Lecture 3: Psychiatric drugs.

Goals:

The objectives are not given.

Focus on the mechanisms, doctor said 90% of MCQ is about mechanisms.

Helpful clips for your own Benefit:

What Causes Depression.mov **(2:51).**
https://www.youtube.com/watch?v=InNhDfDfl5c

The Brain—Lesson 2—How Neurotransmission Works. **(1:34).**
https://www.youtube.com/watch?v=p5zFgT4aofA

How Do Antidepressants Work ? **(1:25).**
https://www.youtube.com/watch?v=G4r3qCkLUDQ

References:

Simpson's Forensic Medicine - Med432 - Notes.

Introduction : Simpson's Forensic Medicine

- Large doses of any medicine may cause cardio- toxicity or neurotoxicity but when toxicity occurs it usually does so as a result of the drug's shared ability to stimulate the same set of brain receptors as are stimulated by abused drugs.

- Members of the benzodiazepine family (alprazolam, clonazepam, diazepam, zolpidem) bind the benzodiazepine receptor located on the γ-aminobutyric acidA (GABAA) receptor acting synergistically with opiates to depress respiration.
- Second- and third-generation antidepressants cause 'serotonin syndrome', but the underlying mechanism is just the same as that of cocaine the antidepressants prevent the reuptake of serotonin, leading to the accumulation of excess serotonin in the synaptic cleft between nerve endings.

- When prescription medications are considered, two disorders have come to predominate most discussion: serotonin syndrome and QT interval prolongation.

Antidepressant Overdose!

What's Available?

1: MAOI's (Monoamine Oxidase Inhibitors), no longer used, it has many side effects.

2: TCA (Tricyclic Antidepressants) , no exam comes without it, you should know every thing about it.

3: SSRI (Selective serotonin reuptake inhibitors)

4: SNRI (serotonin norepinephrine reuptake inhibitors). New one, safe.

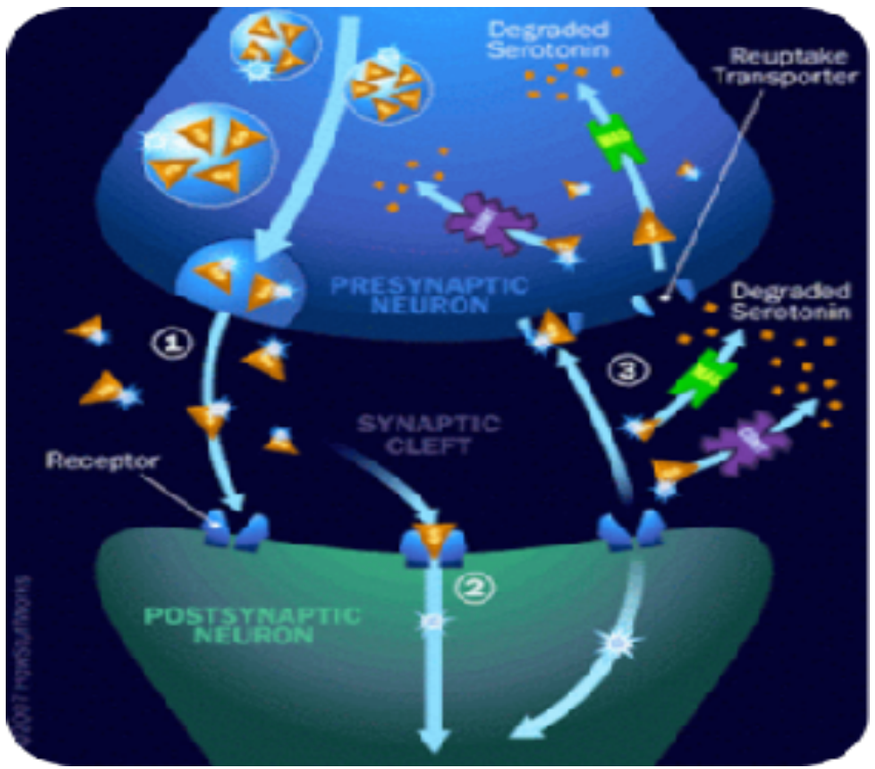
Summary Of Antidepressant:

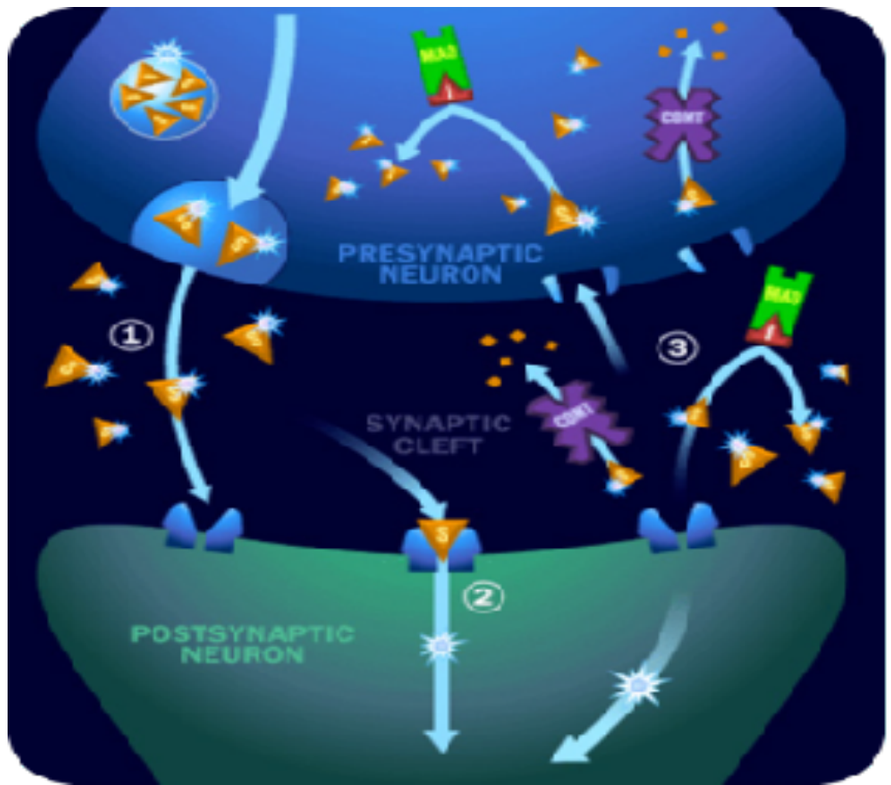
Antidepressants Pharmacology –Soton Brain Hub 6:45.
https://www.youtube.com/watch?v=4X5nqkEBmTo

1: Monoamine Oxidase Inhibitors (MAOIs)

Bind irreversibly to monoamine oxidase thereby preventing inactivation of biogenic amines such as norepinephrine, dopamine and serotonin leading to increased synaptic levels. (Upper effect ➔ euphoria).

Monoamine oxidase ***(light green)*** is an enzyme which degrades excitatory neurotransmitters **(NT*- orange tringles)** into non-active metabolites. Drugs **(red arrow in pic.2)** bind irreversibly to monoamine oxidase ➔ blocking the normal pathway, thereby preventing inactivation of the NT ➔ increase the level of NT in the synaptic cleft ➔ symptoms appear.

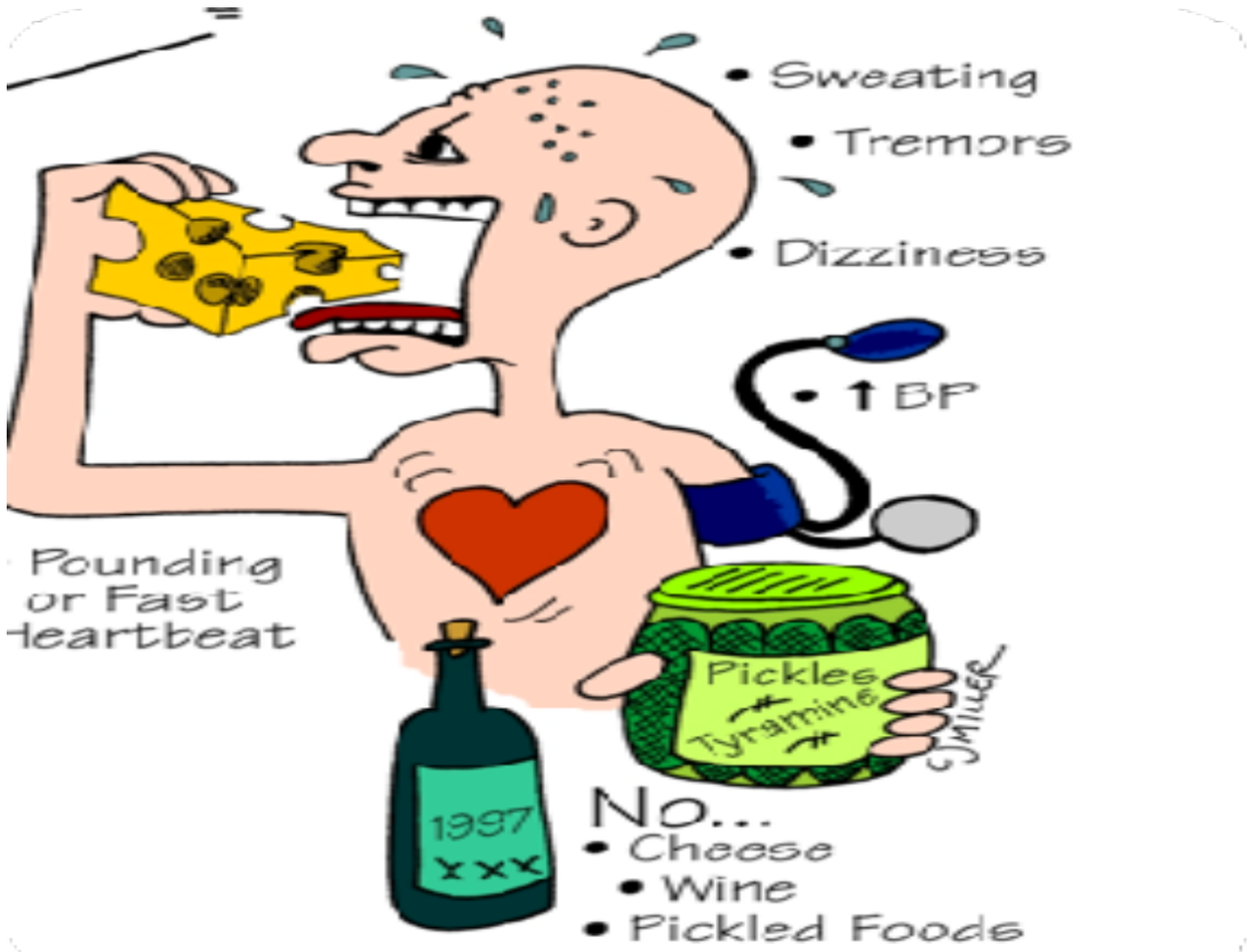




* NT= Neurotransmitter transporters

What Happens in MAOI Toxicity?

Aged cheese and wine have double effect with Monoamine oxidase inhibitors because they both contain: **Tyramine** precursor ➔➔more release of NE ➔➔ **hypertensive crisis.**



2: Tricyclic Antidepressants (TCA)

(other uses: migraine, IBS etc.)
e.g., **amitriptyline**

Peripheral & Central Effects of TCA'S

Anticholinergic
Tachycardia
Hyperthermia
Mydriasis
Anhydrosis
Red skin
Decreased bowel sounds
Ileus
Urinary retention
Distended bladder

Alpha$_1$-Blockade
Reflex tachycardia
Miosis or midrange pupils

Excitation
Agitation
Delirium
Myoclonic jerks
Hyper-reflexia
Clonus
Seizures
Hyperthermia

Inhibition
Sedation
Coma

Symptoms in toxicated Patients.

How many different MOA do TCA'shave?

Very important.
Exam Question.

TCA's Major Pharmacodynamics Effects	
1. Sodium channel blockade (quinidine-like membrane-stabilizing effects).	**1.** Na channel blocking (very cardio-toxic in overdoses cause it **widens QRS ➔ Vtac.)** it makes the QRS more than 160 – in genral over 120 is wide, in overdosed over 100 is considered wide (millisecond).
2. Alpha1-adrenoreceptor blockade.	**2.** Alpha 1 receptor blockade, in blood vessels ➔ **hypotension**.
3. Inhibition of reuptake of biogenic amines. (e.g., norepinephrine, serotonin).	**3.** Reuptake inhibition of the excitatory NT.
4. Muscarinic receptor blockade (anticholinergic effects).	**4.** Muscarinic receptors blocking, anti-cholinergic effects ➔ **nausea, vomiting anorexia, blurred vision, confusion , constipation, tachycardia, urinary retention.**

Note : Early TCA poisoning is characterized primarily by anticholinergic effects. Patients typically present with tachycardia, flushed and dry skin, mydriasis, and altered level of consciousness.

TCA's Major Pharmacodynamics Effects

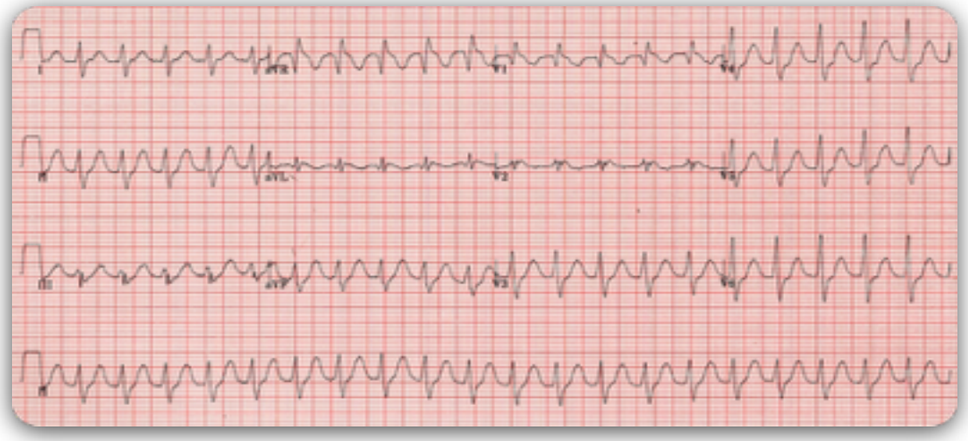
5. Histamine receptor blockade (antihistaminic effects).	**5.** Histamine receptor blockade (also act as anti-cholenergic, prolong **QT interval + tachycardia**).
6. Potassium efflux blockade.	**6.** K channel blocking **(widens QT).**
5,6 – both prolong QT ⇛ torsade.= arrhythmia= death.	
7. Indirect GABAa antagonism caused by binding at picrotoxin receptor.	**7.** In direct GABA antagonism. Ex. Of GABA agonists: benzodiazepine, alcohol.

Effects of TCA'S

Very important.

Exam Question.

WHAT'S ABNORMAL?



1- Sinus Tachycardia
2- Prolonged QT Interval
3 -Widening of the QRS interval
4- RAD (Right axis deviation).
5- Prominent R in aVR

Complications Of TCA

Hypertension (Early and transient)	2ndry to **anticholinergic** effects.
Hypotension.	2ndry to **alpha-receptor** blockage.
Sinus tachycardia	2ndry to **anticholinergic effects** **+ antihistamine.**
Ventricular tachycardia (monomorphic), QRS.	2ndry to **Na channel blockage.**
Ventricular tachycardia (polymorphic), (torsades de pointes). prolong QT.	2ndry to **K channel blockage.**

go through it :

COMPLICATION	MECHANISM: CAUSE		TREATMENT
	CARDIAC	*PERIPHERAL VASCULAR*	
Hypertension (early and transient)	Positive chronotropism: Anticholinergic vagolytic effects Positive inotropism: Increased circulating catecholamines caused by reuptake inhibition	Initial vasoconstriction: Increased circulating catecholamines caused by reuptake inhibition	Not indicated
Hypotension	Negative inotropism: Fast sodium channel inhibition with impairment of excitation-contraction coupling	Vasodilation: $Alpha_1$-adrenoreceptor blockade	IV isotonic crystalloid IV $NaHCO_3$ if QRS >100 msec Norepinephrine or dopamine
Sinus tachycardia	Positive chronotropism: Anticholinergic vagolytic effects Positive chronotropism: Increased circulating catecholamines caused by reuptake inhibition	Reflex tachycardia: $Alpha_1$-adrenoreceptor blockade	Not indicated
Ventricular tachycardia (monomorphic)	Negative dromotropism: Fast sodium channel inhibition with QRS prolongation		IV $NaHCO_3$ Synchronized cardioversion Overdrive pacing
Ventricular tachycardia (polymorphic) (torsades de pointes)	Negative dromotropism: Fast sodium channel inhibition with QRS prolongation and resultant QT prolongation, and potassium efflux inhibition		Magnesium sulfate for torsades de pointes

Specific Management

A: Plasma Alkalization (NaHCO3/ Hyperventilation)
B: Sodium Load (NaHCO3 or 3% Saline)

Plasma Alkalization	Sodium Load
-Promotes **TCA protein binding** -Plasma proteins act as a sink that sequesters TCA's away from the sites of toxicity. -Increases the non-ionized form of the drug which **UNBINDS** TCA's from Na-Channels. * Put in mind: most of the medication when it is bound to protein, it is useless! It can not act on the target cells. We give Sodium bicarbonate (NaHCO3) for alkalization (we also hyperventilate the patient to bring the CO2 down ➔ increasing the pH).	Leads to **over-riding Na-Channel Blockade** due to an increased Na concentration gradient across the cell membrane. * You just overcome the Na blockage by giving more Na in the form of (hypertonic saline and NaHco3).

3: Selective serotonin reuptake inhibitors; (SSRI)

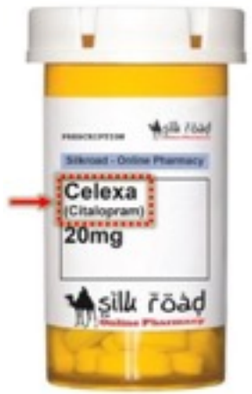
Simple Facts:

Mainstay for treatment of depression (less side effects).

SSRIs have a **wide therapeutic index**

Although they are safer in overdose than MAOIs and TCAs, they do have therapeutic limitations, such as the long delay until onset of antidepressant effect (variable)

Rarely fatal, with ingestions of up to 30 times the daily dose associated with few or no symptoms. (so it is a waist to use SSRI when planning to suicide ☺☺)



Remember:

1- QT prolongation. 2- Seizures

-SSRIs may be associated with SIADH syndrome (inappropriate anti-diuretic hormone secretion) at therapeutic doses.

-Most cases of hyponatremia develop within 1 month (not acute) and frequently within the first 2 weeks.

- Young, Na=115= SSRI;; Old, Diuretics= Thiazides.

Diagnostic Strategies and Management?

Hx mainly for diagnosing & supportive therapy for management.

* NON SPECIFIC!!

Serotonin Syndrome:

Three features of the serotonin syndrome are critical to an understanding of the disorder.

- **First**, the serotonin syndrome is not an idiopathic drug reaction;; it is a predictable consequence of excess serotonergic agonism of central nervous system (CNS) receptors and peripheral serotonergic receptors.
- **Second**, excess serotonin produces a spectrum of clinical findings.
- **Third**, clinical manifestations of the serotonin syndrome range from barely perceptible to lethal. The death of an 18-year-old patient named Libby Zion in New York City more than 20 years ago, which resulted from coadminstration of meperidine and phenelzine, remains the most widely recognized and dramatic example of this preventable condition.

Extra reading: http://www.smbs.buffalo.edu/acb/neuro/readings/SerotoninSyndrome.pdf

Simple Facts:

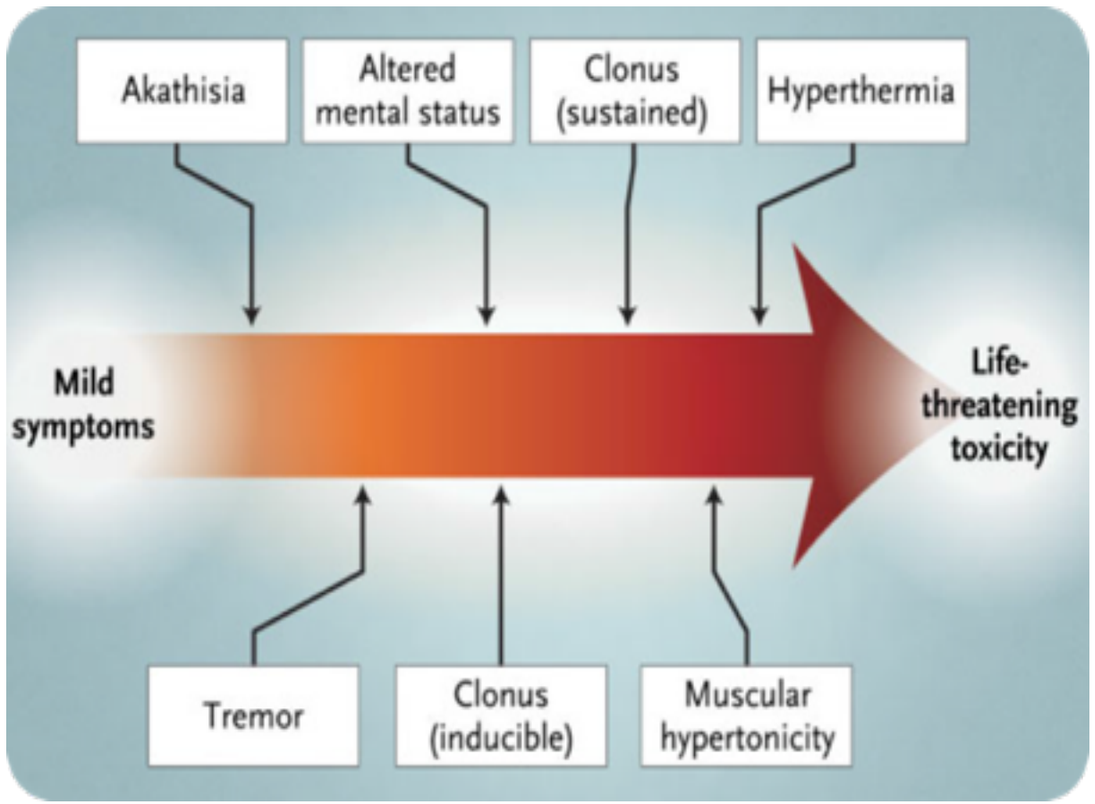
-Potentially lethal condition

-Excess serotonin accumulation in the synaptic cleft

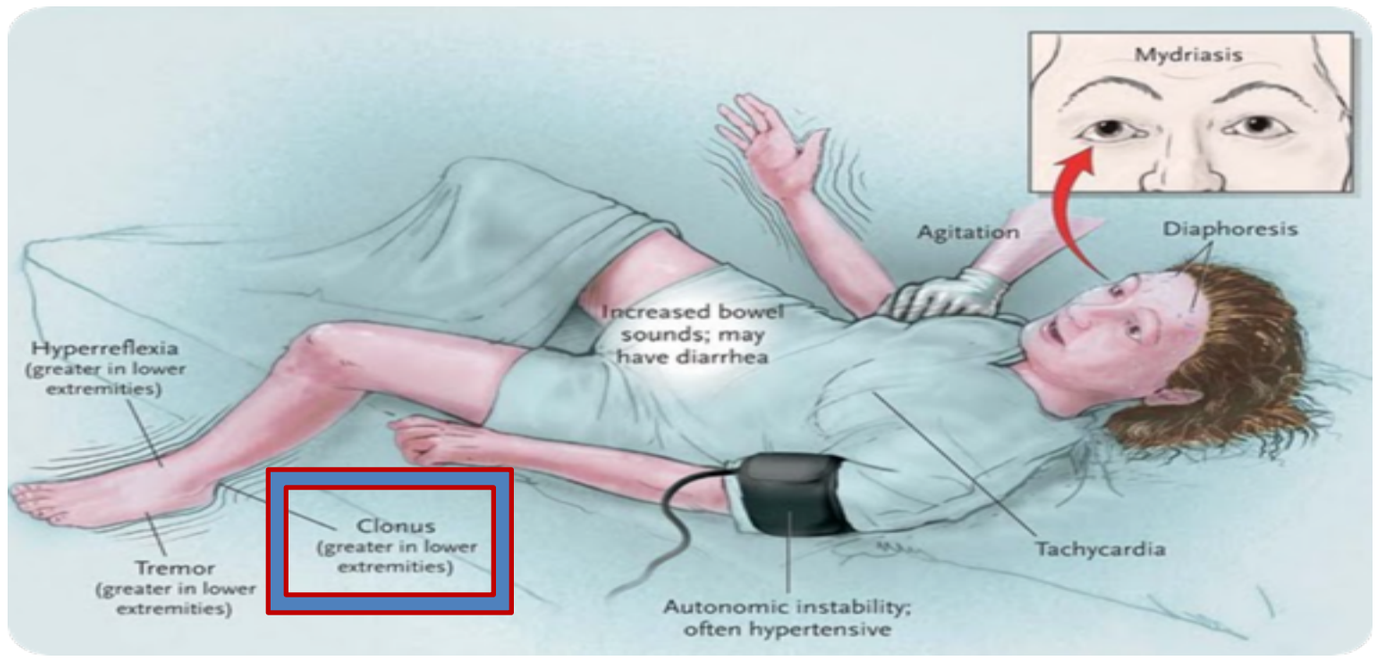
- Likely to develop when drugs from different classes are combined,

e.g. increased release and impaired uptake

-Syndrome occurs in approximately 14 to16 % of persons who overdose on SSRIs



Clinical Features



Clonus associated with overdose in Hx ⇛ think of serotonin Syndrome Immediately. (Important.)

Management of serotonin syndrome:

1- Discontinue the offending agent.
2- Supportive.
3- **Cyproheptadine** (Serotonin Antagonist) **(Antidote for serotonin Syndrome).** **Exam Q.**

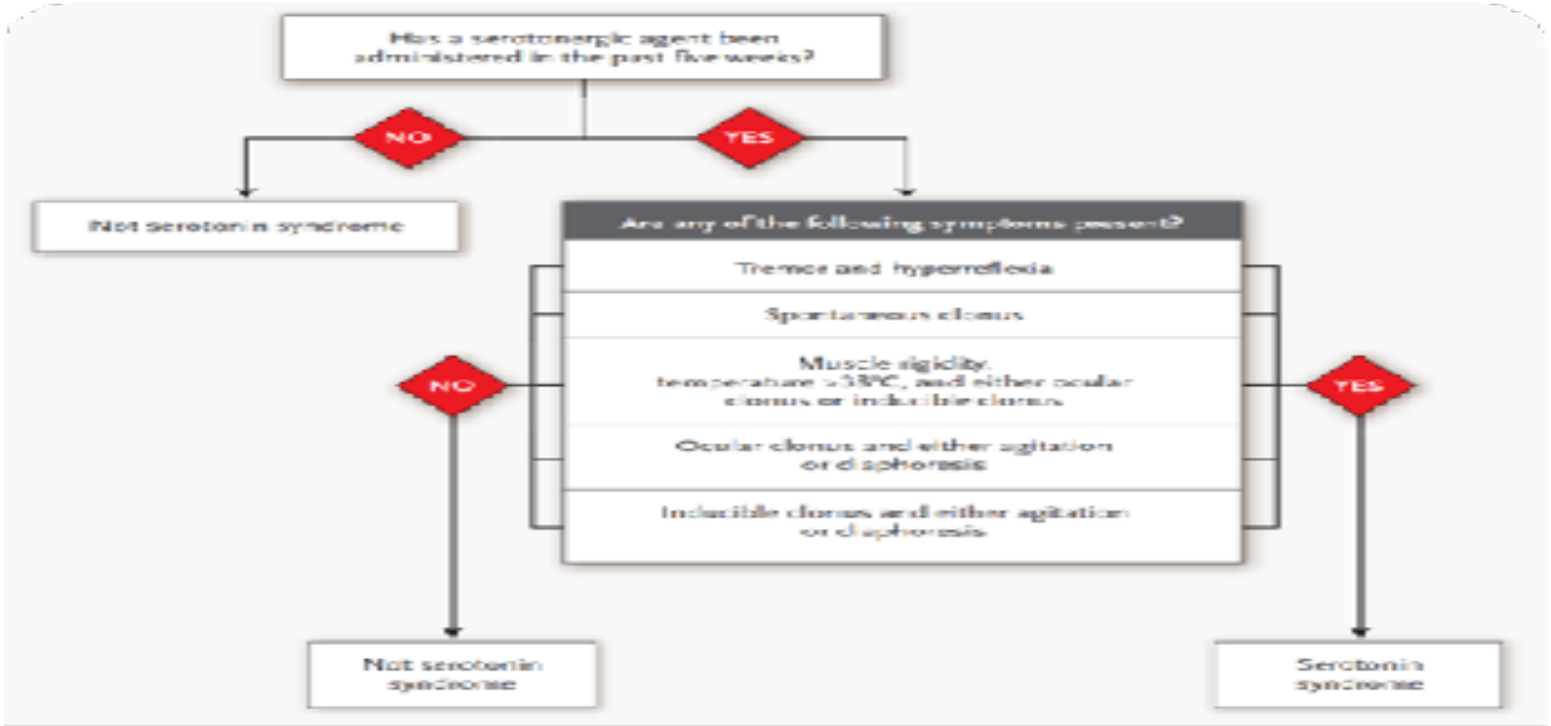


Figure 4. Algorithm for Diagnosis.
The neuromuscular features of clonus and hyperreflexia are highly diagnostic for the serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity can overwhelm other neuromuscular findings and mask the diagnosis.

Hunter's Criteria: (For serotonin Syndrome).

In the setting of exposure to a known serotonergic agent, serotonin syndrome can be diagnosed by the presence of any of the following:

- Spontaneous clonus
- Inducible clonus *and* agitation or diaphoresis
- Ocular clonus *and* agitation or diaphoresis
- Tremor and hyper-reflexia
- Hypertonic with temperature > 38° C *and* ocular clonus or inducible clonus

Differential consideration for Serotonin Syndrome:

Table 2. Manifestations of Severe Serotonin Syndrome and Related Clinical Conditions.

Condition	Medication History	Time Needed for Condition to Develop	Vital Signs	Pupils	Mucosa	Skin	Bowel Sounds	Neuromuscular Tone	Reflexes	Mental Status
Serotonin syndrome	Proserotonergic drug	<12 hr	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Mydriasis	Sialorrhea	Diaphoresis	Hyperactive	Increased, predominantly in lower extremities	Hyperreflexia, clonus (unless masked by increased muscle tone)	Agitation, coma
Anticholinergic "toxidrome"	Anticholinergic agent	<12 hr	Hypertension (mild), tachycardia, tachypnea, hyperthermia (typically 38.8°C or less)	Mydriasis	Dry	Erythema, hot and dry to touch	Decreased or absent	Normal	Normal	Agitated delirium
Neuroleptic malignant syndrome	Dopamine antagonist	1–3 days	Hypertension, tachycardia, tachypnea, hyperthermia (>41.1°C)	Normal	Sialorrhea	Pallor, diaphoresis	Normal or decreased	"Lead-pipe" rigidity present in all muscle groups	Bradyreflexia	Stupor, akinetic mutism, coma
Malignant hyperthermia	Inhalational anesthesia	30 min to 24 hr after administration of inhalational anesthesia or succinylcholine	Hypertension, tachycardia, tachypnea, hyperthermia (can be as high as 46.0°C)	Normal	Normal	Mottled appearance, diaphoresis	Decreased	Rigor mortis–like rigidity	Hyporeflexia	Agitation

Discontinuation Syndrome:

-Rarely life-threatening

-Can result in significant discomfort

-Typically starts within 3 days after therapy is stopped

Note : Psychiatric drugs, such as antidepressants and antipsychotics, are commonly prescribed to treat a wide variety of mental disorders, such as depression, bipolar disorder or schizophrenia. One of the possible side effects of such drugs, however, isn't experienced until one tries to discontinue its use.
This is a well understood and common phenomenon, especially with certain classes of drugs (like most SSRI antidepressants).

Signs & Symptoms: 6 Categories

-**Disequilibrium** (dizziness, ataxia)

-**Sleep disturbances**

-**Gastrointestinal symptoms**

-**Affective symptoms** (irritability, anxiety)

-**Sensory symptoms** (electric shock–like sensation, paresthesias)

-**General somatic symptoms** (H/A, tremor, anorexia, diaphoresis)

Summary from Simpson's Forensic Medicine

Serotonin syndrome:

Serotonin syndrome is a potentially life-threatening adverse drug reaction that occurs when excess serotonin accumulates within the synaptic cleft of neurons in the central nervous system. It may be caused by therapeutic drug use, inadvertent interactions between drugs, overdose of prescription drugs or the recreational use of certain other drugs such as cocaine. A spectrum of specific symptoms, somatic, cognitive and autonomic, may occur. In full-blown serotonin syndrome symptoms include: cognitive effects (mental confusion, hypomania, hallucinations, agitation, headache, coma), autonomic effects (shivering, sweating, hyperthermia, hypertension, tachycardia, nausea and diarrhea) and somatic effects (myoclonus, hyper-reflexia and tremor).

QT interval prolongation (long QT syndrome) :

Individuals with long QT syndrome (LQTS) experience abnormal prolongation of the QT interval, the portion of the electrocardiogram (ECG) that represents repolarization of cardiomyocytes. The QT interval extends from the onset of the Q wave to the end of the T wave. The normal rate adjusted length for the QT interval is less than 440 milliseconds. A prolonged QT interval favors the occurrence of a lethal form of ventricular tachycardia known as torsade des pointes. The QT prolongation may be caused by genetic aberration or it may be acquired.

Drugs with unique modes of action

Lithium, restore normal brain function to those with bipolar disorder, and that it somehow does so by deactivating an enzyme called GSK-3B. Chronic lithium poisoning is characteristically associated with greater toxicity than acute ingestion, and is usually manifested by neurotoxicity of rapid onset. Another feature of lithium poisoning is delayed cardiotoxicity, usually manifesting as bradycardia.

MCQs

1/ All of the following are considered as a MOA of TCA's , except ?

A--Muscarinic receptor blockade
B--Potassium efflux blockade
C-- Indirect GABA agonist
D--Inhibition of reuptake of serotonin

2/ Which of the following is caused by alpha--blockade effect of TCA's ?

A--Decrease bowel sound
B-- Anhydrosis
C--Mydriasis
D--Reflux tachycardia

3/ A patient was admitted to the emergency with TCA's toxicity, what do expect the ECG changes for this patient ?

A--Prolonged QT Interval
B--Prominent R in aVR
C--Sinus Tachycardia
D--All of the above

4/15 years old male who was admitted to the emergency department with tachypnea, on examination he had normal pupils, decreased bowel sounds, rigor mortis--like rigidity, what is the most likely cause for his symptoms ?

A--Proserotonergic drug
B--Inhalation anesthesia
C--Dopamine antagonist
D--Anticholinergic agent

5/Regarding the management of TCA's toxicity, what is the MOA of plasma alkalinization ?

A--Increases the non--ionized form of the drug
B--Decrease the non--ionized form of the drug
C--No change in the non--ionized form of the drug

6/Which one of the following drugs has the safest overdose toxicity ?

A-MAOIs
B--SSRIs
C--TCAs

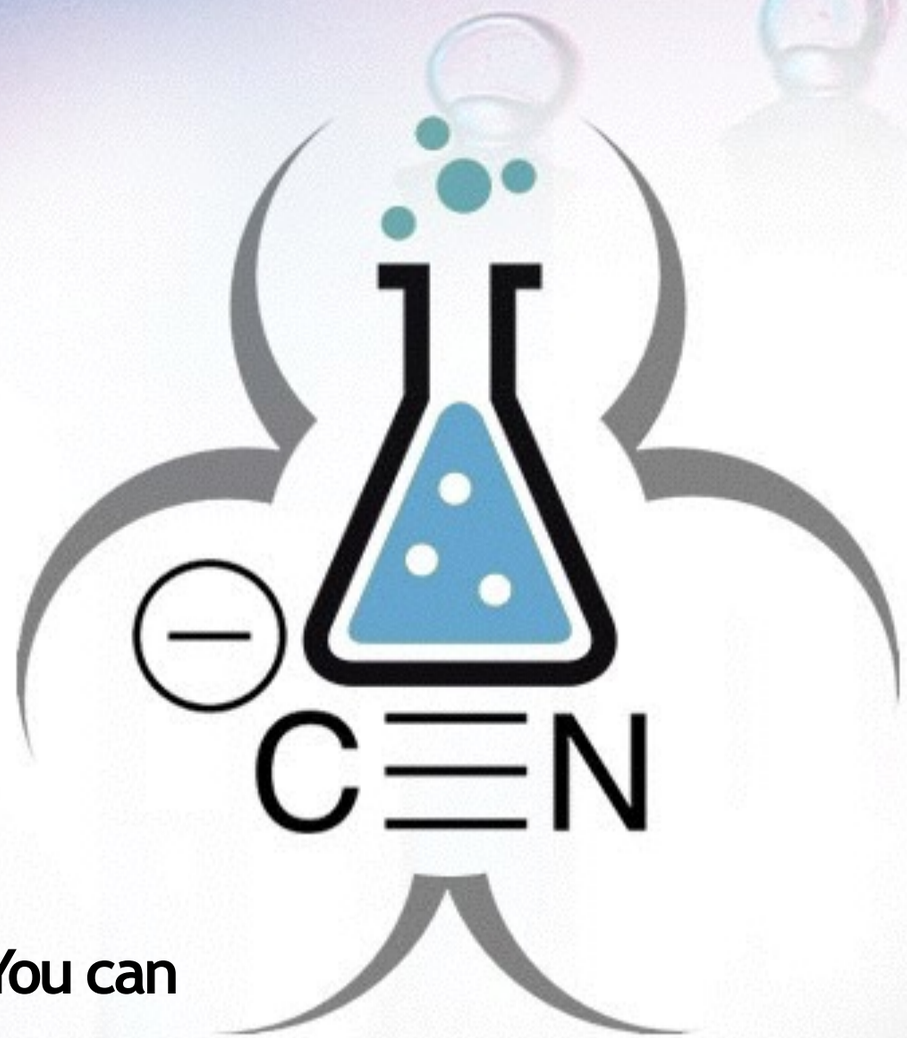
7/68 years old patient seen in ER suddenly with seizures and QT prolongation, after taking full history from the patients' family, the patient was found to had an overdose of citalopram, which one of these is predicted to occure as a complication of this drug ?

A--Hypokalemia
B--Hyponatremia
C--Hypernatremia
D--Hypocalcemia

8/Which one of the following is not included in Hunter's Criteria ?

A--Tremor
B--Tachycardia
C--Clonus
D--Agitation

Answers : 1/C , 2/D, 3/D , 4/B , 5/A ,6/B , 7/B , 8/B



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