Pain, Opioids, Addiction and Buprenorphine

Steven Prakken MD
Director Medical Pain Service
Duke Pain Medicine
Pain: Largest U.S. Public Health Crisis

Prevalence

100M
- Persistent Pain
  - Annual Healthcare & Productivity Cost: $560-630 Billion

80M
- Cardiovascular Disease
  - Annual Healthcare & Productivity Cost: $309 Billion

29M
- Cancer
  - Annual Healthcare & Productivity Cost: $127 Billion

14M
- Diabetes
  - Annual Healthcare & Productivity Cost: $243 Billion

328 Million Prescriptions and $13 Billion in Sales

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1 Institute of Medicine 2011: Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research
2 The Heart Foundation (http://www.theheartfoundation.org/heart-disease-facts/heart-disease-statistics/)
4 American Diabetes Association (http://www.diabetes.org/diabetes-basics/statistics/)
5 IMS Health; 2014 data
National Overdose Deaths
Number of Deaths from Prescription Opioid Pain Relievers (excluding non-methadone synthetics)

Source: National Center for Health Statistics, CDC Wonder
Overdose Deaths Involving Opioids, United States, 2000-2015

- **Any Opioid**
- **Commonly Prescribed Opioids** (Natural & Semi-Synthetic Opioids and Methadone)
- **Heroin**
- **Other Synthetic Opioids** (e.g., fentanyl, tramadol)

National Overdose Deaths
Number of Deaths from Heroin and Non-Methadone Synthetics (captures illicit opioids)

Source: National Center for Health Statistics, CDC Wonder
Number of Reported Law Enforcement Encounters Testing Positive for Fentanyl in the US: 2010 - 2015
Opioid involvement in benzodiazepine overdose

Source: National Center for Health Statistics, CDC Wonder
Addiction Rates
Lifetime prevalence in USA 16.7%, with ETOH at 13.5% and other drug use at 7%

Prevalence in pain patients is quite varied, 2.8–28% current and 23–41% lifetime. Most commonly cited range is 4–26%.

Problematic Opioid Use

- Systematic review from 38 studies (26% primary care settings, 53% pain clinics)

Misuse rates: 21% - 29%

Misuse: Opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects.

Addiction rates: 8% - 12%

Addiction: Pattern of continued use with experience of, or demonstrated potential for, harm (e.g., “impaired control over drug use, compulsive use, continued use despite harm, and craving”).

Substance Use Disorder in the Past Year among People Aged 12 or Older

Percent in Past Year


12 or Older 12 to 17 18 to 25 26 or Older
Illicit Drug Use Disorder in the Past Year among People Aged 12 or Older

SAMHSA 2015
Pain Reliever Use Disorder in the Past Year among People Aged 12 or Older
Past Month Nonmedical Use of Psychotherapeutic Drugs among People Aged 12 or Older, by Age Group: Percentages 2002–2014

Percent Using in Past Month


- ▲ 12 or Older
- ○ 12 to 17
- □ 18 to 25
- □ 26 or Older
Past Year Nonmedical Psychotherapeutic Initiates among Persons Aged 12 or Older
Illicit Drug Use Age 50–64
Past Year Heroin Use among People Aged 12 or Older, by Age Group: Percentages 2002–2015
Heroin and Pain Management

- **Heroin initiates**
  - Nearly 80% used prescription drugs first

- **Nonmedical Pain Reliever Use and Initiation of Heroin**
  - 3.6% of NMPR progressed to heroin in last 5 years
  - .39% of NMPR progressed to heroin in last 12 months
  - .02% of non–NMPR progressed to heroin in last 12 months

- **Alabama 2016**
  - Only 15% of deaths occurred outside of heroin and fentanyl

Muhuri 2013, Jones 2013, Kertesz 2016, CDC 2015
The lifetime risk of depression and other mood disorders among a population has a positive correlation with an increasing Gini coefficient, which is an indicator of greater income inequality.
Buprenorphine, the History

- Discovered in 1966 in England, looking for alternative tx’s for addiction through antagonists or partial agonists.

- Late 1990 with 1–2 million needing opioid addiction tx and only 150,000 able to receive methadone tx.
  - Needing office based tx

- Trials in USA for addiction, in 2000 –2002 successful

- FDA approval in 2002 for opioid addiction, office based

- Limits of 30 patients initially, then to 100 and now to 275 per provider in 2016
Buprenorphine
What kind of opioid is it?
Buprenorphine Pharmacology

- Partial agonist at Mu
- Strong antagonist at Kappa
- Half life 28–37 hrs
- 25–100x more potent than morphine
- High first pass metabolism, high lipophilic, thus SL and transdermal helpful.
- Bioavailable 30%SL, 70%IM, 15% transdermal
- Metabolism CYP3A4 to norbup and glucouronidation
- QT prolongation
**Mu Receptors**

- **Mu receptors**
  - Primarily in the brainstem and medial thalamus
  - Responsible for...
    - supraspinal analgesia
    - respiratory depression
    - euphoria
    - sedation
    - decreased gastrointestinal motility
    - physical dependence.
KAPPA RECEPTORS

- Kappa receptors
  - limbic and other diencephalic areas, brain stem, and spinal cord
  - Responsible for...
    - Dysphoria
    - spinal analgesia
    - Sedation
    - Dyspnea
    - Dependence
    - respiratory depression.
CLASSIFICATION

- Agonists
  - Oxycodone, oxymorphone, hydrocodone, morphine, methadone, codeine, fentanyl, tramadol, tapentadol

- Partial Agonists
  - Buprenorphine

- Antagonists (Mu)
  - Naloxone, naltrexone

- Agonist/Antagonist
  - Butorphanol, nalbuphine, pentazocine
Buprenorphine Pharmacology

Remember!!

- Very high affinity for Mu
  - Will kick other opioids off of the receptor

- Partial Agonist
  - Will turn the receptor on only part way

- Half life 28–37 hrs

- Incomplete reversal by naloxone
Buprenorphine for Addiction Treatment

- **Buprenorphine Waiver**
  - 6 hrs of training
  - DEA with “X” that indicates waiver in place
    - Tx the disease of addiction

- Now 100 patients, up to 275 if tx of 100 for a year

- NP/PA’s now able to treat
Abstinence Rate Exceeds 60% in MAT long-term study

Potter 2015
Buprenorphine and Naloxone

- Addiction formulations
  - With Naloxone
    - Suboxone, Bunavail, Zubsolv
  - Without Naloxone
    - Subutex (least expensive)

- Assumptions
  - IVDU protection?
# Mu Receptor Binding

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Binding Affinity Ki</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufentanil</td>
<td>0.1</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>.3–.9</td>
</tr>
<tr>
<td>Naloxone</td>
<td>.8–1.2</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1.6</td>
</tr>
<tr>
<td>Morphine</td>
<td>5.7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>23.4</td>
</tr>
<tr>
<td>Meperadine</td>
<td>193.0</td>
</tr>
</tbody>
</table>
Buprenorphine Induction

- Decision to begin buprenorphine
- Educate about "precipitated withdrawal"
  - Not naloxone effect
  - Not reversible
- COWS score mild to moderate
- Day 1 and day 2 dosing level obtained and continued.
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Scores</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting pulse rate</td>
<td>0-4</td>
<td>0=80 or less; 1=81-100; 2=101-120; 4=120 or greater</td>
</tr>
<tr>
<td>Sweating</td>
<td>0-4</td>
<td>0=none; 4=sweat streaming from face</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0-5</td>
<td>0=sits still; 5=unable to sit still (even for a few seconds)</td>
</tr>
<tr>
<td>Pupil size</td>
<td>0-5</td>
<td>0=normal; 5=dilated (only iris rim visible)</td>
</tr>
<tr>
<td>Bone or joint aches</td>
<td>0-4</td>
<td>0=none; 4=severe discomfort</td>
</tr>
<tr>
<td>Runny nose or tearing</td>
<td>0-4</td>
<td>0=none; 4=constant</td>
</tr>
<tr>
<td>GI upset</td>
<td>0-5</td>
<td>0=none; 5=multiple episodes of vomiting or diarrhea</td>
</tr>
<tr>
<td>Tremor</td>
<td>0-4</td>
<td>0=none; 4=gross tremor</td>
</tr>
<tr>
<td>Yawning</td>
<td>0-4</td>
<td>0=none; 4=yawning several times/minute</td>
</tr>
<tr>
<td>Anxiety &amp; Irritability</td>
<td>0-4</td>
<td>0=none; 4=severe, precluding participation</td>
</tr>
<tr>
<td>Gooseflesh skin</td>
<td>0-5</td>
<td>0=smooth; 5=prominent piloerection</td>
</tr>
</tbody>
</table>

COWS=Clinical Opiate Withdrawal Scale; GI=gastrointestinal.

Score: 5-12 mild; 13-24=moderate; 25-36=severe.

**Buprenorphine for Addiction**

- **Induction for Suboxone or Subutex**
  - **Day 1**…. 4mg initial dose, repeat in 2 hrs at 2–4mg, may repeat at 2–4 mg in another 2–6 hrs if need, total max of 12 mg if need.
  
  - Stop at the dose that reverses withdrawal
    - Common first day dose is 8mg
  
  - **Day 2**…. repeat once the dose that worked day 1, if after 12 mg the first day there was poor response then may add 4mg for 16mg total dose. No higher for a week and then may increase by 2mg every 2–4 days.
  
  - 32mg max effective dose
Buprenorphine for Pain

- No Waiver needed

- **Butrans** (2013)
  - Schedule III
  - Patch technology
    - 5, 7.5, 10, 15 and 20 mcg/hr
    - 7 day patch

- **Belbuca** (2015)
  - Schedule III
  - Buccal patch, dissolving
  - 75 to 900 mcg patches, bid dosing
  - On Medicaid thanks to Larry Greenblatt MD
Butrans  

Belbuca
## Belbuca Dosing

<table>
<thead>
<tr>
<th>MSE dose prior to tapering to 30 mg</th>
<th>Starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 30 mg oral MSE</td>
<td>75 mcg every 12 hrs</td>
</tr>
<tr>
<td>30–89 mg oral MSE</td>
<td>150 mcg every 12 hrs</td>
</tr>
<tr>
<td>90–160 mg oral MSE</td>
<td>300 mcg every 12 hrs</td>
</tr>
<tr>
<td>Greater than 160 mg oral MSE</td>
<td>Consider alternative tx</td>
</tr>
</tbody>
</table>

- 75 mcg every 12 hrs
- 150 mcg every 12 hrs
- 300 mcg every 12 hrs
- Consider alternative tx
Benefits of Buprenorphine

Pain
- Review showing efficacy in 25/26 trials
- No analgesic ceiling effect
- Some evidence of no antagonistic effect on other Mu opioid agonists
  - Can use full agonists if need
  - Kappa antagonism may reduce euphoria of others

Neuropathic pain
- Effective in review
- May work through antihyperalgesia

Benefits of Buprenorphine

- **Respiratory**
  - Has ceiling effect, safest opioid
  - Full agonists with up to 11% respiratory depression

- **Constipation**
  - Much lower incidence (1–5%)
  - No sphincter of Oddi spasm
    - Use in pancreatic pain?

- **Renal failure**
  - Bile elimination
    - No increase in blood levels
  - Hemodialysis does not effect levels
    - Stable pain control

Benefits of Buprenorphine

- Cognitive
  - Better visual, psychomotor, cognitive function vs morphine or methadone
  - Less impaired driving

- Depression
  - Less depressogenic, may actually have some antidepressant effect

- Both likely due to Kappa antagonist effect

Benefits of Buprenorphine

- **Immunosuppression**
  - Does not—
    - reduce NK cell function
    - Increase cortisol
    - Reduce ACTH levels
    - Change cytokine expression

- **Hormone**
  - Does not—
    - Reduce testosterone
    - Reduce hormone levels

Davis 2012, Aloisi 2011, Bleisener 2005, Hallinan 2009,
Benefits of Buprenorphine

- **Tolerance**
  - Slower than for morphine and fentanyl

- **Antihyperalgesia**
  - Tested by transcutaneous stimulation
  - Effect on antihyperalgesia > analgesia
  - May reduce vs prevent central sensitization

- **QTc**
  - Methadone up to 29% of patients
  - Methadone 4x buprenorphine for cardiac death

Buprenorphine Transitions

- Must be in frank withdrawal or will precipitate w/d
  - Few options
- Full agonists added to buprenorphine
  - fine
- Buprenorphine added to full agonists
  - careful
- Buprenorphine in the ED or Hosp
  - Keep bup if can, careful if not
- Buprenorphine in the future
- Waiver need
Buprenorphine and Psychiatry

- SUD treatment
- Pain treatment as safe option
- Potential mood treatment?
- Consultation liaison exposure
  - Sickle Cell
  - Endocarditis
  - Pain and SUD comorbidity
Can I Use It?
- Waiver for “SUD”
- No waiver needed for:
  - Pain
  - Withdrawal in hospital
    - May discharge with 3 day supply
    - Continuation of SUD tx if hospitalized

Just using this for SUD?
- Suboxone vs subutex
THANK YOU
Elective Surgery

Preoperatively:
Surgical team should assess anticipated postoperative pain and opioid requirements

Minimal to No Pain

Moderate to Severe Pain

Still Taking Buprenorphine
- Continue buprenorphine
- Do NOT routinely prescribe supplemental opioids
- Do NOT change the buprenorphine dose
- Consider adjuncts – NSAIDs, membrane stabilizers, acetaminophen, local anesthetic agents, regional anesthetic techniques

Off Buprenorphine
- Surgical team should contact buprenorphine providers and confirm they are aware of surgery and have a plan to reinstitute therapy
- Assess amount of time since last dose. If the following dose/time intervals are met, treat with traditional opioids using opioid-tolerant dosing:
  - 0-4 mg per day – stop x 24 h before surgery
  - >4-8 mg per day – stop x 48 h before surgery
  - >8-12 mg per day – stop x 72 h before surgery
  - >12 mg – requires preoperative management plan with buprenorphine provider

Still Taking Buprenorphine
- Cancel surgery – Maybe better: postpone or schedule surgery such that the following requirements can be met
- Patient should return to buprenorphine provider and be placed on short-acting opioid or be weaned off before surgery. A plan for follow-up and reinstatement of therapy should be established.
  - 0-4 mg per day – stop x 24 h before surgery
  - >4-8 mg per day – stop x 48 h before surgery
  - >8-12 mg per day – stop x 72 h before surgery

Off Buprenorphine
- Anticipate patient's opioid requirements will be similar to opioid-tolerant or highly-tolerant patient
- Surgical team should ensure appropriate outpatient follow-up with buprenorphine provider
- Consider adjuncts – NSAIDs, membrane stabilizers, acetaminophen, local anesthetic agents, regional anesthetic techniques
Still Taking Buprenorphine

- Surgeons should contact the physician prescribing buprenorphine and ensure that he or she is aware of surgery
- Continue the buprenorphine for postoperative pain
- Do NOT routinely prescribe supplemental opioids
- Consider adjuncts – acetaminophen and/or NSAIDs

Off Buprenorphine

- Assess the amount of time since last dose of buprenorphine
- If ≥5 days off buprenorphine, treat with traditional opioids; may require tolerant or highly-tolerant doses
- Surgeons should contact the physician prescribing buprenorphine and ensure that he or she is aware of surgery
- After postoperative pain normalizes, the patient may work with his or her physician to reinstitute buprenorphine therapy

Still Taking Buprenorphine

1. Discontinue buprenorphine
2. Start PCA – Will likely require high doses; may require some continuous opioid infusion. However, would avoid high-dose, continuous opioids and instead allow the patient to use PCA. Consult APS, PCA to be managed by Acute Pain Service (APS).
3. Patient should be in a monitored setting with close nurse monitoring (ICU, or monitored/moderate care setting)
   - Duration of ICU/monitored setting time will vary
   - Acetaminophen around the clock (ATC)
   - Consider gabapentin or pregabalin
4. Regional anesthesia – consider continuous catheters
5. Maximize adjuncts
   - Dexmedetomidine for ICU patients used according to ICU protocols
   - Acetaminophen around the clock (ATC)
   - Consider gabapentin or pregabalin

Off Buprenorphine

- Anticipate patient’s course to be similar to tolerant patient
- Surgeons should ensure appropriate outpatient follow-up
Figure 38. Heroin Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: Percentages, 2002-2014

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.