PHARMACOLOGICAL MANAGEMENT OF DEPRESSION

OUTLINE

- Classification of Antidepressants
- Mechanism of Action
- SSRIs
- Tricyclic Antidepressants
- Monoamine Oxidase Inhibitors
- 5-HT2 receptor antagonists

CLASSIFICATION OF ANTIDEPRESSANTS

Can be divided into three main classes, depending on their acute pharmacological properties.

1. Monoamine reuptake inhibitors. These are compounds that inhibit the reuptake of noradrenaline and/or serotonin(5-HT).
2. Monoamine oxidase inhibitors (MAOIs). These are compounds that deactivate monoamine oxidase irreversibly or reversibly.
3. 5-HT2 receptor antagonists. These drugs have complex effects on monoamine mechanisms but share the ability to block 5- HT2 receptors

MONOAMINE REUPTAKE INHIBITORS

These are compounds that inhibit the reuptake of noradrenaline and/ or 5- HT (Serotonin). They include:

1. Tricyclic antidepressants
2. Selective serotonin reuptake inhibitors (SSRIs)
3. Selective noradrenaline and serotonin reuptake inhibitors (SNRIs)
4. Selective noradrenaline reuptake inhibitors (NARIs).

Monoamine oxidase inhibitors (MAOIs).

These are compounds that deactivate monoamine oxidase either:

1. Irreversibly E.g. Phenelzine and Tranylcypromine
2. Reversibly E.g. Moclobemide

5-HT2 Receptor Antagonist

- These drugs include mirtazapine and trazodone.
- They have complex effects on monoamine mechanisms but share the ability to block 5- HT2 receptors.

Drug	Advantages	Disadvantages
Tricyclic antidepressants	Well studied Efficacy never surpassed	Cardiotoxic*, dangerous in overdose
		Anticholinergic side effects**
	Useful sedative effect in selected patients	Cognitive impairment
		Weight gain during longer-term treatment
SSRIs/SNRIs	Lack cardiotoxicity***: relatively safe in overdose†	Long-term toxicity not fully evaluated
	Not anticholinergic	Gastrointestinal disturbance, sexual dysfunction
	No cognitive impairment	May worsen sleep and anxiety symptoms initially
	Relatively easy to give effective dose	Greater risk of drug interaction
Trazodone	Lacks cardiotoxicity††, relatively safe in overdose	Daytime drowsiness
Mirtazapine	Useful sedative effect in selected patients	Weight gain common Less well-established efficacy in severe depression

MECHANISM OF ACTION

- The acute effect of **reuptake inhibitors** and **of MAOIs** is to **enhance the functional activity of noradrenaline and/ or 5- HT**.
- These actions can be detected within hours of the start of treatment.
- Full antidepressant effects of drug treatment delayed for several weeks.
- The delay in the onset of therapeutic activity may be due to pharmacokinetic factors e.g. the half- life is around 24 hours, therefore steady- state plasma drug levels will be reached only after 5– 7 days. However, this does not completely account for the lag in antidepressant activity.

MECHANISM OF ACTION

- The delay in onset of obvious therapeutic effect with antidepressant medication led to suggestions that the antidepressant effect of current treatments is a consequence of **slowly evolving neuroadaptive changes in the brain**, which are triggered by acute potentiation of monoamine function.

MECHANISM OF ACTION

- Mechanisms that might underlie this effect, include **desensitization of inhibitory autoreceptors on 5-HT and noradrenaline cell bodies, increased production of neurotrophins**, such as brain-derived neurotrophic factor (BDNF), and **increased synaptogenesis and neurogenesis**.

Selective serotonin reuptake inhibitors (SSRIs)

- First- line treatment of depression.
- They are moderately better tolerated and markedly less toxic in overdose.
- They include:
  - Citalopram
  - Escitalopram
  - Fluoxetine
  - Fluvoxamine
  - Paroxetine
  - Sertraline

SSRIs

Pharmacological properties

- They are a structurally diverse group, but they all inhibit the reuptake of serotonin (5-HT) with high potency and selectivity.
- None of them has an appreciable affinity for the noradrenaline uptake site.
- They have a low affinity for other monoamine neurotransmitter receptors.

SSRIs

- **Pharmacokinetics**
- Generally absorbed slowly and reach peak plasma levels after about 4– 8 hours, although citalopram and escitalopram are absorbed more quickly.
- The half- lives of citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline are between 20 and 30 hours, whereas the half- life of fluoxetine is 48– 72 hours.
- SSRIs are primarily eliminated by hepatic metabolism.
- Fluoxetine is metabolized to norfluoxetine, which is also a potent 5- HT uptake blocker and has a half- life of 7– 9 days.

SSRIs

Side effects

Gastrointestinal effects. Nausea occurs in about 20% of patients, although it often resolves with continued administration. Other side effects include bloating, flatulence, and diarrhoea.

Neuropsychiatric effects. These include insomnia, daytime somnolence, agitation, tremor, restlessness, irritability, and headache.

SSRIs have also been associated with seizures and mania

SSRIs

Other side effects.

- Sexual dysfunction, including ejaculatory delay and anorgasmia.
- Sweating and dry mouth.
- Cardiovascular side effects are rare with SSRIs, but some reduction in pulse rate may occur, and postural hypotension has been reported.
- Associated with skin rashes and, rarely, a more generalized allergic reaction with arthritis.

SSRIs

SSRIs and suicidal behavior

- SSRIs can cause agitation and restlessness early in treatment, and it is possible that in predisposed individuals this might trigger dangerous behavior.
- Studies have shown a fourfold increase in risk of attempted suicide seen with all antidepressants in the first 9 days of treatment.
- In adolescents and children, the risk of self- harm with SSRIs might be greater.
- Patients should be closely monitored when starting antidepressant medication

SSRIs

- **Pharmacodynamics interactions**
- The most serious interaction reported is where simultaneous administration of SSRIs and MAOIs has provoked a 5- HT toxicity syndrome (the 'serotonin syndrome') with:
- Agitation
- Hyperpyrexia
- Rigidity
- Myoclonus
- Coma and death

SSRIs

- Other drugs that increase brain 5- HT function and that must therefore be used with caution in combination with SSRIs include **lithium** and **tryptophan**, which have been reported to be associated with mental state changes, myoclonus, and seizures.
- Other medical drugs that have been implicated in the serotonin syndrome when combined with SSRIs include **tramadol** and **linezolid.**

SSRIs

- **Pharmacokinetic interactions**
- Some SSRIs, particularly fluvoxamine, fluoxetine, and paroxetine, can produce substantial inhibition of hepatic cytochrome P450 enzymes, and can decrease the metabolism of several other drugs, thereby elevating their plasma levels .
- Citalopram, escitalopram, and sertraline cause fewer reactions of this nature.

	CYP 1A2	CYP 2D6	CYP 2C9	CYP 2C19	CYP 3A/4
Inhibitors	Fluvoxamine (+++) Duloxetine (+)	Fluoxetine (+++) Paroxetine (+++) Duloxetine (++) Sertraline (+) Citalopram (+) Escitalopram (+)	Fluoxetine (+++) Fluvoxamine (+++)	Fluvoxamine (+++) Fluoxetine (++) Venlafaxine (+)	Fluvoxamine (++) Fluoxetine (+)
Some substrates (plasma level increased)	Olanzapine Clozapine Haloperidol Tricyclic antidepressants Theophylline	Tricyclic antidepressants Venlafaxine Haloperidol Thioridazine Risperidone Clozapine Olanzapine	Warfarin Tolbutamide Phenytoin	Tricyclic antidepressants Diazepam Propranolol Omeprazole	Benzodiazepines Carbamazepine Quetiapine Clozapine

Differences between SSRIs

Drug	Risk of pharmacokinetic interaction*	Discontinuation syndrome	Other
Citalopram	+	+	Increases QT interval
Escitalopram	+	+	Increases QT interval
Fluoxetine	+++	0	Increased risk of agitation, slower onset of action
Fluvoxamine	+++	+++	Less well tolerated
Paroxetine	+++	+++	Weight gain
Sertraline	++	++	May have dopaminergic effects

SSRIs

- Explain to the patient that they may become more anxious and agitated early during SSRI treatment which is not an indicator that the underlying depression is worsening.
- Anxiety and agitation usually diminish, when treatment persist but short- term treatment with a benzodiazepine may be helpful, particularly if sleep disturbance is a problem.
- Patients should be reviewed frequently during the first few weeks of treatment, to ensure compliance with medication.
- Should be continued for at least 6 months, this lowers the rate of relapse.
- Effective in the prophylaxis of recurrent depressive episodes.
- Should not be stopped suddenly, due to withdrawal reactions (insomnia, nausea, agitation, and dizziness).

Tricyclic antidepressants

Pharmacology

Tricyclic antidepressants have a three- ringed structure with an attached side chain. There are two groups

1. **Tertiary amines** ; Those that have a terminal methyl group on the side chain. Compared with secondary amines they have a higher affinity for the 5- HT uptake site and are more potent antagonists of α1- adrenoceptors and muscarinic cholinergic receptors. Therefore, in clinical use, they are more sedating and cause more anticholinergic effects E.g. Amitriptyline, Clomipramine, and Imipramine
2. **Secondary amines**; Those that do not have a terminal methyl group on the side chain. E.g. Desipramine and Nortriptyline.

Tricyclic antidepressants

Pharmacology

- Tricyclic antidepressants inhibit the reuptake of both 5- HT and noradrenaline.
- They also have antagonist activities at a variety of neurotransmitter receptors. The receptor- blocking actions have been thought to cause adverse effects.
- Although the ability of some tricyclic antidepressants to antagonize brain 5- HT2 receptors may also mediate some of their therapeutic effects.
- Tricyclics have quinidine- like membrane- stabilizing effects, and this may explain why they impair cardiac conduction and cause high toxicity in overdose.

Tricyclic antidepressants

Pharmacokinetics

- They are well absorbed from the gastrointestinal tract, and peak plasma levels occur 2– 4 hours after ingestion.
- Tricyclics are subject to significant first- pass metabolism in the liver and are highly protein- bound. The free fraction is widely distributed in body tissues.
- Tricyclics are metabolized in the liver by hydroxylation and demethylation.
- Demethylation of tricyclics with a tertiary amine structure gives rise to significant plasma concentrations of the corresponding secondary amine.

Tricyclic antidepressants

- **Clomipramine** is the most potent of the tricyclic antidepressants in inhibiting the reuptake of 5- HT.
- Its secondary amine metabolite, desmethylclomipramine, is an effective noradrenaline reuptake inhibitor.
- Unlike other tricyclic antidepressants, clomipramine is useful in ameliorating the symptoms of obsessive– compulsive disorder.
- **Lofepramine** is a tertiary amine which is metabolized to Desipramine.
- Lofepramine is a fairly selective inhibitor of noradrenaline reuptake, and has fewer anticholinergic and antihistaminic properties than amitriptyline.
- It is not cardiotoxic in overdose.

Tricyclic antidepressants

Side effects

- **Anticholinergic effects** include;
  - dry mouth,
  - disturbance of accommodation,
  - difficulty in micturition, leading to retention,
  - constipation, leading rarely to ileus,
  - postural hypotension,
  - tachycardia, and
  - increased sweating.
- Retention of urine, especially in elderly men with enlarged prostates, and worsening of glaucoma are the most serious of these effects.
- Dry mouth and accommodation difficulties are the most common.

Tricyclic antidepressants

Psychiatric effects include;

- Tiredness and drowsiness with amitriptyline and other sedative compounds.
- Insomnia with Desipramine and Lofepramine.
- Acute organic syndromes.
- Mania may be provoked in patients with bipolar disorders.

Tricyclic antidepressants

- **Cardiovascular effects** include;
  - Tachycardia and postural hypotension occur commonly.
  - Prolongation of PR and QT intervals, depressed ST segments, and flattened T- waves.
  - Ventricular arrhythmias and heart block develop occasionally, more often in patients with pre- existing heart disease.
- **Neurological effects** include;
  - Fine tremor (commonly)
  - Incoordination
  - Headache
  - Muscle twitching
  - Epileptic seizures in predisposed patients
  - Peripheral neuropathy (rarely)

Tricyclic antidepressants

- **Other effects** include weight gain and sexual dysfunction.
- **Withdrawal effects**: Sudden cessation may be followed by nausea, anxiety, sweating, gastrointestinal symptoms, and insomnia with vivid dreaming.
- **Toxic effects:** Ventricular fibrillation, conduction disturbances, and low blood pressure. Sedation and coma lead to respiratory depression.

Tricyclic antidepressants

Interactions with other drugs

- They antagonize the hypotensive effects of α2-adrenoceptor agonists such as clonidine, but can be safely combined with thiazides and angiotensin-converting enzyme (ACE) inhibitors.
- The ability of tricyclics to block noradrenaline reuptake can lead to hypertension with systemically administered noradrenaline and adrenaline.
- Tricyclics should not be used in conjunction with antiarrhythmic drugs, particularly amiodarone.

Tricyclic antidepressants

Interaction with other drugs

- Tricyclics increase the QT interval and should not be given with other drugs that can produce a similar effect, for example, pimozide, astemizole, erythromycin, clarithromycin, diphenhydramine, and tamoxifen.
- Plasma levels of tricyclics can be increased by numerous other drugs, including cimetidine, sodium valproate, calcium- channel blockers, and SSRIs.
- Tricyclics may increase the action of warfarin.

Tricyclic antidepressants

Contraindications

- Agranulocytosis
- Severe liver damage
- Glaucoma
- Prostatic hypertrophy
- Uncontrolled epilepsy
- Significant cardiovascular disease.

- Tricyclics must be used cautiously in epileptic patients and in the elderly.

Tricyclic antidepressants

Clinical use of tricyclic antidepressants

- Amitriptyline – sedating.
- Nortriptyline - less sedating.
- Lofepramine can be used for patients who present a risk of overdose.
- Clomipramine can be reserved for patients in whom a depressive disorder is related to obsessive–compulsive disorder.

Tricyclic antidepressants

- Amitriptyline starting dose will depend to some extent on the patient's age, weight, physical condition, and history of previous exposure to tricyclics; daily doses of 25– 50 mg for an outpatient and 50– 75 mg for an inpatient would be reasonable.
- The whole dose can be given at night about 1– 2 hours before bedtime, because the sedative effects of the drug will aid sleep.
- The dose of amitriptyline to be aimed for is about 125 mg daily or above. This dose can usually be reached over a period of 2– 4 weeks.

Tricyclic antidepressants

Maintenance and prophylaxis

- If patients respond to amitriptyline, they should be maintained on treatment for at least 6 months, as continuation therapy greatly reduces the risk of early relapse.
- The same dose of amitriptyline should be maintained if possible.
- In some patients depression is a recurrent disorder, therefore long- term prophylactic treatment may be justified.

Monoamine oxidase inhibitors (MAOIs)

- MAOIs were introduced just before the tricyclic antidepressants.
- Their use has been less widespread due to troublesome interactions with foods and drugs.
- In adequate doses MAOIs are useful antidepressants, often producing clinical benefit in depressed patients who have not responded to other medication or ECT.
- In addition, MAOIs can be useful in refractory anxiety states.

MAOIs

Pharmacological properties

- MAOIs inactivate enzymes that oxidize noradrenaline, 5- HT, dopamine, and tyramine, and other amines that are widely distributed in the body as transmitters, or are taken in food and drink or as drugs.
- Monoamine oxidase (MAO) exists in a number of forms that differ in their substrate and inhibitor specificities.
- MAO- A metabolizes intraneuronal noradrenaline and 5-HT.
- Both MAO- A and MAO- B metabolize dopamine and tyramine.

MAOIs

Compounds available

- **Phenelzine** is the most widely used.
- **Isocarboxazid** has fewer side effects than Phenelzine. Useful in patients who suffer from side effects of Phenelzine such as hypotension or sleep disorder.
- **Tranylcypromine** differs from the other compounds in combining the ability to inhibit MAO with an amphetamine- like stimulating effect, which may be helpful in patients with anergia and retardation. However, some patients become dependent on the stimulant effect of tranylcypromine.

MAOIs

- **Moclobemide** differs from the other compounds in selectively binding to MAO- A, which it inhibits in a reversible way. This results in a lack of significant interactions with foodstuffs, and a quick offset of action.

MAOIs

Pharmacokinetics

- Phenelzine, Isocarboxazid, and Tranylcypromine are rapidly absorbed and widely distributed.
- They have short half- lives (about 2– 4 hours), as they are quickly metabolized in the liver by acetylation, oxidation, and deamination.
- They bind irreversibly to MAO- A and MAO- B by means of a covalent linkage. This means that the enzyme is permanently deactivated and MAO activity can be restored only when new enzyme is synthesized.
- Despite their short half- lives, irreversible MAOIs cause a long- lasting inhibition of MAO.

MAOIs

- **Moclobemide** binds reversibly to MAO- A.
- This compound has a short half- life (about 2 hours), and therefore its inhibition of MAO- A is brief, declining to some extent even during the latter periods of a three times daily dosing regimen.
- Full MAO activity is restored within 24 hours of stopping Moclobemide, whereas with the irreversible MAOIs, a period of 2 weeks or more may be needed for synthesis of new MAO.

MAOIs

Efficacy of MAOIs in depression

- Phenelzine doses of up to 90 mg daily if side effects permit are superior to placebo and are generally equivalent to tricyclic antidepressants in their therapeutic activity.

MAOIs side effects

Central nervous system

Insomnia, drowsiness, agitation, headache, fatigue, weakness, tremor, mania, confusion

Autonomic nervous system

Blurred vision, difficulty in micturition, sweating, dry mouth, postural hypotension, constipation

Other

Sexual dysfunction, weight gain, peripheral neuropathy (pyridoxine deficiency), oedema, rashes, hepatocellular toxicity (rare), leucopenia (rare)

MAOIs

Interactions with foodstuffs

- Some foods contain tyramine, a substance that is normally inactivated by MAO in the liver and the gut wall.
- When MAO is inhibited, tyramine is not broken down and is free to exert its hypertensive effects.
- These effects are due to release of noradrenaline from sympathetic nerve terminals with a consequent elevation in blood pressure.
- The elevated BP may occasionally result in subarachnoid hemorrhage.

MAOIs

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MAOIs

Foods to be avoided during MAOIs use;

- All cheeses except cream, cottage, and ricotta cheeses
- Red wine, sherry, beer, and liquors
- Pickled or smoked fish
- Brewer's yeast products
- Broad bean pods (e.g. Italian green beans)
- Beef or chicken liver
- Fermented sausage (e.g. bologna, pepperoni, salami)
- Unfresh, overripe, or aged food (e.g. unfresh dairy products)

MAOIs

- 80% of all reported reactions between foodstuffs and MAOIs, and nearly all of the deaths, have followed the consumption of cheese.
- Hypertensive reactions should be treated with parenteral administration of an α1- adrenoceptor antagonist.
- Oral Nifedipine has also been advocated.
- Whatever treatment is given, blood pressure must be monitored carefully.

MAOIs

Moclobemide and tyramine reactions

- Tyramine is metabolized by both MAO- A and MAO- B.
- Tyramine has relatively little effect in patients who are receiving Moclobemide because MAO- B (present in the gut wall and the liver) is still available to metabolize much of the tyramine ingested.
- The interaction between Moclobemide and MAO- A is reversible, thus allowing displacement of Moclobemide from MAO when tyramine is present in excess

MAOIs

- **The serotonin syndrome**. A number of drugs that potentiate brain 5- HT function can produce a severe neurotoxicity syndrome when combined with MAOIs
- **Neurological**: Myoclonus, nystagmus, headache, tremor, rigidity, seizures
- **Mental state:** Irritability, confusion, agitation, hypomania, coma
- **Others:** Hyperpyrexia, sweating, diarrhoea, cardiac arrhythmias

MAOIs

Contraindications:

- These include liver disease, Pheochromocytoma, congestive cardiac failure, and conditions that require the patient to take any of the drugs that react with MAOIs.

MAOIs

Clinical use of MAOIs in depression

- **Phenelzine**.
- Treatment should start with 15 mg daily, increasing to 30 mg daily in divided doses (with the final dose taken not later than 3.00 pm) in the first week.
- The dose can be increased by 15 mg weekly if side effects permit.
- Side effects that are likely to be particularly troublesome are insomnia and postural hypotension.

MAOIs

Withdrawal from MAOIs

- Even gradual withdrawal can be associated with increasing anxiety and depression.
- MAOIs produce a more severe discontinuation syndrome than other antidepressants.
- It is emphasized that, because of the time taken to synthesize new MAO, 2 weeks should elapse between the cessation of irreversible MAOI treatment and the easing of dietary and drug restrictions

5-HT2 receptor antagonists

- 5-HT2CRs are Gαq-coupled heteroreceptors that are expressed in several limbic structures including the hippocampus (especially enriched in CA3), amygdala, anterior olfactory and endopiriform nuclei, and cingulate and piriform cortex.
- Over activity of 5-HT2CRs may contribute to the etiology of depression and anxiety as some suicide victims have abnormally high expression of 5-HT2CRs in the prefrontal cortex.

5-HT2 receptor antagonists

- Agomelatine, a mixed melatonergic agonist/5-HT2CR antagonist is an effective anxiolytic and antidepressant in both preclinical and clinical populations.
- Acute administration of SSRIs can lead to negative side effects (such as increased anxiety) presumably through activation of both 5-HT1AR autoreceptors and 5-HT2CR heteroreceptors. (Yohn CN, Gergues MM, Samuels BA. The role of 5-HT receptors in depression. Mol Brain. 2017;10(1):28. Published 2017 Jun 24. doi:10.1186/s13041-017-0306-y)

Agomelatine

- It is a melatonin receptor agonist and a somewhat weaker antagonist at 5- HT2C receptors.
- The mechanism of antidepressant action of Agomelatine is not established, but could be mediated through a melatonin- like action on circadian rhythms.

Agomelatine

- Pharmacokinetics: Agomelatine is rapidly absorbed, reaching maximum levels within 1– 2 hours of ingestion.
- It has a high first- pass metabolism, with a bioavailability of only 5– 10%.
- It has a short half- life of about 2 hours and no metabolites likely to contribute to its therapeutic action.

Agomelatine

Unwanted effects

- The most common adverse effects of Agomelatine are nausea and dizziness.
- Some patients experience somnolence, and insomnia has also been reported.
- Anxiety and fatigue,
- Diarrhoea, and constipation.
- Sexual dysfunction is less frequent than with SSRIs.
- The most serious potential adverse effect of Agomelatine is an increase in liver enzymes (ALT and AST).

Agomelatine

Drug interactions

- The main interaction of Agomelatine is with drugs that inhibit the hepatic microsomal enzymes, CYP1A2 and CYP2C9/ 19. This is because these enzymes metabolize Agomelatine, and higher blood levels of Agomelatine are likely to increase the risk of hepatic dysfunction.
- Agomelatine should not be given with potent CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin.
- Coadministration with more moderate inhibitors (estrogens, propranolol) should be employed with caution.

Mirtazapine

- It is a quadricyclic compound with complex pharmacological actions.
- It is a fairly potent antagonist at several 5- HT- receptor subtypes, particularly 5- HT2 and 5- HT3 receptors.
- Mirtazapine is also a competitive antagonist at histamine H1 receptors and α1- and α2- adrenoceptors (The latter leads to an increase in noradrenaline cell firing and release).

Mirtazapine

Pharmacokinetics

- Mirtazapine is well absorbed, with peak plasma levels being reached between 1 and 2 hours.
- The half- life is about 16 hours, and the daily dose can be given at night.
- Mirtazapine is extensively metabolized by the liver, and has only minor inhibitory effects on cytochrome P450 isoenzymes.

Mirtazapine

Efficacy

- The effective dose is usually between 10 mg and 45 mg daily.

Mirtazapine

Unwanted effects

- The common adverse effects are attributable to its potent antihistaminic actions, and include
  - drowsiness and dry mouth.
  - Increased appetite and body weight.
- Leucopenia is not common however monitoring is recommended.

Mirtazapine

Drug interactions

- May Potentiate other centrally acting sedatives.
- There is a theoretical risk that mirtazapine could reverse the therapeutic effect of α2- adrenoceptor agonists such as clonidine.

Trazodone

- Trazodone is a triazolopyridine derivative with complex actions on 5- HT pathways.
- It has some weak 5- HT- reuptake- inhibiting properties.
- Trazodone has antagonist actions at 5- HT2 receptors, but its active metabolite, m- chlorophenylpiperazine (m-CPP), is a 5- HT receptor agonist.
- Trazodone also blocks postsynaptic α1- adrenoceptors.
- Overall it has a distinct sedating profile.

Trazodone

- Pharmacokinetics :Trazodone has a short half- life (about 4–14 hours). It is metabolized by hydroxylation and oxidation, with the formation of a number of metabolites, including m-CPP.
- Efficacy of trazodone is improved if treatment is started at low doses (50 mg) and increased slowly to 300 mg over 2–3 weeks.
- Once- daily administration of the drug is often sufficient.
- The drug is usually given in the evening to take advantage of its sedative properties.
- Doses above 300 mg daily are usually better given in divided amounts.

Trazodone

Unwanted effects

- Sedation, which can result in significant cognitive impairment.
- Nausea and dizziness
- postural hypotension
- cardiac arrhythmias may be worsened in patients with cardiac disease.
- The most serious side effect of trazodone is **priapism**. This reaction is seen rarely (about 1 in 6000 male patients).

THANK YOU