

Seeking Relief: Opioids and Pain

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Cases

- ▶ Tom, a 46M presents to ED after tripping over some loose boards near his home and landing on his outstretched hands.
- ▶ Diagnosed with an acute fracture of the wrist - given analgesia and plaster to manage fracture.
- ▶ Treated with Paracetamol and Oxycodone IR during hospital stay.
- ▶ Sent home with 5 oxycodone tablets due to hospital policy. Presents the next day to GP as pain is still ongoing asking for more analgesia because the oxycodone helped quite a lot.

Cases

- ▶ Ellen, a 34F presents to clinic a few days early for her repeat MS-Contin script. States that she lost her handbag and the last strip of her meds was in the bag.
- ▶ History of chronic pain post domestic violence a few years ago
- ▶ You note this is not the first time she has presented requesting scripts early - always different excuses.

Cases

- ▶ Mark, a 52M requests an increase in his Oxycodone SR script this month as his pain is getting worse and his usual dose is not holding him anymore.
- ▶ Pain longstanding post MVA 15 years ago. Difficult to treat, has been on a slowly increasing dose of oxycodone SR for years.

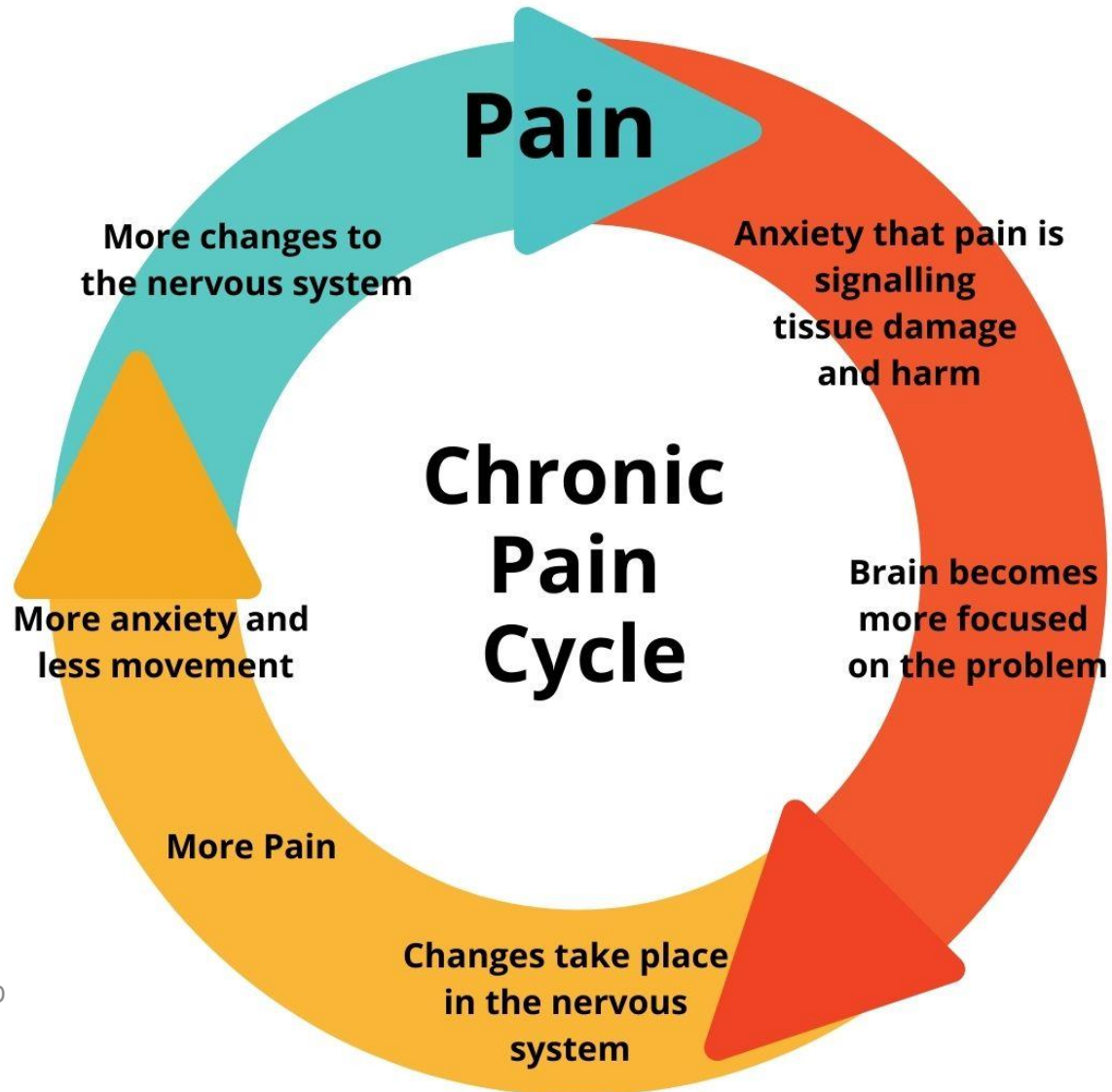
Cases

- ▶ Mary, a 73F presents to GP clinic a week post discharge from hospital - recent TKJR complicated by local haematoma, prosthetic joint infection and long hospital stay.
- ▶ Current meds: Paracetamol, Celecoxib, Oxycodone/Naloxone SR, Tapentadol IR
- ▶ Requests repeat scripts for all the above as pain is still ongoing.

Pain Physiology - updated

- ▶ Neuropathic - pain arising from disease or injury to the somatosensory system - clarified definition in 2010
- ▶ Nociceptive - pain arising from the activation of C fibres and A- Δ small fibres.
 - ▶ C - polymodal activation, but pain specific output
 - ▶ A- Δ - threshold dependent signalling
- ▶ Nociplastic - pain arising due to altered functioning of peripheral and central pathways other than those exclusively defined as neuropathic pain
- ▶ Opioids - anti-nociceptive agents - good in acute nociceptive pain - variable effectiveness in other types of pain

Becoming chronic



Opioids

- ▶ Family of substances originally derived from the opium poppy
- ▶ First seen as long ago as 5700BC
- ▶ Used by most civilisations since. Most commonly used as an analgesic and sedative
- ▶ Greeks used it for its sleep-inducing properties and for pain (Morpheus origin)
- ▶ The Latin phrase “Sedare dolorem opus divinum est” is used to describe its benefits (alleviating pain is the work of the divine)
- ▶ Paracelsus in the early 1500s reintroduced it as Laudanum
- ▶ Thomas Sydenham used a tincture of opium and alcohol that he called Laudanum.

Opioids

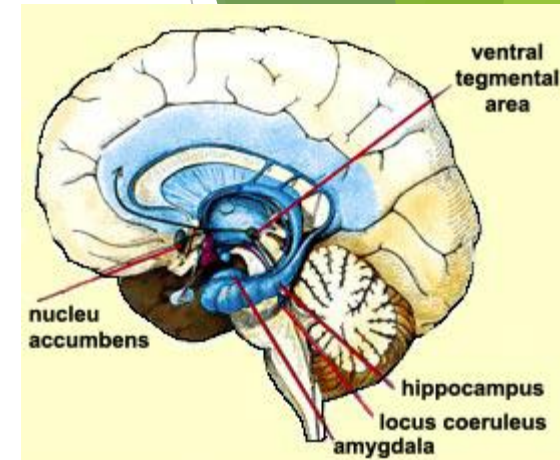
- ▶ Method of action via endogenous opioid receptors (μ , κ , δ)
- ▶ Most opioids act as full agonists at all opioid receptors
- ▶ Buprenorphine primary partial agonist at μ , and antagonist at κ & δ
- ▶ Effects:
 - ▶ Analgesia via opioid receptors
 - ▶ Sedation
 - ▶ Euphoria
 - ▶ Sweating
 - ▶ Constipation
 - ▶ Relaxation, drowsiness
 - ▶ Respiratory depression
 - ▶ Bradycardia
 - ▶ Respiratory arrest
 - ▶ Cardiac arrest

Use vs Use Disorder

- ▶ Difference between opioid use and opioid use disorder
- ▶ Opioid use is a voluntary activity
- ▶ Opioid use disorder is a compulsive behaviour of seeking and use despite negative consequences

Dependence

- ▶ Repeated use of opioids in the absence of painful stimuli activates opioid reward system
- ▶ Active via VTA and mesolimbic reward system releasing DA in the NAc
- ▶ Receptors eventually become less responsive to opioid stimulation - requires larger doses to achieve same effect
- ▶ Also affects the locus coeruleus in the brain stem
 - The LC usually increases noradrenaline production to stimulate wakefulness, breathing, BP, alertness
 - In the presence of opioid molecules - suppress the release of NA
 - Over time the LC adjusts by increasing level of production
 - In the absence of opioids the LC now produces excessive NA
 - jitters, anxiety, cramps, diarrhoea



Dependence

Opioids usurp brain circuitry and compromise dopaminergic reward pathway⁴

Drug and stress innate immune gene induction creates the neurobiology of dependence

Disrupts frontal cortical behavioral control mechanisms

Increases limbic negative affect, craving, and anxiety

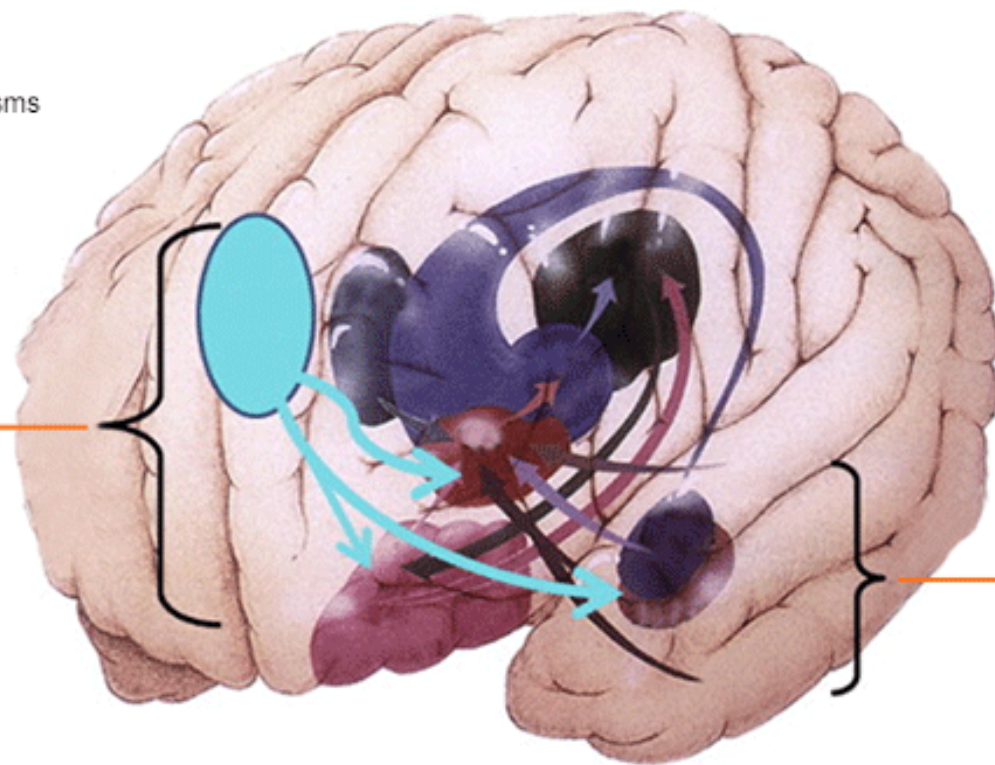
Frontal Cortex:

- Goal setting
- Motivation
- Planning
- Impulse inhibition

Amygdala Hippocampus:

- Anxiety
- Urgency
- Negative Affect
- Craving
- Impulsiveness

Adapted with permission from Crews et al.



Diagnosis of dependence/use disorder

- ▶ Following the ICD10 criteria for substance use disorder will help establish whether there is a dependence or not

- ▶ Three or more of the following must have been experienced or exhibited at some time during the previous year:
 1. A strong desire or sense of compulsion to take the substance;
 2. Difficulties in controlling substance-taking behaviour
 3. A physiological withdrawal when substance ceased or reduced
 4. Evidence of tolerance, such that increased doses are required in order to achieve effects originally produced by lower doses;
 5. Progressive neglect of alternative pleasures or interests because of substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects
 6. Persisting with substance use despite clear evidence of overtly harmful consequences

DSM-V

1. Taking the substance in larger amounts or for longer than you're meant to
2. Wanting to cut down or stop using the substance but not managing to
3. Spending a lot of time getting, using, or recovering from use of the substance
4. Cravings and urges to use the substance
5. Not managing to do what you should at work, home, or school because of substance use
6. Continuing to use, even when it causes problems in relationships
7. Giving up important social, occupational, or recreational activities because of substance use
8. Using substances again and again, even when it puts you in danger
9. Continuing to use, even when you know you have a physical or psychological problem that could have been caused or made worse by the substance
10. Needing more of the substance to get the effect you want (tolerance)
11. Development of withdrawal symptoms, which can be relieved by taking more of the substance

DSM-V - Persistent Pain

1. **Taking the substance in larger amounts or for longer than you're meant to**
2. **Wanting to cut down or stop using the substance but not managing to**
3. Spending a lot of time getting, using, or recovering from use of the substance
4. Cravings and urges to use the substance
5. Not managing to do what you should at work, home, or school because of substance use
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Management options

- ▶ Cut off prescribing
- ▶ Continue prescribing
 - ▶ Typical opioids
 - ▶ Opioid Agonist Treatment agents
- ▶ Difficult discussions

Withdrawal

- ▶ Only occurs in patients that have become neuroadapted to opioids.
 - ▶ Tolerance developed within the brain
 - ▶ Requires regular use
 - ▶ Dose independent
- ▶ Onset depends on type of opioid
 - ▶ Short acting vs long acting
 - ▶ Can be as early as 4 hours post injection of heroin or as long as 2-3 days post last dose of buprenorphine (longer if LAIB)

Withdrawal symptoms

- ▶ Not all patients will get all the listed symptoms
 - ▶ Dilated pupils
 - ▶ Sweats
 - ▶ Tremor
 - ▶ Bone and muscle ache
 - ▶ Nausea, vomiting
 - ▶ Abdominal cramps
 - ▶ Diarrhoea
 - ▶ Yawning
 - ▶ Piloerection
 - ▶ Rhinorrhoea
 - ▶ Cravings for opioids

Acute withdrawal

- ▶ Easing of symptoms is primary goal
- ▶ Patient unwilling or unable to cease opioid use:
 - ▶ Anti-emetics
 - ▶ Anti-diarrhoeals
 - ▶ Diazepam (consider oxazepam in liver failure or advanced age)
 - ▶ Buscopan
 - ▶ May require antipsychotic agent if agitation profound
- ▶ Opioids for analgesia and withdrawal management

Typical Agents

- ▶ May be appropriate in rare cases
- ▶ Closer monitoring
- ▶ Patient contracts
- ▶ Staged supply
- ▶ Opioid rotation
 - ▶ Dose reduce 25-50% (OMEDD)
 - ▶ Reduced tolerance poorly understood
 - ▶ May result in tolerance again and dose escalation
- ▶ Regular reviews

Opioid Agonist Treatment

- ▶ Management of opioid use disorder with an opioid agonist
- ▶ Long history within Australia
- ▶ Two agents primarily used in Australia
 - ▶ Methadone
 - ▶ Buprenorphine

Methadone

- ▶ Full agonist
- ▶ Liquid form, long $t_{1/2}$
- ▶ Slow up-titration over weeks
- ▶ Daily dosing, usually 40-100mg
- ▶ Concerns
 - ▶ Prolonged QTc - especially at higher doses (>100mg) **RARE**
 - ▶ Over-sedation + respiratory depression
 - ▶ Particularly when used in combination with other sedating medication ie benzos, alcohol
- ▶ Interactions
 - ▶ Methadone metabolised by cytochrome p450 pathways so interacts with inducers and inhibitors of these (ie rifampicin)
 - ▶ Methadone dosing may need to be adjusted if starting a new medication

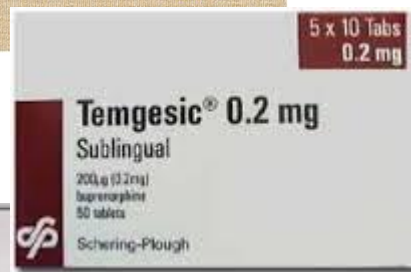
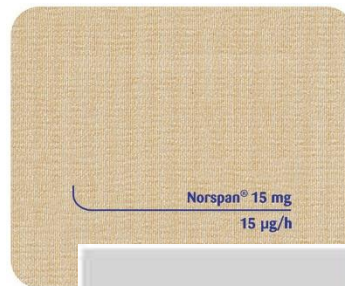


Buprenorphine

- ▶ Synthetic opioid compound developed in 1969 and available in 1978 for human use
- ▶ High binding affinity for the opioid receptors
- ▶ Competitive partial agonist at μ , and antagonist at κ & δ receptors
- ▶ Analgesia via μ found throughout central nervous system
- ▶ Has a “ceiling” effect due to partial activation of opioid receptor
- ▶ Antagonism of κ & δ receptors reduces respiratory depression, dysphoria and sedation

Buprenorphine

- ▶ Usually encountered as:
 - ▶ Suboxone
 - ▶ Norspan
 - ▶ Temgesic
 - ▶ Subutex
 - ▶ Buvidal
 - ▶ Sublocade



Support

- ▶ Colleagues
- ▶ MATOD education
- ▶ Local Pharmacists
- ▶ Addiction Medicine Specialist Services
- ▶ ACECHO
- ▶ PAMS - Pharmacotherapy Advocacy Mediation Support
- ▶ SafeScript

