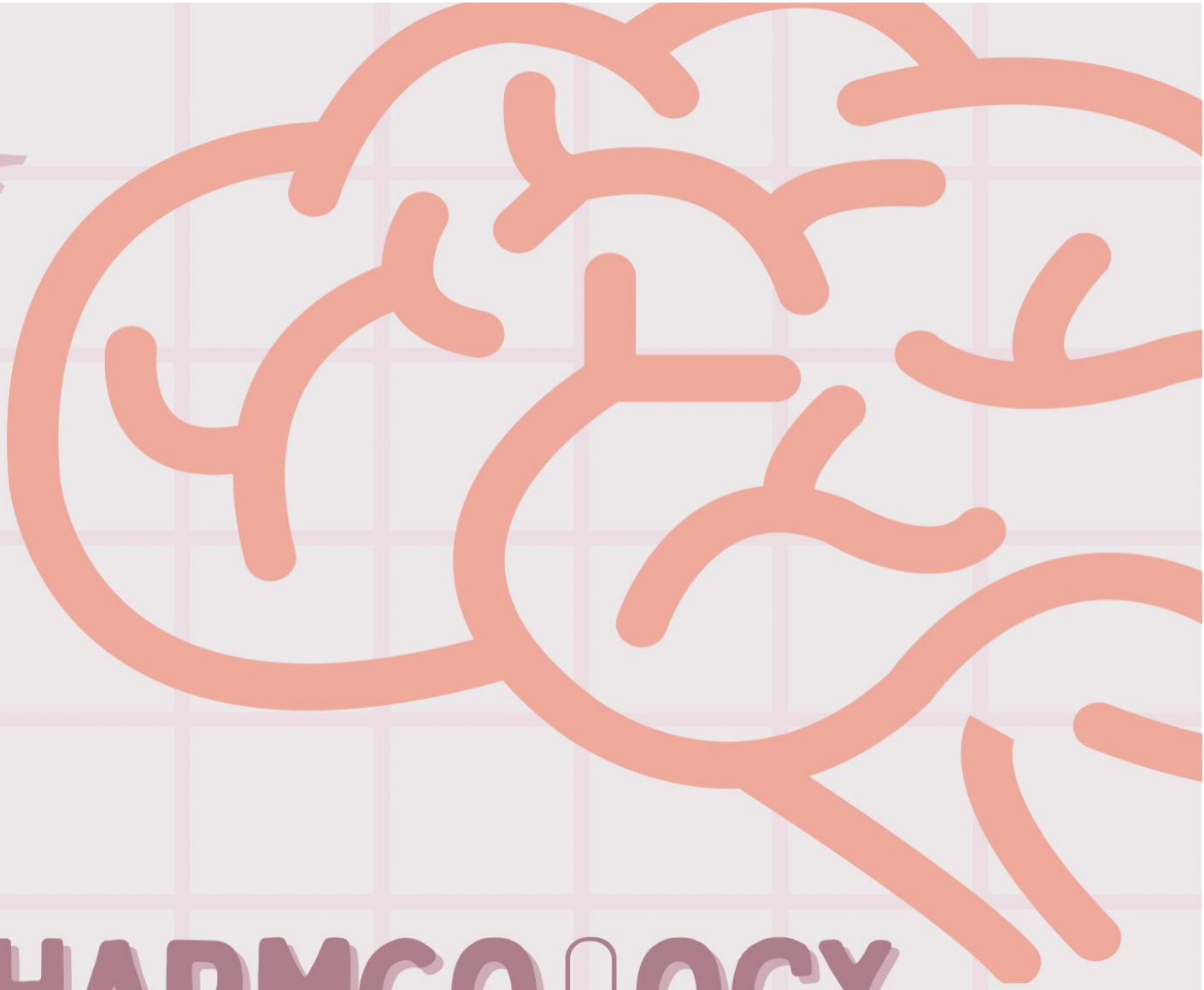

PHARMCOLOGY

SHEET NO. 12

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Antidepressant Drugs:

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.
3. **Melancholic** سوداوي & 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) a growth hormone for neurons, are critical in the regulation of neural plasticity, resilience, & neurogenesis.
• There is evidence that depression is associated with loss of neurotrophic support.

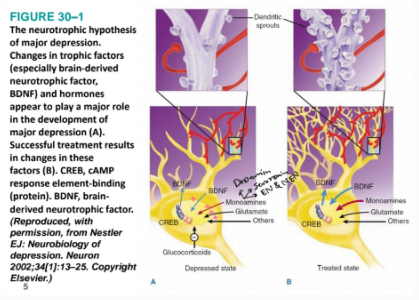
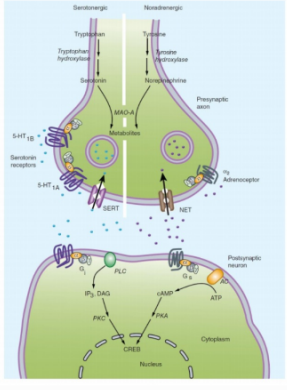


FIGURE 30–1
The neurotrophic hypothesis of major depression. Changes in trophic factors (especially brain-derived neurotrophic factor, BDNF) and hormones appear to play a major role in the development of major depression (A). Successful treatment results in changes in these factors (B). CREB, cAMP response 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.)***

B. **The Monoamine Hypothesis:**
• This hypothesis suggest that depression is related to deficiency in amount or function of cortical & limbic **serotonin, norepinephrine & dopamine**.
• **Reserpine** had been shown to induce depression. It depletes stores of amine neurotransmitters.
• Drugs that increased amine function in certain synaptic areas had relieved depression.
• **Tryptophan-free diet** given to patients taking **fluoxetine** (acts on serotonin receptors) leads to relapse rapidly, but **not** in those given **desipramine**. [Try is a precursor of serotonin synthesis].
• Depletion of catecholamines also leads to relapse.
• 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 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.

• The time required to synthesize neurotrophic factors may be the explanation.

C. **Neuroendocrine Factors:**
• Abnormalities in the hypothalamic-pituitaryadrenal axis.
1. Major depression (and more so psychotic depression) is associated with **elevated cortisol** levels, **non-suppression of ACTH with dexamethasone**, & **chronically elevated level of CRH** (Corticotropin releasing hormone).
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. موجود بس ما بيعطينا تأثير

b) **Elevation of thyroxine** during depressed states.
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.
4. **Severe testosterone deficiency** in men may be associated with depression.
• Sex hormone replacement in hypogonadal men & women improve symptoms.

These 3 theories are interrelated:
1. **HPA & 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 and improve depression.

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.
2. Tricyclic antidepressants (oldest drugs): **imipramine, desipramine.**
C. 5-HT2 Receptor Modulators: **trazodone, nefazodone.**
D. Tetracyclic & Unicyclic Antidepressants: **bupropion, mirtazapine, amoxapine, maprotiline.**
E. Monoamine Oxidase Inhibitors: **phenelzine, tranylcypromine, selegiline.**

Pharmacokinetics:
• Most are incompletely absorbed & undergo significant first-pass metabolism ➡️ active metabolites (drugs).
• High lipid solubility • High tissue protein binding • Very large volume of distribution.

Pharmacodynamics:
A. **Tricyclic antidepressants block** the amine transporters, **NET & SERT** (for norepinephrine & serotonin, respectively). ➡️ **accumulation** of these amines at the synaptic site.
B. **MAOIs block the intraneuronal degradation of the amines** ➡️ more amines to **accumulate** in presynaptic stores, and thus more to be released.
C. **Trazodone, mirtazapine** & similar agents may elicit their action by antagonism of subtypes of serotonin receptors (5-HT2A or 5-HT2C).
• **Mirtazapine** also antagonizes α2-adrenergic receptors.
• **SSRIs** occupy most serotonin uptake sites.
• Actions of bupropion remain poorly understood.
Receptor & postreceptor effects: ৸৩
• 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 downregulation of postsynaptic as well as presynaptic receptors.
*When you increase the agonists you downregulate the receptors.
*The effect is due to downregulation of receptors, **not** due to the amines themselves.
• Enhanced serotonergic transmission (mediated through diverse mechanisms) has been thought to be a common effect of antidepressants even without an increase in synaptic serotonin (whatever you give from the drugs, the treatment of depresstion is related to serotonin).

The table is not for memorizing.

Therapeutic Uses:

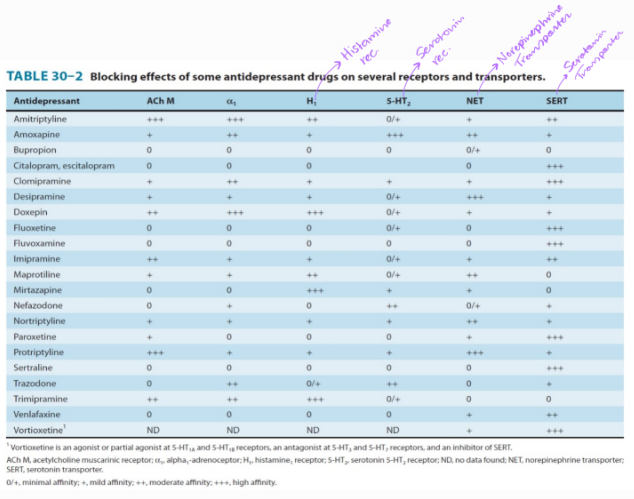


TABLE 30–2 Blocking effects of some antidepressant drugs on several receptors and transporters.

Antidepressant	ACh M	α_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; α_1, alpha$_1$-adrenoceptor; H_1, histamine, 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.

1. **Major depressive disorder**: Maximum benefit of antidepressants may require 1–2 months or longer.
2. **Anxiety disorders**: **panic** الهلع, **generalized anxiety**, and **social phobia**. Require 6-8 weeks of treatment. Better treated with **benzodiazepines**.
3. **Pain disorders**: Antidepressants possess analgesic properties independent of their mood effects. Neuropathic, chronic joint and muscle pain, postherpetic neuralgia (after herpes virus) to chronic back pain.
4. **Premenstrual Dysphoric Disorder:** depressed mood, irritability, insomnia, fatigue, & a variety of other physical symptoms. These symptoms are more severe than those of premenstrual syndrome. The SSRIs **fluoxetine** is beneficial.
5. **Smoking Cessation**: **Bupropion** reduces the urge to smoke. The mechanism is unknown, but it may mimic nicotine's effects on dopamine and norepinephrine & may antagonize nicotinic receptors.
6. **Bulimia**: (excessive eating, then vomiting) (episodic intake of large amounts of food (binges) followed by ritualistic purging through emesis, laxatives, or other methods). **Fluoxetine reduces the binge-purge cycle**.
7. **Attention deficit hyperkinetic disorder**: (was called minimal brain dysfunction syndrome, happens in children, their attention spam become very short).
Atomoxetine has been recently introduced for this purpose (selective NET inhibitor), with no abuse liability like amphetamines (no addiction).

Adverse Effects:

• **All** antidepressants is the risk of **increased suicidality** (suicidal ideation & gestures & suicide) in patients <25 years of age.
• Depressed patients may **tolerate** adverse effects because they are too depressed to care.
• Adverse reactions happens In healthy individuals, even moderate doses are poorly tolerated.
*مروا عالكلام الجاي واعرفوا ال:common things
A. Selective Serotonin Reuptake Inhibitors:
• Increased serotonergic activity in the gut is **commonly** associated with **nausea, GI upset, & 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).
• **Headache, insomnia or hypersomnia**.
• **Weight gain** while taking SSRIs, particularly **paroxetine**.
• A **discontinuation syndrome** characterized by dizziness, paresthesias, & other symptoms beginning 1-2 days after stopping the drug & persisting for 1 week or longer.
• **Teratogenicity** (**paroxetine**).

B. Serotonin-Norepinephrine Reuptake Inhibitors and Tricyclic Antidepressants:
• Have many of the serotonergic adverse effects associated with **SSRIs**.
• **Increased blood pressure & heart rate**.
• CNS activation such as **insomnia, anxiety, & agitation**.
• **Discontinuation syndrome** like that of SSRI.

TCAs:
• **Anticholinergic effects**: dry mouth, constipation, urinary retention, blurred vision, & confusion.
• **Orthostatic hypotension** (α-blocking action).
• H1 antagonism is associated with **weight gain & sedation**.
• **Arrhythmogenicity** • **Sexual effects**.

C. 5-HT Receptor Modulators:
• **Sedation** (**trazodone**) • **GI disturbances** • **Priapism** (**trazodone**).
• **Nefazodone & trazodone** are α-blocking agents & may result in a dose-related **orthostatic hypotension**.
• **Nefazodone** is **hepatotoxic** ➡️ **fatal fulminant hepatic failure** requiring transplantation.

D. Tetracyclics & Unicyclics:
• **Amoxapine** is associated with a **parkinsonian syndrome** due to its D2-blocking action.
• **Mirtazapine** has significant **sedative** effect.
• **Maprotiline** (**seizures**).
• **Agitation, insomnia, & anorexia** (**Bupropion**).

E. Monoamine Oxidase Inhibitors:
• **Orthostatic hypotension** • **Weight gain.**
• **Insomnia & restlessness** • **Sedation & confusion**.

Drug Interactions:

A. Pharmacodynamic interactions:
1. Additive **sedation** with **alcohol** & **sedative-hypnotics**.
2. Dangerous **hypertensive reactions** when **MAOIs** are used with **tyramine rich foods**, and with **sympathomimetic** drugs. They increase sympathomimetic effects مهم جدا
3. **SSRIs + MAOIs** ➡️ **serotonin syndrome** (hyperthermia, muscle rigidity, myoclonus & rapid changes in mental status and vital signs).

B. Pharmacokinetic interactions: (happen due to drug metablism)
1. **Paroxetine & fluoxetine** inhibit **CYP2D6**, & thus clearance of drugs metabolized by it (**desipramine, nortriptyline, flecainide, …**).
2. **Nefazodone & fluvoxamine** may inhibit **CYP3A4** at high concentrations.