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# Serotonin Toxicity: Clinical Recognition and Forensic Interpretation

**Amy L. Patton, NREMT, PhD**

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## Disclosures

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I have no conflicts of interest.

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## Learning Objectives

1. Describe serotonin and the mechanisms underlying serotonin toxicity.
2. Identify key clinical features of serotonin syndrome and differentiate it from other toxidromes.
3. Evaluate the role of polypharmacy, particularly tramadol and trazodone, in precipitating toxicity.
4. Interpret the investigative and forensic implications of serotonin syndrome in drug-impaired and toxicology cases.

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## Module 1

**Overview, History, and Mechanism of Serotonin Toxicity**

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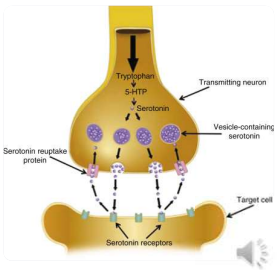
## Serotonin

- **Neurotransmitter also known as 5-hydroxytryptamine, or 5-HT**
- **Synthesized from the amino acid tryptophan**
- **Plays a role in mood regulation, sleep, appetite, pain perception, and thermoregulation**
- **Present in both the central nervous system and peripheral tissues**

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https://www.sciencedirect.com/science/chapter/edited-volume/abs/pii/B9780128194010000067

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## What is Serotonin “Syndrome”?

*A potentially life-threatening drug reaction caused by excessive serotonin receptor activation in the central and peripheral nervous systems*

**Old View: Syndrome**


Idiosyncratic, rare, mysterious

**New view: Toxicity**

Dose-dependent, predictable, spectrum

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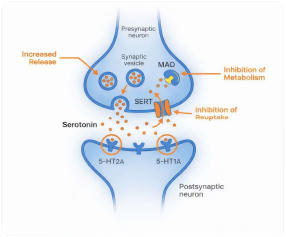
## Mechanisms Leading to Serotonin Toxicity




**Serotonin Reuptake Inhibition**
Drugs like SSRIs and SNRIs blocking serotonin reabsorption into neurons.

**Enhanced Serotonin Release**
Substances like amphetamines and tramadol directly stimulate serotonin release.

**Monoamine Oxidase Inhibition**
MAO inhibitors prevent serotonin breakdown.

**Serotonergic Receptor Agonism**
Certain drugs activate serotonin receptors without altering serotonin concentrat on.

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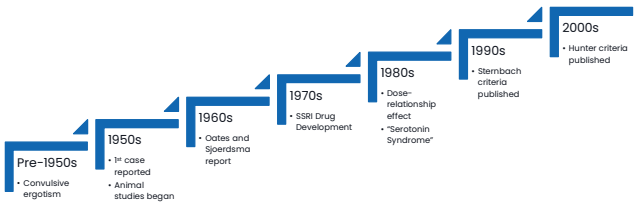
## Historical Perspective

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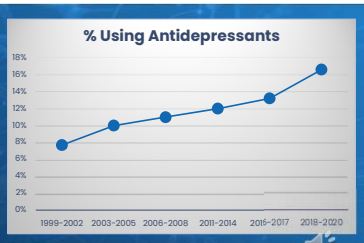
## Why This Matters Today

- Antidepressant prescribing has increased substantially since the 1990s
- Chronic pain treatment frequently includes Tramadol
- Trazodone commonly prescribed for insomnia

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## Module 1 Summary

- Serotonin is a widely distributed neurotransmitter
- Serotonin toxicity represents excessive receptor activation
- Toxicity is pharmacologically predictable
- Understanding mechanism improves recognition

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## Module 2

Clinical Presentation and Diagnostic Criteria

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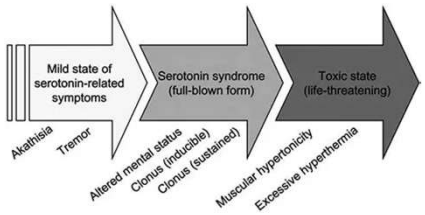
## The Clinical Spectrum

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## The Clinical Triad


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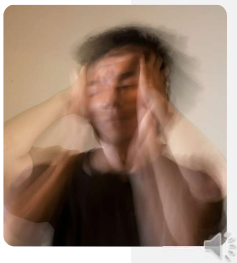
## Mental Status Changes

- Anxiety
- Confusion
- Delirium
- Nonspecific findings
- May resemble stimulant intoxication



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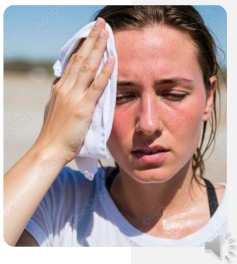
## Autonomic Symptoms

- Tachycardia
- Diaphoresis
- Hypertension
- Hyperthermia



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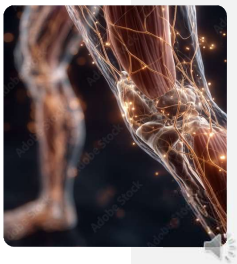
## Neuromuscular Findings

- Hyperreflexia
- Inducible ankle clonus
- Tremor
- Rigidity (severe cases)



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## Ankle Clonus

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https://pmc.ncbi.nlm.nih.gov/articles/PMC4498881/

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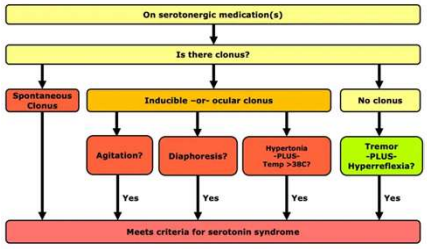
## The Hunter Criteria




Schematic for the various ways to satisfy the Hunter Criteria for serotonin syndrome.

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## Module 2 Summary

- Serotonin toxicity presents along a clinical spectrum
- Neuromuscular findings are key diagnostic clues
- Clonus and hyperreflexia particularly important
- Diagnosis is primarily clinical

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## Module 3

Causes, Polypharmacy, and High-Risk Drugs

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## Polypharmacy

**What is it?**
- Use of multiple medications simultaneously
- Common in treatment of chronic or complex conditions

**Considerations**
- Medications may affect the body in similar ways
- Drug–drug interactions may alter metabolism

**Relevance to Serotonin Toxicity**
- More than one drug may increase serotonin
- Effects can build on each other

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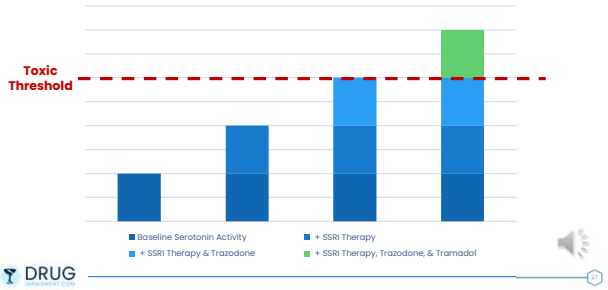
## Cumulative Burden

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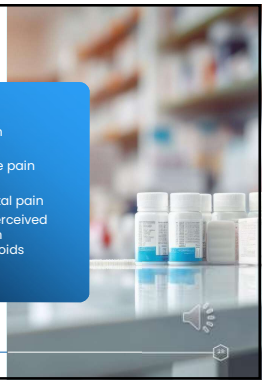
## Tramadol

**Pharmacology**
- Pain medication with opioid effects
- Increases serotonin levels by inhibiting serotonin reuptake
- Levels are affected by how the body metabolizes it
- Active metabolite: O-desmethyltramadol

**Clinical Use**
- Moderate pain management
- Post-operative pain
- Chronic musculoskeletal pain
- Sometimes perceived as "safer" than traditional opioids



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## Trazodone

**Pharmacology**
- Affects serotonin in multiple ways
- Blocks certain serotonin receptors
- Causes sedation
- Metabolized primarily by CYP3A4 in the liver

**Clinical Use**
- Commonly prescribed for insomnia
- Often used as an adjunct to antidepressants
- Lower doses used for sleep
- Higher doses used for depression

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## Pharmacokinetic Interactions

How the body interacts with drugs

**What Are Pharmacokinetic Interactions?**
- Changes in drug absorption, metabolism, or elimination

**Key Enzyme Systems**
- Many serotonergic drugs metabolized by cytochrome P450 enzymes
- Drug interactions may occur when one drug inhibits enzyme activity

**Clinical Example**
- Some SSRIs inhibit CYP2D6
- Tramadol metabolism is CYP2D6 dependent
- Enzyme inhibition → increased tramadol exposure
- Increased exposure → greater serotonergic activity

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## Pharmacogenetics

The genetic differences in drug metabolism in the population

**Common types:**
- Poor metabolizers
- Intermediate metabolizers
- Normal metabolizers
- Ultrarapid metabolizers

**Results:**

Genetic variability can lead to:
- Higher drug concentrations in poor metabolizers
- Reduced drug effect in ultrarapid metabolizers
- Unexpected adverse reactions

**Example:**
- Tramadol metabolism depends on CYP2D6
- Poor metabolizers may accumulate parent drug
- Ultrarapid metabolizers produce more active metabolite

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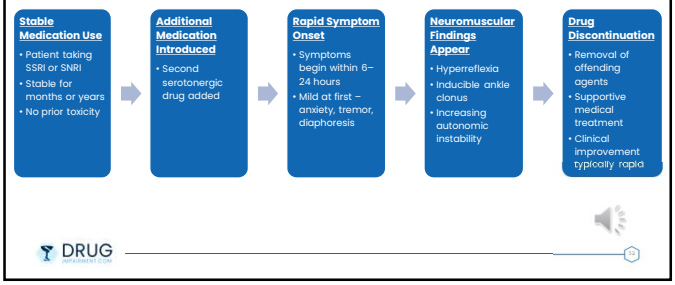
## Case Pattern Walkthrough

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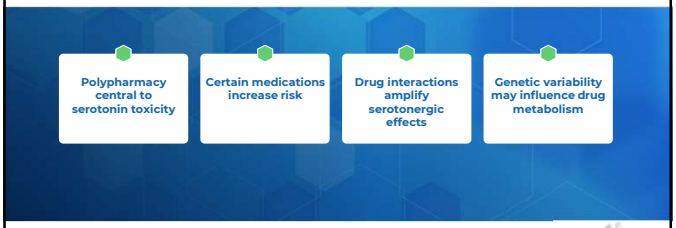
## Module 3 Summary

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## Module 4

Implications for Drug-Impaired Driving and Forensic Toxicology

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## Field Presentation

### Common Observations
- Agitation or restlessness
- Tremor
- Diaphoresis
- Tachycardia
- Confusion or disorientation

### Investigative Challenges
- May resemble stimulant intoxication
- Symptoms may appear rapidly
- Behavior may seem inconsistent

*Key Clue: Clonus and Hyperreflexia*

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## Serotonin Toxicity vs. Stimulant Intoxication

### Serotonin Toxicity
- Appearance:
  - Agitation or confusion
  - Diaphoresis
  - Tachycardia
  - Tremor
- Neuromuscular Findings:
  - Hyperreflexia
  - Inducible ankle clonus
  - Muscle rigidity (severe cases)
- Onset
  - Rapid (often within 6–24 hours)
  - Often follows medication change

### Stimulant Intoxication
- Appearance:
  - Agitation or paranoia
  - Diaphoresis
  - Tachycardia
  - Dilated pupils
- Neuromuscular Findings:
  - Normal or mildly increased reflexes
  - Clonus typically absent
- Onset
  - Related to recent drug use
  - May be dose-dependent

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## DRE Implications

### Evaluation Focus
- Assess neuromuscular activity
- Check for inducible ankle clonus
- Evaluate reflexes and tremor

### Important Considerations
- Overlap with stimulant impairment
- Vital signs may show autonomic instability
- Rapid symptom progression possible

### Documentation
- Record clonus and hyperreflexia findings
- Note medication history if available
- Consider need for medical evaluation

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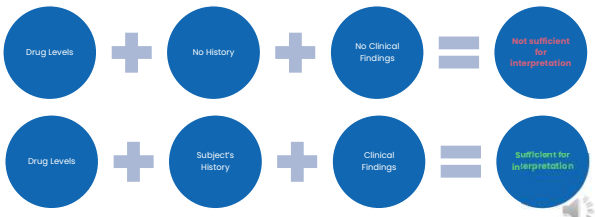
## Toxicology Interpretation




Interpretation requires ALL three components

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## Analytical Limitations

The Impact of Stop Testing

**What is Stop Testing?**
- Testing discontinued after primary drug identified

**Potential Issues**
- Additional drugs may go undetected
- Polypharmacy may be missed

**Example**
- Tramadol detected → testing stops

**Impact**
- Incomplete toxicological picture
- Complicates interpretation

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## Case Study Example

| | |
|---|---|
| **Scenario** | Erratic driving observed; Subject appears agitated and diaphoretic; Unable to remain still |
| **Examination** | Tremor present; Inducible ankle clonus observed |
| **History** | Recent tramadol prescription; Concurrent antidepressant use |
| **Analytical Results** | **+ Tramadol, + Sertraline, – Stimulants** |

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## Module 4 Summary

- Presentation may mimic other causes of impairment
- Neuromuscular findings provide important clues
- Toxicology interpretation requires context
- Polypharmacy may complicate conclusions

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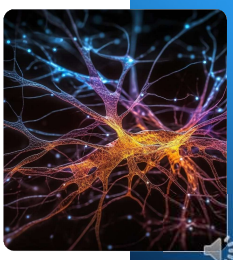
## Final Takeaways

- **Serotonin Toxicity is Predictable**
  It is pharmacologically driven – not idiosyncratic
- **Recognition is Clinical**
  Clonus and hyperreflexia are key
- **Polypharmacy Drives Risk**
  Additive and synergistic effects are observed
- **Interpretation Requires Context**
  Drug levels alone are insufficient



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