AL-Mustaqbal university
College of Nursing

PharmacologyII

Dr. Ghada Ali
ghada.ali@uomus.edu.iq

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Drug Therapy for Depression and Mood Stabilization

Mood disorders include **depression**, **dysthymia**, **bipolar disorder**, and **cyclothymia** .Major depressive disorder is relatively common in adults, and it also occurs in children and adolescents.

❑ Depression

The symptoms of depression are **feelings of sadness** and **hopelessness**, as well as the **inability to experience pleasure** in usual activities, **changes in sleep patterns** and **appetite**, **loss of energy**, and **suicidal thoughts**.

❑ Mania

is characterized by the opposite behavior: **enthusiasm**, **anger**, **rapid thought** and **speech patterns**, **extreme self confidence**, and **impaired judgment**.

Pathophysiology

depression results from interactions among several complex factors. Causes involve

- **the immune system**,
- **monoamine neurotransmitter dysfunction** (deficiency of norepinephrine and/or serotonin)
- **neuroendocrine factors**, Corticotropin releasing factor secretion is increased in people with depression. CRF-secreting neurons are widespread in the CNS, and CRF apparently functions as a neurotransmitter and mediator of the endocrine, autonomic, immune, and behavioral responses to stress as well as a releasing factor for corticotropin.
- **genetic** and
- **environmental factors**.

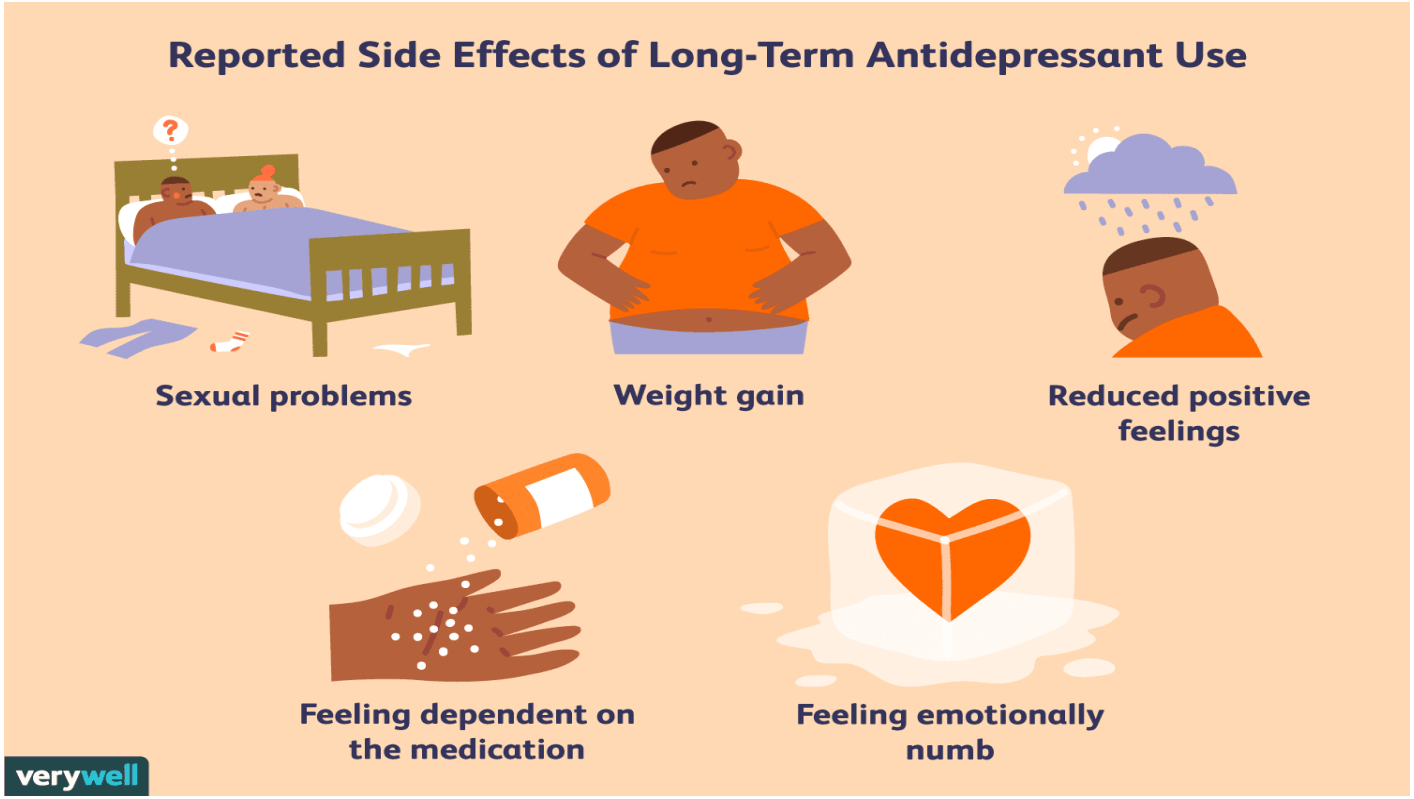
Drug Class	Prototype	Other Drugs in the Class
Antidepressants		
Tricyclic antidepressants	Imipramine	Amitriptyline Amoxapine Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Nortriptyline (Pamelor) Protriptyline hydrochloride Trimipramine
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine (PROzac, Sarafem)	Citalopram (Celexa) Escitalopram (Lexapro) Fluvoxamine (Luvox) Paroxetine (Paxil, Paxil CR, Brisdelle, Pexeva) Sertraline (Zoloft) Vilazodone (Viibryd, Viibryd Starter Pack)
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine (Effexor XR)	Desvenlafaxine (Pristiq) Duloxetine (Cymbalta, Drizalma Sprinkle) Levomilnacipran (Fetzima, Fetzima Titration) Milnacipran (Savella, Savella Titration Pack) Nefazodone
Monoamine oxidase (MAO) inhibitors	Phenelzine (Nardil)	Isocarboxazid (Marplan) Selegiline hydrochloride (Emsam, Zelapar) Tranylcypromine (Parnate)
Atypical antidepressants		Bupropion (Aplenzin, Wellbutrin SR, Wellbutrin XL) Mirtazapine (Remeron) Trazodone
Mood-stabilizing agents	Lithium carbonate (Lithobid)	Aripiprazole (Abilify, Abilify Maintena, Abilify MyCite) Olanzapine (ZyPREXA, ZyPREXA Relprew, ZyPREXA Zydis) Quetiapine (Seroquel) Olanzapine–fluoxetine (Symbyax) Risperidone (Perseris, RisperDAL, RisperDAL Consta) Ziprasidone (Geodon)

Antidepressants are used to regulate mood specifically affecting serotonin, norepinephrine, and dopamine. Antidepressant effects are attributed to **changes in receptors** rather than changes in neurotransmitters.

- **Older antidepressants** include
  - the tricyclic antidepressants (TCAs) and
  - the monoamine oxidase (MAO) inhibitors.
- **Newer drugs** include
  - the selective serotonin reuptake inhibitors (SSRIs),
  - the serotonin–norepinephrine reuptake inhibitors (SNRIs) , and several adjuvant atypical antidepressant drugs that differ from TCAs and MAO inhibitors.

The choice of an antidepressant depends on the

- **patient's age;**
- **medical condition**;
- **previous history of drug response**, if any; and the
- **specific drug's adverse effects**. Also, prescribers often use the **side effect** profile to help determine the best choice for a specific patient.



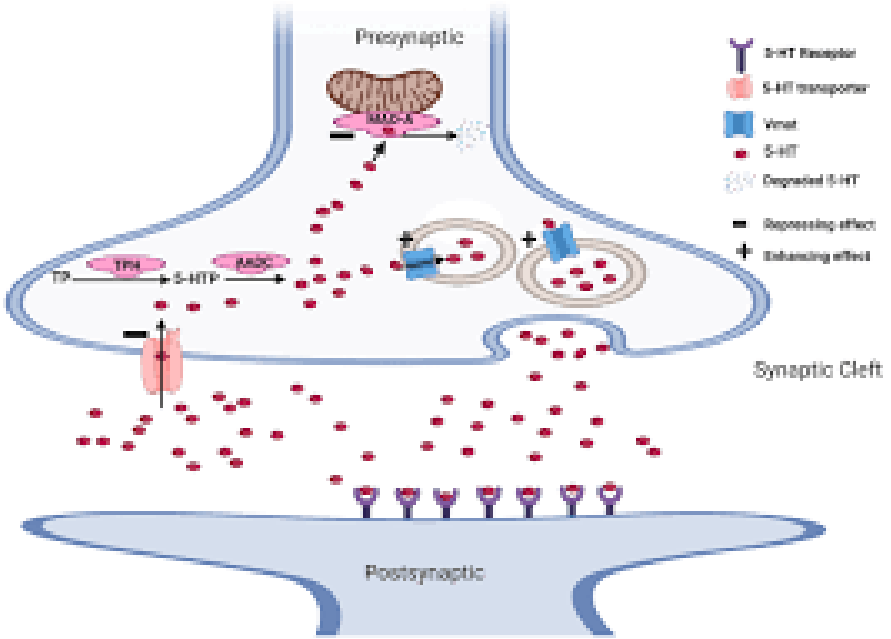
❑ Tricyclic antidepressants

Imipramine is the prototype. it blocks the reuptake of **norepinephrine** and serotonin at the presynaptic nerve endings, increasing the action of both neurotransmitters. The drug's use in enuresis may be due to the fact that imipramine also blocks acetylcholine receptors.

Other Drugs in the Class

Commonly used TCAs include

- **amitriptyline**,
- **clomipramine** (Anafranil),
- **desipramine** (Norpramin),
- **doxepin** (Silenor), and
- **nortriptyline** (Pamelor).



❑ Selective Serotonin Reuptake inhibitors (SSRIs)

fluoxetine is the prototype, (SSRIs are called "selective" because they seem to primarily affect serotonin and not other neurotransmitters.) Fluoxetine blocks the reabsorption of the neurotransmitter serotonin in the brain.

Other Drugs in the Class

Other SSRIs include

- **citalopram (Celexa),**
- **escitalopram (Lexapro),**
- **Paroxetine (Paxil),**
- **sertraline (Zoloft), and**
- **vilazodone**

Serotonin–norepinephrine reuptake inhibitors (SNRIs)

Like the SSRIs, the SNRIs, of which **venlafaxine** (Effexor XR) is the prototype, inhibit the neuronal uptake of serotonin. In addition, they also inhibit the uptake of norepinephrine, increasing the activity of these neurotransmitters in the brain. The SNRIs are similar to SSRIs in terms of therapeutic effects.

Monoamine oxidase inhibitors

MAO inhibitors are third-line agents for the treatment of depression and are rarely used in clinical practice today, mainly because they may interact with some foods and drugs to produce severe hypertension and possible heart attack or stroke.

❑ Atypical antidepressants

Other drugs used to treat depression include bupropion, mirtazapine, and trazodone .

People also use the herbal preparation **St. John's wort** as an antidepressant. inhibits the reuptake of **dopamine**, NE, and serotonin. After an oral dose, peak plasma levels are reached in about 2 hours.

Bipolar disorder

Bipolar disorder is a condition in which people alternate between periods of depression and overexcitement. There are two subtypes of this disorder, which are defined by the presentation of the mood disorder.

Bipolar disorder type I

Is characterized by episodes of major depression plus mania (euphoria or irritability) and occurs equally in men and women.

Bipolar disorder type II

Is characterized by episodes of major depression plus episodes of hypomania (persistent irritable mood but absence of euphoria) and occurs more frequently in women. Bipolar spectrum disorder broadens the definition of bipolar disorder to include conditions such as cyclothymia (a mild type of bipolar disorder) and dysthymia (chronically depressed mood).

Pathophysiology

mania, and hypomania have been associated with

- abnormal functioning of **neurotransmitters or receptors**, such as a relative **excess** of excitatory neurotransmitters (e.g., **NE**) or a relative **deficiency** of inhibitory neurotransmitters (e.g., gamma-aminobutyric acid **[GABA]**).
- Secondary causes of manic and hypomanic behavior include **drugs that stimulate the CNS**, CNS diseases and infections, and electrolyte or endocrine disorders.

Mood-stabilizing agents:
Drugs used to treat bipolar disorder

Mood-stabilizing drugs such as **lithium** stimulate neuronal growth and reduce brain atrophy in people with long-standing mood disorders. **Lithium carbonate** (Lithobid), the prototype, is a naturally occurring metallic salt that is used in patients with bipolar disorder, mainly to treat and prevent manic episodes.

Other Drugs in the Class

Atypical antipsychotics are used to decrease dopamine activity in the treatment of the mania phase of bipolar disorder, including reducing acute mania, psychomotor agitation, and psychosis currently,

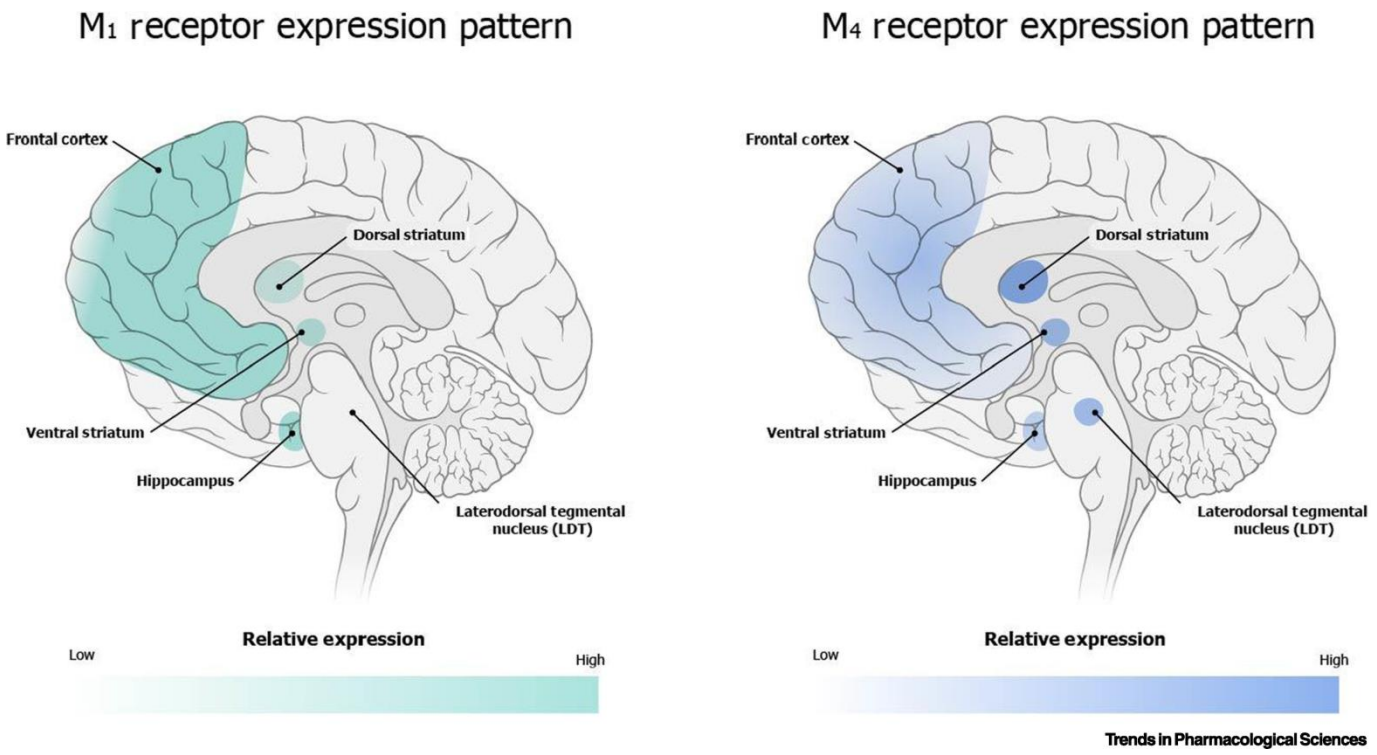
- **aripiprazole**,
- **olanzapine** (monotherapy or combination with fluoxetine),
- **quetiapine**,
- **risperidone**,
- **ziprasidone** are approved by the FDA for this indication

Drug Therapy for Psychotic Disorders

Psychosis may be acute or chronic. Acute episodes, also called **confusion** or **delirium**, have a sudden onset over hours to days and may be precipitated by physical disorders (e.g., brain damage related to cerebrovascular disease or head injury, metabolic disorders, infections); drug intoxication with adrenergics , antidepressants, some anticonvulsants, amphetamines, cocaine, and others; and drug withdrawal after chronic use (e.g., alcohol, benzodiazepine antianxiety or sedative–hypnotic agents). In addition, acute psychotic episodes may be superimposed on chronic dementias and psychoses, such as schizophrenia.

Pathophysiology

There is evidence of **abnormal neurotransmission** systems in the brains of people with schizophrenia, especially in the dopaminergic, serotonergic, and glutamatergic systems. In addition, illnesses or drugs that alter neurotransmission in one system are likely to alter neurotransmission in other systems.



Drug Therapy

The goal of drug treatment is to relieve symptoms with minimal or tolerable adverse effects. In patients with acute psychosis, the goal during the first week of treatment is to **decrease symptoms** (e.g., aggression, agitation, combativeness, hostility) and normalize patterns of sleeping and eating

Drug Class	Prototype	Other Drugs in the Class
First-generation (typical) antipsychotics	Chlorpromazine Haloperidol (Haldol)	Fluphenazine Loxapine Perphenazine Pimozide Thioridazine Trifluoperazine Thiothixene
Second-generation (atypical) antipsychotics	Clozapine (Clozaril, Versacloz)	Aripiprazole (Abilify, Abilify Maintena) Asenapine (Saphris, Secuado) Iloperidone (Fanapt) Lurasidone (Latuda) Olanzapine (Zyprexa, Zyprexa Relprevv) Paliperidone (Invega, Invega Sustenna, Invega Trinza) Quetiapine (Seroquel, Seroquel XR) Risperidone (Risperdal, Perseris, Risperdal Consta) Ziprasidone (Geodon)

❑ First-generation “typical” antipsychotics

- **First-generation phenothiazines**

Chlorpromazine hydrochloride (Largactil)is the prototype drug of the phenothiazine groups,.

- **First-generation non-phenothiazines**

They are effective in treating both psychotic disorders and nonpsychotic depression. The first-generation antipsychotic medication **Haloperidol** (Haldol) is the prototype “typical” non-phenothiazine. This butyrophenone is a frequently used, long-acting antipsychotic

❑ Second-generation “atypical” antipsychotics

The “atypical” antipsychotics are the drugs of choice, especially for patients who are newly diagnosed with schizophrenia. These second-generation antipsychotics differ from first-generation agents in that they have a **broader range of action** due to their effects on the serotonergic, noradrenergic, and dopaminergic systems. **Clozapine** is the prototype “atypical” antipsychotic.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