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The paradox of opioids: pain induced by use and withdrawal

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Faculty/Presenter Disclosure

- **Faculty:** Launette Marie Rieb
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Disclosure of Commercial Support

- Potential for conflict(s) of interest:
 - 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

Death



Overdose

Sleep apnea

Testosterone
Suppression

Myocardial
Infarction

MVAs

Addiction

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

Opioid Adverse Effects

Death



Overdose

Sleep apnea

Testosterone
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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)



Pain 100 (2002) 213–217

PAIN

www.elsevier.com/locate/pain

Topical review

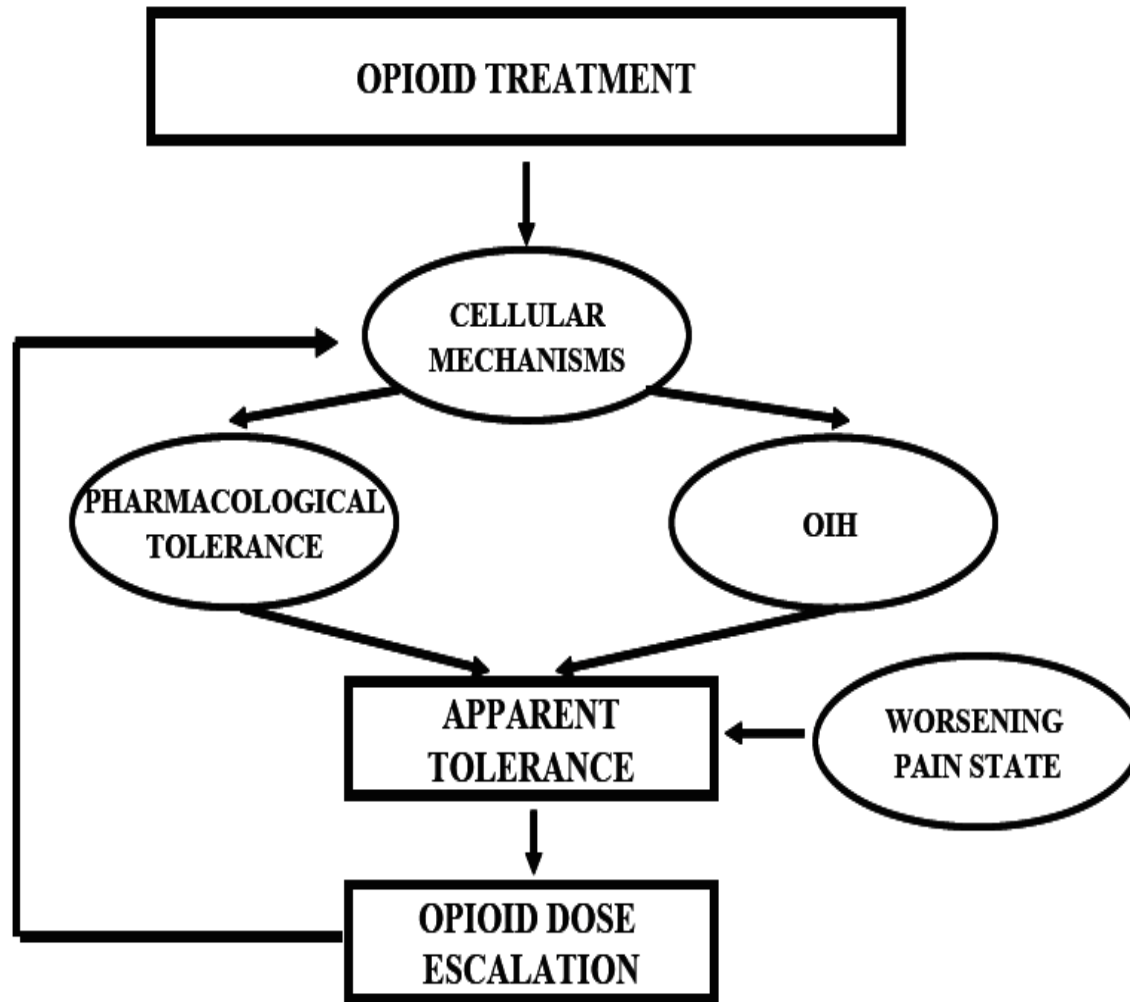
Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy

Jianren Mao*

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ASAM American Society of
Addiction Medicine



(Mao, 2008)



Opioid Tolerance and Hyperalgesia in Chronic Pain Patients After One Month of Oral Morphine Therapy: A Preliminary Prospective Study

Larry F. Chu,* David J. Clark,*[†] and Martin S. Angst*

**Department of Anesthesia, Stanford University School of Medicine, Stanford.*

[†]*Department of Anesthesia, Palo Alto Veterans Affairs Hospital, Palo Alto, California.*

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 remifentanyl

All became hyperalgesic as well as tolerant after 1 mo. oral morphine

Opioid-induced hyperalgesia in community-dwelling adults with chronic pain

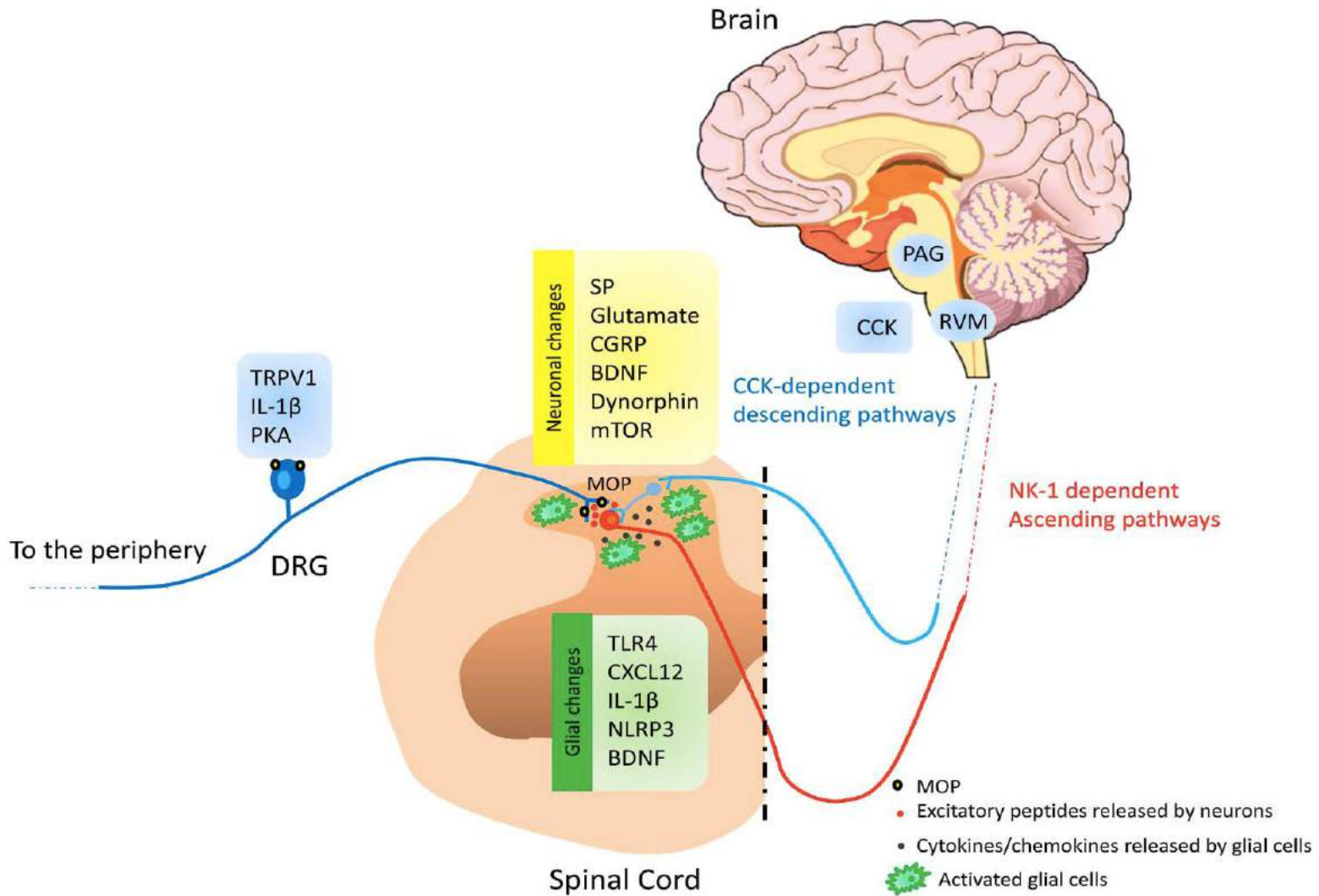
W. Michael Hooten^{a,*}, Tim J. Lamer^a, Channing Twyner^b

June 2015 • Volume 156 • Number 6

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)

Mini-Review

NIDA Special Issue on Frontiers in Addiction Research

TheScientificWorldJOURNAL (2007) 7(S2), 98–111

ISSN 1537-744X; DOI 10.1100/tsw.2007.230

TheScientificWorldJOURNAL

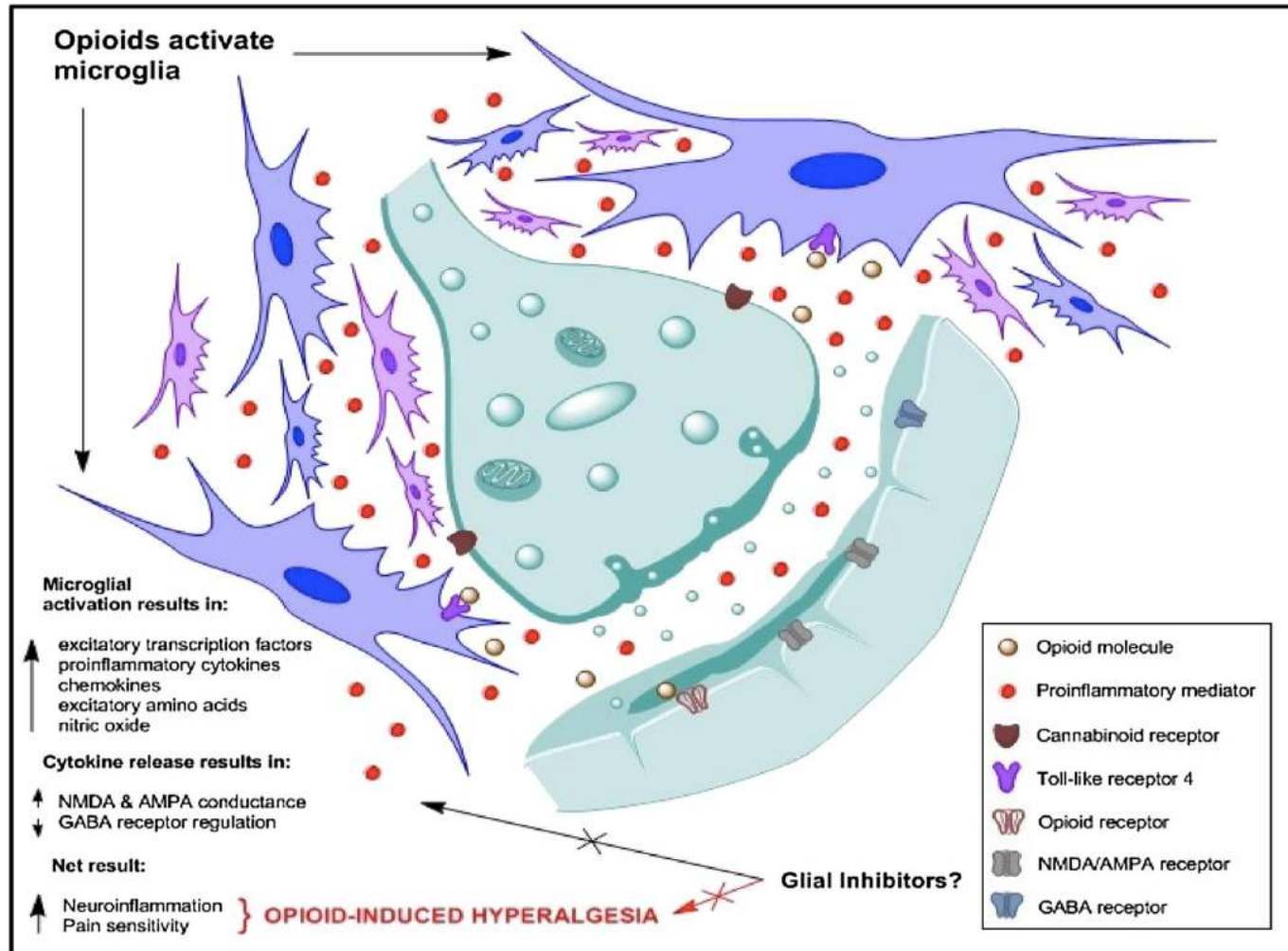
www.thescientificworld.com

Opioid-Induced Glial Activation: Mechanisms of Activation and Implications for Opioid Analgesia, Dependence, and Reward

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OIH Mechanisms - Microglia



(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

Pain. 2003 Nov;106(1-2):49-57.

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

Angst MS¹, Koppert W, Pahl I, Clark DJ, Schmelz M.

Pain Med. 2008 November ; 9(8): 1158–1163. doi:10.1111/j.1526-4637.2008.00475.x.

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.

ORIGINAL RESEARCH ARTICLES

Associations between Heat Pain Perception and Opioid Dose among Patients with Chronic Pain Undergoing Opioid Tapering

W. Michael Hooten, MD,^{*,†} Carlos B. Mantilla, MD, PhD,^{*} Paola Sandroni, MD, PhD,[‡] and Cynthia O. Townsend, PhD[‡]

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[†]Psychiatry and Psychology and

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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

Launette Marie Rieb^{a,b,*}, Wendy V. Nomart^a, Ruth Elwood Martin^c, Jonathan Berkowitz^d, Evan Wood^{b,e},
Ryan McNeil^{b,e}, M.-J. Milloy^{b,e}

December 2016, 157(12) 2865–2874.

Open access:

<http://journals.lww.com/pain/pages/articleviewer.aspx?year=2016&issue=12000&article=00028&type=Fulltext>



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

WISP Discussion

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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c. BC Centre for Excellence in HIV/AIDS, SPH

d. Division of AIDS, Department of Medicine,
University of British Columbia, Canada



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

- Arout CA, Edens E, Petrakis IL, Sofuoglu M. Targeting Opioid-Induced Hyperalgesia in Clinical Treatment: Neurobiological Considerations. *CNS Drugs* 2015;29(6):465-486. <http://www.ncbi.nlm.nih.gov/pubmed/26142224>
- Hooten WM, Mantilla CB, Sandroni P, Townsend CO. Associations between heat pain perception and opioid dose among patients with chronic pain undergoing opioid tapering. *Pain Med* 2010;11(11):1587-1598. <http://www.ncbi.nlm.nih.gov/pubmed/21029354>
- Hooten WM, Lamer TJ, Twyner C. Opioid-induced hyperalgesia in community-dwelling adults with chronic pain. *Pain* 2015;156(6):1145-1152. <http://www.ncbi.nlm.nih.gov/pubmed/25815431>
- Hutchinson MR, et al. Opioid-induced glial activation: mechanisms of activation and implications for analgesia, dependence and reward. *The Scientific World Journal* 2007;7(S2)98-111
<https://www.ncbi.nlm.nih.gov/pubmed/17982582>

References, cont'd

- Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. Pain 2002;100(3):213-217.
<http://www.ncbi.nlm.nih.gov/pubmed/12467992>
- 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/>
- Rieb L, Norman W, Martin R, Wood E, McNeil R, Milloy MJ. Withdrawal-associated injury site pain (WISP): A descriptive case series of an opioid cessation phenomenon. PAIN. December 2016, 157(12) 2865–2874. Open access: <http://journals.lww.com/pain/pages/articleviewer.aspx?year=2016&issue=12000&article=00028&type=Fulltext>
- Rivat C, Ballantyne J. The dark side of opioids in pain management: basic science explains clinical observation. PAIN Reports. 1(2016)e570. http://journals.lww.com/painrpts/Fulltext/2016/08300/The_dark_side_of_opioids_in_pain_management_.3.aspx

Thank you!

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