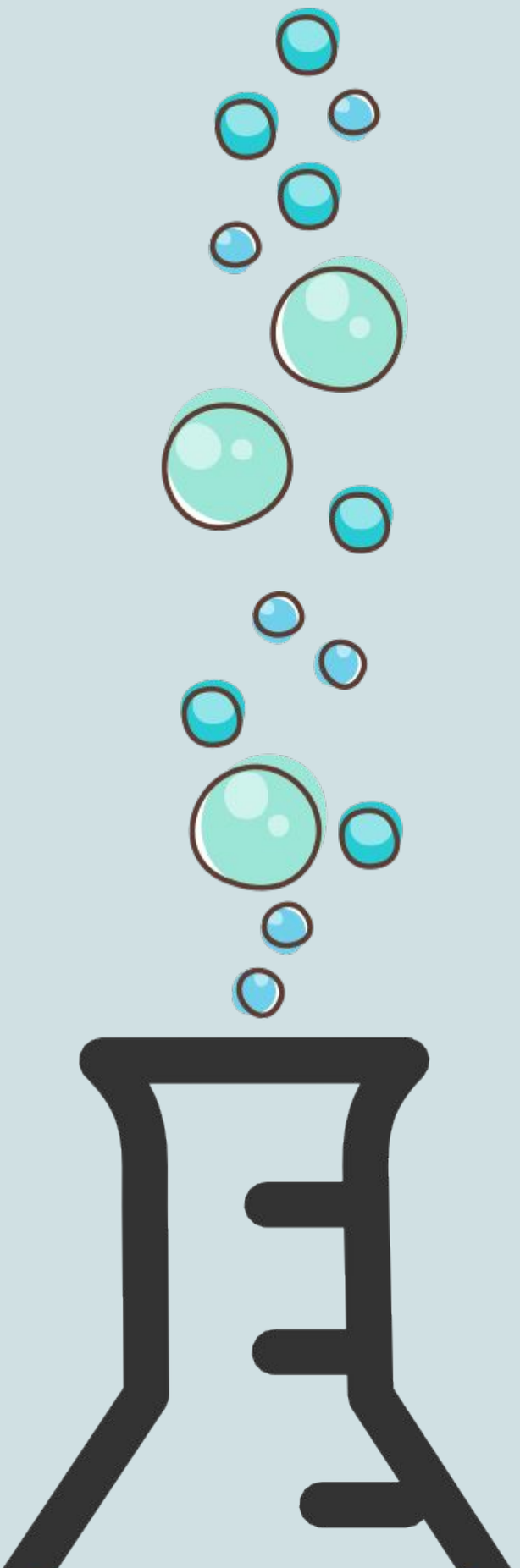
PSYCHIATRIC DRUGS



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Objectives

1. Not mentioned

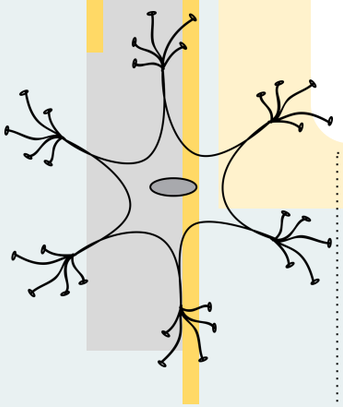
Introduction

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

Other synapses are electrical; in these synapses, ions flow directly between cells.



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.

The fate of this neurotransmitter:

- Taken up by the postsynaptic neuron.
- Re-enters the presynaptic neuron (reuptake).
- Destructed by an 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 neurotransmitters 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 Antidepressant"

It's a good antidepressant, and it's also used for chronic pain. It used in clinical practice today but not as an antidepressant. It used for other stuff

SSRI
"Selective Serotonin Reuptake Inhibitor"

Less toxic than those above, more commonly used.

SNRI
"Serotonin Norepinephrine Reuptake Inhibitor"

Side effects are usually mild and go away after the first few weeks of treatment.

1- Monoamine Oxidase Inhibitors (MAOIs)

MOAIs

Mechanism Of Action (Image)

-Bind irreversibly to **monoamine oxidase** → thereby **preventing inactivation** of biogenic amines such as norepinephrine, dopamine and Serotonin leading to → increased synaptic levels.

-So it increases the serotonin and therefore elevates the mood.

The only physiological reason we are in a balanced state is because there is a balance between two things: excitatory neurotransmitters (dopamine, serotonin, epinephrine, norepinephrine) and inhibitory neurotransmitters (GABA)
That's why we like to divide medications or street drugs as:
1- Uppers: like cocaine (makes you crazy) and amphetamine (like captagon يحطونها مع الشاهي ويمسكون خط عشان يقعدون صاحين وتعرف عندنا بأبو ملف او الأبيض)
2- Downers: like alcohol (you drink then you go to sleep or your speech becomes slow)

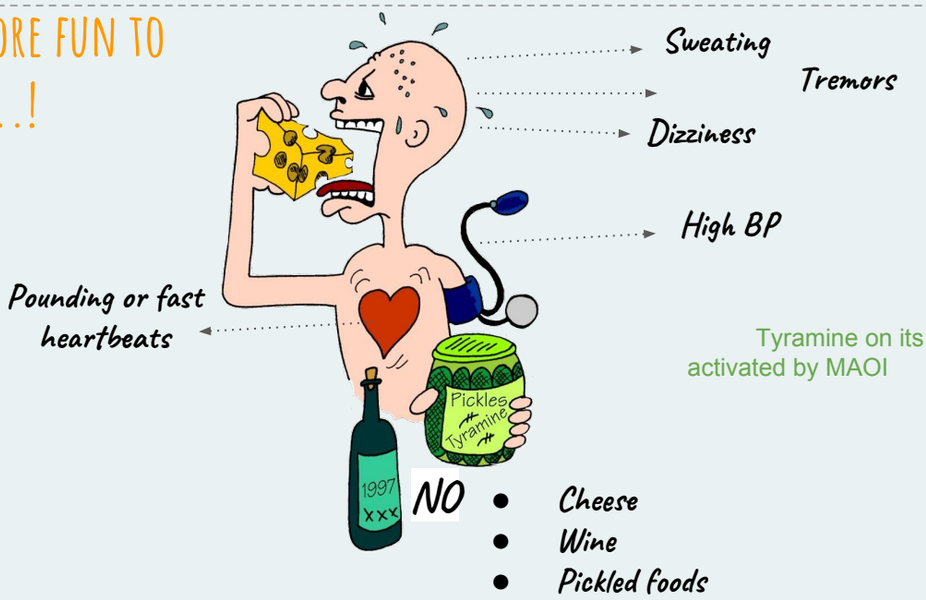
Uppers work by increasing dopamine and norepinephrine in synaptic cleft so when you're depressed there is not enough serotonin, norepi and dopamine in the synaptic cleft

Overdose

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

- Severe headache
- Sweating and severe anxiety
- Fast heartbeat (Tachycardia/Palpitations)
- Changes in vision Confusion
- Nausea and vomiting
- Nosebleeds
- Chest pain
- Shortness of breath
- Seizures
- Rigidity

MAKE IT MORE FUN TO MEMORIZE..!



Tyramine on its own needs to be activated by MAOI

2- Tricyclic Antidepressants

T

C

A

- we are 100% going to have a question on this in the **exam**
- Sometimes we see people on TCAs as an antidepressant but they've been on it for 25 years so we can't stop it and this is the only indication otherwise we don't initiate antidepressant therapy with TCAs.
- We can use it for IBS and migraine for example
- Frequently prescribed as an antidepressant.
- Sometimes it's prescribed for chronic pain.

Mechanism of action :

You have to know all 7 mechanisms for the sake of the exam

It has seven mechanisms of action, that's why they present with different toxic syndromes. (Very important)

1. Sodium channel blockade (quinidine-like membrane stabilizing effect) Causes QRS prolongation leading to ventricular tachycardia (monomorphic)
2. Alpha adrenoceptor blockade There's Alpha in blood vessels so if it blocks Alpha it will cause vasodilation leading the hypotension
3. Inhibition of reuptake of biogenic amines (norepinephrine,serotonin)
4. Muscarinic receptor blockade (anticholinergic effect) Causing QT prolongation
5. Histamine receptor blockade(antihistaminic effect) All antihistamines prolong QT
6. Potassium efflux blockade Causing QT prolongation
7. Indirect GABAA antagonism (caused by binding at picrotoxin receptor)

2- Tricyclic Antidepressants

Peripheral & 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 -Ileus -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 of 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)

2- Tricyclic Antidepressants

Complications:

Others: doctor focus on presentation and management

Complication	Cardiac	Peripheral Vascular	Treatment
Hypertension (early and transient)	**Positive chronotropism:** Anticholinergic 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-adrenoceptor blockade	-IV isotonic crystalloid -IV $NaHCO_3$ if QRS>100 msec -Norepinephrine or dopamine
Sinus tachycardia	**Positive chronotropism:** Anticholinergic vagolytic effect **Positive chronotropism:** increased circulating catecholamines caused by reuptake inhibition	**Reflex tachycardia:** Alpha 1-adrenoceptor 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) Anything that causes QT prolongation will lead to polymorphic V.Tach	**Negative dromotropism:** fast sodium channel inhibition with QRS prolongation and resultant QT prolongation, and potassium efflux inhibition	-	Magnesium sulfate for torsades de pointes

Chronotropic effects are those that change the heart rate. Chronotropic drugs may change the heart rate and rhythm by affecting the electrical conduction system of the heart and the nerves that influence it, by changing the rhythm produced by the sinoatrial node.

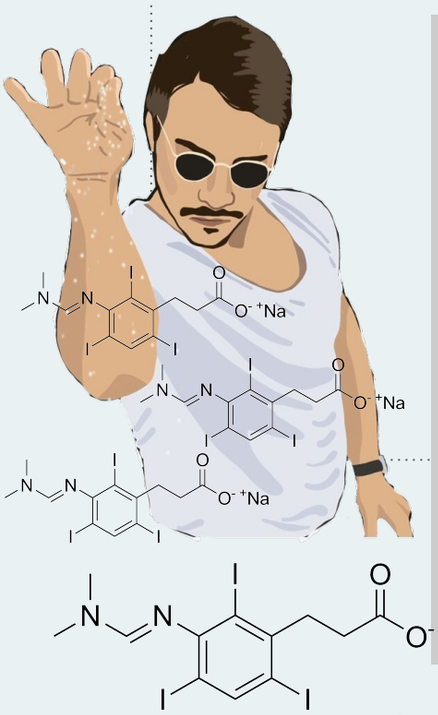
The term **inotropic state** is most commonly used in reference to various drugs that affect the strength of contraction of heart muscle

A dromotropic agent is one which affects the conduction speed in the AV node, and subsequently the rate of electrical impulses in the heart.

2- Tricyclic Antidepressants

Specific Management:

1-Plasma Alkalinization (NaHCO3 \ Hyperventilation)

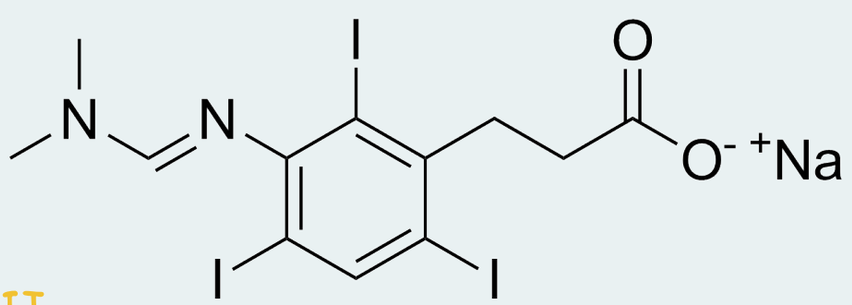


Promotes **TCA protein binding** .

- 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.

2-Sodium Load (NaHCO3 or 3% Saline)



OOPS! WE MAY HAVE ADDED A BIT TOO MUCH OF SODIUM,,,

3- SSRI

Simple facts: (image)

- Mainstay for treatment of depression less side effects. Very common
- 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: (You need to know more from the textbook)

- **QTc prolongation.** What's the problem with QT prolongation? It causes torsades de pointes
- **Seizures.**
- May be associated with **SIADH** at therapeutic doses.
- most cases of **hyponatremia** (young patients, excessive sweating and it is caused by hydrochlorothiazide)develop within 1 month and frequently within 2 weeks) basically when the drug effect in general starts to appear. Antidepressants are a common cause of hyponatremia in young age and adults



Diagnostic strategies and management:

NON SPECIFIC! History and physical examination

- We can't do urine analysis because the patient may have taken cocaine one week before and urine will be positive for cocaine now. Only psychiatrist and police order urine analysis

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

Serotonin Syndrome

What is Serotonin Syndrome : Quite rare

-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. Common scenario: if someone on an antidepressants at the same time he went and smoked cocaine and took something else that increase serotonin
-Syndrome occurs in approximately **14-16%** of people who overdose on **SSRIs** (basically it happens 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 (image)

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.

Serotonin Syndrome

Clinical Features of Serotonin Syndrome

	Major	Minor
Cognitive	Altered level of consciousness - Agitation	Insomnia - Restlessness - Anxiety
Autonomic	Hyperthermia - Diaphoresis	Tachycardia - Hyper or Hypotension - Tachypnea - Mydriasis
Neuromuscular	Muscle rigidity - Hyperreflexia - Myoclonus - Tremor	Akathisia - Incoordination

(Clinical Features of Serotonin Syndrome)

- All uppers cause mydriasis while Downers and opioids cause miosis
- Clonus is specific to serotonin syndrome

Management: (From the book。)

Very important

1-Is it Serotonin Syndrome or not? (Differential diagnosis)

2-Typical symptoms of Serotonin Syndrome (Hunter's criteria)

3-Start the treatment! (Stop & Support)

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

Serotonin Syndrome

Management:

1-Is it Serotonin Syndrome or not?
(Differential diagnosis)

2-Typical symptoms of Serotonin Syndrome
(Hunter's criteria)

3-Start the treatment!
(Stop & Support)

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 oC and ocular clonus or inducible clonus.

Hunter's criteria for Serotonin Syndrome
Important: You need to know about it from the textbook

1-Is it Serotonin Syndrome or not?
(Differential diagnosis) You may want to check next slide (;

2-Typical symptoms of Serotonin Syndrome
(Hunter's criteria)

3-Start the treatment!
(Stop & Support)

Consider **cyproheptadine** (serotonin antagonist) for moderate to severe clinical features refractory to support care.

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

Serotonin Syndrome

Differential diagnosis of Serotonin Syndrome:

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

3- SSRI

Discontinuation Syndrome:

When you on SSRIs for long time, usually it's recommended to stop over a week or two don't stop it suddenly because it may cause discontinuation Syndrome

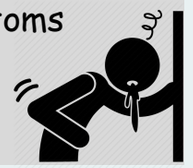
- Rarely life-threatening.
- Can result in significant discomfort.
- typically start within 3 days after therapy is stopped.

Signs & Symptoms: (Not specific) 6 categories

Disequilibrium (dizziness,ataxia).

Sleep disturbances

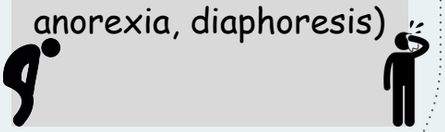
Gastrointestinal symptoms



Affective symptoms (Irritability, anxiety)

Sensory symptoms (Electric shock-like sensation, paresthesias)

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



Summary

	MAOI	TCA	SSRI
Mechanism of Action	Bind irreversibly to **monoamine oxidase** → thereby **preventing inactivation** of biogenic amines such as norepinephrine, dopamine and Serotonin leading to → increased synaptic levels	1. Sodium channel blockade 2. Alpha adrenoceptor blockade 3. Inhibition of reuptake of norepinephrine & serotonin 4. Muscarinic receptor blockade 5. Histamine receptor blockade 6. Potassium efflux blockade 7. Indirect GABAA antagonism	selective serotonin reuptake inhibitor
Toxicity & Effect	• anyone taking MAOI, should avoid tyramine containing food • present with hypertensive emergency	Anticholinergic: Mydriasis Alpha1 Blockade: Miosis Excitation: Agitation Inhibition: Sedation	• QTc prolongation • Seizures • SIADH
Management		• Plasma Alkalinization • Sodium Load	NON SPECIFIC

Serotonin syndrome

Caused by: Excess serotonin accumulation in the synaptic cleft.

Clinical features of serotonin syndrome: Cognitive, Autonomic & Neuromuscular.

Management:
1- should be taking the meds for **AT LEAST 5 WEEKS**
2- should present with typical symptoms of serotonin syndrome: **Hunter's criteria**
3- After that, start treating the patient:

- Stop all serotonergic therapy
- Supportive treatment
- Consider **cyproheptadine**

Hunter's criteria: 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 >38C + ocular or inducible clonus.

Discontinuation syndrome

typically start within 3 days after stopping therapy.

Signs & symptoms:

1- Disequilibrium
2- Sleep disturbances
3- Gastrointestinal Sx
4- Affective Sx
5- Sensory Sx
6- General somatic Sx

How toxic is your knowledge!

1-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

2- **Administration of MAO inhibitor will cause change the CNS concentration of which of the following ?**

A. Acetylcholine.
B. Histamine.
C. norepinephrine.
D.GABA

3-**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 °C, 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?**

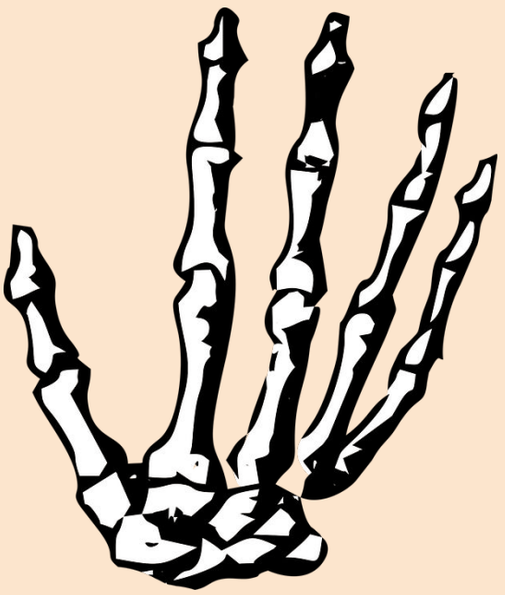
a. Cyproheptadine
b. Dantrolene
c. Ciprofloxacin
d. Succinylcholine

4-**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

1-D
2-C
3-A
4-D

Thank you and good luck!



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A+ is yours (:

- Email us at:

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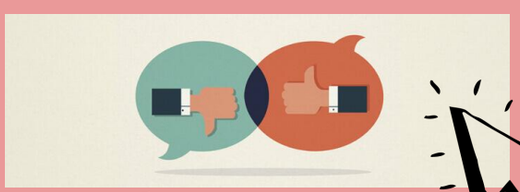

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