

Objective 3

Evaluate a pain patient's regimen to identify common medications used in pain management implicated in serotonin toxicity: analyze a drug-drug interaction report to determine utility of information provided

Drug Interaction Tool

- Can be used to evaluate the risk for drug interactions
- Data obtained from drug interaction tool must be analyzed carefully
- Drug reference databases such as LexiComp™ or Micromedex™ often have a drug interaction option
- Most interaction tools will give you a basic analysis with the option to click on a link for more information

Drug Interaction Tool

- Most interaction tools will give you a key for the severity of the drug interaction

Interaction Analysis

Interaction Monograph

Jump to Section

Filter Item

Filter Risk Ratings

Reset Filters

Jump to Section

All Items

All Risk Ratings

A

 = No known interaction

B

 = No action needed

C

 = Monitor therapy

D

 = Consider therapy modification

X

 = Avoid combination

Lexicomp Online, Interactions Online, Hudson, Ohio: Up-to-date, Inc.; 2013; July, 2020. Available at <https://online.lexi.com/lco/action/interact>

Patient Case – EH: High Risk Medications

- EH, a 62 year old pt with metastatic breast cancer to the spine, is well known to your team. Her cancer has been relatively stable the past 3 years with treatment. EH is in the hospital for spinal fusion surgery for worsening back pain. After surgery she develop confusion, anxiety, myoclonus, increased heart rate, and increased blood pressure.
- PMH: CKD III, DM II (controlled w/diet & exercise), depression
- Meds:
 - Home Meds: Sertraline 100 mg daily, methadone 5 mg PO Q8 hrs., Senna 8.6 mg BID, gabapentin 800 mg BID – discontinued for elevated SCr
 - Hospital Meds: enoxaparin 60 units daily, morphine PCA 7mg every 15 mins. as needed (using 20 doses/day), desipramine 25 mg QHS, ondansetron 8 mg q8 hours as needed
- Labs: WNL except for elevated HR, BP, and SCr
- Possible causes for EH's symptoms?

Patient Case – EH: Drug Interaction Report

- Example of a drug interaction report

Patient Case – EH: Drug Interaction Report

■ Example of a drug interaction report

Drugs in this analysis: Desipramine, Lovenox, Methadone, Morphine (Systemic), Ondansetron, Senna, Sertraline
View interaction detail by clicking on link.

✓ Drug-Allergy Interactions

No interactions identified in the database

✓ Drug-Drug Interactions

- D Desipramine (CNS Depressants) – Methadone (Opioid Agonists)
- D Desipramine (CNS Depressants) – Morphine (Systemic) (Opioid Agonists)
- D Lovenox (Enoxaparin) – Sertraline (Agents with Antiplatelet Properties)
- D Methadone (CNS Depressants) – Morphine (Systemic) (Opioid Agonists)
- D Methadone (QT-prolonging Agents (Highest Risk)) – Ondansetron *Depends on Route*
- C Desipramine (Serotonergic Agents (High Risk)) – Ondansetron
- C Desipramine (Tricyclic Antidepressants) – Sertraline
- C Methadone (Opioid Agonists) – Sertraline (Serotonergic Agents (High Risk))
- C Methadone (QT-prolonging Agents (Highest Risk)) – Sertraline (QT-prolonging Agents (Indeterminate Risk - Caution))
- C Morphine (Systemic) (Opioid Agonists) – Sertraline (Serotonergic Agents (High Risk))
- C Ondansetron – Sertraline (Serotonergic Agents (High Risk))

✓ Duplicate Therapy Interactions

Methadone – Morphine (Systemic)

Patient Case - BP: High Risk Medications

- BP is a 52 year old male with a history of SCC of tonsil – NED x 18 months. He reports to your pain clinic for management of his chronic pain caused by his cancer treatments – mixed nociceptive & neuropathic pain
- BP presents with symptoms of insomnia, dizziness, mild tachycardia, N/V, cramping, and muscle twitching
 - PMH: FM, IBS, RA, GAD, hypothyroid, RLS
- Current Medications:
 - Albuterol 2 puffs q6 prn
 - Amlodipine 5 mg daily
 - Simvastatin 40 mg daily
 - Buprenorphine 15 mcg patch weekly
 - Buspirone 10 mg twice daily
 - Venlafaxine XR 150 mg daily
 - Gabapentin 600 mg TID
 - Hydrocodone 10/325 mg
 - Hydroxyzine 25 mg TID prn
 - Lactulose 15 mg TID
 - Nortriptyline 75 mg daily
 - Ondansetron 8 mg q8 PRN

Patient Case BP: Drug Interaction Report

> Drug-Allergy Interactions

✓ Drug-Drug Interactions

- X** Buprenorphine (Opioids (Mixed Agonist / Antagonist)) – OxyCODONE (Opioid Agonists)
- D** AmLODIPine – Simvastatin *Depends on Dose*
- D** Buprenorphine – Gabapentin (CNS Depressants)
- D** Buprenorphine – HydrOXYzine (CNS Depressants)
- D** Buprenorphine – Nortriptyline (CNS Depressants)
- D** Gabapentin (CNS Depressants) – OxyCODONE
- D** HydrOXYzine (CNS Depressants) – OxyCODONE
- D** Nortriptyline (CNS Depressants) – OxyCODONE
- C** Albuterol (Beta2-Agonists) – Nortriptyline (Tricyclic Antidepressants)
- C** Buprenorphine (Opioid Agonists) – Venlafaxine (Serotonergic Agents (High Risk))
- C** BusPIRone – Nortriptyline (Serotonergic Agents (High Risk))
- C** BusPIRone – Venlafaxine (Serotonergic Agents (High Risk))
- C** Gabapentin (CNS Depressants) – HydrOXYzine

- C** Gabapentin (CNS Depressants) – Nortriptyline (CNS Depressants)
- C** HydrOXYzine – Nortriptyline (CNS Depressants)
- C** Nortriptyline (Serotonergic Agents (High Risk)) – Ondansetron
- C** Nortriptyline (Tricyclic Antidepressants) – Venlafaxine (Serotonin/Norepinephrine Reuptake Inhibitors)
- C** Ondansetron – Venlafaxine (Serotonergic Agents (High Risk))
- C** OxyCODONE (Opioid Agonists) – Venlafaxine (Serotonergic Agents (High Risk))
- B** Albuterol (QT-prolonging Agents (Indeterminate Risk - Caution)) – Ondansetron *Depends on Route*
- B** Buprenorphine (Opioid Agonists) – BusPIRone (Serotonergic Agents (Moderate Risk))
- B** Buprenorphine (QT-prolonging Agents (Indeterminate Risk - Avoid)) – Ondansetron *Depends on Route*
- B** BusPIRone (Serotonergic Agents (Moderate Risk)) – Ondansetron (Antiemetics (5HT3 Antagonists))
- B** BusPIRone (Serotonergic Agents (Moderate Risk)) – OxyCODONE (Opioid Agonists)
- B** HydrOXYzine (QT-prolonging Agents (Indeterminate Risk - Caution)) – Ondansetron *Depends on Route*

✓ Duplicate Therapy Interactions

Buprenorphine – OxyCODONE

Opioids and Serotonin

- Fentanyl
- Tramadol
- Methadone
- Oxycodone

Baldo BA, Rose MA. The anaesthetist, opioid analgesic drugs, and serotonin toxicity: a mechanistic and clinical review. *Br J Anaesth*. 2020;124(1):44-62.

Objective 4

Provide a brief overview of available evidence for the treatment of serotonin toxicity with special attention to any gaps in knowledge and outcomes.

Management...

- Stop all serotonergic agents
- Supportive Care
 - BP management
 - Temp management
 - Respiratory management
 - ICU monitoring (severe)

...Management

- Pharmacologic
 - Benzodiazepines for severe agitation
 - Avoid medications with anticholinergic effects (eg haloperidol)
 - Cyproheptadine
 - 5-HT_{1A} and 5-HT_{2A} antagonist
 - Monitor for hypotension
 - Initial dosing between 4-16mg
 - 2 mg every 2 hrs. until resolved
 - Olanzapine
 - Theoretical

Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol.* 1999;13(1):100-109.

Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. *J Emerg Med.* 1998;16(4):615-619.

McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother.* 2001;35(7-8):870-873.

...Management for our Cases

■ EH

- Restart gabapentin at renal dosing
- Consider stopping desipramine or rotating methadone

■ BP

- Thorough history of why medications were started, length of therapy, benefit, side effects?
- Consider alternate anxiolytic
- Consider opioid rotation
- Consider stopping TCA

References

- Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352:1112-1120.
- Volpi-Abadie, Kaye AM, Kaye AD. Serotonin Syndrome. *Ochsner*. 2013;13:533-40
- Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9): 635-42
- Boyer EW, Traub SJ, Grayzel, J. Serotonin syndrome (serotonin toxicity). In *UpToDate*. Waltham, MA: UpToDate; 2020. Accessed July 2020
- Simon LV, Keenaghan M. Serotonin Syndrome. [Updated 2019 Dec 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing
- Lane R, Baldwin D. Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. *J Clin Psychopharmacol*. 1997;17:208-221.
- Frank C. Recognition and treatment of serotonin syndrome. *Can Fam Physician*. 2008;54:988-992.
- Lexicomp Online, Interactions Online, Hudson, Ohio: UpToDate, Inc.; 2013; July, 2020. Available at <https://online.lexi.com/lco/action/interact>
- Mersfelder TL, Nichols WH. Gabapentin: Abuse, Dependence, and Withdrawal. *Ann Pharmacother*. 2016;50(3):229-233
- Baldo BA, Rose MA. The anaesthetist, opioid analgesic drugs, and serotonin toxicity: a mechanistic and clinical review. *Br J Anaesth*. 2020;124(1):44-62.
- Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol*. 1999;13(1):100-109.
- Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. *J Emerg Med*. 1998;16(4):615-619.
- McDaniel WW. Serotonin syndrome: early management with cyproheptadine. *Ann Pharmacother*. 2001;35(7-8):870-873.