TOXOCOLOGY 434

Lecture 3

Antidepressant Overdose!

Important :
Dr said Qs will be from the book i'll give some hints but u have to study the book I added important Dr's hints on the slides .

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Color Index : Important , doctor`s note

Editing File

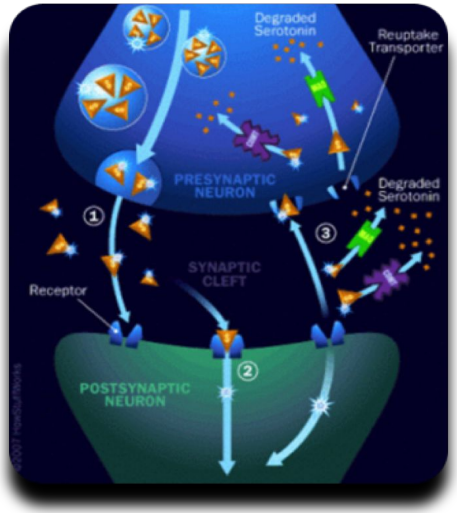
What's Available? MAOI's , **TCA, SSRI,** SNRI.

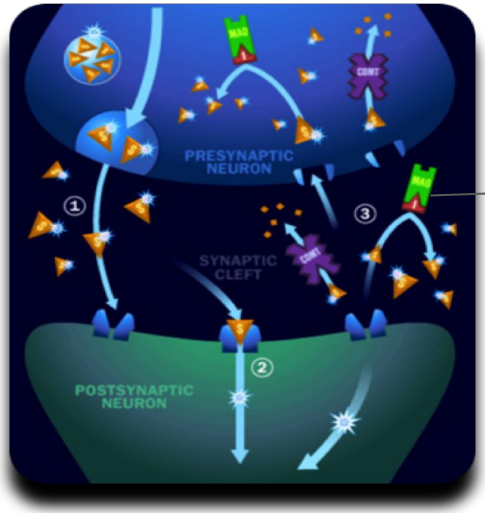
Monoamine Oxidase Inhibitors (MAOIs):

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

MAO cause degradation of those NT.

-What does these Neurotransmitters"NT" "norepinephrine, dopamine and serotonin" do? they make us a wake.
-The uppers are cocaine , amphetamine "they increase excitatory NT ", speed , Zanix "BDz"
-Other names of amphetamine "common in KSA" are لكزس ، captagon, الابيض
قنبلة
-These make us feel high ,active sweating , high BP as they increase these NT.
-As normal person we have balance between inhibitory "GABA" & excitatory NT.
-Heroin "common on KSA" is for low class "homeless"
-Cocaine is for high class .
-Alcohol works in GABA .





MAOI

What Happens in MAOI Toxicity?

tyramine reaction u might Not be asked about it
anything that undergoes fermentation like pickles, wins , bears they develop tyramine , if u take MAOI + tyramine it has synergistic effect.

- Alcohol stimulate GABA, those who are chronic alcoholics there will be continuous + of GABA so there will be up regulation to the +ve NT, that's why Alcohol withdrawal is disaster because GABA goes down & the +ve NT works alone so they'll come with seizure until they die.
-It happens usually like if alcoholic gets appendicitis & he admitted for 4 days without drinking alcohol they will have seizure & die.
-So it's important to ask if they are drinker we give them something to increase GABA As Diazepam regularly.

TCA's

e.g Amitrityline , **definitely u will have 3 Questions on TCAs**.

How many Different MOA do TCA's have? 7

"u have to know all of them "

Major Pharmacodynamic Effects:

1. Sodium channel blockade (quinidine-like membrane-stabilizing effects)
2. Alpha$_1$-adrenoreceptor blockade
3. Inhibition of reuptake of biogenic amines (e.g., norepinephrine, serotonin)
4. Muscarinic receptor blockade (anticholinergic effects)
5. Histamine receptor blockade (antihistaminic effects)
6. Potassium efflux blockade
7. Indirect GABA$_A$ antagonism caused by binding at picrotoxin receptor

To make it easy it blocks Na channel, alpha R, Histamin R , Potassium efflux , GABA R , and anticholinergic effect.
-By blocking Na channel it **cause arrhythmia prolong QRS >** "**extremely important** "
-By blocking pottasium channel it cause arrhythmia **prolong QT** there is a lot of drugs"all antipsychotic & some antibiotic" do the same action so u have to do ECG for all patients before prescribing TCAs to them.
- Alpha R on "BV" blockage so it **causes Hypotension**.
-Anticholinergic cause tachycardia, HTN, **Dryness** ,agitation.
- To differentiate between Sympathomimetic toxicity & anticholinergic"AC" is the dryness as bone with AC while sympathomimetic will come with profuse sweating.

the problem with it is it has very Narrow therapeutic index

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

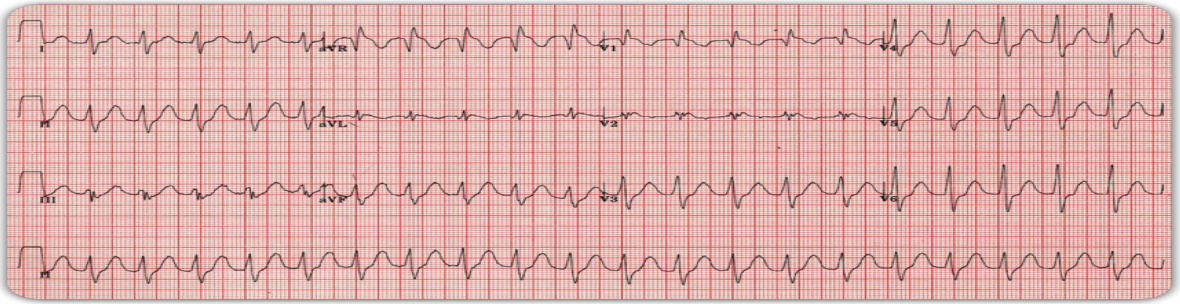
Excitation
Agitation
Delirium
Myoclonic jerks
Hyper-reflexia
Clonus
Seizures
Hyperthermia

Inhibition
Sedation
Coma

BP = CO X SVR
CO= HR X SV
so if for any reason SVR decrease CO needs to go up How? by increasing HR just compensatory mechanism due to alpha blockade hypotension.

TCAs is used for neuropathic pain e.g migraine as Opioid don't work with them. For IBS as well

WHAT'S ABNORMAL? **u might have an ECG image on the exam.**

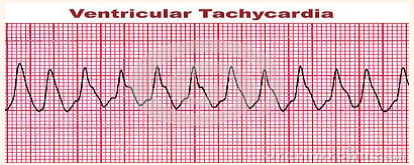


Sinus Tachycardia , **Prolonged QT Interval**, Widening of the **QRS interval**, RAD"right access deviation">don't worry about it , **Prominent R in aVR**, AV nodal reentrant tachycardia "AVNRT".

Hint: it will come on the exam.
aVR is a -ve lead usually **if it's +ve & u see prominent "terminal" R it's Na blocking effect & most likely TCAs overdose this is very classic.**

Complication:

1-Hypertension (early and transient) . 2-Hypotension. 3-Sinus tachycardia. 4-Ventricular tachycardia (monomorphic). 5-Ventricular tachycardia (polymorphic) (torsade de pointes).

	MECHANISM: CAUSE		
COMPLICATION	***CARDIAC***	***PERIPHERAL VASCULAR***	**TREATMENT**
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

Regular Vent tachycardia “mono” > QRS
Vent tachycardia-torsades de pointes-”poly” > QT

Specific Management:

U don't need to know the mechanism , just know that u give NaHCO3

1-**Plasma Alkalinization (NaHCO3/ Hyperventilation)**

-Promotes ***TCA binding to protein*** ***these proteins act as sink*** مجرى

-Plasma proteins act as a sink that sequesters TCA's away from the sites of toxicity.

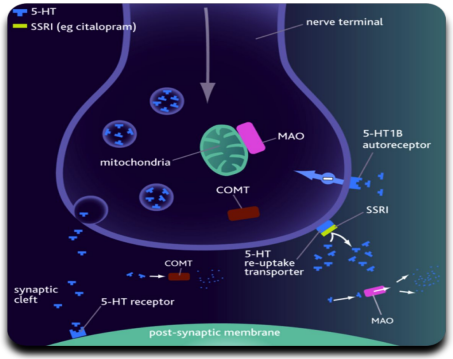
-Increases the non-ionized form of the drug which ***UNBINDS*** TCA's from Na-Channels.

2-**Sodium Load (NaHCO3 or 3% Saline)**

- Leads to ***over-riding Na-Channel Blockade*** due to an increased Na concentration gradient across the cell membrane , u overwhelm the receptors with Na.

SSRI's

e.g Ecitalopram, Paroxetine, Fluoxetine .



Simple Facts:

•Mainstay for treatment of depression "TCA isn't used for depression anymore exept if pt is 70 YO has been on it for 40 years"

•SSRIs have a **wide therapeutic index**"u need to take 30 - 50 times to develop symptoms".

•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)"2 weeks after administration"

•Rarely fatal, with ingestions of up to 30 times the daily dose associated with few or no symptoms

Citalopram"celexa":

•QTc prolongation , Seizures.

SSRI isn't one time medication , u need to take it everyday doesn't cause addiction , Unlike Benzodiazepine u take it only when u are depressed, or having airplane phobia but it has high dependence rate.

"Remember" SSRIs may be associated with SIADH at therapeutic doses,Most cases of hyponatremia develop within 1 month and frequently within the first 2 weeks.

If u have Middle age guy with sizure + hyponatremic > he either took Amphetamine or on SSRI. but in elderly with seizure + hyponatremic it's hydrochlorothiazide until proven otherwise

Diagnostic Strategies and Management?

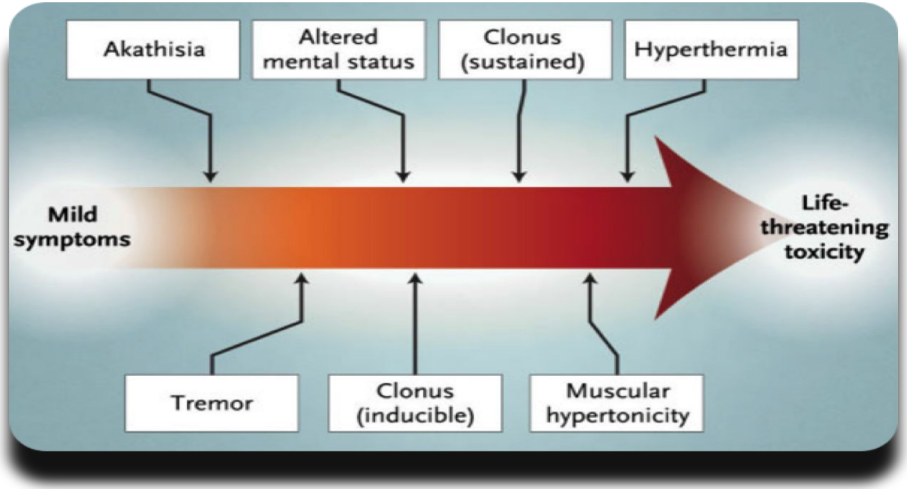
NON SPECIFIC!!

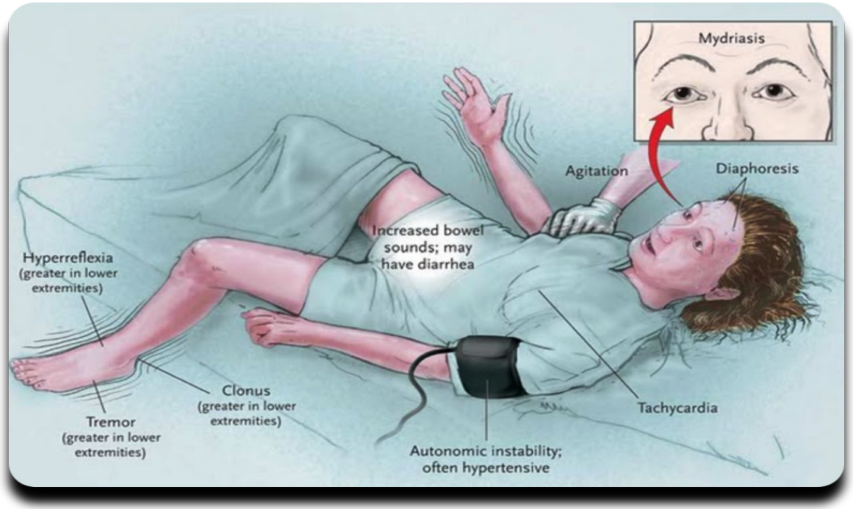
SSRI Dx has no specific Toxidrome but it causes Serotonin syndrome, occur if someone had SSRI with Cocaine , or with TCA or another SSRI.

Serotonin Syndrome 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 is the magic one , remember if u see clonus with other symptoms it's serotonin syndrome

Management:

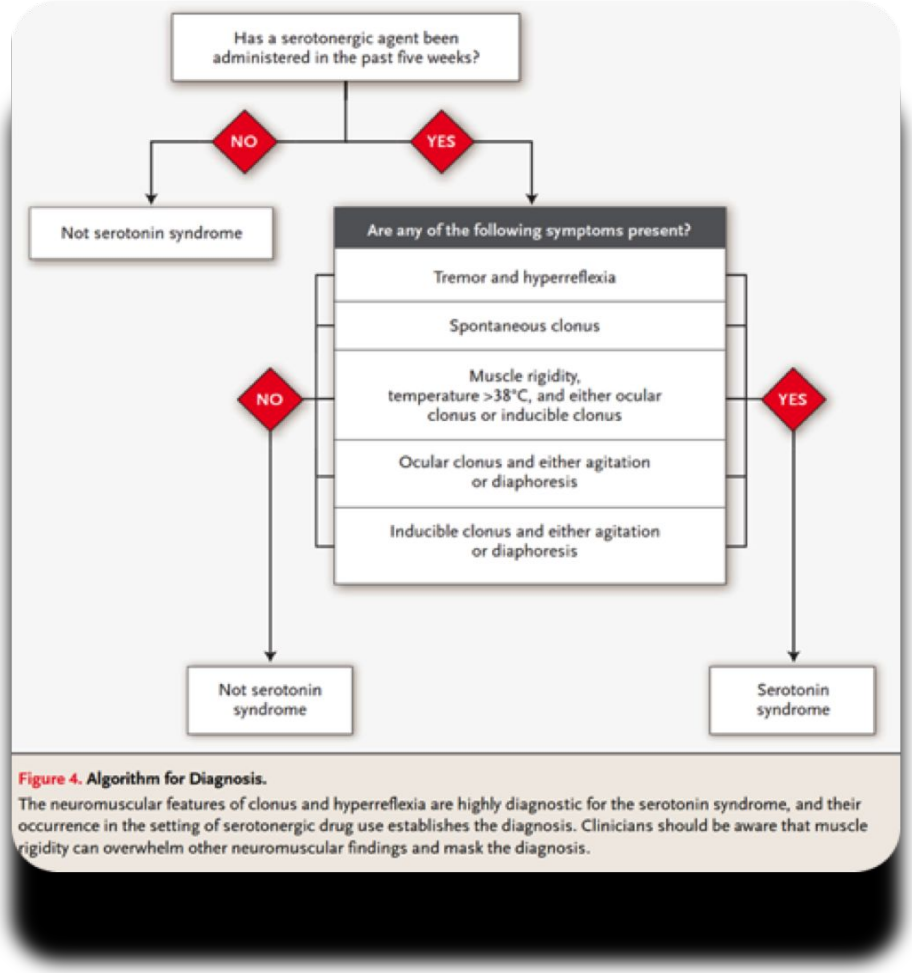


Figure 4. Algorithm for Diagnosis.
The neuromuscular features of clonus and hyperreflexia are highly diagnostic for the serotonin syndrome, and their occurrence in the setting of serotonergic drug use establishes the diagnosis. Clinicians should be aware that muscle rigidity can overwhelm other neuromuscular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

Hunter's criteria for Serotonin Syndrome

You have to know it

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, 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

very spastic

Management: Discontinue the offending agent, Supportive, **Cyproheptadine** (Serotonin Antagonist).

If u had these Symptoms in a patient what would u think of ? "DDx of serotonin syndrome"
1-phyochromocytoma 2-malignant hyperthermia which is reaction to anesthetic Muscle relaxant 3- Nuroleptic malignant syndrome"happens with Dopamenrgic as Haloperidol, antipsychotic,anticholinergic , sympathomimetic " you need to know all these DDx "underlined by Black"

Discontinuation Syndrome: Rarely”Not” life-threatening, Can result in significant discomfort, Typically starts within 3 days after therapy is stopped. “if someone on SSRI & they suddenly ask him to stop , they basically have headache , sleep disturbance , uncomfortable”

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”headache ”, tremor, anorexia, diaphoresis)

So the psychiatrist will put them back on SSRI & Start Tapering the dose gradually