Drugs for Depression & Mania

Anti-depressants : Drugs for Mania & Depression

- **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.
  Biogenic amine theory proposes that depression is **due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain.**

- **Mania** : is characterized by the **opposite behavior**: enthusiasm, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.
  Conversely, the **theory proposes that mania is caused by an overproduction of these neurotransmitters .**

Antidepressant drugs classes

- **Tricyclic antidepressants (TCAs)**
- **Mono amino oxidase Inhibitors (MAOI)**
- **Selective Serotonin Reuptake Inhibitors (SSRI)**
- **Serotonin/norepinephrine reuptake inhibitors (SNRIs)**

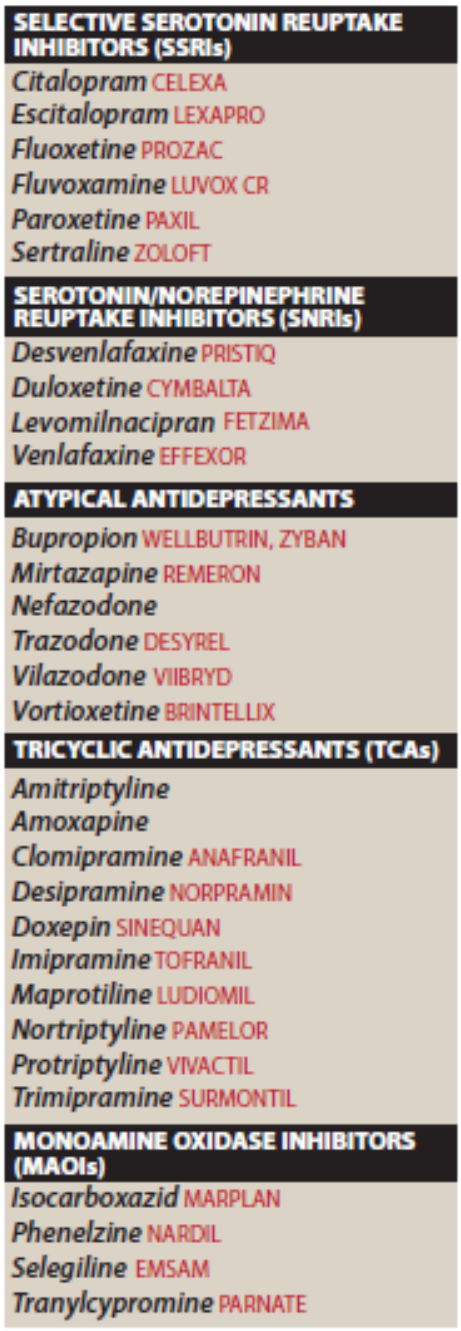

Figure 10.1
Summary of antidepressants.

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MECHANISM OF ANTIDEPRESSANT DRUGS

Most clinically useful antidepressant drugs (Figure 10.1) potentiate, either

directly or indirectly, the actions of norepinephrine and/or serotonin (5-HT)

in the brain.

Although , the pharmacological effects of any of the antidepressant and anti-mania drugs on neurotransmission, which often occur immediately; however, **the time course for a therapeutic response occurs over several weeks.**

This suggests that decreased reuptake of neurotransmitters is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects.

- **TRICYCLIC ANTIDEPRESSANTS (TCAs)**

The TCAs elevate mood, improve mental alertness, increase physical activity of individuals with major depression by blocking norepinephrine and serotonin reuptake into the presynaptic neuron . these old drugs are not preferred today since show different adverse effects relative to other newer class of antidepressants (SSRIs & SNRIs) .

- **the Tertiary Amines:**

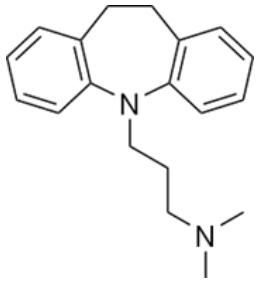
Imipramine [ee-MIP-ra-meen] (the prototype drug)

Desipramine [dess-IP-ra-meen]

Amitriptyline [amee- TRIP-ti-leen]

Clomipramine [kloe-MIP-ra-meen]

Nortriptyline [nor-TRIP-ti-leen]

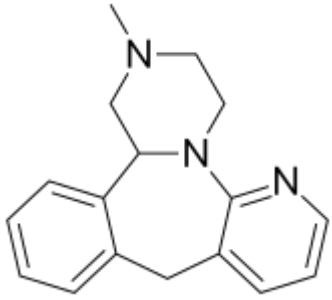


IMMPRAMINE

- **The secondary Amines (** These Antidepressants , Are related "**tetracyclic**" antidepressant agents and are commonly included in the general class of TCAs. **Maprotiline**

Mianserin

Mirtazapine



Mechanism of action :

1- Inhibition of neurotransmitter reuptake: TCAs are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals in the brain The TCAs are effective in treating moderate to severe depression. .

2- Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. It is not known if any of these actions produce the therapeutic benefit of the TCAs. However, **actions at these receptors are likely responsible for many of their adverse effects.**

Therapeutic uses & Adverse effects

The TCAs are effective in treating :

- ✓ moderate to severe depression.
- ✓ Some patients with panic disorder also respond to TCAs.
- ✓ Imipramine has been used to control bed-wetting in children older than 6 years of age; however, it has largely been replaced by desmopressin and non pharmacologic treatments (enuresis alarms).
- ✓ The TCAs, particularly amitriptyline, have been used to help prevent migraine headache and treat chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear.
- ✓ Low doses of TCAs, especially doxepin, can be used to treat insomnia.

Adverse effects

Blockade of muscarinic receptors leads to Anticholinergic side effects :

- blurred vision, dry mouth
- urinary retention
- sinus tachycardia
- Constipation
- Aggravation of angle-closure glaucoma (Figure 10.7).
- **The TCAs also block α-adrenergic receptors**, causing orthostatic hypotension, dizziness, and reflex tachycardia.
  Imipramine is the most likely, and nortriptyline the least likely, to cause orthostatic hypotension.
- Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to **block histamine H1 receptors.**

- **Weight gain** is a common adverse effect of the TCAs.
- **Sexual dysfunction** occurs in a minority of patients, and the incidence is lower than that associated with the SSRIs.
- These agents may precipitate **life-threatening arrhythmias** in an overdose situation.

❖ MONOAMINE OXIDASE INHIBITORS (MAO I)

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver.

In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest.

The MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space.

The MAOIs currently available for treatment of depression include :

- **Phenelzine [FEN-el-zeen],**
- **Tranylcypromine [tran-il-SIP-roe-meen],**
- **Selegiline [seh-LEDGE-ah-leen].**

Mechanism of action

Most MAOIs, such as *phenelzine,* form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space (Figure 10.9).

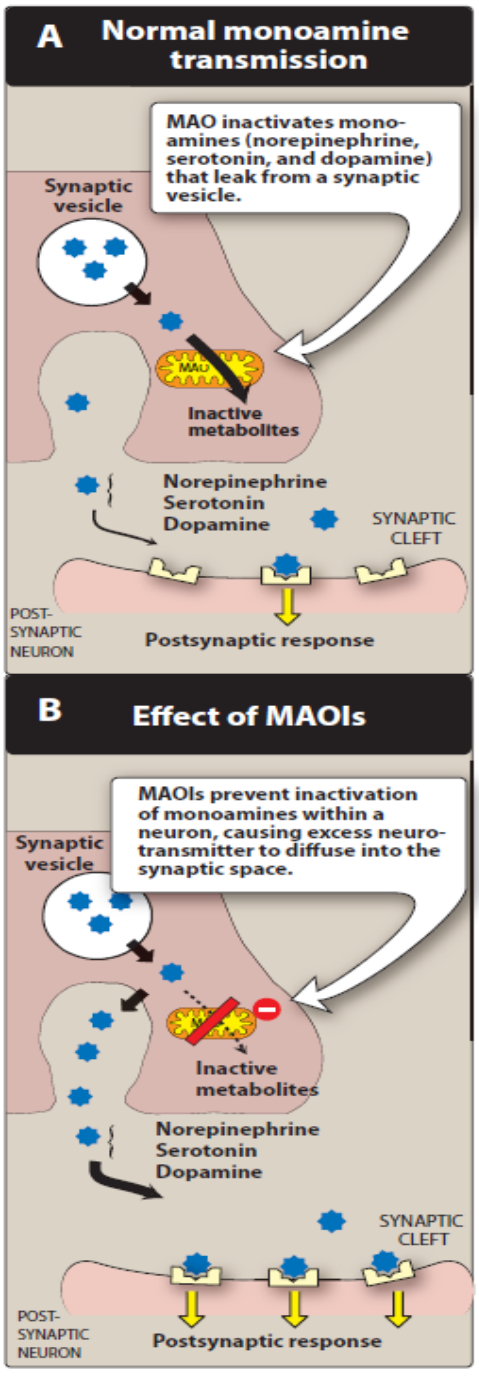


Figure 10.9
Mechanism of action of monoamine oxidase inhibitors (MAOIs).

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Pharmacokinetics

These drugs are well absorbed after oral administration.

MAOIs are hepatically metabolized and excreted rapidly in urine.

D- Therapeutic uses & Adverse effects

The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.

Adverse effects

Severe and often unpredictable side effects, due to

- **Drug–food interactions**, For example, tyramine, which is contained in foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish, and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet.

Tyramine causes the **release of large amounts of stored catecholamines from nerve terminals**, resulting in a **hypertensive crisis, headache, tachycardia, and cardiac arrhythmias. (tyramine crises)**

Patients must, therefore, be educated to avoid tyramine-containing foods when use MAOI drugs .

Phentolamine and prazosin are helpful in the management of tyramine-induced hypertension.

- **Drug-drug interactions :** the use of MAOIs with other antidepressants is contraindicated. For example, SSRIs should not be co-administered with MAOIs. Both SSRIs and MAOIs require a washout period of (2-6) weeks before the other type is administered
- **Other possible side effects** of treatment with MAOIs include : **drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.**

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The SSRIs include :

- **Fluoxetine [floo-OX-e-teen] drug),**
- **Citalopram [sye-TAL-oh-pram] & escitalopram [es-sye-TAL-ohpram],**
- **Paroxetine [pa-ROX-e-teen]**
- **Sertraline [SER-tra-leen]**

المعلومات التالية تشمل الانواع اعلاه

MECHANISM OF ACTION : The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft available to bind to the postsynaptic receptor.

Pharmacokinetics

- All of the SSRIs are well absorbed after oral administration. **Peak levels are seen in approximately 2 to 8 hours on average.**

Food has little effect on absorption for which food increases its absorption, so it is prefered to be given after meal

Therapeutic uses & adverse effects

The primary indication for SSRIs is depression, for which they are as effective as the TCAs.

A number of other psychiatric disorders also respond favorably to SSRIs, including

- ✓ Obsessive–compulsive disorder
- ✓ Panic disorder,
- ✓ Generalized anxiety disorder,
- ✓ Posttraumatic stress disorder,
- ✓ Premenstrual dysphoric disorder
- ✓ Bulimia nervosa (only *fluoxetine* is approved for bulimia).

Adverse effects

Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without adverse effects, such as :

- Headache
- Sweating
- Anxiety
- Agitation
- Gastrointestinal (GI) effects (nausea, vomiting, diarrhea)
- Sexual dysfunction which may include loss of libido, delayed ejaculation, is common with the SSRIs.
- Sleep disturbances : Insomnia and somnolence
- Somnolence (alternatively "sleepiness" or "drowsiness") is a state of strong desire for sleep . Somnolence is often viewed as a symptom rather than a disorder by itself. **Paroxetine and fluvoxamine are generally more sedating (less somnolence) than fluoxetine**
- Drug–drug interactions since SSRI are potent CYP inhibitors , also show drug-drug interaction with some drugs as (ethanol alcohol, adrenergic drugs & MAOI) IF GIVEN TOGETHER). Additionally, SSRIs may interact in elderly using diuretics .

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRI)

- **Venlafaxine [VEN-la-fax-een]**
- **Duloxetine [doo-LOX-e-teen]**

SUMMARY OF ANTIDEPRESSENT THERAPY

- ✓ Moreover, the SSRIs have little blocking activity at muscarinic, α-adrenergic, and histaminic H1 receptors. Therefore, common side effects associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs.

- ✓ Because they have different adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression.

- ✓ Patients who do not respond to one antidepressant may respond to another, and approximately 80% or more will respond to at least one antidepressant drug.

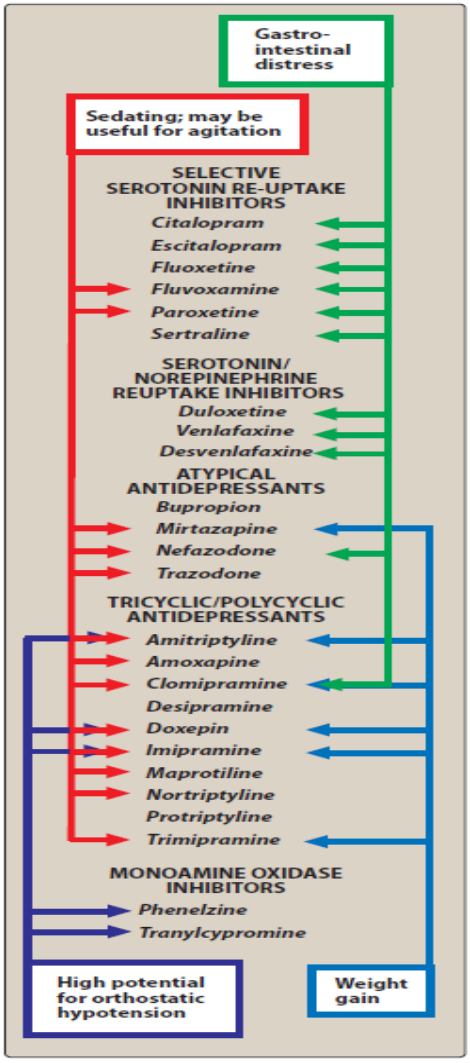

Figure 10.10
Side effects of some drugs used to treat depression.

الجدول للاطلاع لملاحظة الادوية وتاثيراتها الجانبية

Treatment of Mania and Bipolar Disorder

The treatment of bipolar disorder has increased in recent years, due to increased recognition of the disorder and also an increase in the number of available medications for the treatment of mania.

- **Lithium**

Lithium salts are used acutely and prophylactically for managing bipolar patients. *Lithium* is effective in treating 60% to 80% of patients exhibiting mania and hypomania.

Although many cellular processes are altered by treatment with *lithium salts,* the mode of action is unknown.

The therapeutic index of *lithium* is extremely low, and *lithium salts* can be toxic. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give *lithium* with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation.

Adverse effects due to higher plasma levels may indicate toxicity and include ataxia, slurred speech, coarse tremors, confusion, and convulsions.

Thyroid function may be decreased and should be monitored.

Unlike other mood stabilizers, *lithium* is renally eliminated, and though caution should be used when dosing this drug in renally impaired patients, it may be the best choice in patients with hepatic impairment.

- **Other drugs**

- **Several antiepileptic drugs**, including : c**arbamazepine, valproic acid, and lamotrigine,** have been approved as mood stabilizers for bipolar disorder. **ستشرح في محاضرات لاحقة**
- Other agents that may improve manic symptoms include the older (**chlorpromazine and haloperidol)** and newer antipsychotics. **ستشرح في محاضرات لاحقة**

ANTIPSYCHOTIC DRUGS

Overview

The antipsychotic drugs (also called **neuroleptics or major tranquilizers**) are used primarily to **treat schizophrenia**, but they are also effective in other **psychotic and manic states.**

The use of antipsychotic medications involves a difficult balance between the benefit of alleviating Symptoms and reducing adverse drug effects .

SCHIZOPHRENIA

Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances.
The onset of illness is often during late adolescence or early adulthood.
It occurs in about 1% of the population and is a chronic and disabling disorder.
Schizophrenia has a strong genetic component and probably
reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic dopaminergic neuronal pathways.

Dopamine & Dopaminenergic neuronal pathway

Neurons that use dopamine as a neurotransmitter are called dopaminergic neurons. Neurons that have dopamine receptor proteins on the postsynaptic membrane, and that therefore respond to dopamine, have been identified & highly concentrated in the midbrain.

Aim of drug therapy in schizophrenia

Antipsychotic drugs (Figure 11.1) are not curative and do not eliminate chronic thought disorders, but they often :

- Decrease the intensity of psychotic symptoms (hallucinations and delusions) & Permit the person with schizophrenia to function in a supportive environment.
- Decrease the risk of a wide variety of troubling drug adverse effects.

Antipsychotic Drugs classes

The antipsychotic drugs are divided into first- and second-generation agents.

❖ **First-generation Antipsychotics**

- **Chlorpromazine**
- **Thioredazine**
- **Trifluoperazine**
- **Haloperidol**
- **Pimozide**

❖ **Second -generation Antipsychotics**

- **Clozapine**
- **Olanzapine**
- **Risperidone**

No one drug is clinically more effective than another.

التقسيم واسماء الادوية

Mechanism of Action :

1-Dopamine antagonism: All of the first-generation antipsychotic drugs block D2 dopamine receptors in the brain and the periphery (Figure 11.2).

2. Serotonin receptor–blocking activity: Most of the second generation agents appear to exert part of their unique action
through inhibition of serotonin receptors (5-HT), particularly
5-HT2A receptors and most of the second-generation antipsychotic drugs block D2 dopamine receptors in the brain and the periphery , with some drugs indirectly block cholinergic receptors showing Anti-cholinergic side effects .

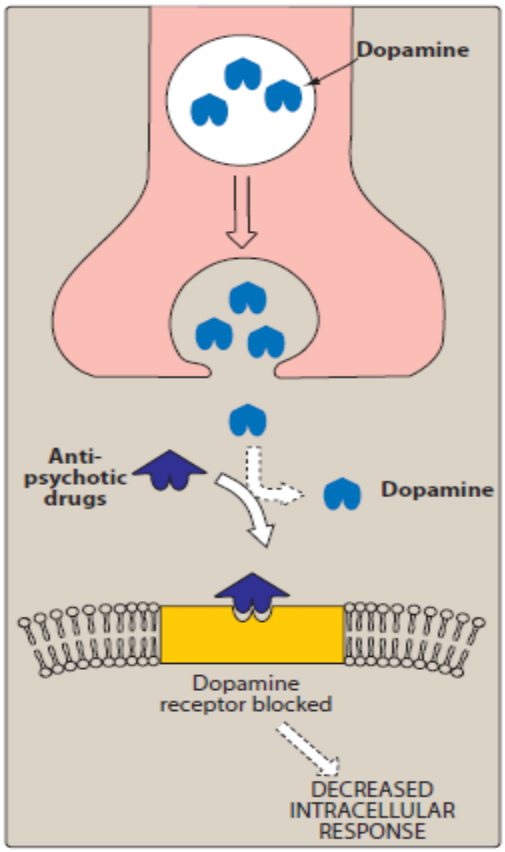

Figure 11.2
Dopamine-blocking actions of antipsychotic drugs.

Diagram for neuroleptic drugs action

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❖ Pharmacokinetics : Absorption and metabolism

- ✓ After oral administration, the antipsychotics show variable absorption that is unaffected by food.
- ✓ These agents readily pass into the brain and have a large volume of distribution.
- ✓ They are metabolized to many different metabolites، usually by the cytochrome P450 system in the liver

❖ Therapeutic uses & adverse effects :

1- Treatment of schizophrenia: The antipsychotics are considered the only efficacious pharmacological treatment for schizophrenia.

The first-generation antipsychotics are most effective in treating **positive symptoms of schizophrenia (**hallucinations and delusions) associated with schizophrenia (known as "positive" symptoms) by blocking D2 receptors in the mesolimbic system of the brain.

2- **Treatment of Mania** : Many antipsychotic agents are approved for the management of the manic and mixed symptoms associated with bipolar disorder.

3- **Prevention of nausea and vomiting:** most commonly, prochlorperazine useful in the treatment of drug-induced nausea , and vomiting having **Antiemetic effects** mediated by blocking D2 receptors of the chemoreceptor trigger zone of the medulla which contains vomiting center and induce nasua & vomiting .

3- Other uses: The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior secondary to other disorders.

Adverse effects

Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80% , First-generation antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors, such as **haloperidol .**

❖ **Anticholinergic side effects:**

1- **Extrapyramidal effects:** Anticholinergic side effects arise from blockade of dopamine receptors in the nigrostriatal pathway of the brain which are normally balanced by the excitatory actions of cholinergic neurons , Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects probably causes unwanted movement symptoms characterized by :

- **Dystonias** (sustained contraction of muscles leading to twisting, distorted postures)
- **Parkinson-like symptoms**
- **Akathisia** (motor restlessness)
- **Tardive dyskinesia** (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs) can occur with both acute and chronic treatment.

The second generation antipsychotics exhibit a lower incidence of EPS.

2- Some of the antipsychotics, particularly Thioridazine, chlorpromazine , show anti-cholinergic effects include **blurred vision, dry mouth (Except** Clozapine which increases salivation**)** , **confusion**, **constipation and urinary retention.**

❖ **Adrenergic Blockade of α-adrenergic receptors** causes **orthostatic hypotension** .

❖ **Dopamine receptor blocking** In the pituitary, antipsychotics block D2 receptors, leading to an increase in prolactin release.

❖ **Histamine blocking : Sedation** occurs with those drugs that are potent antagonists of the H1-histamine receptor.

❖ **Hormonal disturbances** : The antipsychotics depress the hypothalamus, affecting thermoregulation and causing amenorrhea, galactorrhea, infertility.

❖ **Metabolic side effects** : The second-generation antipsychotic drugs associated with a higher risk of metabolic side effects, such as : diabetes, hypercholesterolemia, and weight gain.

❖ **Heart ECG rythum changes** Some antipsychotics have been associated with mild to significant QT prolongation of heart ECG rythum ,used with caution in patients with ventricular arrhythmia .

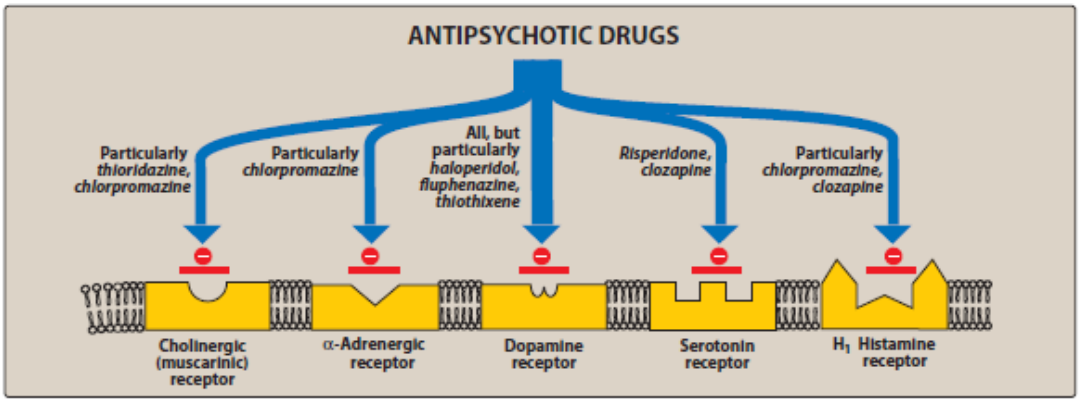

Figure 11.4
Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors.

الرسم مطلوب مع التاشير للتمييز بين pharmacological effect & Adverse drug action