distress or preventing some dreaded event or situation but either clearly excessive or not connected in a realistic way with what they are designed to neutralize or prevent

Recognition, by the affected person (unless he or she is a child), at some point during the course of the disorder, that the obsessions or compulsions are excessive or unreasonable

Obsessions or compulsions that cause marked distress, are time consuming (take more than 1 hr/day), or interfere substantially with the person's normal routine, occupational or academic functioning, or usual social activities or relationships

Content of the obsessions or compulsions not restricted to any other Axis I disorder, such as an obsession with food in the context of an eating disorder, that is present

Disturbance not due to the direct physiological effects of a substance or a general medical condition

Specified as OCD with poor insight if, for most of the time during the current episode, the person does not recognize that the obsessions and compulsions are excessive or unreasonable

\* DSM-IV denotes *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, and OCD obsessive-compulsive disorder.

## Behavioural Therapy Cognitive Therapy Medications

**Table 2. Recommended Treatments for OCD.\***

| Treatment                                          | Initial Daily Dose | Target Daily Dose | Common Side Effects                                                                                                                                        |
|----------------------------------------------------|--------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                    | mg                 |                   |                                                                                                                                                            |
| Selective serotonin-reuptake inhibitors†           |                    |                   | Anxiety, decreased libido, sexual dysfunction, diarrhea, sedation, headache, insomnia, dizziness, nausea                                                   |
| Fluoxetine (Prozac)                                | 20                 | 80                |                                                                                                                                                            |
| Fluvoxamine (Luvox)                                | 50                 | 300               |                                                                                                                                                            |
| Sertraline (Zoloft)                                | 50                 | 200               |                                                                                                                                                            |
| Paroxetine (Paxil)                                 | 20                 | 60                |                                                                                                                                                            |
| Citalopram (Celexa)                                | 20                 | 60                |                                                                                                                                                            |
| Escitalopram (Lexapro)                             | 10                 | Unknown           |                                                                                                                                                            |
| Clomipramine (Anafranil, tricyclic antidepressant) | 25–50              | 250               | Dizziness, sedation, dry mouth, weight gain, sexual dysfunction                                                                                            |
| Venlafaxine (Effexor)                              | 75                 | 375               | Accommodation disorder, blurred vision, headache, sexual dysfunction, paresthesias, nausea, weight loss, withdrawal syndrome (dizziness, nausea, weakness) |

\* OCD denotes obsessive-compulsive disorder.

† All selective serotonin-reuptake inhibitors except escitalopram have been formally studied in patients with OCD. Side-effect profiles may vary among these agents; an alternative agent in this class should be tried if one agent proves to be ineffective or is associated with substantial side effects.



# *Selective Serotonin Reuptake Inhibitors(SSRI's)- Adverse Effects*

- “Less serious”
- Anorexia/Nausea
- Hypomania/Mania/Nervousness/Headache/Insomnia/ Dizziness/EPS
- QT Prolongation(Citalopram)
- Hyponatremia(5-HT<sub>1C</sub> & 5-HT<sub>2</sub> Receptors ADH release)
  - Citalopram/Fluoxetine/Fluvoxamine/Paroxetine/Sertraline
- Sexual dysfunction
- Serotonin syndrome

[Ray S, et al. The [use of antidepressant medication in pregnancy](#). Best Practice & Research Clinical Obstetrics & Gynecology 2014; 28: 71-83.]

[Isbister GK, et al. [Serotonin toxicity: a practical approach to diagnosis and treatment](#). Medical Journal of Australia 2007; 187: 361-5.]

[Jacob S & Spinler SA. Hyponatremia associated with selective serotonin reuptake inhibitors in older adults. Ann Pharmacother 2006; 40: 1618-22.]

# *Selective Serotonin Reuptake Inhibitors(SSRI's)- Drug-Drug Interactions*

## ■ Fluvoxamine

- (↓↓CYP 1A2 & 2C19)
- (↓CYP 3A4 & 2C9)

## Fluoxetine/Paroxetine

- (↓↓CYP 2D6)

# *Selective Serotonin Reuptake Inhibitors(SSRI's)- Drug-Drug Interactions*

|            |                                                                                               |
|------------|-----------------------------------------------------------------------------------------------|
| SSRI       | Significant PK Interactions(↑ Plasma Levels & Potential Adverse Effects )                     |
| Sertraline | Clozapine<br>Unlikely to cause other clinically significant pharmacokinetic drug interactions |

# *Selective Serotonin Reuptake Inhibitors(SSRI's)- Drug-Drug Interactions*

|                             |                                                                                                                                                |
|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| SSRI                        | Significant PK Interactions(↑ Plasma Levels & Potential Adverse Effects )                                                                      |
| Citalopram/<br>Escitalopram | Unlikely to cause clinically significant pharmacokinetic drug interactions but contra-indicated with other drugs which can prolong QT interval |

# *Selective Serotonin Reuptake Inhibitors(SSRI's)- Drug-Drug Interactions*

| SSRI                                       | Significant PD Interactions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sertraline/<br>Citalopram/<br>Escitalopram | <p>Potential Serotonin Syndrome when combined with:<br/>Other Antidepressants(5-HT-enhancing)<br/>Buspirone/Fentanyl/Linezolid/Lithium/Ondansetron/St. John's Wort/Tramadol</p> <p>Increased risk of bleeding (particularly upper GI bleed) with:<br/>NSAIDs/Warfarin and other anticoagulants/Antiplatelets</p> <p>Other PD interactions to consider: Other drugs which can also cause sexual dysfunction(antipsychotics), GI effects(acetylcholinesterase inhibitors) or hyponatremia (thiazide diuretics)</p> |

# *Serotonin Syndrome*

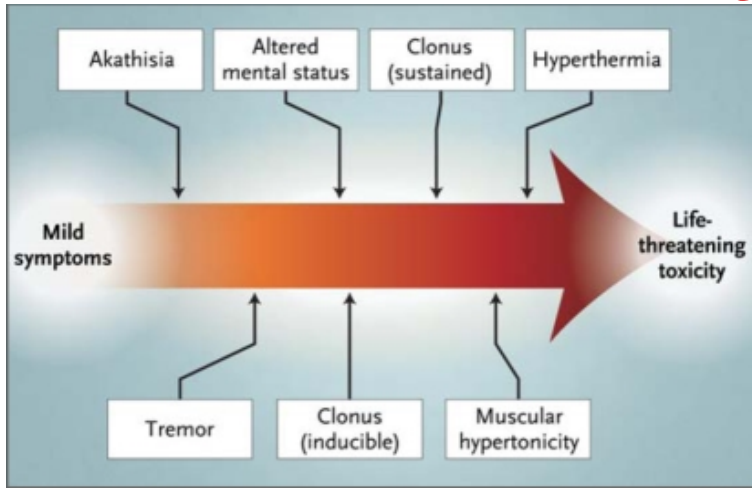
- Potentially life-threatening condition caused by excessive serotonergic activity in CNS
- Characterized by:
  - Mental status changes
  - Autonomic instability, &
  - Neuromuscular hyperactivity
- Most cases reported in patients:
  - Using multiple serotonergic drugs or
  - Who have had considerable exposure to a single serotonin-augmenting drug
- Diagnostic Criteria: Dursun/Hunter/Radomski/Sternbach

# *Serotonin Syndrome*

- Diagnosis is made using the **Hunter Serotonin Toxicity Criteria**
- Require the presence of ONE of the following classical features or groups of features:
  - Spontaneous clonus
  - Inducible clonus + [agitation OR diaphoresis]
  - Ocular clonus + [agitation OR diaphoresis]
  - Tremor + hyperreflexia
  - Hypertonia + Temperature > 100.4<sup>o</sup>F(38<sup>o</sup>C) +[ocular clonus OR inducible clonus]

[Ables AZ, Nagubilli R. Prevention, recognition and management of serotonin syndrome. Am Fam Physician 2010; 81(9): 1139-42.]

# Serotonin Syndrome



## 1 Drugs that have been associated with serotonin toxicity

### Serotonin reuptake inhibitors

- *Selective serotonin reuptake inhibitors*: fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline, escitalopram
- *Other antidepressants*: venlafaxine, clomipramine, imipramine
- *Opioid analgesics*: pethidine, tramadol, fentanyl, dextromethorphan
- St John's wort

### Monoamine oxidase inhibitors

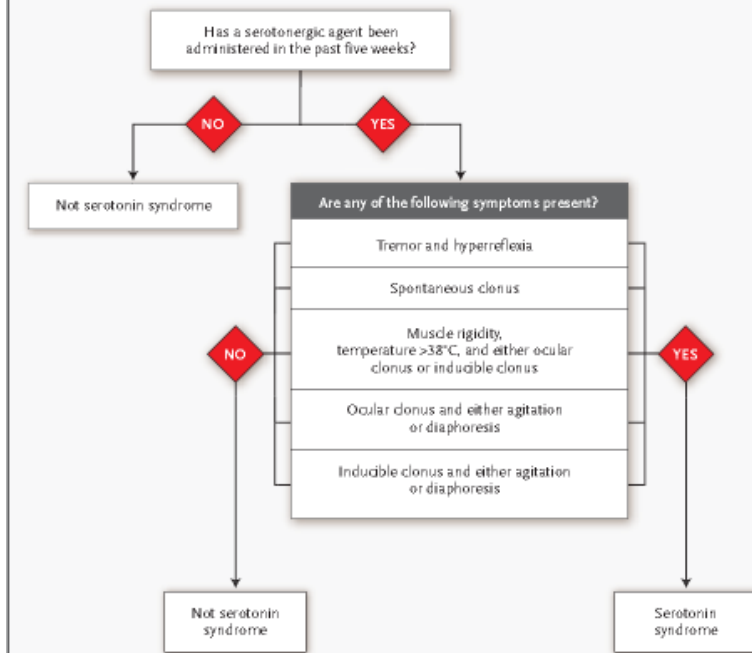
- *Irreversible monoamine oxidase A inhibitors*: phenelzine, tranylcypromine
- *Reversible monoamine oxidase A inhibitors*: moclobemide
- *Others*: linezolid

### Serotonin-releasing agents

- Fenfluramine
- Amphetamines
- Methylenedioxymethamphetamine (MDMA; ecstasy)

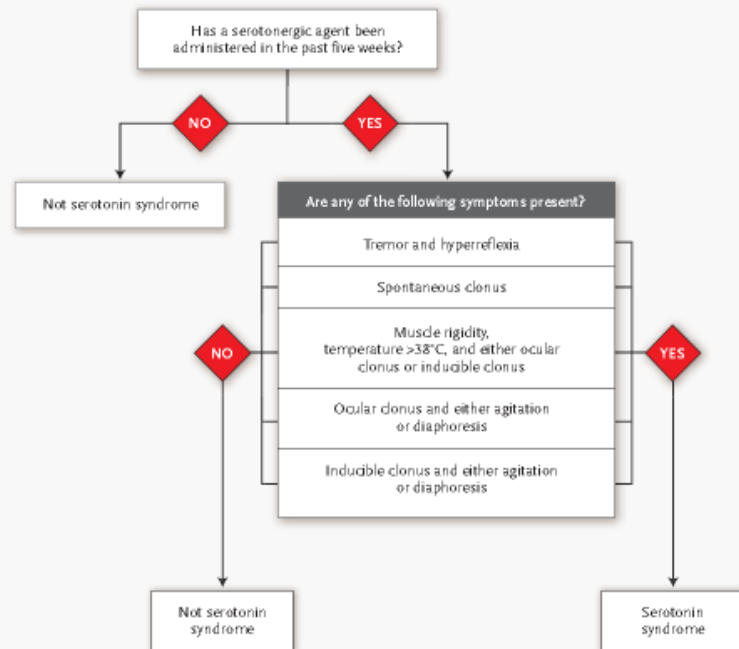
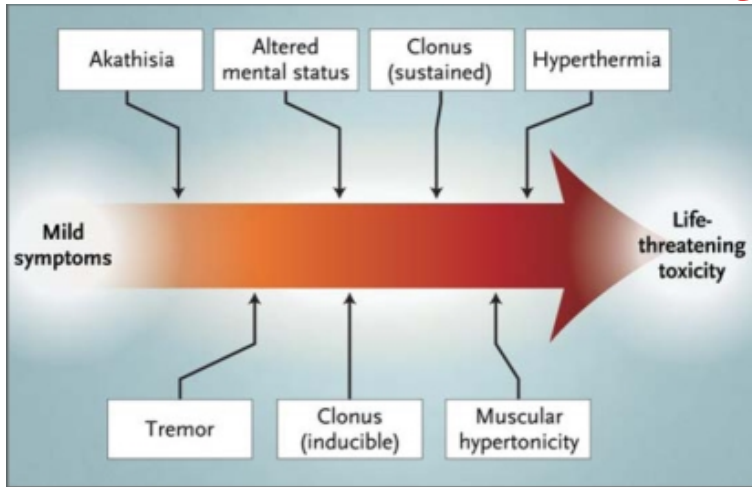
### Miscellaneous

- Lithium
- Tryptophan





# Serotonin Syndrome



**Table 2**

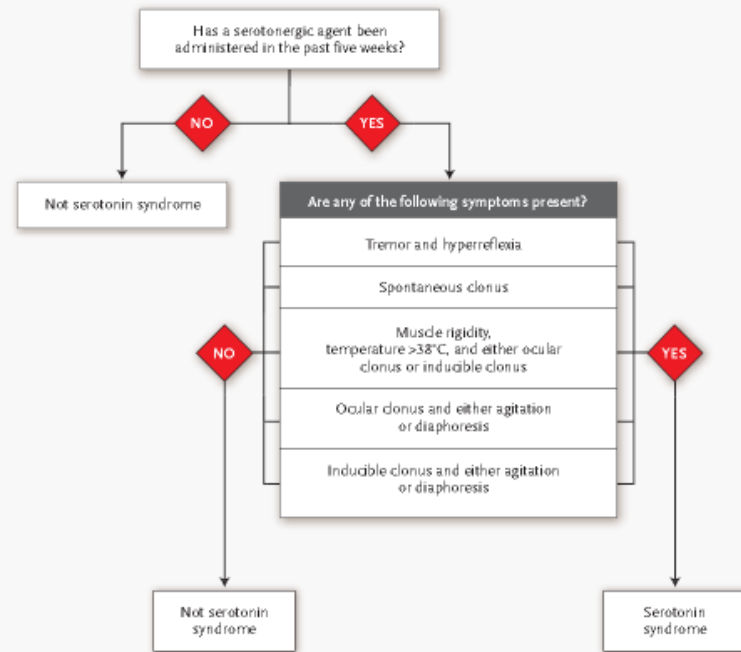
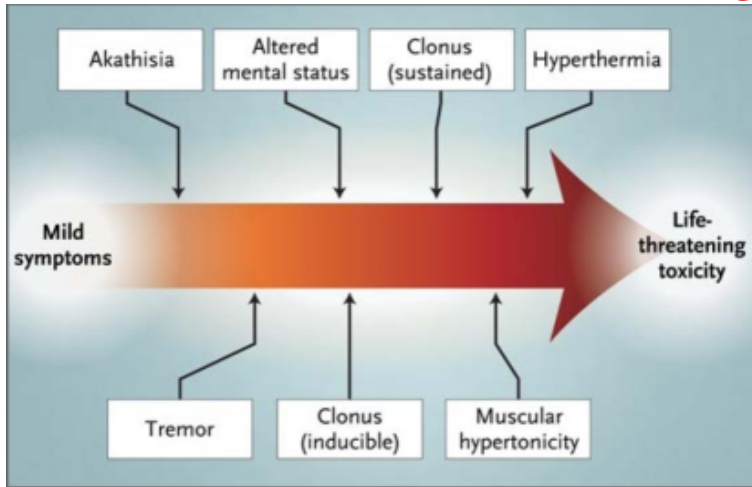
## Combinations That May Result in Serotonin Syndrome

- All SSRIs in combination
- Venlafaxine & lithium
- Venlafaxine & moclobemide
- Venlafaxine & fluoxetine
- Venlafaxine & mirtazapine
- Fluoxetine & sertraline
- Fluoxetine & tramadol
- Trazodone & buspirone
- Clomipramine & MAOI
- Clomipramine & trazodone
- Clomipramine & moclobemide
- Dextromethorphan & paroxetine
- Dextromethorphan & moclobemide
- Linezolid & citalopram
- SSRI & St. John's wort
- SSRI & MAOI
- Meperidine & MAOI

*SSRI: selective serotonin reuptake inhibitor; MAOI: monoamine oxidase inhibitor.*

*Source: References 2, 6, 9.*

# Serotonin Syndrome



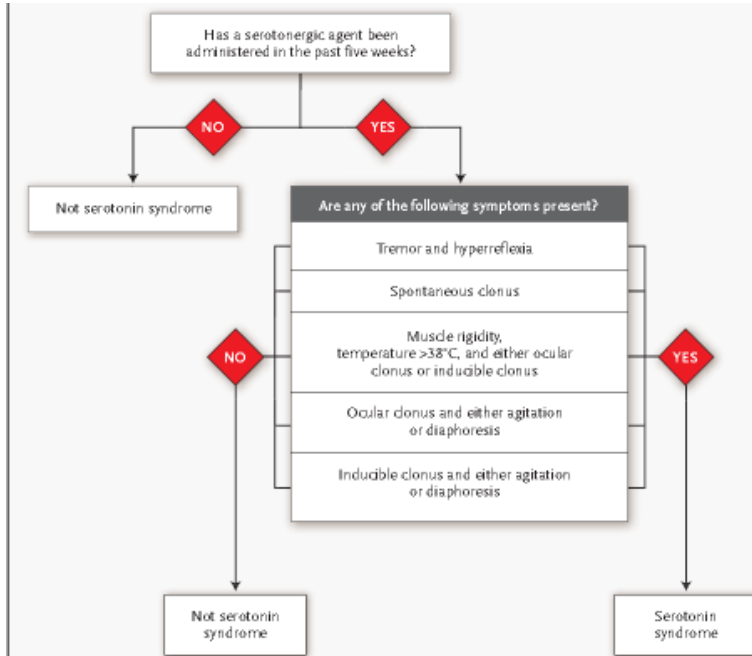
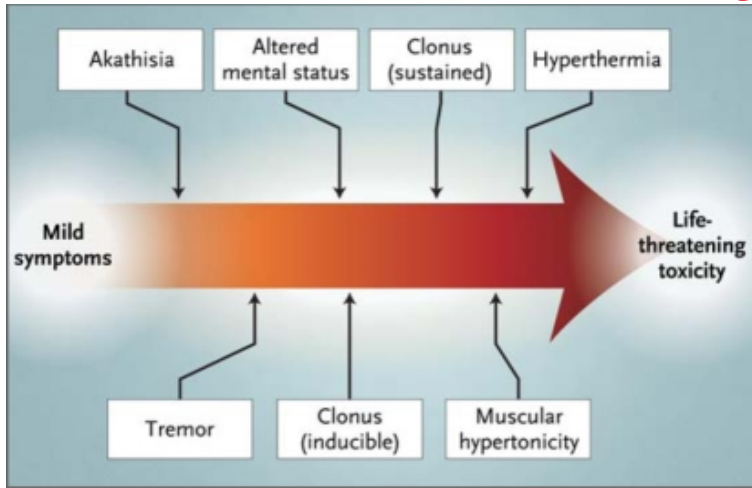
**Table 4**

## Clinical Presentation of Serotonin Syndrome and Differential Diagnosis

| Clinical Presentation              | Serotonin Syndrome | NMS | Anticholinergic Delirium |
|------------------------------------|--------------------|-----|--------------------------|
| Tachycardia                        | +                  | +   | +                        |
| Hypertension                       | +                  | +   | +                        |
| Muscle rigidity                    | +                  | +   | -                        |
| Hyperthermia >41.1°C               | +                  | +   | -                        |
| Hyperreflexia                      | +                  | -   | -                        |
| Myoclonus                          | +                  | -   | -                        |
| Shivering                          | +                  | -   | -                        |
| Acute onset                        | -                  | -   | +                        |
| Restlessness, confusion, agitation | +                  | -   | +                        |
| Bowel sound                        | +                  | -   | -                        |

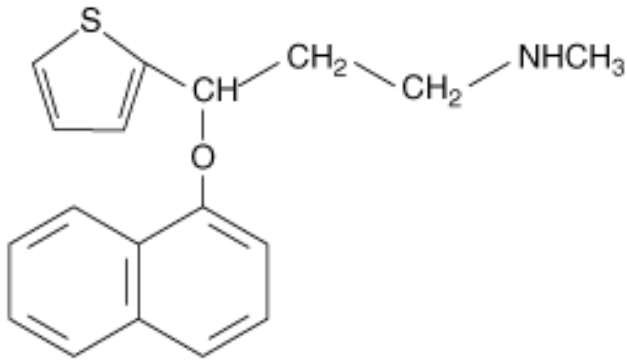
*NMS: neuroleptic malignant syndrome; +: present; -: not present.  
Source: Reference 2.*

# Serotonin Syndrome

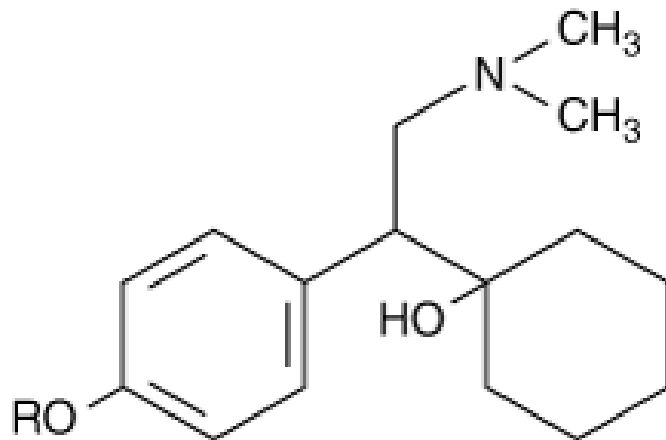


- Most cases of SS are mild
- Treated by
  - Withdrawal of the offending agent +
  - Supportive care
- Benzodiazepines used to treat agitation + tremor
- Cyproheptadine used as an antidote
- Patients with moderate or severe cases of SS require hospitalization
- Critically ill patients may require:
  - Neuromuscular paralysis
  - Sedation, &
  - Intubation

# Serotonin NE Reuptake Inhibitors (SNRI's)



Duloxetine

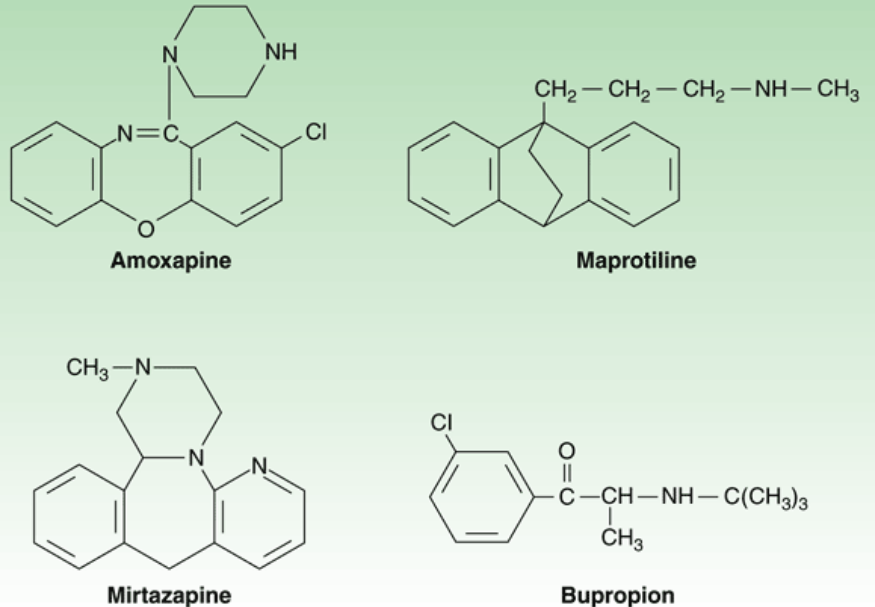


R = CH<sub>3</sub> : Venlafaxine

R = H : Desvenlafaxine

- Bind to transporters for both serotonin and NE (NET + SERT)
- Enhance actions of both neurotransmitters
- SNRIs differ from the TCAs in lacking significant blocking effects on peripheral receptors including
  - Histamine (H<sub>1</sub>)/Muscarinic/  
α-adrenergic receptors

# Heterocyclics



## ■ Bupropion

- Mechanism of antidepressant action unknown
- Drug has no effect on 5-HT or NE receptors nor on amine transporters

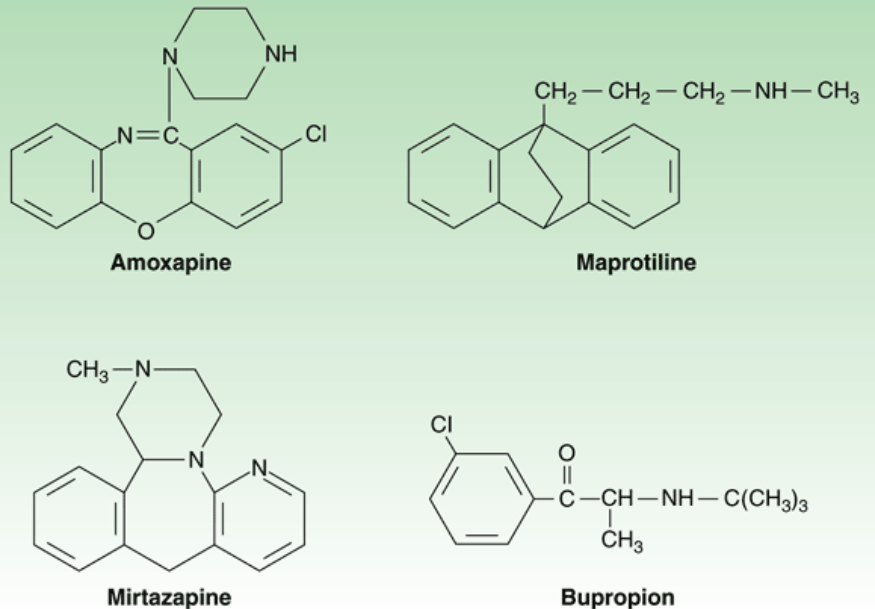
## ■ Mirtazapine

- Increases amine release from nerve endings by antagonism of presynaptic  $\alpha_2$  adrenoceptors involved in feedback inhibition
- Is also an antagonist at serotonin 5-HT<sub>2</sub> receptors

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition: www.accessmedicine.com

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# Heterocyclics

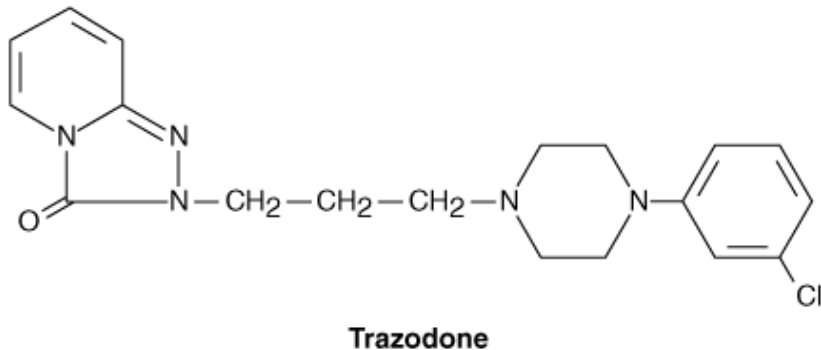


- Amoxapine/Maprotiline
  - Are **potent NET inhibitors** + less potent SERT inhibitors
  - Both possess **anticholinergic properties**

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition: [www.accessmedicine.com](http://www.accessmedicine.com)

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# 5-HT<sub>2</sub> Antagonists



## ■ 5-HT<sub>2</sub> Antagonists

- Major antidepressant actions result from block of the 5-HT<sub>2A</sub> receptor
- G-protein-coupled receptor located in several CNS regions including the neocortex
- Antagonism of this receptor is equated with both the antianxiety + antidepressant actions of these drugs