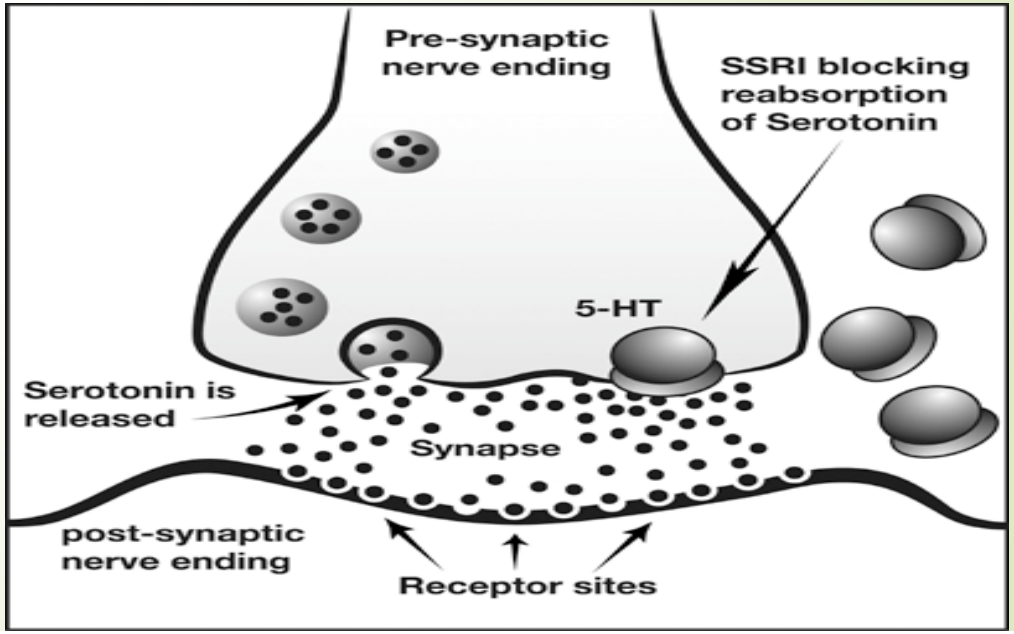
Antidepressants

By Dr. Swathi Swaroopa. B

- Depression is the most common of the affective disorders (disorders of mood rather than disturbances of thought or cognition);
- it may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions
- Antidepressants are the drugs used to treat depression

Medications for Depression

- The Aim of an Antidepressant is to stabilize and normalize the neurotransmitters in our brain. Neurotransmitters such as serotonin, dopamine and norepinephrine play a role in regulating our mood.



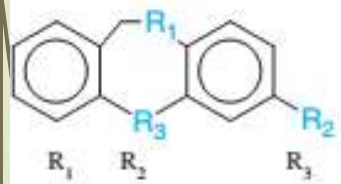
	Usual Adult Daily Dose (mg)	Neurotransmitter Effects[a]	Toxicity[b]
Tricyclic antidepressants			
Amitriptyline	75–200	NE, 5-HT	A, H, QRS, Sz
Amoxapine	150–300	NE, DA	A, H, Sz
Clomipramine	100–250	NE, 5-HT	A, H, QRS, Sz
Desipramine	75–200	NE	A, H, Sz
Doxepin	75–300	NE, 5-HT	A, H, QRS, Sz
Imipramine	75–200	NE, 5-HT	A, H, QRS, Sz
Maprotiline	75–300	NE	A, H, QRS, Sz
Nortriptyline	75–150	NE	A, H, QRS, Sz
Protriptyline	20–40	NE	A, H, QRS, Sz
Trimipramine	75–200	NE, 5-HT	A, H, QRS, Sz

Newer, noncyclic drugs			
Bupropion	200–450	DA, ?NE	Sz
Citalopram	20–40	5-HT	Sz, SS
Fluoxetine	20–80	5-HT	Sz, SS
Fluvoxamine	50–300	5-HT	Sz, SS
Mirtazapine	15–45	alpha-2	
Nefazodone	100–600	5-HT, alpha-2	H
Paroxetine	20–50	5-HT	Sz, SS
Sertraline	50–200	5-HT	Sz, SS
Trazodone	50–400	5-HT, alpha-2	H, Sz, SS
Venlafaxine	30–600	5-HT, NE	Sz, SS

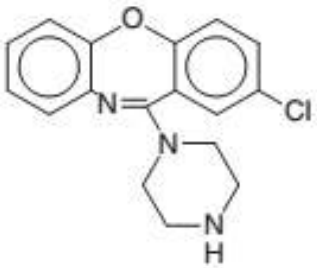
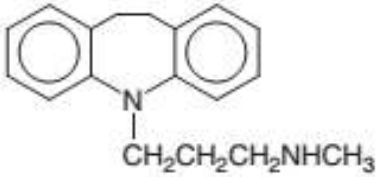
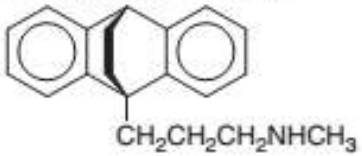
Classification

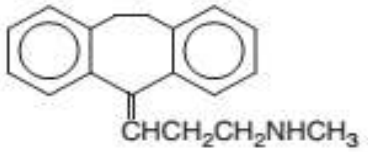
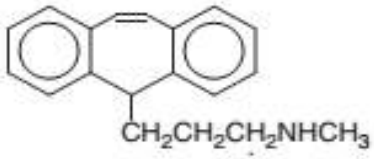
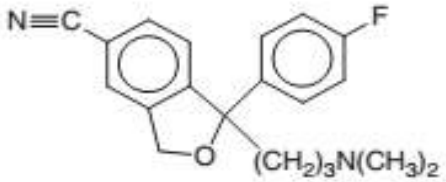
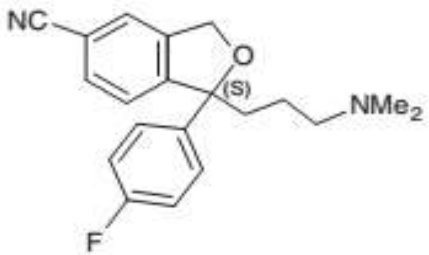
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs
- Monoamine oxidase inhibitors (MAOIs
- Atypical antidepressants

Antidepressants: Chemical Structures, Dose and Dosage Forms, and Side Effects

Nonproprietary Name (TRADE NAME)	Dose and Dosage Forms			Amine Effects	Side Effects								
	Usual Dose, mg/day	*Extreme Dose, mg/day*	*Dosage Form*		*Agitation*	*Seizures*	*Sedation*	*Hypo-tension*	*Anti-cholinergic Effects*	*Gastro-intestinal Effects*	*Weight Gain*	*Sexual Effects*	*Cardiac Effects*
Norepinephrine Reuptake Inhibitors: **Tertiary Amine Tricyclics**													
 R_1 R_2 R_3													
Amitriptyline (ELAVIL and others) C H $C{=}CH(CH_2)_2N(CH_3)_2$	100–200	25–300	O, I	NE, 5-HT	0	2+	3+	3+	3+	0/+	2+	2+	3+
Clomipramine (ANAFRANIL) C Cl $N{-}(CH_2)_3N(CH_3)_2$	100–200	25–250	O	NE, 5-HT	0	3+	2+	2+	3+	+	2+	3+	3+
Doxepin (ADAPIN, SINEQUAN) O H $C{=}CH(CH_2)_2N(CH_3)_2$	100–200	25–300	O	NE, 5-HT	0	2+	3+	2+	2+	0/+	2+	2+	3+
Imipramine (TOFRANIL and others) C H $N{-}(CH_2)_3N(CH_3)_2$	100–200	25–300	O, I	NE, 5-HT	0/+	2+	2+	2+	2+	0/+	2+	2+	3+
(+)-Trimipramine (SURMONTIL) C H $N{-}CH_2CH(CH_3)CH_2N(CH_3)_2$	75–200	25–300	O	NE, 5-HT	0	2+	3+	2+	3+	0/+	2+	2+	3+

Antidepressants: Chemical Structures, Dose and Dosage Forms, and Side Effects (*Continued*)

Nonproprietary Name (TRADE NAME)	Dose and Dosage Forms			Amine Effects	Side Effects								
	Usual Dose, mg/day	*Extreme Dose, mg/day*	*Dosage Form*		*Agitation*	*Seizures*	*Sedation*	*Hypo-tension*	*Anti-cholinergic Effects*	*Gastro-intestinal Effects*	*Weight Gain*	*Sexual Effects*	*Cardiac Effects*
Norepinephrine Reuptake Inhibitors:													
Secondary Amine Tricyclics													
Amoxapine (ASENDIN) 	200–300	50–600	O	NE, DA	0	2+	+	2+	+	0/+	+	2+	2+
Desipramine (NORPRAMIN) 	100–200	25–300	O	NE	+	+	0/+	+	+	0/+	+	2+	2+
Maprotiline (LUDIOMIL) 	100–150	25–225	O	NE	0/+	3+	2+	2+	2+	0/+	+	2+	2+

Nortriptyline (PAMELOR)	75–150	25–250	O	NE	0	+	+	+	+	0/+	+	2+	2+
													
Protriptyline (VIVACTIL)	15–40	10–60	O	NE	2+	2+	0/+	+	2+	0/+	+	2+	3+
													
Selective Serotonin Reuptake Inhibitors													
(±)-Citalopram (CELEXA)	20–40	10–60	O	5-HT	0/+	0	0/+	0	0	3+	0	3+	0
													
(+)- Escitalopram (LEXAPRO)	20–40	10–60	O	5-HT	0/+	0	0/+	0	0	3+	0	3+	0
													

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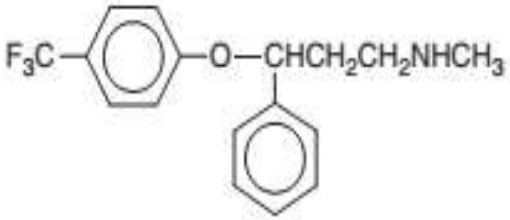
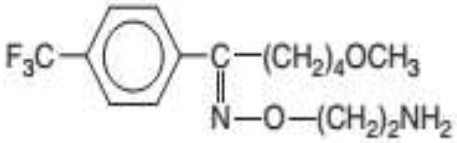
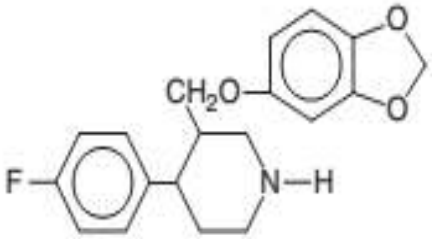
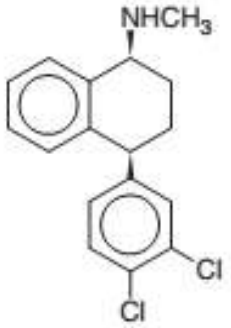
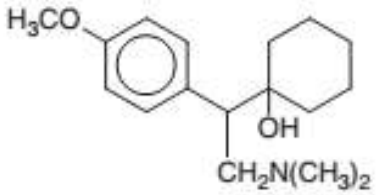
(±)-Fluoxetine (PROZAC)	20–40	5–50	O	5-HT	+	0/+	0/+	0	0	3+	0/+	3+	0/+
													
Fluvoxamine (LUVOX)	100–200	50–300	O	5-HT	0	0	0/+	0	0	3+	0	3+	0
													
(–)-Paroxetine (PAXIL)	20–40	10–50	O	5-HT	+	0	0/+	0	0/+	3+	0	3+	0
													

(+)-Sertraline (ZOLOFT)	100–150	50–200	O	5-HT	+	0	0/+	0	0	3+	0	3+	0

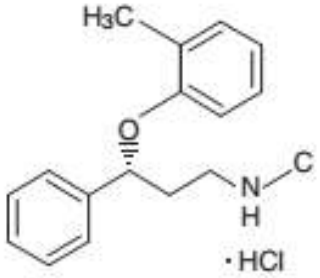


(±)-Venlafaxine (EFFEXOR)	75–225	25–375	O	5-HT, NE	0/+	0	0	0	0	3+	0	3+	0/+



Atypical Antidepressants

(–)-Atomoxetine (STRATTERA)	40–80 (children: 1.0–1.4 mg/kg)	20–150	O	NE	0	0	0	0	0	0/+	0	0	0



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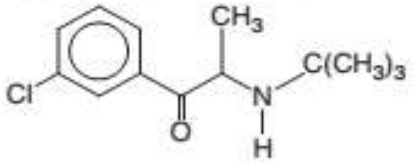
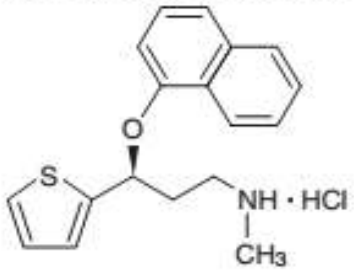
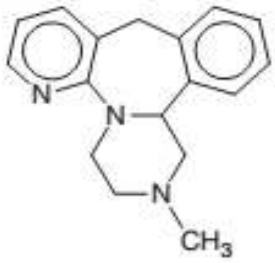
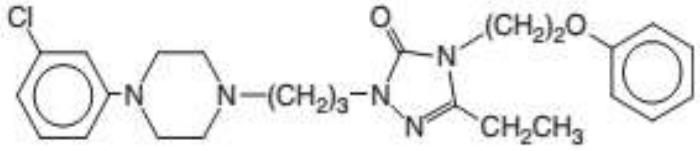
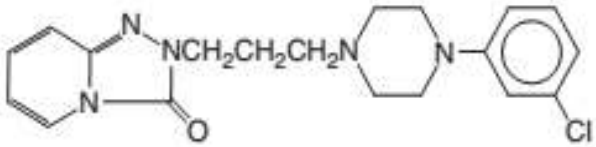
Bupropion (WELLBUTRIN)	200–300	100–450	O	DA, ?NE	3+	4+	0	0	0	2+	0	0	0
													
(+)-Duloxetine (CYMBALTA)	80–100	40–120	O	NE, 5-HT	+	0	0/+	0/+	0	0/+	0/+	0/+	0/+
													
(±)-Mirtazapine (REMERON)	15–45	7.5–45	O	5-HT, NE	0	0	4+	0/+	0	0/+	0/+	0	0
													

Nefazodone* (SERZONE)	200–400	100–600	O	5-HT	0	0	3+	0	0	2+	0/+	0/+	0/+

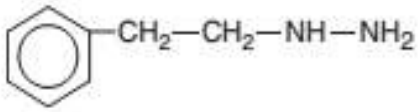


Trazodone† (DESYREL)	150–200	50–600	O	5-HT	0	0	3+	0	0	2+	+	+	0/+

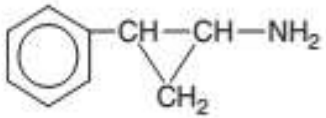


Monoamine Oxidase Inhibitors

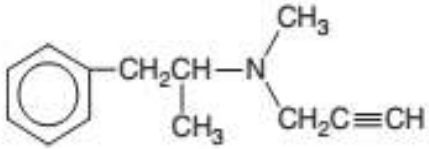
Phenelzine (NARDIL)	30–60	15–90	O	NE, 5-HT, DA	0/+	0	+	+	0	0/+	+	3+	0



Tranylcypromine (PARNATE)	20–30	10–60	O	NE, 5-HT, DA	2+	0	0	+	0	0/+	+	2+	0



(–)-Selegiline (ELDEPRYL)	10	5–20	O	DA, ?NE, ?5-HT	0	0	0	0	0	0	0	+	0



Cyclic Antidepressants

Possess a 3-ring molecular structure

Uses

- Depression ,
- Panic disorder,
- Social phobia,
- Bulimia,
- Narcolepsy,
- Attention deficit disorder,
- Obsessive compulsive disorder,
- Childhood enuresis, and
- Chronic pain syndromes.

Toxicokinetics

- Absorbed from the GI tract
- Volumes of distribution Vd is high (10 to 50 L/kg).
- Most of them bind to plasma protein alpha1-glycoprotein with varying affinity.
- Highly lipophilic, sparingly water soluble, and substantially metabolised by first-pass in the liver.

Toxicokinetics

- Metabolites retain significant pharmacologic activity until hydroxylation occurs by microsomal enzyme system.
- The half-lives of these compounds are highly variable (4 hrs to 93 hrs).
- Approximately 30% of the absorbed dose is eliminated by gastric and biliary secretion, while renal clearance accounts for 3 to 10% of the parent compound.

Mode of action and mechanism of toxicity

- Act by inhibiting voltage-gated sodium channels in myocardial cells,
- Blocking of H1, H2, and D2 receptors, as well as muscarinic receptors,
- Inhibiting alpha-adrenergic receptors
- Interacting with GABA receptors,
- Inhibiting the transport and reuptake of biogenic amines at nerve terminals

Mode of action and mechanism of toxicity

- The toxicity of cyclic antidepressants is mainly due to effects on
- Myocardium,
- CNS, and
- Peripheral vasculature.

Mode of action and mechanism of toxicity

- **Cardiovascular toxicity** is related to their sodium channel blockade and α-adrenergic blockade.
- TCAs bind to and inhibit the movement of sodium ions into the fast sodium channel thereby slowing phase O depolarization in the His-Purkinje system and ventricular myocytes.
- Results in slowed cardiac conduction by slowing the propagation of ventricular depolarization which is manifested as a prolonged QRS on the ECG

Mode of action and mechanism of toxicity

- TCAs inhibit outward potassium current by blocking potassium channels in phase 3, which ultimately results in prolongation of the QT interval
- Competitive blockade at muscarinic receptors and norepinephrine reuptake inhibition play a role in **Sinus tachycardia**
- Norepinephrine reuptake inhibition can lead to hypertension

Mode of action and mechanism of toxicity

- Prolonged blockade can cause depletion of norepinephrine from the presynaptic nerve terminal, and inhibition of α1-adrenergic receptors results in the subsequent **development of refractory hypotension and bradycardia** in cases of serious overdose.

B. Central nervous system effects

- **Sedation** and **coma** result in part from anticholinergic toxicity.
- **Seizures** result by inhibition of reuptake of norepinephrine or serotonin in the brain or other central effects
- Convulsions resulting from overdose are caused by complicated interactions within the brain due to altered concentrations of GABA, dopamine, noradrenaline and acetylcholine.

Usual Fatal Dose

- Serum drug level of more than 1000 ng/ml (10 to 20 mg/kg PO) is usually fatal.
- Ten times the therapeutic daily dose of a cyclic antidepressant is potentially fatal.
- Fatal poisonings have occurred in children following the ingestion of as little as 250 mg of imipramine or amoxapine.

Usual Fatal Dose

- Presence of following factors are more likely to cause Death in severe cyclic antidepressant overdose
  - Age > 30 years.
  - Serum drug level > 800 ng/ml (2880 mmol/L).
  - Ingestion of amitryptiline.
  - Heart rate > 120.
  - QRS duration > 100 ms.
  - QRS axis > 90°.
  - Terminal 40-ms axis > 135°.
  - QTc interval > 480 ms

Clinical presentation

- Anticholinergic effects
- It include sedation, delirium, coma, dilated pupils, dry skin and mucous membranes, diminished sweating, tachycardia, hyperthermia diminished or absent bowel sounds, and urinary retention.
- Myoclonic or metonymic jerking is common with anticholinergic intoxication and may be mistaken for seizure activity.

Clinical presentation

- Severe cardiac toxicity generally develops within six hours, although ECG changes may persist beyond 48 hours.
- Myocardial infarction
- Tachycardia, Hypotension.
- Prolongation of the PR, QRS, and QT intervals. Various degrees of atrioventricular(AV) block may be seen
- T-wave flattening or inversion, ST segment depression, right bundle branch block, junctional rhythm and atrioventricular block

Clinical presentation

CNS effects

- Seizures, agitation, hallucinations, confusion
- Coma is usually short-lived, and most patients waken within 24 hours.
- Miosis may be present in deeply comatose patients
- Rhabdomyolysis and renal failure may result from prolonged seizures or coma

- The muscular hyperactivity from seizures and myoclonic jerking, combined with diminished sweating, can lead to severe hyperthermia, resulting in rhabdomyolysis, brain damage, multisystem failure, and death

Clinical presentation

Others

- Peripheral neuropathy, polyradiculoneuropathy, and extrapyramidal manifestations.
- Pulmonary oedema is present in 10 to 15% of patients
- Metabolic acidosis may develop in patients with prolonged seizures or hypotension
- Neuroleptic malignant syndrome (NMS) has been reported.
- Respiratory depression

Clinical presentation

- Uncommon manifestations
- Fulminant hepatic failure, bowel ischaemia, and acute intestinal pseudo obstruction
- Pruritic erythematous rash, vesicular eruption, blistering and skin discolouration have also been reported.

Clinical presentation

- Symptoms associated with tricyclic antidepressant withdrawal may include nausea, diarrhoea, malaise, myalgias, headache, rhinorrhoea, anxiety, agitation, mania, insomnia, nightmares, arrhythmias and ventricular ectopy.

Diagnosis

- Serum tricyclic levels
- Monitor serum electrolytes, renal and hepatic function in patients with significant toxicity
- Follow CPK levels in patients with prolonged seizures or coma.

ECG changes

- A terminal 40 ms QRS axis of >120 degrees or an R wave in lead aVR of > 3 mm are thought to be a more sensitive indicator of tricyclic antidepressant toxicity than QRS interval
- Elevation of creatine kinase and lactic acid dehydrogenase levels.
- Chest X-ray to detect pulmonary oedema

Treatment

Supportive measures:

- Maintain airway and intubate if indicated.
- Monitor arterial blood gases.
- Administer oxygen if necessary.
- Treat hypotension with IV crystalloids, inotropes (dopamine), vasopressors (noradrenaline), etc. necessary.
- Intra-aortic balloons have been used successfully when pressors have failed

Treatment

Reduce drug absorption:

a. Stomach wash (within the first 6 hours).

b. Activated charcoal (1 gm/kg).

Enhance drug elimination:

a. Multiple-dose activated charcoal.

b. Diuresis and haemodialysis are not effective.

c. Haemoperfusion is not routinely recommended, but has been used in patients with severe intoxication.

Treatment

Treat convulsions:

a. Diazepam 0.1 mg/kg IV

b. Phenytoin 15 mg/kg IV infusion.

c. If seizures cannot be controlled with diazepam or phenytoin, or recur, administer phenobarbitone.

If phenobarbitone is ineffective, consider paralysis(by neuromuscular blocking agent) and/ or barbiturate coma.

Treatment

Treat arrhythmias:

Patients with arrhythmias or QRS widening- Serum alkalinisation to a pH of 7.45 to 7.55 using intravenous boluses of sodium bicarbonate is recommended.

Intubation and hyperventilation as an adjunct to sodium bicarbonate with careful monitoring of blood gases to avoid profound alkalaemia

Quinidine, disopyramide, and procainamide are type 1a and are contraindicated, as their effects on myocardial conduction are similar to that of the tricyclic antidepressants.

- Sinus tachycardia—supportive measures only.

- Supraventricular arrhythmias- 1 to 2 mEq/kg of sodium bicarbonate is administered as needed to achieve a physiologic pH, or slightly above (7.45 to 7.55).

Ventricular tachycardia-

- Lignocaine 1mg/kg IV, bolus, followed by infusion of 2 to 4 mg/min;
- Synchronized cardioversion if these measures are ineffective;
- isoprenaline infusion 0.5 to 5.0 mcg/min and
- overdrive pacing for torsade de pointes.

Ventricular fibrillation-Defibrillate;

- Sodium bicarbonate 1 to 3 mmol/kg, and hyperventilation for achieving a pH of 7.45 – 7.50;
- 1: 1000 adrenaline,
- 0.5 to 1.0 mg IV; lignocaine 1 mg/kg IV bolus, followed by 2 to 4 mg/min infusion;
- Beta blockers if these measures are ineffective.

Bradycardia or heart block—alkalinise to 7.40 to 7.45 pH; isoprenaline; pacemaker.

Refractory cardiac arrest—basic and advance life support for a minimum of 1 hour; alkalinise to 7.5 pH.

- Hypertonic saline has been found to be useful in some cases.
- Physostigmine use in tricyclic antidepressant overdose is controversial because it can lead to seizures and fatal dysrhythmias (recommended to treat only when life-threatening symptoms that have been unresponsive to other therapies).
- Use of flumazenil in the setting of tricyclic antidepressant overdose has been associated with the onset of seizures and ventricular arrhythmias

Selective Serotonin Reuptake Inhibitors (SSRI) & selective serotonin-noradrenaline reuptake inhibitors (SNRIs),

- These are second generation of antidepressant drugs and are much safer and better tolerated than the first generation drugs (cyclics and monoamine-oxidase inhibitors).

- SSRI-citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, oxaflozane, paroxetine, pizotifen, sertraline.

- SNRIs- venlafaxine, milnacipram, and duloxetine

Uses

- Depression
- Panic disorder
- Obsessive-compulsive disorder
- Sleep disorders
- Migraine
- Substance abuse.

Toxicokinetics

- SSRIs (except paroxetine and sertaline-cz of slower absorption toxicity also delayed) are rapidly absorbed on oral administration
- Peak plasma concentrations reach within 2 to 8 hours depending on the drug
- Sertraline; peak plasma concentrations are reached approximately 5 to 8 hours after oral dosing.
- SSRIs are metabolized in the liver by cytochrome P-450 mixed function oxidase (MFO) microsomal enzymes.

- They are highly bound to plasma proteins and have a large volume of distribution.
- Protein binding ranges from 50% (for citalopam) to 99% (for sertraline).
- Fluoxetine binds to plasma proteins to the extent of 94%.
- Half-lives for SSRIs are variable, but most have a half-life of 20 to 24 hours.

- A notable exception is fluoxetine (Prozac) and its active metabolite, norfluoxetine, which have half-lives of 2 to 4 days and 8 to 9 days, respectively.

- Patient's regimen must not occur until 2 to 3 weeks after discontinuation of an SSRI. Some recommend a 5-week "wash-out" period for fluoxetine prior to initiation of an MAOI.

Mechanism of action

- The SSRIs specifically inhibit the reuptake of serotonin, thereby potentiating the activity of neuronally released serotonin.
- They also alter the sensitivity of serotonin subtype 5HT1A or 5HT1C receptors.

Mechanism of action

- The physiologic manifestations of SS are largely due to stimulation of $5HT_{1a}$ and $5HT_2$ receptors, with the symptoms of serotonin toxicity arising from the specific location of the 5HT receptors in the body.

- For example, serotonergic projections to the thalamus and cortex result in effects on sleep-wake cycles, mood, thermoregulation, appetite, pain perception, and sexual function.

- Excess 5-HT in these pathways causes the mental status changes, confusion, agitation, ataxia, and fever associated with SSRI toxicity and SS.

Mechanism of action

- Toxicity of descending pathways to the brainstem and medulla results in hyperreflexia, myoclonus, and tremor.
- Seizures are rare in SSRI overdose, with the exception of citalopram, which has an increased risk of inducing seizures in both adults and children.
- Autonomic nervous system effects include diaphoresis, mydriasis, hypertension, tachycardia, hyperthermia, piloerection, and muscular rigidity.

Mechanism of action

- Cardiovascular effects most commonly include sinus tachycardia, flushing, hypertension, and in rare cases, hypotension.
- Dose-dependent QT prolongation has been reported with citalopram (Celexa).
- Citalopram is contraindicated in individuals with congenital long QT syndrome, and the dose should not exceed 40mg daily. [18]

Mechanism of action

- Due to the high levels of serotonin in gastric and intestinal mucosal enterochromaffin cells, the most common minor adverse effects of SSRI therapy are gastrointestinal;
- eg, abdominal cramping, nausea, and diarrhea.
- SSRIs have also been shown to moderately increase the risk of upper gastrointestinal bleeding.

Mechanism of action

- Most agents cause CNS depression.
- Serotonin uptake inhibitors (often called selective serotonin reuptake inhibitors or SSRIs) such as fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine produce the "serotonin syndrome"
- None of the drugs in this group has significant anticholinergic effects
- Anorexia, dry mouth, nausea, vertigo, blurred vision, tremor, drowsiness, sexual dysfunction, seizures; suicidal ideation, mania, and paranoia; extrapyramidal effects;

Clinical presentation

- Signs and symptoms that manifest in the neuromuscular, autonomic nervous, and gastrointestinal systems, in which concentrations of serotonin receptors are highest

Clinical presentation

- Cardiac arrhythmias; hyponatraemia and SIADH; and serum sickness or flu-like symptoms.
- Serotonin syndrome: which increase serotonin availability
- SSRIs may cause the development of this syndrome when used alone, or (more commonly) when administered along with other serotonergic agents especially monoamine oxidase inhibitors (MAOIs).

- Main features include agitation, restlessness, confusion, disorientation, hallucinations, drowsiness or insomnia, tachypnoea, flushing, abdominal pain, ataxia, tremor, hypomania, myoclonus, muscle rigidity, opisthotonus, trismus, hyperactivity, convulsions, sweating, salivation, tachycardia, mydriasis, nystagmus, teeth chattering, hyper- or hypotension, hyperpyrexia, coma and diarrhea

- Hyperthermia is characteristic of serotonin syndrome


opisthotonous

- Serotonin syndrome has many similarities with neuroleptic malignant syndrome (NMS)

- NMS tends to have a slower onset and more prolonged duration of symptoms. Also, it is more frequently associated with fever and muscle rigidity than serotonin syndrome.

- The syndrome usually occurs in the first 2 hours of the first dose of the drug and usually resolves within 6 to 24hours of stoppage of the medication

- Sometimes however, complications ensue including metabolic acidosis, lactic acidosis, rhabdomyolysis, myoglobinuria, renal and hepatic dysfunction, DIC, or ARDS.

- Abdominal pain, nausea, vomiting, diarrhoea, vertigo, lethargy, insomnia, diplopia, CNS depression, tremors, and rarely convulsions
- ECG abnormalities-junctional rhythm, bigeminy and ventricular tachycardia, and QTc prolongation associated with ventricular tachycardia
- Left bundle branch block with citalopram

Abrupt withdrawal symptoms

- Vertigo, nausea, vomiting, fatigue, and myalgia
- Discontinuation syndrome of dizziness, lightheadedness, insomnia, fatigue, anxiety, agitation, nausea, headache, and sensory disturbances with **fluoxetine.**
- Fatigue, nausea, abdominal cramps, diarrhoea, shortness of breath, memory impairment, dizziness, insomnia, chills, headache, eye discomfort, tinnitus, ataxia, abnormal sensations with **sertraline therapy**.
- Paroxetine exposure in utero has resulted in a neonatal syndrome with effects including jitteriness, vomiting, irritability, hypoglycaemia, and necrotising enterocolitis

Treatment

- Involves supportive measures.
- Syrup of ipecac is contraindicated, while stomach wash is usually not necessary.
- Monitor for evidence of serotonin syndrome, including seizures or persistent lethargy or arrhythmias.

- Sodium bicarbonate may be useful in treating QRS prolongation or arrhythmias.
- A reasonable starting dose is 1 to 2 mEq/kg intravenous bolus, repeated as necessary.
- Monitor arterial blood gases to maintain a pH of 7.45 to 7.55.
- Because of the large volume of distribution and high degree of protein binding of SSRIs, haemodialysis, forced diuresis, haemoperfusion and exchange transfusion would not be expected to be useful in overdose.

Diagnosis for syndrome

- Serum electrolytes, glucose, renal function tests, CK and an ECG are recommended in all patients with suspected serotonin syndrome.

- Obtain liver function tests, PT or INR, platelets, and arterial blood gases in patients with severe hyperthermia, hypotension or other severe effects.

Sternbach's diagnostic criteria for serotonin syndrome

At least three of the following features

- Mental status changes (confusion, hypomania),
- agitation,
- myoclonus,
- hyperreflexia,
- sweating,
- shivering,
- tremor,
- diarrhoea,
- Incoordination and fever.

Hunter serotonin toxicity criteria:

Following the use/overdose of a serotonergic agent, a diagnosis of serotonin toxicity can be made if the patient meets any of the following 5 criteria:

- If the patient has spontaneous clonus.
- If the patient has inducible clonus, and agitation or diaphoresis.
- If the patient has ocular clonus, and agitation or diaphoresis.
- If the patient has tremor and hyperreflexia.
- If the patient is hypertonic, and has a temperature greater than 38°C and ocular clonus or inducible clonus.

- It was found that the presence of a temperature equal or greater than 38.5°C and/or marked hypertonia or rigidity (particularly truncal) indicated severe serotonin toxicity with a high risk of progression to respiratory compromise.

Treatment of serotonin syndrome:

- Benzodiazepines for agitation.
- Rapid external cooling.
- Benzodiazepines or barbiturates for convulsions.
- Neuromuscular blockade (with non-depolarizing paralytics) in severe cases.
- Nitroprusside for severe hypertension; noradrenaline, adrenaline, or (NOT dopamine) for severe hypotension.
- Benefit may be obtained in some cases with cyproheptadine (4 mg/hr), methysergide (2 mg twice daily), or propranolol.
- Chlorpromazine has also been used to treat cases of serotonin syndrome.

Monoamine Oxidase Inhibitors (MAOIs)

- MAOIs have been largely replaced by the cyclic antidepressants for the treatment of a variety of psychiatric disorders

- MAOIs include clorgyline, isocarboxacid, iproniazid, lazabemide, moclobemide, pargyline, phenelzine, pimozide, selegiline, toloxatone, and tranylcypromine

- Irreversible MAOIs such as clorgyline, isocarboxacid, phenelzine, tranylcypromine, and selegiline

Uses

- Depression,
- Agoraphobia,
- Anxiety disorders,
- Bulimia,
- Migraine,
- Panic disorders,
- Obsessive-compulsive disorders,
- Phobic disorders,
- Narcolepsy and Parkinson’s disease

Toxicokinetics

- MAOIs are rapidly and completely absorbed orally reaching peak blood levels within 2 h.
- MAOIs are acetylated in the liver to many active and inactive metabolites.
- The volume of distribution is estimated to range from 1 to 4 l /kg
- The inactive metabolites are excreted by the kidneys.
- The elimination half-lives of MAOI parent compounds range from 15 min to 3.5 h.

Mode of Action

- Two categories of MAOs exist: MAO-A and MAO-B
- Monoamine oxidase-A enzyme, located primarily in the placenta, intestines and liver and Monoamine oxidase enzyme B, located primarily in the platelets, brain.
- The MAOIs act (obviously) by inhibiting monoamine oxidase which is a flavin-containing enzyme.

Mode of Action

- MAO-A which is found in the liver and the intestinal wall, metabolizes tyramine and therefore limits its entry into the systemic circulation

- Monoamine oxidase oxidatively deaminates and inactivates monoamines, some of which are essential as neurotransmitters or modulators of nervous system transmission.

e.g. noradrenaline, dopamine, adrenaline, and serotonin

Mode of Action

Toxicity results from release of

- Excessive neuronal stores of vasoactive amines,
- Inhibition of metabolism of catecholamines or
- Interacting drugs, or absorption of large amounts of dietary tyramine(which in turn releases catecholamines from neurons)

- As a result of MAO inhibition, the pool of noradrenaline in the presynaptic sympathetic nerve terminal is expanded which causes the elevation of CNS noradrenaline and dopamine.

Mode of Action

- This is presumed to be the reason for the antidepressant effect of MAOIs.

- Some MAOIs are selective for the monoamine oxidase-A.
- Others are selective for the monoamine oxidase-B.

- Others are non-selective. Selectivity is lost in overdose.
- Meclobemide (reversible) and clorgyline (irreversible)are selective MAO-A inhibitors.
- Lazabemide, pargyline and selegiline are selective MAO B inhibitors.
- Phenelzine, tranylcypromine and isocarboxazid are non-selective MAOIs.

Toxic effects

- Overdose presentation will be delayed upto 12 hours or more
- Anxiety, flushing, headache, nausea, tachycardia/bradycardia, hypertension/hypotension, agitation, delirium, hallucinations, nystagmus, tremors, muscle rigidity, trismus, opisthotonus, convulsions, hyperthermia, profuse sweating, tachypnoea, respiratory depression, and cardiovascular collapse.
- Pupils may be dilated and minimally reactive to light after MAOI overdose or MAOI-induced serotonin syndrome. Ping pong gaze (rhythmic and pendular, conjugate horizontal eye movements) has been described in some cases of MAOI overdose

Toxic effects

- Death occurs in some cases from complications such as ARDS, DIC, and myoglobinuric renal failure.
- Overdose complicated by rhabdomyolysis or hypotension often leads to myoglobinuria, acute tubular necrosis and renal failure.
- Coagulopathy, haemolysis and thrombocytopenia may develop with MAOI overdose.

Toxic effects

- The newer reversible, selective inhibitors of MAO-A (e.g. moclobemide) appear to have a less severe toxicity profile when used in overdose.

- Chronic use of these drugs (especially phenelzine and tranylcypromine) can lead to withdrawal reaction on abrupt cessation, characterised by anxiety, depression, confusion, hallucinations, nausea, vomiting, diarrhea and chills.

Fatal Dose

- Ingestion of greater than 2 to 3 mg/kg of an MAOI should be considered potentially life-threatening, and 4 to 6 mg/kg or greater is consistent with reported fatalities.

Treatment

- Due to the potential for delayed and severe toxicity, any patient with a history of acute MAOI overdose, even in the absence of symptoms in the first 4 to 6 hours, should be admitted for ICU monitoring and remain until stable for 24 hours.

The following measures are suggested for the treatment of adverse as well as toxic effects of MAOIs:

- Maintenance of airway, oxygen, assisted ventilation, etc. (as needed).
- Cardiac monitoring.
- Electrolytes should be monitored closely, particularly for hyperkalaemia.

- Monitor liver and renal function, and CPK level.
- Severe hypertension should be treated with IV sodium nitroprusside or phentolamine.
- Methyldopa and guanethidine are contraindicated as they may potentiate hypertensive crises.
- Hypotension (or shock) can be managed by IV fluids, and vasopressors such as noradrenaline or dopamine, i.e. direct-acting alpha-adrenergic agonists

- Ventricular tachyarrhythmias usually respond to lignocaine, phenytoin, or procainamide.
- If the patient is seen within a short time of overdosing, gut decontamination must be carried out—lavage, activated charcoal, cathartics.
- Acidic diuresis and haemodialysis have been tried with varying degree of success but are probably best avoided.

- Although MAO inhibitor excretion is enhanced by forced acid diuresis, there is no evidence that it is effective in reducing the severity of an overdose.
- In fact, such a procedure may be dangerous in this situation because of the instability of the cardiovascular system.
- Muscle rigidity and agitation may respond to phenothiazines such as chlorpromazine.
- Diazepam is however safer, and phenytoin is a good alternative

- In the presence of intractable muscle rigidity, neuromuscular paralysis with pancuronium may be necessary.*
- Seizures are best treated with benzodiazepines or barbiturates.
- Hyperthermia can be managed with paracetamol and external cooling. In severe cases (malignant hyperthermia type), IV dantrolene is given at a dose of 2.5 mg/kg, every6 hours, for 24 hours.
- As an alternative, bromocriptine can be administered.

- For rhabdomyolysis: Early aggressive fluid replacement is the mainstay of therapy and may help prevent renal insufficiency.
- Diuretics such as mannitol or furosemide may be needed to maintain urine output.
- Urinary alkalinisation is not routinely recommended.

- Treat acute metabolic disturbances such as hyperkalaemia, hyperthermia, and hypovolaemia.
- Control seizures, agitation, and muscle contractions.
- Patients should be placed on special diets low in tyramine- containing foods for at least 2 weeks post-exposure.

- Drug interactions and adverse effects of all antidepressants
- Atypical antidepressants

Thank you