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NYSPANA District 14

Serotonin Syndrome in the Perioperative Period

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Case Study #1

- Patient H&P: 38yo F, no significant med hx
- Case: D&C hysteroscopy, Mirena IUD insertion
- Home meds: None
- DOS meds
  - Preop: midazolam 2 mg, **ondansetron** 4 mg
  - Intraop: **Fentanyl** 100 mcg, Propofol 140 mg, lidocaine 70 mg; desflurane in O2
- OR emergence: uneventful, LMA w/ spontaneous respirations, all VS WNL
- PACU
  - Initial emergence routine; pt coherent & talking
  - Dilaudid 0.5 mg.
  - **Clonic BUEs followed by BLEs, tachycardic 180s-200s, decline in mental status**, afebrile, no HTN.
  - Labetalol 15 mg, + effect then rebounded; Ativan 0.5 mg without improvement in mental status
  - MHAUS protocol initiated, reintubated & sedated, dantrolene 80 mg administered. Initial labs (electrolytes, ABG, CK) WNL; EKG sinus tach. Tremors resolved in PACU.
- Post op course: Transfer to ICU intubated. Pt's husband noted past rare resting tremor. Subsequent labs showed **increased CK** otherwise nl. **Febrile** overnight. Dantrolene readministered on POD 1 for repeated **clonus** episode; sz r/o w/ EEG

Case Study #2

- Patient H&P: 44yo F, hx major depression, polysubstance abuse >1 yr prior, preop labs/exam WNL
- Case: hysterectomy, BSO, endometrial fulguration, LOA
- Home meds: **clonazepam (benzo), duloxetine (SSRI), lamotrigine & topiramate (anticonvulsants), lithium (serotonin secretagogue), quetiapine (serotonin receptor blocker).**
- DOS meds: All home meds taken in a.m.; Preop anxiolytic (Midazolam 5 mg); uneventful induction & intubation analgesic (**fentanyl** 100 ug), hypnotic (propofol 120 mg), paralytic (rocuronium 50 mg); unremarkable maintenance of anesthesia (O2 & desflurane), paralysis (rocuronium 20 mg), & analgesia (hydromorphone 2 mg); fluid replacement (~3L LR & ½ L Hextend); reversal of paralysis (neostigmine 5 mg, glycopyrrolate 0.7 mg).
- EBL 350 ml; UOP 200ml; last OR T 36.7°C
- OR emergence**: BUE & BLE rigidity; B pupillary horizontal nystagmus; unresponsive to verbal and tactile stimuli**. VSS/WNL
- PACU: still intubated, **spontaneous BUE clonus; T 37.7°C**; Resolved/extubated in 45 mins
- Post op course: nl except pt self-report of "difficulty finding words and concentrating" through POD 6

Case Study #3

- Pt H&P: 42yo F; hx depression
- Case: Closed reduction nasal fx
- Home meds: **atypical antipsychotic (quetiapine), SSRI (citalopram); CNS stimulant (Adderall)**
- DOS meds: None indicated
- OR emergence: VSS
- PACU: **Clonus with rhythmic left-right head movement. Progressive agitation, restlessness, and inability to follow commands. SBP fluctuations from 180-90mm Hg. BLE rigidity. Vertical ocular clonus. T 38.5° C.**
- Treatment: Benzos administered without effect. Cyproheptadine administered. Increased alertness, decreased rigidity. Ocular clonus and BP volatility resolved after 2 hours.

Case Study #4

- Pt H&P: 77 yo M; PMH IDDM (optimized), HTN, mild depression, chronic lymphedema, diabetic neuropathies; labs WNL
- Primary case uneventful: hemimaxillectomy for primary squamous carcinoma of the palate
- Post op course
  - POD 7: pt started **fluoxetine** for acute depression.
  - POD 10: neutrophilia & swinging pyrexia; **Linezolid** started after MRSA grew in gangrenous toe and then blood cultures; **pyrexia** and **agitation** continued; **HTN, tachycardia, rigors, ataxia & insomnia** developed and worsened over 3 days; neuro exam showed generalized **hypertonicity, weakness of all limbs without sensory change, inducible clonus, and brisk reflexes**. Sepsis suspected.
- Return to OR
  - Toe amputation 2° suspected sepsis. Pt reintubated in PACU for **respiratory failure & reduced consciousness**. Admitted to ICU with **tachycardia, T>39°C, SBP>220mmHg, clonus, hyperreflexia, confusion, agitation & insomnia**. CT r/o CVA.
  - Discontinued serotonin drugs. Extubated 4d later. Drowsy for a week. Recovered fully.

Serotonin Syndrome Overview

- A drug induced condition that results from the effects of toxic levels of the neurotransmitter serotonin (5-HT)
- Rare occurrence and resemblance to other conditions makes it difficult to diagnose
- Classic triad
  - Mental state changes
    - Agitation, confusion
  - Autonomic hyperactivity
    - Sweating, fever, tachycardia, tachypnea
  - Neuromuscular abnormalities
    - Tremor, clonus, hyperreflexia, rigidity

Serotonin Physiology

Table 2 Role of serotonin (5-HT) receptor subtypes in relation to serotonin syndrome

Receptor	Action related to serotonin syndrome
5-HT_{1A}	Neuronal inhibition, sleep regulation, appetite, thermoregulation, anxiety and hyperactivity, depression with hypoactivity
5-HT_{1D}	Locomotion, muscle tone
5-HT_{2A}	Neuronal excitation, learning, peripheral vasoconstriction, platelet aggregation
5-HT_{2B}	Stomach contraction
5-HT_{3}	Nausea and vomiting, anxiety

From Boyer and Shannon[7]

Serotonin Drug Mechanisms

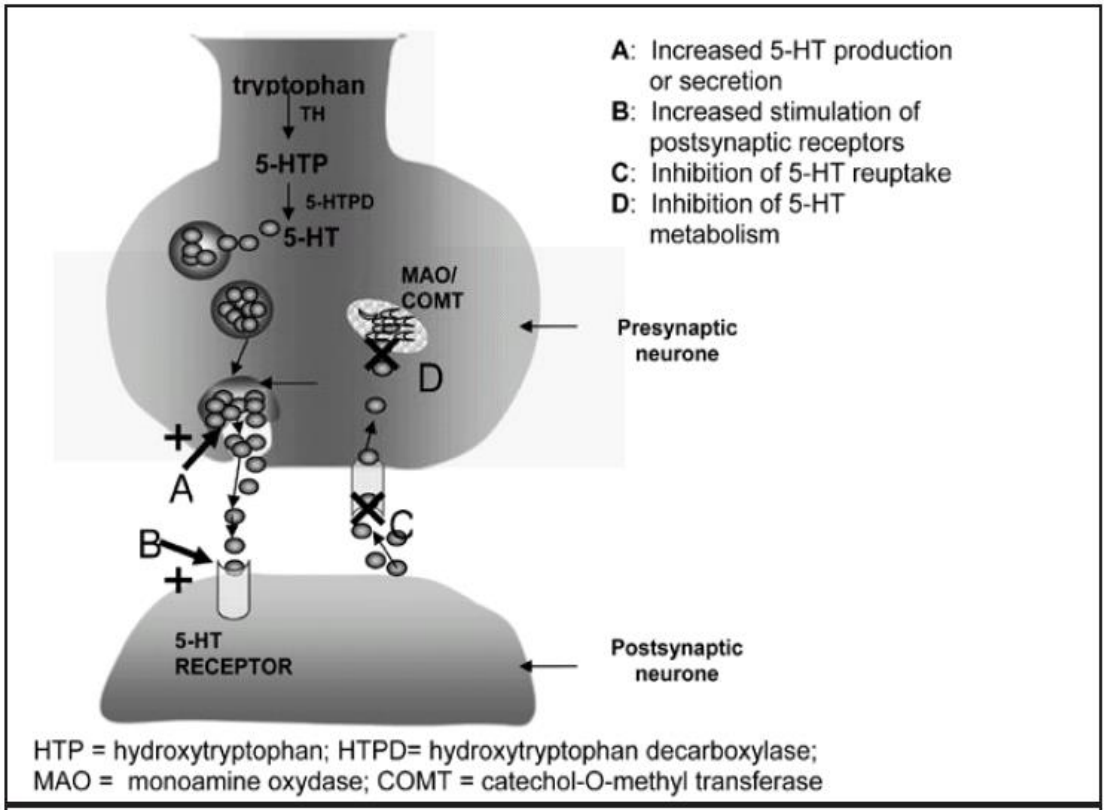

Figure 1 Schematic diagram illustrating mechanisms of serotonin syndrome (see Table 2 for specific actions of different 5-HT receptors)

Serotonin Enhancing Drugs by Mechanism

Mechanism of action	Drug class	Examples
Serotonin precursor	Herbals	L-tryptophan
Inhibition of serotonin metabolism	MAOIs	Isocarboxazid Phenelzine Selegiline
	Antibiotics	Linezolid
	Herbals	St John's Wort Ginseng
Increase in serotonin release	Psychotropics	Lithium
	Recreational drugs	Amphetamines (crystal meth, dextroamphetamine) MDMA (Ecstasy) Cocaine Ethanol

Serotonin Enhancing Drugs by Mechanism

Mechanism of action	Drug class	Examples
Inhibition of serotonin reuptake	Phenylpiperidine opioids	Fentanyl Dextromethorphan Meperidine Methadone Sufenta / Alfenta/ Remi Tramadol
	Recreational drugs	MDMA (Ecstasy)
	SSRIs	Fluoxetine Paroxetine Sertraline Trazodone
	Tricyclic antidepressants	Amitriptyline Nortriptyline Imipramine
	SNRIs	Duloxetine Venlafaxine

Serotonin Enhancing Drugs by Mechanism

Mechanism of action	Drug class	Examples
Serotonin receptor agonism	Anxiolytics & antipsychotics	Buspirone Lithium Olanzapine
	Anti-migraine	Triptans Sumatriptan
	Antiemetic	Ondansetron Granisetron Aprepitant Metoclopramide
	Recreational drugs	LSD
	Dye	Methylene blue

Serotonin Toxicity Incidence

- 2012 data from National Poison Database
  - 47,115 toxicity events related to SSRIs
    - 1,723 moderate adverse events
    - 152 major adverse events
    - 7 deaths
- Probably underestimated
  - Lack of recognition
  - Increasing SSRI prescriptions

Antidepressant Rx Data from NIH & CDC

- 10% (leading cause) of disability in U.S and Canada is depression
- 11% of Americans 12+ take antidepressant(s)
- Most common Rx med taken by Americans aged 18-44
  - 3rd most common Rx drug taken overall
- More common in females and Caucasians
- Of Americans on antidepressants, 60% take > 2 yrs, 14% > 10 years
- Rate of antidepressant use increased ~400% from 1988-2008
- 80% of antidepressants not prescribed by psychiatrists
- 1/3 of population with severe depressive symptoms take antidepressant(s)
- <1/3 on antidepressant (and <1/2 on multiple antidepressants) have seen a mental health professional in the past year

Serotonin Syndrome Presentation

	Mild	Moderate
Mental status changes	Anxiety Restlessness Insomnia	Agitation Easily startled Hypervigilance Mild confusion Pressured speech
Autonomic hyperactivity	Diaphoresis Mild HTN Mydriasis Shivering Tachycardia	Hyperactive bowel sounds T>40°C
Neuromuscular abnormalities	Akathisia Hyperreflexia Muscle twitching Tremor	Inducible clonus Myoclonus Ocular clonus

Serotonin Syndrome Presentation

	Severe
Mental status changes	Coma Delirium
Autonomic hyperactivity	ARDS DIC Dramatic swings in HR & BP Respiratory failure Tachycardia & HTN>>>shock T>41.1°C
Neuromuscular abnormalities	↑serum aminotransaminases / creatinine Hypotonicity Metabolic acidosis Muscle rigidity Myoglobinuria Renal failure Rhabdomyolysis Seizures Spontaneous clonus

Serotonin Syndrome Diagnosis

Table 1 Comparison of the Sternbach and Hunter diagnostic criteria for serotonin syndrome (SS)

Diagnostic criteria	Clinical features required	Sensitivity/specificity[4]
Sternbach[2]	1. Recent addition or increase in a known serotonergic agent 2. Absence of other possible aetiologies (infection, substance abuse, withdrawal etc) 3. No recent addition or increase of a neuroleptic agent 4. At least 3 of the following symptoms: • mental status changes (confusion, hypomania) • agitation • myoclonus • hyperreflexia • diaphoresis • shivering • tremor • diarrhoea • incoordination • fever	75% / 96%
Hunter[3]	In the presence of a serotonergic agent: 1. spontaneous clonus = SS 2. ELSE IF inducible clonus AND agitation OR diaphoresis = SS 3. ELSE IF ocular clonus AND agitation OR diaphoresis = SS 4. ELSE IF tremor AND hyperreflexia = SS 5. ELSE IF hypertonic AND pyrexia >38ºC AND ocular clonus OR inducible clonus = SS 6. ELSE NOT SS	84% / 97%

Differential Diagnoses

- Serotonin syndrome
- Adverse drug reaction
- Neuroleptic malignant syndrome
- Sympathomimetic toxicity
- Anticholinergic poisoning
- Opioid-induced muscle rigidity
- Delirium tremens
- Malignant hyperthermia
- Seizure disorder
- Heat stroke
- Meningoencephalitis
- Severe sepsis

Differential Diagnoses

Diagnosis	Similarities to SS	Differences from SS
Adverse drug reaction	Unpredictable change in VS and MS	Rarely causes muscle rigidity or fever
Neuroleptic malignant syndrome	Hyperpyrexia, sweating, tachycardia, tachypnea, muscle rigidity, MS change, BP change, caused by neurotransmitter (dopamine) toxicity	Paranoia, specific to neuroleptic drugs (antipsychotics / tranquilizers)
Sympathomimetic toxicity	Tachycardia, HTN, diaphoresis, hyperpyrexia, agitation, mydriasis, delirium, sz	Combativeness, bruxism, rapid onset after ingestion of ecstasy, meth, or ephedrine

Differential Diagnoses

Diagnosis	Similarities to SS	Differences from SS
Anticholinergic poisoning	Hyperpyrexia, MS changes, mydriasis, sz, myoclonus	Flushed dry skin, hallucinations, decreased bowel sounds, urinary retention
Opioid-induced muscle rigidity	Muscle rigidity	Transient, chest / truncal rigidity, no VS changes, responds to naloxone
Delirium tremens	Hyperpyrexia, tachycardia, HTN, agitation	48-72 hrs after last ETOH, gradual onset, hallucinations
Malignant hyperthermia	Muscle rigidity, hyperpyrexia, tachycardia	Severe hypercapnia, electrolyte abnormalities, responds to dantrolene

Differential Diagnoses

Diagnosis	Similarities to SS	Differences from SS
Seizure disorder	Clonus, hyperpyrexia	Usually recurrent, rarely presents during periop period
Heat stroke	Hyperpyrexia, MS changes, tachycardia, tachypnea	Lack of sweating, flushed skin, headache
Meningoencephalitis	Confusion, MS change, hyperpyrexia	Headache, stiff neck, photophobia, lumbar puncture + cx
Severe sepsis	Confusion, MS change, pyrexia, tachycardia, tachypnea	Slow onset, + blood cx, change in CBC, responds to abx, hypotension

Serotonin Syndrome Treatment

- Stop all serotonin enhancing drugs
- Provide supportive care
- Consider cyproheptadine
  - Approved indication: Hypersensitivity reactions
    - Multiple off label uses, including SS
  - Oral agent (syrup or tablets)
  - Serotonin and histamine antagonist
    - Competitively inhibits H1 receptor, mediating bronchial constriction, smooth-muscle contraction, edema, hypotension, CNS depression, and cardiac arrhythmias
    - Prevents histamine release in blood vessels
    - http://reference.medscape.com/drug/cyproheptadine-343389#10

Recommendations

Preoperatively

- Ask about depression /anxiety hx
- Verify current home med list
- Ask about OTC drugs, illicit drug use, & herbals
- Identify high-risk patients

Postoperatively

- Identify high-risk patients
- Note serotonin enhancing OR drugs (fentanyl, methylene blue)
- Maintain a high level of vigilance for s/sx in PACU
- Consider alternatives to common serotonergic agents
  - Avoid redosing ondansetron
  - Avoid administering fentanyl
- Report suspected cases voluntarily
  - FDA MedWatch classifies SS as an adverse drug reaction
  - https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home

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