Pain, Addiction, and Opioid Strategies

Launette Rieb, MD, MSC, CCFP, FCFP, CCSAM, dip. ABAM
Clinical Associate Professor, Department of Family Practice,
University of British Columbia

Medical Consultant, Department of Family and Community Medicine,
St. Paul’s Hospital, Vancouver

Canadian Addiction Medicine Research Fellow

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Faculty/Presenter Disclosure

- **Faculty:** Launette Rieb

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  - **Bias:** No perceived bias to mitigate
Learning objectives

1. Discuss key studies of non-opioid management for CNCP

2. Explore pain induced by opioids and review opioid tapering and substitution protocols

3. Name key strategies for opioid use risk reduction
Non-pharmacological Therapies
Cochrane Reviews

- Psychological therapies – CBT
  - Mild-mod effect: depression, disability, +/- pain (Williams, 2012)
- Physical therapy – Some evidence for shoulder (Green, 2003)
- TENS – Conflicting evidence (Khadilkar, 2008)
- Prolotherapy – Not effective alone, unclear with co-interventions (Dagenaise 2007)
- Spinal manipulation for CLBP – No better/worse than tx like PT/exercise, unclear compared to sham (Rubinstein 2011)
- Massage – Beneficial, especially combined with stretching and education (Furlan 2008)
Opioid Adverse Effects

- Overdose
- Sleep apnea
- Testosterone
- Death
- Myocardial Infarction
- MVAs
- Addiction

(Chou et al., 2015; Dowell et al., 2016; Ballantyne, 2015; )
Opioids Causing Pain

Opium use causes “internal rheumatism”
(Quincey TD, 1821)

Morphine “tends to encourage the very pain it pretends to relieve”
(Albutt, 1870)
Topical review

Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy

Jianren Mao*

MGH Pain Center, Department of Anesthesia and Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
OPIOID TREATMENT

CELLULAR MECHANISMS

PHARMACOLOGICAL TOLERANCE

OIH

APPARENT TOLERANCE

WORSENING PAIN STATE

OPIOID DOSE ESCALATION

(Mao, 2008)
Opioid-induced Pain Sensitization

(Ravat and Ballantyne, 2016)
OIH Mechanisms - Microglia

Microglial activation results in:
- excitatory transcription factors
- proinflammatory cytokines
- chemokines
- excitatory amino acids
- nitric oxide

Cytokine release results in:
- NMDA & AMPA conductance
- GABA receptor regulation

Net result:
- Neuroinflammation
- Pain sensitivity

OPIOID-INDUCED HYPERALGESIA

(Glial Inhibitors?)

(Opioid molecule
- Proinflammatory mediator
- Cannabinoid receptor
- Toll-like receptor 4
- Opioid receptor
- NMDA/AMPA receptor
- GABA receptor)

(Arout, 2015)
Significant Pain Reduction in Chronic Pain Patients after Detoxification from High Dose Opioids

• Baron and MacDonald, 2006
• Retrospective study of opioid detoxification
• 21/23 patients had significant decrease in pain after detoxification
Withdrawal-induced hyperalgesia (WIH)

• Unmasking OIH with opioid cessation
  – PAIN

• AND release of catecholamines due to withdrawal
  – Causes neuroinflammatory and neuroimmune response
  – PAIN
Reduced Cold Pain Tolerance in Chronic Pain Patients Following Opioid Detoxification

Jarred Younger, PhD, Peter Barelka, MD, Ian Carroll, MD, MA, Kim Kaplan, MD, Larry Chu, MD, Ravi Prasad, PhD, Ray Gaeta, MD, and Sean Mackey, MD, PhD
Stanford University School of Medicine, Department of Anesthesia, Division of Pain Management, Palo Alto, California, USA

Conclusions—These findings suggest that the withdrawal of opioids in a chronic pain sample leads to an acute increase in pain sensitivity.
Higher starting dose = more hyperalgesia, AND Tapering from higher doses was associated with lower values of Heat Pain (i.e. more hyperalgesia) in a dose dependent manner N=109
Possible OIH/WIH Mitigators – pre/clinical

- NMDA antagonists (ketamine, etc.)
- NSAIDs (ketorolac, ibuprofen, etc.)
- Gabapentinoids (gabapentin, pregabalin)
- Alpha and beta blockers
- Cannabinoids?
- Melatonin
- Microglia TLR-4 antagonists, e.g. (+)-naloxone, (+)-naltrexone, ibudilast
- Opioid tapering, or rotation then tapering, instead of abrupt stop

(Arout, 2015; Chu, 2012; Mao, 2006; Grace, 2014; Xin 2012; Hutchinson. 2012)
Clinical Note

PAIN

Withdrawal-associated injury site pain (WISP): a descriptive case series of an opioid cessation phenomenon


December 2016, 157(12) 2865–2874.
Open access:

Mixed methods study of patients on opioids for CNCP or addiction

• 5 screening Q – option to do full survey of 35 Qs
• 58 screened, 47 confirmed WISP, of these
• 34 completed the full surveys (21 by interview)
• WISP median pain intensity 8/10 (original injury 10/10), more painful than general withdrawal
• WISP median duration 2 wks, but 18% >1 mo.
• WISP can be a risk factor for opioid reinitiation
• Mitigators included gabapentin and NSAIDS
“God, it felt just like it did when it was healing when it was broken, yeah. I don’t know how—any other way to describe it.”

• Participant #2, 53 year-old white male, original injury - fractured arm at age 12

“I was pounding my legs...old injury sites are horrendous. So, like it’s more severe in those spots. The other part you can like go, get through with a hot cloth, or whatever, with Gravol and stuff, but old injury sites come back with like, severe severity.”

• Participant #17, 58 year old Indigenous female, original injury—foot fractures requiring plating and lower leg injuries requiring fasciotomies after a home invasion, capture, and repeated assault with a hammer
“There’s also not just physical pain...I was run over by a semi so I suffered some physical injuries that come up in withdrawal, but also there’s anxiety from it too...It’s like PTSD from that big time”

- Participant #8, 38 year old white male with previous multiple bilateral lower leg and foot fractures after being struck and pulled underneath a semi-trailer
WISP Theories

• “all part of the drug withdrawal”
• “I don’t think it healed right”
• “might be psychological”
• “I thought, okay, it’s such a strong pull to do the drugs that my brain figured out that because I started taking opiates when I sprained my ankle, it’s going to start kicking the pain out at the ankle to get more opiates…”
  – Participant # 5, 35 year old white male, original injury—right ankle tendon tear requiring casting
CPSBC - Opioid Use Guidelines

- Do complete Hx + Px and generate a DDx
- Screen – SUD, mood disorders, family Hx
- Opioid Manager, PharmaNet, UDS, contracts
- Dose within guidelines for new starts
- MEDD 30-50mg moderate, up to 90 for severe
- Short course for acute pain – exit strategy
  – FUNCTION must change to continue Rx
Opioid Issues - Pearls

• Generally avoid caffeinated products

• Long acting formulations for baseline control if a SUD, no evidence of advantage over short

• Use short acting formulations as occasional prn doses, or if chronic - dose on the half life

• Use THE SAME opioid for both long acting and short acting breakthrough (or acute pain), do not mix (unless patch, or methadone used)
When to Suggest Opioid Taper?

- Patient on opioids without significant improvement in pain and function
- Safety sensitive position
- Spread of pain in the absence of disease progression
  - allodynia and hyperalgesia
- Active substance abuse/dependence where harm reduction not viable
- Patient requests to come off
Opioid Withdrawal

Withdrawal is not life threatening

- Unless patient has a history of seizures, is dehydrated, suicidal or pregnant

- Warn patients of OD risk post detox
Opioid Withdrawal

- DSM-5...3+ within minutes to days of stopping:
  - Dysphoria
  - N or V
  - muscle aches
  - lacrimation or rhinorrhea
  - diarrhea
  - yawning
  - fever
  - insomnia
  - Pupillary dilation, piloerection or sweating
Typically...opioid tapering is not an emergency!

- As out patients most can drop 5-10% every 1-2 weeks, sometimes slowing to every 2-4 weeks for the last 20-30% of the opioid.

- For patients on LOT for many years who have failed more rapid tapering, just slow it down to drop every 1-3 months.

- Even if you drop the dose 5% every 3 months, in a year they will be down 20%, and by 2 years 40%. But this is ridiculously slow if they are on extremely high doses or have only been on a couple of years or less.
Opioid Lowering Options

1. Convert to long acting opioid – taper
2. Taper with short acting opioid
3. Withdrawal symptom management
4. Opioid substitution/rotation - taper
Opioid Short > Long Conversion

- Long acting can provide smoother control
- But beware of high peak of some long acting formulations which can produce euphoria
- Change 50-75% of the total dose over to the long acting formulation – provide the rest in short acting with a warning for sedation
- Review in 1 week and convert more to long
- Ideally very little to no breakthrough
Opioid Dose Adjustments - Pearls

- Physician adjusts dose as required:
  - Increase or decrease by 5-10% at a time
  - The earliest dose change should be after 5 half lives of that particular drug
  - Morphine (1/2 life 3 hr) daily adjust in hospital
  - Methadone (1/2 life 24-36h) adjust q5+ days
  - Comfortable change is every 1-4 weeks – PT input

- If unsuccessful (no change pain + function)
  - taper off, might try a diff opioid, or not

- Go slower at the end of a taper – last 20%
Opioid Tapering – Example

• Pt taking hydromorphone (short) 200 mg/d
• 1\textsuperscript{st} conversion: Hydromorphone (long) 75 mg q12 h plus hydromorphone (short) 4mg 1q4h prn – warn about driving, sedation
• 2\textsuperscript{nd} week: see if prn doses needed – if so add in as long acting, e.g. 100 mg q12h
• 3\textsuperscript{rd} week on...taper 5-10%, typically faster at first and slower at the end of the taper
• Taper until on lowest dose strength long 3q12h
• Then re-introduce short to complete weekly taper, e.g. hydromorphone (short) 2mg q8h; 1mg q6h; 1mg q8h; 1mg am and hs;1mg hs; off
Opioid Tapering – Short

• Sometimes easiest to simply taper what the patient is currently using
  – E.g. Percocet 16-20/d, taken 6 tid +/- 2/d

• If it is a dual agent first switch to eliminate the ASA or acetaminophen (bloodwork?)
  – E.g. Oxycodone 5 mg 18/d

• Next spread out the daily dose evenly based on the ½ life of the medication
  – E.g. Oxycodone 5 mg 5/4/4/5 spread q6h
Opioid Tapering – Example

• Next taper the medication – depending on the patient’s symptoms the drop can be ever 4 -14 days, always dropping nighttime dose last
• Oxycodone 5 mg 4/4/4/5 spread q6h
• Oxycodone 5 mg 4/4/4/4 spread q6h
• Oxycodone 5 mg 4/3/4/4 spread q6h
• Oxycodone 5 mg 4/3/3/4 spread q6h
• Oxycodone 5 mg 3/3/3/4 spread q6h
• Oxycodone 5 mg 3/3/3/3 spread q6h
• Continue this pattern until 0/0/0/1, then off
**Opioid Tapering – Combo**

- If patient using a combination of short and long acting – conventional wisdom is to taper short first, but since often this is what patients “feel” and are attached to you can taper it last
- Oxycodone ER 80 mg q12 h plus oxycodone 10mg 1-2 prn 4/d max
- Taper Oxycodone ER first by 10 mg every 4-14 days dropping morning dose, then evening dose
- Hold the oxycodone short 10 mg at q6h until off the Oxycodone ER then taper by 5 mg as per previous schedule leaving the hs to be last off
Screening and Assessment Tools

• **SUD**
  – AUDIT – alcohol
  – DAST - drugs
  – COMM – Current Opioid Misuse Measure

• **Mood**
  – PHQ9 or BDI – depression

• **Pain**
  – BPI - Brief Pain Inventory

• **Function**
  – PDI – Pain Disability Index
  – 5As (Universal Precautions)
Functional Assessment

Universal Precautions for Opioid Prescribing—The 5 As (Gourley, 2005)

1. Activities of daily living
   - Work, self care, mobility, leisure, sport, sleep
2. Analgesia
3. Adverse effects
4. Affect
5. Aberrant drug-related behaviors
## Opioid Risk Tool

By Lynn R. Webster MD

<table>
<thead>
<tr>
<th>Item (circle all that apply)</th>
<th>Item score if female</th>
<th>Item score if male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family History of Substance Abuse:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Illegal Drugs</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Prescription Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2. Personal History of Substance Abuse:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Illegal Drugs</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Prescription Drugs</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>3. Age (mark box if 16-45)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4. History of Pre-adolescent Sexual Abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5. Psychological Disease:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention Deficit Disorder, Obsessive-Compulsive Disorder, or Bipolar, Schizophrenia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>Total Score Risk Category:</th>
<th>Low Risk: 0 to 3, Moderate Risk: 4 to 7, High Risk: 8 and above</th>
</tr>
</thead>
</table>

(Furlan 2010)
Risk of SUD

- Those at highest risk:
  - Active SUD
  - Past Hx of SUD
  - Family Hx of SUD
  - Active psychiatric illness
  - Childhood trauma, esp. sexual abuse in women
  - Youth

Exposure:
- Dose dependent rise in risk of SUD
Canadian Opioid Use Guidelines-NOUGG
Best Practice for Opioid Therapy

• Complete history, physical, differential Dx
• Risk assessment SUD, psychiatric issues
• Medication review + urine drug screen
• Appropriate trial of non-opioid alternatives
• Pre/post-opioid pain and function questions
• Treatment agreement: 1 MD, visits, scripts
• Taper off benzodiazepines first – contraindicated
• Sufficient trial of opioid, establish efficacy
• Use Opioid Manager + PharmaNet each visit
Common Tx Goals for Pain and SUD

• Correct sleep disturbance
• Stabilize mood
• Eliminate unnecessary medications
• Restore function
Canadian Opioid Use Guidelines-NOUGG
Patients at High Risk for SUD

• Prescribe only for **well-defined** somatic or neuropathic pain conditions

• Relatively **contraindicated in headache and fibromyalgia**

• Start with lower doses and titrate in small dose increments

• **Monitor closely** for signs of aberrant drug related behaviors
Opioid Detox Options

- Patients with physiologic dependence on opioids who need to come off can be assisted by a variety of approaches:
  - Symptom management (CINA, clonidine etc)
  - Replacement and tapering (if Rx for pain)
  - Agonist therapy (methadone or buprenorphine) for detox or maintenance
  - Antagonist therapy (naltrexone)
  - Screen for and address addiction processes
  - Engage in non-pharmacologic strategies
Co-management of SUD and Pain

- When an Substance Use Disorder is active, pain is much harder to treat due to dysregulation of all pathways involved with mood, pain, and behavioral reinforcement.
- Must co-manage pain and addiction issues be it alcohol, cocaine or opioid use disorder.
- No take home opioid doses if any active SUD.
- No opioid prescribing if any alcohol use.
- Short acting opioid added temporarily to MATx.
Pain and OUD

- Typically conversion to medication assisted treatment (MATx) with buprenorphine, or methadone is done to stabilize.
- Buprenorphine has the same or better pain relieving effect as morphine.
- No evidence to add a 2\textsuperscript{nd} opioid for CNCP.
- For those wanting abstinence, post detoxification can give naltrexone 50 mg PO daily or 25mg twice daily (high OD rate if d/c).
Conversion from High-Dose Full-Opioid Agonists to Sublingual Buprenorphine Reduces Pain Scores and Improves Quality of Life for Chronic Pain Patients


Retrospective chart review of CNCP patients on over 200 MEDD - converted from other opioids to bup/nx
- pain scores averaged 8/10 pre-conversion, 4/10 post conversion
Pre- and postconversion pain scores by pre-conversion morphine equivalents dosage

Bup/nx and Methadone

• Buprenorphine/naloxone (bup/nx) and methadone as maintenance therapy or to detoxify from other opioids
• Do online and/or in-person classes first
• For bup/nx induction
  – Buprenorphine 20 mcg/h patch on day other op stopped
  – Next day ensure COWS score >13 to start
  – Induction - Bup/nx 1mg test dose, 2 mg q2h prn...12
  – Then taper 1-2mg/d
  – ...or increase by up to 4/d for opioid maintenance treatment
• For methadone 10-30mg starting dose, taper 5mg/d
  – Or consider maintenance therapy – increase q5d by 5-10mg
  – If on MMT long-term and wants off – taper 5% q 2-8 weeks
Advantages of methadone for CNCP:

- Theoretically good for neuropathic pain: binds to NMDA receptor, blocks glutamate (one of the pathways of tolerance and opioid induced hyperalgesia, though can get)
- Long half life (24-36 hrs) so it can lower withdrawal induced pain if dosed daily, may need q6-8h dosing for analgesia

Disadvantages of methadone for CNCP:

- Methadone vs morphine 43% increased risk of death, even methadone 20mg or less \( \text{HR} = 1.5 \) (Ray, 2015)
- Review, 3 studies - limited info, efficacy (Haroutiunian 2012)

Methadone should NOT be first line for CNCP (unless OUD)
Benzodiazepine Tapering Strategies

• Taper with the same benzo, drop q1-4 wks:
  – Eg. Zopiclone 7.5mg ii hs
  – Taper: 7.5+5, 5 ii, 7.5, 5, 7.5 ½ (3.5), 5 ½ (2.5)
  – Can also put into a suspension and taper 1mg/mo.

• Taper using a different long acting benzo:
  – Diazepam 10mg, decrease by 2mg q1-4 wks

• Fast taper or eliminate using another med:
  – Gabapentin 300 mg tid titrated to symptoms up to 600-900 tid then taper over 1-3 months
Ashton Protocol

• Dr. Heather Ashton from the UK
• Protocol for very slow benzo conversion and taper of diazepam
• Conversion to diazepam in steps 5mg at a time & then very slow taper over 6-12 months
• Use for highly sensitive patients
  – Those on for many years
  – Elderly
  – Failed conventional tapering
Harm Reduction – Safety

• Medication review
• Daily witnessed ingestion
• Call backs for pill counts
• Bubble packing
• Safe storage
• Patch return to pharmacy
• Overnight oximetry
• Naltrexone
Take Home Naloxone

- Towardstheheart.com
Medications are a fantastic tool, but if they are not working...

- Review the diagnosis – Repeat Hx/Px
- Screen for depression, anxiety, and PTSD
- Explore perception of disability & meaning
- Screen for a Substance Use Disorder
- Expand non-pharmacological treatments
- Ensure your prescribing is \textit{safe, effective}, and cannot possibly do more harm than good
- Take an \textit{empathetic, consistent approach}
Case

Mr. B: 48 yr old HIV+ HCV+ male with peripheral neuropathy, sleep disturbance, cocaine & alcohol use disorders now both in sustained abstinence (6 years), pain 8/10

Meds:

– Oxycodone/acetaminophen (5/325) 6 q6h– no evidence of current OUD, no pain relief
– Thus oxy 120 mg = 180 mg MEDD
– Temazepam 60mg hs 2-3x/wk (from his wife)
– Intolerable experience in the past with duloxetine, venlafaxine, and amitriptyline
Mr. C – Treatment:

1. Taper off oxycodone/acetaminophen 5/325:
   - Lower by 1 tablet q4 days until at 1 q6h
   - Then lower by ½ tab q4 days until off

2. Titrate onto gabapentin
   - Begin with HS dose - 100 mg, incr. q4d until at 300 mg hs
   - Titrate up daytime doses by 100 mg until 300 tid - qid, then by 300 mg weekly until 600 tid (2400 mg/d)
   - If no pain relief in 6 weeks at 2400 mg/d then taper off
   - If 2400 mg/d helpful can push the dose further to 3600
   - Neuromodulators can help ameliorate opioid withdrawal symptoms too which can help Mr. C.
Mr. C – Treatment, cont’d:

3. Taper temazepam
   • Stabilize nightly benzo to half current episodic dose
   • Slowly taper, or can use diazepam, remembering that neuromodulators can also help benzo withdrawal
   • Ashton protocol for benzo tapering may be needed

4. Nortiptyline may be better tolerated for sleep but he declined, can try quetiapine 25 mg hs and titrate up

5. Sleep hygiene techniques + relaxation/anger mgt
Case, cont’d

• **Result:** Pain better controlled, sleep still a challenge but improving with time

• **What if he was binging on alcohol and benzos?**
  • Offer residential detox. Not eligible for opioids – stop (or fast taper 10% per day).

• **What if he had requested more opioids instead of less?**
  • Explain that other medications are first line and need to be tried in sufficient doses. Explain that opioids have risks associated with use – outline them. Explain why this is considered a failed treatment attempt = opioids are no longer indicated
What if he had some pain relief and increased function with oxy/acetaminophen and was unresponsive to all other med categories?

- Once daily oral morphine formulation – which could go to a daily witnessed ingestion (DWI) if needed during initial monitoring, and be reverted back to DWI if there is cocaine or other drugs in the UDS
- **NOT eligible for carry doses of opioids if using cocaine or other illicit drugs**
1. Use non-opioid medications and therapies primarily

2. Rare use of opioids beyond acute setting

3. If restores function, use opioids with screening and monitoring and informed consent

4. Have an opioid exit strategy and recall these techniques of tapering and rotation
Thank you!
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