# Antidepressant Drugs

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# Depression

- **Major depression is one of the most common psychiatric disorders.**
- **Depression is a heterogeneous disorder that can be classified as follows:**

1. **Brief reactive (secondary) depression occurring in response to real stimuli (the most common).**
2. **Depression associated with bipolar affective, manic-depressive, disorder.**

# Depression

3. **Melancholic (سوداوي) and recurrent depression, a genetically determined biochemical disorder manifested by an inability to experience ordinary pleasure or to cope with ordinary life events. [major depression]**

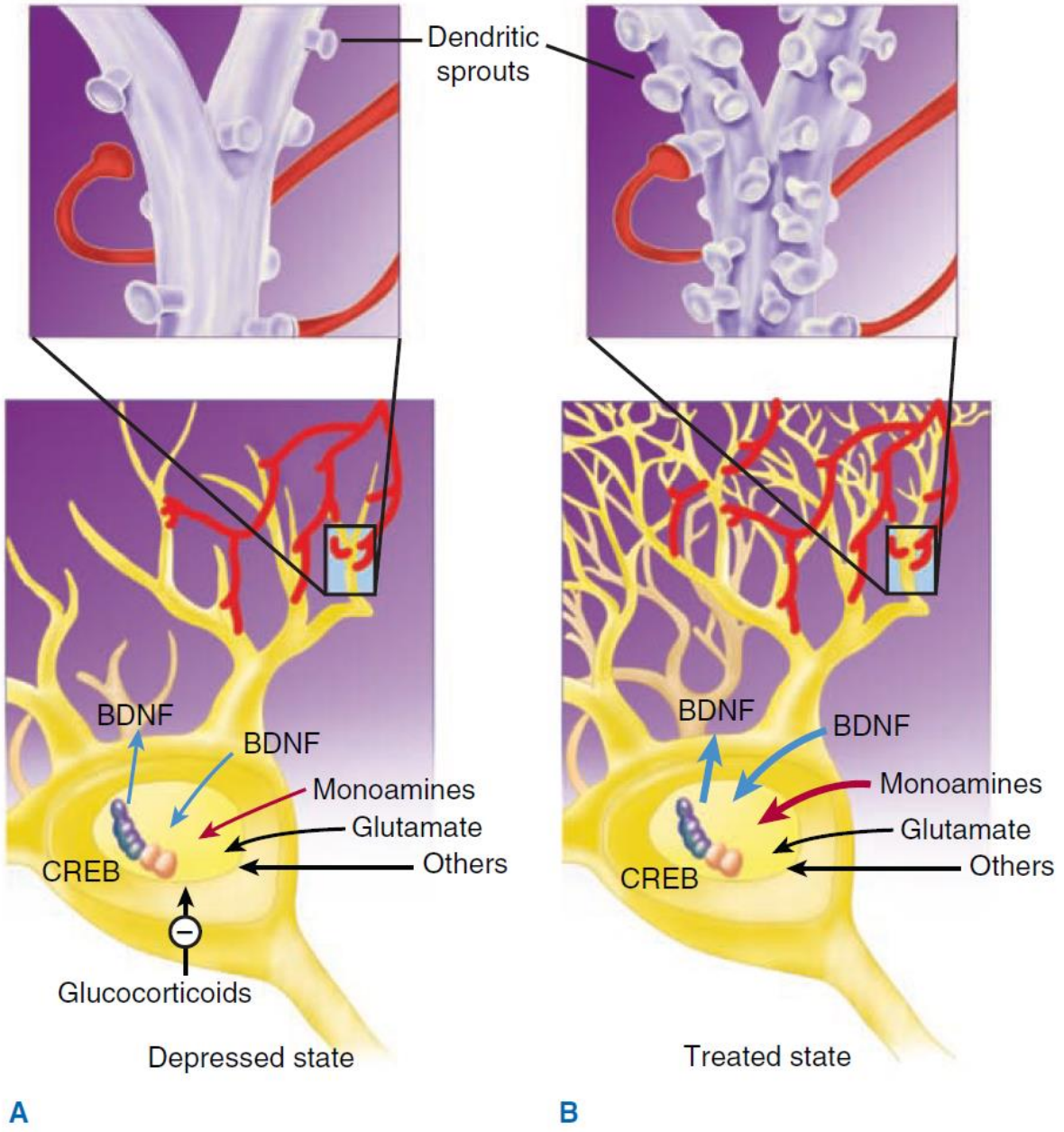
# Pathogenesis of Major Depression

## A. Neurotrophic hypothesis:

- **There is evidence that nerve growth factors, such as "brain-derived neurotrophic factor" (BDNF), are critical in the regulation of neural plasticity, resilience, and neurogenesis.**
- **There is evidence that depression is associated with loss of neurotrophic support.**

## FIGURE 30–1

**The 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 (A). Successful treatment results in changes in these factors (B). CREB, cAMP response element-binding (protein). BDNF, brain-derived neurotrophic factor.** ***(Reproduced, with permission, from Nestler EJ: Neurobiology of depression. Neuron 2002;34[1]:13–25. Copyright Elsevier.)***



# Pathogenesis of Major Depression

## B. The Monoamine Hypothesis:

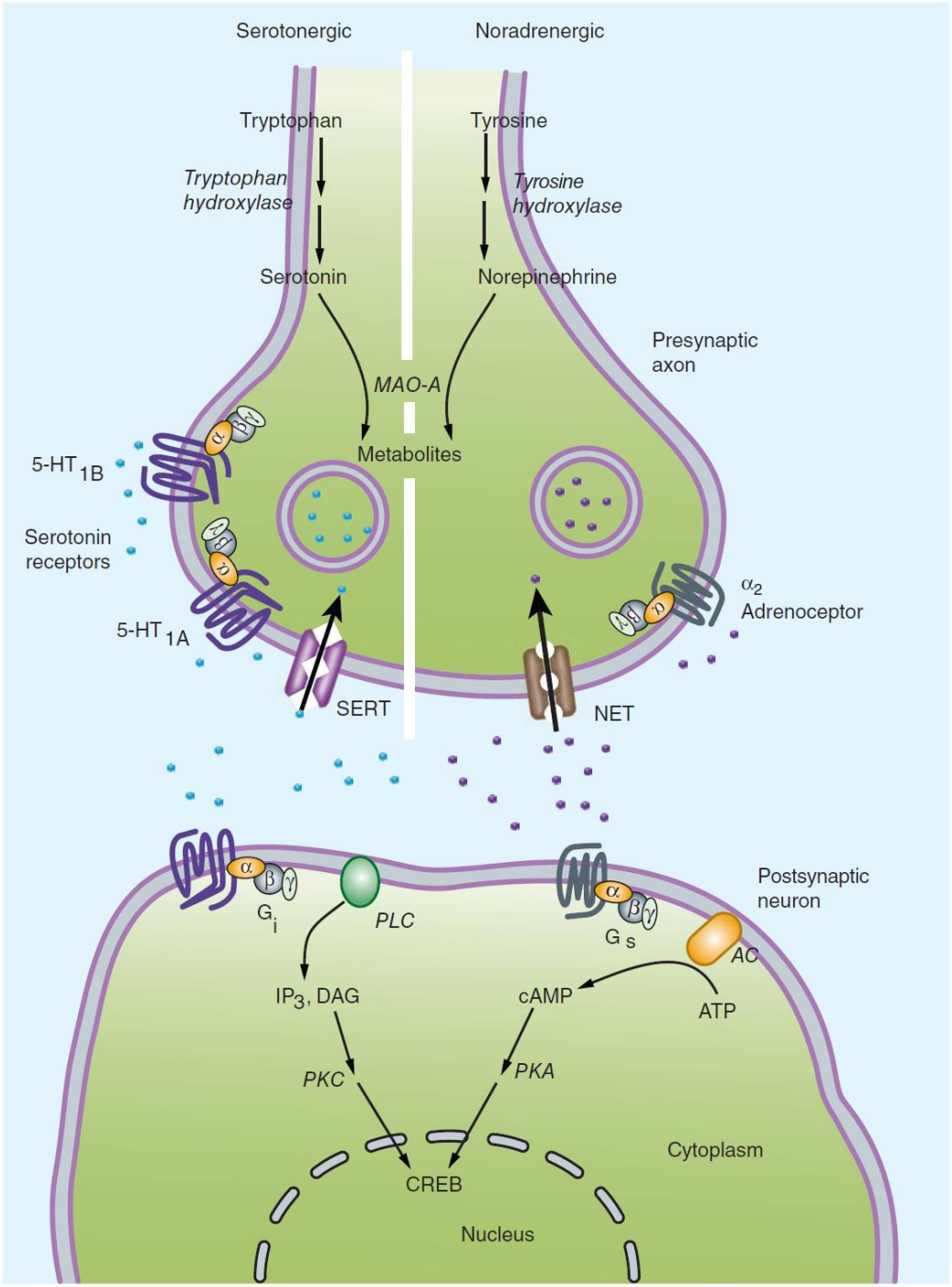
- **This hypothesis suggest that depression is related to deficiency in amount or function of cortical and limbic serotonin, norepinephrine and dopamine**
- **Reserpine had been shown to induce depression. It depletes stores of amine neurotransmitters.**

# Pathogenesis of Major Depression

- **Drugs that increased amine function in certain synaptic areas had relieved depression.**
- **Tryptophan-free diet given to patients taking fluoxetine leads to relapse rapidly, but not in those given desipramine. [Try is a precursor of serotonin synthesis]**
- **Depletion of catecholamines also leads to relapse.**

# Pathogenesis of Major Depression

- **One of the weaknesses of the monoamine hypothesis is that amine levels increase immediately with antidepressant use, but maximum beneficial effects of most antidepressants are not seen for many weeks.**
- **The time required to synthesize neurotrophic factors may be the explanation.**




**The amine hypothesis of major depression. Depression appears to be associated with changes in serotonin or norepinephrine signaling in the brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element-binding (protein); DAG, diacyl glycerol; IP3, inositol trisphosphate; MAO, monoamine oxidase; NET, norepinephrine transporter; PKC, protein kinase C; PLC, phospholipase C; SERT, serotonin transporter.**

# Pathogenesis of Major Depression

## C. Neuroendocrine Factors:

- **Abnormalities in the hypothalamic-pituitary-adrenal axis.**

1. **Major depression ( and more so psychotic depression) is associated with elevated cortisol levels, non-suppression of ACTH with dexamethasone, and chronically elevated level of CRH.**

# Pathogenesis of Major Depression

2. **Thyroid dysregulation has also been reported in depression.**

- **Up to 25% of depressed patients are reported to have abnormal thyroid function:**

a) **A blunting of response of thyrotropin (TSH) to thyrotropin-releasing hormone.**

b) **Elevation of thyroxine during depressed states.**

# Pathogenesis of Major Depression

c) Clinical hypothyroidism may be associated with depressive symptoms which resolves with thyroid replacement.

- Thyroid hormones augment the effects of antidepressants.

3. Estrogen deficiency states which occur in the postpartum and postmenopausal periods are thought to be associated with depression in certain women.

# Pathogenesis of Major Depression

4. **Severe testosterone deficiency in men may be associated with depression.**

- **Sex hormone replacement in hypogonadal men and women improve symptoms.**

# Pathogenesis of Major Depression

**These 3 theories are interrelated:**

1. **HPA and steroid abnormalities may suppress transcription of BDNF gene.**
2. **Cortisol binding to hippocampus receptors during stress may decrease BDNF synthesis.**
3. **Antidepressants increase BDNF gene transcription, and down-regulate the HPA axis, and may normalize HPA fuction**

# Antidepressant Drugs

**Classification:**

A. **Selective Serotonin Reuptake Inhibitors: Fluoxetine, Citalopram, Escitalopram, Paroxetine, Fluvoxamine**

B. **Serotonin-Norepinephrine Reuptake Inhibitors:**

1. **Selective serotonin-norepinephrine reuptake inhibitors: venlafaxine, desvenlafaxine, duloxetine**

# Antidepressant Drugs

2. Tricyclic antidepressants: imipramine, desipramine

C. 5-$HT_2$ Receptor Modulators: trazodone, nefazodone

D. Tetracyclic and Unicyclic Antidepressants: bupropion, mirtazapine, amoxapine, maprotiline

E. Monoamine Oxidase Inhibitors: phenelzine, tranylcypromine, selegiline

# Antidepressant Drugs

**Pharmacokinetics:**

- **Most are incompletely absorbed and undergo significant first-pass metabolism → active metabolites (drugs).**
- **High lipid solubility.**
- **High tissue protein binding.**
- **Very large volume of distribution.**

# Antidepressant Drugs

**Pharmacodynamics:**

A. **Tricyclic antidepressants block the amine transporters, NET and SERT (for norepinephrine and serotonin, respectively). → accumulation of these amines at the synaptic site.**

B. **MAOIs block the intraneuronal degradation of the amines, which cause more amines to accumulate in presynaptic stores, and thus more to be released.**

# Antidepressant Drugs

C. Trazodone, mirtazapine and similar agents may elicit their action by antagonism of subtypes of serotonin receptors (5-$HT_{2A}$ or 5-$HT_{2C}$).

- Mirtazapine also antagonizes $\alpha_2$-adrenergic receptors.
- SSRIs occupy most serotonin uptake sites.
- Actions of bupropion remain poorly understood.

# Antidepressant Drugs

## Receptor and postreceptor effects:

- **The number of receptors for the neurotransmitters can decrease over the same time course as clinical improvement occurs in patients.**
- **Thus, the increase in neurotransmitter seen early in treatment appears to produce down-regulation of postsynaptic as well as presynaptic receptors.**

# Antidepressant Drugs

- **Enhanced serotonergic transmission (mediated through diverse mechanisms) has been thought to be a common effect of antidepressants even without an increase in synaptic serotonin.**

**TABLE 30–2 Blocking effects of some antidepressant drugs on several receptors and transporters.**

| Antidepressant | ACh M | $\alpha_1$ | $H_1$ | 5-$HT_2$ | NET | SERT |
|---|---|---|---|---|---|---|
| Amitriptyline | +++ | +++ | ++ | 0/+ | + | ++ |
| Amoxapine | + | ++ | + | +++ | ++ | + |
| Bupropion | 0 | 0 | 0 | 0 | 0/+ | 0 |
| Citalopram, escitalopram | 0 | 0 | 0 | | 0 | +++ |
| Clomipramine | + | ++ | + | + | + | +++ |
| Desipramine | + | + | + | 0/+ | +++ | + |
| Doxepin | ++ | +++ | +++ | 0/+ | + | + |
| Fluoxetine | 0 | 0 | 0 | 0/+ | 0 | +++ |
| Fluvoxamine | 0 | 0 | 0 | 0 | 0 | +++ |
| Imipramine | ++ | + | + | 0/+ | + | ++ |
| Maprotiline | + | + | ++ | 0/+ | ++ | 0 |
| Mirtazapine | 0 | 0 | +++ | + | + | 0 |
| Nefazodone | 0 | + | 0 | ++ | 0/+ | + |
| Nortriptyline | + | + | + | + | ++ | + |
| Paroxetine | + | 0 | 0 | 0 | + | +++ |
| Protriptyline | +++ | + | + | + | +++ | + |
| Sertraline | 0 | 0 | 0 | 0 | 0 | +++ |
| Trazodone | 0 | ++ | 0/+ | ++ | 0 | + |
| Trimipramine | ++ | ++ | +++ | 0/+ | 0 | 0 |
| Venlafaxine | 0 | 0 | 0 | 0 | + | ++ |
| Vortioxetine[1] | ND | ND | ND | ND | + | +++ |

[1] Vortioxetine is an agonist or partial agonist at 5-$HT_{1A}$ and 5-$HT_{1B}$ receptors, an antagonist at 5-$HT_3$ and 5-$HT_7$ receptors, and an inhibitor of SERT.

ACh M, acetylcholine muscarinic receptor; $\alpha_1$, alpha$_1$-adrenoceptor; $H_1$, histamine$_1$ receptor; 5-$HT_2$, serotonin 5-$HT_2$ receptor; ND, no data found; NET, norepinephrine transporter; SERT, serotonin transporter.

0/+, minimal affinity; +, mild affinity; ++, moderate affinity; +++, high affinity.

# Antidepressant Drugs

**Therapeutic Uses:**

1. **Major depressive disorder: Maximum benefit of antidepressants may require 1–2 months or longer.**
2. **Anxiety disorders: panic, generalized anxiety, and social phobia. Require 6-8 weeks of treatment. Better treated with benzodiazepines.**

# Antidepressant Drugs

3. **Pain disorders:** **Antidepressants possess analgesic properties independent of their mood effects. Neuropathic, chronic joint and muscle pain, postherpetic neuralgia to chronic back pain.**

# Antidepressant Drugs

4. **Premenstrual Dysphoric Disorder:** depressed mood, irritability, insomnia, fatigue, and a variety of other physical symptoms. These symptoms are more severe than those of premenstrual syndrome. The SSRIs fluoxetine is beneficial.

# Antidepressant Drugs

5. **Smoking Cessation:** **Bupropion reduces the urge to smoke. The mechanism is unknown, but it may mimic nicotine's effects on dopamine and norepinephrine and may antagonize nicotinic receptors.**
6. **Bulimia:** **(episodic intake of large amounts of food (binges) followed by ritualistic purging through emesis, laxatives, or other methods). Fluoxetine reduces the binge-purge cycle.**

# Antidepressant Drugs

7. **Attention deficit hyperkinetic disorder:**
   **Atomoxetine has been recently introduced for this purpose (selective NET inhibitor), with no abuse liability like amphetamines.**

# Antidepressant Drugs

## Adverse Effects:

- All antidepressants is the risk of increased suicidality (suicidal ideation and gestures and suicide) in patients <25 years of age.
- Depressed patients may tolerate adverse effects because they are too depressed to care.
- In healthy individuals, even moderate doses are poorly tolerated.

# Antidepressant Drugs

**A. Selective Serotonin Reuptake Inhibitors:**

- **Increased serotonergic activity in the gut is commonly associated with nausea, gastrointestinal upset, and diarrhea.**
- **Increasing serotonergic tone at the level of the spinal cord and above is associated with diminished sexual function and interest (loss of libido, delayed orgasm, or diminished arousal).**

# Antidepressant Drugs

- **Headache, insomnia or hypersomnia.**
- **Weight gain while taking SSRIs, particularly paroxetine.**
- **A discontinuation syndrome characterized by dizziness, paresthesias, and other symptoms beginning 1 - 2 days after stopping the drug and persisting for 1 week or longer.**
- **Teratogenicity (paroxetine).**

# Antidepressant Drugs

**B. Serotonin-Norepinephrine Reuptake Inhibitors and Tricyclic Antidepressants:**

- **Have many of the serotonergic adverse effects associated with SSRIs.**
- **Increased blood pressure and heart rate**
- **CNS activation such as insomnia, anxiety, and agitation.**
- **Discontinuation syndrome like that of SSRI.**

# Antidepressant Drugs

**TCAs:**

- **Anticholinergic effects: dry mouth, constipation, urinary retention, blurred vision, and confusion.**
- **Orthostatic hypotension (α-blocking action).**
- **$H_1$ antagonism is associated with weight gain and sedation.**
- **Arrhythmogenicity.**
- **Sexual effects.**

# Antidepressant Drugs

**C. 5-HT Receptor Modulators:**

- **Sedation (trazodone).**
- **Gastrointestinal disturbances.**
- **Priapism (trazodone).**
- **Nefazodone and trazodone are α-blocking agents and may result in a dose-related orthostatic hypotension.**
- **Nefazodone is hepatotoxicity → fatal fulminant hepatic failure requiring transplantation.**

# Antidepressant Drugs

## D. Tetracyclics and Unicyclics:

- **Amoxapine is associated with a parkinsonian syndrome due to its $D_2$-blocking action.**
- **Mirtazapine has significant sedative effect.**
- **Maprotiline (seizures).**
- **Agitation, insomnia, and anorexia (Bupropion).**

# Antidepressant Drugs

**E. Monoamine Oxidase Inhibitors:**

- **Orthostatic hypotension.**
- **Weight gain.**
- **Insomnia, and restlessness**
- **Sedation and confusion**

# Antidepressant Drugs

## Drug Interactions:

### A. Pharmacodynamic interactions:

1. Additive sedation with alcohol and sedative-hypnotics.
2. Dangerous hypertensive reactions when MAOIs are used with tyramine rich foods, and with sympathomimetic drugs.

# Antidepressant Drugs

**3. SSRIs in conjunction with MAOIs → serotonin syndrome (hyperthermia, muscle rigidity, myoclonus and rapid changes in mental status and vital signs.**

# Antidepressant Drugs

## B. Pharmacokinetic interactions:

1. **Paroxetine and fluoxetine inhibit CYP2D6, and thus clearance of drugs metabolized by it (desipramine, nortriptyline, flecainide, …).**
2. **Nefazodone and fluvoxamine may inhibit CYP3A4 at high concentrations.**