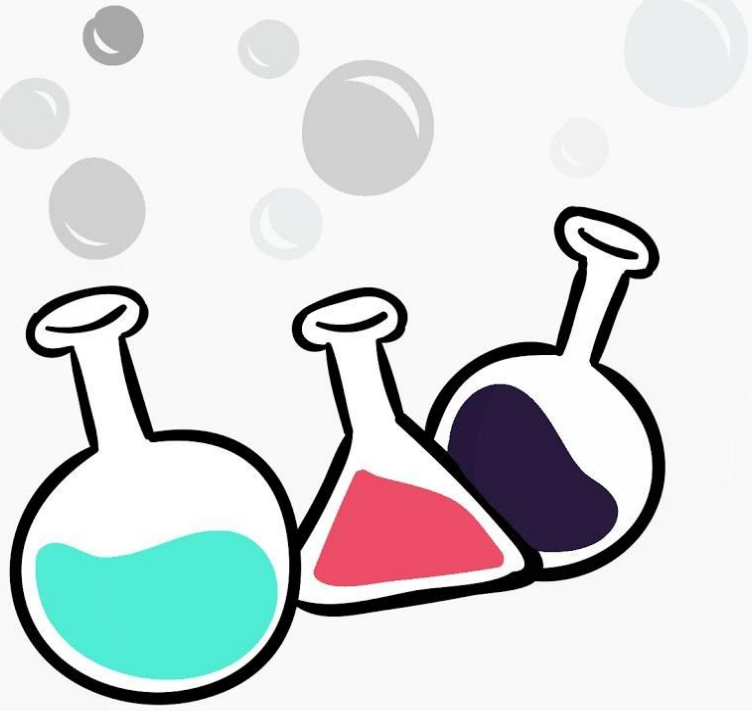


Antidepressant overdose

Team leaders: Khalid alzahrani - Abdullah aljunaydil - Futoon alsaleh

Objectives:

- Not mentioned in the lecture but the doctor said the slides are not enough and you should go back to your book, review your basics , i tried my best to include the basics ..

Done by:

Futoon alsaleh -Sarah alkhaliefa

Revised

[Color index : Important | Notes | Extra | Editing file]

Introduction:

(physiology watch this 3 minutes video https://www.youtube.com/watch?v=m4PXHeHqnmE)

basic science review

- Neurons communicate with one another at junctions called **synapses**.
- At a synapse, one neuron sends a message to a target neuron—another cell.
- Most synapses are **chemical**; these synapses communicate using chemical messengers.
  - At a chemical synapse, an action potential triggers the presynaptic neuron to release neurotransmitters → Then they bind to receptors on the postsynaptic cell → make it more or less likely to fire an action potential.
- Other synapses are electrical; in these synapses, ions flow directly between cells.
- **The fate of this neurotransmitter:**
  - **Taken up** by the postsynaptic neuron.
  - Renters the presynaptic neuron (**reuptake**).
  - **Destructed** by enzyme presented in the synaptic cleft .
- **Drugs mechanism of action:** most of CNS drugs work on this synaptic cleft .. they can **increase** the level of neurotransmitter by two ways:
  - **Preventing the reuptake (SSI)**
  - **Inhibiting the destructing enzyme (MAOI)**

What's available?

-**MAOI** (monoamine oxidase inhibitor): old group of drugs , has a lot of complications, it's still used but less commonly than before.

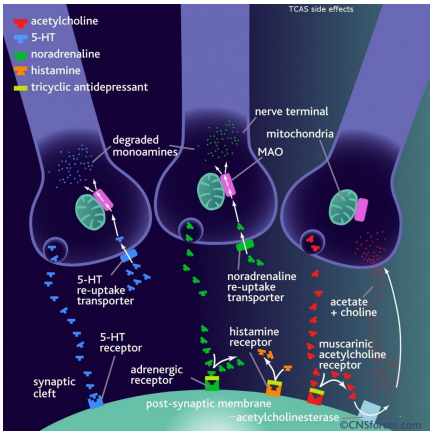
-**TCA** (tricyclic antidepressants) : it's a good antidepressant , and it's also used for chronic pain.

-**SSRI** (selective serotonin reuptake inhibitor): less toxic than those above , more commonly used.

-**SNRI** (serotonin norepinephrine reuptake inhibitor).

1-Monoamine Oxidase Inhibitors (MAOIs):

Mechanism of action:



- Bind irreversibly to **monoamine oxidase**[1] → thereby **preventing inactivation** of biogenic amines such as norepinephrine, dopamine and serotonin leading to → increased synaptic levels.
- So it increases the serotonin, so it will elevate the mood .

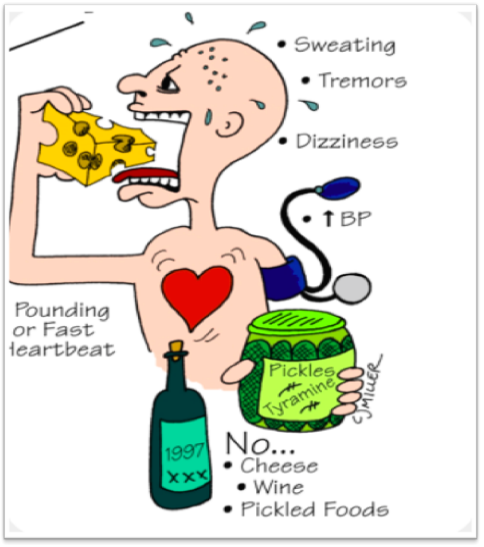
What Happens in MAOI Toxicity?

- In general, depressed patient are more prone to toxicity.
- In general anyone taking MAOI, should avoid tyramine containing food (anything that undergoes fermentation like pickles, wine and bears contain tyramine) .
- They usually present with hypertensive emergency (fatal).

[1]Monoamine oxidases (MAOs) catalyze the breakdown of monoamine neurotransmitters including dopamine, serotonin, and epinephrine in the CNS

- Tyramine is an amino acid that helps regulate blood pressure.
- It occurs naturally in the body and it's found in certain foods.
- Medications called monoamine oxidase inhibitors (MAOIs) block an enzyme known as monoamine oxidase, which breaks down excess tyramine in the body.
    - Blocking this enzyme helps relieve depression.
- If you take an MAOI and you eat high-tyramine foods, tyramine can quickly reach dangerous levels. Then → tyramine is taken up into adrenergic neurons and converted to octopamine[2] (which is a false neurotransmitter that causes massive release of NE) and may result in hypertensive crisis.
- The emergency signs of a rapid and severe rise in blood pressure (hypertensive crisis), which may include:

Severe headache	Nausea and vomiting
Sweating and severe anxiety	Nosebleeds
Fast heartbeat	Chest pain
Changes in vision	Shortness of breath
Confusion	



2-Tricyclic antidepressants

- Frequently prescribed as an antidepressant.
- Sometimes it's prescribed for chronic pain.

Mechanism of action:

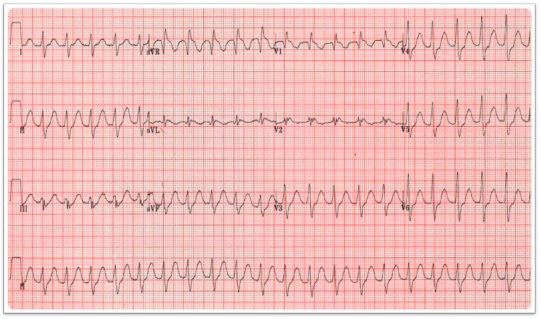
It have seven mechanisms of action , that's why they present with different toxic syndromes

- **How many different mechanisms?** 7
    1. Sodium channel blockade (quinidine-like membrane stabilizing effect)
    2. Alpha$_1$ adrenoceptor blockade
    3. Inhibition of reuptake of biogenic amines (norepinephrine, serotonin)
    4. Muscarinic receptor blockade (anticholnergic effect)
    5. Histamine receptor blockade (antihistaminic effect)
    6. Potassium efflux blockade
    7. Indirect GABA$_A$ antagonism (caused by binding at picrotoxin receptor)

[2] organic chemical closely related to norepinephrine

Peripheral and central effects of TCAs Important (MCQ); TCA toxicity can present with both mitosis and mydriasis.			
Anticholinergic	**Alpha$_1$ Blockade**	**Excitation**	**Inhibition**
◆ Tachycardia ◆ Hyperthermia ◆ Mydriasis ◆ Anhidrosis ◆ Red skin ◆ Decreased bowel sounds ◆ lleus ◆ Urinary retention ◆ Distended bladder	◆ Reflex tachycardia ◆ Miosis or midrange pupils	◆ Agitation ◆ Delirium ◆ Myoclonic jerks ◆ Hyper—reflexia ◆ Clonus ◆ Seizures ◆ Hyperthermia	◆ Sedation ◆ Coma

Complications:



- **ECG Changes:**
  - **patient can come with:**
    1. Sinus tachycardia.
    2. Prolonged QT interval.
    3. Widening QRS interval (more than 2.5 to 3 small squares) Any patient with drug toxicity is more prone to QRS widening, but what does that mean? the QRS represents ventricular contraction, if it's prolonged, it means that the heart muscle is weakened so it's taking more time to contract. So what? The heart will be more prone to fatal arrhythmias e.g. ventricular tachycardia, ventricular fibrillation
    4. Right axial deviation (RAD).
    5. Prominent R wave in aVR lead. We usually call this changes pro arrhythmic changes, it's easier to treat patients with those symptoms, rather than to treat fatal ventricular arrhythmias or ventricular fibrillation.

★ So ECG is important to know if the patient is "pre-arrhythmic"! علشان نلحق عليه قبل لا يدخل بمشكلة كبيرة

- **Others:doctor focus on presentation and management**

Complications			
Complication	**Cardiac**	**Peripheral vascular**	**Treatment**
Hypertension (early and transient)	Positive chronotopism: Anticholnergic vagolytic effect Positive Inotropism: increased circulating catecholamines caused by reuptake inhibition	Increased vasoconstriction: increased circulating catecholamines caused by reuptake inhibition	**Not indicated.** Just monitor the patient, it's a transient thing.
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: Anticholnergic vagolytic effect 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: IMP

Plasma Alkalinization (NaHCO3 \ Hyperventilation):	**Sodium load** (NaHCO3 or 3% Saline):
• 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.	• Leads to **overriding Na-Channel Blockade** due to an increased Na concentration gradient across the cell membrane.

3-SSRIs:

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) (it takes 1-2 weeks).
- Overdose **rarely fatal**, with ingestions of up to 30 times the daily dose associated with few or no symptoms(but got a lot of toxic syndromes)

Effects:

- **QTc prolongation.**
- **Seizures.**
- May be associated with **SIADH** at therapeutic doses (most cases of **hypo**natremia develop within 1 month and frequently within 2 weeks) - basically when the drug effect in general starts to appear.

Diagnostic strategies and management:

- NON SPECIFIC!!

★ Hint: Middle age guy + seizure + hyponatremia = Amphetamine or on SSRI, Elderly +seizure + hyponatremia = hydrochlorothiazide until proven otherwise

Serotonin syndrome:

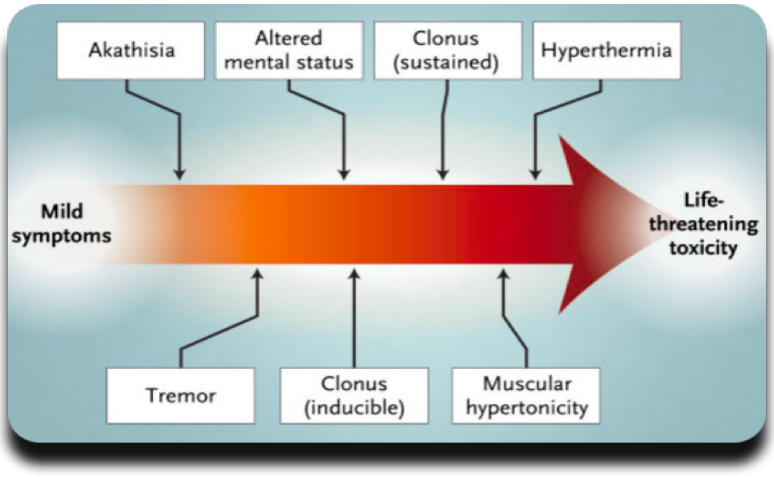
- Potentially **lethal** condition.
- **Caused by:** **Excess** serotonin accumulation in the synaptic cleft.
- Likely to develop when drugs from different classes are **combined**, e.g. increased release and impaired uptake.
- Syndrome occurs in approximately **14-16%** of persons who overdose on **SSRIs** (it happens basically if the patient is taking multiple medication, that's why we need clinical pharmacist with us to identify possible drug drug interaction.

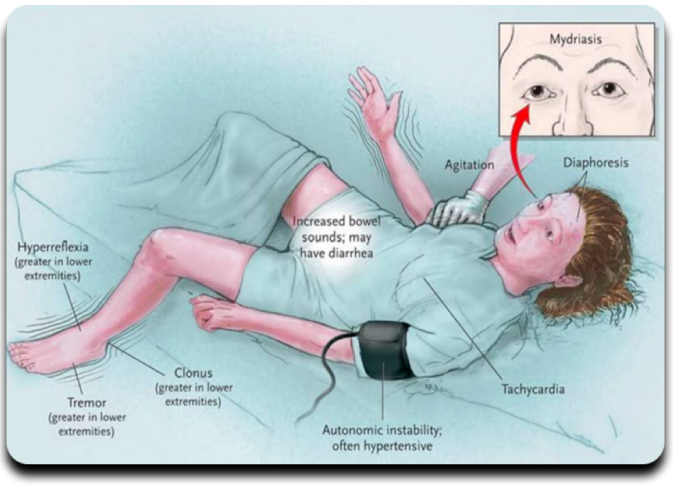
★ This syndrome occurs after an isolated overdose of an SSRI, but it is more commonly a result of drug-drug interactions, especially with drug combinations that raise synaptic serotonin concentrations by different mechanisms.

Clinical features: Serotonin syndrome is described as a triad of mental status changes, autonomic instability, and increased neuromuscular activity, but the condition exists along a spectrum

Severity pattern of serotonin syndrome:	
Category:	**Clinical Features:**
Mild:	Mild agitation, mild fever (<40), tremor, myoclonus, hyperreflexia, diaphoresis, mydriasis, elevated blood pressure and heart rate. We have to treat them while they are in the mild symptoms , because once they develop severe life threading symptoms it will be hard bringing them back
Moderate:	Marked agitation, hyperthermia (>40), myoclonus, hyperreflexia, ocular clonus, increased bowel sounds.
Severe:	Hyperthermia (>41.1), delirium, marked muscle rigidity, marked swings in blood pressure and heart rate.

Clinical features of serotonin syndrome:		
	Major:	**Minor:**
Cognitive:	Altered level of consciousness - Agitation	Insomnia - Restlessness - Anxiety
Autonomic:	Hyperthermia - Diaphoresis	Tachycardia - Hyper or hypo tension - Tachypnea - Mydriasis
Neuromuscular:	Muscle rigidity - Hyperreflexia - Myoclonus - Tremor	Akathisia - Incoordination





Management:

- Before you start managing the patient, you have to make sure this is serotonin syndrome. How ?
  - the patient should be taking the meds for **AT LEAST 5 WEEKS** !! If the patient is taking them for only 2 weeks this isn't serotonin syndrome:

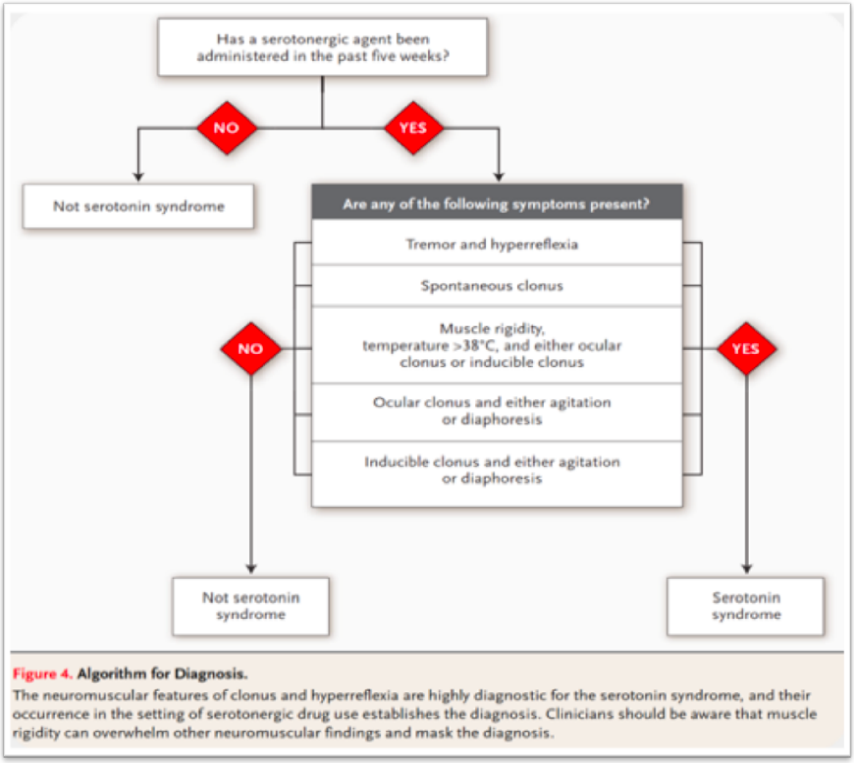


Figure 4. **Algorithm for Diagnosis.**
The neuromuscular features of clonus and hyperreflexia are highly diagnostic for the serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity can overwhelm other neuromuscular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

- They should present with typical symptoms of serotonin syndrome:

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 hyperreflexia.
- Hypertonic with temperature >38°C and ocular clonus or inducible clonus.

- **After that, start treating the patient:**
  - **Stop all serotonergic therapy.**
  - **Supportive treatment:**
    - Initiate cardiopulmonary monitoring, establish peripheral IV access, and obtain ECG
    - IV fluid rehydration
    - External cooling measures for hyperthermia
    - Benzodiazepines for agitation
    - Short acting IV antihypertensives (nitroprusside or esmolol) for severe hypertension
    - Use direct acting IV vasopressors (norepinephrine, epinephrine, or phenylephrine) for hypotension resistant to IV fluid resuscitation
  - **Consider cyproheptadine** (serotonin antagonist) for moderate to severe clinical features refractory to supportive care.

Differential diagnosis of 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, alert 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 start within 3 days after therapy is stopped.

Signs & symptoms : 6 categories

1. Disequilibrium (dizziness, ataxia).
2. Sleep disturbances.
3. Gastrointestinal symptoms.
4. Affective symptoms (irritability, anxiety).
5. Sensory symptoms (electric shock–like sensation, paresthesias).
6. General somatic symptoms (H/A, tremor, anorexia, diaphoresis).

MCQs :

- **A 26-year-old female presented after taking overdose of tricyclic antidepressants "TCA", you have requested ECG to be done, which one of the following will be seen?**
  A. Bradycardia
  B. 1st degree heart block
  C. Left bundle branch block
  D. Prominent R in aVR
  Answer: D
- **Administration of MAO inhibitor will cause change the CNS concentration of which of the following ?**
  A. Acetylcholine.
  B. Histamine.
  C. norepinephrine.
  D.GABA
  Answer: C
- **Which of the following is the mechanism of action of TCA's toxicity?**
  A- Blockage of sodium channels
  B- Blockage of calcium channels
  C- Blockage of uptake
  D- Blockage of monoamine oxidase
  Answer:There is probably a mistake in the choices , because TCA both block the NA channel and inhibits the reuptake of biogenic amines (dopamine, norepinephrine, epinephrine, histamine and serotonin)
- **A 25-year-old male with history of depression on regular treatment for the past year, brought in by his friend to your emergency department with fever measuring 41 ℃, profusely sweating and altered mental status, on examination he was found to have generalized rigidity and hyperreflexia plus inducible clonus. After initiating all your supportive management measures, which of the following medications is most appropriate for his condition?**
  a. Cyproheptadine
  b. Dantrolene
  c. Ciprofloxacin
  d. Succinylcholine
  Answer: A
- **A 35-year-old female patient was being treated for depression with tricyclic antidepressants. She took an overdose of her medication at home and an ambulance has brought her to your emergency department. After initial control of her airway, breathing and circulation, you notice on the monitor that patient has developed wide complex tachycardia. Which of the following drugs should be used to treat this patient?**
  A- Amiodarone
  B- Beta blockers
  C- Calcium channel blockers
  D- Sodium bicarbonate
  Answer: D