BENZODIAZEPINES AND OPIOIDS: LULLING PATIENTS TO SLEEP

Pain Symposium 2017
Intermountain Healthcare

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LEARNING OBJECTIVES

• Describe the responsible mechanism of increased respiratory depression with opioids and benzodiazepines.
• Recall the recommendations from the CDC and FDA concerning the combination of opioids and benzodiazepines.
• List two strategies to decrease the use of the combination of benzodiazepines and opioids.
INTRODUCTION – PATIENT BH

• Past Medical History
  o Chronic back pain
  o Fractured pelvis
  o Fractured rib
  o Neuropathy
  o Sciatic nerve palsy
  o Morbid obesity
  o Depression
  o Anxiety
  o Drug abuse (heroin, THC, cocaine)

• Current Medications
  o Clonazepam 1mg PO BID PRN
  o Albuterol Inhaler
  o Gabapentin 800mg PO TID
  o Nortriptyline 150mg PO Daily
  o Fluoxetine 20mg PO Daily
  o Oxycodone 15mg PO QID
  o Tizanidine 4mg PO BID
BH TIMELINE

- 8/19/08 – First received Lortab 7.5 BID for acute back pain
- 12/08 – Lortab taper was started
- 7/09 – Change to new PCP – Continued on Lortab – Injured Achilles tendon
- 5/2010 – Began clonazepam 0.5mg daily due to anger/anxiety. Also using flexeril for back pain
- 7/2011 – Psych admit due to depression/alcoholism – discharged on ambien and vistaril – now taking Lortab q6h.
- 8/2012 – Transitioned to new PCP – Lortab replaced by oxycodone 15mg BID
- 9/2013 – Oxycodone increased to #75 per month

- 10/13 – Oxycodone increased to #90 per month – started Cymbalta
- 3/2014 – BH found out wife was cheating on him. Started Xanax
- 4/14 – Xanax changed to Klonopin due to Xanax wearing off
- 6/14 – Positive UDS for Cannabis – pt denies using
- 6/14 – Claims daughter flushed medications down toilet – needs early refill
- 7/14 – Transfer to new PCP – Now on oxycodone 15mg #120 per month and clonazepam 0.5mg PO TID – New PCP tapers clonazepam to BID
BH TIMELINE

- 8/2014 – Severe injuries from car accident
  - Transitioned to MS Contin 30mg PO TID with a small amount of oxycodone for breakthrough pain
- 9/2014 – BH did not tolerate MS contin – back to oxycodone
- 10/2014 – Started gabapentin
- 1/2015 – Discussed decreased use of Ambien
- 3/2015 – Stopped clonazepam
- 4/2015 – Stopped ambien and started nortriptyline

- 11/2015 – BH called saying anxiety is getting worse - #15 clonazepam called in
- 2/2016 – Clinic received phone call from pharmacy stating that the patient had been getting Percocet from a dentist
- 3/3/2016 – BH stated that this time of year causes anxiety due to it being the time that he found out his wife was cheating on him. Clonazepam 1mg PO BID #30 prescribed
- 3/6/2016 – Patient found unresponsive in his home. Pronounced dead upon arrival to the ED.
PHARMACOLOGY

Benzodiazepines and Opioids
OPIOIDS

Respiratory Depression

- Agonist at the μ (mu)-opioid receptor
- Can produce significant respiratory depression by inhibiting brainstem respiratory mechanisms.
- Dose related μ (mu)-opioid receptor activity in the medulla is thought to contribute to respiratory depression

Source: Bertram G. Katzung; Basic & Clinical Pharmacology, Fourteenth Edition
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BENZODIAZEPINES

Respiratory Depression

- Bind to GABA<sub>A</sub> subunits in the CNS
- Facilitate GABA-mediated chloride ion channel opening frequency
- Enhance membrane hyperpolarization
- Respiratory depression – rare in healthy patients
- Fatal Overdose – rare in healthy patients

Source: Bertram G. Katzung:
Basic & Clinical Pharmacology, Fourteenth Edition
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EVIDENCE

Benzodiazepine and Opioids
COHORT STUDY OF THE IMPACT OF HIGH-DOSE OPIOID ANALGESICS ON OVERDOSE MORTALITY

- 2,182,374 opioid analgesic patients in North Carolina followed for 1 year
- Secondary outcome looked at the contribution of benzodiazepines and long acting opioids to overdose death
- 478 overall opioid overdose deaths were reported – Rate of 0.7 per 10,000 person years
- 80% of patients taking opioids were also taking a benzodiazepine
- Rate of death with combination – 7 per 10,000 person-years

RECOMMENDATIONS

NEUROLOGY, CDC AND FDA
<table>
<thead>
<tr>
<th>Opioid treatment agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen for prior or current substance abuse/misuse (alcohol, illicit drugs, heavy tobacco use)</td>
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<tr>
<td>Screen for depression</td>
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<tr>
<td>Prudent use of random urine drug screening (diversion, nonprescribed drugs)</td>
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<td>Do not use concomitant sedative-hypnotics or benzodiazepines</td>
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<tr>
<td>Track pain and function to recognize tolerance and track effectiveness</td>
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<tr>
<td>Track daily MED using an online dosing calculator</td>
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<tr>
<td>Seek help if MED reaches 80-120 mg and pain and function have not substantially improved</td>
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<tr>
<td>Use the state Prescription Drug Monitoring Program to monitor all sources of controlled substances</td>
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</tbody>
</table>

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible. (Recommendation category: A; evidence type: 3)

- Although there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient taking long-term, stable low dose benzodiazepine therapy), clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible.

- In addition, given that other central nervous system depressants (e.g., muscle relaxants, hypnotics) can potentiate central nervous system depression associated with opioids, clinicians should consider whether benefits outweigh risks of concurrent use of these drugs.

“It is nothing short of a public health crisis when you see a substantial increase of avoidable overdose and death related to two widely used drug classes being taken together,” said FDA Commissioner Robert Califf, M.D. “We implore health care professionals to heed these new warnings and more carefully and thoroughly evaluate, on a patient-by-patient basis, whether the benefits of using opioids and benzodiazepines – or CNS depressants more generally – together outweigh these serious risks.”
INTERMOUNTAIN ACTIVITIES

Benzodiazepines and Opioids
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
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<tbody>
<tr>
<td>1</td>
<td>Porter FM Opioid Patient List</td>
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<td>2</td>
<td>Marion D.: 801 - 387-3772</td>
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<td>3</td>
<td>4-12-17</td>
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<tr>
<td>4</td>
<td>Criteria for inclusion</td>
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<tr>
<td>5</td>
<td>Includes pharmacy orders, for encounters with a discharge date between 4/1/2016 and 12/31/2016</td>
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<td>6</td>
<td>Encounter location = Porter FM</td>
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<td>7</td>
<td>Medication must be in the Opioid list of drugs (defined by Tim Drake)</td>
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<tr>
<td>8</td>
<td>Patient that also have a benz type medication, have a Y in the second to last column</td>
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<tr>
<td>9</td>
<td>Patients with a diagnosis for sleep apnea (Intermountain systems) within last 12 months are shown by a date in the last column</td>
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<tr>
<td>10</td>
<td>Opioid medication strength, for morphine equivalent calculation, requires the position of the opioid in the generic name description field</td>
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<tr>
<td>11</td>
<td>12</td>
<td>Opioid strength is the same as the strength in the med strength desc (not always the case but appears to work for our subset)</td>
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<tr>
<td>12</td>
<td>-- for iCenta, assumed it is always the first named ...</td>
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<tr>
<td>13</td>
<td>LAST ORDER</td>
<td>PRV</td>
<td>LST ORDER</td>
<td>C</td>
<td>AVG_MORPH_EQUIV</td>
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<table>
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<tr>
<th>MMA</th>
<th>LAST_MMA</th>
<th>EVENT</th>
<th>MMA, SOURCE, TEXT</th>
<th>OPIATE LIST</th>
<th>BENZO_RX</th>
<th>FL</th>
<th>SLEEP</th>
<th>APNEA</th>
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<td>3/28/2016 12:02</td>
<td>109</td>
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<td>7/20/2012 22:01</td>
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<td>9/20/2016 17:38</td>
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<td>Dias, Valarie</td>
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<td>hydrocodone-acetaminophen (hydrocodone-acetaminophen 10 mg-325 mg oral tablet), tramadol (tramadol 50 mg oral tablet)</td>
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<td>10/19/2016 7:49</td>
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<td>Martindale, Brett</td>
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</tbody>
</table>
Population Health Intervention Data

- DME >80mg
- Chronic Opioid with benzodiazepine
- Chronic Opioid with OSA
- Patients without a current OTA
ACUTE CARE SCENARIOS

Scenario 1
Patient was found unresponsive and diaphoretic at 1940. Patient was breathing with RR of 12, O2 sats were 94, but would not wake up even with sternal rub. I was called into the room, we administered 0.4mg IV naloxone at 1945 to which the patient responded and woke up. Vital signs continued to be stable although HR increased to 126, which came back down within the half hour. The patient had not had any pain meds since 1715 when hydromorphone was administered. Promethazine and alprazolam were also administered at 1845.
ACUTE CARE SCENARIOS

Scenario 2
5 mg IV diazepam and 50 mcg IV fentanyl were ordered and administered for sedation. Shortly after receiving both doses, the patient quickly decompensated and was bagged with supplemental oxygen. Naloxone and flumazenil were given and the patient promptly improved.
RESULTS FROM GARDNER AND DRAKE STUDY, 2017

Study Population

- **174,404** In-Patient Opioid Encounters
  - **115,269** With Sedative/hypnotic
    - **1,702** With Naloxone
    - **113,567** Without Naloxone
  - **58,482** Without Sedative/hypnotic
    - **653** With Naloxone
    - **59,135** Without Naloxone

Statistical Analysis

<table>
<thead>
<tr>
<th>Received Naloxone</th>
<th>No Event</th>
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<tbody>
<tr>
<td>Sedative</td>
<td>1,702</td>
</tr>
<tr>
<td>Without Sedative</td>
<td>653</td>
</tr>
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</table>

<table>
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<tr>
<th>Relative Risk</th>
<th>1.35</th>
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<tbody>
<tr>
<td>95% CI</td>
<td>1.23 – 1.47</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>NNH</td>
<td>260</td>
</tr>
<tr>
<td>95% CI</td>
<td>200 – 369</td>
</tr>
</tbody>
</table>
POWERPLAN REVIEW

• Over 2000 powerplans reviewed
• 127 contain both a benzodiazepine and an opioid option
• Zero-Harm?
• Alerts?
CONCLUSIONS

• Benzodiazepines increase the central nervous system risks associated with opioid therapy
• These risks extend into the acute-care setting
• Simple activities such as prescriber notifications can reduce the use of the combination of opioids and benzodiazepines
DISCUSSION

What are you doing in your areas in response to the statement from the FDA and the change in labeling for the opioids and benzodiazepines?

What plans do you have to implement changes in your areas?

What barriers to you anticipate?