Complex pain and substance use: concepts and management

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Disclosure

- Faculty**: Dr. Launette Rieb**
- No interests in nor $ received from a pharmaceutical, medical device or communications company
- Relationship with commercial interests:
  - Talks for numerous organizations for CME approved events
  - Clinically work for ActumHealth, WorkSafeBC, St. Paul's Hospital
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- No perceived potential conflicts of interest
- No perceived bias to mitigate

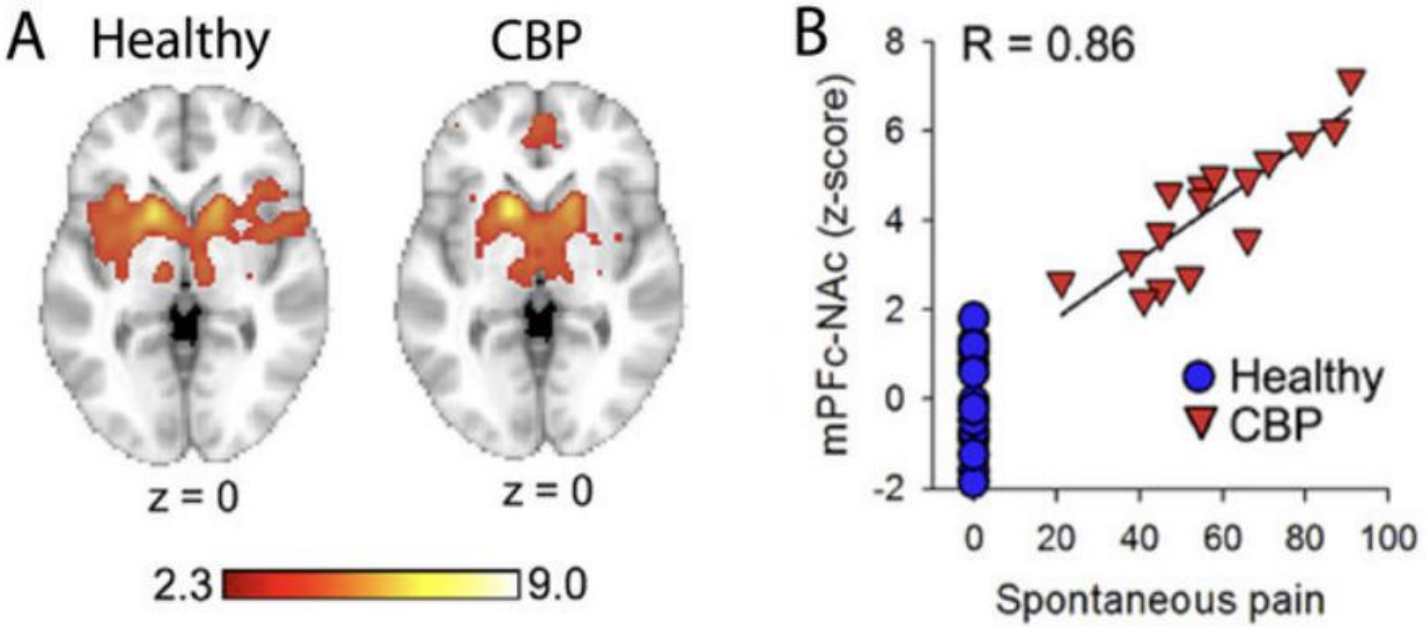
Learning objectives

1. Grasp key concepts related to the neurophysiology and psycho-social overlapping of complex pain and substance use
2. Integrate key principles of management for those with pain and addiction
3. Explore complex cases and reflect on your own patients

Challenge - Pain is primal

- Pain is a primitive and essential warning system
- It serves to alter behaviour – keep still, fight, avoid
- Feeling pain maximizes your chance at survival
- Numerous pathways keep pain systems alert
- Pain, mood, and addiction pathways overlap
- Highly adaptive for acute pain – not chronic pain
- Chronic pain is a different disease – maladaptive
- Coach patients on learning to turn down attention to signal
- Focus on functional restoration instead of pain

Apkarian. Pain and the Brain. PAIN 2011



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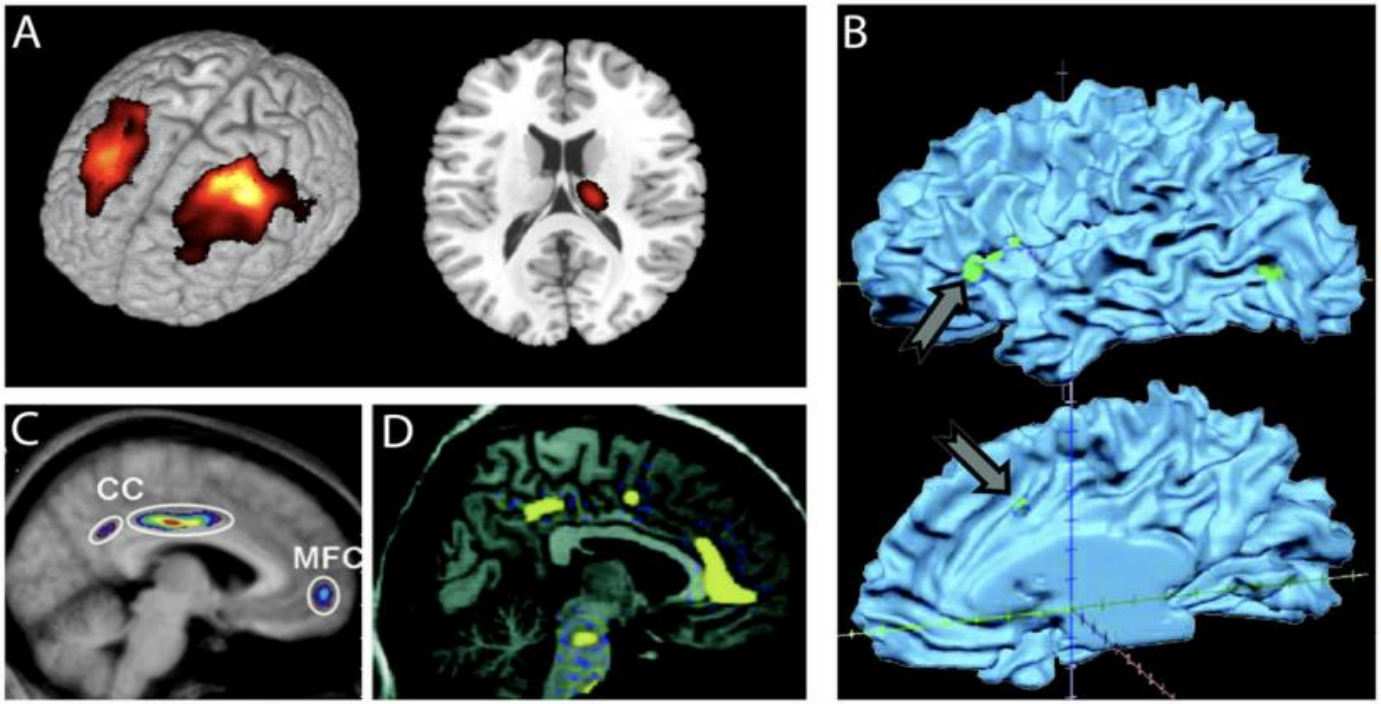
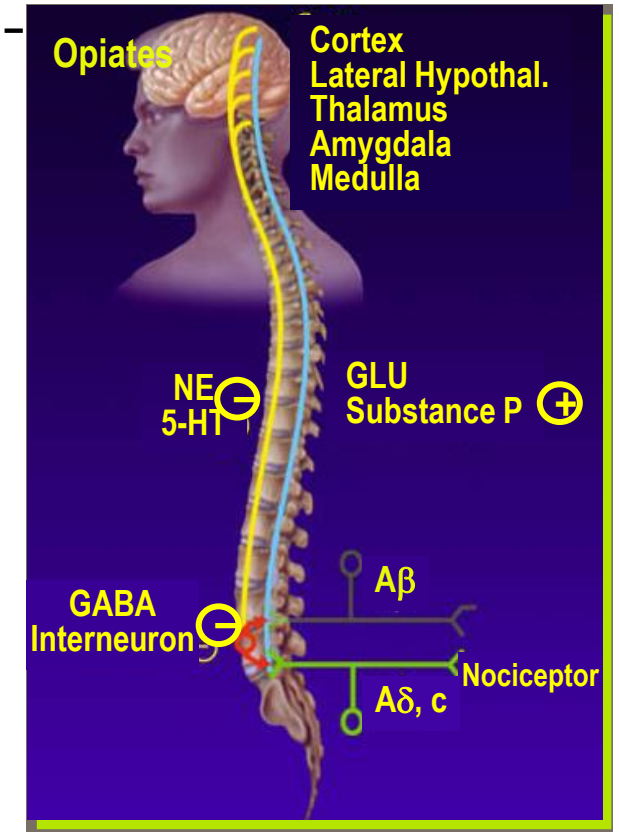


Depression and chronic pain

- Serotonin (5-HT) and norepinephrine (NE)…
- Key mediators of mood
- Part of the body's endogenous analgesic system



Evidence-Based Non-Pharmacological Therapy for LBP	# trials
Exercise	122
Chiropractic/manipulation	61
Acupuncture	49
Multidisciplinary rehabilitation	44
Psychological therapy	32
Massage	26
Yoga	14
Mindfulness-based stress reduction	3
Tai chi	2

Chou, Ann Intern Med 2016; slide courtesy of K. Kroenke

Pharmacological treatments for pain

Non-opioid analgesics

- Acetaminophen
- NSAIDs
  - Systemic
  - Topical

Co-analgesics

- Tricyclic antidepressants
- SNRIs
- Gapapentin/pregabalin
- Other anticonvulsants
- Capsaicin
- Skeletal muscle relaxants
- Cannabinoids

Opioids

- Buprenorphine
- Codeine
- Fentanyl
- Hydromorphone
- Methadone
- Morphine
- Oxycodone
- Tapentadol
- Tramadol

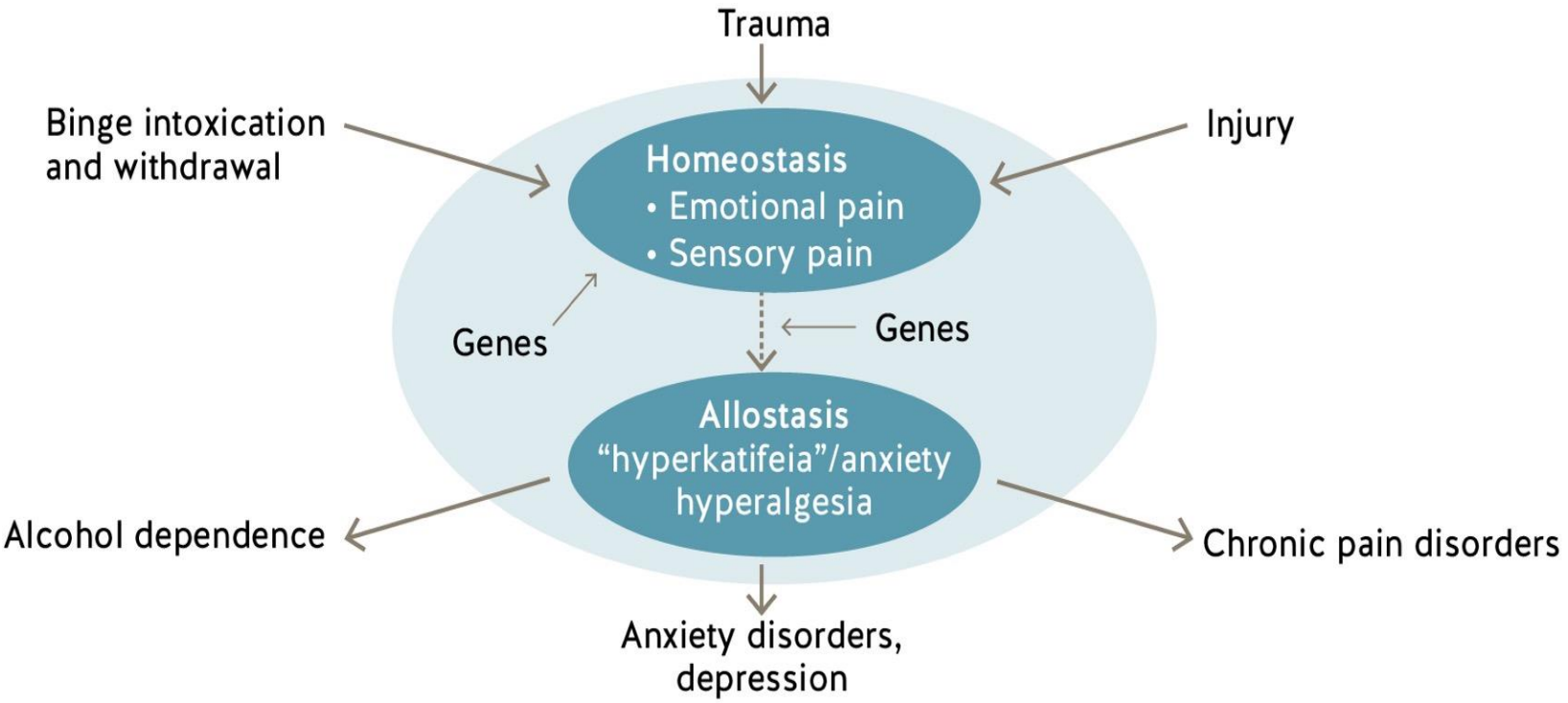
N.B. Benzodiazepines are not on this list

8 med classes in four common conditions

#	Drug	LBP	OA	FM	Neuropathic
1a	**Acetaminophen**		+		
1b	**NSAIDs**	+	+		
2a	**Tricyclics**			+	+
2b	**Muscle relaxants**	+		+	
3a	**Gabapentinoids**			+	+
3b	**SNRIs**	+		+	+
4a	**Tramadol**	+	+	+	+
4b	**Opioids**	?	+(*)		+ (**)
-	**Topical analgesics**	+	+		+/-

Slide courtesy of K. Kroenke – modified L. Rieb added notes: *SPACE trial showed opioids had greater side effects and no improved efficacy over non-opioid tx; **Cochrane review of neuropathic pain oxycodone was ineffective

Alcohol, trauma, and injury



Egli, et al. 2012

Analgesic Efficacy of Opioids

- Average **20–30% analgesia** (Ballantyne, 2006)

- **Only 1 in 7-11 get relief** for CNCP (Busse, 2018)
  - The non-responders should be taken off right away, not left on with other medications added
  - Fantasy that endless dose escalations will provide further reductions in pain

Prescription opioid treatment for non-cancer pain and initiation of injection drug use

- Large retrospective cohort study
- **Chronic opioid prescription users: 4% became injection users**
- Episodic opioid users: 1.3%
- Acute opioid users: 0.7%
- No hx prescription opioid use: 0.4%
- Higher opioid dose and younger age increased risk

- **The risk of initiation of IDU was 8.4 X higher** in those with chronic prescription opioid use than those who were opioid naïve (95% CI, 6.4-10.7)

Wilton J, et. Al. BMJ 2021; 375:e066965 doi: https://doi.org/10.1136/bmj-2021-066965

Factors Associated with OD

- Aberrant behaviors
- Recent initiation of opioids
- Methadone
- Concomitant use of benzodiazepines
- Obtaining opioid prescriptions from multiple providers
- Substance abuse and other psychological comorbidities
- **Higher dose**

Opioid Adverse Effects

Death

Overdose

Sleep apnea

Testosterone Suppression

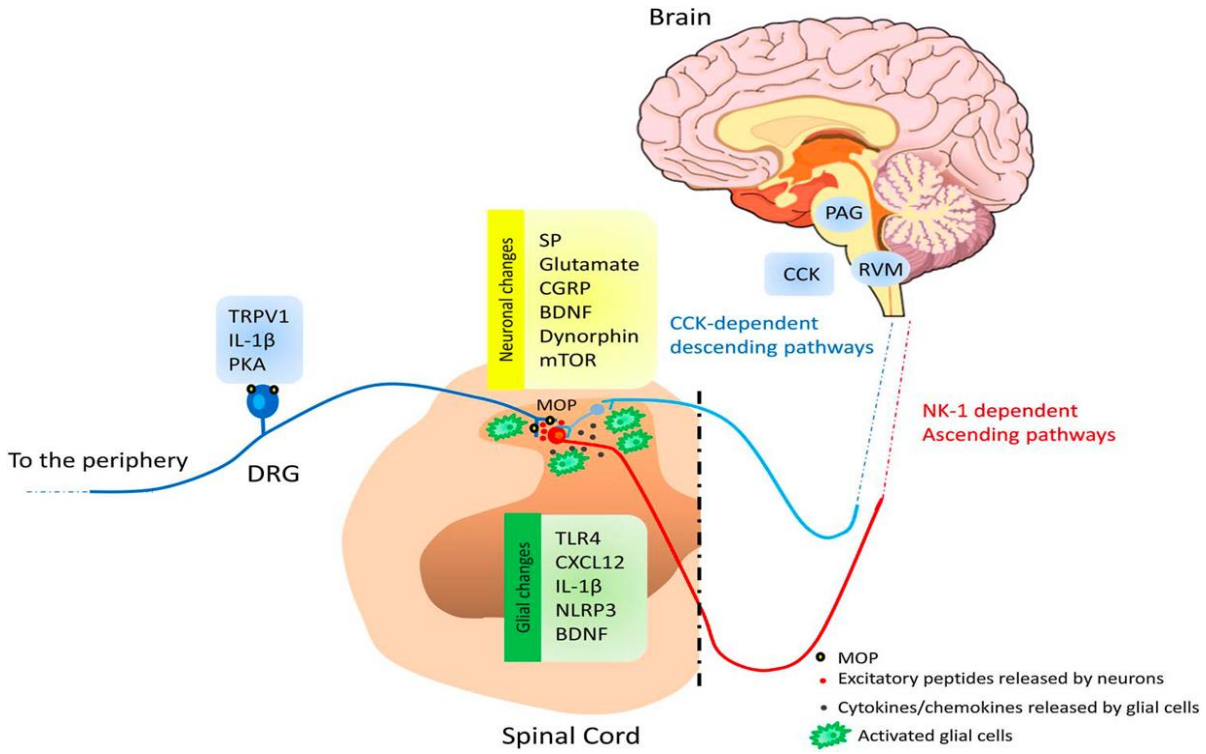
Myocardial Infarction

MVAs

Addiction

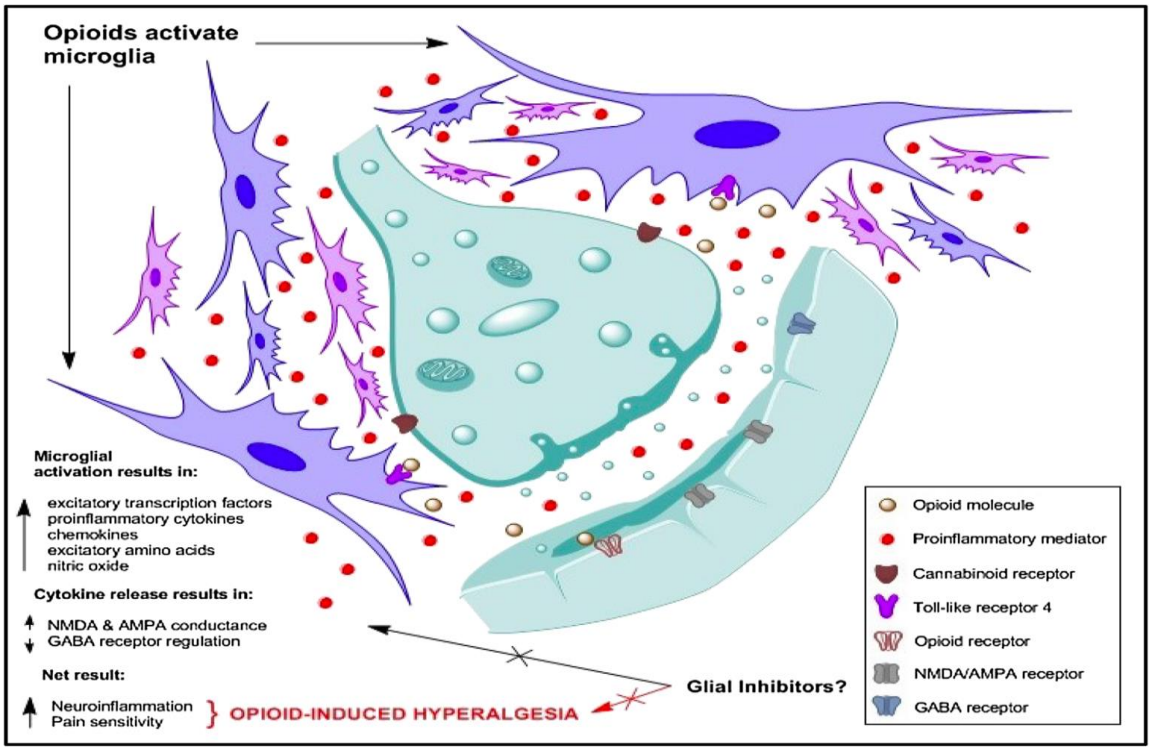
(Chou et al., 2015; Dowell et al., 2016; Ballantyne, 2015)

Opioid-induced pain sensitization



Ravat and Ballantyne, 2016

OIH mechanisms - microglia



Arout, 2015

Clinical Note

PAIN

OPEN

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

Launette Marie Rieb[a,b,*], Wendy V. Norman[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

- Document and characterize our clinical observation

- Pain can return temporarily to old healed (and previously pain-free) injury sites during opioid withdrawal

Results

- Most recruited from the inner-city research office from BC
- 58 completed screening (31 by interview)
- 47 screened positive for WISP
- Of those, **34** (72%) completed full survey (21 by interview)

Demographics:

- Median age: 45 years (IQR: 18), 62% male
- 71% White, 27% First Nations, 3% Black
- 68% Grade 12 education or higher, 67% unemployed

Original injuries:

- fracture 62%, soft tissue 35%, other 3%

WISP

- Healed injury sites can hurt again during opioid withdrawal and vanish when withdrawal is over, a phenomenon we called withdrawal-associated injury site pain (WISP)
- Participants in this mixed methods study reported that WISP was reminiscent of the original injury in quality of pain and often intensity of pain (8/10), on average lasted 2 weeks post opioid cessation, but lasted over 1 month in 18% of participants
- WISP contributed to relapse in 44% and was a barrier to detoxification
- Beyond opioids, NSAIDs and gabapentinoids relieved WISP in many, as did full detoxification

WISP descriptions

"I was pounding my legs…old injury sites are horrendous.

God, it felt just like it did when it was healing when it was broken."

…the sensitivity to touch was increased."

"There's also not just physical pain,… but also there's anxiety from it too… it's like PTSD.

Pain Rep. 2018 Apr 5;3(3):e648. doi: 10.1097/PR9.0000000000000648. eCollection 2018 May.

Linking opioid-induced hyperalgesia and withdrawal-associated injury site pain: a case report.

Rieb LM[1], Norman WV[1], Martin RE[1,2], Berkowitz J[3], Wood E[4,5], Milloy MJ[4,5], McNeil R[4,5].

https://www.ncbi.nlm.nih.gov/pubmed/29922741

"Alice"

- 34 year-old white woman recruited from a CHC providing OAT
- In depth interview and survey in 2014, and follow-up in 2017

- Age 13-15 several twisting injuries to R knee, resolved in few days
- Age 30 began recreational snorting oxycodone, developed OUD
- Upon detoxification she had return of right knee pain (WISP 8/10)
- WISP lasted 6 weeks (general withdrawal 4 wks, left knee 0-2/10)

- With each subsequent relapse due to OUD, right knee pain escalated as the oxycodone dose went up, WISP worsened 10/10

"Alice" – cont'd

- 200 detoxification attempts – and 3 times made it through 6 weeks and was pain free for months afterwards until relapsing again
- WISP produced aversion and worsening mood (bipolar disorder?)
- Reported mitigators: NSAIDs, gabapentin
- Methadone: Helped detoxify, then 200mg help OUD not WISP
- BUP-NX: treated both her OUD and WISP – stable and pain free

- Conclusion: First case linking OIH and WISP, demonstrating that opioids may induce clinically significant pain upon use and withdrawal

- WISP = Clinical correlate of OIH?

Drug and Alcohol Dependence 216 (2020) 108242

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Withdrawal-associated injury site pain prevalence and correlates among opioid-using people who inject drugs in Vancouver, Canada

Launette Marie Rieb[a], Kora DeBeck[b,c], Kanna Hayashi[c,d], Evan Wood[c,e], Ekaterina Nosova[c], M-J Milloy[c,e,*]

Methods

- Qs added to three ongoing prospective cohort studies of PWID in Vancouver, Canada, June-Dec. 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 (43.7%) 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

= 17.7% of all PWID

Results

79 (70.5%) said that having WISP affected their opioid use behavior:

- 57 (72.2%) used more opioids to relieve WISP
- 19 (24.1%) avoided opioid withdrawal
- 3 (3.8%) no longer used opioids in order to avoid WISP

Results

In multivariable analysis:

- WISP was positively associated with…
  - High school diploma or higher education
    - AOR = 2.23, CI: 1.18-3.63
  - Taking pain medications daily
    - AOR = 2.06, CI: 1.18-3.63
  - Use of heroin in the last 6 months
    - AOR = 2.00, CI: 1.14-3.57
- WISP was negatively associated with…
  - Age at first drug use
    - AOR = 0.96, CI: 0.93-0.99

WISP not association with having chronic pain, this it is not a result of any underlying chronic pain issue

Those with neuropathic pain who did not develop WISP were associated with NSAID and gabapentin use, indicating these medications may be protective (AOR 4.06; CI:1.13-15.09)

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)

Pain Relief Seeking VS OUD?

Both can request early refills

Pain Relief:

Takes to relieve pain

No euphoria

If dosing is on ½ life – compliant

Discusses changes with MD

Takes meds in route prescribed

Tolerance/hyperalgesia may occur

OUD:

Takes to get high or feel "normal"

Seeks euphoria (though may not get it)

Binges on meds, craves, compulsive

Changes own med doses frequently

Chews, snorts or injects meds at times

Accesses illicit sources

Tolerance/hyperalgesia may occur

Summary from BCCSU Pain and Addiction Module

1. Substance use, injury and traumatic events can alter pain sensitivity.
2. Pain can alter sleep, substance use and mental health – all must be co-managed.
3. Prioritize the use of non-pharmacologic and non-opioid strategies for acute pain and chronic non cancer pain in those with substance use disorder.
4. Generally, avoid opioids for chronic non cancer pain in those with a non-opioid active substance use disorder or who have significant risk factors for addiction.
5. For those with an active opioid use disorder and pain, use opioid agonist treatment to manage both. Buprenorphine is first line treatment for this population.
6. Avoid co-prescribing a second opioid in addition to opioid agonist treatment for chronic non cancer pain
7. For severe acute pain when other treatments have failed and an opioid is indicated, limit prescribing to as short as possible.
8. For surgical pain management in those on opioid agonist treatment – maintain on current dose (or taper buprenorphine to 12 mg) then add acute opioid for a limited time.

Case - Lisa

- I was called to the home for palliative care
- 29-year-old woman with abdominal pain
- Friends shared heroin at a party - relief
- Presented 9x to emerg. over 1 year – no exam
- **Finally examined – liver edge in pelvis**
- **Adenocarcinoma of the bowel**
- **Father had died age 35 of bowel cancer**
- **Mother and brother hysterical, she was in shock – pain control overnight poor**
- Admitted next day to hospital, no level of morphine could comfort, nurses pushed her under with morphine

Case - Ms. J.

- 19-year-old street entrenched female youth
- Pierced, tattooed, black clothes torn
- Presents asking for methadone

- **Past Medical History**
  - Severe ankle sprain a year prior, air cast
  - X-ray negative
  - Ongoing pain, ER visits – "drug seeking"
  - Friends helped out with pills then heroin
  - No mood issues, sleep broken

Ms. J., cont'd

- **Medications**
  - Ibuprofen 400 mg 1-2 OD prn
  - Acetaminophen ineffective
- **Substance Use History**
  - Tobacco started age 12, currently 1ppd
  - Marijuana started age 13, currently 2-3 jnts/d
  - Alcohol started age 13, 2 beer/wk, rare binges
  - Heroin – started 6 months prior with smoked heroin escalating to ¾ gm/d iv divided TID

Ms. J., cont'd

Social history

–On the street since age 17

–Father alcoholic, violent, she left home

–Recent breakup with boyfriend

–Has a dog which makes housing a challenge

- **Exam**
  - bony tenderness right ankle
- **What are the next steps?**

Ms. J., cont'd

- **Management**
  - Converted to methadone 85 mg/d
  - Referred to community counselor for housing
  - X-ray, CT, bone scan – occult fracture and low grade osteomyelitis
  - Antibiotics
  - Surgical intervention – internal fixation
  - Temporary oxycodone for several weeks following surgery

Ms. J., cont'd

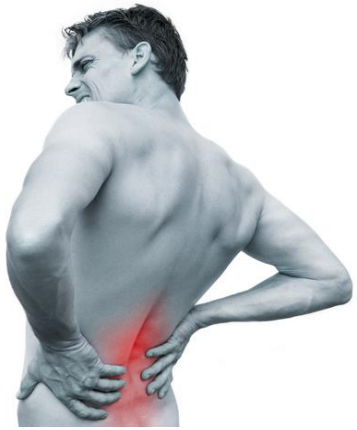
- **Management, cont'd**
  - Physiotherapy
  - Tapered off methadone
  - Decreased tobacco and marijuana

- **Social follow-up**
  - Grade 12 equivalent study and exam
  - Applied and accepted to be a youth counselor

Ms. J., Case Highlights

- What can begin as pseudo-addiction (seeking pain relief but labeled as drug seeking) can become full blown addiction
- People who fall outside the average (due to class, race, sexual orientation, body ornamentation, age, lifestyle, etc.) can be misdiagnosed or not fully seen
- Treat the underlying condition
- Challenge yourself to see whole the person

Case - Mr. D.



- 47 year old married at home father, degree is psychology, no family history of SUD
- Age 19: L4-5 discectomy for prolapse
- Post-op give Tylenol #3
  - He mixed these with ETOH to get high
- 10 years later – recurrent disc – surgery
- Initially successful then increasing low back pain over the next year

Mr. D, cont'd

- GP managed
  - Tried different medications, low dose at 1st
  - Hydromorphone short acting up to 80 mg/d
    - Would run out early, would crush and smoke
  - Fluoxetine 60 mg/d
  - Lorazepam 4 mg/d
  - Pain still unmanageable on above regime
  - Referred on

Mr. D., cont'd

- Multidisciplinary hospital-based pain clinic
  - Medications altered, various medications combined
  - Opioids were increased over time to the level below:
  - Fentanyl Patch 150 mcg/h q2 d (prescribed q3d)
  - +/- fentanyl solution 100 mcg/2ml vile 3-5/d
  - Fentanyl film 600 mcg bid = 1200 mcg/d
  - Tramadol (24h) 50 mg ii bid = 6 tabs/d = 300 mg/d
  - Methadone tablets 60 mg bid = 120 mg/d
  - Hydromorphone - short acting 80 mg/d (snorting)
  - Morphine equivalent daily dose > 2,500 mg/d

Mr. D., cont'd

- Other medications
  - Fluoxetine 80 mg/d (adverse rxn - duloxetine)
  - Diazepam 2.5 mg bid (+still using lorazepam)
  - Decongestant with pseudoefedrine 2 tabs/d
  - Caffeine pills and energy drinks
- He still felt pain, otherwise felt "Great!"
- Function: ran triathlons, others see sedation
- Total cost to wife's insurance = $3,000/wk
- Insurance cut off coming so came for help

- What are your suggestions?

Mr. D., cont'd

- Voluntary admission to a medically supervised residential treatment facility: education, 12 step, group, 1:1, CBT, etc.
- Methadone and fluoxetine same dose at 1st
- Stopped tramadol on admission
- Stopped all fentanyl after 2 d taper
- Added quetiapine 25 mg q6h

- No withdrawal seen – why?

Mr. D., cont'd

- Tapered the methadone over 3 weeks to 5 mg tid
- Dose held until in withdrawal
- Switched to buprenorphine patch 10 mcg initially – not quite enough
- Then over to sublingual bup/nx titrated to 6 mg/d prior to discharge – pain now 2/10

Mr. D. f/u

Follow-up at 12 months – doing great!

- Meds
  - Bup/nx 6 mg/d
  - Fluoxetine 60 mg/d and tapering
  - Quetiapine 125 mg/d and tapering
- Has attended 12 step daily, has a sponsor
- No relapses or slips, despite divorcing
- No more pain issues
- GAF 95/100

Mr. D., Reflections

- Primary pain disorder or substance use disorder?
- Opioid induced hyperalgesia?
- How can the opioids besides methadone be stopped abruptly without withdrawal?
- How can bup/nx and 12 step combined control both the pain and addiction issues?

Case - Mr. X.

- **56 year old left-hand-dominant sailor**
- Seen Sept. 12, 2018 through WorkSafeBC referral
- 2000 L shoulder rotator cuff tear - surg x4, resolved
- 2001 R rotator cuff tear and repair
- **2011 fall at work, complete re-tear R rotator cuff**
- 3 subsequent surgeries to repair failed repairs R sh.
  - Post op infection Dec. 2011, increased pain
  - Last surgery May 2012, not eligible for more
  - Pain 6+/10, pain and mood induced insomnia/disturbance
- Adjustment disorder, then Major Depressive Disorder with hospitalization for suicide attempt, retrained and back at work but struggling with pain

Case - Mr. X., Cont'd

- 3 multidisciplinary pain programs, PT, IMS

PMHx:

- Sleep apnea requiring CPAP
- HTN
- 2 years prior workup for CVD neg. – Stress test neg.

Medications:

Morphine started with initial L shoulder injury 18 years prior and never stopped, as high as 800 mg/d tapered to 400mg/d, has remained on same dose for many years (NB. no change after R shoulder injury)

Case - Mr. X, Cont'd

Current medications:

- **Morphine (ER)** 400mg/d lowered by his family MD abruptly 2 mo. prior to 300mg/d, then pain spiked, withdrawal, insomnia
- **Gabapentin** 800 Q6H halved abruptly 1 mo. prior to visit with me by his family MD to 800 Q12H, then worse pain
- Rare use **codeine** 30 mg + acetaminophen 300mg + caffeine 15 mg; also uses rabeprazole 20mg for reflux
- **Tadalafil** prn for erectile dysfunction
  - Testosterone not tested?
- **Trazodone** 150 mg 1/3-1/2 hs – taken off by his MD who was concerned about meds, then worse sleep/pain
- **Zopiclone** 7.5 mg tapered off in the last year
- Past tried SSRIs, SNRIs, TCAs all side effects, stopped

Case - Mr. X, Cont'd

Substance Use History:

- Previous **tobacco** smoker, quit 4 years ago
- **Cannabis** – occasionally in teens, none since
- Previous **binge drinke**r as a young adult, by 2016 drank a bottle of wine every 1-2 weeks. Warned about potential side effects but persisted. In 2018 with med changes and pain - began daily drinking, escalated to 4-9 drinks/day which he found relieved pain temporarily but overall increased pain sensitivity, loss of control, craving, use despite consequences, hiding his use, understands it is contraindicated, etc.
- **Cocaine**: 3 months in youth, brother went to rehab for this
- No reported abuse of opioids (no alternate routes, binges, running out, double doctoring, or illicit use, etc.)

Case - Mr. X, Cont'd

Initial physical exam:

- 5'7" 190 lbs
- Good range of affect
- No impaired in office

Right shoulder:

- Multiple scars, wasting, detached biceps
- Sensation intact to touch and sharp, motor 5/5
- Flexion 135, abduction 105, ext 45, ext rot 35

Case - Mr. X, Cont'd

- **What is the differential diagnosis?**
  - Chronic pain secondary to severe rotator cuff injuries, repair, infection
  - Opioid induced hyperalgesia? Withdrawal-induced hyperalgesia? Gabapentin was helping at higher dose?
  - Alcohol use disorder – severe, adds risk for OD++
  - Sleep apnea, adds risk for OD++
  - MDD and insomnia

Case - Mr. X, Cont'd

- **What are the options for treatment ?**
  - Residential treatment is most prudent for detoxification of alcohol under medical supervision and opioid rotation to buprenorphine + naloxone
  - Provide him with a naloxone kit

Case - Mr. X, Cont'd

Arranged to admit him to treatment Oct. 1, 2018

The night prior to arriving, on top of morphine…:

- Binge drank+++ son brought over "specialty cocktails"
- Took tadalafil x2 for evening with wife
- Sweaty and uncomfortable overnight

On arrival at the treatment centre… BP 140/90

- 80 BPM irreg/irreg = new onset A-Fib
- Sent to hospital for workup – No MI, anticoagulant (rivaroxaban 20 mg) and beta blocker (metoprolol 25 oD titrated to 75 BID) given, no electrocardioversion

Case - Mr. X, Cont'd

- Stayed 42 days in D+A treatment – did well
- Never cardioverted with medication alone
- Apt. for cardiac echo pending and electro-cardioversion scheduled

- To reduce potential of cardiac stress due to precipitated withdrawal, we decided to do micro-induction of buprenorphine (Suboxone)

Case - Mr. X, Cont'd

- **Morphine:** Tapered by 10 mg q 2 days, until down to 70 mg TID, then (once adding buprenorphine) tapered 20-30 mg q 2d (ie. 60 mg TID, 50 mg TID, 40 TID, 30 TID, 20 TID, 20 BID, then stop)

- **Buprenorphine:** Butrans patch 10 mcg/h started when morphine was 70 TID – next day Suboxone 0.5 mg x 2d, 1 mg x 2d, 1.5 mg x 2d, 1 mg x 2d, 1 mg BID x 2d, 1.5 mg BID x 1d, **2 mg BID** at discharge with view to taper off in community over 2 weeks

- Gabapentin changed to **pregabalin** 150 mg BID

Case - Mr. X, Cont'd

- If you had asked Mr. X before detox he would have told you…
  - He needed more morphine to treat his pain
  - He needed alcohol to get by with the pain
  - He was considering adding cannabis to help pain

Yet after detox…

  - He reported having "less pain" rated as just "1.5/10" and the "deep ache was gone", seeping 7-8 h/night. He reported being "more clear headed", realized he had an alcohol use disorder and so did his parents, wanted off all opioids to advance in safety sensitive jobs. He saw treatment as a lifesaving intervention
  - His overall appraisal = "It's amazing!"

Mr. G

- 52-year-old contractor
- Increasing low back pain and stiffness x 7 years
- NSAIDs and acetaminophen minimal impact, and not worth the GI upset
- Oxycodone (Percocet) started by family MD
- Later Oxycontin up to 300 mg/d – when MD stopped prescribing
- W/D syndrome drove him to heroin and later fentanyl
- Lost his wife and child, along with his business
- Trials of buprenorphine and methadone failed
- Stabilized morphine 1000 mg/d at RAAC
- I saw him – listened to pattern, suspected AS so tested:
- HLA B-27 +, MRI for spinal inflammation + = Ankylosing spondylitis
- Sent to rheumatology – on third biologic, swimming and walking daily
- Now has visitations with daughter again and on good terms with family

Thank you!