The paradox of opioids: pain induced by use and withdrawal

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Faculty/Presenter Disclosure

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  - None
Mitigating Potential Bias

• I will not mention OrionHealth USA in my talk
Objectives

1. List three pain phenomena associated with opioid use or cessation

2. Discuss possible mechanisms for opioids increasing pain with use and withdrawal

3. Identify potential mitigators of opioid associated pain
Opioid Benefits

- Pain relief
- Calming
- Diarrhea relief

- COPD
- Anesthesia
- End of life
Opioid Adverse Effects

- Overdose
- Sleep apnea
- Testosterone Suppression
- Addictive Use
- Myocardial Infarction
- MVAs
- Death

(Chou et al., 2015; Dowell et al., 2016; Ballantyne, 2015)
Opioid Adverse Effects

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

(Chou et al., 2015; Dowell et al., 2016; Ballantyne, 2015)
Opioids & Pain – case 2003

- 39 year-old Caucasian male crane operator, upper limb crush, surgeries+
- Dx 4 limb CRPS, numerous tx including spinal cord stimulator
- Oxycodone SR 360 mg = MEDD 540 mg
- Rotated: fentanyl 75 mcg/h patch + oxy IR 5 mg QID = MEDD 330 mg
- Within 3 weeks, pain 1-2/10
- hyperalgesia and allodynia vanished
- He went back to work

(Rieb, 2011)
Opioids causing pain

“Morphia tends to encourage the very pain it pretends to relieve”

(Albutt, 1870)
Topical review

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

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OPIOID TREATMENT

CELLULAR MECHANISMS

PHARMACOLOGICAL TOLERANCE

OIH

APPARENT TOLERANCE

WORSENING PAIN STATE

OPIOID DOSE ESCALATION

(Mao, 2008)
N = 6 chronic low back pain patients
Assessed before and 1 month after initiating oral morphine therapy
Cold pressor test before morphine initiation, then pre/post infusion with remifentanil

All became hyperalgesic as well as tolerant after 1 mo. oral morphine
N = 187 consecutive pts entering a pain management program with 85 on opioids + 102 not on opioids but matched pain conditions

Those taking opioids had lower heat pain tolerance i.e. More hyperalgesia
Opioid-induced Pain Sensitization

(Rivat and Ballantyne, 2016)
Opioid-Induced Glial Activation: Mechanisms of Activation and Implications for Opioid Analgesia, Dependence, and Reward

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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

\[
\text{OPIOD-INDUCED HYPERALGESIA}
\]

\(\text{(Arout, 2015)}\)
OIH Mitigators – pre/clinical

- Opioid rotation, lowering or elimination
- NMDA antagonists (ketamine – too sedating, DM-mixed)
- NSAIDs (ketorolac, ibuprofen, COX-2 inhibitors, etc.)
- Gabapentinoids (gabapentin, pregabalin)
- Alpha and beta blockers
- Melatonin
- Lidocaine, ondansetron, cannabinoids?
- Microglia TLR-4 antagonists (enantiomers of naloxone & naltrexone, minocycline)

(Hutchinson 2014; Arout, 2015; Chu, 2012; Mao, 2008; Grace, 2014; Xin 2012)
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
Opioid Withdrawal Pain

“Internal rheumatism”

(de Quincey, 1821)
Emotional Pain of Withdrawal

- ↓ dopamine ➔ depression, grief, loss, lethargy, amotivation

- ↑ noradrenalin ➔ anxiety, insomnia, worry, perseveration, agitation, aggression, activation of traumatic memories, flight
Withdrawal-induced hyperalgesia (WIH)

• Unmasking OIH with opioid cessation
  – PAIN

• AND release of catecholamines due to withdrawal
  – Causes neuroinflammatory and neuroimmune response
  – PAIN
WIH after Anesthesia


Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal.

Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M.
Reduced Cold Pain Tolerance in Chronic Pain Patients Following Opioid Detoxification

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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

Tapering from higher doses was associated with lower values of heat pain (i.e. more hyperalgesia) in a dose dependent manner

N= 109
Possible 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
- Opioid tapering, or rotation then tapering, instead of abrupt stop

(Arout, 2015; Chu, 2012; Mao, 2006; Grace, 2014; Xin 2012)
Withdrawal-associated injury site pain (WISP): a descriptive case series of an opioid cessation phenomenon

WISP – descriptive case series

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
• Typically less painful than original injury (10/10)
• Typically 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
WISP VS original injury

“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
WISP VS original injury & w/d pain

“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
WISP - Emotional Aspects

“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, developed an opioid use disorder and had treatment
Severe OI > WISP > W/D
2 weeks ++
Aversive Relapse
Theories

Central sensitization
High opioid dose
Many w/d episodes
Abrupt cessation
Noradrenaline Neuroinflammatory Neuroimmune

(Woolf, 1983; Barron et al., 2013; Hooten, et al. 2015; Prosser, et al., 2008; Wang et al., 2011; Celerier et al., 2001; DeLeo et al 2004; Raghavendra et al. 2002; Bie et al., 2003; Treister et al, 2012; Karasz et al., 2004)
OPIOID WITHDRAWAL-ASSOCIATED INJURY SITE PAIN AMONG PEOPLE WHO INJECT DRUGS: A CROSS-SECTIONAL STUDY

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Methods

• Qs added to three ongoing prospective cohort studies of PWID in Vancouver, Canada, June-Nov. 2015
• RN administered questionnaire in 1:1 interviews
• Inclusion:
  – Age 18+,
  – Injection drug use in last 6 months
  – Daily opioid use in last 6 months
  – Not intoxicated at the time of the survey
• Screened for an old healed injury, typically pain free
• Outcomes: Lifetime prevalence of WISP and correlates using multivariate logistical regression
Results

- **631 PWID** who were daily opioid users in previous 6 months were identified
  - Median age: 46 (IQR 34-53) years
  - 388 (61.5%) identified as male
  - 360 (57.1%) white, and 104 (34%) aboriginal
  - 147 (48%) completed high school or higher education

- **276 (44%)** PWID had an old, healed injury that was typically pain free
Results

• Among PWID with a previous injury that was typically pain free:

112 (40.6%) had WISP

= 18% of all PWID
Results

70 (70.5%) said that having WISP affected their opioid use behavior:

- 57 (72%) used more opioids to relieve WISP
- 19 (24%) avoided opioid withdrawal
- 3 (4%) no longer used opioids to avoid WISP
Results

In multivariable analysis:

• WISP was negatively associated with chronic neuropathic pain
  – Adjusted Odds Ratio (AOR) = 0.79; 95% CI: 0.6 - 0.9

• Neuropathic and not having had WISP was associated with being on gabapentin or NSAIDS thus these meds may be protective
  – AOR 4.06; 95% CI, 1.13 – 15.09

• WISP had NO association with other types of chronic pain or with a particular opioid, mental health status, HIV status, or other stimulant drug use
Discussion

• 1 in 5 PWID experienced WISP, > 1 in 3 with injury
  – Addiction Medicine specialists see this phenomenon yet previously undocumented, worth screening for

• WISP affects opioid use behavior
  – May be one of the drivers in the current opioid crisis

• Puts into question the etiology of the high rates of reported pain in those with opioid use disorders, including in those on opioid replacement therapy

• Future research is needed on WISP mitigation, including the role of NSAIDS and gabapentinoids
  (Dennis, 2015; Trafton, 2012; Arout, 2015)
The paradox of opioids - Summary

Pain relief, but also pain from...
- Opioid induced hyperalgesia (OIH)
- Withdrawal-induced hyperalgesia (WIH)
- Withdrawal-associated injury site pain (WISP)
- General myalgias and arthralgias of withdrawal

Primary Mechanisms
- Neuroinflammatory/neuroimmune changes
- Microglia activation
- NMDAr – glutamate pathway activation

Possible Mitigators
- NSAIDS, gabapentinoids, alpha blockers, NMDAr blockers, minocycline, opioid rotation, opioid lowering, elimination, etc.
References


• Rieb, L. Spreading pain with neuropathic features may be induced by opioid medications. This Changed my Practice. Sept. 12, 2011 [http://thischangedmypractice.com/pain-with-neuropathic-features/](http://thischangedmypractice.com/pain-with-neuropathic-features/)


Thank you!

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Your Stories

- Cases
- Thoughts
- Observations
- Theories
- Questions
a place of mind
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