Antidepressants

- Symptoms of depression:
  - Intense feelings of sadness, hopelessness and despair
  - Inability to experience pleasure in usual pleasurable activities
  - Change in sleep patterns
  - Suicidal thoughts

- Mania is characterized by:
  - Enthusiasm
  - Rapid thought and speech pattern
  - Extreme self confidence and impaired judgment

Depression may be secondary to:

- Organic problems like hypothyroidism, dementia, anemia
- Psychiatric problems like schizophrenia, drug abuse, anxiety disorders
- Use of depressants drugs such as alcohol

Depression in the Elderly:

- Not natural part of aging
- Underdiagnosed and misdiagnosed in elderly
- 10-15% of elderly have clinically significant depression
- Drug responsiveness similar to younger patients

Mechanisms of antidepressant drugs

- Biogenic amine theory of depression and mania proposes that:
  - Depression is due to a deficiency of monoamines such as norepinephrine and serotonin, at certain sites in the brain
  - Mania is caused by an overproduction of these neurotransmitters

- **Antidepressants potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain**

Mechanisms of antidepressant drugs

- The amine theory of depression and mania is too simplistic and fails to explain why the pharmacologic effects of antidepressant and anti-mania drugs on neurotransmission occur immediately, whereas therapeutic response occurs after several weeks

- Decreased reuptake of neurotransmitters is only an initial effect which may not be directly responsible for the antidepressant effects

Antidepressants:

- First-generation
  - Tricyclics antidepressants (TCAs)
  - Monoamine oxidase inhibitors (MAOIs)
- Second-generation
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Atypical antidepressants

Selective serotonin reuptake inhibitors (SSRIs)

- Antidepressant drugs that specifically inhibit serotonin reuptake
- They are relatively safe even in overdose
- Have largely replaced TCAs and MAOIs as the drugs of choice in treating depression

Selective serotonin reuptake inhibitors (SSRIs)

- Fluoxetine
- Citalopram
- Escitalopram
- Fluvoxamine
- Paroxetine
- Sertraline

SSRIs

Actions

- Block the reuptake of serotonin, increasing its concentrations in the synaptic cleft and its postsynaptic neuronal activity

SSRIs

- Antidepressants, including SSRIs, take at least <u>2 weeks</u> to produce significant improvement in mood
  - Maximum benefit may require≥12 weeks
  - Do not usually produce CNS stimulation or mood elevation in normal individuals

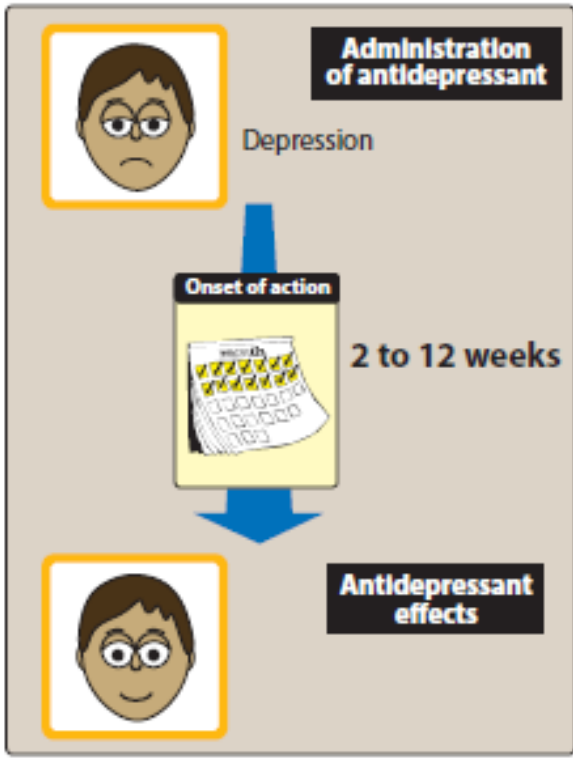


Figure 10.3
Onset of therapeutic effects of the major antidepressant drugs requires several weeks.

SSRIs

Therapeutic uses

- Depression
- OCD
- Panic disorder
- GAD
- PTSD
- Social anxiety disorder
- Premenstrual dysphoric disorder
- Bulimia nervosa (only fluoxetine is approved)

PK

- 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
  - eexcept with sertraline, Food increases its absorption
- $t_{1/2}$16-36 hours
  - Fluoxetine $t_{1/2}$ 50 hours, $t_{1/2}$ of its active metabolite ~ 10 days
- It is available as a sustained-release preparation allowing once-weekly dosing
- Metabolism by CYP450 enzymes and glucuronide or sulfate conjugation
- Dosages should be reduced in patients with hepatic impairment

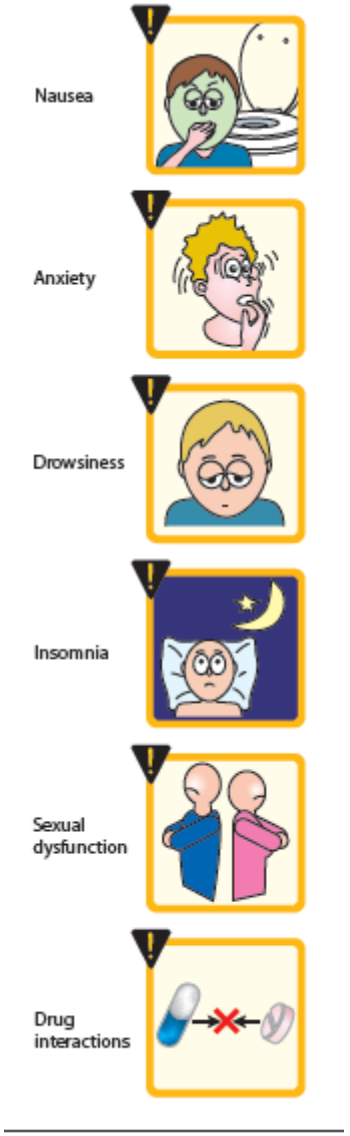
SSRIs

- Fluoxetine and paroxetine are potent inhibitors of CYP2D6 which is responsible for the elimination of TCAs, neuroleptic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs

SSRIs

Adverse effects

- Headache
- Sweating
- Anxiety and agitation
- GI effects (nausea, vomiting, diarrhea)
- Weakness and fatigue
- Sexual dysfunction
- Changes in weight
- Sleep disturbances (insomnia and somnolence)
  - Paroxetine and fluvoxamine are more sedating (may be useful in sleeping difficulty)
  - Fluoxetine or sertraline are more activating SSRIs (Useful in fatigue and excessive somnolence)



SSRIs

- Overdose: Large intakes of SSRIs do not usually cause cardiac arrhythmias (compared to the arrhythmia risk for the TCAs)
  - An exception is citalopram, it may cause QT prolongation
- Seizures can occur in over dose
- All SSRIs have the potential to cause serotonin syndrome when used in the presence of a MAOI or other highly serotonergic drug
  - Serotonin syndrome include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus, and changes in mental status and vital signs

SSRI in children and teenagers

- Should be used cautiously in children and teenagers
  - ~ 2% children report suicidal ideation with SSRI
- Pediatric patients should be observed for worsening depression and suicidal thinking with initiation or dosage change of any antidepressant
- Fluoxetine and escitalopram are approved for childhood depression
- Fluoxetine, sertraline, and fluvoxamine are approved for OCD in children

SSRI

Discontinuation syndrome:

- All of the SSRIs have the potential to cause a discontinuation syndrome after abrupt withdrawal,
- Fluoxetine has the lowest risk of causing an SSRI discontinuation
- Signs and symptoms of SSRI discontinuation syndrome
  - Headache, malaise, flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

Serotonin/norepinephrine reuptake inhibitors (SNRI)

- Inhibit the reuptake of both serotonin and norepinephrine
- May be effective in treating depression in patients where SSRI are ineffective
- Effective against chronic painful symptoms, such as backache and muscle aches, against which SSRIs are relatively ineffective

(This pain is modulated by serotonin and norepinephrine pathways in the CNS)

- Both SNRIs and TCAs, with their dual actions of inhibiting both serotonin and norepinephrine reuptake, are sometimes effective in relieving physical symptoms of neuropathic pain such as diabetic peripheral neuropathy

SNRIs

- Unlike TCA SNRIs have little activity at adrenergic, muscarinic, or histamine receptors
- TCAs might have been referred to as SNRIs except for their differences in adverse effects relative to this newer class of antidepressants
- SNRI precipitate a discontinuation syndrome if treatment is abruptly stopped

SNRI

- Duloxetine
- Venlafaxine
- Desvenlafaxine
- Levomilnacipran

Venlafaxine and desvenlafaxine

Venlafaxine

- A potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake

Desvenlafaxine

- Active metabolite of the parent compound venlafaxine
- No significantly different clinical or adverse effects than venlafaxine.

Side effects of venlafaxine and desvenlafaxine

- Nausea, headache, sedation, dizziness, insomnia
- Sexual dysfunction
- Constipation

Duloxetine

- Inhibits serotonin and norepinephrine reuptake at all doses
- It is extensively metabolized in the liver, should not be administered to patients with hepatic insufficiency
- Metabolites are excreted in the urine, and the use of duloxetine is not recommended in patients with end-stage renal disease
- Adverse effects
  - Nausea
  - Dry mouth
  - Constipation
  - Insomnia
  - Sexual dysfunction
  - Risk for an increase in either blood pressure or heart rate
- Duloxetine inhibits CYP2D6 and CYP3A4

Tricyclic antidepressants (TCAs)

- Imipramine
- Clomipramine
- Desipramine
- Trimipramine
- Amitriptyline
- Maprotiline
- Nortriptyline
- Protriptyline
- Amoxapine
- Doxepin

Tricyclic antidepressants (TCAs)

- Block norepinephrine and serotonin reuptake into the neuron
- Mechanism of action
  - Inhibition of neurotransmitter reuptake: TCAs are potent inhibitors of neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals
  - By blocking the major route of neurotransmitter removal, TCAs cause increased concentrations of monoamines in the synaptic cleft, resulting in antidepressant effects
  - Maprotiline and desipramine are relatively selective inhibitors of norepinephrine reuptake
  - TCAs also block α-adrenergic, histaminic, and muscarinic receptors causing many adverse effects

Tricyclic antidepressants

- Actions
  - Elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70 percent of individuals with major depression
  - The onset of the mood elevation is slow taking ≥ 2 weeks
  - No CNS stimulation or mood elevation in normal individuals
  - Physical and psychological dependence is rare
  - Slow withdrawal to minimize discontinuation syndromes and cholinergic rebound effects
  - Can be used for prolonged treatment of depression

TCAs

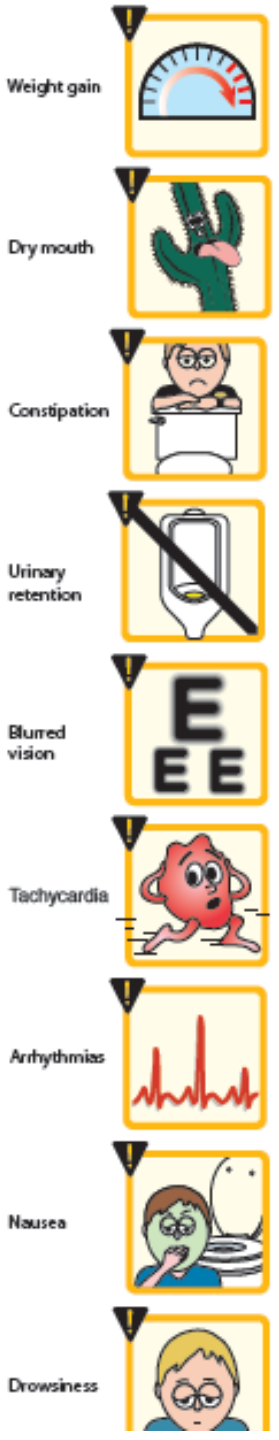
Therapeutic uses

- 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 age 6 years) by causing contraction of the internal sphincter of the bladder
- Used cautiously at present because of inducement of cardiac arrhythmias and other cardiovascular problems
- The TCAs, particularly amitriptyline, are used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of the pain is unclear
- Low doses of TCAs, especially doxepin, can be used to treat insomnia

TCAs

Adverse effects

- Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation
- Affect cardiac conduction which may precipitate life-threatening arrhythmias in overdose
- 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, especially during the first weeks of treatment due to blockade of histamine H1 receptors
- Weight gain
- Sexual dysfunction



TCAs

Precautions

- TCAs and all antidepressants should be used with caution in bipolar disorder because antidepressants may cause a switch to manic behavior
- The TCAs have a narrow therapeutic index, suicidal patients should be given only limited quantities of these drugs and be monitored closely
- The TCAs may exacerbate certain medical conditions, such as unstable angina, benign prostatic hyperplasia, epilepsy, and preexisting arrhythmias

Monoamine oxidase inhibitors (MAOIs)

- MAO inactivates norepinephrine, dopamine, and serotonin

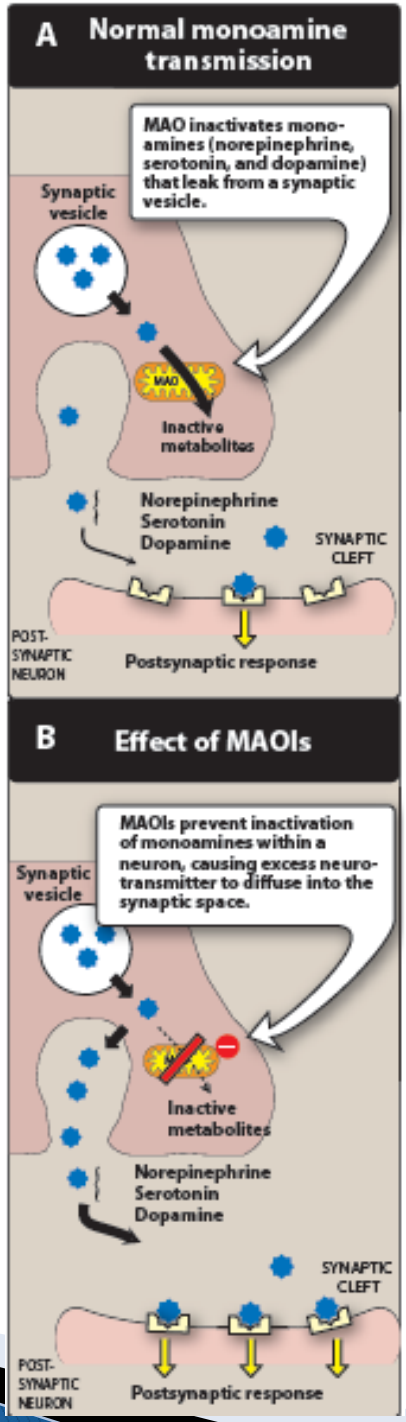
- MAO inhibitors (MAOIs) inactivate MAO, permitting neurotransmitter molecules to accumulate within the presynaptic neuron and leak into the synaptic space causing activation of norepinephrine and serotonin receptors

MAOIs

- Isocarboxazid
- Phenelzine
- Tranylcypromine
- Selegiline

MAOIs

- Mechanism of action: Most MAOIs form stable complexes with MAO causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and diffusion of excess neurotransmitter into the synaptic space
- These drugs also inhibit MAO in the liver and gut that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods causing a high incidence of drug-drug and drug-food interactions
  - Selegiline may produce less inhibition of gut and hepatic MAO


A Normal monoamine transmission
MAO inactivates monoamines (norepinephrine, serotonin, and dopamine) that leak from a synaptic vesicle.
Synaptic vesicle
MAO
Inactive metabolites
Norepinephrine
Serotonin
Dopamine
SYNAPTIC CLEFT
POST-SYNAPTIC NEURON
Postsynaptic response
B Effect of MAOIs
MAOIs prevent inactivation of monoamines within a neuron, causing excess neurotransmitter to diffuse into the synaptic space.
Synaptic vesicle
Inactive metabolites
Norepinephrine
Serotonin
Dopamine
SYNAPTIC CLEFT
POST-SYNAPTIC NEURON
Postsynaptic response

MAOIs

- Actions
  - The antidepressant action of the MAOIs, like that of the SSRIs and TCAs, is delayed several weeks
  - Selegiline and tranylcypromine have an amphetamine- like stimulant effect that may produce agitation or insomnia

MAOIs

- Therapeutic uses
  - Indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety
  - Treatment of phobic states
  - Treatment of atypical depression (labile mood, rejection sensitivity, and appetite disorders)
  - Considered to be last-line agents in treatment because of their risk for drug-drug and drug-food interactions

- Enzyme regeneration when irreversibly inactivated occurs several weeks after termination of the drug, 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

MAOIs

Adverse effects

- Severe side effects, due to drug-food and drug-drug interactions
  - Tyramine, found in aged cheeses, meats, chicken liver, pickled or smoked fish, red wines, is inactivated by MAO in the gut
  - Individuals receiving a MAOI are unable to degrade tyramine causing the release of large amounts of stored catecholamines from nerve terminals, resulting in "hypertensive crisis," (headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, stroke)
  - Patients must be educated to avoid tyramine-containing foods
  - Phentolamine and prazosin are helpful in the management of tyramine-induced hypertension
  - This may be dangerous in severely depressed patients with suicidal tendencies
- Drowsiness
- Orthostatic hypotension

MAOIs

- MAOIs and SSRIs should not be coadministered due to the risk of the life-threatening "serotonin syndrome" that include symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status
  - Both types of drugs require washout periods of at least 2 weeks before the other type is administered
  - Fluoxetine should be discontinued at least 6 weeks before a MAOI is initiated
- Combination of MAOIs and bupropion can produce seizures

Atypical antidepressants

- Act at several different sites
- Similar antidepressant effects to TCA and SSRIs, but different side effects
- Include
  - Bupropion
  - Mirtazapine
  - Nefazodone
  - Trazodone

Bupropion

- Weak dopamine and norepinephrine reuptake inhibitor
- Bupropion also assists in decreasing the craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking
- Can help with cocaine withdrawal
- Side effects
  - Dry mouth
  - Nervousness
  - Tremor
  - Increased risk for seizures at high doses

Mirtazapine

- Enhances serotonin and norepinephrine neurotransmission by blocking presynaptic α_2 receptors and 5-HT_2 receptors
- It is a sedative because of its potent antihistaminic activity
- No antimuscarinic side effects
- No interference with sexual functioning
- Side effects
  - Increased appetite and weight gain
  - Marked sedation

Nefazodone and trazodone

- Weak inhibitors of serotonin reuptake
- Block postsynaptic 5-HT_{2A} receptors
- With chronic use may desensitize 5-HT_{1A} presynaptic autoreceptors increasing serotonin release
- Both are sedating because of their potent H_1-blocking activity
- Side effects
  - Orthostatic hypotension and dizziness due to α_1-receptor antagonism
  - Nefazodone: hepatotoxicity

Bipolar Disorder

- In bipolar disorder patients go through episodes of an elevated or agitated mood known as mania alternating with episodes of depression

- Mania is characterized by enthusiasm, rapid thought and speech pattern, extreme self confidence and impaired judgment

Criteria for a Manic Episode:

- Mood disturbance
  - Distinct period
  - Elevated, expansive, or irritable mood
- Behavioral Symptoms (at least three)
  - Increased activity and productivity
  - Pressure to keep talking
  - Flight of ideas
  - Decreased need for sleep
  - Distractibility
  - Risk-seeking behaviors
- Duration: at least 1 week

Lithium

- Used as salt: lithium carbonate
- Lithium salts are used prophylactically for treating manic-depressive patients and in the treatment of manic episodes
- Considered “mood stabilizer”
- Effective in patients with mania and hypomania
- Mode of action is unknown
- Safety factor and therapeutic index are extremely low

Lithium

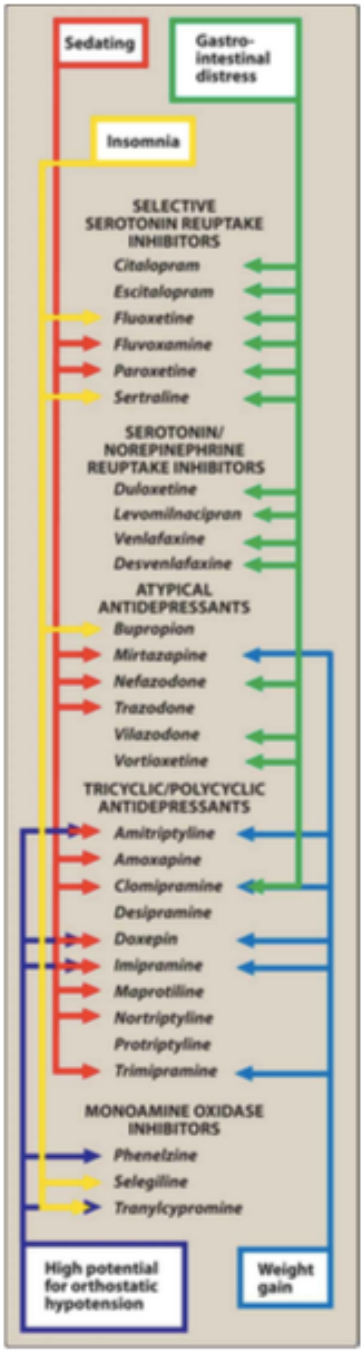
- Adverse effects:
  - Headache, dry mouth
  - Polydipsia, polyuria, polyphagia
  - GI distress

  (give lithium with food)
  - Tremor
  - Dizziness
  - Fatigue
  - Dermatologic reactions
  - Sedation
  - Convulsions (At higher doses)
- Diabetes insipidus that results from taking lithium can be treated with amiloride
- Thyroid function may be decreased and should be monitored
- Lithium causes no noticeable effect on normal individuals

Drugs used for Mania

Other drugs

- Several antiepileptic drugs like carbamazepine, valproic acid, and lamotrigine, have been approved as mood stabilizers and are used in the treatment of bipolar disorder
- Older (for example, chlorpromazine and haloperidol) and newer antipsychotics
- The atypical antipsychotics (risperidone, olanzapine, aripiprazole, and quetiapine)
- Benzodiazepines are also frequently used as adjunctive treatments for the acute stabilization of patients with mania


Sedating
Gastro-intestinal distress
Insomnia
SELECTIVE SEROTONIN REUPTAKE INHIBITORS
Citalopram
Escitalopram
Fluoxetine
Fluvoxamine
Paroxetine
Sertraline
SEROTONIN/ NOREPINEPHRINE REUPTAKE INHIBITORS
Duloxetine
Levomilnacipran
Venlafaxine
Desvenlafaxine
ATYPICAL ANTIDEPRESSANTS
Bupropion
Mirtazapine
Nefazodone
Trazodone
Vilazodone
Vortioxetine
TRICYCLIC/POLYCYCLIC ANTIDEPRESSANTS
Amitriptyline
Amoxapine
Clomipramine
Desipramine
Doxepin
Imipramine
Maprotiline
Nortriptyline
Protriptyline
Trimipramine
MONOAMINE OXIDASE INHIBITORS
Phenelzine
Selegiline
Tranylcypromine
High potential for orthostatic hypotension
Weight gain