Pain management: an update on assessment, management and opioid use

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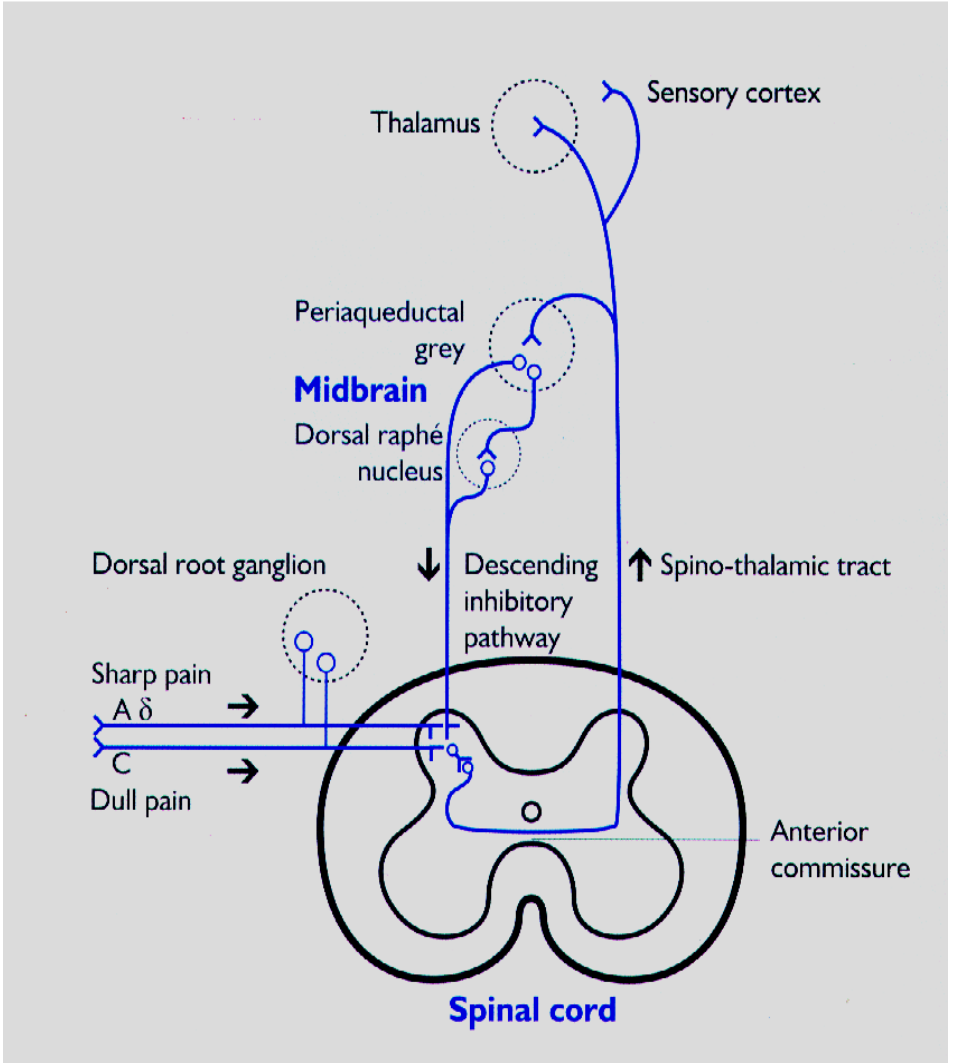
painaustralia™
working to prevent and manage pain

- Advisory Group, Victorian Dept of Health, *Safescript,* Drugs of Dependence
- Advisory and educational activity for *Mundipharma, Seqiris, Spectrum Therapeutics*

Pain: a multidimensional experience

- *"**Nociceptive**"* pain: structural
  - sensory, affective, motivational aspects
- *"**Neuropathic**"* pain: nervous system damage
- Sensitisation *("**nociplastic**")* pain
  - Kosek E. *Pain* 2016; 157: 1382
    - peripheral (transduction)
    - spinal (transmission)
    - supra-spinal/brain (perception)
  - down-regulation (modulation)
    - reduced descending inhibition implicated
- Most pain states have a degree of sensitisation
  - heightened sensations, emotion, meaning
  - Impact on bio-psycho-social domains

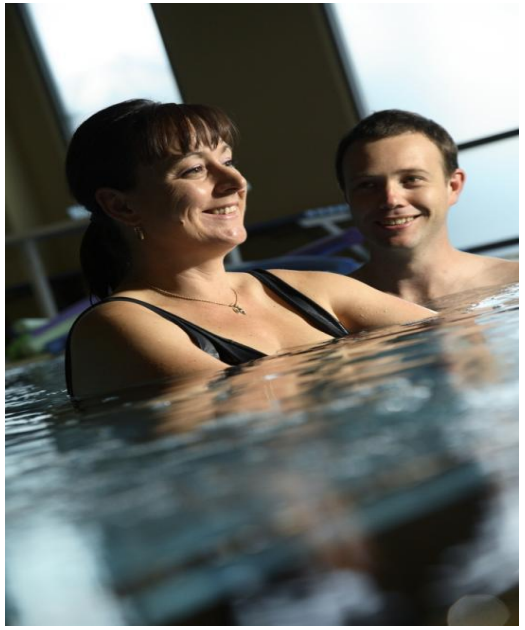


An approach to pain management

- Patient education
  - include family, medical team → for perception

- Pharmacological
  - opioids, clonidine, LA's → for nociceptive pain
  - NSAIDS, biologicals, anti-oxidants → for inflammation
  - blocks/LA's, ketamine, Mg, clonidine, TCAD/SNRI, GBP → for neuropathic, sensitisation
    - ? medical cannabis → for ? perception

- Non-pharmacological → for nociceptive, neuropathic and sensitisation components
  - neuromodulation e.g. spinal cord stimulation
  - physical rehabilitation, re-exposure, desensitisation strategies
  - psychology assessment/management
    - education, cognitive re-appraisals, acceptance, mindfulness
  - social
    - judicious support, lessen solicitation, legal (? need for apology)



Psychiatric illness and pain

- High incidence of depression
  - 40-50%+ with persistent/chronic pain
    - poorer prognosis: mutually promote severity, progress
      - shared neuronal pathways
        - Sheng *J Neural Plasticity* 2017; 9724371

- Suicide risk >2x control
  - chronic pain independent risk factor
    - higher in unemployed/disabled, ? neuropathic pain
    - hopelessness, mental defeat, catastrophising implicated
      - Racine M. *Prog NeuroPsychoPharm Biol Psych* 2018; 87: 269
  - higher risk with higher opioid dose
      - Ilgen M. *Pain* 2016; 157: 1079

- High dose opioid more common in those with history of anxiety, depression, PTSD, SUD
  - co-dependent relationship to opioid use and chronic pain
    - Eklund M. *Clin J Pain* 2010; 26; 1
    - Feingold D. *J Affect Disord* 2017; 218; 1

Addiction/dependence and pain

- Shared risk factors for chronic pain and substance use disorder
  - childhood adversity, genetics, psychiatric, social
  - risk injury/trauma in those with dependence
    - commonly triple diagnosis: pain/SUD/psychiatry
      - Salsitz E. *J Med Toxicol* 2016; 12: 54
- Opioids post acute pain carry risk of dependence/addiction
  - risk <1% if no risk factors (0.2% at 1 yr, 0.6% at 3 yr)
    - 3-6% with risk factor, but up to 20% of “chronic pain on opioids” cohort
      - dependence behavour identified in those with chronic pain
        - Campbell G. *Pain* 2015; 156: 231 & 2016; 157: 1489
- Repeat prescriptions are associated with higher rates of SUD at 3 yrs
  - ? marker of risk or is continued prescribing causing increased risk
  - young male 3x higher; hydromorphone, depression, tobacco use also risk
    - Brat G. *BMJ* 2018; 360: j5790
  - psychiatric, high pain, past addiction
    - Fishbain D. *Pain Med* 2008; 9: 444
  - provider and system factors
    - Cragg A. *Systematic Reviews* 2017; 6: 265

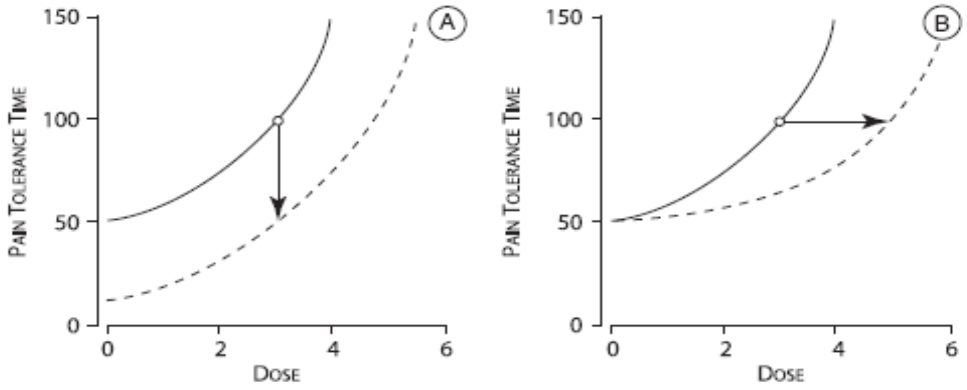
Opioid philosophy

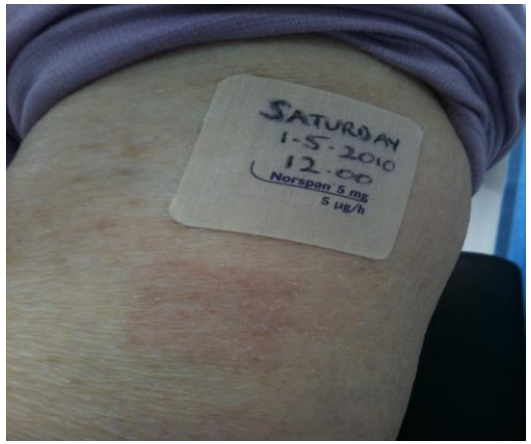
- Opioids are anti-nociceptive
  - 63% respond in enriched enrollment trials >3 mths
    - Meske DS. *J Pain Res* 2018; 11: 923

- Reasons for failure of opioid response
  - OIHA and tolerance
  - disease progression/mechanistic change
  - psycho-social e.g. anxiety, misuse/addiction, diversion

- Co prescribe anti-hyperalgesics
  - monitor, dose limit/wean
  - physical and psychological Mx

- “atypical” opioids with dual MOA preferred
  - synergy to gain analgesia, less OIHA/tolerance

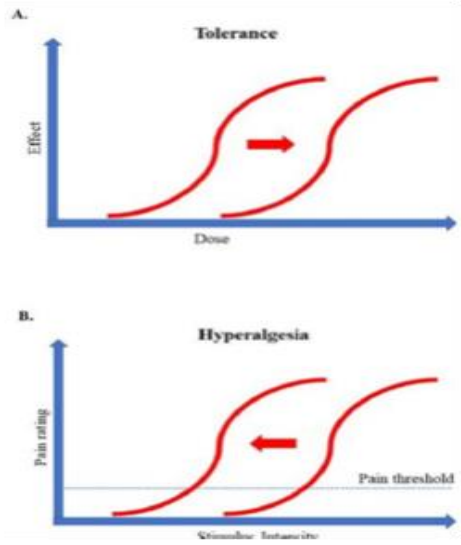




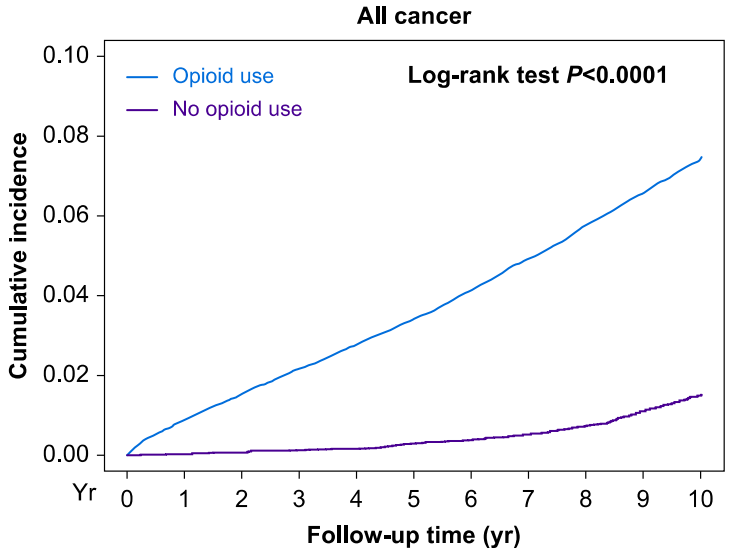
OIHA, tolerance, depression, Ca risk

- Exogenous opioid exposure induces hyperalgesia (OIHA)
  - Appears related to dose, potency, exposure time e.g. remifentanil
  - NMDA, NOS, glial cell activation
  - Heightened pain experience despite opioid; myalgia, arthralgia with withdrawl
    - Codeine specifically activates glia
      - Lee M. *Pain Physician* 2011; 14: 145
- Tolerance: reduced anti-nociception with prolonged exposure

→Opioids fail over time even in nociceptive pain without anti-hyperalgesic strategy



- Association of opioid use with depression: complex relationship, includes pain
  - Bates, N. *Curr Treat Options in Oncology* 2022; 23: 348
- Association of opioid use with Ca risk, including recurrence
  - Solid tumours, HR 2.6; ? immunosupression, ? DNA effects
    - Sun M. *BJA* 2022; 129: 84



Ketamine

- Ketamine: 0.1-0.3 mg/kg/hr anti-hyperalgesia
  - Psych, analgesia, bronchodilation, anaesthesia with increasing at doses
  - Pre-emptive NMDA antag prevents receptor up-regulation with nerve injury and hyperalgesia in animals
    - Wilson *Pain* 2005; 117: 421
  - RCT ketamine intra-op spine surgery pts on opioids
    - 30% less opioid pca use, less pain at 6 weeks, 70% less opioid use
      - Loftus *Anesthesiology* 2010; 113: 639

- Cochrane review
  - Modest but statistically significant reduction in chronic pain after surgery
    - Chaparro L. *Cochrane Database Syst Rev* 2013; 7: CD008307

- Limited evidence in chronic pain
  - No RCT, short heterogenous experimental trials in chronic neuropathic pain
    - Israel J. *Health Psychol Res* 2021; 9(1)
  - No benefit with oral ketamine (40-400 mg/d) in Ca neuropathic pain: mostly chemo neuropathy
    - Fallon M. *JAMA Oncol* 2018; 4: 870

Lignocaine

- Nerve conduction block at high concentration/proximity to nerve structure
  - regional analgesia > iv

- Antinociceptive and anti-neuropathic effects when given iv: 1.5 mg/kg load, up to 1.5 mg/kg/hr, 24 hr
  - acute pain: visceral pain states reduce opioid use, pain scores, promotes rehabilitation
  - role in acute neuropathic pain: SCI, peripheral nerve, CRPS
  - Na channel, anti-inflammatory, ? Other effects
    - Hyland S. *Healthcare* 2021; 9: 333

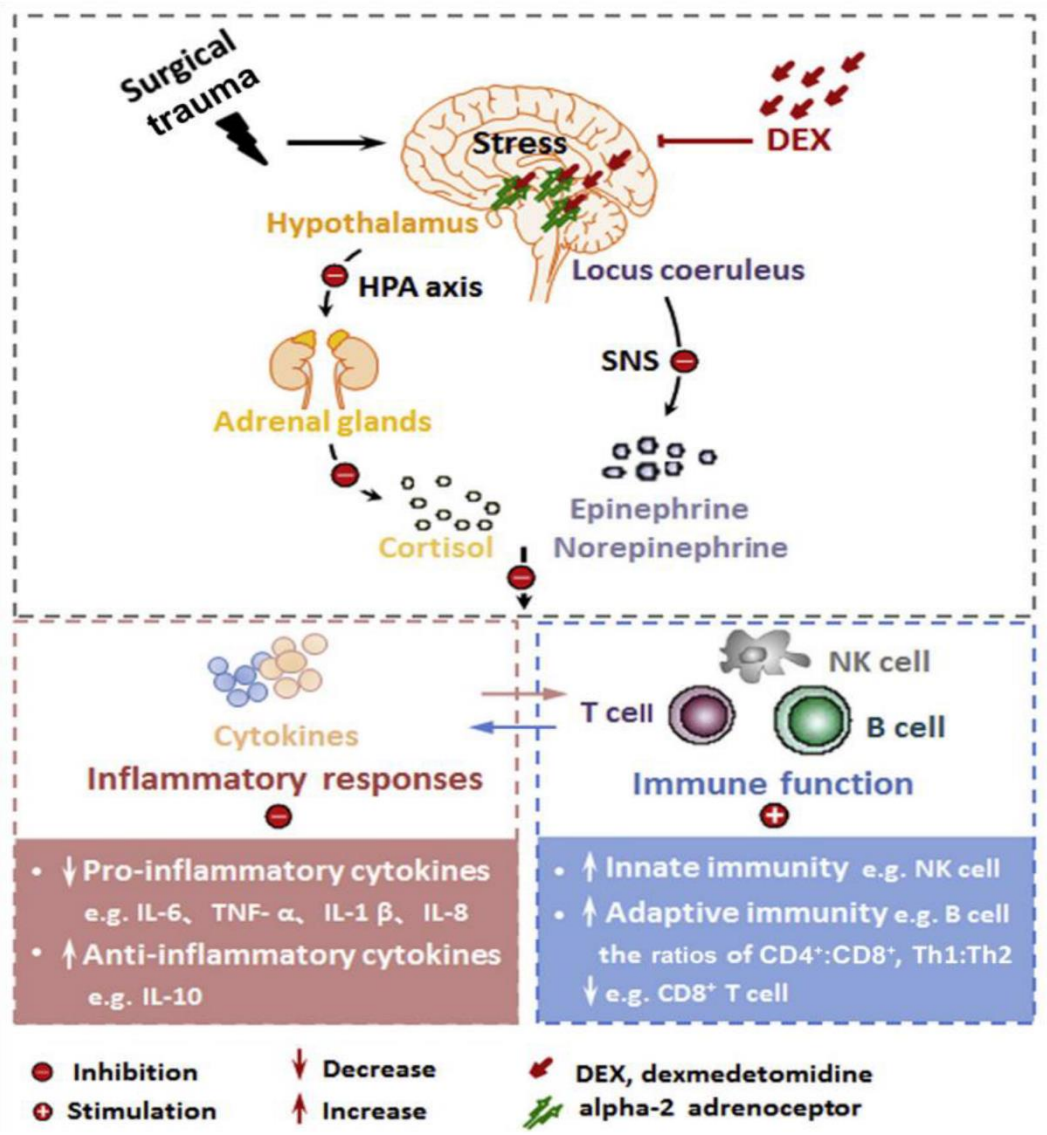
- Experimental evidence in chronic neuropathic states
  - Na1.8, TRPV1, glial, CCB, other actions
  - peripheral nerve injury: neuroma
    - Hermanns H. *BJA* 2019; 123: 335

Table 1 Effects of systemic lidocaine on different chronic pain modalities.

Effects on chronic pain	Spontaneous pain	Hyperalgesia	Allodynia
Neuropathic pain	Reduced[25,27]		
Diabetic neuropathy	Reduced[28]		
Peripheral nerve injury	Reduced[19,23]	Reduced[19,23]	
Post-herpetic neuralgia	Reduced[17,23]	Reduced[23]	Reduced[17,23]
Chronic regional pain syndrome	Reduced at high (3 μg ml^{-1}) plasma concentration[20]	Reduced for cold threshold only[20]	Reduced for cold and mechanical threshold[20]
Central pain	Reduced[21,24]	Reduced[21]	Reduced[21]

Dexmedetomidine/Clonidine

- Apla-2 adrenoceptor agonists reduce NA release (LC, SC)
  - reduced nociception at SC
  - reduced CNS/autonomic response to nociception
  - anti-hyperalgesia
  - anxiolysis
  - anti-inflammatory
    - Wiatrwski R. *AANA Journal* 2021; 89: 77
- Intra-op infusion to PACU
  - reduce propofol/MAC/opioid
  - reduce OIHA
    - Lee C. *Korean J Anaesthesiol* 2013; 64: 301
  - reduce ketamine emergence phenomena
  - transition to clonidine po
    - Hyland S. *Healthcare* 2021; 9: 333



Safety strategies: chronic opioid use

- Active management approaches
  - sleep study, dental, HPA assessment, Ca screen
  - mood, anxiety management: TCAD, SNRI, SSRI
  - permits, legal, family engagement
  - de-prescribing/tapering discussion/plan
    - Fishbain D. *Pain Med* 2019; 20: 2179
    - ? ketamine, ? clonidine
      - Frank J. *Annals Int Med* 2017; 167: 181
  - LAIB as option for pain, dependence
    - Barnett A. *Drug Alcohol Depend* 2021; 227: 108959

- Potential risk of tapering
  - psychiatric, including O/D risk
    - Darnall B. *Pain Med* 2019; 20: 429

- Therapeutic drug monitoring
  - morphine, oxycodone: 20-80 ng/ml therapeutic, >200 toxic
    - Bodor G. *eJIFCC* 2012; 23: 55

AL NEWS

Advocates hail 'game changing' PBS listing of buprenorphine

Harm-reduction advocates have long called for an end to the surprisingly high cost of opioid substitution therapy.

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Pharmaceutical giant Mundipharma hit with hefty fine over misleading opioid drug information

By the Specialist Reporting Team's Alison Branley

Updated 23 Dec 2019, 2:05pm

The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

eJIFCC

2012; 23(2): 55

The Laboratory's Role in Opioid Pain Medication Monitoring

Geza S. Bodor
Veterans Administration, Eastern Colorado Health Care System (VA ECHCS), Denver

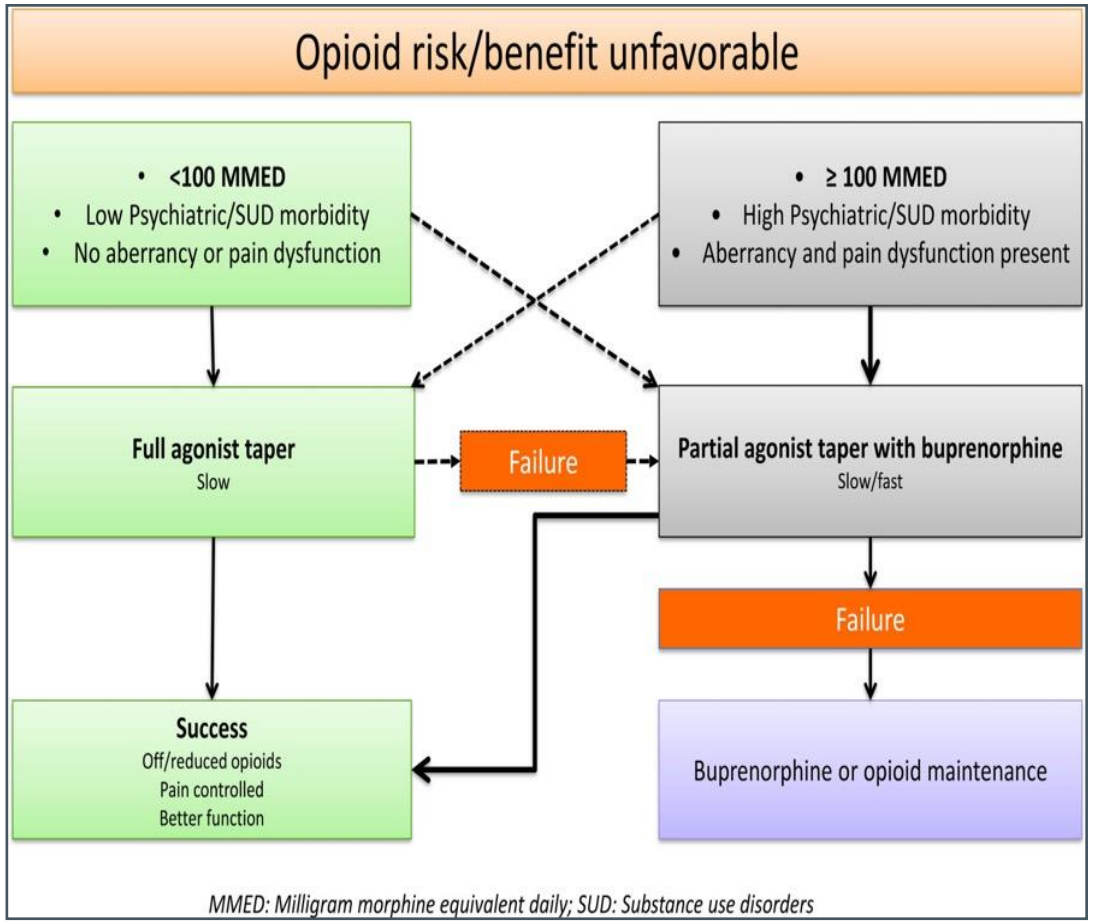
Table 1
Reported lowest and highest daily doses of opioid medications and lowest and highest blood concentrations as observed in chronic pain patients who were fully functional (modified from (8))

Opioid	Previously reported therapeutic range (ng/mL)	Previously reported toxic concentration (ng/mL)	n	Lowest - Highest dose (mg/day)	Lowest - Highest blood concentration (ng/mL)
Codeine	10 - 100	>200	1	120	480
Hydrocodone	8-32	>100	11	50 - 300	18 - 396
Hydromorphone	8-32	>100	11	20 - 540	9.4 - 230
Oxycodone	10 - 100	>200	15	15 - 2700	5 - 3077
Oxycodone (LA)	10 - 100	>200	33	40 - 960	10 - 650
Morphine	10-80	>200	10	100 - 1800	22 - 828
Morphine (LA)	10-80	>200	17	60 - 2000	16 - 2837
Meperidine	70 - 500	>1000	xx		
Normeperidine	50 -280	>8000	xx		
Fentanyl	1 - 3	>8	26	n/a (b)	1.2 - 9.5
Propoxyphene	100 - 400	>500	2	400 - 1300	227 - 240

(LA): denotes sustained release / long acting formulation
(b): all patients received fentanyl via sustained release transdermal or trabsmucosal patches
(xx): not reported in reference (8).

Adverse outcomes of opioid revision

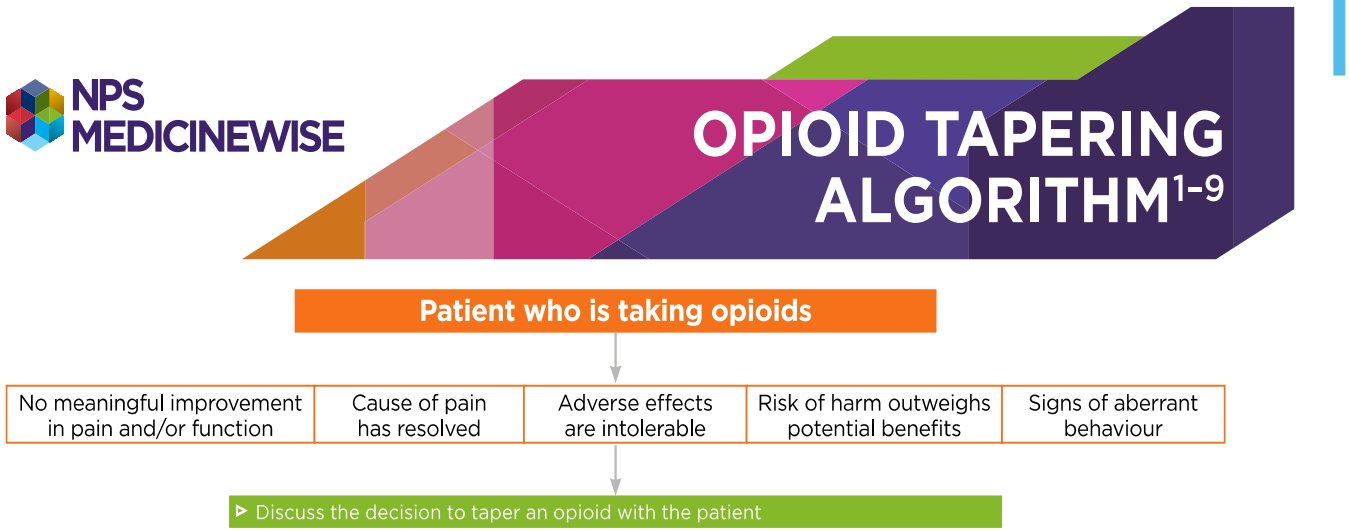
- Risks with opioid wean
  - acute: withdrawal, anxiety, agitation
  - chronic: anhedonia, hyperkatafeia
    - Manhapra A. *Subst Abus* 2018; 39: 152
    - Koob G. *Biol Psychiatry* 2020; 87: 44
  - subsequent ↑ mortality
    - overdose risk
    - undefined other death causes
      - James J. J *Gen Intern Med* 2019; 34: 2749
    - death by suicide or O/D increased > stopping opioids
    - greatest the longer the Rx, up to 7x ↑
    - first 3 months at risk time
      - Oliva E. *BMJ* 2020; 368: m283
  - social stigma
  - service provision issues
    - limited access to pain, addiction med
      - ? bed access for rotation
    - role for depot buprenorphine



Opioid tapering/safety

- Develop personalized management plan
  - re-consent/prescribing agreement
  - endocrine, sleep, Ca check

- TGA, NPS: consensus opinion re taper
  - engagement/MI
  - fast/slow taper
    - 10% dose ↓ per 2-4 weeks
  - specialist support re OUD
    - https://www.tga.gov.au/opioid-resources



- Low quality evidence for less/equivalent pain and improved function
  - RCT of MI/taper support strategy 43% vs 19% dose reduction
    - 18 weekly sessions, only 35 of 144 screened engaged
      - Sullivan M. *J Pain* 2017; 18: 308
  - range of approaches with opioid dose as secondary outcome: MDT pain management, buprenorphine
      - Frank J. *Ann Int Med* 2017; 167: 181
      - Fishbain D. *Pain Med* 2019; 20: 2179
  - case series only for ketamine, clonidine
    - buprenorphine: improved pain control, mood, for higher dose OMED
      - Chong j. *AJGP* 2020; 49: 339

Cannabis and opioids

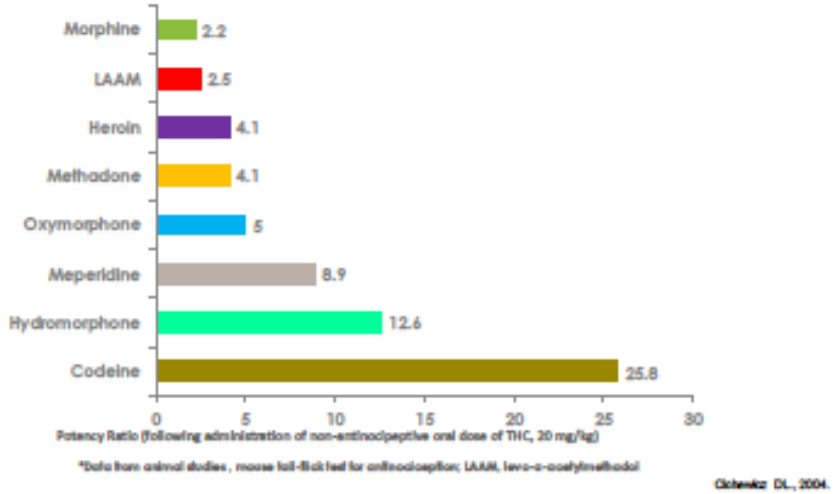
- Reduced deaths in US states with access reversed over time
  - Shover C. *PNAS* 2019; 116(26)
  - ? reduced opioid misuse
    - Wendelboe A. *JPCRR* 2019; 6: 268

- Synergy in animal studies
  - 17/19 studies +
    - 3.6x lower morphine effective dose
  - 1/9 clinical studies demonstrated reduction
    - Nielson S. *Neuropsychopharm* 2017; 42: 1752
  - codeine reduction greatest
    - ? anti-neuro-inflammatory effect

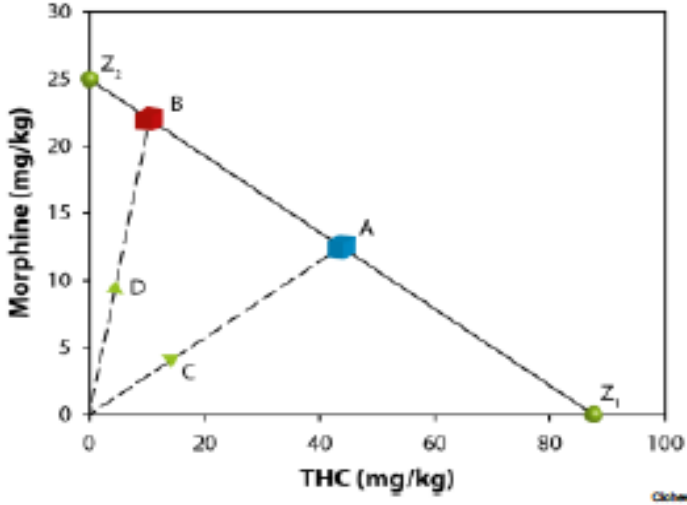
- Systematic review: 9 studies, reduced opioids in CNCP
  - high risk of bias, no causal inference
    - Okusanya O. *Syst Rev* 2020; 9: 167

- POINT study of opioids in chronic pain
  - 1/3rd used cannabis: no evidence lowed opioid
    - higher pain interference, anxiety
      - Campbell G. *Lancet Pub Health* 2018; 3: e341

Opioid Sparing Effects of THC



Cannabinoid-Opioid Synergism



Comments/questions

- Waiting in pain
  - >6 mth wait associated with symptom progression, function ↓
  - Median wait time for pain clinic 60 days
    - large variability, rural > city, public >> private
    - telehealth availability improving
      - Hogg M. *Pain Medicine* 2020; doi 10.1093
- National Facility Directory
  - https://www.painaustralia.org.au/getting-help/pain-directory

Brain man videos
https://www.youtube.com/watch?v=5KrUL8tOaQs
Tame the beast video
https://www.tamethebeast.org
Pain toolkit
http://www.paintoolkit.org