Moving into the Post-opioid Chronic Pain Treatment Era – Opportunities and Challenges

William C. Becker, MD
Core Investigator, PRIME Center of Innovation
VA Connecticut Healthcare System
Associate Professor, Yale School of Medicine
I have no conflicts of interest related to the content of this presentation.
Outline

Background:
- Chronic pain: pathophysiology and epidemiology
- Opioids’ role in chronic pain

Intervention development:
- Management strategies for when harm outweighs benefit
- Novel use of buprenorphine
- Testing/implementing non-pharmacologic approaches
Case presentation

Mr. M is 66-year-old white man with chronic low back pain who presents for evaluation.

CC: “I’m in a rut.”

PMHx: lumbar spondylosis, PTSD

Pertinent data:
– Morphine SA 60 mg TID, oxycodone IR 10 mg q6 hours;
– Opioid therapy started 2004 at 30 mg MEDD→240 mg MEDD
– Sedentary but intermittent high intensity activity

ROS: Daily moderate-severe back pain interfering with ADLs, nightmares, snoring, erectile dysfunction
Problem list

• Poorly controlled chronic pain
• Opioid tolerance
• Poorly controlled PTSD
• Sleep-disordered breathing
• Erectile dysfunction

• Sub-optimal treatment of chronic pain
• Elevated risk of overdose death
• Mismatch between needs and healthcare resources
Outline

Background:
- Chronic pain: pathophysiology and epidemiology
- Opioids’ role in chronic pain

Intervention development:
- Management strategies for when harm outweighs benefit
- Novel use of buprenorphine
- Testing/implementing non-pharmacologic approaches
Acute pain

von Hehn CA et al. Neuron 2012
Chronic inflammatory pain

Adapted from von Hehn CA et al. Neuron 2012
Chronic pain: neuronal plasticity and central sensitization

Neuronal plasticity
Peripheral nerve injury → recruitment of macrophages and glial cells → dysregulated nerve regeneration of both AB and c-fibers

Central sensitization
Excess of AB and c-fibers in dorsal horn → compensatory changes to NMDA receptors → lowered pain thresholds

Woolf CJ. Pain 2011
Chronic pain: hyperalgesia and allodynia

Woolf CJ. Pain 2011
Complexity of chronic pain

- Maladaptive behaviors
- Maladaptive thoughts
- Disuse/de-conditioning
- Pain behaviors

- Reframe thoughts
- Decrease pain
- Coping skills/self-management techniques
- Increase activity
- Increase pain

Deardorff, WW. APA 2008.
Becker, WC; Heapy AA et al. JGIM 2017.
Chronic pain epidemiology

• In 2016: 20.4% of U.S. adults had chronic pain; 8.0% had high-impact chronic pain
• Both more prevalent among adults:
  – living in poverty
  – with less than a high school education
  – with public health insurance.
• Among veterans: 29.1%; 10.3%
• Prevalence increasing

Dahlhamer et al. MMWR 2018.
Opioid analgesics (opiates + opioids)

**Opiates**
- Naturally present in opium from seedpod of *Papaver somniferum*
- Morphine, codeine

**Opioids**
- Manufactured
- **Semi-synthetics**: hydrocodone, hydromorphone, oxycodone
- **Synthetics**: fentanyl, methadone
- **Illicitly-manufactured synthetics**: fentanyl analogues
Morphine equivalent dose

- Method of standardizing potency across various opioid compounds
- Based on equianalgesic tables from dose ranging studies
- Example:
  - 20 mg oxycodone TID = 90 mg morphine equivalent daily dose

<table>
<thead>
<tr>
<th>Equianalgesic dose (MG)</th>
<th>Opioid (oral)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Morphine</td>
</tr>
<tr>
<td>7.5</td>
<td>Hydromorphone</td>
</tr>
<tr>
<td>20</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>30</td>
<td>Hydrocodone</td>
</tr>
</tbody>
</table>
Activation of mu receptors
Sequelae of long-term opioids

Tolerance → higher doses required to achieve same analgesic effect over time
• High prevalence
• Also develops to some of the toxic effects

Withdrawal → characteristic symptoms upon abrupt cessation or lowering of opioid dose

Opioid-induced hyperalgesia → paradoxical worsening of pain with higher doses
• Prevalence unknown
• Correlation with total opioid exposure (dose x time)
Mu receptors and reward pathways
Opioid use disorder (DSM-5)

**Physiologic sequelae**
- Tolerance
- Withdrawal
- Opioid craving

**Loss of control**
- Greater amounts of use or longer period of use than intended
- Persistent desire but unsuccessful efforts to cut down
- Inordinate amount of time obtaining, using, or recovering

**Adverse consequences**

Summary of 5 criteria:
- Important social, occupational or recreational activities given up or reduced due to opioid use or recurrent opioid use despite physical or psychological problems caused or worsened by use
Other important toxicities

- Constipation
- Itching
- Nausea/vomiting
- Hypogonadism
- Opioid-induced hyperalgesia
- Sedation
- Impaired cognition
- Falls/motor vehicle accidents
- Blunted respiratory drive
- **Non-fatal and fatal overdose**
Direct association between prescribed dose and overdose

<table>
<thead>
<tr>
<th>Dose* (mg/day)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-&lt;20</td>
<td>1.00 (REF)</td>
</tr>
<tr>
<td>20-&lt;50</td>
<td>1.9 (1.3-2.7)</td>
</tr>
<tr>
<td>50-&lt;100</td>
<td>4.6 (3.2-6.7)</td>
</tr>
<tr>
<td>≥100</td>
<td>7.2 (4.9-10.7)</td>
</tr>
</tbody>
</table>

*morphine equivalent

Bohnert et al. JAMA 2011
Long-term opioid therapy’s questionable efficacy

- Martell BA, O’Connor PG, Kerns RD, Becker WC et al. *Ann Intern Med*, 2007: No RCTs longer than 16 weeks; non-significant pooled effect size in trials where opioids were compared to placebo or non-opioids.


- Krebs et al. *JAMA*, 2018: Opioid group – significantly worse pain intensity; no better in terms of functional interference; significantly more side effects.
Opioids for chronic pain: important limitations

- Central sensitization may not be responsive to opioids
- Chronic pain has prominent psychological component; unclear role for opioids
- Long term therapy induces tolerance, necessitating higher doses
- Higher doses chronically $\rightarrow$ increased risk of opioid-induced hyperalgesia
- Higher doses $\rightarrow$ increased risk of toxicity, both acute and chronic
- Little evidence that opioids improve outcomes in chronic pain
Nearly 40% increase in rate ≥ 30-day prescriptions: 2006-2017

Schieber LZ et al. JAMA Network Open 2019
VHA doing better

Hadlandsmyth, K et al. JGIM 2018.
How did we get here?

• Public health campaigns against pain

• Aggressive & sometimes deceptive marketing
  • Extrapolation from cancer/acute pain data
  • Purdue pharma officials found guilty of misbranding; fined $600 million

• Clinical inertia
If benefits do not outweigh harms of continued opioid therapy, **optimize other therapies** and **work with patients** to taper to lower dosages or discontinue opioids.

Non-pharmacologic therapy and non-opioid pharmacologic therapy **are preferred** for chronic pain.
Outline

Background:
• Chronic pain: pathophysiology and epidemiology
• Opioids’ role in chronic pain

Intervention development:
• Management strategies for when harm outweighs benefit
• Novel use of buprenorphine
• Testing/implementing non-pharmacologic approaches
Problem list

Poorly controlled chronic pain with pervasive pain-related functional interference $\rightarrow$ BENEFIT is absent

Poorly controlled PTSD

Sleep-disordered breathing

Erectile dysfunction

Elevated risk of overdose death (240 mg MEDD) $\rightarrow$ HARM/RISK are prohibitive
Mismatch between needs and healthcare resources

• Needs:
  – Optimized pain care, including opioid tapering/discontinuation
  – Optimized mental health care
  – Optimized medical disease management

• Resources:
  – Brief, infrequent primary care visits
  – Fragmented specialty care visits
Opioid Reassessment Clinic (ORC)

- Integrated pain team, embedded in primary care
- Multidisciplinary: Psychiatry, Health Psychology, Internal Medicine, Nurse Case Management
- Longitudinal co-management
- Addictions expertise, buprenorphine-certified prescribers

ORC approach

• Biopsychosocial, patient-centered pain assessment eliciting functional goals

• Assessment of harm/benefit of current opioid regimen

• Multi-modal treatment planning designed to help the patient achieve functional goals

• Modifying the opioid regimen to help meet functional goals

We can support you to feel better overall if you’re willing to work with us.

Becker WC et al. ASCP. 2016
Evidence-based high value chronic pain care

Integrated Health System

Behavioral therapies

Self Management

Self Efficacy

Pharmacotherapy

Physical modalities

AP Wright, WC Becker, GD Schiff - JAMA IM, 2016
Evidence-based non-pharmacologic treatments for chronic pain

### Active physical modalities
- **Structured exercise**
- **Physical therapy**
- Yoga
- Tai Chi
- Aqua-therapy

### Behavioral treatments
- **Cognitive behavioral therapy**
- **Mindfulness based stress reduction**

### Passive techniques
- Chiropractic
- Acupuncture
- Massage
- TENS
Opioid Reassessment Clinic flow

PCP discusses referral with patient
PCP makes electronic referral
Referral reviewed; discuss with PCP
ORC intake scheduled

Follow up visits:
- APRN or MD visit
- Clinical health psychologist assessment and treatment
- Structured opioid prescribing
- Care coordination of multi-modal mental health, pain and addiction treatment

Intake visit:
- Psychiatrist assessment
- Internist assessment
- Team discussion
- Treatment planning with patient and team

Structured chart review by APRN

• 67 studies (3 good quality, 13 fair, 51 poor)
• Very low quality evidence across many different programs/protocols
• Pain, function & quality of life may improve with voluntary opioid tapering supported by multidisciplinary team
• Important gaps:
  – Few studies in primary care
  – Few studies of adverse effects of tapering

Frank JW et al. Ann Intern Med 2017
Tapering pearls

• Lead with empathy
• Express concern
• Acknowledge shared responsibility
• Highlight tangible potential benefits
• Highlight other patients’ success
• Partnership/reassurance
• Celebrate micro-successes
• Offer choice whenever possible

Becker WC et al. ASCP. 2016
Sleep Better

Sleep is often disrupted when taking opioids, which is why this program focuses on sleep. This section will address ways to improve your sleep.

- **Learn Why Sleep Matters**
  Learn why sleep is so important, and how opioid medications and pain may impact your sleep.

- **Veterans' Stories**
  Hear from other Veterans about their sleep and their experiences with tapering opioids.

- **Coping Strategies**
  Learn strategies to improve your sleep.

- **FAQs**
  See answers to common questions about sleep and opioids.

- **Additional Resources**
  Find additional support to help address sleep problems.
Neuro-adaptation and fear of tapering

Patient: “I also had lots of fears about, let’s say there was an apocalypse in our society… What would happen to me? Where would I get my medication from? What was going to happen?”

Rationale for buprenorphine

• Potential for quicker taper off

• Addresses neuro-adaptation

• Observational data suggest chronic pain efficacy

• Multiple studies in the opioid use disorder literature demonstrate improved functioning

• Caveat: requires total discontinuation of other opioids and induction with withdrawal symptoms

Becker WC et al. JSAT. 2015
Buprenorphine: a partial $\mu$ agonist

Opioid dose

- Full Agonist
- Partial Agonist (Buprenorphine)
- Full Antagonist

Opioid effect:
- sedation
- respiratory depression

%
Starting buprenorphine: overlapping approach

• Starting with very low dose bup, increase in stepwise fashion over 4-5 days
• Once bup at therapeutic dose, stop full-agonist opioids; can decrease full-agonists on last day of bup/nx up titration

<table>
<thead>
<tr>
<th>Day</th>
<th>Buprenorphine/naloxone (buprenorphine component listed)</th>
<th>Morphine SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5mg BID or 1 mg x 1</td>
<td>90 mg TID</td>
</tr>
<tr>
<td>2</td>
<td>1mg BID</td>
<td>90 mg TID</td>
</tr>
<tr>
<td>3</td>
<td>1mg TID</td>
<td>90 mg TID</td>
</tr>
<tr>
<td>4</td>
<td>2mg TID</td>
<td>90 mg in AM</td>
</tr>
<tr>
<td>5</td>
<td>4mg TID</td>
<td>none</td>
</tr>
<tr>
<td>5 and onward</td>
<td>Adjust dose to symptoms</td>
<td>none</td>
</tr>
</tbody>
</table>

Becker WC; Edens EL, Frank JW, Ann Int Med 2020
ORC study

Among patients on high-dose, full agonist opioids:

• Assessment and engagement with care team

• If no opioid use disorder:
  
  – “We now know more about safety problems related to opioids and we are concerned about your health and safety. We recognize that we prescribed you these medications so now we want to help you be safer while still managing your pain.”
  
  – Constrained choice: slow taper (e.g. 10% decrease every 2-4 weeks) vs. quick taper off and switch to buprenorphine

Oldfield BJ, Edens EL, Edmond SN, Cervone D, Becker WC et al. Pain Medicine, 2018
### ORC study results

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention (N = 66)</th>
<th>Control (N = 39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opted for slow taper, No. (%)</td>
<td>24 (37)</td>
<td>1 (3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Opted for partial agonist, No. (%)</td>
<td>41 (62)</td>
<td>1 (2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Oldfield BJ, Edens EL, Edmond SN, Cervone D, Becker WC et al. Pain Medicine, 2018
ORC study results

Changes in morphine equivalent daily dose among patients engaging in the ORC compared to those who did not

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (N = 66)</th>
<th>Control (N = 39)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDD at referral, median (IQR), mg</td>
<td>85 (35–180)</td>
<td>60 (30–156)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MEDD at reengagement with PCP, median (IQR), mg, No. (%), mg</td>
<td>25 (0–80)</td>
<td>53 (30–165)</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepine co-prescription at referral, No. (%)</td>
<td>20 (30)</td>
<td>11 (28)</td>
<td>0.44</td>
</tr>
<tr>
<td>Benzodiazepine co-prescription at reengagement, No. (%)</td>
<td>19 (29)</td>
<td>11 (28)</td>
<td></td>
</tr>
<tr>
<td>Cannabinoids on urine drug test at referral, No. (%)</td>
<td>10 (15)</td>
<td>5 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cannabinoids on urine drug test at reengagement, No. (%)</td>
<td>10 (15)</td>
<td>4 (11)</td>
<td></td>
</tr>
</tbody>
</table>

IQR = interquartile range; MEDD = morphine equivalent daily dose; ORC = Opioid Reassessment Clinic; PCP = primary care provider.

Oldfield BJ, Edens EL, Edmond SN, Cervone D, Becker WC et al. Pain Medicine, 2018
Veterans’ Pain Care Organizational Improvement Comparative Effectiveness (VOICE) Study

- RCT of integrated pain team (IPT) vs. pharmacist-led telecare collaborative management (TCM)

- Patients on high-dose therapy: standard vs. “plus” taper

Figure 2: Study design

Enrolled participants

Moderate dose

- IPT
- Std taper

- TCM
- Std taper

High dose

- IPT
- Std taper
- Plus taper

- TCM
- Std taper
- Plus taper

OPD-1511-33052. PI: Krebs, EE; co-PIs: Becker, WC; Seal, KA
Veterans’ Voices
The “Post-Opioid” Era
VA’s Whole Health Model

- Personal Health Inventory
- Personal Health Planning
- Whole Health Coaching
- Emphasis on non-pharm treatments
• Multi-site pragmatic trial of ~750 veterans with moderate to severe chronic pain

• Compare two approaches on primary outcome pain functional interference:
  
  (1) Whole Health Team vs.
  
  (2) Primary Care Group Education

1 UH3 AT009765-01. NICCH. PIs: Becker, WC; Seal, KA
Summary

- Opioid-centric chronic pain management has largely failed: harm > benefit

- CDC/VA/DoD Guidelines chart the course for change

- Promising interventions:
  - Collaborative multi-disciplinary management
  - Technology assists
  - Switch to buprenorphine
  - Non-pharm and self-management based approaches
Thank you

• Veterans

• Collaborators

• Funders
Questions