Target Audience: Emergency Medicine Residents, Medical Students

Primary Learning Objectives:

1. Recognize signs and symptoms of serotonin syndrome
2. Describe the drug/drug interactions at risk for precipitating serotonin syndrome
3. Discuss the risks and complications of serotonin syndrome, including hyperthermia and rhabdomyolysis
4. Recognize the role of sedation with benzodiazepines and supportive care as the foundation of treatment of serotonin syndrome
5. Describe the role of cyproheptadine (anti-serotonergic agent) in the treatment of serotonin syndrome

Secondary Learning Objectives: detailed technical/behavioral goals, didactic points

1. Check reflexes in a patient with possible serotonin syndrome
2. Obtain a medication history and understand risk for drug/drug interactions
3. Recognize that serotonin syndrome is a spectrum of disease that if untreated may progress
4. Recognize similarities and differences between the Sympathomimetic Toxidrome and Serotonin Syndrome

Critical actions checklist:

1. Obtain a medication and social history
2. Perform a thorough physical exam including reflexes
3. Volume resuscitate with isotonic IVF
4. Initiate appropriate benzodiazepine therapy to control neuromuscular agitation
5. Begin active cooling measures for hyperthermia
6. Screen for rhabdomyolysis

Environment:

1. Room Set Up – ED acute care area
    a. Manikin Set Up – Mid or high fidelity simulator, simulated sweat
    b. Props – Standard ED equipment
2. Distractors – ED noise

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CASE SUMMARY

SYNOPSIS OF HISTORY/ Scenario Background

The setting is an emergency department.

Patient is a 24-year-old female with a history of depression and anxiety. The patient is brought to the emergency department by EMS for vomiting, agitation, and “seizures.” The patient was initially brought to the medical tent at a rave by her boyfriend.

PMHx: Anxiety, Depression
PSHx: None
Medications: Stopped fluoxetine few days ago
Allergies: NKDA
SocHx: Occasional tobacco, occasional alcohol, used 2C-B at rave this evening

SYNOPSIS OF PHYSICAL

Patient is anxious, tachycardic, and appears to be shaking, which is worse when she moves/is moved.
She is actively vomiting in ED but appears to be protecting her airway.
She is agitated, confused, but is able to tell you her name.
Skin is diaphoretic.

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CRITICAL ACTIONS

1. **Obtain a detailed medication and social history**

   Cueing Guideline: Nurse will ask the doctor if they obtained medication history

2. **Perform a thorough physical exam including reflexes**

   Must include reflexes as part of the physical assessment in the context of an acutely poisoned patient.
   Cueing Guideline: The nurse can ask if the doctor if they think the patient is having seizures.

3. **Order serum diagnostic tests**

   Order point-of-care glucose, chemistry panel, salicylate concentration, and CK.
   Cueing Guideline: The nurse can ask if the doctor would like any labs or any levels on the patient.

4. **Volume resuscitate with IV normal saline**

   Give 1-to-2 liters of normal saline solution for volume resuscitation.
   Cueing Guideline: The nurse will say, “We have a line in place. Would you like any fluids?” Alternatively, the nurse can mention the tachycardia. If not done the patient will become more tachycardic (progressing from the 130’s/minute to the 140’s-to-150’s/minute) and more hypotensive (progressing from the 140/90 to 120/85 to 105/83 mmHg)

5. **Initiate appropriate benzodiazepine therapy to control neuromuscular agitation**

   Cueing Guideline: Patient will have worsening agitation, confusion, and develop spontaneous myoclonus if adequate benzodiazepines or a benzodiazepine plus antiserotonergic agent are not administered. **If an antimuscarinic agent without antiserotonergic properties is administered,** the patient will develop worsening hyperthermia (until adequate treatment is given).

6. **Begin active cooling measures for hyperthermia**

   Start active external cooling measures for hyperthermia. Administration of acetaminophen **will not** improve patient’s condition.
   Cueing Guideline: The nurse will ask the doctor if they would like to treat the patient’s fever.

7. **Screen for rhabdomyolysis**

   Start IV fluid therapy at a rate twice the maintenance fluid rate once the patient has been resuscitated with initial boluses of fluid and rhabdomyolysis is diagnosed.

8. **Consult the intensive care unit**

   Consult the intensive care unit for definitive disposition and admission.

Critical Actions Checklist[1]

Resident Name	
Case Description	

Skills measured **Core competencies: PC** Patient care, **MK** Medical knowledge, **IC** Interpersonal and communication skills **P** Professionalism, **PB** Practice-based learning and improvement **SB** Systems-based practice	**Very Unacceptable**		**Unacceptable**		**Acceptable**		**Very Acceptable**	
Data Acquisition (D) PC MK I	1	2	3	4	5	6	7	8
Problem Solving (S) PC MK PB	1	2	3	4	5	6	7	8
Patient Management (M) PC MK IC P PB SB	1	2	3	4	5	6	7	8
Resource Utilization (R) PC PB SB	1	2	3	4	5	6	7	8
Health Care Provided (H) PC SB	1	2	3	4	5	6	7	8
Interpersonal Relations (I) IC P	1	2	3	4	5	6	7	8
Comprehension of Pathophysiology (P) MK PB	1	2	3	4	5	6	7	8
Clinical Competence (C) PC MK IC P PB SB	1	2	3	4	5	6	7	8

Critical Actions

Yes	No		Comments:
		Obtain a detailed medication and social history	
		Perform a thorough physical exam including reflexes	
		Order serum diagnostic tests (must include POC serum glucose, BMP, and toxicology panel)	
		Volume resuscitate with IV normal saline	
		Initiate appropriate benzodiazepine therapy to control neuromuscular agitation	
		Begin active cooling measures for hyperthermia	
		Screen for rhabdomyolysis	
		Consult intensive care unit	

Yes	No	
		Dangerous actions

[1] Modified ABEM Oral Certification Examination checklist and scoresheet

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HISTORY

You are called to see a new patient (24-year-old female) in the emergency department. You see an anxious, diaphoretic patient who appears to be shaking, which is worse when she moves/is moved. She is actively vomiting in ED but appears to be protecting her airway. She is agitated, confused, but is able to tell you her name.

Onset of Symptoms: About an hour prior to arrival

Background Info: 24-year-old female with a history of depression and anxiety. The patient is brought to the emergency department by EMS for vomiting, agitation, and "seizures." The patient was brought to the medical tent at a rave by her boyfriend.

Additional History

From EMS: They report they picked up the patient at the medical tent at a rave. Her condition did not significantly change during transport.

From Boyfriend: He admits they used designer drugs together this evening. [If asked, he will report that they used the drug 2C-B which he believes works like "Ecstasy."

Chief Complaint: Agitation

Past Medical Hx: Anxiety, Depression

Past Surgical Hx: None

Habits: Smoking: Occasional
ETOH: Occasional, none tonight
Drugs: Did use drugs at rave tonight

Family Med Hx: Hypertension

Social Hx:

Marital Status:	Single
Children:	None
Education:	Unable to state

ROS: Patient is unable to answer.

CASE CONTINUATION

Shortly after patient is triaged the nurse asks if you could evaluate the patient for seizures.

Vital Signs: BP: 140/90 mmHg P: 130/minute R: 24/minute T: 38.5C (101.3F)
POx: 97% (room air)

Airway – Patent, intermittent vomiting but appears to be protecting airway
Breathing – Tachypneic but lungs CTAB
Circulation – Tachycardia (130's), extremities warm/flushed
Disability – Patient is agitated, anxious. Poor attention but can answer simple questions.
Exposure – No trauma, rash, drug patches. Patient is diaphoretic

Required Actions at the Beginning of the Case

- Establish safety net (IV, oxygen, cardiac monitor, two large bore IVs, draw blood for labs)
- A/B – May consider oxygen as above
- C – Cardiac monitor; 2L bolus isotonic IVF for presumed volume depletion; may consider ECG
- D – Finger stick glucose = 115 mg/dL; serum diagnostics should be sent; may consider initial dose medication

Branch Point:

- **IF EITHER LORAZEPAM (2 MG IV OR MORE) – OR – DIAZEPAM (10 MG IV OR MORE) IS ADMINISTERED,** then the patient's tachycardia will lower to 120/minute.
- **IF CYPROHEPTADINE IS ADMINISTERED,** the patient's symptoms will improve, but more slowly. Cyproheptadine alone will be insufficient for control of the patient's symptoms.
- **IF INSUFFICIENT IV FLUID IS GIVEN,** then the patient's tachycardia will worsen.

PHYSICAL EXAM

General Appearance: Pale, diaphoretic female. Unresponsive.

Vital Signs: BP: 140/90 mmHg P: 130/minute R: 24/minute T: 38.5C (101.3F) POx: 97% (room air)

Head: Normal

Eyes: PERRLA, pupils 6 mm → 5 mm bilaterally

Ears: TMs/nares clear.

Mouth: Vomitus around mouth noted; MM slightly dry.

Neck: No tenderness or deformity on exam, full range of motion

Skin: Diaphoretic/flushed; no rash/lesions appreciated.

Chest: No trauma.

Lungs: Mild tachypnea noted. Clear to auscultation bilaterally.

Heart: Tachycardic, S1 S2, no murmurs/gallops/rubs.

Back: Normal

Abdomen: Soft, mild diffuse tenderness. Bowel sounds increased.

Extremities: No signs of trauma, no edema, pulses are present.

Genital: Negative for retained foreign body.

Rectal: Normal tone, guaiac negative; negative retained foreign body.

Neurological: Moving all extremities. Increased tone in all extremities noted, greater in lower extremities than upper. Diffuse hyperreflexia with sustained inducible clonus bilateral ankles. [**If participant asks,** occasional spontaneous clonus will be noticed, which will cease after the administration of benzodiazepines].

Mental Status: Somnolent, able to answer simple questions but confused to date, situation. Poor attention.

Required Actions Over the Next Several Minutes of the Case

- Resuscitation with isotonic IV fluid should be in progress by this time
- Medical therapy (benzodiazepine and cyproheptadine administration) should be started at this time
- External cooling should be initiated by this time
- Serum diagnostics should be ordered by this time
- Placement of a bladder catheter should be performed at this time (to monitor input and output)
- ICU consultation should be considered

Branch Point:

- **IF DIAGNOSTIC LABS HAVE BEEN ORDERED,** then the results should be available at this time.
- **IF ADDITIONAL DOSES OF A BENZODIAZEPINE ARE ADMINISTERED,** then the patient's tachycardia will continue to lower to 100/minute. Blood pressure will continue to stabilize (129/93 mmHg). Hyperreflexia will also improve following administration of benzodiazepines.
- **IF ADDITIONAL DOSES OF A BENZODIAZEPINE ARE <u>NOT</u> ADMINISTERED,** then the tachycardia and the hypertension will continue to worsen.
- **IF CYPROHEPTADINE IS ADMINISTERED,** the patient's symptoms will improve, but more slowly. Cyproheptadine alone will be insufficient for control of the patient's symptoms.
- **IF INSUFFICIENT IV FLUID IS GIVEN,** then the patient's tachycardia and blood pressure will worsen. Progressively increase the heart rate from 130s/minute to 140-150s/minute. Progressively lower the blood pressure from 140/90 mmHg to 120/85 to 105/83).
- **IF A BLADDER CATHETER IS PLACED,** 300 mL of urine is obtained.

Required Actions Toward the Completion of the Case

- Rhabdomyolysis should be recognized as a complication of serotonin syndrome by this time
- Poison Center/Toxicology Consultation should be made by this time
- ICU consultation and definitive disposition/admission should be completed by this time
- **AT FACULTY DISCRETION,** hyperreflexia could recur while patient is awaiting admission

Branch Point

- **IF HYPERREFLEXIA RECURS WHILE PATIENT IS AWAITING ADMISSION TO THE ICU,** then additional benzodiazepines should be administered.
- **IF RHABDOMYOLYSIS IS RECOGNIZED,** maintenance fluid at twice the maintenance rate should be started.

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STIMULUS INVENTORY

#1	Complete blood count
#2	Basic metabolic panel
#3	Urinalysis
#4	Liver function tests
#5	Toxicology
#6	Venous blood gas
#7	Cardiac markers
#8	CXR
#9	CT head
#10	ECG

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LAB DATA & IMAGING RESULTS

Stimulus #1	
Complete Blood Count (CBC)	
WBC	12,500/mm^3
Hemoglobin	10.5 g/dL
Hematocrit	31.5%
Platelets	286,000/mm^3

Stimulus #2	
Basic Metabolic Profile (BMP)	
Sodium	137 mEq/L
Potassium	3.6 mEq/L
Chloride	109 mEq/L
Bicarbonate	17 mEq/L
Glucose	85 mg/dL
BUN	20 mg/dL
Creatinine	1.0 mg/dL

Stimulus #3	
Urinalysis	
Color	Dark
Specific gravity	1.010
Glucose	Negative
Protein	Trace
Ketones	Trace
Blood	Moderate
Leuk. Esterase	Negative
Nitrites	Negative
WBC	1/hpf
RBC	1/hpf
Hyaline casts	Few

Stimulus #4	
Liver Function Tests	
AST	63 U/L
ALT	36 U/L
Alk Phos	133 U/L
T. Bilirubin	1.0 mg/dL
Albumin	4.2 mg/dL

Stimulus #5	
Toxicology	
Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	< 10 mg/dL

Stimulus #6	
Venous Blood Gas	
pH	7.35
pCO_2	35 mm Hg
pO_2	55 mm Hg
HCO_3	18 mEq/L

Stimulus #7	
Cardiac markers	
Troponin	0.01 ng/mL
CPK	1,200 U/L
CK-MB	15 ng/mL

Stimulus #8	
CXR	Normal

Stimulus #9	
CT head	Normal

Stimulus #10	
ECG	Sinus tachycardia with rate:128/minute Normal axis and intervals No ST/T-wave abnormalities

Stimulus #1

Complete Blood Count (CBC)

WBC	12,500/mm^3
Hemoglobin	10.5 g/dL
Hematocrit	31.5%
Platelets	286,000/mm^3

Stimulus #2

Basic Metabolic Profile (BMP)

Sodium	137 mEq/L
Potassium	3.6 mEq/L
Chloride	109 mEq/L
Bicarbonate	17 mEq/L
Glucose	85 mg/dL
BUN	20 mg/dL
Creatinine	1.0 mg/dL

Stimulus #3

Urinalysis

Color	Dark
Specific gravity	1.010
Glucose	Negative
Protein	Trace
Ketones	Trace
Blood	Moderate
Leuk. Esterase	Negative
Nitrites	Negative
WBC	1/hpf
RBC	1/hpf
Hyaline casts	Few

Stimulus #4

Liver Function Tests

AST	63 U/L
ALT	36 U/L
Alk Phos	133 U/L
T. Bilirubin	1.0 mg/dL
Albumin	4.2 mg/dL

Stimulus #5

Toxicology

Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	< 10 mg/dL

Stimulus #6

Venous Blood Gas

pH	7.35
pCO_2	35 mm Hg
pO_2	55 mm Hg
HCO_3	18 mEq/L

Stimulus #7

Cardiac markers

Troponin	0.01 ng/mL
CPK	1,200 U/L
CK-MB	15 ng/mL

Stimulus #8	
CXR	Normal

Stimulus #9	
CT head	Normal

Stimulus #10	
ECG	Sinus tachycardia with rate of 128/minute Normal axis and intervals No ST/T-wave abnormalities

Debriefing Materials – <u>Serotonin Syndrome</u>

Implicated Agents:

- SSRI
  - Citalopram, Fluoxetine, Paroxetine, Sertraline, etc.
  - St John's Wort
- SNRI
  - Venlafaxine, Duloxetine, Bupropion
- MAO-I
  - Phenylzine, Isocarboxazid
- Analgesics
  - Fentanyl
  - Tramadol
  - Meperidine
- Antitussive
  - Dextromethorphan
- Antibiotics
  - Linezolid
- Triptans (anti-migraine agents)
  - Sumatriptan, Rizatriptan
- Lithium
- Drugs of abuse
  - Lysergic acid diethylamide (LSD)
  - 3,4-methylenedioxy-methamphetamine (MDMA) and related phenethylamines
- Methylene Blue (thyroid/parathyroid operations)

Pathophysiology:

- Serotonin syndrome may occur in the presence of MAO-I or lithium overdose (but not usually as single agents)
- A drug-drug interaction in the setting of multiple serotonergic agents is the most common cause of serotonin syndrome
- Serotonergic neurons in the CNS are implicated in control of alertness, mood, mediation of headache, nausea/vomiting, and motor tone
- Serotonergic neurons in the peripheral nervous system are involved in the regulation of gastrointestinal motility and vascular tone
- **Agents with prolonged metabolism/excretion (e.g. fluoxetine) may remain in body for days to weeks and can result in serotonin syndrome even after discontinuation if another serotonergic agent is initiated**

Severity of Ingestion:

- Serotonin syndrome is a spectrum disorder
  - Symptoms may range from mild restlessness, tremor, and hyperreflexia to coma with hyperthermia and rhabdomyolysis
- Some drug-drug interactions are associated with more severe clinical manifestations
  - MAO-I & meperidine (Libby Zion, 1984)

- May be difficult to predict in advance

Organ System Effects:

- Psychiatric:
  - Agitation/anxiety
  - Confusion

- Pulmonary:
  - Usually none
  - Respiratory failure may occur due to inability to protect the airway in severe serotonin syndrome

- Cardiovascular:
  - Tachycardia, hypertension
  - Beware late hypotension related to dehydration and/or cardiovascular collapse

- Neurologic:
  - Hyperreflexia
  - Neuromuscular excitation
    - Rhabdomyolysis
    - Hyperthermia
    - Not “fever”
  - Myoclonus (inducible or spontaneous)
  - Confusion which may progress to coma
    - Not always present
  - Final common pathway: [?seizure], coma, death

- Gastrointestinal:
  - Nausea, vomiting, and diarrhea may occur
    - Note similarity to carcinoid syndrome

- Dermatologic:
  - Diaphoresis

Diagnostic Testing:

- Clinical exam paramount
  - Hunter Serotonin Syndrome Criteria
    - Serotonergic drug administered within 5 weeks AND any one of the following
      - Tremor and Hyperreflexia
      - Spontaneous clonus
      - (Inducible Clonus OR Ocular Clonus) AND any of the following
        - Agitation
        - Diaphoresis
      - Muscle rigidity AND hyperthermia (> 38 C) AND inducible clonus or ocular clonus

- Glucose/Chemistry panel
- Serial CK measurements
    - if more than mild disease
    - evaluate for presence/severity of rhabdomyolysis
- Serial lithium concentrations if history of use/overdose
- Urinalysis: Screen for evidence nephrotoxicity
- Consider CT head if alteration in Mental Status

Treatment:

- Decontamination
    - Discontinue the offending agent(s)
    - Usually no acute decontamination is indicated
    - May consider decontamination measures if known MAO-I overdose and no contraindication
        - Higher risk mortality
- Supportive Care:
    - Airway:
        - Consider airway protection if significant alteration in mental status
    - Breathing:
        - Support as needed
    - Circulation
        - Administer lactated Ringer's or isotonic sodium chloride solution to restore/maintain euvolemia
            - Additional IVF may be required for treatment of rhabdomyolysis
        - Autonomic hyperactivity common
            - Control of neuromuscular agitation critical in controlling autonomic hyperactivity
            - If control of hypertension is required, short-acting agents should be used as abrupt cardiovascular collapse may occur
        - If cardiovascular collapse occurs, direct-acting vasopressors should be used
    - Disability
        - Control neuromuscular agitation with aggressive use of benzodiazepines titrated to clinical response
            - If inadequate response to aggressive benzodiazepines, proceed to intubation, sedation (e.g. propofol), and consider paralysis
        - Start active external cooling if hyperthermia
            - Not a fever
        - Consider adjunctive use cyproheptadine (anti-serotonergic antihistamine)
            - Load: Initial: 12 mg PO, then 2 mg PO q2 hr until symptoms controlled (may crush and put in NGT or OGT)
            - Maintenance: 8 mg PO q6 hr
            - Caution: Antimuscarinic properties may inhibit sweating
                - Start cooling measures to control hyperthermia before initiation
            - Caution: If diagnosis is in doubt, cyproheptadine should be avoided

Consultations:

- Consult the regional poison center or a local medical toxicologist for additional information and patient care recommendations.
- Consult Nephrology if kidney failure develops due to rhabdomyolysis or if lithium intoxication present

Disposition:

- Admit patients with major signs and symptoms to an ICU.
- Consult Psychiatric service personnel for stabilized patients with intentional overdose.
- Patients with accidental drug-drug interactions and mild symptoms can be considered for discharge home with discontinuation of offending drug(s), careful return precautions, and caution advised to patient and prescribing providers regarding serotonin syndrome

Take-Home Points:

- Serotonin syndrome may be caused by overdose, but is usually caused by a drug-drug interaction and may be caused by the interaction of an illicit drug with a prescribed one
- Serotonergic drugs with long half-lives may still be implicated in serotonin syndrome even after discontinuation
- Serotonin syndrome is characterized by neuromuscular agitation (usually with hyperreflexia and myoclonus), associated adrenergic hyperactivity, diaphoresis, gastrointestinal disturbance
- Rhabdomyolysis, hyperthermia, and various degrees of alteration in mental status may occur
- Aggressive supportive care and aggressive sedation with benzodiazepines are the mainstay of treatment of serotonin syndrome
- Patients with clear diagnosis of serotonin syndrome, with a protected airway and without hyperthermia may be candidates for cyproheptadine therapy (anti-serotonergic antihistamine)

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4. Ramsay RR, Dunford C, Gillman PK. Methylene blue and serotonin toxicity: inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction. British journal of pharmacology. 2007;152(6):946-51.
5. Sternbach H. The serotonin syndrome. The American journal of psychiatry. 1991;148(6):705-13.