

Antidepressants drugs

Depression

- The symptoms of **depression** are feelings of sadness and hopelessness.
- Inability to experience pleasure in usual activities.
- Changes in sleep patterns and appetite.
- loss of energy.
- Suicidal thoughts.
- **Mania** is characterized by the opposite behavior: **enthusiasm**, anger, rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

MECHANISM OF ANTIDEPRESSANT DRUGS

- Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of **norepinephrine and/or serotonin (5-HT)** in the brain.
- This, along with other evidence, led to the **biogenic amine theory**, which proposes that **depression** is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain.
- Conversely, the theory proposes that **mania** is caused by an overproduction of these neurotransmitters.
- The biogenic amine theory of depression and mania is overly simplistic. It fails to explain the pharmacological effects of any of the antidepressant and antimania 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.

Summary of Antidepressants

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Amitriptyline

Amoxapine

Clomipramine ANAFRANIL

Desipramine NORPRAMIN

Doxepin SINEQUAN

Imipramine TOFRANIL

Maprotiline LUDIOMIL

Nortriptyline PAMELOR

Protriptyline VIVACTIL

Trimipramine SURMONTIL

MONOAMINE OXIDASE INHIBITORS (MAOIs)

Isocarboxazid MARPLAN

Phenelzine NARDIL

Selegiline EMSAM

Tranylcypromine PARNATE

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Citalopram CELEXA

Escitalopram LEXAPRO

Fluoxetine PROZAC

Fluvoxamine LUVOX CR

Paroxetine PAXIL

Sertraline ZOLOFT

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

Desvenlafaxine PRISTIQ

Duloxetine CYMBALTA

Levomilnacipran FETZIMA

Venlafaxine EFFEXOR

ATYPICAL ANTIDEPRESSANTS

Bupropion WELLBUTRIN, ZYBAN

Mirtazapine REMERON

Nefazodone

Trazodone DESYREL

Vilazodone VIIBRYD

Vortioxetine BRINTELLIX

Selective Serotonin Reuptake Inhibitors (SSRIs)

- The selective serotonin reuptake inhibitors (SSRIs) are a group of antidepressant drugs that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter.
- This contrasts with the tricyclic antidepressants (TCAs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) that nonselectively inhibit the reuptake of norepinephrine and serotonin
- 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.

➤ **The SSRIs include:**

- **Fluoxetine** [*floo-ox-e-teen*] (the prototypic drug),
- **Citalopram** [*sy-e-tal-oh-pram*]
- **Escitalopram** [*es-sye-tal-ohpram*]. *Escitalopram is the pure S-enantiomer of citalopram.*
- **Fluvoxamine** [*floo-vox-e-me-en*].
- **Paroxetine** [*pa-rox-e-teen*].
- **Sertraline** [*SER-tra-leen*].

Actions

- The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft.
- Antidepressants, including SSRIs, typically take **at least 2 weeks** to produce significant **improvement in mood**, and **maximum** benefit may require up to **12 weeks** or more .
- 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.

Therapeutic uses

- 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, social anxiety disorder, premenstrual dysphoric disorder, and **bulimia** nervosa (only **fluoxetine** *is approved for bulimia*).

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 (except with **sertraline**, *for which food **increases** its absorption*).
- The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by cytochrome P450 (CYP450)–dependent enzymes and glucuronide or sulfate conjugation occur extensively.
- **Fluoxetine** *differs from the other members of the class* by having a much **longer half-life (50 hours)**, and the half life of its active metabolite S-norfluoxetine *is quite long, averaging 10 days*.
- It is available as a sustained-release preparation allowing once-weekly dosing.

- **Fluoxetine** and *paroxetine* are **potent inhibitors** of a CYP450 isoenzyme (CYP2D6) responsible for the elimination of TCAs, antipsychotic drugs, and some antiarrhythmic and β -adrenergic antagonist drugs.
- Other CYP450 isoenzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs.
- Dosages of the SSRIs should be reduced in patients with hepatic impairment.

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 and agitation, gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and the potential for drug–drug interactions.**
- SSRIs have been associated with **hyponatremia**, especially in the **elderly** and patients who are volume depleted or taking diuretics.

- 1. Sleep disturbances:** **Paroxetine** and **fluvoxamine** are generally more sedating than activating, and they may be **useful in patients who have difficulty sleeping.**
 - Conversely, patients who are fatigued or complaining of excessive **somnolence** may benefit from one of the more activating SSRIs, such as **fluoxetine or sertraline.**
- 2. Sexual dysfunction:** Sexual dysfunction, which may include loss of libido, delayed ejaculation, and **anorgasmia**, is common with the SSRIs.
 - ✓ One option for managing SSRI-induced sexual dysfunction is to change the antidepressant to one with fewer sexual side effects, such as **bupropion or mirtazapine.** *Alternatively,* the dose of the drug may be reduced.

3. Use in children and teenagers antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 children report suicidal ideation as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant. **Fluoxetine, sertraline, and fluvoxamine** are approved for use in children to treat **obsessive–compulsive disorder**, and **fluoxetine** and **escitalopram** are approved to treat **childhood depression**.

4. Overdose: Overdose with SSRIs does not usually cause **cardiac arrhythmias**, with the exception of **citalopram**, which may cause QT prolongation. [Note: The TCAs have a significant risk for arrhythmias in overdose.] **Seizures** are a possibility because, all antidepressants may lower the seizure threshold. All SSRIs have the potential to cause **serotonin syndrome**, especially when used in the presence of a MAOI or other highly serotonergic drug. **Serotonin syndrome may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs.**

- 5. Discontinuation syndrome:** All of the SSRIs have the potential to cause a **discontinuation syndrome** after their **abrupt withdrawal**, particularly the agents with shorter half-lives and inactive metabolites. **Fluoxetine** *has the lowest risk of causing an SSRI discontinuation syndrome* due to its longer half-life and active metabolite.
- Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise, and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS

- **Venlafaxine** [*VEN-la-fax-eeen*], **desvenlafaxine** [*dez-VEN-la-fax-eeen*], **levomilnacipran** [*leevo-mil-NA-si-pran*], and **duloxetine** [*doo-LOX-e-teen*] inhibit the reuptake of both serotonin and norepinephrine.
- These agents, termed **SNRIs**, **may be effective in treating depression in patients in whom SSRIs are ineffective.**
- Depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which **SSRIs** are also relatively **ineffective.**

- This pain is, in part, modulated by serotonin and norepinephrine pathways in the central nervous system (CNS).
- Both **SNRIs** and the **TCAs**, with their dual inhibition of both serotonin and norepinephrine reuptake, are sometimes effective in relieving pain associated with diabetic peripheral neuropathy, **postherpetic** neuralgia, **fibromyalgia**, and low back pain.
- The SNRIs, unlike the TCAs, have little activity at α -adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs.
- ❖ The SNRIs may precipitate a discontinuation syndrome if treatment is abruptly stopped.

A. Venlafaxine and desvenlafaxine

- **Venlafaxine** is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake.
- *Venlafaxine* has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme.
- **Desvenlafaxine** is the active, demethylated metabolite of *venlafaxine*.
- The most common side effects of *venlafaxine* are **nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation**.
- At high doses, there may be an increase in blood pressure and heart rate.
- The clinical activity and adverse effect profile of *desvenlafaxine* are similar to that of *venlafaxine*.

B. Duloxetine

- **Duloxetine** *inhibits serotonin and norepinephrine reuptake at all doses.*
- It is extensively metabolized in the liver to inactive metabolites and should be avoided in patients with liver dysfunction.
- **GI side effects** are common with **duloxetine**, *including nausea, dry mouth, and constipation.* Insomnia, dizziness, somnolence, sweating, and sexual dysfunction are also seen.
- **Duloxetine** *may increase blood pressure or heart rate.*
- *Duloxetine is a moderate inhibitor of CYP2D6 isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics.*

C. Levomilnacipran

- **Levomilnacipran** is an enantiomer of **milnacipran** (*an older SNRI used for the treatment of depression in Europe and fibromyalgia in the United States*).
- The adverse effect profile of *levomilnacipran is similar* to other SNRIs.
- It is primarily metabolized by CYP3A4, and, thus, activity may be altered by inducers or inhibitors of this enzyme system.

Atypical Antidepressants

- The atypical antidepressants are a mixed group of agents that have actions at several different sites.
- This group includes:
 - **Bupropion** [*byoo-proe-pee-on*]
 - **Mirtazapine** [*mir-taz-a-peen*]
 - **Nefazodone** [*ne-fazoh- done*]
 - **Trazodone** [*traz-oh-done*]
 - **Vilazodone** [*vil-az-oh-done*]
 - **Vortioxetine** [*vor-TEE-ox-e-teen*].

A. Bupropion

- **Bupropion** is a weak dopamine and norepinephrine reuptake inhibitor that is used to alleviate the symptoms of depression.
- **Bupropion** is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to quit smoking.
- **Side effects** may include dry mouth, sweating, nervousness, tremor, and a dose dependent increased risk for seizures.
- It has a very low incidence of sexual dysfunction.
- **Bupropion** is metabolized by the *CYP2B6* pathway and has a relatively **low risk for drug–drug interactions**, given the few agents that inhibit/induce this enzyme. *bupropion* may inhibit *CYP2D6* and, thus, increase exposure to substrates of this isoenzyme.
- Use of *bupropion* should be avoided in patients at risk for seizures or those who have eating disorders such as **bulimia**.

C. Nefazodone and trazodone

- These drugs are weak inhibitors of serotonin reuptake.
- Their therapeutic benefit appears to be related to their ability to block postsynaptic 5-HT_{2a} receptors.
- Both agents are sedating, probably because of their potent histamine H₁-blocking activity.
- **Trazodone** *is commonly* used off-label for the management of insomnia.
- **Trazodone** has been associated with **priapism**, and **nefazodone** *has been associated* with a risk for hepatotoxicity.
- Both agents also have mild to moderate α ₁ receptor antagonism, contributing to orthostasis and dizziness.

D. Vilazodone

- *Vilazodone is a serotonin reuptake inhibitor and a 5-HT1a partial agonist.*
- Although the extent to which the 5-HT1a receptor activity contributes to its therapeutic effects is unknown, this possible mechanism of action renders it unique from that of the SSRIs.
- The adverse effect profile of vilazodone is similar to the SSRIs, including a risk for discontinuation syndrome if abruptly stopped.

E. Vortioxetine

- Vortioxetine utilizes a combination of serotonin reuptake inhibition, 5-HT1a agonism, and 5-HT3 and 5-HT7 antagonism as its suggested mechanisms of action to treat depression.
- It is unclear to what extent the activities other than inhibition of serotonin reuptake influence the overall effects of *vortioxetine*.
- The common adverse effects include nausea, vomiting, and constipation, which may be expected due to its serotonergic mechanisms.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

- The TCAs block norepinephrine and serotonin reuptake into the presynaptic neuron and, thus, if discovered today, might have been referred to as SNRIs, except for their differences in adverse effects relative to this newer class of antidepressants. The TCAs include the tertiary amines
- **Imipramine** [ee-mip-ra-meen] (the prototype drug),
- **Amitriptyline** [amee-trip-ti-leen],
- **Clomipramine** [kloe-mip-ra-meen],
- **Doxepin** [doxe-pin]
- **Trimipramine** [trye-mip-ra-meen],
- **Desipramine** [dess-ip-ra-meen] and **nortriptyline** [nor-trip-ti-leen] (the *n-demethylated metabolites of imipramine and amitriptyline, respectively*)
- **Protriptyline** [proe-trip-ti-leen]. *Maprotiline* [ma-proe-ti-leen]
- **Amoxapine** [a-MOX-a-peen] are related “tetracyclic” antidepressant agents and are commonly included in the general class of TCAs.
- Patients who do not respond to one TCA may benefit from a different drug in this group.

A. Mechanism of action

1. Inhibition of neurotransmitter reuptake:

- **TCAs** and **amoxapine** are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals. **Maprotiline** and **desipramine** are relatively selective inhibitors of norepinephrine reuptake.

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. actions at these receptors are likely responsible for many of their adverse effects.
- **Amoxapine** *also blocks 5-HT₂ and dopamine D₂ receptors.*

Actions

- The TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50% to 70% of individuals with major depression.
- The onset of the mood elevation is slow, **requiring 2 weeks or longer.**
- Patient response can be used to adjust dosage.
- After a therapeutic response, the dosage can be gradually reduced to improve tolerability, unless relapse occurs.
- ❖ Physical and psychological dependence have been rarely reported.
- This necessitates slow withdrawal to minimize discontinuation syndromes and cholinergic rebound effects.

Therapeutic Uses

- 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 nonpharmacologic 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*.

Pharmacokinetics

- TCAs are well absorbed upon **oral administration**.
- Because of their **lipophilic** nature, they are widely distributed and readily **penetrate into the CNS**.
- As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsistent bioavailability.
- These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid.
- Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

Adverse Effects

- Blockade of **muscarinic** receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of angle-closure glaucoma.
- These agents affect **cardiac conduction** similarly to **quinidine** and may precipitate **life-threatening arrhythmias** in an overdose situation.
- 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.

- TCAs (like all antidepressants) should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior.
- The **TCAs have a narrow therapeutic index** (five- to six fold the maximal daily dose of **imipramine** *can be lethal*).
- Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely.
- The TCAs may exacerbate certain medical conditions, such as benign prostatic hyperplasia, epilepsy, and preexisting arrhythmias.

Monoamine Oxidase Inhibitors

- 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 four MAOIs currently available for treatment of depression include **phenelzine** [FEN-el-zeen], **tranylcypromine** [*tran-il-SIP-roe-meen*], **isocarboxazid** [eye-soe-car-BOX-ih-zid], and **selegiline** [*seh-LEDGE-ah-leen*].
- [*Note: **Selegiline** is also used for the treatment of Parkinson’s disease. It is the only antidepressant available in a **transdermal delivery system**.*]
- Use of MAOIs is limited due to the complicated **dietary restrictions** required while taking these agents.

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.
- These drugs inhibit not only MAO in the brain but also MAO in the liver and gut that catalyzes oxidative deamination of drugs and potentially toxic substances, such as **tyramine, which is found in certain foods**.
- The MAOIs, therefore, show a high incidence of drug–drug and drug–food interactions.
- Selegiline administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism.

Actions

- Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed several weeks.
- **Selegiline** and **tranylcypromine** have an **amphetamine-like stimulant** effect that may produce agitation or insomnia.

C. Therapeutic uses

- The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.
- A special subcategory of depression, called **atypical depression**, may respond preferentially to MAOIs.
- Because of their risk for drug–drug and drug–food interactions, the MAOIs are considered **last-line agents** in many treatment settings.

➤ Pharmacokinetics:

- These drugs are well absorbed after **oral administration**.
- Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug.
- Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class.
- MAOIs are hepatically metabolized and excreted rapidly in urine.

➤ Adverse effects:

- Severe and often unpredictable side effects, due to drug–food and drug–drug interactions, limit the widespread use of MAOIs.
- 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, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke.

- Patients must, therefore, be educated to avoid tyramine-containing foods.
- **Phentolamine** and **prazosin** are helpful in the management of tyramine-induced hypertension.
- Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.
- ✓ Due to the risk of serotonin syndrome, the use of MAOIs with other antidepressants is contraindicated.
- ✓ For example, SSRIs should not be coadministered with MAOIs.
- ✓ Both **SSRIs and MAOIs** require a **washout period of at least 2 weeks before** the other type is administered, with the exception of **fluoxetine**, which should be discontinued **at least 6 weeks before a MAOI is initiated**.
- ✓ In addition, the MAOIs have many other critical drug interactions, and caution is required when administering these agents concurrently with other drugs.

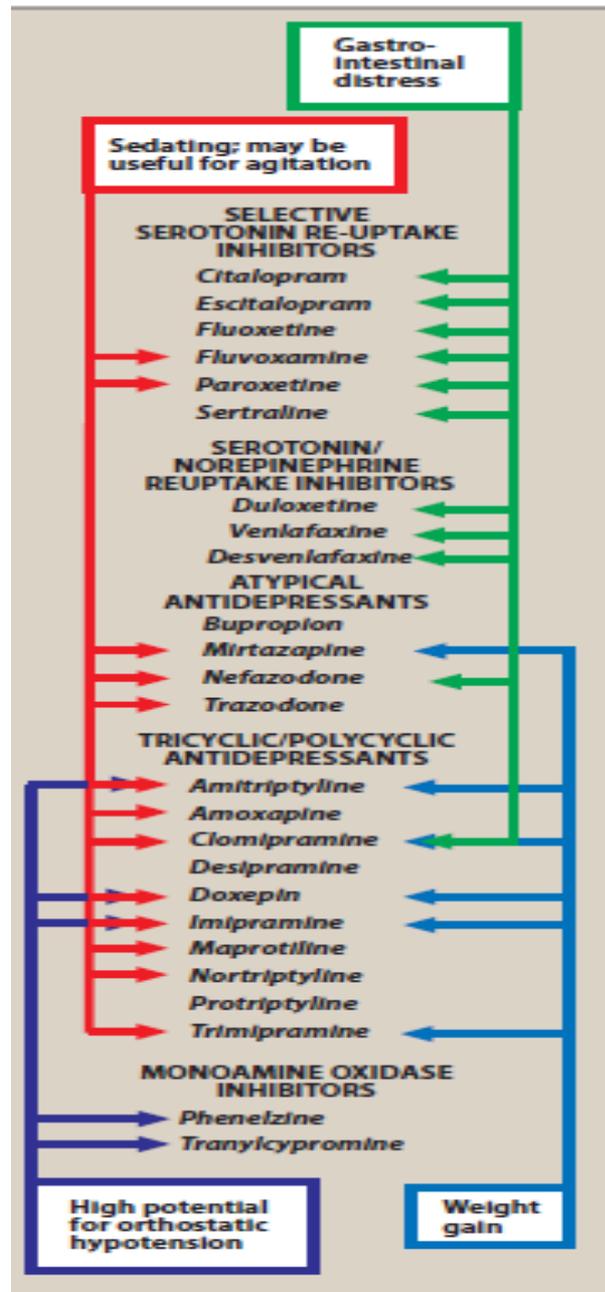


Figure 10.10
Side effects of some drugs used to treat depression.

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.

A. 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.

B. Other drugs

- Several **antiepileptic** drugs, including **carbamazepine**, **valproic acid**, and **lamotrigine**, *have been approved as mood stabilizers for bipolar disorder.*
- Other agents that may improve **manic symptoms** include the older (**chlorpromazine** and **haloperidol**) *and newer antipsychotics.*
- The atypical antipsychotics **risperidone**, **olanzapine**, **ziprasidone**, **aripiprazole**, **asenapine**, *and quetiapine are also used for the management of mania.*
- **Quetiapine**, **lurasidone**, *and the combination of **olanzapine** and **fluoxetine** have been approved for bipolar depression.*