Antidepressant Overdose!

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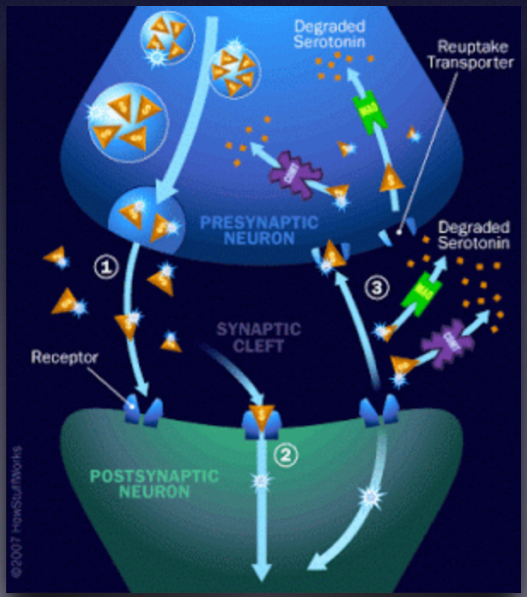
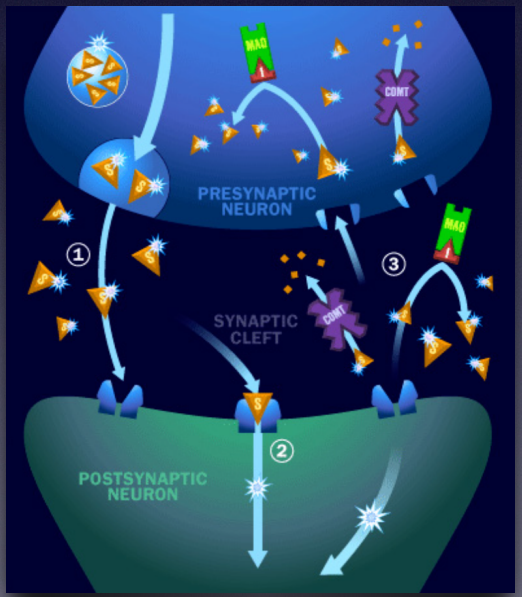
What's Available?

- MAOI's
- **TCA**
- **SSRI**
- SNRI

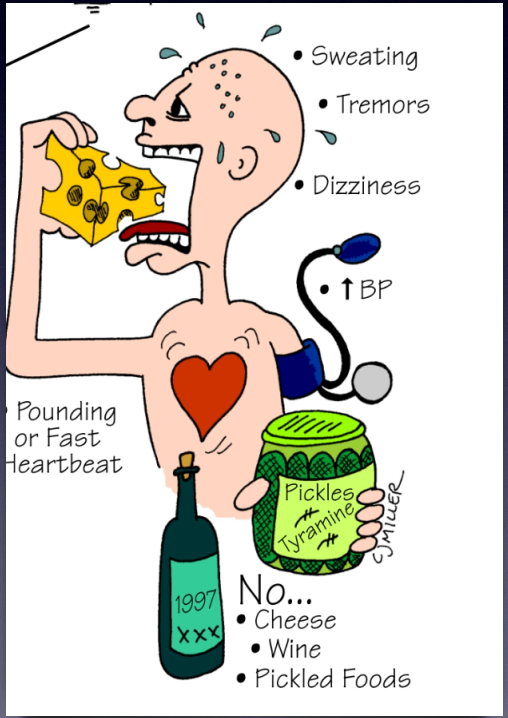
Monoamine Oxidase Inhibitors (MAOIs)

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





What Happens in MAOI Toxicity?



TCA's


Amitriptyline HCl
Tablets, USP
10 mg
100 Tablets
Rx only
Manufactured by Sandoz Inc., Broomfield, CO 80020
SANDOZ

How many different MOA do TCA's have?

- 3
- 4
- 5
- 6
- 7

How many different MOA do TCA's have?

- 3
- 4
- 5
- 6
- **7**

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

Peripheral & Central Effects of TCA'S

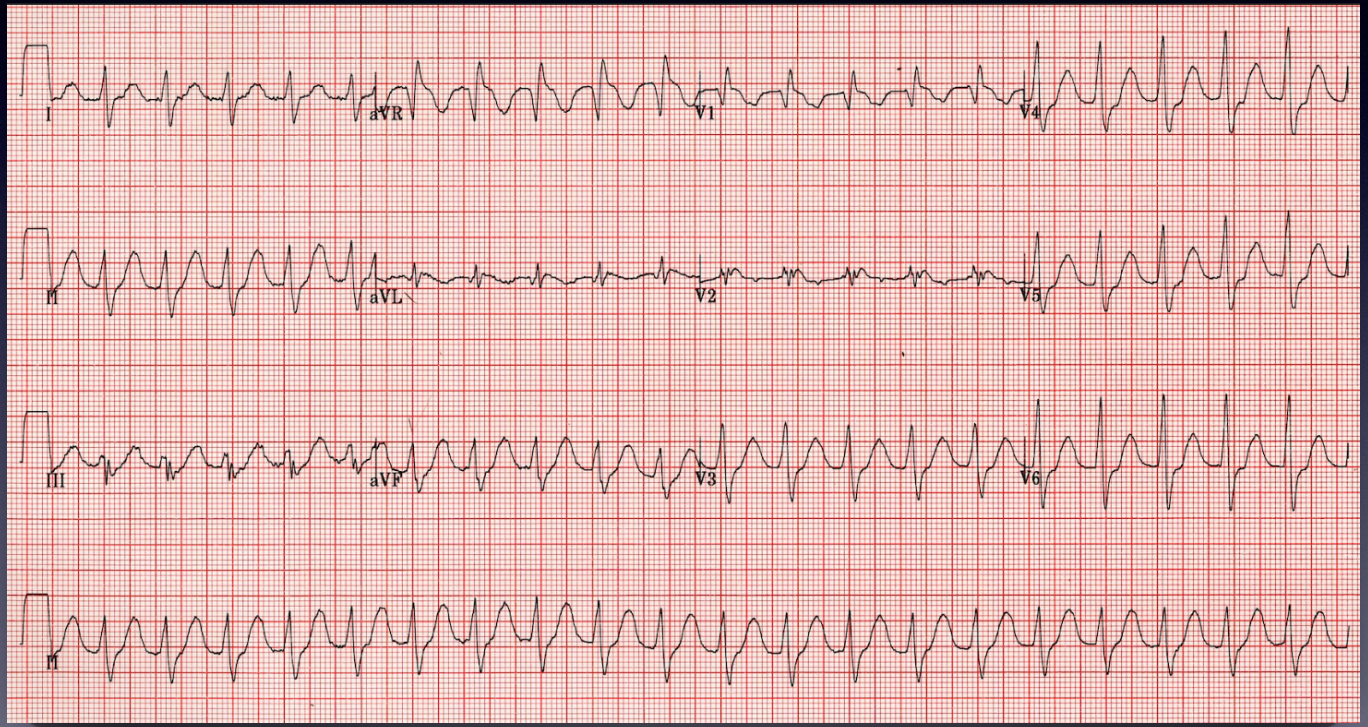
Anticholinergic
Tachycardia
Hyperthermia
Mydriasis
Anhydrosis
Red skin
Decreased bowel sounds
Ileus
Urinary retention
Distended bladder

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

Excitation
Agitation
Delirium
Myoclonic jerks
Hyper-reflexia
Clonus
Seizures
Hyperthermia

Inhibition
Sedation
Coma

WHAT'S ABNORMAL?



- Sinus Tachycardia
- Prolonged QT Interval
- Widening of the QRS interval
- RAD
- Prominent R in aVR

COMPLICATION
Hypertension (early and transient)
Hypotension
Sinus tachycardia
Ventricular tachycardia (monomorphic)
Ventricular tachycardia (polymorphic) (torsades de pointes)

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

- **Plasma Alkalinization ($NaHCO_3$/ Hyperventilation)**
- **Sodium Load ($NaHCO_3$ or 3% Saline)**

Plasma Alkalinization

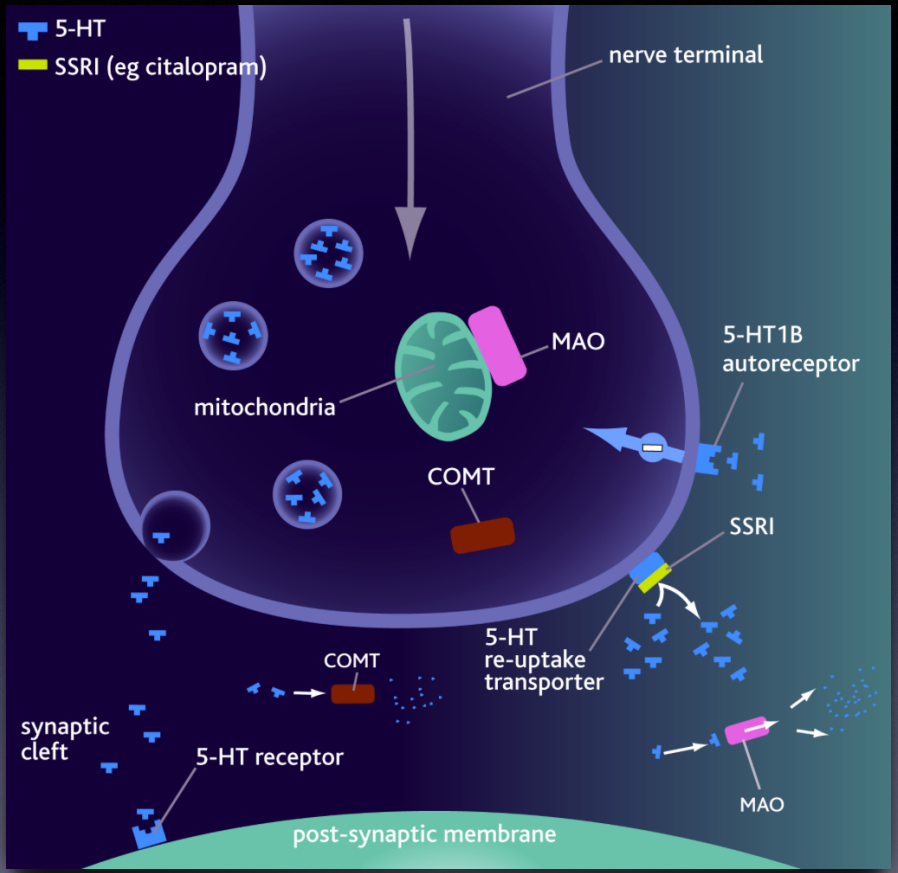
- Promotes ***TCA protein binding***
- Plasma proteins act as a sink that sequesters TCA's away from the sites of toxicity

Sodium Load

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

SSRI's


10mg
PAXIL
PAROXETINE HCl
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
- 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

- QTc prolongation
- Seizures

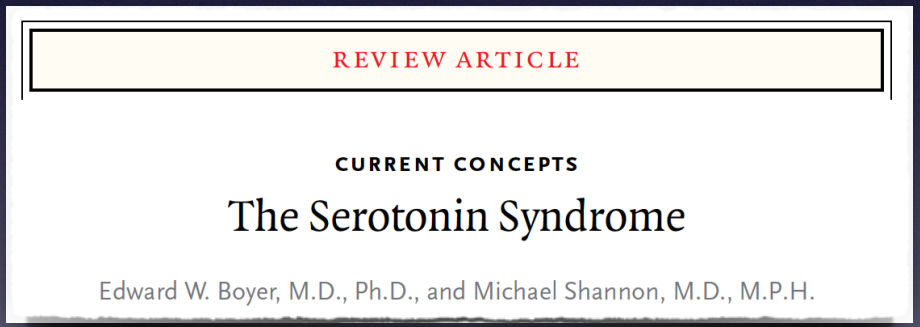
Remember

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

Diagnostic Strategies and Management?

NON SPECIFIC!!

Serotonin Syndrome



REVIEW ARTICLE

CURRENT CONCEPTS

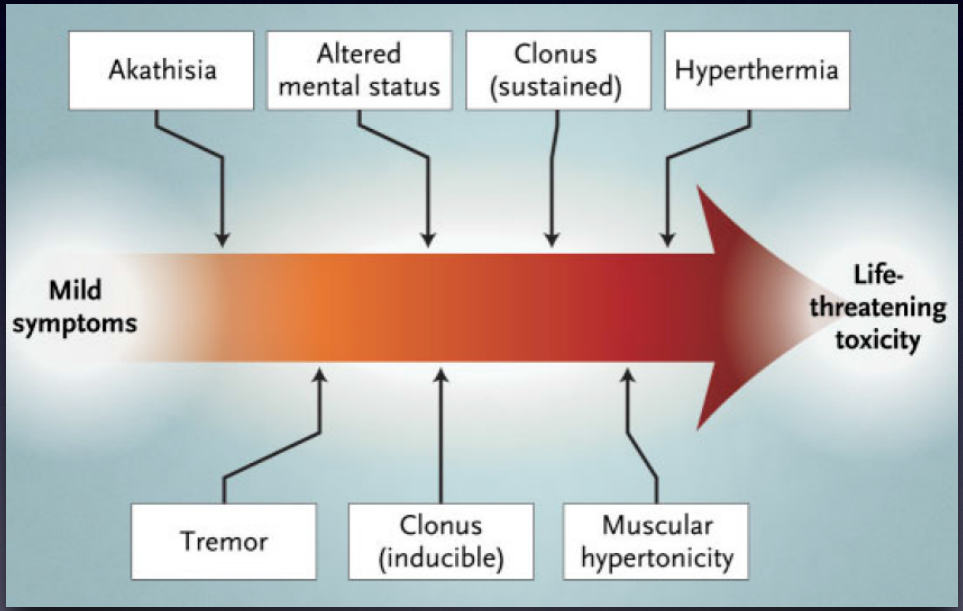
The Serotonin Syndrome

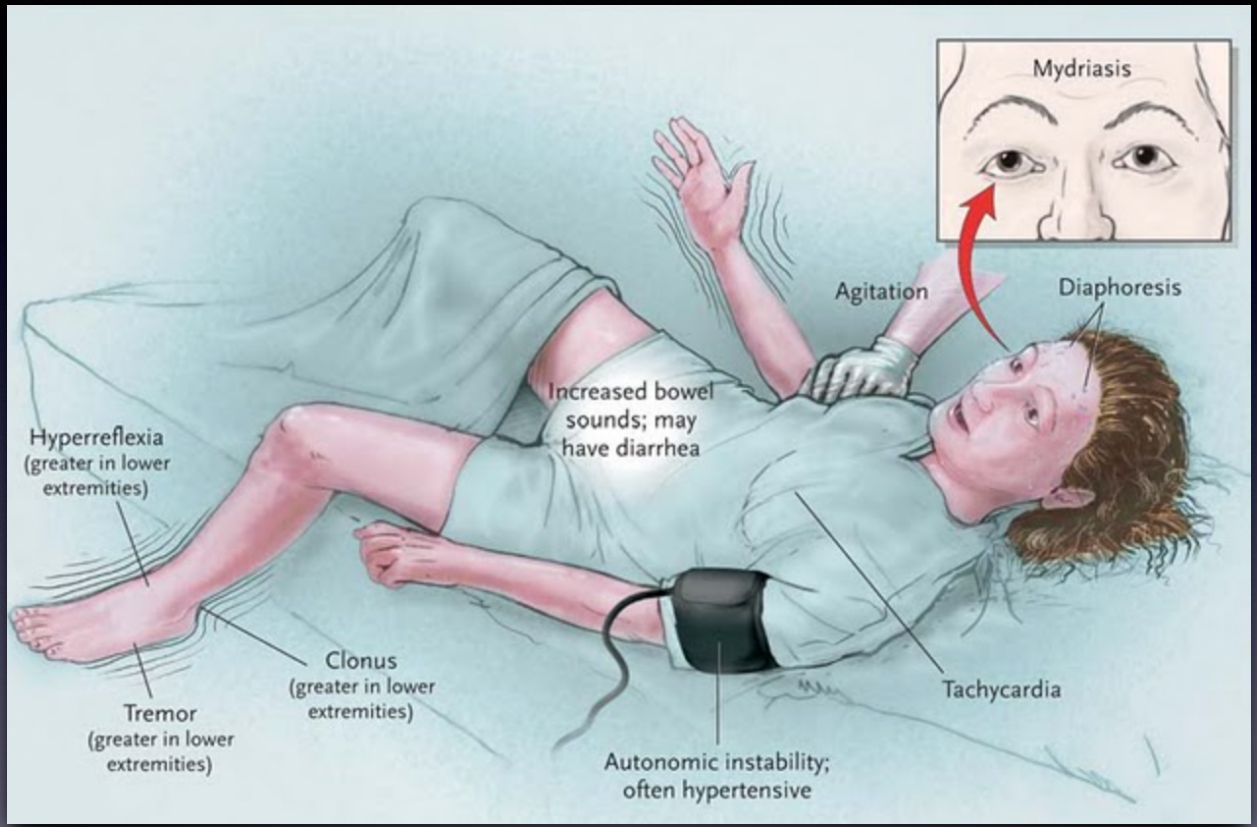
Edward W. Boyer, M.D., Ph.D., and Michael Shannon, M.D., M.P.H.

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

Clinical Features




Mydriasis
Agitation
Diaphoresis
Increased bowel sounds; may have diarrhea
Hyperreflexia (greater in lower extremities)
Clonus (greater in lower extremities)
Tremor (greater in lower extremities)
Tachycardia
Autonomic instability; often hypertensive

Management

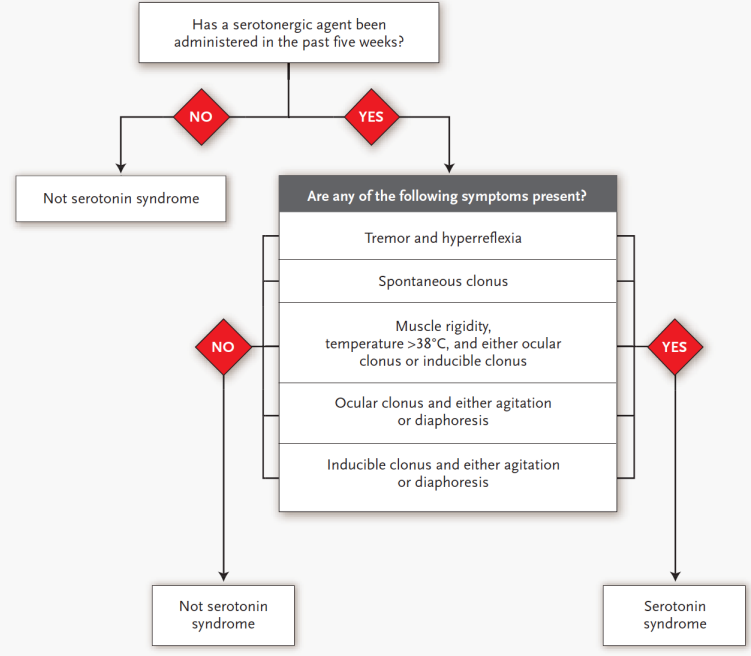


Figure 4. Algorithm for Diagnosis.

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 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

Management

- Discontinue the offending agent
- Supportive
- ***Cyproheptadine*** (Serotonin Antagonist)

Discontinuation Syndrome

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

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)

QUESTIONS?

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