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CLINICAL TOXICOLOGY

848806

ANTIDEPRESSANT TOXICITY

TCA TOXICITY

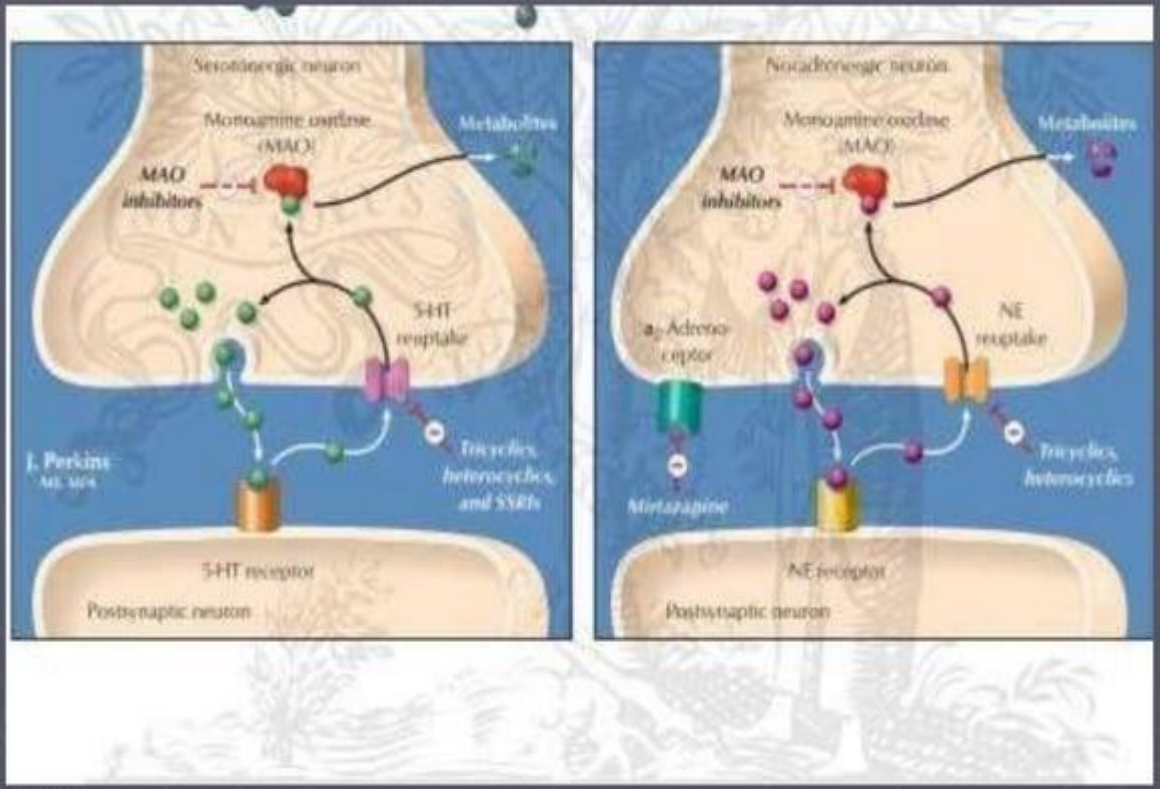
PREPARED BY:
Dr. Monvi Sachdev
Assistant Professor
PharmD

Tricyclic antidepressants

- Tricyclic antidepressants (TCAs) were one of the most important causes of mortality resulting from poisoning until 1993 and still continue to be a major cause of death from self-poisoning.
- Although selective serotonin reuptake inhibitors (SSRIs) have overtaken them to become first-line therapy for depression, TCAs remain widely prescribed for depression and an increasing number of other indications including anxiety disorders, attention deficit disorder, pediatric enuresis, and chronic pain syndromes.

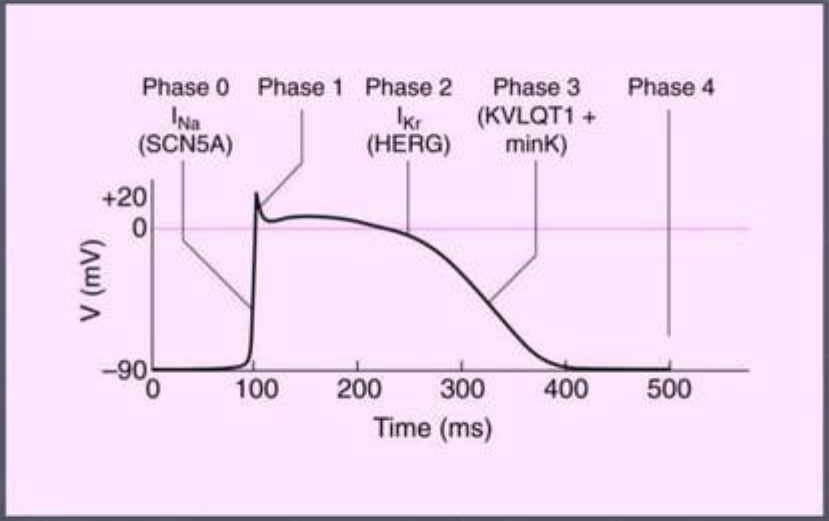
pathophysiology

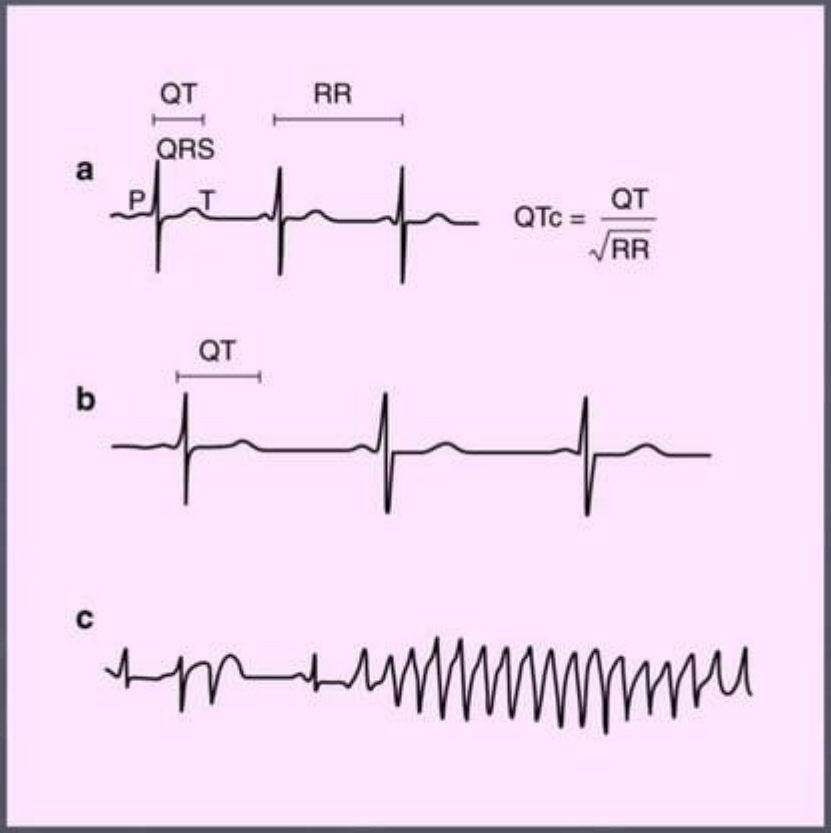
- inhibiting the presynaptic reuptake of biogenic amines, primarily serotonin and norepinephrine.
- TCAs affect many other receptor systems, resulting in many of their toxic effects. They are antagonists at muscarinic acetylcholine receptors, peripheral alpha-adrenergic receptors, and histamine receptors.
- The cardiovascular toxicity, which is the most common cause of morbidity and mortality from TCAs, is related to their membrane-stabilizing effect through sodium channel blockade and alpha-adrenergic blockade.

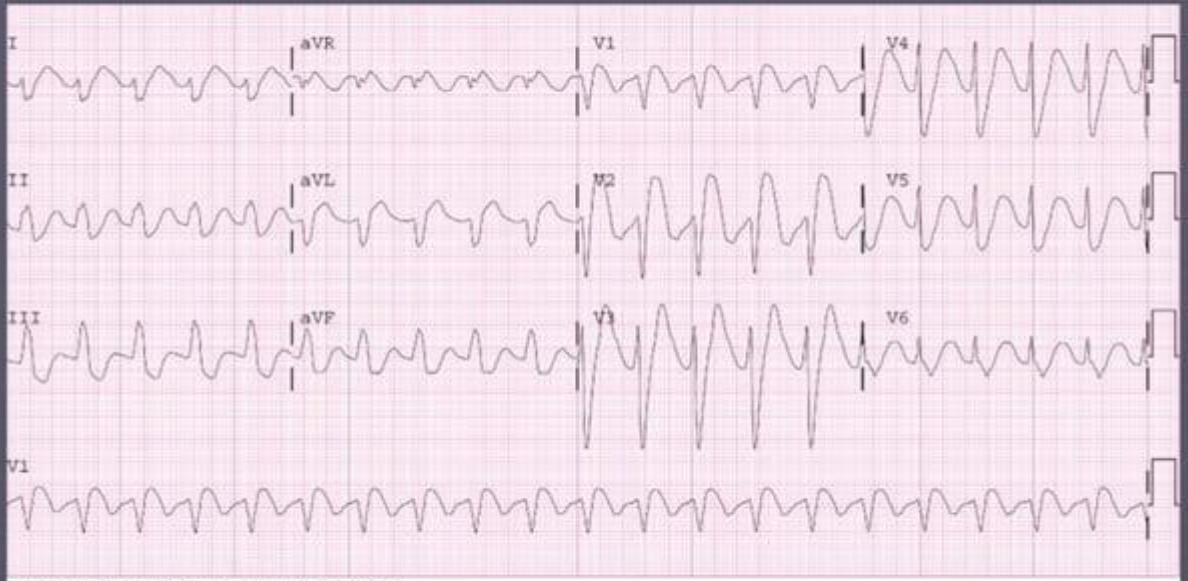

Serotonergic neuron
Monoamine oxidase (MAO)
MAO inhibitors
Metabolites
5-HT reuptake
Tricyclics, heterocyclics, and SSRIs
5-HT receptor
Postsynaptic neuron
Noradrenergic neuron
Monoamine oxidase (MAO)
MAO inhibitors
Metabolites
NE reuptake
Tricyclics, heterocyclics
Mirtazapine
NE receptor
Postsynaptic neuron

- 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. This results in slowed cardiac conduction by slowing the propagation of ventricular depolarization which is manifested as a prolonged QRS on the ECG.

- Specifically, TCAs inhibit outward potassium current by blocking potassium channels in phase 3, which ultimately results in prolongation of the QT interval.


Phase 0
I_{Na}
(SCN5A)
Phase 1
Phase 2
I_{Kr}
(HERG)
Phase 3
(KVLQT1 +
minK)
Phase 4
+20
0
–90
V (mV)
0
100
200
300
400
500
Time (ms)


QT
RR
QRS
a
P
T
QTc = QT / √RR
QT
b
c



Source: Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine, 3rd Edition:* http://www.accessmedicine.com

- Sinus tachycardia is the most common cardiac disturbance seen following TCA overdose. Competitive blockade at muscarinic receptors plays a primarily role, although norepinephrine reuptake inhibition also contributes to the tachycardia.
- Although initial reuptake inhibition of norepinephrine in the central and peripheral nervous systems can result in a patient initially presenting with hypertension and tachycardia, prolonged blockade can cause depletion of norepinephrine from the presynaptic nerve terminal, which results in the subsequent development of refractory hypotension and bradycardia in cases of serious overdose.

- Refractory hypotension, caused primarily by the inhibition of alpha1-adrenergic receptors, is one of the most common causes of mortality seen with TCA overdose.
- This hypotension can be exacerbated by hypoxia, acidosis, and volume-depletion.

- Neurologic effects of TCAs, including agitation and delirium, primarily result from CNS blockade of muscarinic receptors

Clinical manifestations

- Clinical symptoms of antidepressant toxicity often progress rapidly and unpredictably, and, many times, patients present asymptomatically or minimally symptomatic and progress to life-threatening cardiovascular and neurologic toxicity within an hour.

NERVOUS SYSTEM

- Early manifestations include altered mental status, delirium, psychotic behavior, and agitation, and hallucinations. These symptoms can later proceed rapidly to coma.
- Drowsiness, slurred speech, sedation and weight gain (H_1 block)
- Seizures are usually generalized and often occur within 1-2 hours of ingestion. Seizures occurs in 4% of patients with overdose and in 13% of fatal cases

Cardiovascular effects

- Hypertension (early)
- Hypotension
- Dysarrhythmia
- Delayed conduction
- Long QT

- urinary retention; hyperthermia; dry, flushed skin, mydriasis, and constipation from anticholinergic effect.

- Tricyclic antidepressant toxicity can be caused by either an acute ingestion or a chronic ingestion.
- Toxicity secondary to chronic ingestions usually presents with symptomatology that is an exaggeration of the usual side effects of tricyclics.

TREATMENT

- ECG is the most important for diagnosis and follow up.
- Dysrhythmias

- Sodium bicarbonate is the first-line therapy if TCA ingestion is known or strongly suspected (life saving)..... why?

- Procainamide, quinidine, beta-blockers, and calcium channel blockers are contraindicated.

- Hypotension
- Hypotension is treated with sodium bicarbonate and intravenous fluids.
- Vasopressors are recommended for refractory hypotension.
- Seizures
- Benzodiazepines
- Hemodialysis is not effective why?

SSRIs toxicity

- Selective serotonin reuptake inhibitors (SSRIs), widely prescribed medications for the treatment of depression, obsessive-compulsive disorder, anorexia nervosa, panic disorder, anxiety, and social phobia.
- have a high therapeutic to toxicity ratio.
- However, although they are associated with less toxicity than tricyclic antidepressants, they are often involved in co-ingestions that can precipitate the potentially lethal serotonin syndrome (SS).
- fluoxetine (Prozac), sertraline, paroxetine, citalopram, escitalopram, and fluvoxamine

- SS represents a group of signs and symptoms that manifest in the neuromuscular, autonomic nervous, and gastrointestinal systems, in which concentrations of serotonin receptors are the highest.
- Less frequently, SS can be precipitated by an overdose of a single SSRI.

- SS is often caused by combinations of SSRIs with other proserotonergic agents, including the following:
- Monoamine oxidase inhibitors (MAOIs)
- TCAs
- Trazodone (Desyrel)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs) Venlafaxine and duloxetine
- Norepinephrine-dopamine reuptake inhibitors
- Lithium
- Opioids
- Amphetamines and cocaine

pharmacokinetics

- SSRIs are metabolized in the liver by cytochrome P-450
- They are highly bound to plasma proteins and have a large volume of distribution. Peak plasma levels are reached in 2-8 hours.
- Half life variable but about 22 hours. A notable exception is fluoxetine (Prozac) and its active metabolite, norfluoxetine, which have half-lives of 2-4 days and 8-9 days, respectively.

Complications of toxicity

- Seizures
- Aspiration pneumonia
- Rhabdomyolysis
- Disseminated intravascular coagulation
- Acute renal failure
- Respiratory failure

Signs and symptoms

- 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

1. mental status changes, confusion,
2. agitation, ataxia
3. Fever
4. Toxicity of descending pathways to the brainstem and medulla results in hyperreflexia, myoclonus, and tremor.

- Autonomic nervous system effects include diaphoresis, mydriasis, hypertension, tachycardia, hyperthermia, piloerection, and muscular rigidity.
- Cardiovascular effects most commonly include sinus tachycardia, flushing, hypertension, and in rare cases, hypotension.
- Dose-dependent QT prolongation has been reported with citalopram (Celexa).

- 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.

- Most cases fully resolve without residual deficits if supportive care has been provided. The prognosis is generally favorable. Most fatalities occur within the first 26 hours. Patients who remain asymptomatic for 6-8 hours after ingestion are unlikely to require further treatment.

Patient education

- All patients started on SSRIs by psychiatrists or primary care physicians should be educated about symptoms of serotonin toxicity and SS.
- Patients should be counseled about potential interactions among any medications they take—including over-the-counter medications (particularly dextromethorphan-containing cold remedies), illicit drugs (especially

amphetamines, cocaine, and mescaline), and herbal dietary supplements (eg, St. John's wort, ginseng)—that might affect the patient's tissue concentrations of serotonin.

- A minimum of 2 weeks should elapse between termination of an SSRI or MAOI and initiation of a new one.
- Drugs with a longer half-life (ie, fluoxetine) require up to 5 weeks of wash out.
- Elderly patients and those taking liver Mixed Function Oxidases inhibitors may require an extended wash-out period as well.

Managment

- ABCD
- Treat hyperthermia with cooling blankets, fans, ice packs, and IV fluids. Antipyretics are not indicated.
- Administer activated charcoal if a potentially lethal amount or combination of proserotonergic agents has been ingested and if the presentation is within 1-2 hours.
- Treat neuromuscular abnormalities with benzodiazepines.

- Severely ill patients can be treated pharmacologically with 5HT antagonists, such as cyproheptadine. It is available only in oral form, which can be crushed and infused via nasogastric tube. Caution should be exercised in hyperthermic patients, because cyproheptadine has anticholinergic properties and theoretically can worsen hyperthermia.

- Autonomic instability requires treatment with short-acting agents that are amenable to titration, such as nitroprusside and esmolol.
- Treat rahabdomyolysis with aggressive hydration, and alkalinize urine with sodium bicarbonate for renal protection.
- Symptomatic patients with citalopram/escitalopram overdose may require admission to a monitored bed for 24 hours because of the risk of delayed toxicity, which can cause prolonged QT interval and consequent cardiac dysrhythmias (eg, torsades de pointes).

Toxicity of MAOIs

- Two categories of MAOs exist: MAO-A and MAO-B.
- The widely prescribed MAOIs are rather unique in the fact that they bind irreversibly (moclobemide is an exception, since it is a reversible inhibitor) at their sites of action, are eliminated from circulation by such binding
- Additionally, MAOs are located in many tissues, including the gut wall.

- MAOIs absorbed through the gastrointestinal tract bind significantly to MAO in the gut mucosa and liver producing significant first pass effect.
- MAO in the gut mucosa essentially breaks down potentially toxic dietary monoamines, such as tyramine, and "prevent" their absorption.
- The inhibition of gut MAO by these medications coupled with ingestion of substances containing tyramine may produce significant toxicity.

Tyramine-containing foods

- Aged cheeses
- Aged, pickled, or smoked meats (eg, salami) or fish
- Yeast extracts
- Beer
- Red wine more than white wine
- Avocado
- Ginseng

- Recently, a transdermal preparation of a "selective" MAO-B drug, selegiline, has appeared on the market, which by by-passing the first pass effect of gut and hepatic MAOI effects, appears to produce antidepressant effects with significantly reduced risk for dietary-induced toxicity

MAOI poisoning is classified into the following 3 subtypes:

- Actual poisoning from an overdose is uncommon
- Drug-food interaction is so-called tyramine reaction or cheese reaction. It is usually rapid in onset, occurring within 17-90 minutes after ingestion. Most symptoms resolve in 6 hours. Fatalities have been reported due to complications from hypertensive emergencies.
- Drug-drug interaction

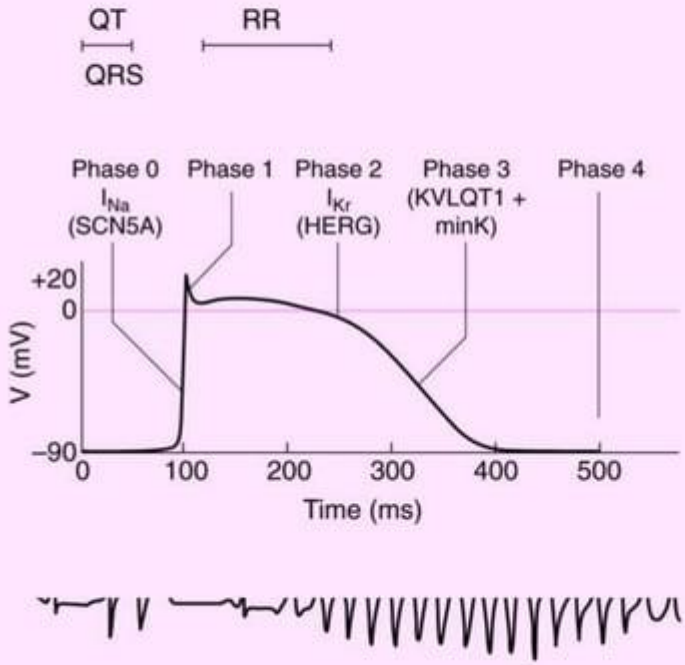
Symptoms are that of increased catecholamines activity

- hypertension, tachycardia, tremors, seizures, and hyperthermia.

Managment

- Decontamination because of the potential for severe toxicity and lack of antidotes, an aggressive decontamination is very important.
- Consider gastric lavage, particularly in patients with recent ingestion (within an hour).
- Administer charcoal: Secure unprotected airway prior to lavage and charcoal administration if needed.
- Hemodialysis is less effective

- Fluid therapy is of paramount importance. Patients may be significantly dehydrated from hyperthermia.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minK)
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V (mV)
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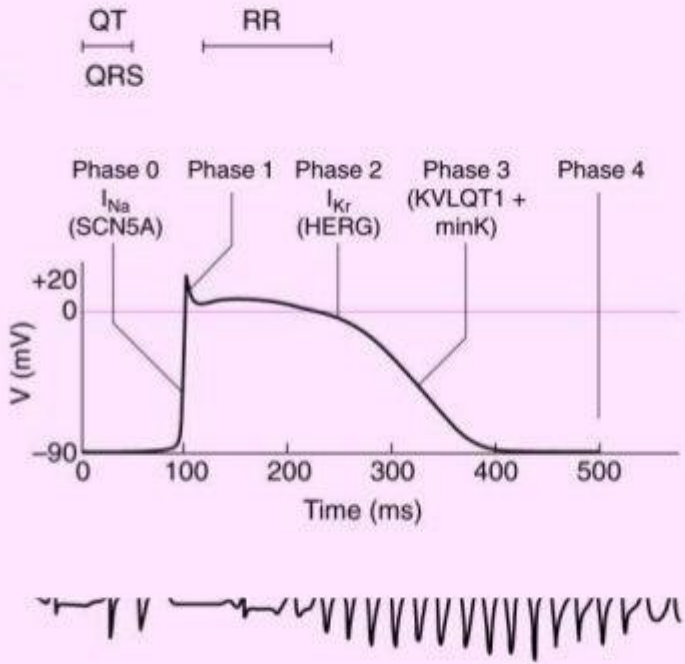
Time (ms)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