Affective or Mood Disorders

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Affective or Mood Disorders

Reactive Depression.

Secondary: Medical

Neurological

Drugs

Major (Endogenous) Depression = Unipolar:

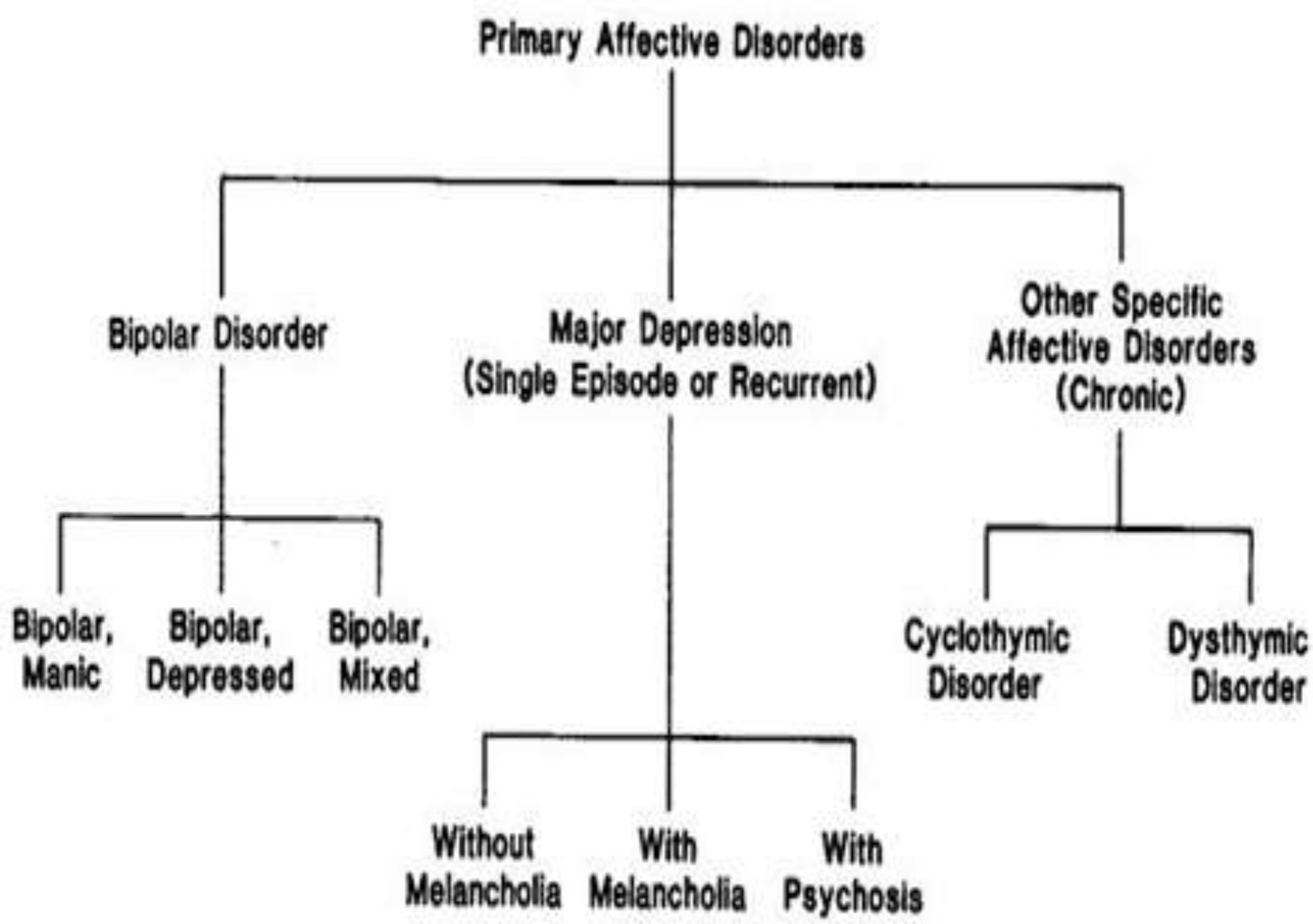
Depressed mood, decreased interest in normal activities, anorexia, weight loss, insomnia, fatigue, and decreased concentration.

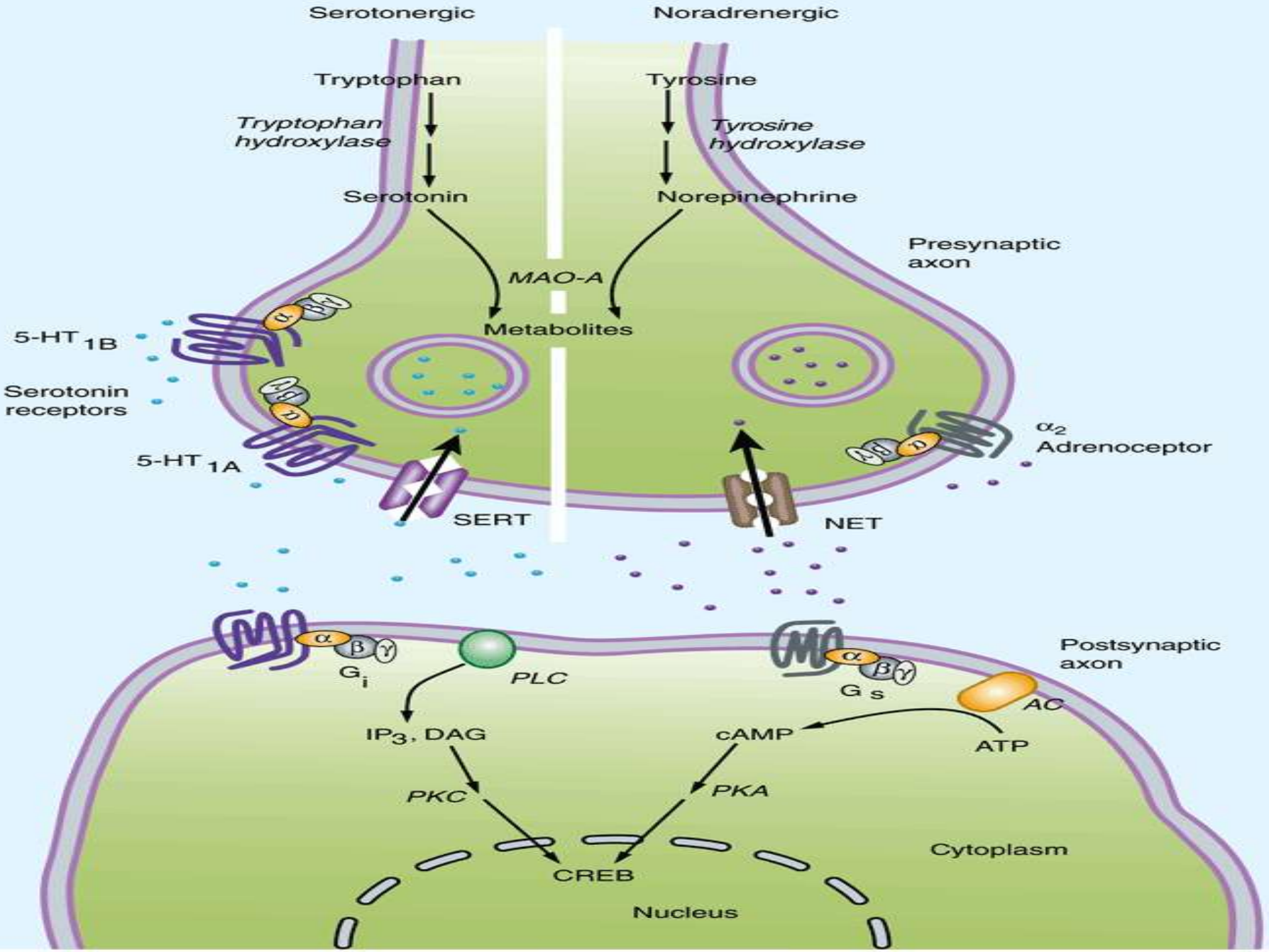
Affective or Mood Disorders

Mania:

Expansive mood, grandiosity, inflated self-esteem, pressured speech, flight of ideas and poverty of sleep.

Manic-Depressive Psychosis = Bipolar


Primary Affective Disorders
Bipolar Disorder
Major Depression
(Single Episode or Recurrent)
Other Specific
Affective Disorders
(Chronic)
Bipolar,
Manic
Bipolar,
Depressed
Bipolar,
Mixed
Cyclothymic
Disorder
Dysthymic
Disorder
Without
Melancholia
With
Melancholia
With
Psychosis



Source: Fattinger BD, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 13th Edition*: www.accessmedicine.com

Biogenic Amine Theory

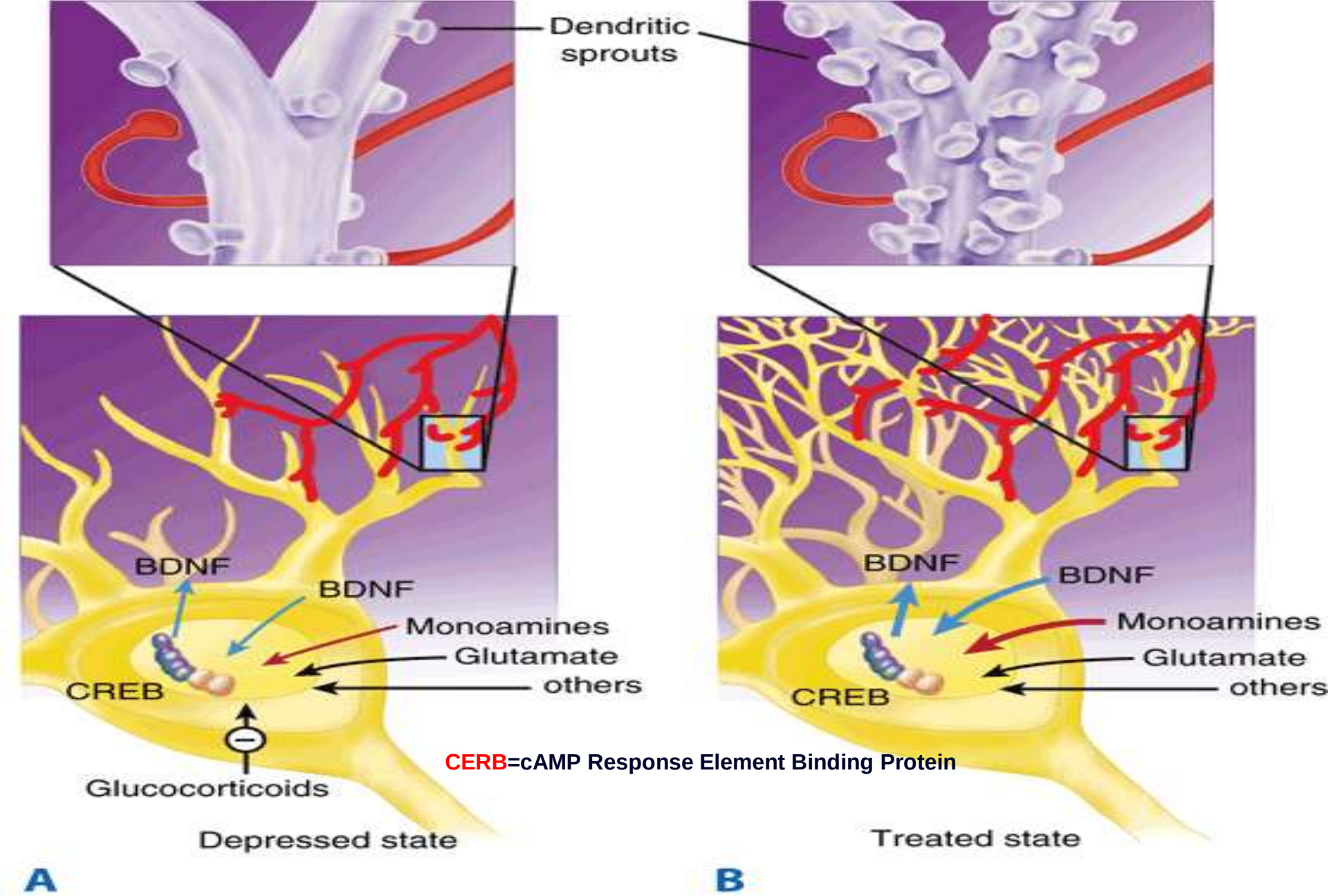
- Depression appears to be associated with changes in central serotonin and/or norepinephrine signaling in the brain.
- Most antidepressant drugs cause changes in amine signaling.

Biogenic Amine Theory

- Reserpine.
- Deficiency in central serotonergic activity predisposes to an affective disorder.
- If this is accompanied with decreased adrenergic activity, depression is observed.
- If accompanied with increased adrenergic activity, mania is observed.

Neurotrophic hypothesis of major depression

- Changes in **trophic factors** (especially brain-derived neurotrophic factor, **BDNF**) and **hormones** appear to play a major role in the development of major depression.
- Successful treatment results in changes in these factors.



CERB=cAMP Response Element Binding Protein

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

Treatment of Affective Disorders

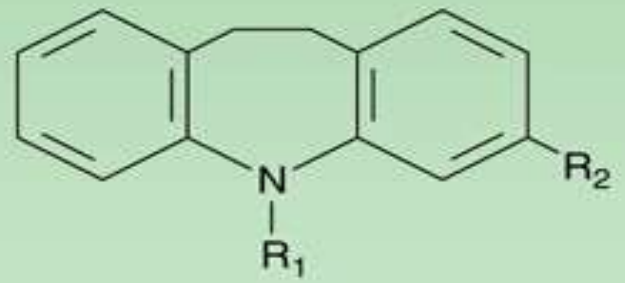
- All modalities of treatment produce immediate effects on some mechanisms of neurotransmission, but the antidepressant or anti manic activity is **delayed for a few weeks**.
- So, action may be due to desensitization of receptors.
- There are **risks** due to this delay.

Clinical Uses of Antidepressants

- Depression
- Anxiety Disorders:
  - Panic Attacks.
  - Social Phobia.
- Obsessive-Compulsive Disorders.
- Nocturnal Enuresis.
- Chronic Pain.
- Bulemia.
- Premenstrual Dysthymic Disorder.
- Attention Deficit Hyperactivity Disorder (ADHA).

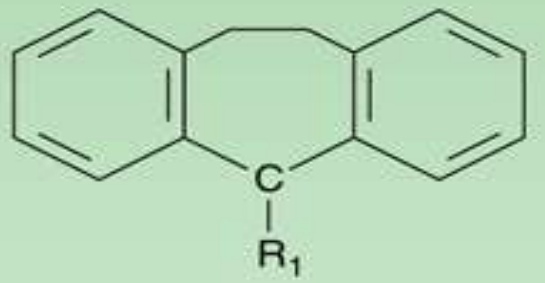
Tricyclic Antidepressants

- **Tertiary Amines:**
  - **Imipramine…..1950s**
  - **Amitriptyline**
  - **Doxepine**
- **Secondary Amines:**
  - **Desipramine**
  - **Protriptyline**
  - **Nortriptyline**



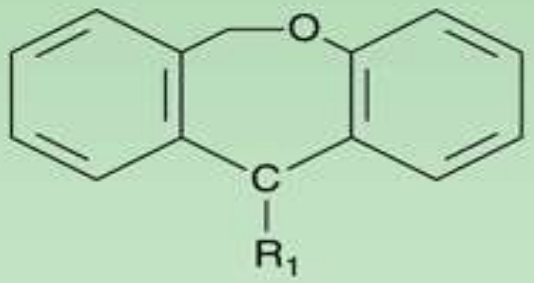
R_1:–$(CH_2)_3N(CH_3)_2$
R_2: H

Imipramine



R_1: = $CH(CH_2)_2N(CH_3)_2$

Amitriptyline



R_1: = $CH(CH_2)_2N(CH_3)_2$

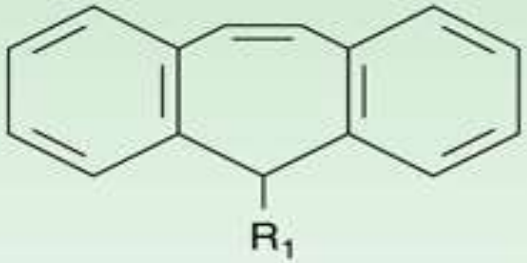
Doxepin

R_1: = $(CH_2)_3NHCH_3$
R_2: H

Desipramine

R_1: = $CH(CH_2)_2NHCH_3$

Nortriptyline



R_1: = $(CH_2)_3NCH_3$

Protriptyline

R_1: = $(CH_2)_3N(CH_3)_2$
R_2: – Cl

Clomipramine

R_1: = $CH_2CH(CH)_3CH_2N(CH_3)_2$
R_2: – H

Trimipramine

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

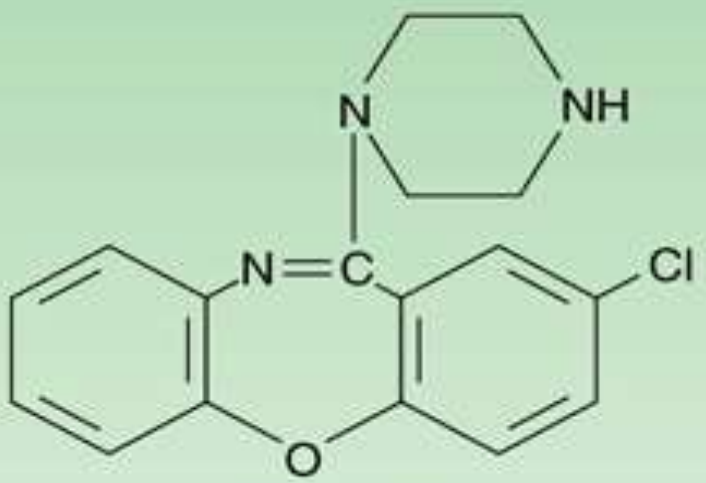
Heterocyclic Antidepressants

- **Maprotiline:**

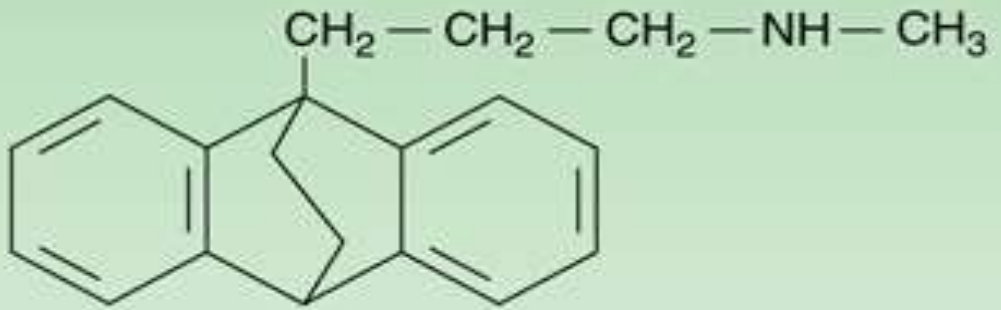
  Less anticholinegic effects but enhances seizures.

- **Amoxapine:**

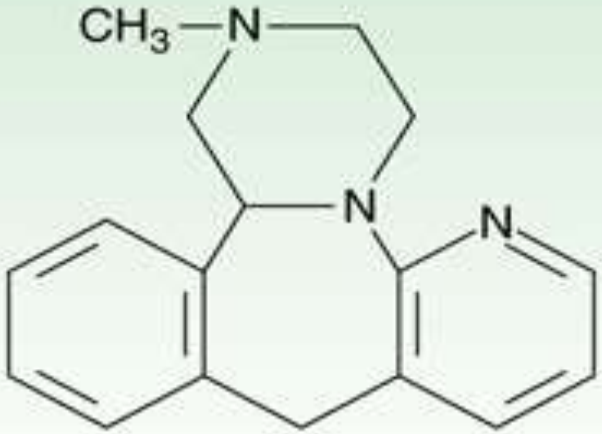
  Less cardiovascular effects but has more dopamine antagonistic activity.



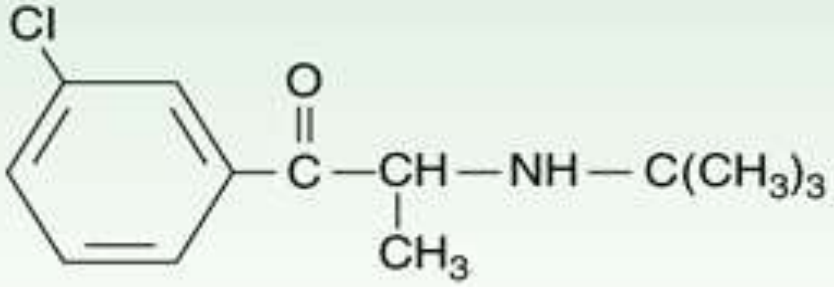
Amoxapine



Maprotiline



Mirtazapine



Bupropion

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

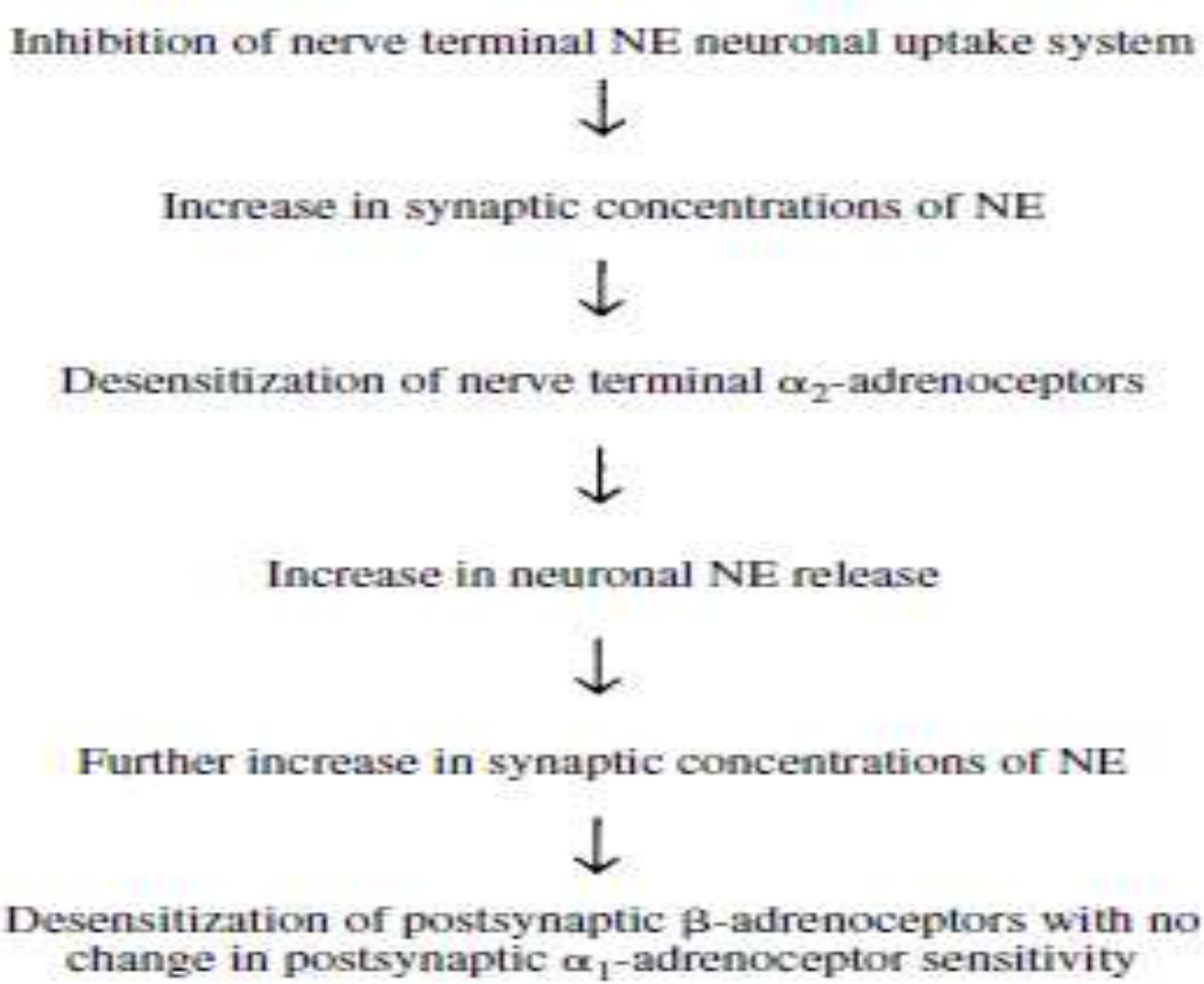


FIGURE 33.2
Cascade of adaptive changes occurring at norepinephrine (NE) synapses following chronic TCA drug treatment.

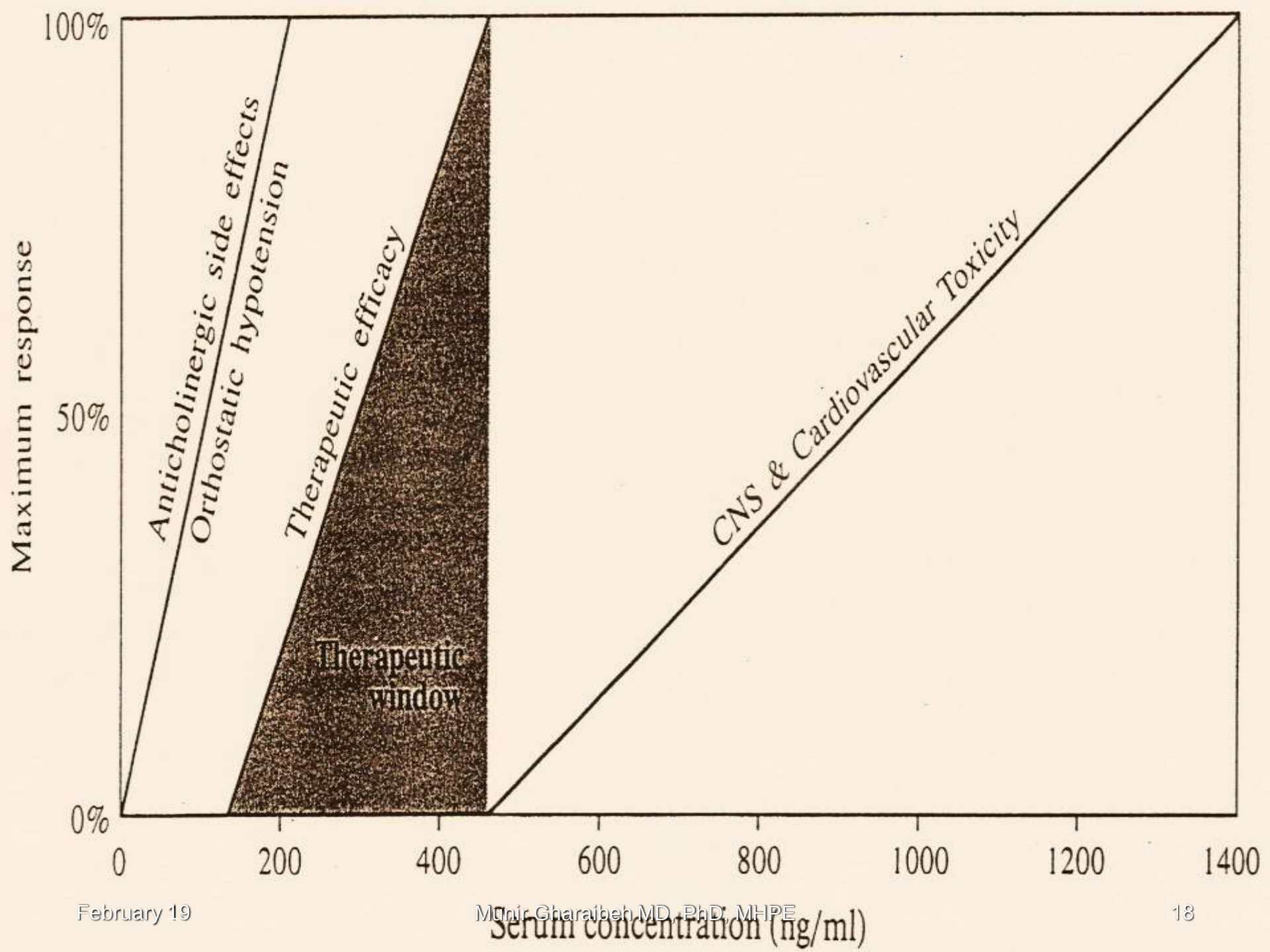
Side Effects and Toxic Reactions of TCA

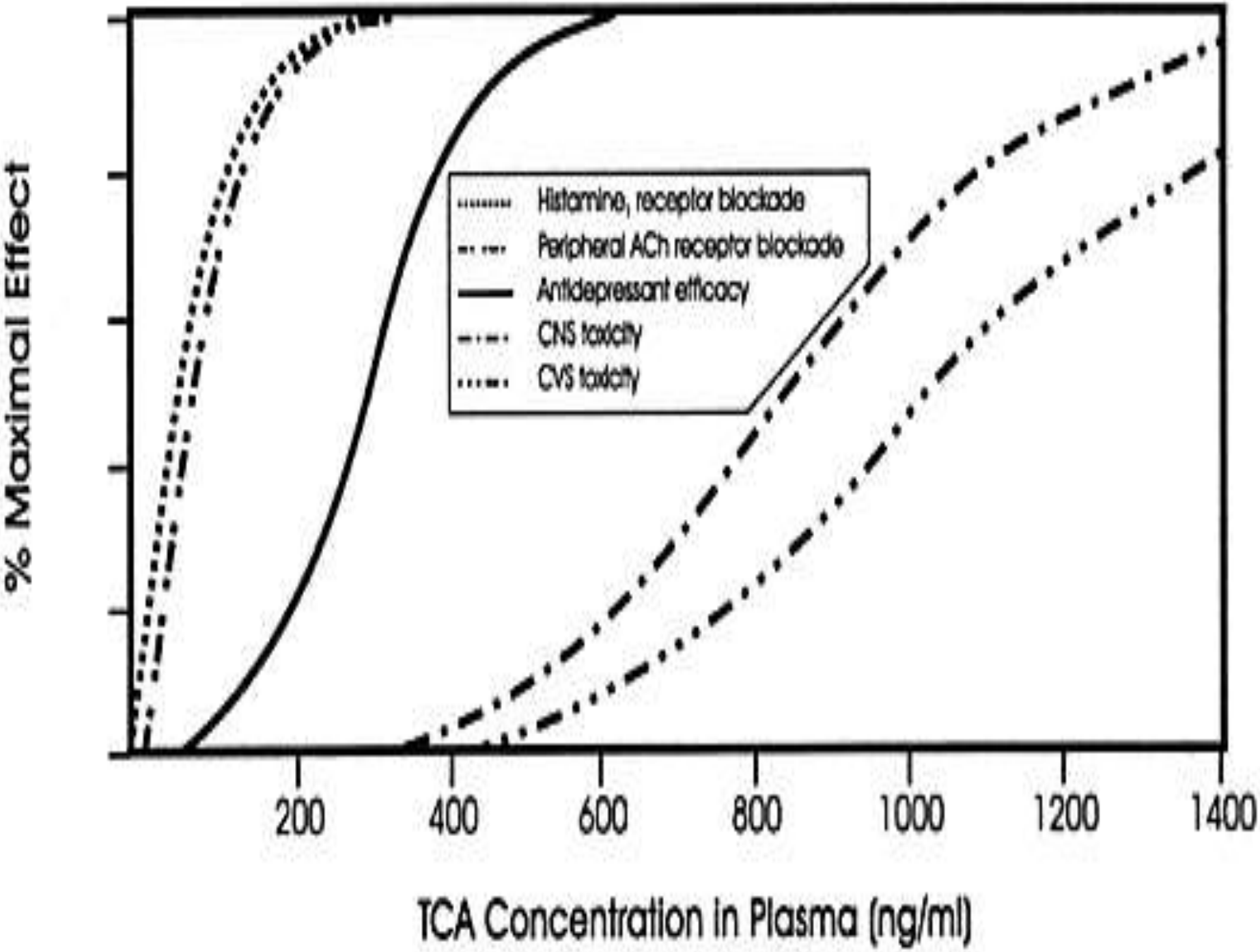
- Very toxic TI=3, so drug monitoring.
- Antimuscarinic Reactions:

  Tachycardia, Blurring of vision, confusion, constipation, dry mouth, urinary retention, etc.
- Cardiovascular:

  Orthostatic hypotension, arrhythmias, conduction defects.
- Sedation.

ide effects appear early in the treatment before therapeutic effects are established


100%
50%
0%
Maximum response
Anticholinergic side effects
Orthostatic hypotension
Therapeutic efficacy
CNS & Cardiovascular Toxicity
Therapeutic window
0
200
400
600
800
1000
1200
1400
Serum concentration (ng/ml)

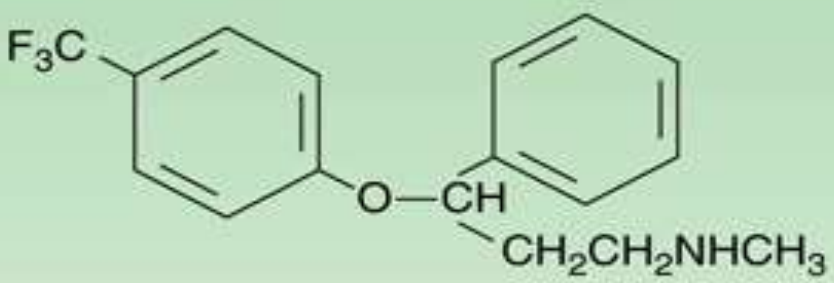

% Maximal Effect
Histamine, receptor blockade
Peripheral ACh receptor blockade
Antidepressant efficacy
CNS toxicity
CVS toxicity
200
400
600
800
1000
1200
1400
TCA Concentration in Plasma (ng/ml)

Side Effects and Toxic Reactions of TCA

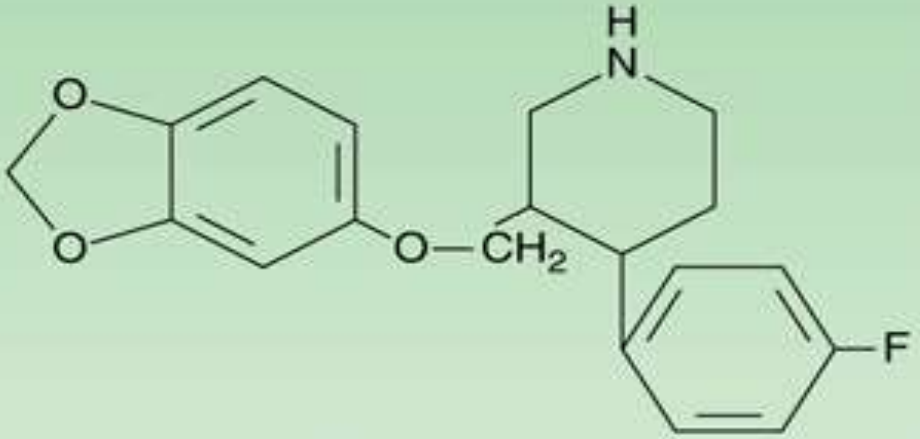
- Toxic delirium, seizures, withdrawal syndrome.
- Weight gain, sexual disturbances.
- Involuntary movements, Lactation; Gynecomastia, neuroleptic malignant syndrome.

Selective Serotonin Reuptake Inhibitors ”SSRI”

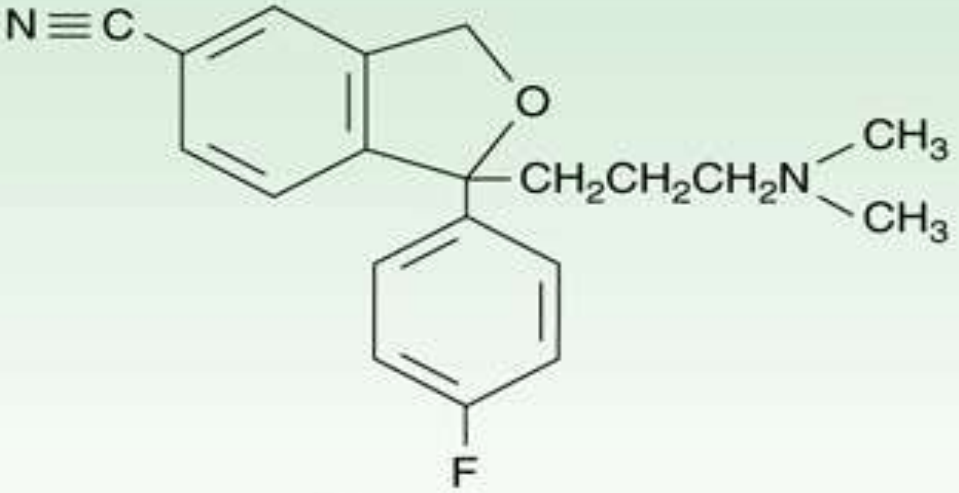
- Very safe drugs.
- No sedative or anticholinergic or cardiovascular effects .
- Can cause stimulation rather than sedation, N,V, D, and sexual dysfunction.



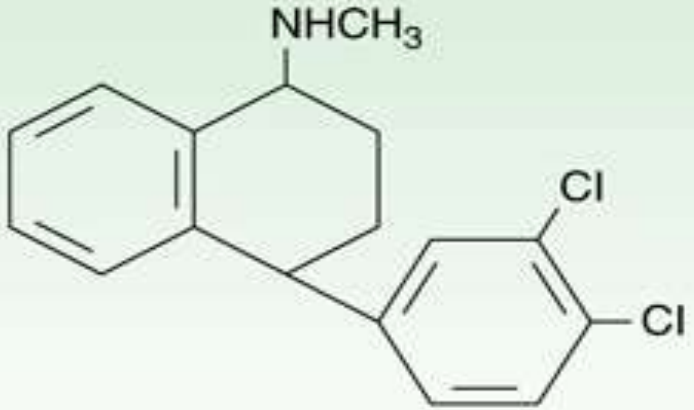
Fluoxetine



Paroxetine



Citalopram, escitalopram



Sertraline

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

Selective Serotonin Reuptake Inhibitors ”SSRI”

Mechanism of Action:

- Selective inhibition of 5HT reuptake.
- Desensitization of :
  - $5HT_{1A}$ receptors leading to increased firing rate.
  - $5HT_{1B}$ receptors leading to increased 5HT release.

Consequently, 5HT neurotransmission is enhanced.

Selective Serotonin Reuptake Inhibitors ”SSRI”

Fluoxetine: ”Prozac”, 1987.

- Greatly revolutionized the treatment of depression.
- Highly bound to plasma proteins.
- Inhibits P450 enzymes.

Fluvoxamine.

Selective Serotonin Reuptake Inhibitors ”SSRI”

Paroxetine:

- Increases weight, more sedating

Citalopram:

- Least effect on P450 enzymes.

Sertraline.

Monoamine Oxidase Inhibitors

- Very effective.
- Considered as old fashioned drugs.
- Considered very toxic (headache, drowsiness, weight gain, postural hypotension, sexual disturbances).
- Mostly cause CNS stimulation.
- Hypertension due to dietary interactions.
- May still be used.

Monoamine Oxidase Inhibitors

Phenelzine:

Hepatotoxic.

Isocarboxamide.

Tranycypromine:

Increases weight.

Selegiline:

No liver toxicity or dietary-induced hypertension.

Miscellaneous Agents

Venlafaxine: "Effexor".

Decreases the reuptake of both 5HT& NE.

Elevates BP.

Bupropion:

Weak reuptake inhibitor.

Causes CNS stimulation, ? Convulsions.

No impotence.

Mirtazapine

- Noradrenergic and specific serotonergic antidepressant (NaSSA).
- Doesn’t have effects as monoamine reuptake inhibitor.
- A significant feature is its effect as histamine 1 antagonist. This effect is linked to sedation and weight gain.
- Commonly used in the elderly. In this group of patients insomnia and low weight might benefit from sedation and weight gain.
- Mirtazapine has no significant drug-drug interactions, this makes it attractive for use in combination with other antidepressants as augmenting option.

TABLE 33.2 Common Side Effects of Therapeutic Doses of Antidepressants

Agent	Sedation	Anticholinergic	Orthostasis	Weight Gain	Sexual Dysfunction
SSRIs	+/−	0	0	+/−	+++
TCAs	+++	+++	+++	++	++
Miscellaneous					
Trazodone	+++	0	++	++	+[a]
Bupropion	0	0	0	0	0
Nefazodone	++	0	0	0	0
Venlafaxine	+/-	0	0[b]	0	++
Mirtazapine	++	0	0	++	0
MAOIs	0	+	+++	++	+

TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.
0, no effect; +, + +, +++ indicate increasing effect.
[a]Priapism.
[b]Venlafaxine can cause a dose-dependent increase in blood pressure.

Electroconvulsive Therapy

- Causes decreased β- receptor activity and number.
- Highly indicated in severe bipolar depression associated with suicidal thoughts or attempts.
- Seems inhumane !!!.
- Other options include **quetiapine**, and **olanzapine/fluoxetine combination(OFC)**

Lithium Carbonate

- Drug of choice for **acute mania and bipolar** depression.
- No actions in normal people.
- Blocks manic behavior in combination with phenothiazines and anxiolytics.
- Inhibits release and increases reuptake of NE, does not interfere with 5HT.
- High Na lowers Li and vice versa. ?Diuretics
- Competes with Na causing altered neuronal function.
- Competes with Mg on G-proteins.

Lithium Carbonate

Toxicity Reactions

- TI = 2-3, so drug monitoring
- Has delayed action(2-3 weeks), so do not increase the dose.
- **Mild toxicity**:

  N,V, abdominal pain, diarrhea, polyurea, thirst and edema.

  Fatigue, muscular weakness, slurred speech, ataxia, sedation and tremor.

Lithium Carbonate
Toxicity Reactions

- **Severe toxicity:**

  Impaired consciousness, confusion, rigidity, increased reflexes, tremor, seizures , coma and death.

- **Chronic toxicity:**

  Hypothyroidism(5%).

  DI.

  Leukocytosis.

  Renal toxicity.

Other Drugs

- **Lamotrigine, Carbamazepine and Valproic acid:**

Anticonvulsants, but also used for maintenance and prophylaxis of bipolar affective disorders.

- **Clonazepam and Lorazepam, alone or with neuroleptics:**

Antipsychotics, but also used for acute mania.

Table 30–4 Some Antidepressant–CYP450 Drug Interactions.

Enzyme	Substrates	Inhibitors	Inducers
1A2	Tertiary amine tricyclic antidepressants (TCAs), duloxetine, theophylline, phenacetin, TCAs (demethylation), clozapine, diazepam, caffeine	Fluvoxamine, fluoxetine, moclobemide, ramelteon	Tobacco, omeprazole
2C19	TCAs, citalopram (partly), warfarin, tolbutamide, phenytoin, diazepam	Fluoxetine, fluvoxamine, sertraline, imipramine, ketoconozole, omeprazole	Rifampin
2D6	TCAs, benztropine, perphenazine, clozapine, haloperidol, codeine/oxycodone, risperidone, class Ic antiarrhythmics, β blockers, trazodone, paroxetine, maprotiline, amoxapine, duloxetine, mirtazapine (partly), venlafaxine, bupropion	Fluoxetine, paroxetine, duloxetine, hydroxybupropion, methadone, cimetidine, haloperidol, quinidine, ritonavir	Phenobarbital, rifampin
3A4	Citalopram, escitalopram, TCAs, glucocorticoids, androgens/estrogens, carbamazepine, erythromycin, Ca^{2+} channel blockers, protease inhibitors, sildenafil, alprazolam, triazolam, vincristine/vinblastine, tamoxifen, zolpidem	Fluvoxamine, nefazodone, sertraline, fluoxetine, cimetidine, fluconazole, erythromycin, protease inhibitors, ketoconazole, verapamil	Barbiturates, glucocorticoids, rifampin, modafinil, carbamazepine