Antidepressant Overdose!

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What's Available?

Hello there

Doctor said the contents of the lecture only cover 20% of the objectives (which are not given) and you need to read extra resources, so it's your choice ^^

Please focus on the mechanisms, doctor said 90% of MCQ is about mechanisms

Added notes are colored by blue (dark and light) , Good luck everyone,

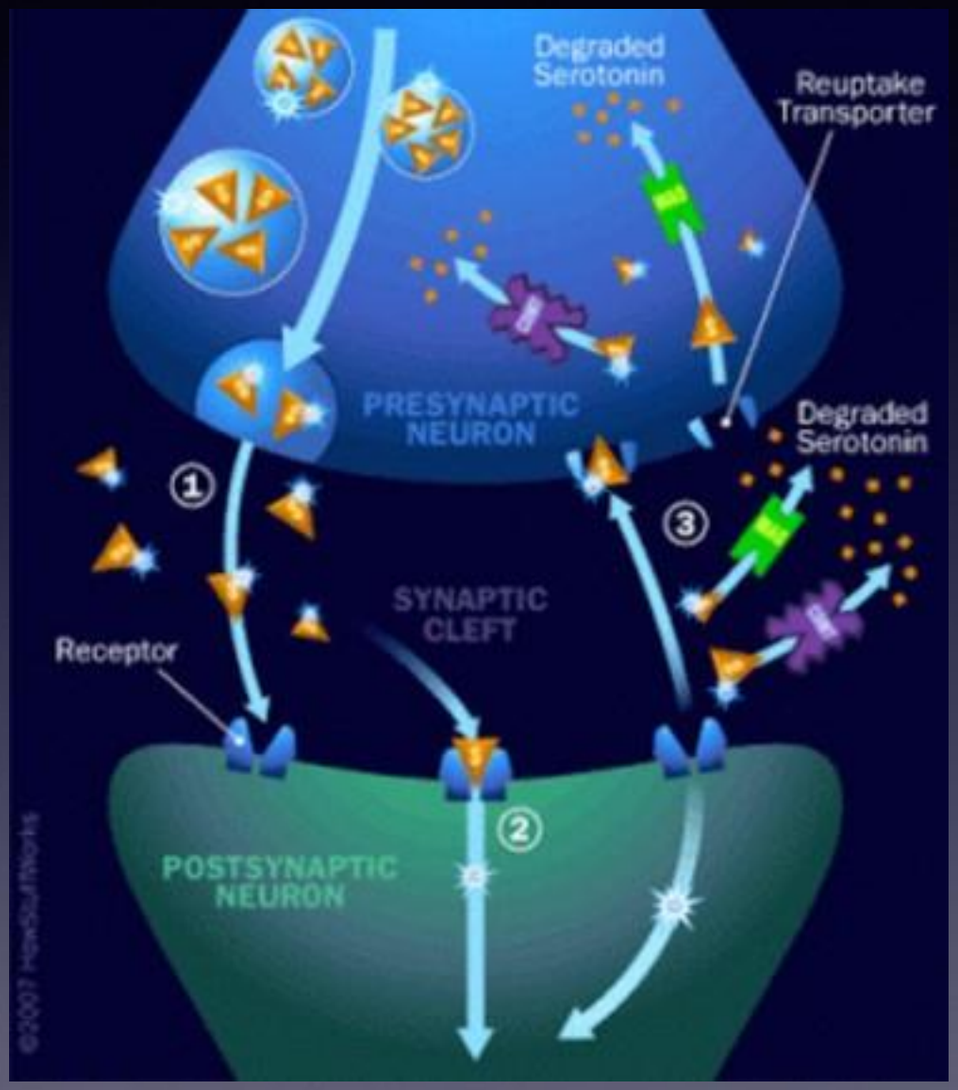
your colleague: Raghad Al Mutlaq

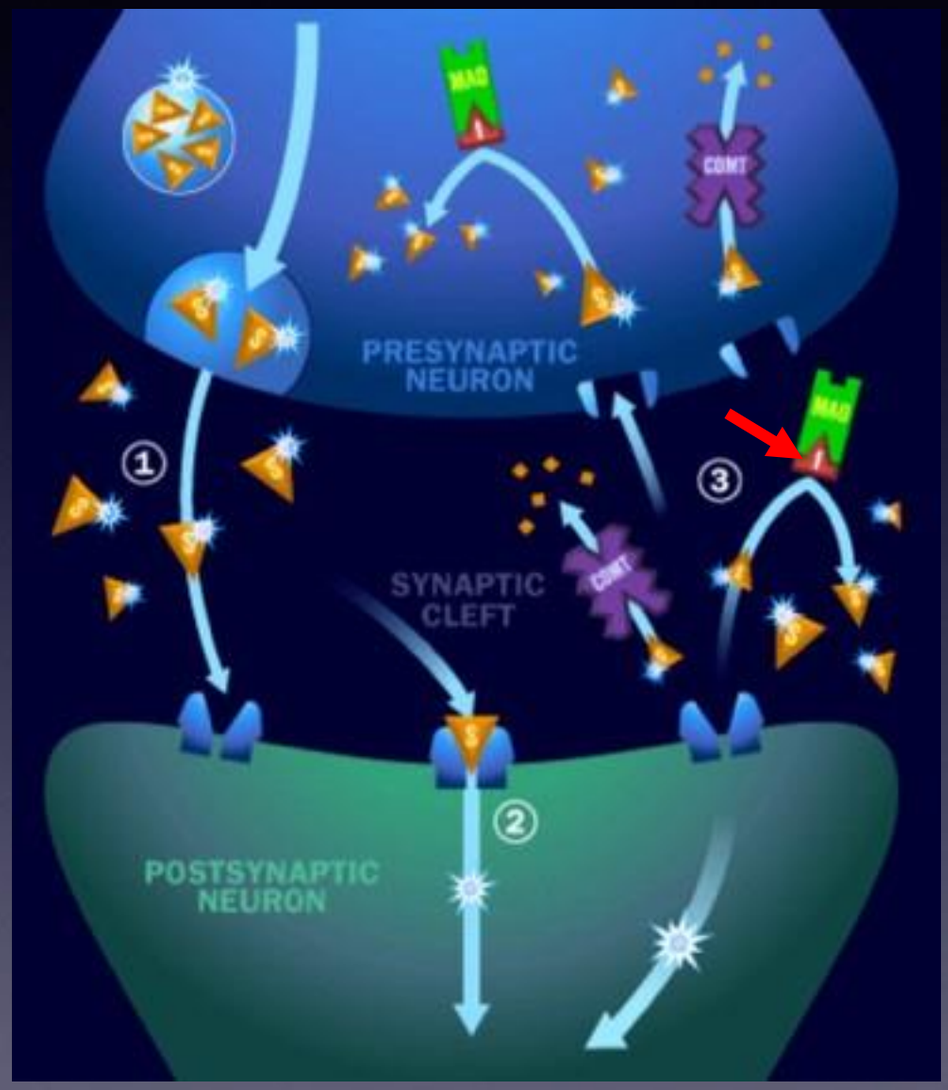
MAOI’s (no longer used, it has many side effects)

- **TCA** (Tricyclic Antidepressants)
- **SSRI** (Selective serotonin reuptake inhibitors)
- SNRI (serotonin norepinephrine reuptake inhibitors)

Monoamine Oxidase Inhibitors (MAOIs)

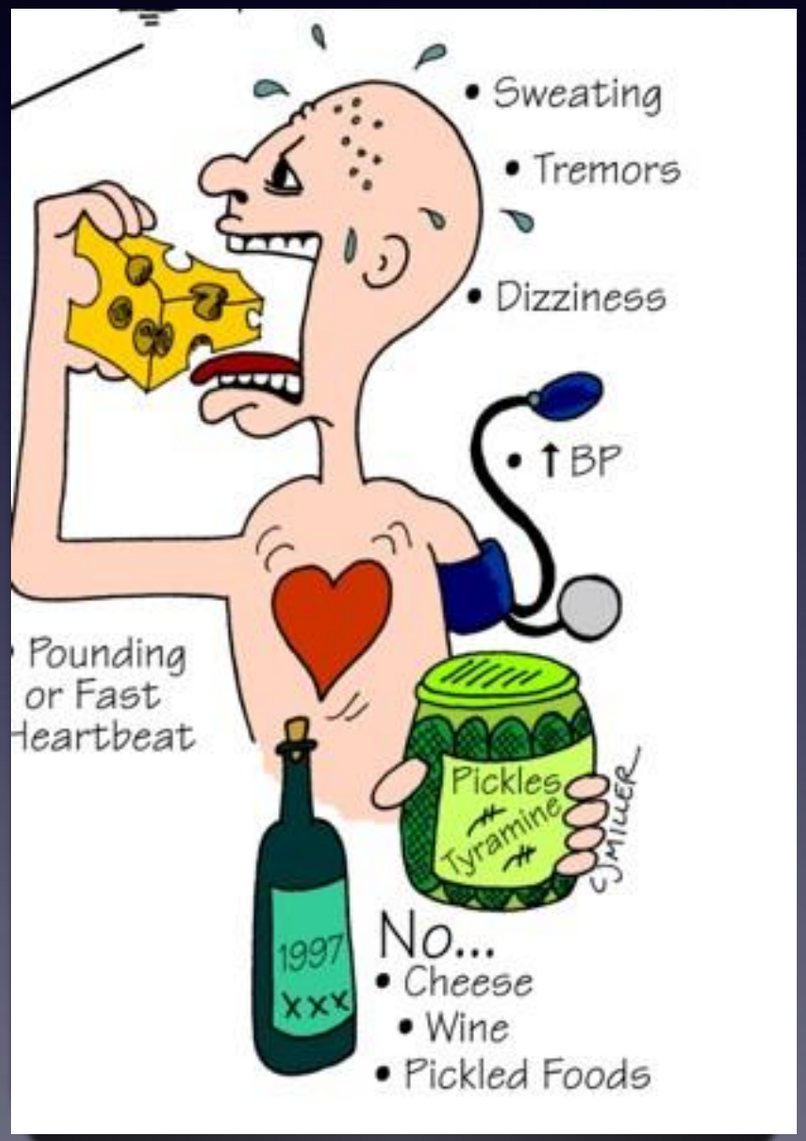
Monoamine oxidase *(light green)* is an enzyme which degrades excitatory neurotransmitters (NT - *orange tringles*) into non-active metabolites. Drugs *(red arrow in pic 2)* bind irreversibly to monoamine oxidase → blocking the normal pathway, thereby preventing inactivation of the NT → increase the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





Toxicity?

Aged cheese and wine have double effect with Monoamine oxidase inhibitors because they both contain: Tyramine precursor → more release of NE → hypertensive crisis (theoretical - not important)



TCA's

You NEED to know everything about them

(other uses: migraine)

e.g., amitriptyline

How many different MOA do TCA's have?

- 3
- 4
- 5
- 6
- **7 (YOU SHOULD KNOW THEM ALL)**

TCA's

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

Everything in this slide is IMPOTANT

1- Na channel blocking (very cardio-toxic in overdoses cause it widens QRS → Vtac.) it makes the QRS more than 160 – in general over 120 is wide, in overdosed over 100 is considered wide (millisecond)

2- Alpha 1 receptor blocade, in blood vessels → hypotension

3- Reuptake inhibition of the Excitatory NT

4- Muscarinic receptors blocking, anti-cholinergic effect → sympatho-mimetic (on examination you'll find: sweat skin, wide pupil, low bowel sounds, extended bladder in ultrasound)

5- Histamine receptor blockade (also act as anti-cholenergic, prolong QT interval + tachycardia)

6- K channel blocking (widens QT)

5,6 - both prolong QT → torsade

difference between Vtac and torsade on ECG: monomorphic and polymorphic (respectively)

7- Indirect GABA antagonism.

Examples of GABA agonists: benzodiazepine, alcohol

TCA's

Symptoms in toxicated Patients:

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

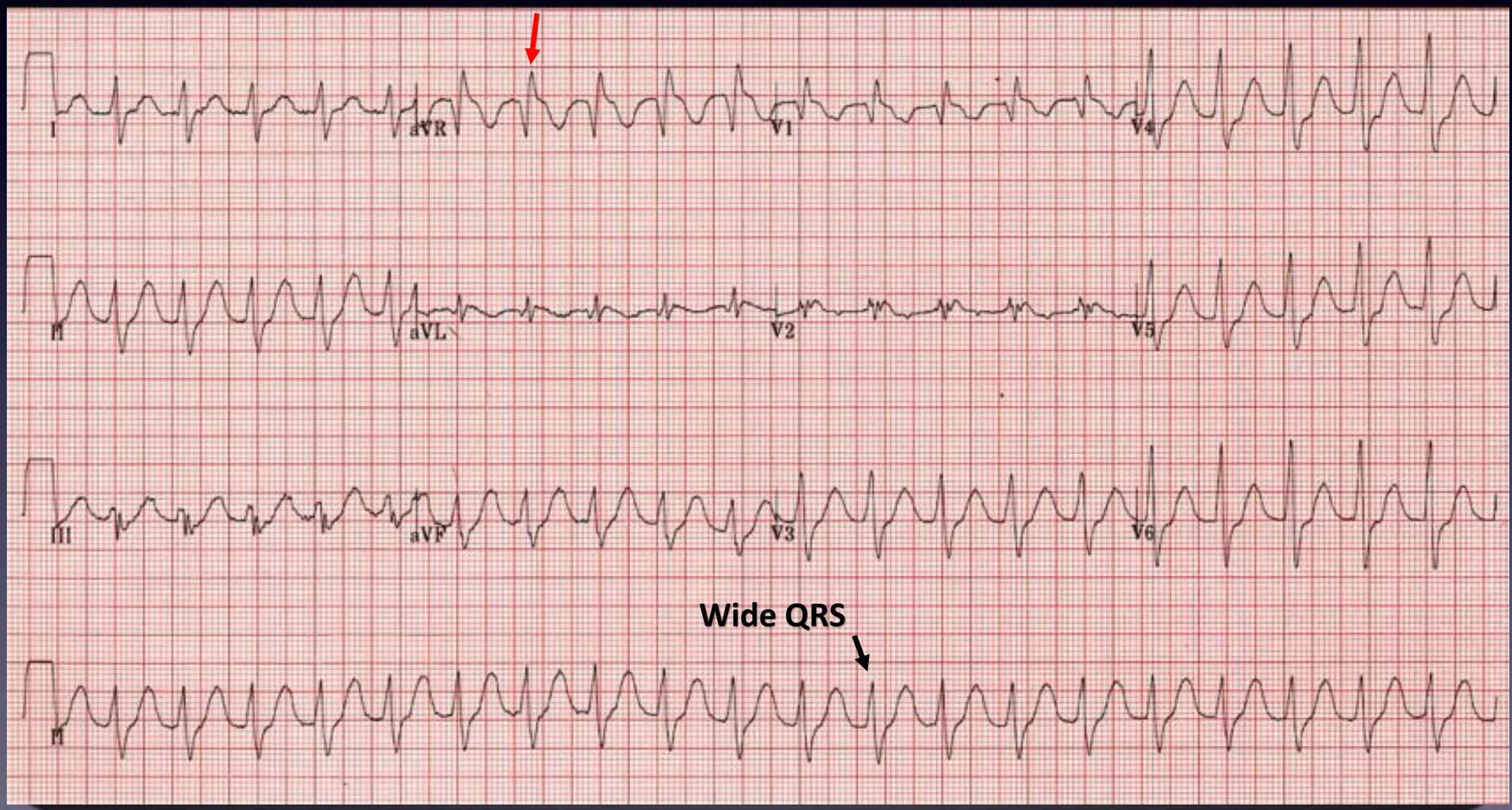
Alpha$_1$-Blockade
Reflex tachycardia
Miosis or midrange pupils

Excitation
Agitation
Delirium
Myoclonic jerks
Hyper-reflexia
Clonus
Seizures
Hyperthermia

Inhibition
Sedation
Coma

WHAT'S ABNORMAL?

Prominent (or terminal) R in aVR when seeing it in the exam think of TCA



- Sinus Tachycardia
- Prolonged QT Interval
- Widening of the QRS interval
- RAD (right axis deviation)
- Prominent R in aVR

Those colored in RED are the most important you most know them!

COMPLICATION
Hypertension (early and transient) 2ndry to anticholinergic effect
Hypotension 2ndry to alpha-receptor blockage
Sinus tachycardia 2ndry to anticholinergic effect + anti-histamine
Ventricular tachycardia (monomorphic) 2ndry to Na channel blockage
Ventricular tachycardia (polymorphic) (torsades de pointes) 2ndry to K channel blockage

Doctor skipped this but he said 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

Doctor promised not to ask about details in the exam because there are still papers on the management

However, you SHOULD know, at least, these two mechanisms:

- **Plasma Alakalinization (NaHCO3/ Hyperventilation)**
- **Sodium Load (NaHCO3 or 3% Saline)**

Plasma Alakalinization

Put in mind: most of the medications when it's bound to protein, it's useless! It can't act on the target cells. We give Sodium bicarbonate ($NaHCO_3$) for alkalization (we also hyperventilate the patient to bring the CO_2 down → increasing the pH)

MOA:

- 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** (**prevent Vtac**)

* للفهم فقققط ومو مطالبين فيه وإذا مو مفهوم تجاهلوه

تأين الأحماض:

الأحماض عبارة عن شقين: موجب وسالب. في المحاليل المتعادلة، الأحماض تتحلل للشقين الأساسين المكونين لها (بمعنى تتأين)، الأحماض القوية تتأين تماماً (بمعنى كل الجزئيات تتحلل لشقين)، الأحماض الضعيفة تتأين جزئياً، بمعنى جزء منها يتحلل وجزء يبقى على صورة الحمض.

pKa: It is the PH (of the solute) at which 50% of the added substance will be in the ionized form, and 50% in the non-ionized form

الآن، وش يصير لما يكون المحلول غير متعادل أو قاعدي تحديداً؟ (تذكير: القاعدة تميل إلى كسب بروتون والحمض العكس)

اللي يحصل إن القاعدة تأخذ البروتون من الجزء الغير متأين (اللي على صورة حمض) وتحوله إلى متأين – تزيد عملية التأين

$HA + Y \leftrightarrow HY^{+} + A^{-}$ (المحلول قاعدي أخذ البروتون من الحمض وطلع أيون سالب)

العكس إذا كانت المادة المضافة قاعدة، وجودها في محلول قاعدي يضعف عملية تأينها.

Now depending on the substance:

In acids: alkalinizing the solute → more ionized form

In bases: alkalinizing the solute → more non-ionized form

TCA is a base → alkalinizing means increasing the non-ionized form which is the inactive form, it acts by unbinding the active form from Na channels

hope it’s clear ☹

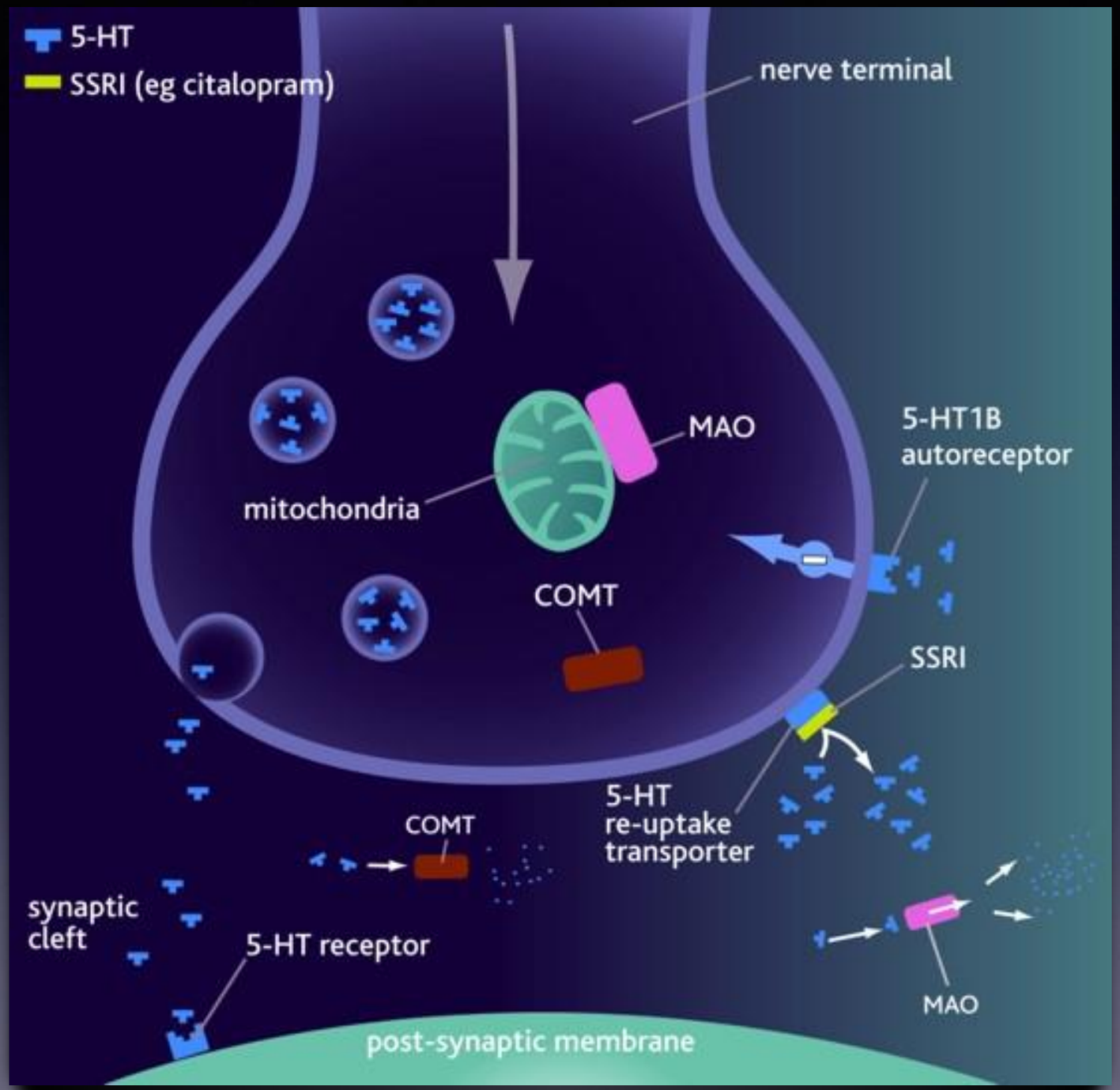
Sodium Load

You just overcome the Na blockage by giving more Na in the form of (hypertonic saline and $NaHCO_3$)

- Leads to ***over-riding Na-Channel Blockade*** due to an increased Na concentration gradient across the cell membrane

SSRI’s


10mg
PAXIL
TABLETS
Lexapro
PROZAC
FLUOXETINE
HYDROCHLORIDE
10 mg Tab
Lilly


5-HT
SSRI (eg citalopram)
nerve terminal
MAO
5-HT1B
autoreceptor
mitochondria
COMT
SSRI
5-HT
re-uptake
transporter
COMT
synaptic
cleft
5-HT receptor
MAO
post-synaptic membrane

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's a waist to use SSRI when planning to suicide ☺)

- QT prolongation
- Seizures

Remember

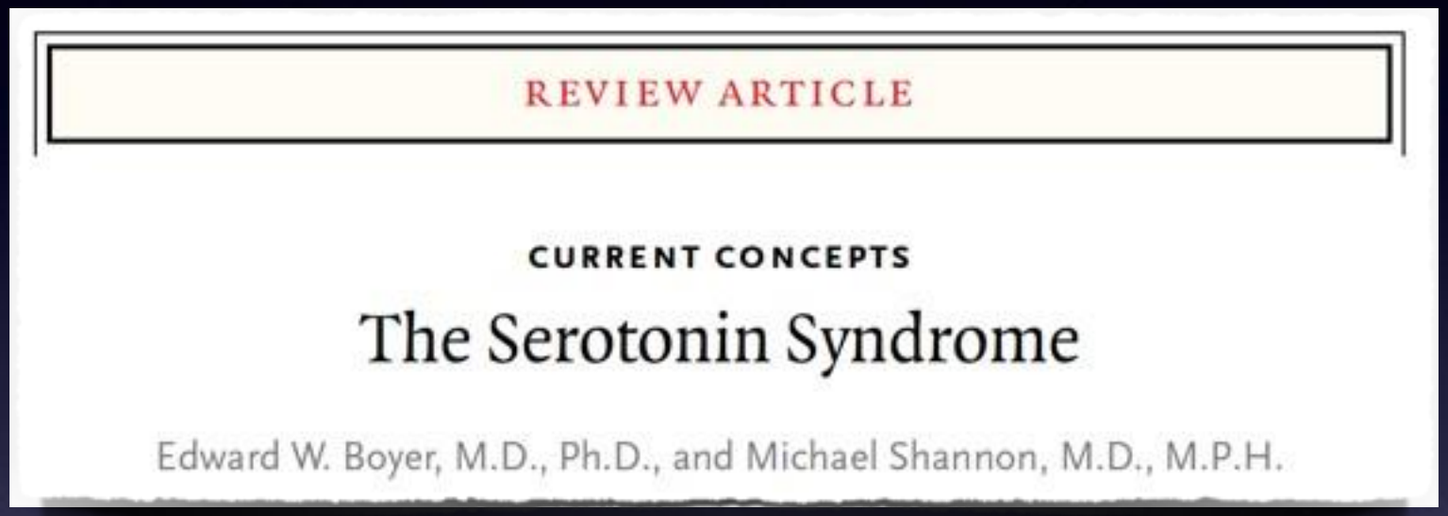
- SSRIs may be associated with SIADH (synd. Of inappropriate anti-diuretic hormone) at therapeutic doses

- Most cases of hyponatremia develop within 1 month and frequently within the first 2 weeks

Diagnostic Strategies and Management?

THEY ARE NOT SPECIFIC!!
Hx mainly for diagnosing
And supportive therapy for management

Serotonin Syndrome



REVIEW ARTICLE

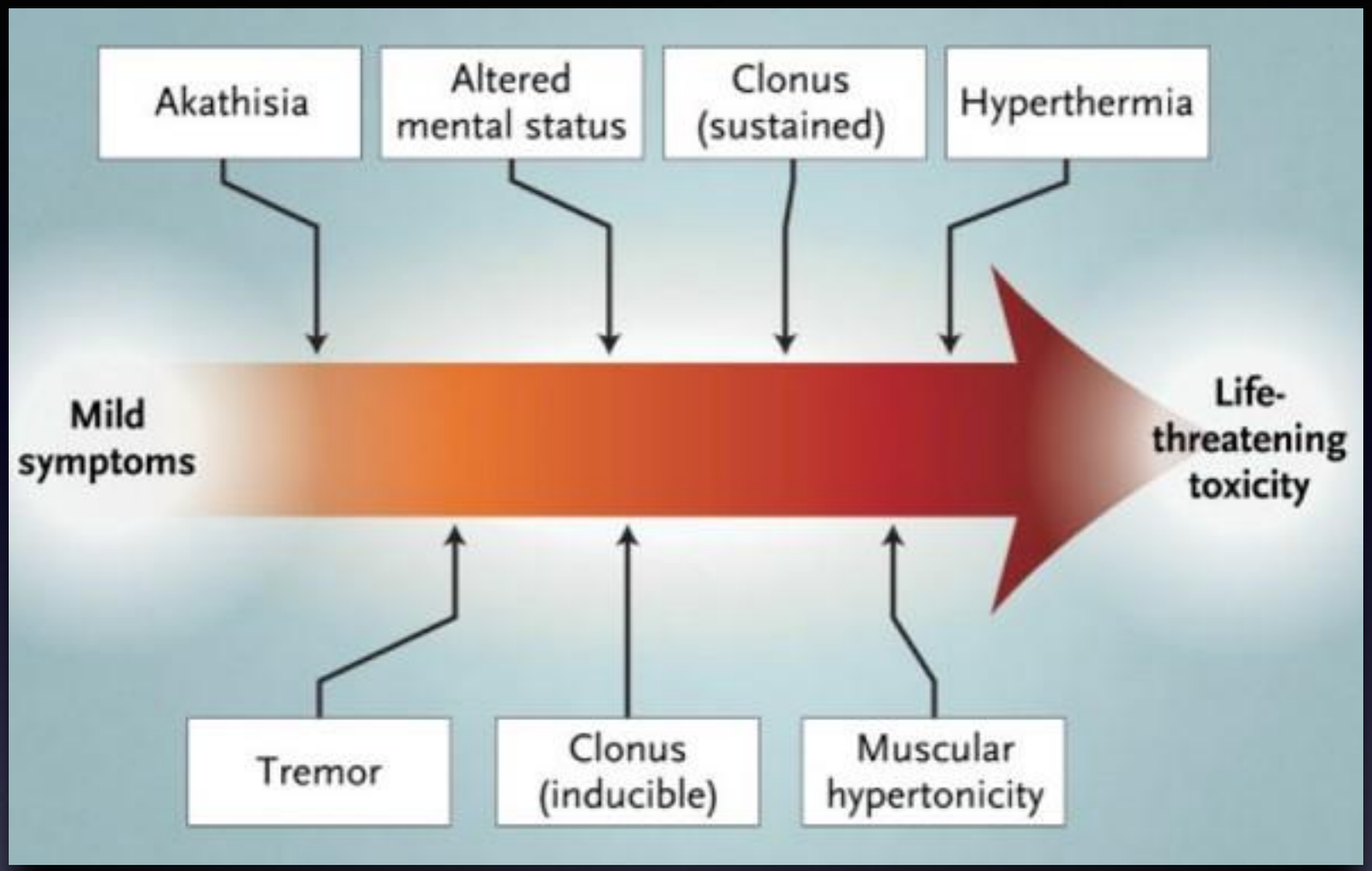
CURRENT CONCEPTS

The Serotonin Syndrome

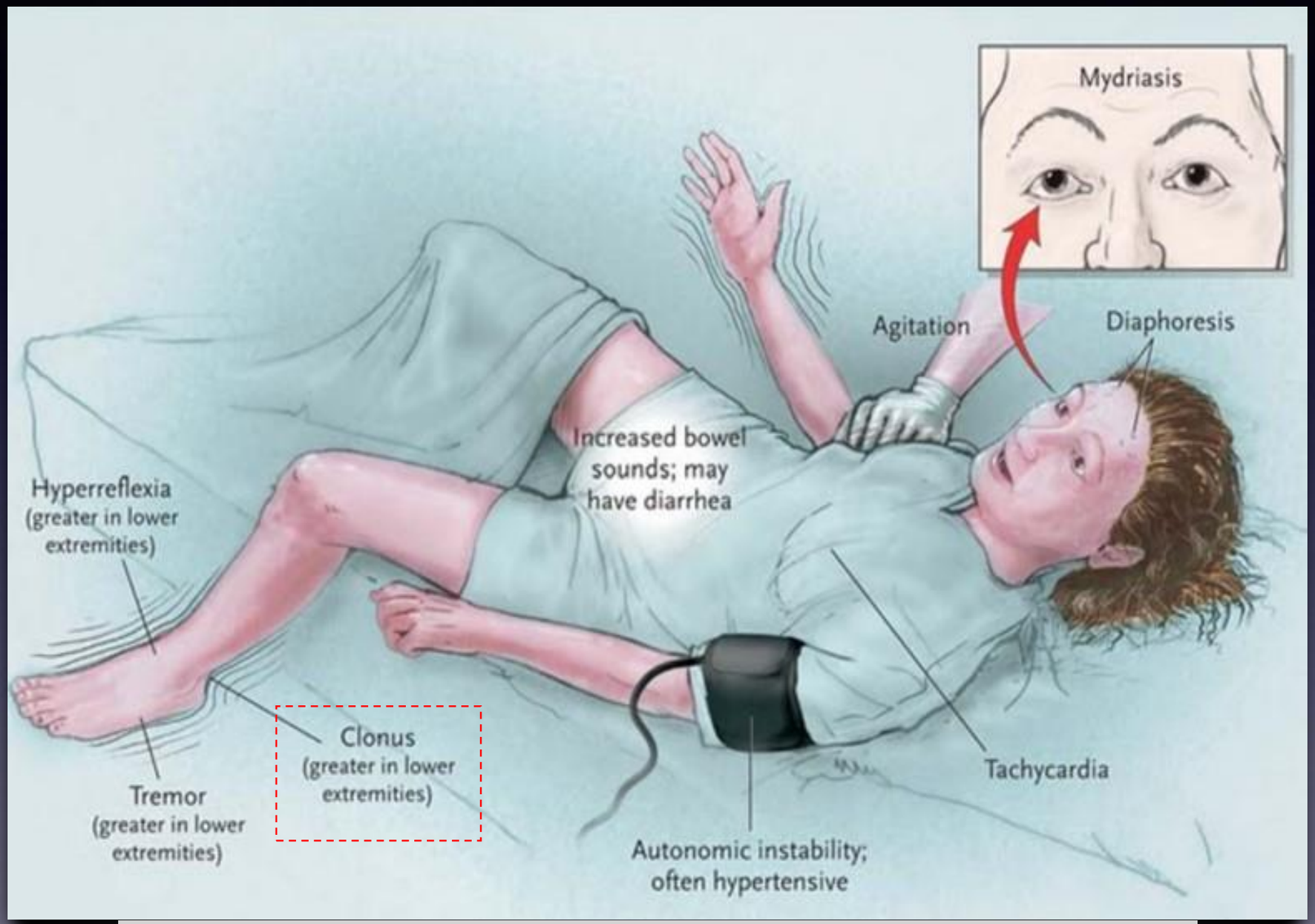
Edward W. Boyer, M.D., Ph.D., and Michael Shannon, M.D., M.P.H.

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


Akathisia
Altered mental status
Clonus (sustained)
Hyperthermia
Mild symptoms
Life-threatening toxicity
Tremor
Clonus (inducible)
Muscular hypertonicity

Clinical Features



Clonus associated with overdose in Hx → think of Serotonin Synd. Immediately

Management

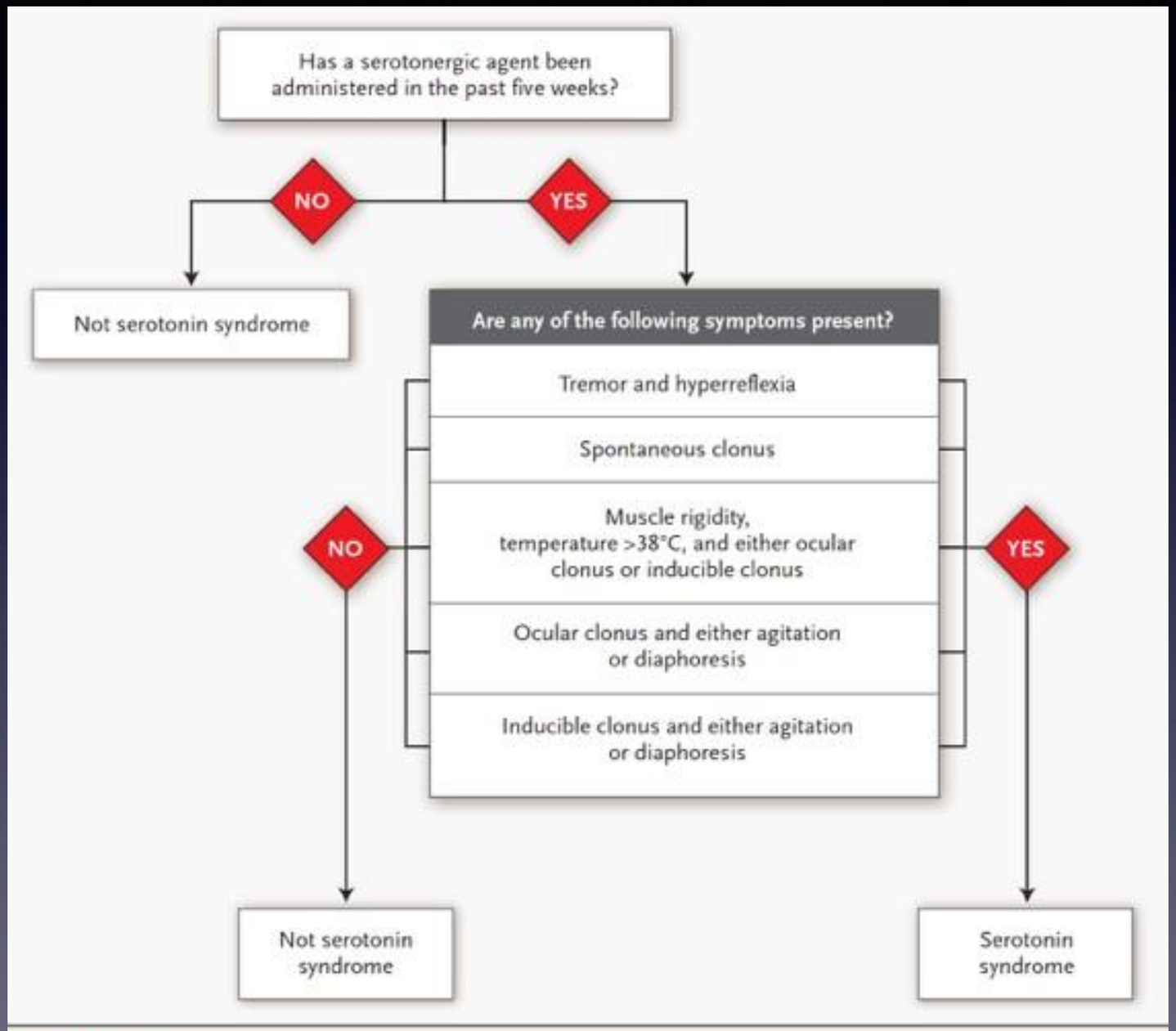


Figure 4. Algorithm for Diagnosis.

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

The Hunter 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

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

Serotonin Syndrome

Management

- Discontinue the offending agent
- Supportive
- Cyproheptadine (know the name only - Serotonin Antagonist) (antidote)

Discontinuation Syndrome

Psychiatric drugs, such as antidepressants and antipsychotics, are commonly prescribed to treat a wide variety of mental disorders, such as depression, bipolar disorder orschizophrenia. 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). http://psychcentral.com/lib/what-is-discontinuation-syndrome/0001305

- Rarely life-threatening
- Can result in significant discomfort
- Typically starts within 3 days after therapy is stopped

Signs & Symptoms

6 Categories

Dysequilibrium (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)

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