Do Prescribed Opioids Impact CD4 Count Restoration among HIV+ Patients Initiating Antiretroviral Therapy?


Society of General Internal Medicine
National Annual Meeting
April 24, 2015
Prescription Opioids in HIV

- HIV-infected (HIV+) patients commonly prescribed opioids for pain

- Important to examine benefits and harms
  - Benefit for acute pain, unclear benefit for chronic pain
  - Growing evidence demonstrating harms
    - Overdose, death; opioid use disorders; falls, fractures; hypogonadism

- All of these harms may be more common in HIV
Opioids and Immune Effects

• Myriad immune-mediated effects

• Epidemiological data focus on patients with addiction

• No studies focused on:
  – Prescription opioids
  – Response to antiretroviral therapy (ART) as a measure of immune function

• Need studies examining effects of opioids on HIV disease
Study Aims

• To examine association between prescription opioid duration and CD4 count restoration among HIV+ patients initiating ART

• To determine whether this relationship varies by baseline CD4 count
Design

• Veterans Aging Cohort Study
  – 47,805 HIV+ and 99,061 uninfected patients
  – Data include pharmacy, laboratory, diagnostic codes

• Analytic sample:
  – Initiated ART Oct., 2002 – Sept., 2010; available labs
  – Excluded if:
    • Cancer or opioid use disorder;
    • Immunosuppressive medications;
    • ART < 1 month, HIV viral load ≤ 500 copies/mL

• Longitudinal analysis followed for 24 months after ART initiation
Measures

• Outcome: CD4 count over time

• Main Predictor: Prescription opioid duration
  – Pharmacy fills over 24 months:
    • None: no opioids
    • Short-term: <90 consecutive days
    • Long-term: ≥90 consecutive days
  – Standardized to average daily milligrams of morphine equivalents
    • High dose: ≥120 mg
# Prescription Opioids

<table>
<thead>
<tr>
<th>Property</th>
<th>Included</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>• Outpatient</td>
<td>• Inpatient</td>
</tr>
<tr>
<td>Formulation</td>
<td>• Transdermal</td>
<td>• Cough syrup/elixir without codeine dose</td>
</tr>
<tr>
<td></td>
<td>• Oral</td>
<td>• Rectal suppositories</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Crystals, powders</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Films</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Injection</td>
</tr>
<tr>
<td>Opioid Type</td>
<td>• Codeine</td>
<td>• Non-formulary opioid</td>
</tr>
<tr>
<td></td>
<td>• Hydrocodone</td>
<td>• Opium</td>
</tr>
<tr>
<td></td>
<td>• Oxycodone (SA)*</td>
<td>• Buprenorphine</td>
</tr>
<tr>
<td></td>
<td>• Morphine (SA)*</td>
<td>• Methadone for methadone maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>• Fentanyl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hydromorphone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Methadone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other low potency opioids (tramadol, propxyphene, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

*SA = sustained action
Covariates

- Demographics: age, gender, race/ethnicity
- Antiretroviral Regimen: type, year of initiation, time on treatment
- VACS Index: age, HIV biomarkers, hepatitis C status, hemoglobin, eGFR and FIB-4
- Clinical Characteristics: pain-related diagnoses, major depression, hepatitis C virus, diabetes mellitus, alcohol and drug use-related diagnoses
Analysis

- Descriptive statistics
- Plotted mean CD4 counts at 6 month intervals
- Linear, mixed-effects models with random intercept and random slope to analyze square root transformed CD4 count over time
  - Likelihood ratio tests
  - Overall and stratified by baseline CD4 count
Patient Characteristics by Prescription Opioid Duration

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>None, N=2246 (52%)</th>
<th>Short-Term, N=1592 (37%)</th>
<th>Long-Term, N=520 (12%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>48 (11)</td>
<td>48 (10)</td>
<td>51 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/Ethnicity, %</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>White</td>
<td>31</td>
<td>34</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>56</td>
<td>55</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Other</td>
<td>13</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Gender, male, %</td>
<td>97</td>
<td>97</td>
<td>98</td>
<td>0.50</td>
</tr>
<tr>
<td>ART-regimen, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitor-based</td>
<td>32</td>
<td>35</td>
<td>37</td>
<td>0.04</td>
</tr>
<tr>
<td>NNRTI-based</td>
<td>66</td>
<td>63</td>
<td>60</td>
<td>0.006</td>
</tr>
<tr>
<td>Year of ART Initiation, %</td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>2002-2004</td>
<td>29</td>
<td>30</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>2005-2007</td>
<td>35</td>
<td>36</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>2008-2010</td>
<td>36</td>
<td>33</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>
Comorbid Conditions by Prescription Opioid Duration

- **Acute Pain-Related Diagnosis**
- **Chronic Pain-Related Diagnosis**
- **Major Depression**
- **Hepatitis C Virus**
- **Diabetes Mellitus**
- **Alcohol or Drug Use Disorder**

Proportion, %

Comorbid Condition

- None
- Short-Term
- Long-Term

p<0.05 for all
## Prescription Opioid Use Characteristics, n=2112

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Short-Term Opioids</th>
<th>Long-Term Opioids</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days, median (IQR)</td>
<td>25 (10-55)</td>
<td>368 (213-556)</td>
<td>n/a</td>
</tr>
<tr>
<td>Average daily dose, mg morphine equivalents, median (IQR)</td>
<td>18 (12-27)</td>
<td>28 (18-47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High dose (&gt; 120 mg morphine equivalent) average daily dose, %</td>
<td>0.4</td>
<td>8.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Observed CD4 Count Over Time after Antiretroviral Therapy Initiation

Months since antiretroviral therapy initiation

CD4 count, cells/mm³, mean

- None
- Short-Term Opioids
- Long-Term Opioids
CD4 Count Over Time, Mixed Models

- Prescription opioid*time interaction:
  - Short-term p=0.11;
  - Long-term p=0.98

Months since antiretroviral therapy initiation

- None
- Short-Term Opioids
- Long-Term Opioids
CD4 Count Over Time, Stratified by Baseline CD4 Count

Baseline CD4 < 500 cells/mm³

Baseline CD4 ≥500 cells/mm³

Prescription opioid*time interaction:
- Short-term p=0.24; long-term p=0.84

Prescription opioid*time interaction:
- Short-term p=0.04; long-term p=0.93

Months since antiretroviral therapy initiation

CD4 count, cells/mm³

None, Short-Term Opioids, Long-Term Opioids
Summary

• No evidence of significant effects of either short-term or long-term prescription opioid exposure on CD4 counts over time

• Findings persisted after accounting for important covariates, including overall disease severity
Next Steps and Conclusions

• Future studies will examine:
  – Dose
  – Immunosuppressive properties
  – Other immune-related outcomes

• Prescription opioids do not appear to adversely impact CD4 count recovery among patients initiating antiretroviral therapy
Acknowledgements

Co-Authors:
• Janet P. Tate
• Kirsha S. Gordon
• William C. Becker
• Kendall Bryant
• Kristina Crothers
• Julie Gaither
• Cynthia Gibert
• Adam Gordon
• Brandon D.L. Marshall
• Maria C. Rodriguez-Barradas
• Jeffrey H. Samet
• Melissa Skanderson

Co-Authors and Mentors:
• David A. Fiellin
• Amy C. Justice

Other Mentors:
• Lynn E. Fiellin
• Patrick G. O’Connor
• Marjorie S. Rosenthal

VACS Opioids Workgroup

Funding:
• Lawrence Linn Award
• NIDA DAHRS K12
• Yale Center for Clinical Investigation
• NIAAA
Questions/Comments

Jen Edelman

ejennifer.edelman@yale.edu
## Opioid Classification by Immunosuppressive Properties

<table>
<thead>
<tr>
<th>Immunosuppressive Properties</th>
<th>Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Morphine, codeine, fentanyl, dihydrocodeine,</td>
</tr>
<tr>
<td>No</td>
<td>Hydrocodone, oxycodone, hydromorphone, tramadol, naltrexone, oxymorphone, buprenorphine</td>
</tr>
<tr>
<td>Unknown</td>
<td>Propoxyphene, meperidine, methadone, levorphanol, pentazocine, tapentadol</td>
</tr>
</tbody>
</table>
Opioids and Immunosuppression

Roy et al. 2011
Type of Opioid Received by HIV Status, n=22,542

Asterix (*) indicates statistical significance.
APPENDIX 1

We made the following assumptions to determine the milligram of morphine equivalents for each opioid: 1) If the quantity of pills was less than the intended days supply of the prescription, then days supply was considered equal to the quantity of pills as we assumed patients did not take less than one pill; 2) Each fentanyl patch was dispensed over 72 h, consistent with previous literature; 3) Cough elixirs were prescribed to be taken as 7.5 mL (between 5 and 10 mL) every 4–6 h (37.5 mL per day) for 7 days; 4) We assumed that patients were taking no less than 10 mL per day of a opioid given solution (excluding cough elixirs); if a quantity of solution/days supply was less than 10 mL, then days supply was set equal to the quantity divided by 10 and we assumed that an equal amount was taken on each day. For a quantity of one, we assumed this was equal to one bottle of 500 mL of solution; and 5) For solutions (1% of all formulations), we accounted for differences in concentration such that for XX mg opioid in YY mL solution, then quantity was divided by YY.