New Opioid Limits: Are They Evidence Based?

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H-E-B PHARMACY/UT PGY1 COMMUNITY RESIDENCY PROGRAM
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PHARMACOTHERAPY ROUNDS

Objectives

Learner should be able to:
- Describe the current state of the opioid epidemic
- Describe Opioid Use Disorder and it’s prevalence
- Outline the pharmacology of opioid analgesics
- Review current guidelines for opioid prescribing for chronic pain
- Review the current strategies to limit opioid diversion and misuse
- Analyze the evidence used to create opioid guidelines and insurance limits
Opioids: A Brief History\textsuperscript{1,2}

- 3400 BC
  - Sumerians introduced Opium as a pain reliever and cure for other ailments

- 19th Century
  - Morphine discovered and used as a common medication
  - Discovery that patients could become addicted to morphine

- 20th Century
  - Heroin introduced as cough suppressant and “non-addictive” substitute for morphine
  - Young Americans began to crush heroin for recreational drug use
  - 1920's: heroin made illegal, and use of oxycodone, morphine, and codeine are mainstays in therapy
  - 1950-80: New medications introduced, “War on Drugs” began, phase of “opioidphobia”
  - 1990's: resurgence of pain treatment and new long acting formulations

- Early 2000's
  - Highest amount of opioid prescribing since discovery
  - Abuse of OxyContin, Vicodin, and Percocet doubles

\textsuperscript{1} Exp Clin Psychopharmacol 2009.
Opioid Use/Abuse Today: An Epidemic\textsuperscript{3,4}

- One of the biggest public health emergencies facing our country today
- 2016
  - Opioid Related Deaths
    - More than 116 Americans die every day from an opioid overdose
    - Deaths from prescription opioids have quadrupled since 1999
    - In 2016, an estimated 17,087 people died from prescription opioid overdose
  - Prescribing
    - Opioid prescribing has also nearly quadrupled since 1999
    - Estimated 11.5 million people misused prescription opioids
    - Estimated cost of $78.5 billion

Mortality in the United States, 2016 NCHS Data Brief No. 293, December 2017

Opioid Prescriptions By State\textsuperscript{3}
Drug Overdoses By State

Number and age-adjusted rates of drug overdose deaths by state, US 2016

National Opioid Overdose Deaths

Number of Deaths Involving Prescription Opioid Pain Relievers (excluding non-methadone synthetics)
Knowledge Check

The estimated number of opioid related deaths and the amount of opioids have nearly quadrupled since 1999.

True or False

Opioid Use Disorder

- Chronic disease with episodes of remission and relapse
- Defined as a pattern of opioid use leading to distress or impairment characterized by at least 2 of the following:

1. Use of larger amount or duration than intended
2. Desire or unsuccessful efforts to control or decrease use
3. Drug seeking behavior
4. Craving or strong urge to use
5. Interference with work/school/home life
6. Change in social, work, or recreational activities because of use
7. Use in dangerous situations
8. Use despite knowledge of physical or psychological problem due to use
9. Tolerance defined by increase in need
10. Withdrawal symptoms

DSM-5 2013.
Opioid Use Disorder\textsuperscript{5,6}

- Epidemiology
  - Estimated 2.1 million people have an opioid use disorder
  - All educational and socioeconomic backgrounds
  - Women have higher rates
  - All ages are effected
    - 150,000 adolescents (12-17) estimated to have an opioid addiction in 2015
- Risk Factors
  - Past or current substance abuse
  - Untreated psychiatric disorders
  - Younger age
  - Family history

Opioid Pharmacology\textsuperscript{7}

- $\mu$ or mu opioid receptors - analgesia, euphoria, adverse event
- $\kappa$ or kappa opioid receptors - dysphoria, physical dependence, psychomimetic
- $\delta$ or delta opioid receptors - respiratory depression, reduced gastrointestinal motility
- Gamma aminobutyric acid (GABA) $\rightarrow$ Dopamine release $\rightarrow$ pleasure

\textsuperscript{J Psychoactive Drugs. 1991;23(2):123-33}
Opioid Class Overview

- **Indications:**
  - Chronic pain in patients requiring a long-term daily around the clock opioid analgesic
  - Moderate to severe pain; non-responsive to non-narcotic analgesics
- **Drug interactions:**
  - CYP3A4 (most), CYP2D6 (tramadol/codeine), QT prolonging agents (methadone), CNS depressants (all)
- **Adverse Reactions:**
  - Constipation (no tolerance)
  - CNS effects- sedation, dizziness, confusion, delirium
  - Flushing, pruritus
  - Physical dependence
  - Respiratory depression
  - Nausea/vomiting

Pharmacokinetic Properties of Opioids

<table>
<thead>
<tr>
<th></th>
<th>codeine</th>
<th>hydrocodone</th>
<th>hydromorphone</th>
<th>methadone</th>
<th>morphine</th>
<th>oxycodone</th>
<th>oxymorphone</th>
<th>tramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>30-60 min</td>
<td>30-60 min</td>
<td>IR: 15min ER: 6h</td>
<td>30-60 min</td>
<td>IR: 30 min</td>
<td>IR: 10-15min</td>
<td>N/A</td>
<td>IR: 1h</td>
</tr>
<tr>
<td>Duration</td>
<td>4-6h</td>
<td>4-6h</td>
<td>IR: 3-4h ER: 13h</td>
<td>4-8h</td>
<td>IR: 3-5h ER: 8-24h</td>
<td>IR: 3-6h ER: 12h</td>
<td>IR: 4-6h ER: 12h</td>
<td>IR: 3-6h</td>
</tr>
<tr>
<td>T1/2</td>
<td>2.5-3.5h</td>
<td>3.5-4h</td>
<td>IR: 2-3h ER: 11h</td>
<td>8-59h</td>
<td>IR: 2-4h ER: 11-24h</td>
<td>IR: 2-4h ER: 5h</td>
<td>IR: 7-9h ER: 9-11h</td>
<td>6-8h AM: 7-9h</td>
</tr>
<tr>
<td>Protein binding</td>
<td>7-25%</td>
<td>36%</td>
<td>8-19%</td>
<td>80-95%</td>
<td>20-35%</td>
<td>45%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic CYP3A4</td>
<td>Hepatic CYP3A4</td>
<td>Hepatic</td>
<td>Hepatic CYP3A4</td>
<td>hepatic</td>
<td>Hepatic CYP3A4</td>
<td>Hepatic</td>
<td>Hepatic CYP3A4 CYP2D6</td>
</tr>
</tbody>
</table>
Morphine Milligram Equivalences (MME)\(^9\)

<table>
<thead>
<tr>
<th></th>
<th>Parenteral (mg)</th>
<th>Oral (mg)</th>
<th>Conversion Factor per the CDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>---</td>
<td>20</td>
<td>1.5</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.3</td>
<td>0.4 (sl)</td>
<td>--</td>
</tr>
<tr>
<td>Codeine</td>
<td>100</td>
<td>200</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.1</td>
<td>Transdermal: mcg is approximately 50% of oral morphine TDD</td>
<td>2.4</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>---</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td>4</td>
</tr>
<tr>
<td>Meperidine</td>
<td>100</td>
<td>300</td>
<td>--</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Tramadol</td>
<td>---</td>
<td>120</td>
<td>--</td>
</tr>
<tr>
<td>Methadone</td>
<td>Linear conversion not possible</td>
<td></td>
<td>1-20mg/day: 4, 21-40mg/day: 8, 41-60 mg/day: 10, ≥ 61-80mg/day:12</td>
</tr>
</tbody>
</table>

JAMA 2016; 315: pp. 1624-1645

CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016\(^9\)

- Initiation of opioid therapy should be with immediate release opioids
- Use lowest dose, and slowly titrate
  - Evaluate risk/benefit when considering a dosage of 50 MME/day
  - Avoid 90 or greater MME/day or carefully justify need
- Long-term opioid use often begins with treatment of acute pain
  - Use lowest dose effective
  - Most often 3 days or less will be needed, rarely will more than seven days be needed
- Pain management should be assessed per individualized patient

JAMA 2016; 315: pp. 1624-1645
Current Mitigation Strategies\textsuperscript{10,11}

- Prescription Drug Monitoring Programs
  - Enables prescribers, and pharmacists to track and monitor prescribing and dispensing data
- Education
  - Efforts to improve pain and opioid use disorder education in medical and pharmacy schools
- Naloxone
  - Made more readily available through state dispensing protocols
- Risk Evaluation and Mitigation Strategies
  - Expanded from Extended Release and Long Acting formulations to all opioids
- Insurance limits on coverage

Using the Guidelines to Limit Reimbursement\textsuperscript{12,13}

- Insurance companies using guidelines to create opioid limits
  - CVS Caremark will require a step therapy before starting a long acting opioid formulation
  - Cigna Health Insurance has dropped coverage of OxyContin™ (Oxycodone ER), and will now cover only Xtampza™ ER (Oxycodone ER)
  - Express Scripts and others will enforce a 7 day limit on acute care medications
  - Center for Medicare and Medicaid Services (CMS) move to place a 90 MME limit on opioids
- Hard stop limits and/or Prior Authorization
Has anyone seen any of these limits in practice?

The Controversy

- Effects on patients
  - Decreasing and delaying access to necessary pain medications
  - Patients are experiencing fear
- Individualized patient care
  - CDC guidelines recommend treating each patient on a case by case basis
- Are these opioid limits an evidence based approach?
Exploring the Evidence

Acute Opioid Limits on Day Supply Evidence
Alam et al. Arch Intern Med. 2012¹⁴

### Long-term Analgesic Use After Low-Risk Surgery: A Retrospective Cohort Study

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess the effects of opioid therapy for acute pain on long-term use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Retrospective cohort study</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Elderly: 66 years and older</td>
</tr>
<tr>
<td></td>
<td>Low-pain short stay surgeries: cataract surgery, laparoscopic</td>
</tr>
<tr>
<td></td>
<td>cholecystectomy, transurethral resection of prostate, varicose vein</td>
</tr>
<tr>
<td></td>
<td>stripping surgery</td>
</tr>
<tr>
<td>Exclusion Criteria</td>
<td>1 or more cohort-specific analgesic in the previous year</td>
</tr>
<tr>
<td></td>
<td>Pts who died within 425 days of surgery</td>
</tr>
<tr>
<td></td>
<td>Hospital admittance &gt;3 days</td>
</tr>
<tr>
<td></td>
<td>Pts. Hospitalized in previous 100 days</td>
</tr>
<tr>
<td></td>
<td>Emergency surgeries, palliative care or cancer patients</td>
</tr>
</tbody>
</table>

### Methods

Analysis of administration data in Ontario from April 1997 to December 2008 for opioid exposure 7 days post surgery and long-term use

### Outcome Measures

- **Opioid exposure**
  - Defined as 1 or more opioids dispensed w/in 7 days
- **Long-term opioid use**
  - Defined as additional claim for any opioid within 60 days of 1 year anniversary of surgery (305-425 days post surgery)

### Statistical Methods

Multivariate logistic regression to examine analgesic initiation and long-term analgesic use

### Population Characteristics

N: 391,139

40% males, 25% in teaching hospital

Almost 94% of patients given codeine over other opioids

Other characteristic similar

| Results | Early opioid exposure: 27,636 (7.1%)  
|         | Early opioid exposure and use at 1 year: 2857 (10.3%)  
|         | Adjusted odds ration: 1.4 (95% CI, 1.39-1.50)  

| Author’s Conclusions | Patients with early exposure are 44% more likely to have long-term opioid use in the elderly  

| Strengths | -Methods designed to limit some confounding  
|          | -Large population size  
|          | -Demonstrated rates of different opioids prescribed for acute pain  

| Weaknesses | -Initial medication dosing not evaluated  
|           | -Indication for use of 1 year not explored  
|           | -Exclusion of patients with death w/in 425 days could exclude opioid related deaths  
|           | -Not generalizable to total population (surgery, age, etc.)  

| My Conclusion | Study shows some association between use of opioids for acute pain and long-term use, BUT unpreventable confounding and low generalizability limit application  

Webster B et al. Spine. 2007

| Objective | To assess the effects of opioid therapy for acute pain on late use, disability duration, medical costs, and low back surgery  

| Design | Retrospective cohort study  

| Inclusion Criteria | Lost time began within 10 days of LBP onset  
|                    | Received 1 paid medical service within 15 days of injury  

| Exclusion Criteria | Prior LBP cases  
|                    | Treatment for fracture or any other condition  


Webster B et al. Spine. 2007

**Relationship Between Early Opioid Prescribing for Acute Occupational Low Back Pain and Disability Duration, Medical Costs, Subsequent Surgery and Late Opioid Use**

| Intervention | Examination of Worker’s Compensation claims for opioid treatment within 15 days of onset of pain/injury.
|             | Examination of endpoints and association with no early opioid treatment, MMEs of 1–140, 141–225, 226–450, and >450.
| Outcome Measures | Late opioid prescriptions (30-730 days post onset/5 or more prescriptions), Disability duration, Medical costs, Surgical procedures.
| Statistical Methods | Multivariate linear regression.
| Population Characteristics | All baseline characteristics similar (age, gender, tenure). N= 8443 in final study sample.

**Results**

Disability duration, medical costs, and low back surgery: increased in those with early use and increased as MEA increased.

Late Opioid Use

Early opioid prescribing was associated with increased risk of late opioid prescribing.

Risk increases as MEA increases.

**Table 5. Logistic Regression Model Examining Association Between Morphine Equivalent Amount (MEA) and Late Opioid Use After Controlling for Severity, Age, Gender, and Job Tenure**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Intervals</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEA (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>490+</td>
<td>6.14</td>
<td>4.92 to 7.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>226–450</td>
<td>3.69</td>
<td>2.88 to 4.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>141–225</td>
<td>2.89</td>
<td>2.25 to 3.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–140</td>
<td>2.08</td>
<td>1.55 to 2.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High severity</td>
<td>2.02</td>
<td>1.74 to 2.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.02</td>
<td>1.01 to 1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.02</td>
<td>0.87 to 1.20</td>
<td>0.783</td>
</tr>
<tr>
<td>Tenure (yr)</td>
<td>0.98</td>
<td>0.97 to 0.99</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Webster B et al. Spine. 2007

<table>
<thead>
<tr>
<th>Relationship Between Early Opioid Prescribing for Acute Occupational Low Back Pain and Disability Duration, Medical Costs, Subsequent Surgery and Late Opioid Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author’s Conclusions</strong></td>
</tr>
</tbody>
</table>
| **Strengths** | - Linear regression with controlling for variables (severity, age, gender)  
- Large homogeneous sample size from 46 states  
- Late opioid use was defined as 5 or more prescriptions |
| **Weaknesses** | - Patient’s injury severity were identified by ICD-9 codes  
- Confounding variables: psychosocial factors, pain intensity  
- Generalizability to other types of acute pain  
- No association shown with duration of initial prescription |
| **My Conclusion** | Study shows strong association between early use and late use of opioids, as well as increase in risk as dose increases. BUT does not show relationship to initial duration of therapy |

### Morphine Milligram Equivalence Limits Evidence
**Bohnert et al. JAMA. 2011**

### Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths

<table>
<thead>
<tr>
<th>Objective</th>
<th>To examine the association between different prescribing patterns and overdoses: MME doses, scheduled and/or as-needed opioids, for different indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective case-cohort study conducted in the Veterans Health Administration from 2004 through 2008</td>
</tr>
</tbody>
</table>
| Inclusion Criteria | -Patients who died of opioid overdose from FY2004-2008 treated with opioids  
                     -Random sample of VA patients who received opioid treatments |
| Exclusion Criteria | -Palliative or hospice care patients  
                     -Intentional overdose  
                     -Methadone, buprenorphine |

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cohort (overdose group vs. control group) analysis of MME dose ranges (0, 1-&lt;20, 20-&lt;50, 50-&lt;100, 100+ mg/day); scheduled, as needed, both; by indication: chronic pain, cancer, substance use disorder, and acute pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome Measure</td>
<td>Hazard rates for opioid overdose in each subgroup</td>
</tr>
</tbody>
</table>
| Statistical Methods | Multivariable modeling  
                     Cox proportional hazards models |
| Population Characteristics | (n)=750 patients with opioid overdose  
                     (n)=154,684 random patients with opioid therapy  
                     94% male, 72% white |
### Results

**Bohnert et al. JAMA. 2011**

#### Patients With Chronic Noncancer Pain Diagnoses

<table>
<thead>
<tr>
<th>Maximum prescribed daily opioid dose, mg/d</th>
<th>Overdose Deaths, No.</th>
<th>Person-Months</th>
<th>Overdose Death Rate per 1000 Person-Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>243</td>
<td>2,729,022.7</td>
<td><strong>0.09 (0.08-0.10)</strong></td>
</tr>
<tr>
<td>1–&lt;20</td>
<td>44</td>
<td>395,205.0</td>
<td><strong>0.11 (0.08-0.15)</strong></td>
</tr>
<tr>
<td>20–&lt;50</td>
<td>108</td>
<td>458,296.2</td>
<td><strong>0.24 (0.19-0.28)</strong></td>
</tr>
<tr>
<td>50–&lt;100</td>
<td>86</td>
<td>129,491.6</td>
<td><strong>0.68 (0.53-0.82)</strong></td>
</tr>
<tr>
<td>≥100</td>
<td>125</td>
<td>100,479.3</td>
<td><strong>1.24 (1.04-1.46)</strong></td>
</tr>
</tbody>
</table>

Fill types

- Regularly scheduled only: 115 (323,304.7) 0.36 (0.29-0.43)
- As needed only: 152 (672,276.0) 0.23 (0.19-0.27)
- Simultaneous as needed and regularly scheduled: 95 (87,891.5) 1.09 (0.88-1.33)

#### Risk of Opioid Overdose Death, HR (95% CI)

<table>
<thead>
<tr>
<th>Opioid fill type</th>
<th>Chronic Pain (n = 111,759)</th>
<th>Cancer (n = 36,803)</th>
<th>Acute Pain (n = 29,379)</th>
<th>Substance Use Disorders (n = 15,491)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regularly scheduled only</td>
<td><strong>1 (Reference)</strong></td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>As needed only</td>
<td>1.10 (0.85-1.43)</td>
<td>2.75 (1.31-5.78)</td>
<td>0.94 (0.59-1.49)</td>
<td>0.97 (0.64-1.46)</td>
</tr>
<tr>
<td>Simultaneous as needed and regularly scheduled</td>
<td>1.34 (0.99-1.79)</td>
<td>1.84 (0.83-4.05)</td>
<td>1.12 (0.68-1.86)</td>
<td>1.22 (0.72-2.05)</td>
</tr>
</tbody>
</table>

Maximun prescribed daily opioid dose, mg/d

| 1–<20 | **1 (Reference)** | 1 (Reference) | 1 (Reference) | 1 (Reference) |
| 20–<50 | 1.88 (1.33-2.67) | 1.74 (0.69-4.30) | 1.58 (0.87-2.86) | 1.42 (0.85-2.38) |
| 50–<100 | 4.63 (3.18-6.74) | 6.01 (2.29-15.78) | 4.73 (2.55-8.79) | 2.76 (1.54-4.94) |
| ≥100 | 7.18 (4.85-10.66) | 11.99 (4.42-32.56) | 6.64 (3.31-13.31) | 4.54 (2.46-8.37) |

Pain-related diagnoses

- Cancer: 0.99 (0.72-1.36) 0.66 (0.35-1.23) 1.03 (0.63-1.66)
- Chronic body pain: 0.69 (0.39-1.33) 1.53 (0.74-3.16) 0.56 (0.24-0.94) 0.74 (0.46-1.21)
- Headache: 1.02 (0.74-1.41) 0.72 (0.23-2.10) 1.17 (0.69-1.98) 0.76 (0.43-1.34)
- Neuropathy: 0.64 (0.38-1.08) 0.21 (0.03-1.56) 0.84 (0.40-1.79) 0.43 (0.16-1.18)
- Injuries and acute pain: 1.37 (1.06-1.74) 0.94 (0.50-1.77) 1.24 (0.86-1.83)
Bohnert et al. JAMA. 2011

**Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths**

| Author’s Conclusions | There is a clear relationship between opioid prescribing and opioid overdose.  
- Overdose risk increases at opioid doses of 50 MME, and again at 100+MME  
- Scheduled opioids did not have significant change in risk compared to scheduled and as needed opioids. |
| Strengths | - Large sample linked to mortality data  
- Multiple indications, dose ranges, and scheduled and/or as-needed analysis |
| Weaknesses | - Assumptions: taking max prescribed, only source is VHA prescriptions  
- Exclusion of methadone, semi-synthetic opioids  
- Misclassification of cause of death-suicide, misdiagnosed overdose  
- Generalizability |
| My Conclusion | - Risk of overdose more than doubles when increasing from 20-<50 to 50-<100 MME, and the risk is even greater at doses >100MME.  
- Even taking into account the limitations of the study, there is a clear association of increased risk and increased dose. |

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**Extended Release and Long Acting Formulation Limits Evidence**
### Miller et al. JAMA Intern Med. 2015

**Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy**

<table>
<thead>
<tr>
<th>Objective</th>
<th>To examine if risk of opioid overdose is associated with opioid formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Cohort study using populations data from the Veterans Administration data from 2000-2009</td>
</tr>
</tbody>
</table>
| Inclusion Criteria                 | - New opioid users defined as no opioid within 6 months  
                       - Patients with chronic pain diagnosis (defined by previous study)  
                       - Opioid monotherapy |
| Exclusion Criteria                 | - Those not eligible for VHA benefits  
                       - Patients without at least 1 encounter in year before prior to opioid prescription  
                       - Hospice patients  
                       - Formulations used solely for opioid addiction  
                       - Intentional overdose |

**Intervention**

Risk of overdose in those initiated with long-acting opioid and those initiated with short-acting opioid

**Outcome Measures**

Unintentional opioid overdose or opioid overdose of undetermined intent

**Statistical Methods**

- Propensity score adjustment model  
- Cox proportional hazards regression models

**Population Characteristics**

- \( n = 840,606 \)  
- Similar baseline characteristics  
- 95% male, 71-75% white, majority age >50
Miller et al. JAMA Intern Med. 2015

### Results

Table 2. Incidence Rate and HR for Unintentional Overdose Comparing Long-Acting With Short-Acting Opioids*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Events</th>
<th>No. of Person-years</th>
<th>Crude Rate (95% CI)*</th>
<th>Crude HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>319</td>
<td>104,683</td>
<td>0.31 (0.27-0.35)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Short-acting</td>
<td>282</td>
<td>91,274</td>
<td>0.31 (0.27-0.35)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>37</td>
<td>13,409</td>
<td>0.31 (0.27-0.35)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>≤14 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td>70</td>
<td>27,762</td>
<td>0.25 (0.21-0.30)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>10</td>
<td>6,091</td>
<td>0.31 (0.27-0.35)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>15-49 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td>79</td>
<td>49,266</td>
<td>0.16 (0.12-0.21)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>6</td>
<td>1,866</td>
<td>0.06 (0.05-0.08)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>≥50 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td>133</td>
<td>115,398</td>
<td>0.11 (0.07-0.13)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>21</td>
<td>8,188</td>
<td>0.25 (0.18-0.32)</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
</tbody>
</table>

- 319 total event  
- 2-fold risk increase in LA group  
- Risk is greatest in first two weeks  
- In addition, risk was double when dose was >50 compared to 1-20MME.

---

### Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy

**Author’s Conclusions**  
- First study to show there is a relationship between unintentional overdose and duration of opioid action.  
- First two weeks of treatment should be limited to short-acting opioids

**Strengths**  
- Propensity scores used to adjust the association between opioid use and overdose for covariates (other medications used, comorbidities)  
- Large population

**Weaknesses**  
- Unable to adjust for misclassification  
- Unable to measure adherence, other sources of opioids  
- Application to females, patients without chronic medical conditions, and younger patients is not known

**My Conclusion**  
Study showed a large increase in risk when initiating opioid therapy with LA opioids. Adjustment for confounding strengthens validity.
An Evidence Based Approach?

- Limited evidence with limited strength
  - No randomized controlled trials
  - Case and cohort study’s with clear limitations and limited application
- One Size Fits all solution vs. individualized patient care model
- Importance: being adopted by states to create laws and insurance companies to create limits

Recommendations$^{18}$

- Medication Therapy Management
- Gaps in Care
  - Recommendations to physicians for alternative treatments
    - Non-prescription medications, clonidine, alternative opioids or prescription pain medication
    - Switch to different opioid based on MME
- Naloxone Protocols
- Substance Abuse Referral
Future Research

- New non-analgesic medications and treatments
- More research into pain, addiction
- The effects limiting access have on the illicit market
- The effects these limits will have on patients, and on opioid use

Knowledge Check

What recommendations could you make to help care for patients effected by these opioid limits?
Conclusion

- This will be something we will encounter in practice more as we enter the new year
- The evidence is limited and there is much to be researched
- We do not yet know the consequences or benefits when limiting opioid prescriptions
- Be prepared to help your patients who might be impacted or experience a gap in care

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Evaluator
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Seton Healthcare Family
Questions?

References

References cont.


New Opioid Limits: Are They Evidence Based?

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PHARMACOTHERAPY ROUNDS