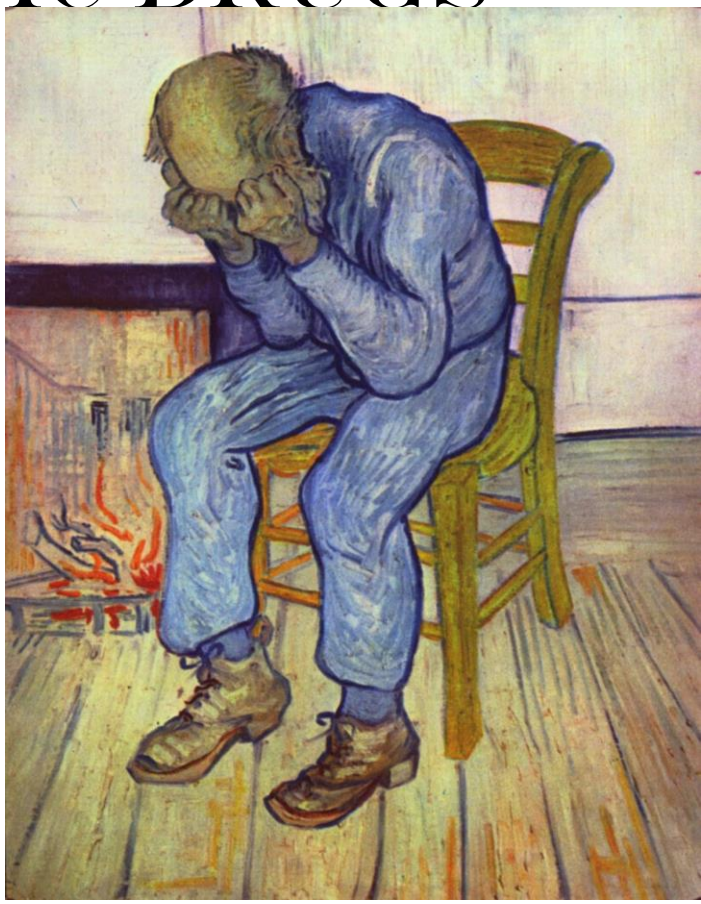
DRUGS AFFECTING CENTRAL NERVOUS SYSTEM

PSYCHOTHERAPEUTIC DRUGS

ANTIDEPRESSANTS



VINCENT VAN GOGH,
25.07.1890

Depression

Depression is an affective illness, whose pathomechanism is not completely known. It can have different degrees of intensity.

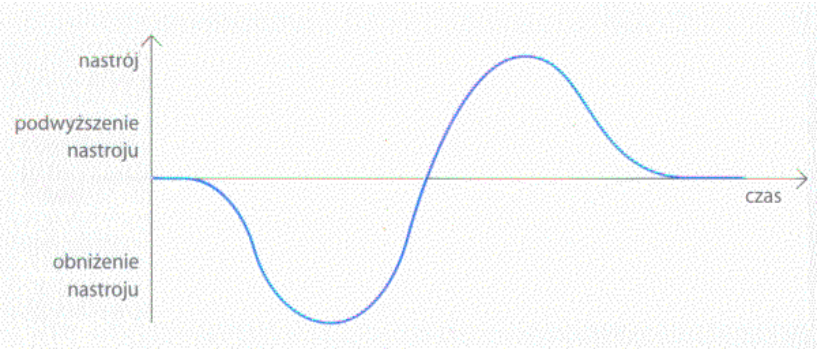
- **Physiological depression** may appear after a loss of a loved one, a change of the environment, a failure at work or school and many others. It is the mildest form of depression and it usually disappears spontaneously.

- **Neurotic depression** is caused by an emotional problem of which a person is not aware. In this type of depression psychotherapy is recommended, but sometimes treatment using antidepressants is effective.

Depression

- **Psychotic depression**, which is the most serious form of depression, is usually caused by pathologic changes and requires hospital treatment with psychotropic drugs. Melancholia is the most serious form of endogenic psychotic depression. This depression type often affects pedantic people who pay too much attention to order and who are extremely conscientious. They suffer from it because of their sudden feeling of the pointlessness of life.

- **Bipolar disorder**, also called manic-depressive psychosis, is characterized by alternating periods of deep depression and decreased activity and periods of euphoria accompanied by increased activity. The manic phase of a euphoric mood can last for only several days, but it sometimes lasts for weeks, months and even up to two years. Periods of remission occur between the two phases. The frequency of changes is unpredictable and in some individuals changes can occur even in daily cycles.



Depression

Depressions are the most common diseases in psychiatry and affect about 10-12% per cent of the world population. On the basis of their clinical symptoms it is possible to distinguish the following types of depressions.

- Depression accompanied by an inhibition of basic psychical and locomotor activity and characterized by a low level of anxiety, when excessive day-time sleepiness is observed, but without any distinct disturbances of sleep at night. In this type of depression it is most likely that the activity of **adrenergic neurons decreases and the activity of cholinergic neurons increases**.

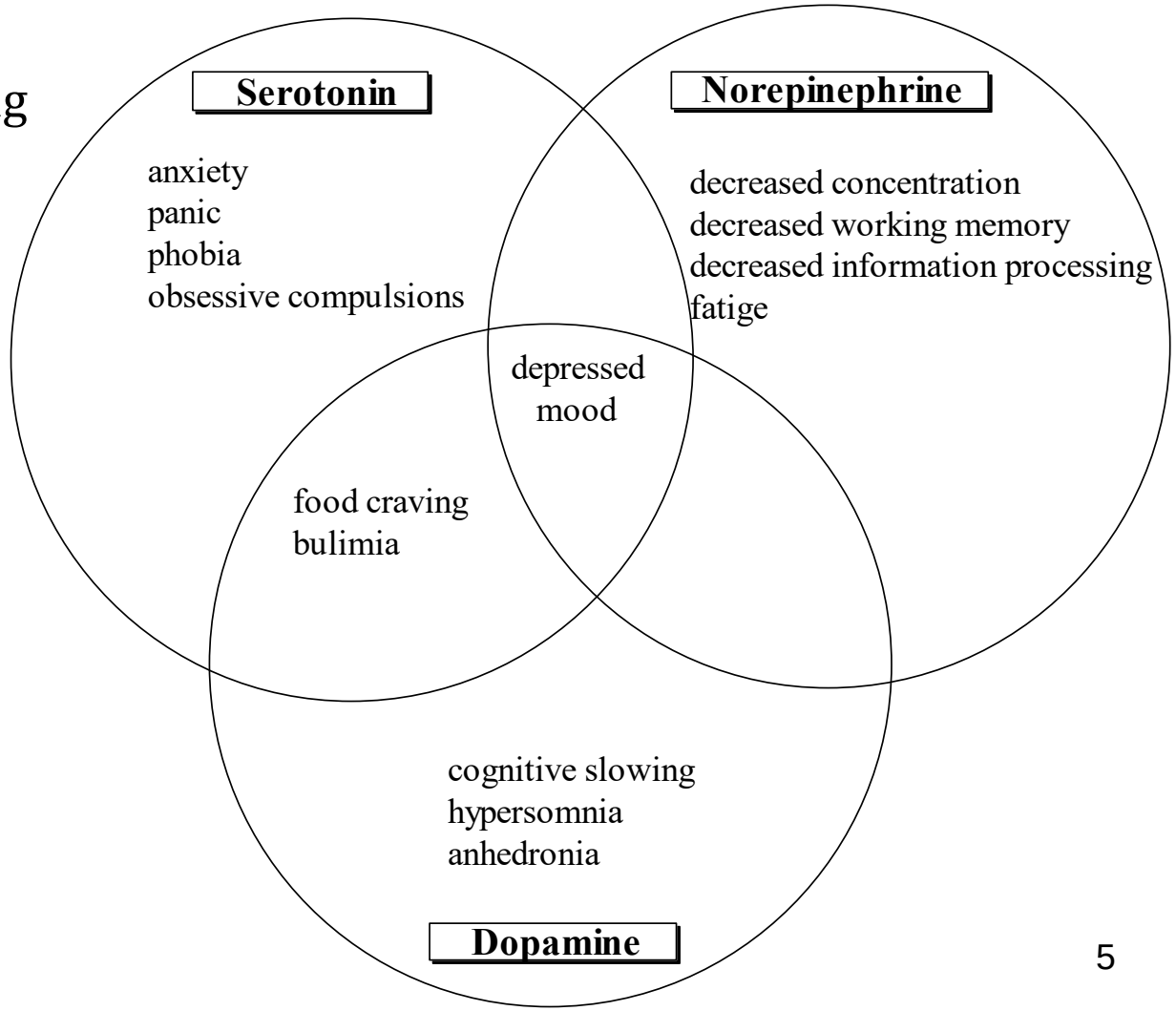
- Depression with symptoms of psychical and locomotor anxiety, when sleeping difficulties, light sleep or total sleeplessness occur. This type of depression can be caused by the **decreased activity of serotoninergic neurons and the increased activity of adrenergic and cholinergic neurons**.

In both types of depression changes in the activity of the dopaminergic neurons can also take place. Stimulation of these neurons may cause manic symptoms.

Biological basis of depression

Monoamine hypothesis

Current theories regarding the causes of depression support the role of the neurotransmitters serotonin and NE in depression and their interrelationships with each other and with dopamine.



Receptor sensitivity hypothesis

- According to this hypothesis, relief from the symptom of depression following chronic administration of ADs comes from a normalization of receptor sensitivity (reducting receptor hypersensitivity) by increasing the concentration of NE and 5-HT in the synaptic cleft.
- Therefore, the use of reuptake inhibitors and the MAOIs as ADs increases the concentration of NE and/or 5-HT in the synaptic cleft and, over time, causes the postsynaptic neuron to compensate by decreasing receptor sensitivity (desensitization) and the number of receptor sites (decrease in the expression of NE and 5-HT receptors: downregulation).
- **About one-third of depressed patients, however, fail to respond to ADs therapy.** For some unknown reason, the increased concentration of NE and/or 5-HT fail to desensitize the postsynaptic receptors.

Permissive hypothesis

- **The permissive hypothesis emphasizes the importance of the balance between 5-HT and NE in regulating mood, not the absolute levels of these neurotransmitters or their receptors.**
- If 5-HT levels are too low, the balanced control of the NE system is lost, permitting abnormal levels of NE to cause mania, as seen in bipolar disorders.
- If the NE levels fall, the balanced control of the 5-HT system is lost, allowing abnormal levels of 5-HT to cause the person to exhibit the symptom of depression.

Hormonal hypothesis

- **The hormonal hypothesis suggests that changes in the hypothalamus – pituitary – adrenal axis (HPA) can influence the levels of 5-HT and NE released by nerve cells in the brain, and subsequently, their function.**
- In the event of stress, the hypothalamus produces a hormone locally in the brain called corticotrophin-releasing factor, which in turn stimulates the pituitary gland to secrete adrenocorticotropic hormone into the blood, where it stimulates the adrenal glands to release hydrocortisone, which prepares the body for dealing with stress. Stress also directly stimulates the adrenal gland to secrete epinephrine and NE.
- Hydrocortisone can cause depression, especially when released in higher-than-usual amounts. The release of hydrocortisone may push the individual over the edge into depression or contribute to the component of anxiety, which so often accompanies depressive illnesses. **Approximately 50% of those with depression have elevated hydrocortisone levels.**

The mechanism of the action of antidepressants

The mechanism of the action of antidepressants has not been completely explained yet.

It is believed that depressive states result from the decreased activity of adrenergic and/or serotoninergic neurons, while manic states are related to the excessive stimulation of adrenergic and dopaminergic neurons, and, according to other research, to the inhibition of the activity of serotoninergic neurons.

Changes in the sensitivity and number of adrenergic and serotoninergic receptors are also considered when trying to determine the pathogenesis of depression.

The mechanism of the action of antidepressants

At present it is thought that the action of antidepressants occurs in two stages.

The first stage is termed acute action and involves a change in the concentration of neurotransmitters, which is caused by:

- The inhibition of NE and/or 5-HT-reuptake by blocking the NE/5-HT pump in the presynaptic membrane of neurons; as a result of this reaction the concentration of these neurotransmitters near receptors increases and leads to increased neurotransmission.

- The inhibition of MAO that results in the diminished metabolism of neurotransmitters, which leads to their increased concentration.

- The action of receptors which involves blocking the α_2-adrenergic, 5-HT and ACh-ergic receptors, leads to an increased release of neurotransmitters to the synaptic cleft and results in increased neurotransmission.

The mechanism of the action of antidepressants

The primary action causes adaptative changes that involve changes of the density and number of receptors and changes in the affinity of neurotransmitters for receptors. Adaptative changes of the adrenergic synapse involve the decreasing of the density of β-receptors and the decreasing of the affinity of NE for them, which is called **"Down"-regulation**.

These changes also involve the diminished density of α_2-receptors and the increased affinity of neurotransmitters for them, which is called **"Up"-regulation**.

Similar changes occur in the serotoninergic synapse.

Antidepressive drugs vary in the degree to which they affect adrenergic and serotoninergic neurotransmission.

The mechanism of the action of antidepressants

Lithium compounds, which are used to treat manic-depression psychosis, demonstrate multidirectional action, but the mechanism of their action in depression has not been completely explained yet.

It is thought that the inhibition of the transformation of inozytoltriphosphate (IP_3) to inozytol (a substrate to resynthesis of $PhIP_2$) is very important.

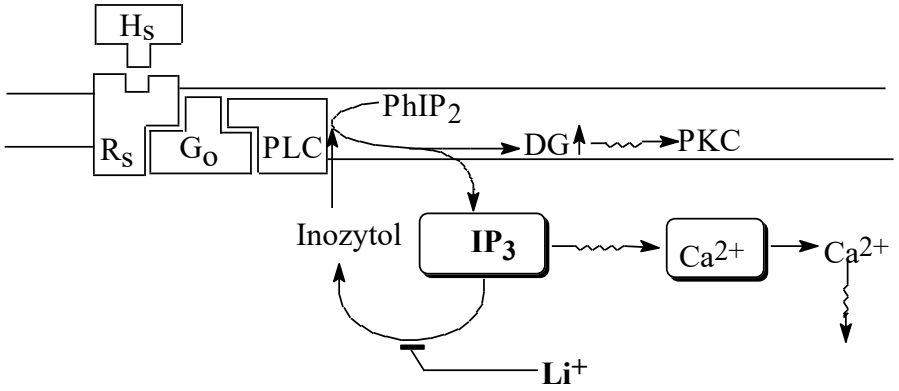


Fig. 1. The influence of lithium compounds on the transformation of IP_3.

The classification, of antidepressants (ADs)

If the mechanism of action is to be the criterion for the classification of ADs, it is possible to distinguish the following groups of ADs:

- **drugs inhibiting 5-HT and/or NE-reuptake**

  - **selective NE-reuptake inhibitors (SNRIs):** Protriptyline, Nortriptyline, Desipramine, Maprotiline, Amoxapine, Reboxetine, Nisoxetine, **Atomoxetine**

  - **selective 5-HT-reuptake inhibitors (SSRIs):** Citalopram, **Escitalopram**, Fluoxetine (PROZAC), Fluvoxamine, Paroxetine, Sertraline

  - **NE and 5-HT reuptake inhibitors (NSRIs)**: Amitryptyline, Clomipramine, Doxepine, Imipramine, Milnacipran, Trimipramine, Venlafaxine, **Duloxetine, Opipramol**

- **Dopamine and NE-reuptake inhibitors (DNRIs): Bupropion**

The classification, of antidepressants (ADs) (2)

- **Serotonin receptor modulators (SRMs)**
  - **- Serotonin-2 antagonists/serotonin reuptake inhibitors (SARIs):** Trazodone
  - **- α_2-Noradrenergic antagonists/serotonin antagonists (NaSSAs): Mirtazepine**
- **Monoamine oxidase inhibitors (MAOIs):** Meclobemide, Phenelzine, Tranylcypromine
- **Mood stabilizers:** Lithium, Valproic acid, Carbamazepine

The classification, of antidepressants (ADs) (3)

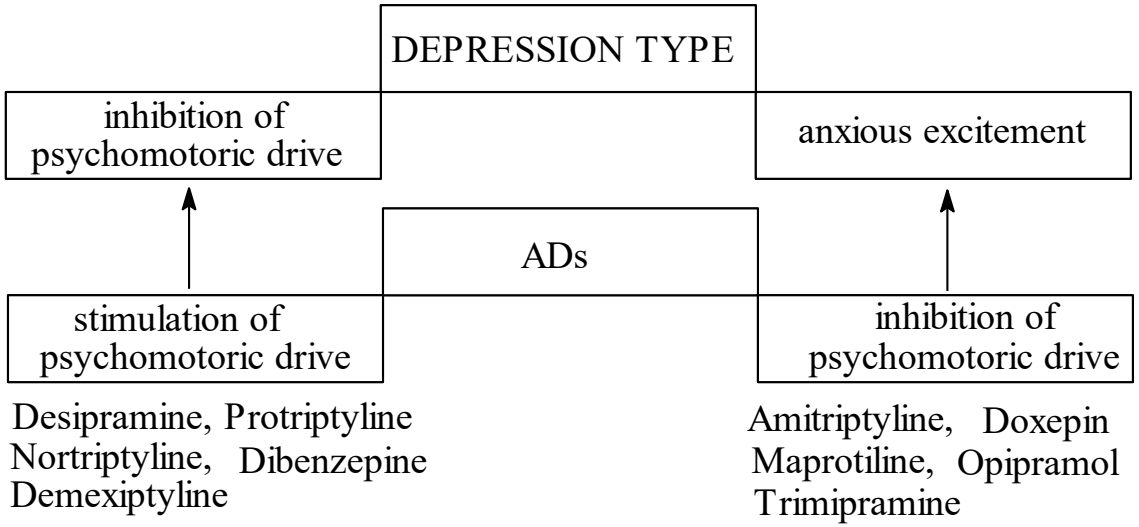
- **other antidepressants**

- **neuroleptics that are used to treat depression (promazine, levopromazine, perphenazine, sulphoridazine, trifluopromazine, sulpyride).**

MAO inhibitors and serotonine-reuptake inhibitors should not be co-administered due to the risk of life-threatening "serotonin syndromes". Both groups of drugs require washout periods of 6 weeks before administering the other type.

In the treatment of depression it is extremely important to know the direction of the action of a particular AD and to use an apprioprate drug to treat a specific kind of depression.

Antidepressants influence the mood a depressed person, psychomotoric drive and anxiety. Different drugs demonstrate various actions. Drugs that stimulate the psychomotoric drive are referred to as stimulating ADs, while those that inhibit this drive are called inhibiting ADs.



Bipolar action ADs

Imipramine,
Lofepramine,
Noxyptyline

Depression types and antidepressive drugs.

In therapy it is possible to use additionally, for some time, drugs from the benzodiazepine group.

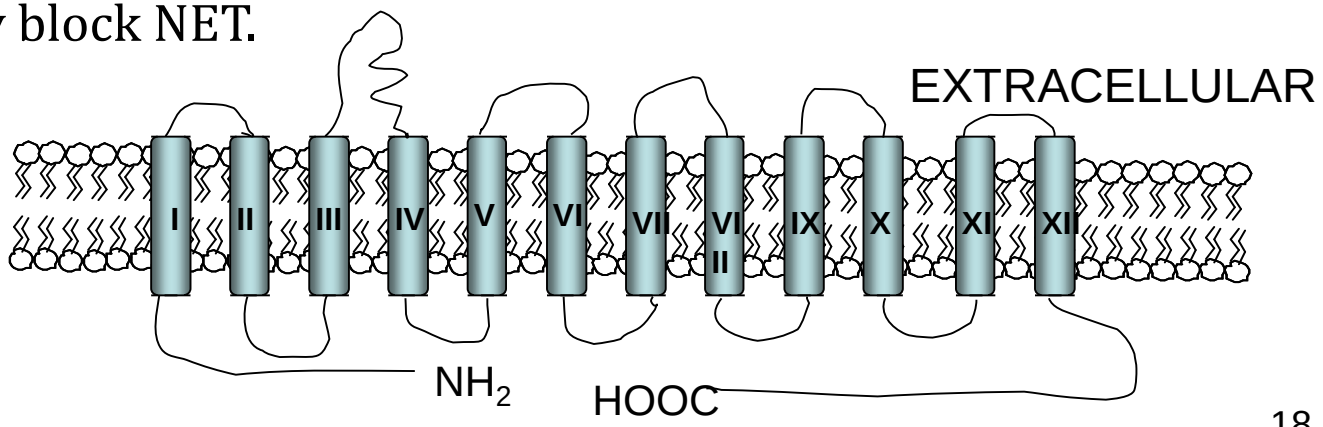
To treat manic depression, it may be necessary to use neuroleptics together with ADs.

For the effective treatment of depression it is very important to use appropriate doses and to continue treatment for a sufficiently long period of time (6 months minimum) to prevent the relapse of depression.

If treatment proves ineffective, it is necessary to consider using a different antidepressant (after 4 weeks) and monitor drug concentration in the patient's blood.

Transporter proteins

- **Transporter proteins are specific to their respective neurotransmitter:**
  - **– SERT (*serotonin reuptake transporter*) for 5-HT**
  - **– NET (NE reuptake transporter) for NE**
  - **– DAT for dopamine**
- None of the reuptake AD exhibit significant affinity for dopamine transmitter.
- TCAs and nontricyclic NSRIs nonselectively block the reuptake transporters for both NE and 5-HT.
- SSRIs selectively block SERT.
- SNRIs selectively block NET.



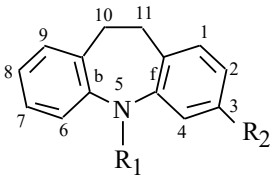
Monoamine reuptake transporter.

Selective Norepinephrine Reuptake Inhibitors (SNRIs)

- **Tricyclic and tetracyclic Secondary Amine Antidepressants (TCAs)**

Protriptyline, Nortriptyline, Desipramine, Maprotiline, Amoxapine, Reboxetine, **Nisoxetine, Atomoxetine**

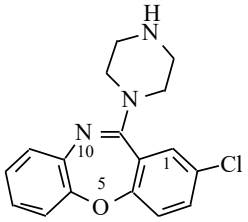
Pochodna dibenzoazepiny



Desipramine

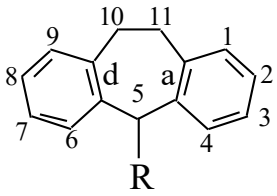
- R_2 = H
- R_1 = $-CH_2-CH_2-CH_2-NHCH_3$;

dibenzooksazepiny



Amoxapine

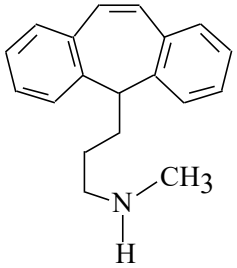
dibenzo[a,d]-1,4-cykloheptadienu



Nortriptyline

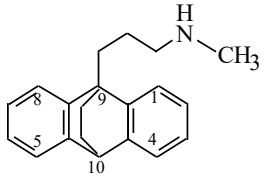
R = $-CH_2-CH_2-CH_2-NHCH_3$

dibenzo[a,d]cykloheptatrienu



Protriptyline

dibenzo[b,e]bicyklo[2.2.2]oktadien



Maprotiline

In tricyclic ADs, the middle ring is condensed with two benzene rings.

Most often it is

- a seven-segment ring (azepine, diazepine, cycloheptane, oxepine, tiepine),

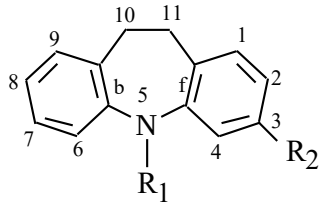
less often it is

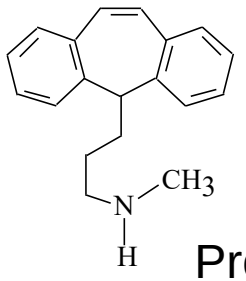
- the six-segment ring of cyclohexane (antracen derivatives) or of piperidine (acridin derivatives).

Dibenzoazepine and dibenzocycloheptadiene derivatives are the most common ADs.

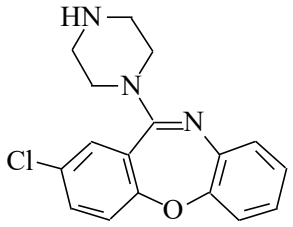
The tricyclic ring system has little significancy regarding selectivity for inhibiting the NET or SERT, it appears to be important for dopamine transport inhibition.

Substituting a halogen (chlorine; clomipramine) or cyano group into the 3 position of the dihydrodibenzazepine ring enhances preferential affinity for SERT.



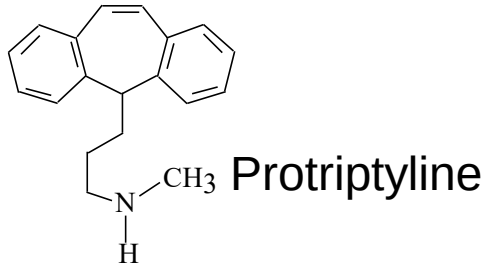


Protriptyline



Amoxapine

The side chain is attached to any one of the atom in the central 7-membered ring.
It must be three carbon atoms, either saturated (propyl) or unsaturated (propilidine), and have a terminal amine group (secondary or tertiary).



Protriptyline

The kind of a substituent bonded with the central ring affects the action of TADs in the following ways:

- The secondary amine TCAs (desipramine, protriptyline, nortriptyline) exhibit substantially more affinity than the SSRIs and the tertiary TCAs for inhibiting NET. None of the secondary TCAs has significant affinity for DAT.

- The introduction of piperazine as the basic center of the molecule leads to the diminishing or disappearance of antidepressive action and a simultaneous increases of neuroleptic action.

- The *Z* (*cis*) geometry of the propylidine group in chiral TCAs appears to be important for transporter selectivity and affinity (e.g., doxepin)

- TCAs and SSRIs bind to different sites on the transporter. The TCAs may act as a modulator of monoamine reuptake by producing conformational changes in the transporter, affecting affinity of the monoamine neurotransmitter.

Pharmacokinetics common to secondary amine TCAs

The secondary amine TCAs have relatively high bioavability. Their primary routes of hepatic metabolism are *N*-demethylation to inactive primary amine metabolites and aromatic ring hydroxylation. Dispite the fact that serum plasma levels are reached with 1 to 2 days, their onset of antidepressant action typically is at least 2 to 3 weeks or longer.

Their volume of distribution is very high, suggesting distribution into the CNS and protein binding.

Renal and liver function can affect the elimination and metabolism of the parent secondary amine TCA and its metabolites, leading to increased potential for adverse effects, especially in those patients (i.e., the elderly) with renal disease.

Mechanisms of action common to secondary amine TCAs

Blocking the reuptake of NE increases its concentration in the synaptic cleft and its ability to interact with synaptic NE receptors.

When drugs are selective for a transporter, differences in potency become clinically irrelevant, because the plasma concentration can be dose-adjusted to achieve inhibition of the desired transporter without affecting the other transporters.

During chronic therapy with the TCAs, adaptive changes at the noradrenergic receptor occur (i.e., downregulation) as a result of neurotransmitter hypersensitivity from low concentration of NE at the postsynaptic receptor. These changes involve the α_1-adrenergic receptor.

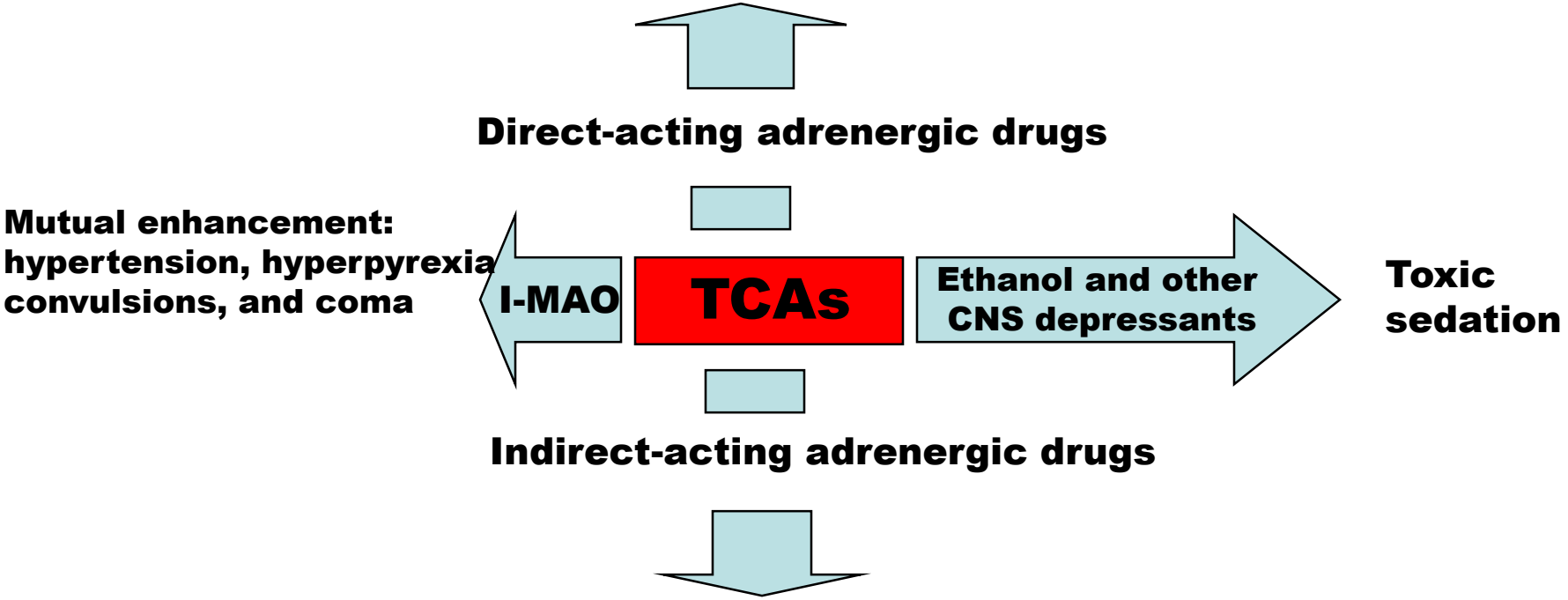
The adverse effects to all TCAs

Disturbance of CNS. TCAs cause the state of excitement and confusion, sleeplessness, muscular tremor, attacks of spasms and myoclony and increased appetite, which leads to weight gain.

Other reactions. Disorders of liver function (increased concentration of transaminases, cholestase), sexual disorders, alergic reactions.

Contraindications. TCAs should be used with caution in manic-depressive patients. TCAs have a narrow therapeutic index, for example 5-6 times of the maximal daily dose of imipramine can be lethal. Depressed patients with suicidal tendencies should be given only limited quantities of these drugs and should be monitored closely.

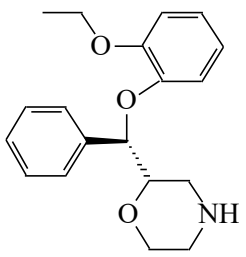
Potentate effects of biogenic amines drugs by preventing their removal from synaptic cleft



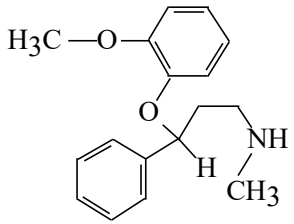
Block effects of indirect-acting sympathomimetic drugs by preventing the drugs from reaching their intracellular sites of action

TCAs = Tricyclic ADs

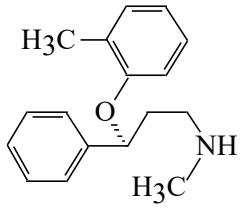
❑ Nontricyclic Secondary Amines Antidepressants



S,S-Reboxetine



(±)-Nisoxetine



***R*(-)-Atomoxetine**

In reboxetine the propylamine side chain of the TCAs is constrained into a morpholine ring.

The antidepressant activity for reboxetine appears to reside with the *S,S*-(+)-enantiomer, which has approximately two fold the inhibition potency of the *R,R*-enantiomer but it is marketed as a racemic mixture of *R,R*- and *S,S*-reboxetine**.**

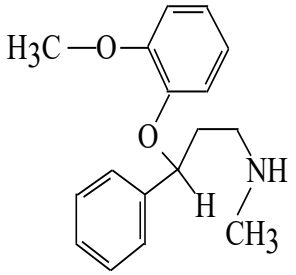
Reboxetine may offer a valuable alternative to the secondary amine TCAs in the treatment of major depression. Reboxetine is likely to become a promising alternative for patients who have failed treatment with or do not tolerate serotoninergic antidepressants.

Reboxetine was the first SNRI. Its effectiveness in the treatment of depression is equal to that of TADs but, unlike TADs, it very weakly inhibits 5-HT-reuptake, does not influence DA-reuptake and does not have an affinity for adrenergic and cholinergic receptors. As a result, reboxetine exhibits only very weak cardiovascular, anticholinergic and sedating adverse effects.

When compared with SSRIs, reboxetine is associated with lower rates of nausea, somnolence, and diarrhea.

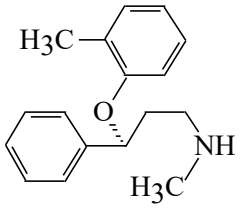
After a single, 4-mg dose, the plasma concentration in the elderly (mean age, 81 years) was twice that of younger subjects, although in both groups, the plasma concentration was similar after 2 hours. AUC was nearly four times greater in the elderly than in the younger subjects, and the elimination half-life was twice as long (24±6 *vs*. 12±3 hours). Because of reduced metabolic clearance, reboxetine plasma concentrations also are increased in those patients with hepatic or renal dysfunction. In these population, reboxetine should be used with caution, and a dosage reduction is indicated.

(±)-Nisoxetine



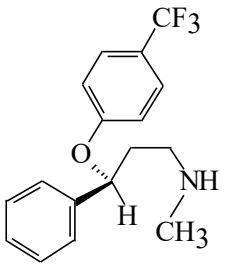
- Nisoxetine is phenoxyphenylpropyloamine derivative.
- The type and position of the ring substitution plays a critical role in the mechanism of action for these phenoxyphenylpropyloamines.
- The unsubstituted molecule is a weak SSRI.
- 2-Substitutions into the phenoxy ring (except for the 2-trifluoro-methyl) are potent and selective NET inhibitors (SNRI).
- 4-Substitute derivatives are potent and selective SERT inhibitors (SSRI; fluoxetine with 4-trifluoromethyl group).
- *R*-Nisoxetine has 20 times greater affinity than its *S*-isomer for NET.
- Its tertiary amine is approximately 100 times less effective at inhibiting NET.
- Increasing the size of the dimethylamino with ethyl or larger alkyl eliminates all activity.

R(-)-Atomoxetine

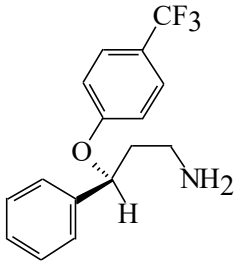


- Atomoxetine was marketed in 2003 as a „nonstimulant" treatment for ADHD (*attention-deficit hyperactivity disorder*), in both adults and children and for treatment of adult depression.
- The 2-methyl substitution confers selectivity for inhibiting NE reuptake.
- The *R*-enantiomer is 10 times more potent than the *S*-enantiomer as a NET reuptake inhibitor.
- Atomoxetine has a low propensity for antycholinergic and adverse cardiovascular effects.
- *Adverse effects*. Adverse effects have included modest increases in diastolic blood pressure and heart rate, anorexia, weight loss, somnolence, dizziness, GI effects (nausea), dry mouth, and skin rash.

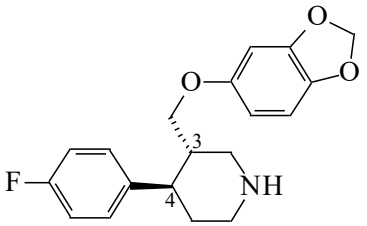
Selective 5-HT reuptake inhibitors (SSRI)



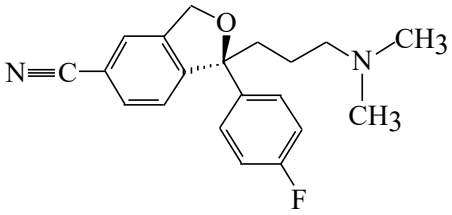
S-Fluoxetine



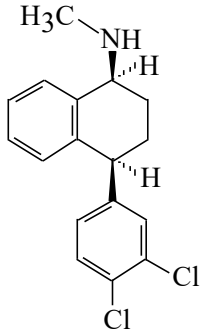
S-Norfluoxetine



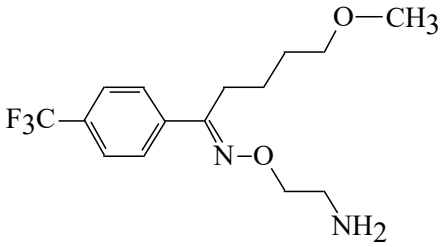
(-)3*S*,4*R*-Paroxetine



S-Citalopram



1*S*,4*S*-Sertraline

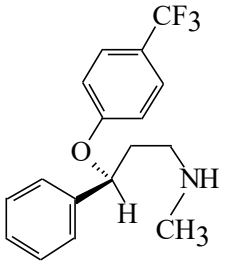


E-Fluvoxamine

In the case of some SSRIs, the influence of optical and substitution isomerism on their activity is observed, for example:

- *S*-Enantiomers of citalopram and fluoxetine and its metabolite, norfluoxetine, are active serotonin-reuptake inhibitors, also characterized by antimigraine action, which is not observed in the case of *R*-fluoxetine.

- The presence of CF_3 group in fluoxetine results in the inhibition of serotonine-reuptake. The elimination of that group or its presence in the *orto* position changes the profile of action towards NE-reuptake inhibition.



Mechanism of action common to the SSRIs

- The SSRIs preferentially inhibit SERT with minimal or no affinity for NE and dopamine transporters.
- SSRIs block 5-HT from binding to SERT and being absorbed into presynaptic cells. The excess 5-HT in the synaptic cleft means overactivation of the postsynaptic receptors. Over an extended period of time, this causes down-regulation of pre- and postsynaptic receptors, a reduction in the amount of 5-HT produced in the CNS and a reduction in the number of SERTs expressed.
- Long-term administration of SSRIs causes downregulation of the SERT, but not the NET. Substantial loss of 5-HT transporter binding sites takes 15 days to occur and is accompanied by a marked reduction of SERT function in vivo.
- Drugs of abuse, such as cocaine, fenfluramine, and 3,4-methylenedioxy-methamphetamine („Ecstasy”) are also SERT inhibitors, but not as selective as the SSRIs.
- The SSRIs have less affinity for α_1, α_2, H_1 and muscarinic receptors, which may explain the adverse-effects profile differences between TCAs and SSRIs.

Adverse effects common to the SSRIs

- SSRIs have fewer side effects than the TCAs, which have strong antycholinergic and cardiotoxic properties.
- Among the SSRIs, there are few differences in adverse effects.
- Adverse effects: nausea, diarrhea, anxiety, agitation, insomnia and sexual dysfunction. Fewer patients have discontinued SSRIs than TCAs (amitriptyline and imipramine, and not nortriptyline, desipramine, doxepin and clomipramine).
- The SSRI overdoses can result in drowsiness, tremor, nausea, and vomiting, including seizures, electrocardiographic changes, and coma. Fatalities are uncommon with pure SSRI overdoses.

Therapeutic uses common to the SSRIs

- Major depression and bipolar depression (fluoxetine, paroxetine, sertraline, citalopram)
- „Atypical" depression (i.e., depressed patients with unusual symptoms, e.g., hypersomnia, weight gain, and interpersonal rejection sensitivity; fluoxetine, paroxetine, sertraline, citalopram)
- Anxiety disorders, panic disorder (sertraline and paroxetine)
- Dysthymia, premenstrual syndrome, postpartum depression, dysphoria, bulimia nervosa (fluoxetine)
- Obesity, bordeline personality disorder, obsessive-compulsive disorder (fluvoxamine, fluoxetine, paroxetine i sertraline)
- Alcoholism, rheumatic pain, and migraine headache.

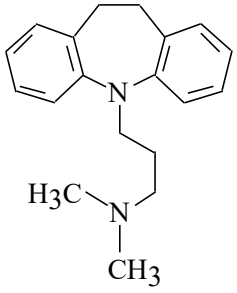
The SSRIs, such as paroxetine and fluoxetine, need stronger pediatric use warnings because of the possible risks of suicidal thoughts and behavior in some children and teenagers. Such risks may be unrelated to any specific SSRIs. 2 or 3 of every 100 young people treated with ADs might be at higher risk of suicidal behavior. Only fluoxetine has been proven to be effective and is approved for the treatment of pediatric depression.

This group of drugs should be used with caution in patients with liver function disorders.

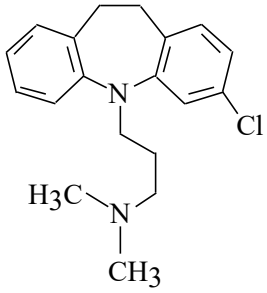
These drugs reach a maximal level in plasma after 2-10 hrs, and a steady-state after several weeks of treatment.

Norepinephrine and serotonin reuptake inhibitors (NSRIs)

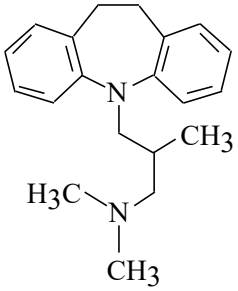
- Tricyclic tertiary amine ADs



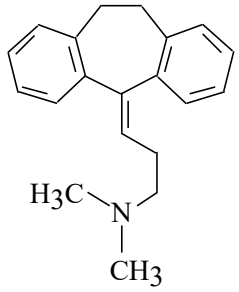
Imipramine



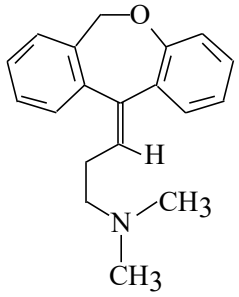
Clomipramine



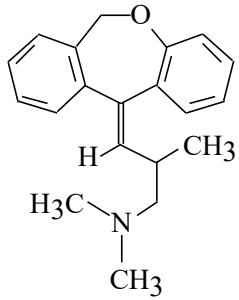
Trimipramine



Amitriptyline



Isomer E



Isomer Z

Doxepin (E/Z = 85/15%)

- **The NSRIs block NET and SERT.**
- **The in vivo antidepressant activity for these TCAs is more complex, because of the formation of secondary amine TCA metabolites, which in many cases annuls the 5-HT affinity of the parent TCA, leading to NE transport selectivity.**
- The plasma concentrations for the secondary amine metabolites usually are higher than that of their parent tertiary amine TCA because of rapid *N*-demethylation metabolism.
- Note that none of the tertiary amine TCAs have any significant affinity for the DA transporter.
- During chronic therapy with the tertiary amine TCAs, downregulation of the noradrenergic and serotoninergic receptors occurs, which is a result of neurotransmitter hypersensitivity caused by the continued high concentrations of NE and 5-HT at the postsynaptic receptor.
- **The tertiary TCAs are less potent inhibitors than the SSRIs for SERT.**

- **The tertiary TCAs may offer an option in the treatment of major depression for patients who have failed treatment with or who do not tolerate SNRIs or SSRIs.**
- **Imipramine also has been used for the treatment of functional enuresis in children who are at least 6 years of age.**

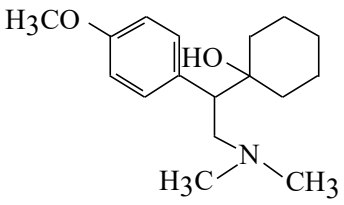
- The relatively low bioavailability for the tertiary amine TCAs suggests first-pass metabolism (*N*-demethylation) to their secondary amine active metabolites and aromatic ring hydroxylation.
- **Despite the fact that steady-state serum plasma levels are reached within 1 to 2 days, their onset of antidepressant action typically is at least 2 to 3 weeks or longer.**
- Excretion is primarily as metabolites via renal elimination. Renal and liver function can affect the elimination and metabolism of the parent TCA and its metabolites, leading to increased potential for adverse effects, especially in those patients (i.e., elderly) with renal disease.

Adverse effects

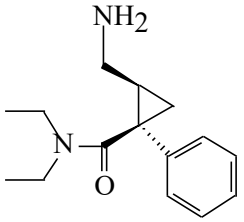
- **The tertiary TCAs exhibit greater antycholinergic, antihistaminic and α_1-antiadrenergic advere effects than the secondary TCAs do.**
- **Increased cardiotoxity or frequency of seizures is higher for the tertiary TCAs than for the secondary TCAs, because they are potent inhibitors of sodium channels, leading to changes in nerve conduction.**
- Cardiotoxity can occur at plasma concentrations approximately 5- to 10 times higher than therapeutic blood levels. These concentrations can occur in individuals who take an overdose of the TCA or who are slow metabolizers and develop higher plasma concentrations on what usually are therapeutic doses.
- Sexual dysfunction in men.

Nontricyclic serotonin and norepinephrin reuptake inhibitors

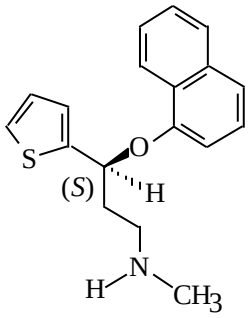
- Clinical studies suggest that compounds which increase the synaptic availability of both NE and 5-HT have greater efficacy than single-acting drugs in the treatment of major depression.



(±)-Venlafaxine

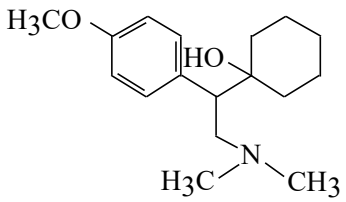


(±)-cis-Milnacipran



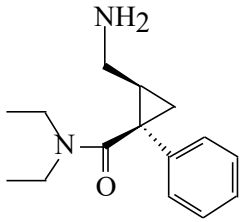
***S*(+)-Duloxetine**

Venlafaxine



- Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), have dual mechanisms of action, with preferential affinity for 5-HT reuptake and weak inhibition of NE and dopamine reuptake.
- **Venlafaxine is approximately 30 times more potent as an inhibitor of SERT than of NET.**
- Because of the 30 times difference in transporter affinities, increasing the dose of venlafaxine from 75 to 375 mg/day can sequentially inhibit SERT and NET.

Milnacipran



- In clinical studies, milnacipran shoved antidepressant efficacy similar to that of TCAs and SSRIs. Its mechanism of action is similar to that of imipramine.

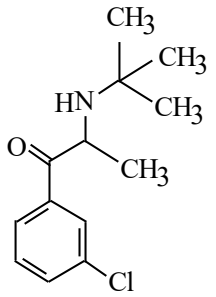
Duloxetin

Duloxetin has been approved for the treatment of depression and diabetic peripheral neuropathic pain.
Duloxetine exhibits dual inhibition with high affinity for the SERTs and NETs, with a five times preferential inhibition of the SERT.

Duloxetine has a low affinity for the other neuroreceptors, suggesting low incidence of unvanted adverse effects.

Adverse effects have included insomnia, somnolence, headache, nausea, diarrhea, and dry mouth.

Dopamine and norepinephrine reuptake inhibitors



(±)-Bupropion

The tertiary butyl group in bupropion prevents its *N*-dealkylation to metabolites that could posses sympathomimetic and/or anorexigenic properties.

Bupropion in vitro is a selective inhibitor of dopamine reuptake at the dopamine presynaptic neuronal membrane and minimal inhibition of NE and 5-HT reuptake.

Bupropion does not exhibit clinically significant anticholinergic, antihistaminic, α_1-adrenergic blocking activity, or MAO inhibition.

Bupropion is extensively metabolized in humans with its major hydroxylated metabolites reaching plasma levels higher than those of bupropion itself.

These hydroxylated metabolites share many of the pharmacological properties of bupropion, so they may play a greater role in attenuating the withdrawal and relapse by which bupropion exerts its activity in smoking cessation.

Hydroxybupropion is appoximately 50% as potent as bupropion, whereas threo-hydrobupropion and erythro-hydrobupropion have 20% of the potency of bupropion.

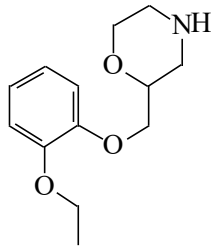
Te mean half-lives for hydroxybupropion and treo/ erytro-hydrobupropion and (±)-hydrobupropion were increased by five- and two times, respectively, in patient with severe hepatic cirrhosis compared with healthy volunteers.

Therapeutic uses

Besides being used to treat depression, bupropion is a nonnicotine aid in the cessation of smoking.

The efficacy of bupropion in smoking cessation is comparable to that of nicotine replacement therapy and should be considered as a second-line treatment in smoking cessation.

Viloxazine



Viloxazine selectively inhibits the presynaptic reuptake of NET (approximately half as potent as imipramine) and is a weak inhibitor of mouse brain 5-HT reuptake.
It differed from the TCAs in not exhibiting the TCA adverse effect profile.
Viloxazine produces antidepressant activities both similar to and different from the tricycles desipramine, imipramine, and amitriptyline.
These actions appear to be relevance with respect to the antidepressant action of this drug.

Presently, viloxazine is classified as an orphan drug, under the trade name CATATROL, for the treatment of narcolepsy and catalepsy.

Viloxazine (2)

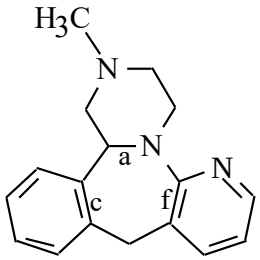
Narcolepsy: reccurent, uncontrollable, brief episodes of sleep, often associated with hypnagogic or hypnopompic hallucination, catalepsy, and sleep paralysis. Called also *Gelineau syndrome* and *paroxysmal sleep*.

Catalepsy: indefinitely prolonged maintenance of a fixed body posture; seen in severe cases of catatonic schizophrenia. The term is sometimes used to denote *cerea flexibilitas*.

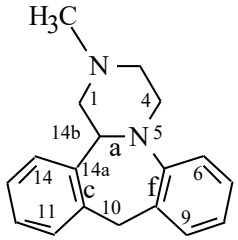
Serotonin receptor modulators

5-HT receptor modulator antidepressants exert their antidepressant effects by mechanisms that enhance noradrenergic or serotoninergic transmission by acting as:

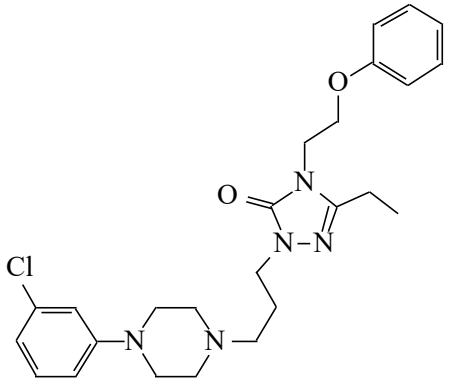
- mixed 5-HT_2 antagonists/5-HT reuptake inhibitors (SARI; trazodone) and
- α_2-adrenergic antagonists/5-HT_2 and 5-HT_3 antagonists (NaSSA; mirtazapine)



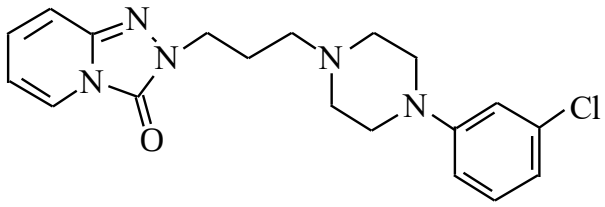
Mirtazapine



Mianserin



Nefazodone



Trazodone

5-HT_2 antagonists/5-HT reuptake inhibitors (SARI; trazodone

Trazodone acts as an antagonist at 5-HT_{2A} receptors and is a weak inhibitor of 5-HT reuptake at the presynaptic neuronal membrane, potentiating the synaptic effects of 5-HT. Its mechanism of action is complicated by the presence of its metabolite, m-chlorophenylpiperazine, which is a 5-HT_{2C} agonist. At therapeutic dosages, trazodone does not appear to influence the reuptake of dopamine or NE within the CNS. It has little anticholinergic activity and is relatively devoid of toxic cardiovascular effects. The increase in serotoninergic activity with long-term administration of trazodone decreases the number of postsynaptic serotoninergic and β-adrenergic binding sites in the brains of animals, decreasing the sensitivity of adenylate cyclase to stimulation by β-adrenergic agonists. It has been suggested that postsynaptic serotoninergic receptor modification is mainly responsible for the antidepressant action observed during longer administration of trazodone.

Trazodone therapy has been associated with several cases of idiosyncratic hepatotoxicity. Although the mechanism of hepatotoxicity remains unknown, the generation of an iminoquinone, an epoxide reactive metabolite or both may play a role in initiation of trazodone-mediated hepatotoxicity.

Trazodone is used primarily in the treatment of mental depression, or depression/anxiety disorders.

The drug also has shown some efficacy in the treatment of benzodiazepine or alcohol dependence, diabetic neuropathy, and panic disorders.

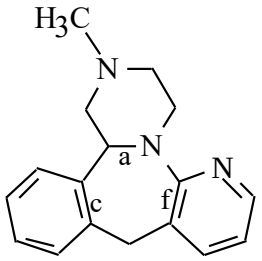
Noradrenergic specific serotoninergic antidepressants

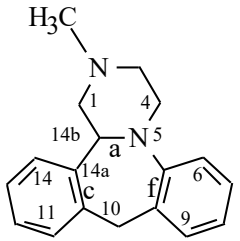
- **Mirtazapine**

  Mirtazapine is a piperazinodibenzoazepine antidepressant that is an isostere of the antidepressant mianserin. A seemingly simple isosteric replacement of an aromatic methine group (CH) in mianserin with a nitrogen to give a pyridine ring (mirtazapine) has profound effects on the physicochemical properties, pharmacokinetics, mechanisms of action and antidepressant activities.

  Mianserin is a potent inhibitor of NET, whereas mirtazapine has negligible effects on the inhibition of NET.

  Mianserin is currently marketed in Europe as an antidepressant. Mianserin has not been approved for use in the United States because of its serious adverse effects of agranulocytosis and leukopenia. Mirtazapine has not exhibited this adverse effect.





- The efficacy of mirtazapine as an antidepressant results from enhancing central noradrenergic and serotoninergic activity, possibly through blocking central presynaptic α_2-adrenergic receptors. Blocking these receptors inhibits the negative feedback loop, which increases the release of NE into the synapse.
- Mirtazapine also is a potent antagonist at 5-HT_2 and 5-HT_3 receptors, and it shows no significant affinity for 5-HT_{1A} and 5-HT_{1B} receptors.
- Additionally, it displays some anticholinergic properties, and it produces sedative effects (because of potent histamine H_1 receptor atagonism) and orthostatic hypotension (because of moderate antagonism at peripheral α_1-adrenergic receptors).
- Its antidepressant effect is comparable to the TCAs and may be better than some SSRIs, especially in patients with depression of the melancholic type, but at higher doses, it may cause drowsiness and weight gain.

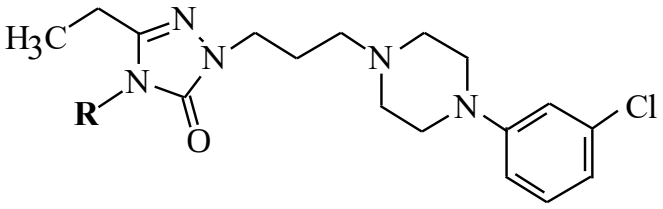
Other serotoninergic drugs

Nefazodone also inhibits serotonin transport, but unlike fluoxetine, paroxetine and sertraline, it blocks the postsynaptic 5-HT_2 receptors in neurons. These receptors do not participate in the desired serotonin action, but are only responsible for the adverse effects. Therefore it is better to use nefazodone.

Nefazodone does not act on the noradrenergic system. Although it inhibits NE-reuptake, it simultaneously blocks α_2-adrenergic receptors.

Nefazodon demonstrates antidepressive activity similar to TADs and SSRIs.

Its adverse effects can be nausea, xerostomia, dizziness, stupor and blurred vision. Nefazodon does not demonstrate negative influence on sexual functions. Nefazodon also acts strongly on opioid (μ_1, μ_2) receptors and because of that it acts analgetically.

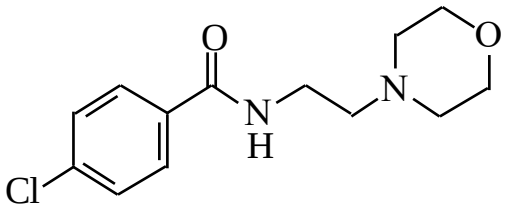


R = -CH_2-CH_2-O-C_6H_5; *Nefazodone*, NEFADAR

Monoamine oxidase inhibitors (MAOIs)

At present selective MAO-A inhibitors (moclobemide, toloxatone) are more widely used than nonselective MAO-Is (tranylcypromine, isocarboxazid). Other MAOIs (cimoxatone, almoxatone, clorgiline) are undergoing clinical trials.

Moclobemide and toloxatone inhibit MAO-A reversibly and selectively. Moclobemide has similar activity to TADs, but is considerably less toxic. Because of its selectivite action, no interaction with food or drugs, typical of non-selective MAOIs, is observed. Moclobemide is used to treat depression syndromes characterized by supression as well as excitation and anxiety.



Moclobemide, AURORIX, MOCLOXIL

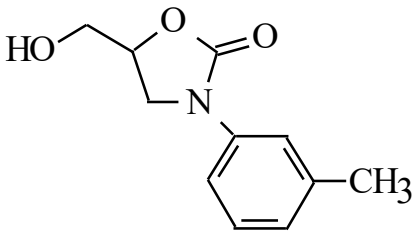
Monoamine oxidase inhibitors (MAOIs)

Toloxatone does not act anxiolitically.

It is mainly used to treat a reactive type of depression in which psychomotor supression occurs.

It shouldn't be used simultaneously with other MAOIs.

Toloxatone increases the action of hypotensive drugs.



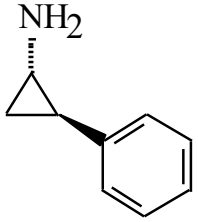
Toloxatone

Monoamine oxidase inhibitors (MAOIs)

Tranylcypromine (non-selective, irreversible MAOI) is used to treat endogenic depression with psychomotor inhibition and a low level of anxiety.

It shouldn't be used in patients with hypertension or other cardiovascular diseases.

Tranylcypromine is a relatively toxic drug, which can cause intracranial bleeding and exceptionally serious complications.



***Tranylcypromine*, PARNATE**

Monoamine oxidase inhibitors (MAOIs)

MAOIs and SSRIs should not be co-administered because of the risk of causing a life-threatening “serotonin syndrome”.

When MAOIs are used the consumption of products containing tyramine (aged cheese, beer, red wine) is contraindicated, to avoid the so-called “yellow cheese syndrome”.

Tyramine is metabolised by MAO in the intestinal wall and in the liver and only a small amount reaches circulation.

Patients receiving MAOIs are unable to degrade tyramine obtained from the diet. **Tyramine releases large amounts of stored catecholamines from nerve terminals, resulting in headache, tachycardia, nausea, hypertension, cardiac arrythmias and stroke.**

Patients must therefore be educated to avoid tyramine-containing foods.

Monoamine oxidase inhibitors (MAOIs)

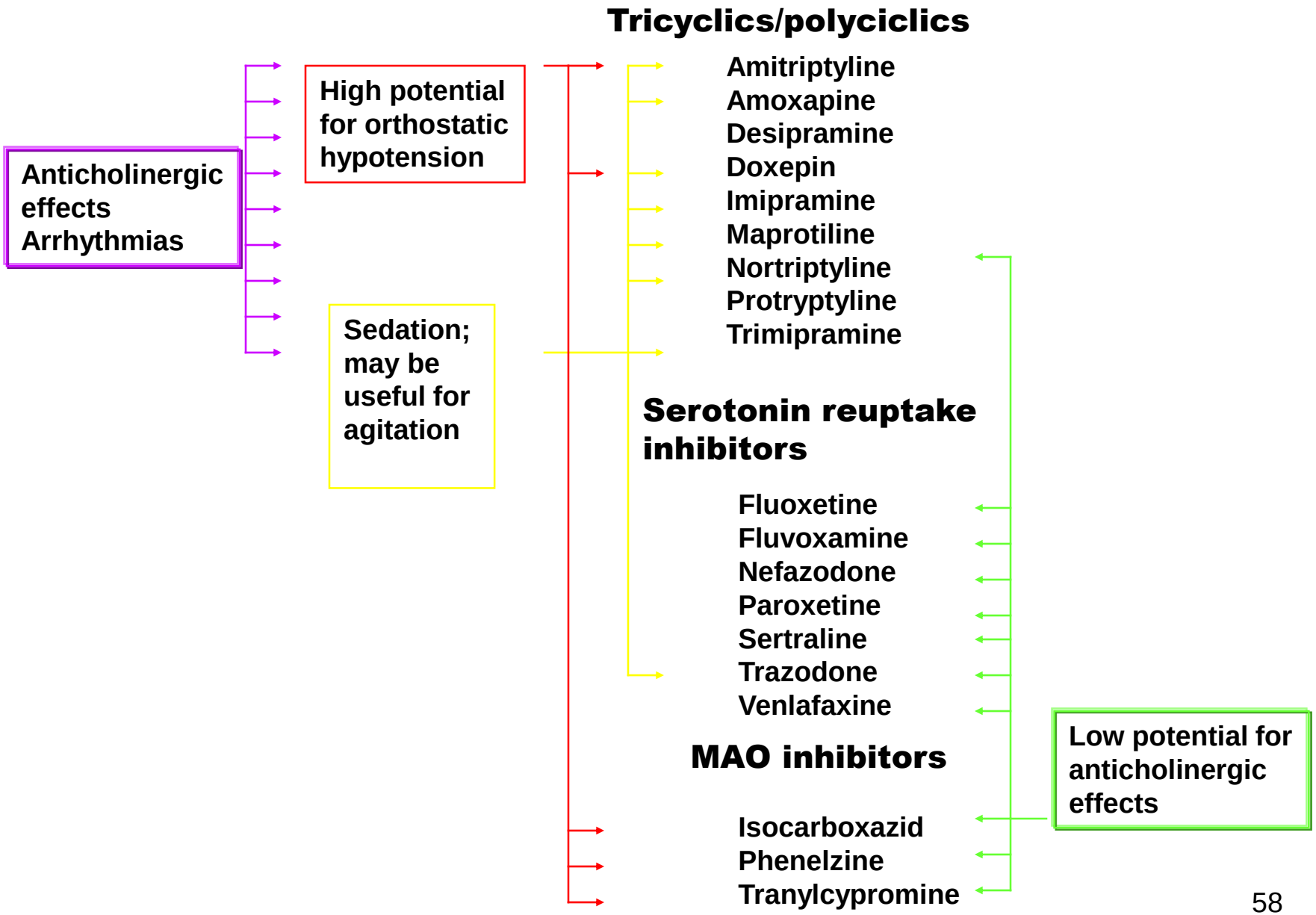
Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dryness of the mouth, dysuria and constipation.

In some patients increased body weight, caused by excessive appetite, is observed. In such cases administration of the drug should be stopped.

Cholinolitic effects are more frequent than during treatment with TADs but they are less intensive.

Therapeutic disadvantages of antidepressant agents

Therapeutic advantages of antidepressant agents



Mood stabilizers - Lithium salts

Lithium salts (bromide, citrate, gluconate, acetate, orothate, sulphate, carbonate, hydroaspargate) are used to treat manic states and are preventivel administered in psychosis of affective,mono- and bipolar and schizoaffective types.

Additionally, lithium salts are used to treat granulocytopenia.

Lithium salts (2)

Lithium carbonate is used in such forms as tablets, sustained-action tablets, slow-release tablets, intestinal tablets, capsules and slow-release capsules. Tablets made by different manufacturers contain from 150 mg to 500 mg of lithium carbonate.

The therapeutic level of lithium ions in blood is from 0.5 to 0.8 mMol/L. This level is obtained if a daily dose of 500 mg to 1.5 g of lithium carbonate, divided into 2 to 3 doses, is used.

The concentration of lithium ions in blood exceeding 1.6 mMol/L threatens severe complications.

Lithium carbonate is easily absorbed from the gastrointestinal tract. A maximal concentration in blood occurs after 1-3 hours.

Lithium ions permeate to cellular and extracellular fluids and do not bind with proteins. However, the distribution of lithium ions is slow.

Lithium salts (3)

The level of lithium ions in cerebrospinal fluid is about 40 per cent of the concentration of lithium ions in plasma.

About 95% of a lithium dose is eliminated by the kidneys. Kidney clearance of lithium ions is 20% of creatinine clearance (15-30 ml/min) and differs in relation to the age and kidney efficiency of the patient. Kidney clearance is less in older patients than in young ones and in those with insufficient kidney function.

The mean half-time elimination is 24 hours (a range of 17-36 ; adults - 24 h, young people 18 h, elderly up to 36 h).

The stationary state is reached after 5-7 days.

In the kidneys, 80% of lithium ions is reabsorbed.

Lithium salts (4)

Lithium and sodium ions compete for reabsorption in the proxymal tubule.

At a diminished level of sodium ions (dehydration, use of diuretics) the reabsorption of lithium ions from the proximal tubule is greater than 80%.

An increased reabsorption of lithium ions increases their level in plasma and can cause toxic syndromes.

An excessive number of sodium ions increases the elimination of lithium ions and decreases the level of lithium ions in plasma.

Lithium ions change the transport of sodium ions in nerve and muscle cells and affect the intraneuronal metabolism of catecholamines.

Lithium salts (5)

The exact mechanism of the action of lithium ions in manic states, depression and granulocytopenia is not known.

At present it is thought that, most probably, lithium ions inhibit the transformation of inozytoltriphosphate (IP_3) to inozytol (a substrate for the resynthesis of $PhIP_2$).

It is known that mono- and divalent cations affect the synthesis, storage, release and reuptake of central neurotransmitters – catecholamines and serotonin.

These neurotransmitters are involved in the pathogenesis of manic states and depression.

There is much evidence that the antimanic action of lithium ions is a result of increased NA-reuptake and the increased sensibility of serotonin receptors.

Other antidepressants

To treat depression products derived from plants (*Hypericum perforatum*) are also used.

The active substances of hypericum, hypericines, relieve stupor and related symptoms, such as a defficient motivation to act, concentration difficulties, exhaustion and sleep disorders.

Electroconvulsive therapy (ECT)

ECT has been in use since the late 1930s to treat a variety of severe mental illnesses, most notably major depression.

Use of ECT is beneficial particularly for individuals whose depressions is severe or life threatening or who cannot take antidepressant medication. Often, ECT is effective in cases where antidepressant drugs do not provide sufficient relief of symptoms.

In recent years, ECT has been much improved. A muscle relaxant is given before treatment, which is done under brief anesthesia.

ECT appears to increase the sensitivity of postsynaptic 5-HT receptors and upregulation of 5-HT_{1A} postsynaptic receptors.

Side effects may result from anesthesia, the ECT treatment, or both. Common side effects include temporary short-term memory loss, nausea, muscle aches, and headache. Some people may have longer-lasting problems with memory after ECT. Sometimes, a person's blood pressure or heart rhythm changes.