Association of long-term opioid and/or benzodiazepine receipt and medication count with mortality among HIV-infected and uninfected patients

DF Weisberg, K Gordon, DT Barry, WC Becker, S Crystal, EJ Edelman, J Gaither, AJ Gordon, J Goulet, R Kerns, BA Moore, J Tate, AC Justice, DA Fiellin

Yale School of Medicine

Veterans Aging Cohort Study
Prescribing of Opioids and Benzodiazepines

• Increasing in the United States
• Concerns over efficacy
  – Long-term treatment of chronic pain, driver of prescriptions
  – Treatment of anxiety and insomnia given safety and efficacy of alternative medications
• Safety concerns
  – Increasing rates of fatal and non-fatal overdose
Overlapping Concern

- Addiction potential
- Respiratory depression
- High-risk populations
  - Mental health
  - Substance use
HIV and Polypharmacy

• HIV-infected patients
  – High prevalence of polypharmacy (≥5 medications)
  – Diminished drug metabolism and elimination
  – Drug-drug interactions and adverse events

• Polypharmacy associated with mortality

• Additional mortality risk associated with opioid and/or benzodiazepine receipt is not known
Purpose

1) Among HIV-infected and uninfected patients, to quantify and compare the risk of mortality for long term
   – Opioid receipt
   – Benzodiazepine receipt
   – Opioid and benzodiazepine receipt

2) To assess these relationships accounting for opioid dose
Design and Subjects

• Prospective observational cohort

• Veterans Aging Cohort Study-Virtual Cohort, 2009
  – HIV-infected patients matched 1:2 by age, sex, race/ethnicity, and site of care to uninfected

• Exclusion criteria
  – Without 1 inpatient or outpatient encounter in 2009
  – Without active pharmacy data
  – With a diagnosis of cancer
  – HIV-infected patients not on anti-retroviral medications
Exposure and Outcome

- Long-term medication receipt, VA pharmacy data
  - 90 days of receipt, allowing 30 day-refill anytime in fiscal year 2009
    - Opioid
    - Benzodiazepine
    - Opioid and benzodiazepine
    - Polypharmacy, medication count
Exposure and Outcome

- All-cause mortality
  - Veterans Health Administration Vital Status File
  - Surveillance for death until Sept 2010
Propensity Score Matching

• Observational studies, risk for confounding by indication
  – Exposed patients at baseline differential likelihood of outcome

• Propensity score matching on likelihood of exposure
Propensity Analysis

• Logistic regression of 43 variables
  – Propensity score, likelihood to receive long-term opioids and/or benzodiazepines
Survival Analysis

- Cox proportional hazards established risk of mortality
- Sensitivity analysis
  - Stratification by HIV status
  - Opioid receipt divided into MEDD categories
    - 0 to <20mg
    - 20 to <50mg
    - 50 to <100mg
    - ≥ 100mg
## Propensity Matched Sample

### Opioid and/or Benzodiazepine Receipt

<table>
<thead>
<tr>
<th></th>
<th>Yes, n (%)</th>
<th>No, n (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Subjects, n</strong></td>
<td>13564</td>
<td>13564</td>
<td>-</td>
</tr>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>47.5 (8.3)</td>
<td>47.8 (9.1)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Male Gender, n (%)</strong></td>
<td>13202 (97.3)</td>
<td>13227 (97.5)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>White Race, n (%)</strong></td>
<td>6632 (48.9)</td>
<td>6627 (48.8)</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>HIV+</strong></td>
<td>2908 (22.6)</td>
<td>2866 (22.3)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Serious Mental Illness, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Major Depression</strong></td>
<td>1496 (11.0)</td>
<td>1440 (10.6)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>PTSD</strong></td>
<td>2510 (18.7)</td>
<td>2538 (18.5)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Bipolar Disorder</strong></td>
<td>1127 (8.1)</td>
<td>1099 (8.3)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Schizophrenia</strong></td>
<td>884 (6.5)</td>
<td>949 (7.0)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Substance Use Disorder, n (%)</strong></td>
<td>1644 (12.1)</td>
<td>1725 (12.7)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Alcohol Use Disorder, n (%)</strong></td>
<td>1591 (11.7)</td>
<td>1645 (12.1)</td>
<td>0.31</td>
</tr>
</tbody>
</table>
## Association with Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Uninfected</th>
<th>HIV +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Opioid*</td>
<td>1.40 (1.22 – 1.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>1.26 (1.08 – 1.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid and Benzodiazepine</td>
<td>1.56 (1.26 – 1.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term medication count**</td>
<td>1.05 (1.03 – 1.06)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant (p = 0.01) interaction between opioid receipt and HIV status

** Medication count includes all long-term medications excludes anti-retroviral medications, opioids, and benzodiazepines
## Association with Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Uninfected</th>
<th>HIV +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Opioid*</td>
<td>1.40 (1.22 – 1.61)</td>
<td>1.25 (1.05 – 1.49)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>1.26 (1.08 – 1.48)</td>
<td>1.31 (1.08 – 1.58)</td>
<td></td>
</tr>
<tr>
<td>Opioid and Benzodiazepine</td>
<td>1.56 (1.26 – 1.92)</td>
<td>1.29 (0.98 – 1.71)</td>
<td></td>
</tr>
<tr>
<td>Long-term medication count**</td>
<td>1.05 (1.03 – 1.06)</td>
<td>1.05 (1.03 – 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

- Statistically significant (p = 0.01) interaction between opioid receipt and HIV status

** Medication count includes all long-term medications excludes anti-retroviral medications, opioids, and benzodiazepines
## Association with Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Uninfected</th>
<th>HIV +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Opioid*</td>
<td>1.40 (1.22 – 1.61)</td>
<td>1.25 (1.05 – 1.49)</td>
<td>1.46 (1.15 – 1.87)</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>1.26 (1.08 – 1.48)</td>
<td>1.31 (1.08 – 1.58)</td>
<td>1.05 (0.79 – 1.41)</td>
</tr>
<tr>
<td>Opioid and Benzodiazepine</td>
<td>1.56 (1.26 – 1.92)</td>
<td>1.29 (0.98 – 1.71)</td>
<td>1.65 (1.15 – 2.38)</td>
</tr>
<tr>
<td>Long-term medication count**</td>
<td>1.05 (1.03 – 1.06)</td>
<td>1.05 (1.03 – 1.08)</td>
<td>1.03 (1.00 – 1.06)</td>
</tr>
</tbody>
</table>

- Statistically significant (p = 0.01) interaction between opioid receipt and HIV status

** Medication count includes all long-term medications excludes anti-retroviral medications, opioids, and benzodiazepines
Opioid Dose and Mortality

Overall Hazard Ratio for Long-term Medication Receipt:
- **Opioid**
- **Opioid and Benzodiazepine**

Morphine equivalent daily dose

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>1 to &lt;20</th>
<th>20 to &lt;50</th>
<th>50 to &lt;100</th>
<th>≥100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Opioid Dose and Mortality

Overall

<table>
<thead>
<tr>
<th>Morphine equivalent daily dose</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to &lt;20</td>
<td>1</td>
</tr>
<tr>
<td>20 to &lt;50</td>
<td>1.5</td>
</tr>
<tr>
<td>50 to &lt;100</td>
<td>2.5</td>
</tr>
<tr>
<td>≥100</td>
<td>5</td>
</tr>
</tbody>
</table>

Long-term Medication Receipt

- Red: Opioid
- Blue: Opioid and Benzodiazepine

HIV-Infected Patients

<table>
<thead>
<tr>
<th>Morphine equivalent daily dose</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to &lt;20</td>
<td>1</td>
</tr>
<tr>
<td>20 to &lt;50</td>
<td>1.5</td>
</tr>
<tr>
<td>50 to &lt;100</td>
<td>2.5</td>
</tr>
<tr>
<td>≥100</td>
<td>5</td>
</tr>
</tbody>
</table>

Uninfected Patients

<table>
<thead>
<tr>
<th>Morphine equivalent daily dose</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to &lt;20</td>
<td>1</td>
</tr>
<tr>
<td>20 to &lt;50</td>
<td>1.5</td>
</tr>
<tr>
<td>50 to &lt;100</td>
<td>2.5</td>
</tr>
<tr>
<td>≥100</td>
<td>5</td>
</tr>
</tbody>
</table>

HIV-Infected Patients

<table>
<thead>
<tr>
<th>Morphine equivalent daily dose</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to &lt;20</td>
<td>1</td>
</tr>
<tr>
<td>20 to &lt;50</td>
<td>1.5</td>
</tr>
<tr>
<td>50 to &lt;100</td>
<td>2.5</td>
</tr>
<tr>
<td>≥100</td>
<td>5</td>
</tr>
</tbody>
</table>
Limitations

• Propensity score matching control for known/observed characteristics

• Accounted for opioid and/or benzodiazepine receipt from VA pharmacy
  – Other licit/illicit sources of medications

• May not have been receiving medications at time of death
Summary

• Long-term opioid receipt
  – Associated with 40% increased risk of mortality
  – Greater with long-term benzodiazepine receipt
  – Greater among HIV-infected patients

• Long-term benzodiazepine receipt
  – Increased risk, regardless of opioid receipt

• Higher opioid doses, increased risk
  – Risk at lower doses with long-term opioid and benzodiazepine receipt
Conclusions

• Results invite further research
  – Pharmacokinetic and pharmacodynamic drug-drug interactions
  – Overdose

• VA Opioid Safety Initiative

• Mitigate risks, caution co-prescribing, particularly HIV-infected populations
Thank You

Questions/Comments:

Daniel F. Weisberg
dfweisberg@gmail.com
Propensity Model

- Demographics:
  - Age
  - Gender
  - Race/Ethnicity

- Clinical Diagnoses:
  - HIV
  - Hypertension
  - Diabetes
  - Cardiovascular disease
  - Coronary artery disease
  - CHF
  - Peripheral vascular disease
  - Stroke (ischemic/hemorrhagic)
  - Cirrhosis
  - End stage liver disease
  - Decompensated end stage liver disease
  - GERD
  - Renal Disease
  - Chronic kidney disease
  - HepC
  - HepB
  - Osteoarthritis
  - Fracture
  - Neuropathy
  - COPD
  - Schizophrenia
  - Major Depression
  - Bipolar Depression
  - PTSD
  - Alcohol use disorder
  - Drug use disorder
  - Acute pain (abd pain, chest pain, kidney stones)
  - Chronic pain (back pain, extremity pain, headache, menstrual pain, neck pain, RA, TMJ pain)

- Other
  - Hospitalizations
  - Smoking history
  - Medication count
Opioid/Benzodiazepine Exposure

• Based on VA formulary
• Opioids:
  – codeine, dihydrocodone, oxycodone, oxycodone sustained action (SA), morphine, morphine (SA), fentanyl, hydromorphone, and methadone, meperidine, pentazocine, propoxyphene, levorphanol, tramadol, and tapentadol
  – buprenorphine and methadone used for opioid agonist treatment were excluded

• Benzodiazepines:
  – alprazolam, chlordiazepoxide, clorazepam, diazepam, estazolam, flurazepam, lorazepam, midazolam, temazepam, triazolam, and oxazepam
Propensity Matched Sample

<table>
<thead>
<tr>
<th>Exposure</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term Opioid</td>
<td>9945 (73.3)</td>
</tr>
<tr>
<td>Long-Term Benzodiazepine</td>
<td>5831 (43.0)</td>
</tr>
<tr>
<td>Both</td>
<td>2212 (16.3)</td>
</tr>
</tbody>
</table>