Perspectives on pain: mechanisms and management

Malcolm Hogg

Royal Melbourne Hospital

painaustralia™
working to prevent and manage pain

- EAG, *Safescript*, Victorian Dept. Health and Human Services
- Advisory Committee, Drugs of Dependence, Victorian Dept. Health and Human Services
- Advisory and educational activity for *mundipharma* and *seqiris*

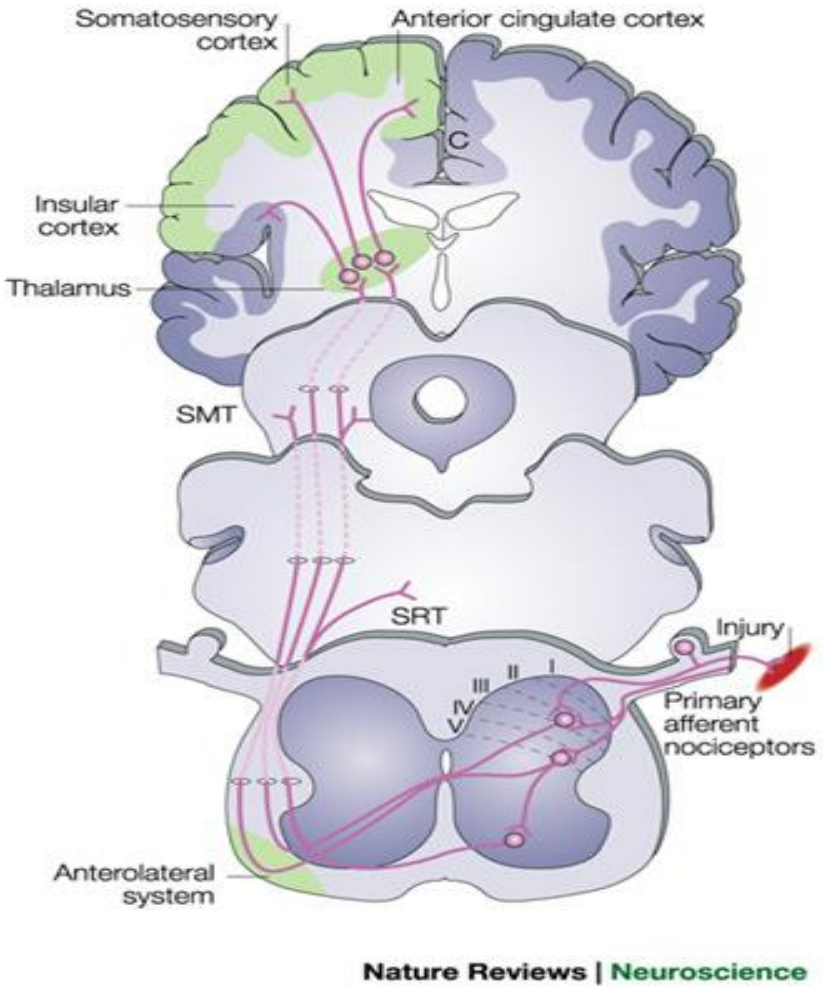
Pain pathways

- Nociception
  - respond to thermal, chemical and mechanical stimuli
  - somatic
    - deep, superficial
  - visceral
    - include vagal afferents

- Multiple brain sites activated
  - sensory-discriminative: *SS1, SS2*,
  - affective-motivational: *ACC, Insular*
  - cognitive-evaluative: *PFC*

- Pain is a multidimensional experience

Fields H. *Nature Reviews Neuroscience* 5, 565-575 (2004)



Clinical pain

- Sensitisation
  - peripheral: inflammatory mediators, nerve changes
    - primary hyperalgesia
  - spinal cord sensitisation: up-regulation (NMDA, NOS, PG's, glia activation)
    - secondary hyperalgesia
  - supraspinal sensitisation: focus, synaptic change/re-organisation
    - ? tertiary hyperalgesia

- Behavoural change
  - sleep, mood, fear-avoidance, hyper-vigilance, social interactions

- Descending modulation
  - inhibition (e.g. CPM)
  - facilitation

- Catastrophising associated with ↑ TS, ↓ DINC
    - Yarnitsky D. *Pain* 2012; 153: 1193

Consider a persons nociceptive spectrum in assessing current pain

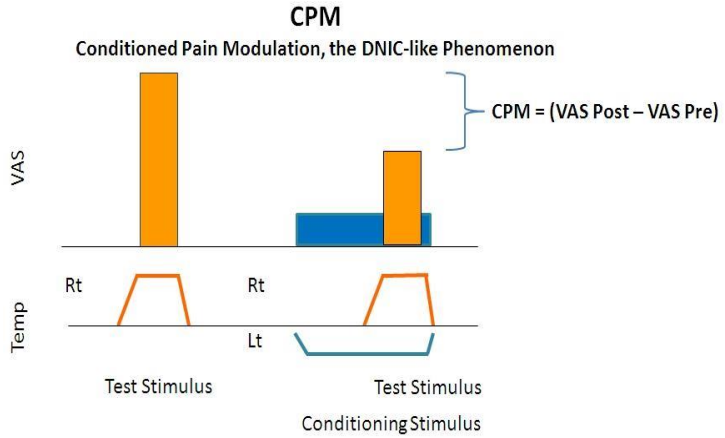
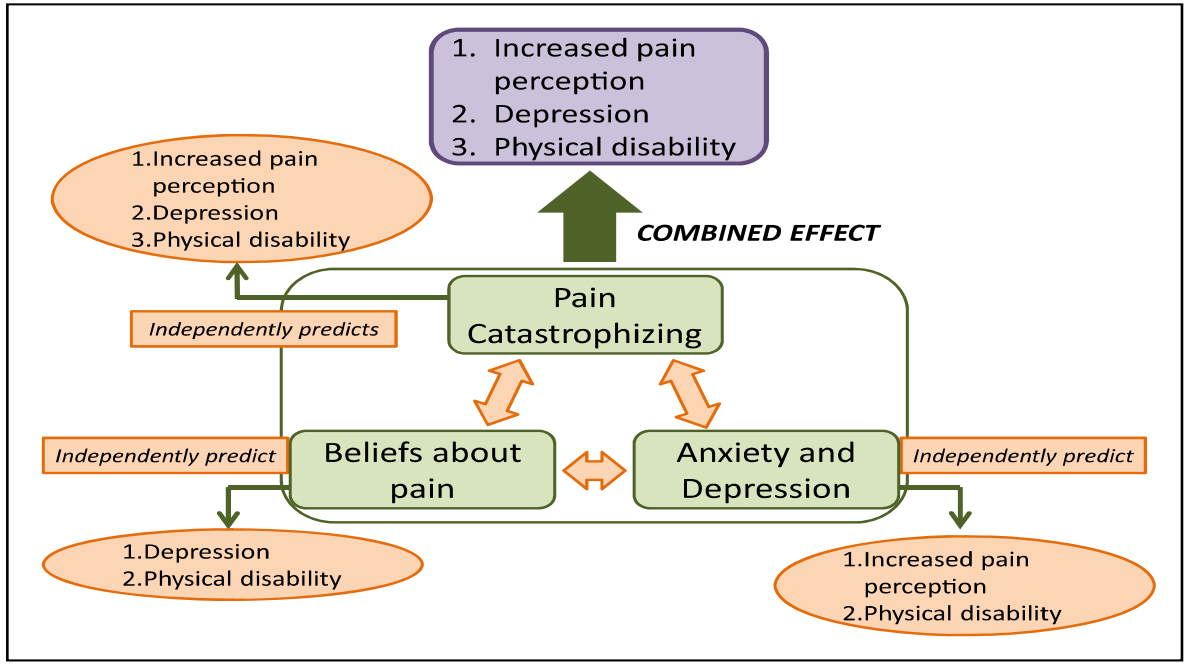


Figure 1. An Example of a Conditioned Pain Modulation (CPM) Test Protocol.

Factors associated with pain severity and persistence

- Acute pain severity biggest predictor of chronic pain following acute injury
  - surgical factors, post-operative care, rehabilitation
    - ? neurogenic inflammation, ? reduced descending inhibition
  - nerve injury: commonly hypo-aesthesia initially

- Psycho-social aspects important, although vary over time/trajectory
  - genetic
    - including anxiety, catastrophising
  - adverse childhood experiences
    - Scott K. *Arch Gen Psych* 2011; 68: 838
    - plus parental style
      - Anno K. *BMC Psychiatry* 2015; 15: 181
  - past pain and pain cognitions
    - catastrophising post pain onset
      - Khan R. *Am J Surgery* 2011; 201: 122
      - Theunissen M. *Clin J Pain* 2012; 28: 819
  - compensation/solicitous systems

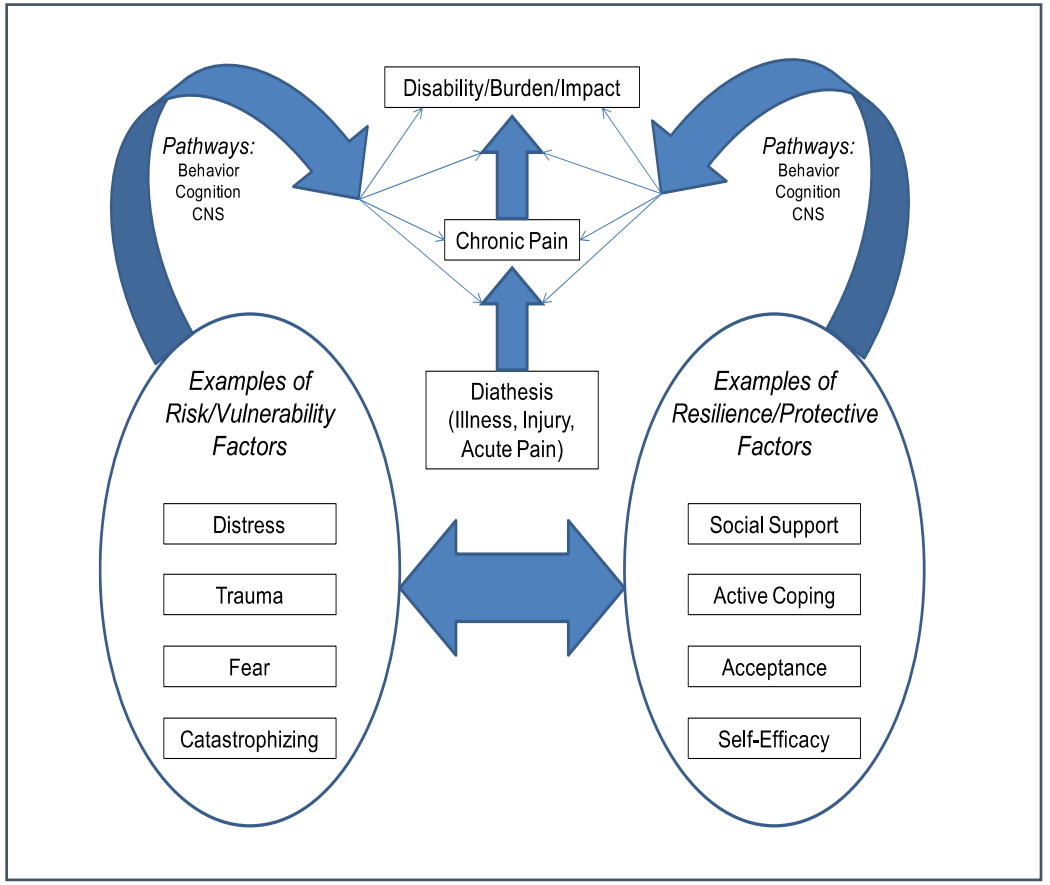


Fear-Avoidance Model and beyond

- F-A model for “chronic pain” development
  - pain cognitions promote disuse
    - pain catastrophising, low self-efficacy
  - disability, distress develops
  - social reinforcement

- Alternative approach to transition
  - cumulative risk/protective factors
    - + avoidance/endurance model
    - consider perceived injustice

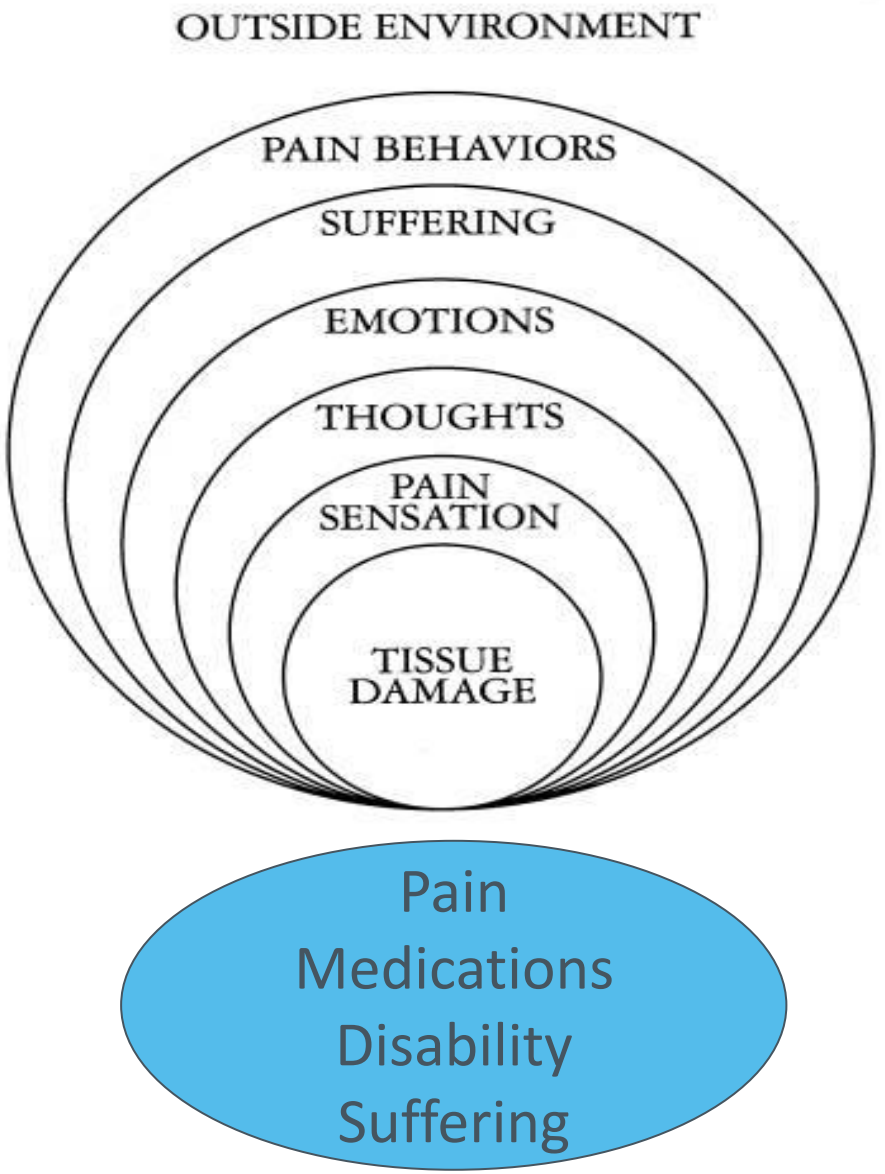
- Early intervention
  - education, balanced analgesia
    - reduce sensitisation
  - cognitive and social management



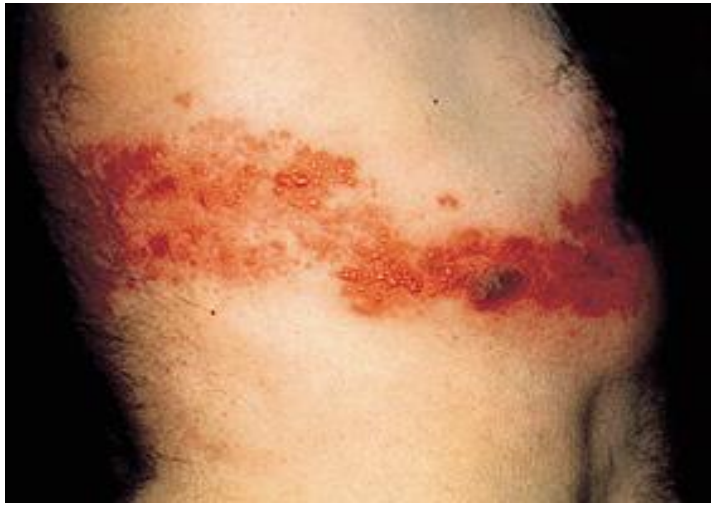
Edwards R. *J Pain* 2016; 17: S2, T70

Effects of persistent/chronic pain

- Bio
  - hyperalgesia
  - concentration/cognitive
  - sleep disturbance
  - physical de-conditioning
- Psychological
  - mood disturbance
  - anxiety
  - health worries
- Social
  - decreased socialisation
  - carer stress
  - financial



Classifying pain



- Duration, mechanism, etiology, site

- **Nociceptive pain**
  - somatic vs visceral; e.g. inflammatory, degenerative, ca

- **Neuropathic pain**
  - damage or disease of somatosensory nervous system
    - injured nerve/CNS reacts abnormally to stimuli or discharge spontaneously
  - neurogenic pain: includes “transitory perturbation

- **Mixed**: neuropathic or neurogenic component in many chronic pain states

Table II
Common sensory abnormalities in neuropathic pain

Quantitative	Qualitative	Spatial	Temporal
Hypoesthesia	Allodynia	Dyslocalization	Aftersensation
Hyperesthesia	Dysesthesia	Radiation	Abnormal latency
Hypoalgesia	Paresthesia		
Hyperalgesia			

Do we need a third mechanistic descriptor for chronic pain states?

Eva Kosek[a,*], Milton Cohen[b], Ralf Baron[c], Gerald F. Gebhart[d], Juan-Antonio Mico[e], Andrew S.C. Rice[f], Winfried Rief[g], A. Kathleen Sluka[h]

Kosek E. *Pain* 2016; 157: 1382

- Other term required for clinical description of pain sensitisation
  - clinical and psychophysical evidence of altered nociception
    - ***nociplastic*: change in function** (IASP endorsed 2017)
    - *algopathic*: pathologic perception of pain
    - *nocipathic*: pathological nociception
  - imprecise, causality questioned
    - Grannan LP. *Pain* 2017; 158: 179
  - ? centralisation
  - ? neurogenic inflammation
  - ? psycho-pathology

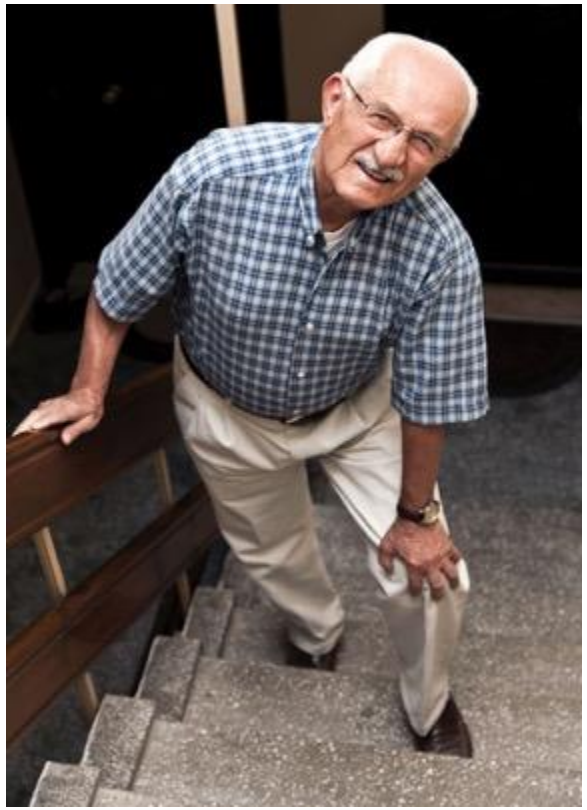
In reality: complex, combination, inferred but often unknown mechanisms

Pain changes with ageing

- Pain system changes
  - increased threshold to activate pain system
  - heightened pain report when intense, prolonged stimulation
    - Riley J. *J Pain* 2014; 15: 272
  - reduced CPM (DNIC)
    - Marouf R. *Pain* 2014; 155: 494

- Accumulate pain experiences
  - surgeries, falls/fractures
  - musculoskeletal system pain ↑
    - but headaches and bowel pain ↓
  - more sensitive to medication side effects
  - increased health related anxiety

- These changes likely contribute to pain presentation in older person
  - **slower to report pain, may have higher pain experience, slower to recover**



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
    - Edlund M. *Clin J Pain* 2010; 26(1); 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

- 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

Pain Assessment

- **Who is the person?**
  - age, medical conditions/medications, presenting pathology
  - psychosocial status: depression, anxiety, pain appraisals

    yellow flags: *psycho-social factors associated with increased risk of disability, distress*

- **What are the potential mechanisms?**
  - nociceptive, neuropathic, "sensitisation" (nociplastic)
  - pain site, character, radiation, ↑ factors

    red flags: *clinical indicators of possible serious medical conditions (ischaemia, bleed, etc)*

- **What is the impact?**
  - biological, psychological, social

    functional state: *ultimate goal is to restore/maximise function; multidimensional measurement required*

- **What is the expected/actual journey?**
  - tissue recovery/injury
  - social response/interactions

    blue/black flags*: solicitous systems, including health care response*

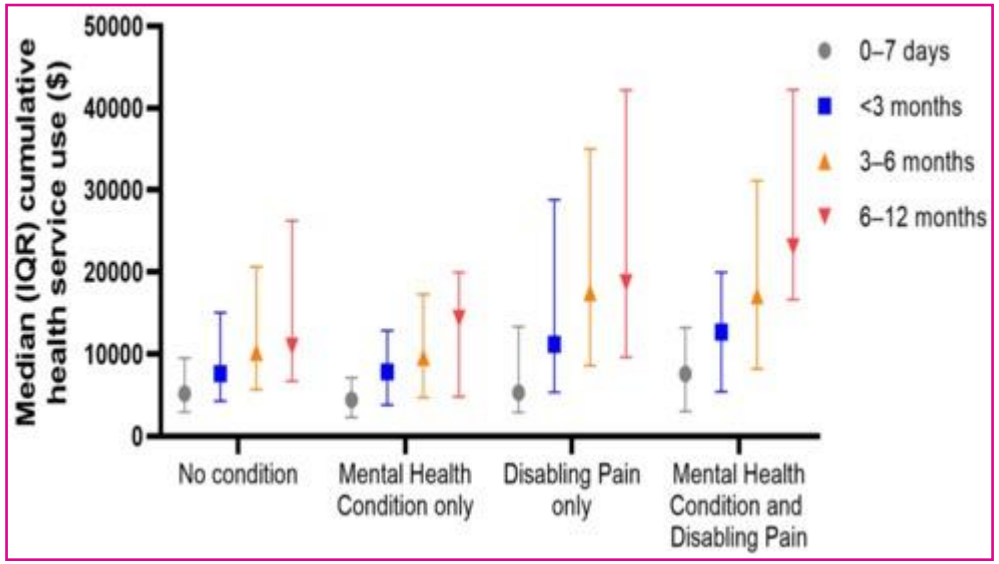
pain score or comfort level?

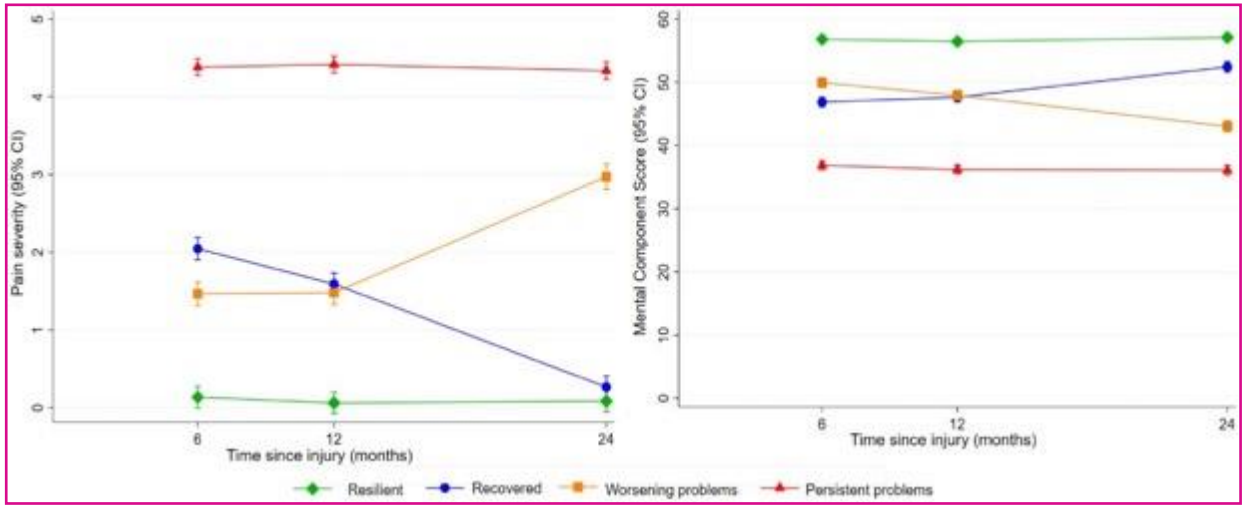
Trauma recovery

- Associated with mental health complaints at 12 mths
  - 1/3rd disabling pain, mental health condition; 1/4th both
    - Nguyen T. *Int J Environ Res Public Health* 2020; 17: 7320

- Pain and disability reduce over 12-18 mth > major trauma
  - rates ↑ after 24 mths; 50% pain/discomfort reported at 3 yrs
  - high impact at 3 yrs: consider it a chronic disorder
    - Gabbe BJ. *PLoS Med* 2017; 14: e1002322

- Different trajectories described re pain, mental health
  - Resilient: early recovery
  - Recovered
  - Worsening: post 12 mths
  - Persistent: high distress from start
    - Giummarra M. *Pain Medicine* 2020; 21: 291
  - RRR 2.6-4.2 for compensable





An approach to pain management

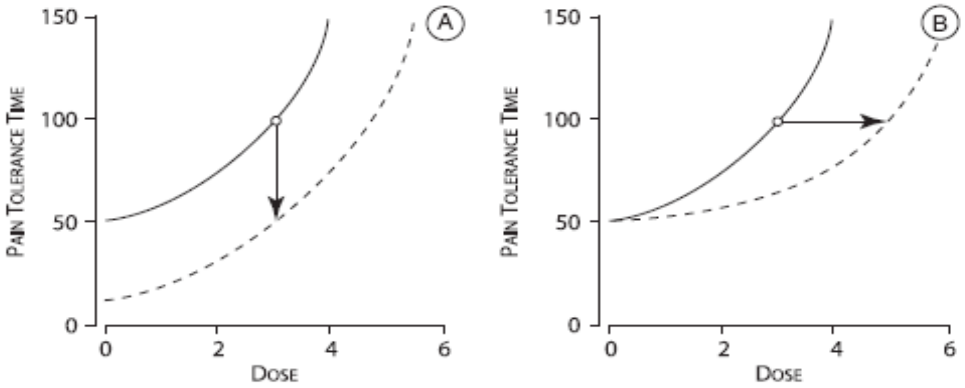
- **Manage from a socio-psycho-biological perspective**

- **Patient education**
  - include family, medical team ➔ for perception

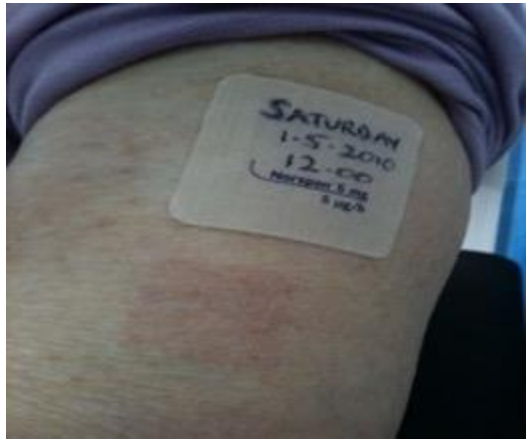
- **Pharmacological**
  - opioids, clonidine, LA's ➔for nociceptive pain
  - NSAIDS, biologicals, anti-oxidants ➔ for inflammation
  - blocks/LA's, ketamine, Mg, clonidine, TCAD/SNRI, GBP ➔ for neuropathic, sensitisation
    - ? cannabinoids → ? perception; ? anti-inflammatory
- Non-pharmacological ➔for nociceptive and sensitisation components
  - neuromodulation
  - physical rehabilitation, re-exposure, desensitisation
  - psychology assessment/management
    - education, cognitive re-appraisals, acceptance, mindfulness
  - social
    - judicious support, lessen solicitation, legal (?early apology)

Opioid philosophy

- Opioids are anti-nociceptive
  - for nociceptive pain
    - Meske DS. *J Pain Res* 2018; 11: 923
  - reasons for failure of opioid response
    - OIHA
      - acute-subacute-chronic, including neuro-inflammatory change
    - 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

Comments/questions

- Perceived injustice (via IEQ)
  - severity and irrepairability of loss
  - blame
  - sense of loss

  - can influence experimental pain intensity
    - McParland J. *Eur J Pain* 2016; 20: 1392
  - ass. with poor outcomes in rehabilitation, RTW
    - Scott W. *Disabil Rehabil* 2016; 38: 2365
  - ↑ 3-6 mths in those not recovering with neck pain
    - Ferrari R. *Clin Rheum* 2015; 34: 975

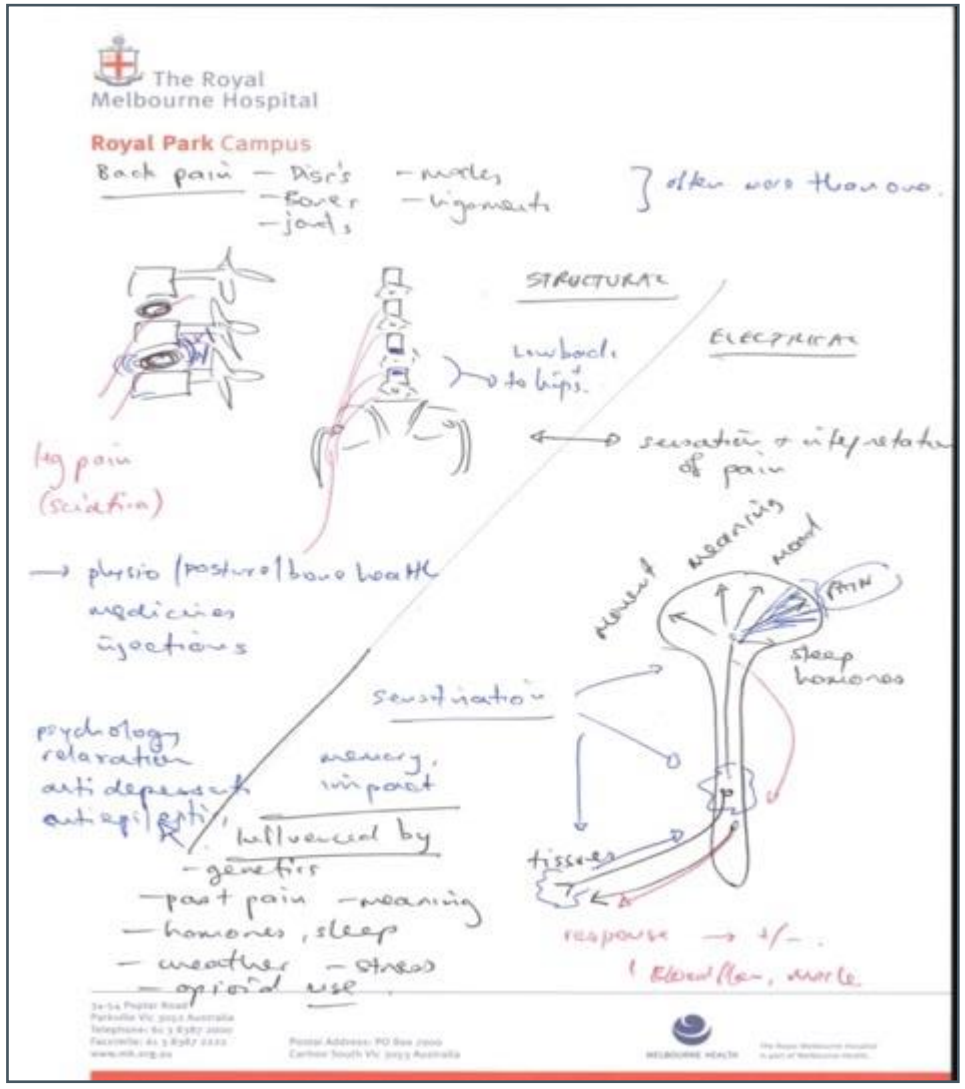
Fifteen Years of Explaining Pain: The Past, Present, and Future

G. Lorimer Moseley*,† and David S. Butler*,‡

- Education psychology
  - conceptual change: pain is dynamic
  - pain as a perceived need to protect (rather than damage)
  - doesn't deny peripheral nociceptor activity
  - not behavioural or educational therapy per se
    - rather cognitive modulation

- Effective
  - improves knowledge, decreases catastrophising
  - short term reduction in pain, disability
  - assists (should integrate) with MDT rehab
    - *Journal of Pain* 2015; 16(9): 807-13

- Patient expectations influences outcome of pain rehab
  - "pre-habilitation" should include education, consent
    - Eklund M. *Eur J Pain* 2019; 23: 1378



Basic Analgesic Plan

- Paracetamol: anti-hyperalgesic
- Anti-inflammatories
  - celecoxib, meloxicam, naproxen, ibuprofen: issues with renal, GIT, CVS disease
  - steroids
  - adjuvants: curcumin/turmeric, low dose naltrexone, melatonin (anti-neuro-inflammatory)
- Opioids
  - morphine, oxycodone, fentanyl, hydromorphone, methadone

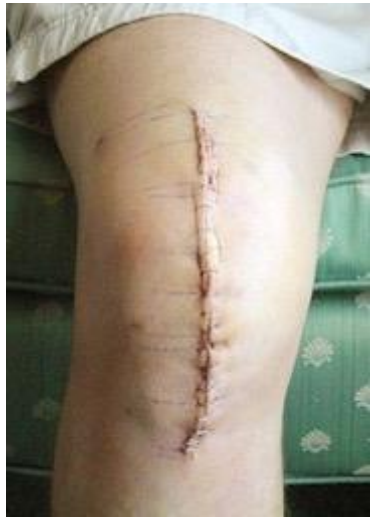
- Neuromodulators: anti-hyperalgesics, anti-neuropathic pain
  - clonidine 50-100 mcgm tds; anxiolytic, analgesic, antihypertensive
  - TCAD's: nortriptyline 1—50 mg nocte
  - SNRI: duloxetine, venlafaxine
  - gabapentinoids: pregabalin, gabapentin: weight gain, oedema, suicidality
  - atypical anti-epileptics: valproate 200 mg tds+, topiramate, carbamazepine
  - ketamine: iv vs po, low dose (0.1-0.3 mg/kg/hr; for depression 0.5 mg/kg over 40 min, 2x week, 4 weeks)

Atypical opioids: tapentadol, buprenorphine

- Benefits in
  - efficacy: via synergistic modes of action
    - better match to mechanism of pain post acute nociception
    - suitable/effective for acute pain, less GI effects
      - Wang X. *Clin J Pain* 2020; 36: 399
    - model suggests 60% tapentadol analgesia related to NRI
      - Raffa R. Adv Ther 2018; 35: 1471
  - safety: reduced MOR adverse effects
    - respiratory, GIT
    - immuno-suppression, HPA axis suppression
      - Davis M. *J Support Oncol* 2012; 10: 209
      - Stollenwerk A. *Adv Ther* 2017; Dec
- Clinical utility/experience
  - can co-prescribe with typical opioids
  - potential for opioid withdrawal with acute rotation
    - Raffa RB. *J Clin Pharm Therapeutics* 2014; 39: 577

Varied interpretations: acute

- Opioids post acute pain carry risk of dependence
  - 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% in chronic pain on opioid cohort
  - repeat prescriptions are associated with higher rates of SUD at 3 yrs
    - ? marker of risk or is continued prescribing causing increased risk
    - young male, depression, tobacco use, high pain, hydromorphone, past addiction
      - Brat G. *BMJ* 2018; 360: j5790
      - Fishbain D. *Pain Med* 2008; 9: 444
  - provider and system factors
    - Cragg A. *Systematic Reviews* 2017; 6: 265
- Analgesia post acute pain should be time limited
  - association with dose, duration initial prescribing and use at 1 yr
    - Shah, A. *MMWR* 2017; 66(10)
  - high rates of persistent pain post orthopaedic trauma: 65% at 3 mths, 1/3rd on opioids
    - Edgley C. *BJA* 2019; 123: 350



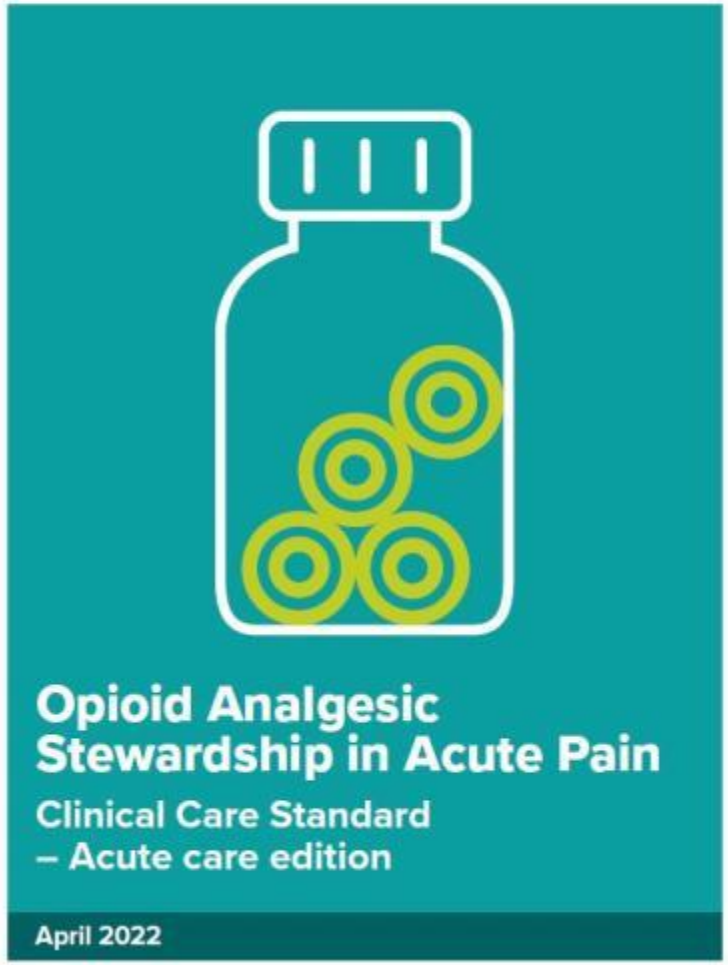
Clinical Care Standards

- Focus on opioids in acute care
  - previous submission re pain in hospital standards (2014)
    - Governance: pain services, policies
    - Medication safety: high risk medicines
    - Communicating for safety

- Measures to be considered
  - documentation of benefit/risk assessment, pain assessment
  - naloxone use, prescribing processes, discharge plans

- Government, TGA encouraged re opioids
  - discourage SR opioids, aim <7 days re discharge

- Limited re referral pathway for those at risk of persistent pain
  - “transitional services”



Opioid stewardship program: what's viable

- Education
  - Consumers of risks, dispensing/disposal
  - Intern/HMO/surgeons/physicians/ED
- Perioperative care
  - ERAS pathways, clinical standards/recommendations
  - *Safescript* integration, specifically for discharge scripts
- GP communication
  - Planned follow-up appointments
  - Medication outreach programs
- Pathways for early access
  - Primary team
  - Transitional pain services
    - pre/post op, for those at risk, incorporating education, "pre-habilitation"

Perioperative opioid stewardship

"Judicious use opioids to treat surgical pain and optimise outcomes"

PAC → DOSA → OP → postop → D/C → follow-up

Peri-operative plans
Wean opioids if possible preop
Multimodal analgesia throughout
(NSAID, GBP, regional/iv-lignocaine, ketamine)
Pharmacist led follow-up within 7 days

O-NET + modifiers

Uncontrolled psychiatric conditions
Behavioral tendencies: catastrophizing, anxiety
Hx of Substance Use Disorder
High risk surgery eg thoracotomy, spine

S Hyland et al. *Healthcare* 2021; 9: 333

Varied interpretations: chronic

- Opioids have limited role in chronic non-cancer pain
  - concern re risks of harm short, longer term
  - evidence based on short term studies, often unimodal
    - Mincha E. *Pain Med* 2014; 15: 79
  - no evidence benefit >1 yr
    - Chou R. *Ann Int Med* 2015; 162: 276
  - Faculty Pain Medicine statement re role, trial, taper
    - PM01 2015, PS01 2020

- TGA/PBS reforms 2020
  - not indicated in CNCP, “exceptional circumstances”
    - new PBS codes, strict re fentanyl transdermal, yet state permits relaxed
  - https://www.tga.gov.au/prescription-opioids-information-health-professionals

Opioid trials are not all negative

PAIN IN OLDER PERSONS
IASP Special Interest Group

- Rehabilitation units within 7 days of lower limb orthopaedic surgery (n=249)
  - interdisciplinary pain protocol with opioid (oxycodone) protocol vs control units
  - higher OMED (24 vs 17 mg), better walk times, similar side effects after 7 days acute rehab
  - less mod-severe pain (4 vs 15%), pain interference (7 vs 14%) and analgesia at (35 vs 51%) at 6 months
    - Morrison RS. *J Amer Geriat Soc* 2009; 57: 1-10

- RCT opioid alone vs multimodal pharmacotherapy for chronic MSK pain
  - improved pain score, function compared to baseline in both groups
    - trajectory over time slightly different
  - opioid alone (not ideal) comparable to multimodal strategy (P/NSAID/GBP +/- Tramadol)
    - less anxiety in opioid alone group
    - ? targeting mechanisms: nociceptive vs sensitisation
      - Krebs E. *JAMA* 2018; 319(9); 872-882

Table 2. Patient-Reported Primary and Secondary Outcomes Among Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain Randomized to Opioid vs Nonopioid Medication

Outcome	Opioid Group, Mean (SD) (n = 119)	Nonopioid Group, Mean (SD) (n = 119)
Pain-Related Function (Primary Outcome)		
BPI Interference scale (range, 0-10; higher score = worse)[c]		
Baseline	5.4 (1.8)	5.5 (2.0)
3 mo	3.7 (2.1)	3.7 (2.2)
6 mo	3.4 (2.1)	3.6 (2.4)
9 mo	3.6 (2.2)	3.3 (2.4)
12 mo	3.4 (2.5)	3.3 (2.6)
Pain Intensity (Secondary Outcome)		
BPI severity scale (range, 0-10; higher score = worse)[d]		
Baseline	5.4 (1.5)	5.4 (1.2)
3 mo	4.3 (1.8)	4.0 (1.7)
6 mo	4.1 (1.8)	4.1 (1.9)
9 mo	4.2 (1.7)	3.6 (1.7)
12 mo	4.0 (2.0)	3.5 (1.9)

ACI NSW Agency for Clinical Innovation

Pain Management Programs – Which Patient for Which Program?

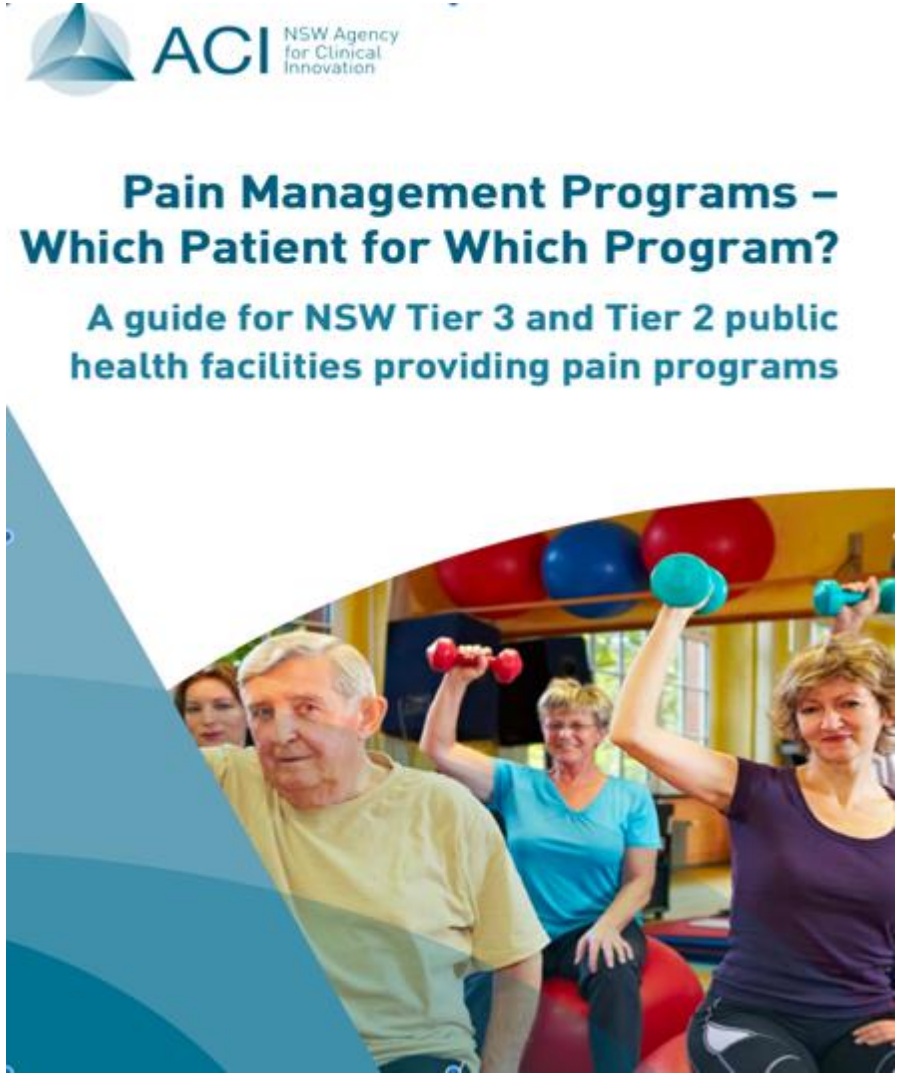
- Interdisciplinary pain management programs
  - "ready-ness" to change: pain management rather than pain reduction
  - identify barriers
    - pain cognitions
    - solicitous spouse/compensation/legal/health systems

- Goals include cognitive restructure, function, less HCU
  - education: 1-6 hrs
  - low intensity: 6-24 hrs
  - medium intensity: 24-60 hrs
  - high intensity: 60-120 hrs

- Community delivered allied health programs reduce wait times
  - Davies S. *Pain Med* 2011; 12: 59

Multi(inter)-disciplinary Pain Management programs

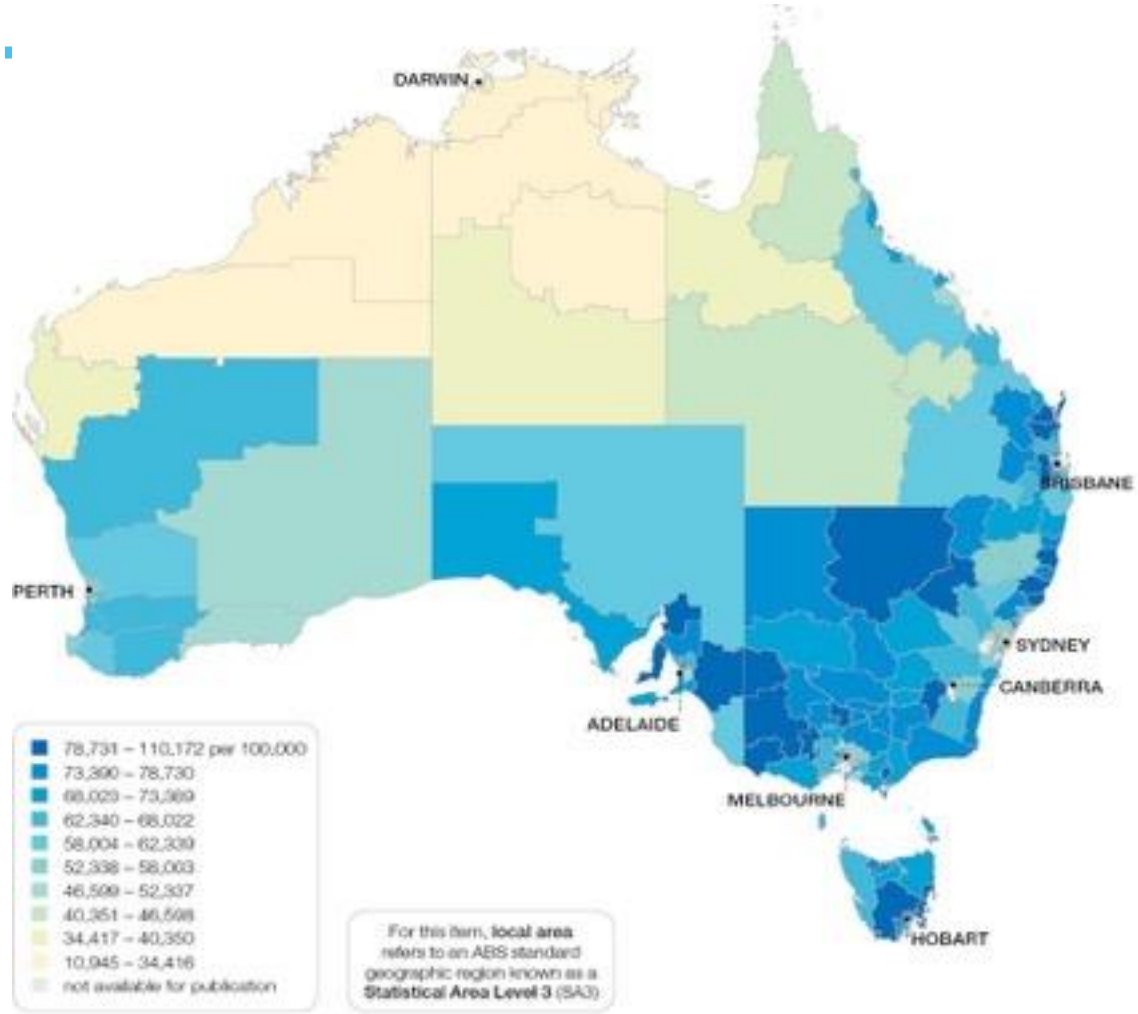
- Group vs Individual
  - co-ordinated program with PT/CP/OT/medical +/- SW, RTW
  - directed to self management of pain: moderate effect size
    - Du S. *Patient Educ Couns* 2017; 100: 37
- Themes
  - graded exposure (>graded activity)
    - Lopez-de-Uralde-Villanueva I. *Pain Med* 2016; 17: 172
  - pacing: tackle boom-bust cycling
  - cognitive restructure
    - challenge catastrophic beliefs, increase self-efficacy
  - target solicitous systems
- Mindfullness: acceptance-commitment therapy
  - Meditators: cortical control
  - Yoga
    - Cramer H. *Clin J Pain* 2013; 29: 450
  - Tai Chi: motor planning activation



Questions/comments

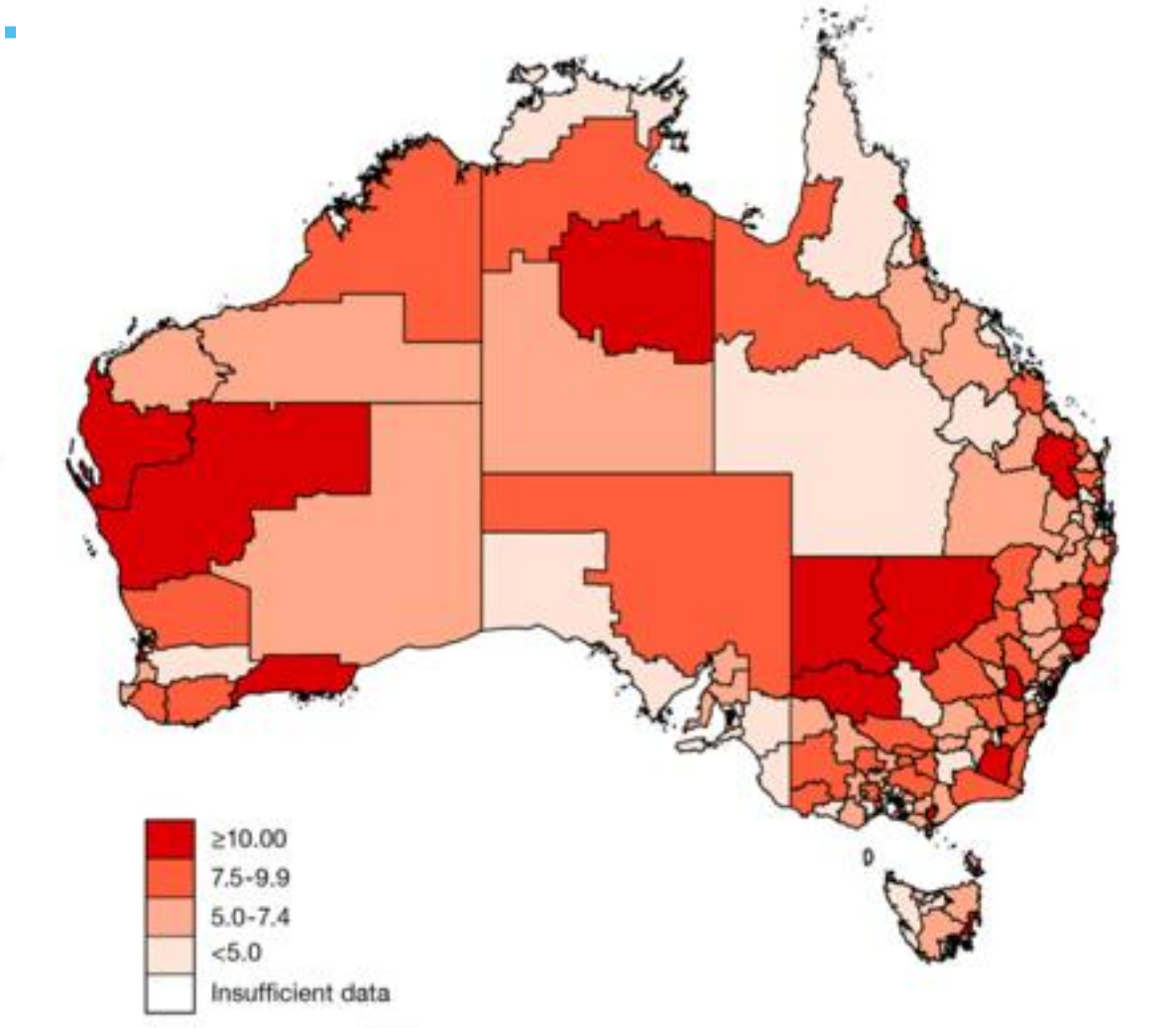
- Chronic LBP in ex elite athletes
  - rowers > skiers > control > orienterers
  - relationship to training load
    - Foss I. *Am J Sports Med* 2012; 40: 2610

- Operating related MSK injury common
  - female > male
  - rate highest in general surgery
    - Tran M. *Plast Reconstr Sug Glob Open* 2022; 10: e4142



Number of PBS prescription of opioid per 100,000

Australian Atlas of Healthcare Variation 2015



Unintentional drug induced death 2013-2017

Australia's Annual Overdose Report 2019, Penington Institute

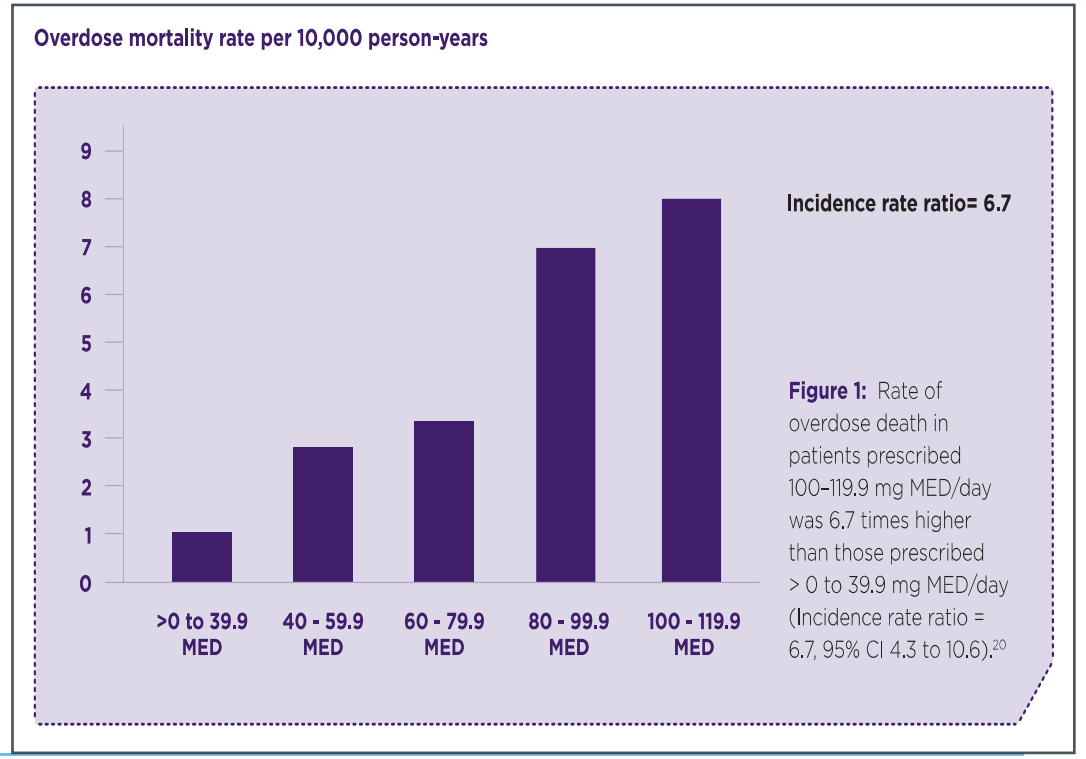
Opioid related deaths

- Prescription opioids associated with drug related deaths
  - often slow, hypoxia related: IN naloxone
    - https://www.health.gov.au/initiatives-and-programs/take-home-naloxone-pilot
- Consider 3 cohorts re risk assessment/management
  - Drug misuse/accidental OD
  - Inadvertent, mixed prescription toxicity (benzo, GBP)
  - Self harm, including mixed drug toxicity
    - 14-30%
- Methadone appears ↑ rate
  - ? past addiction cohort, ? specific toxicity
    - Pennington OD Report 2020
- Tapentadol
  - can cause respiratory depression, dose related but < equi-analgesia
    - van der Schrier *BJA* 2017; 119: 1169
  - low rates of death and misuse of tapentadol related to dispensing data
    - Nielsen S. *Addiction* 2020; 115: 1075

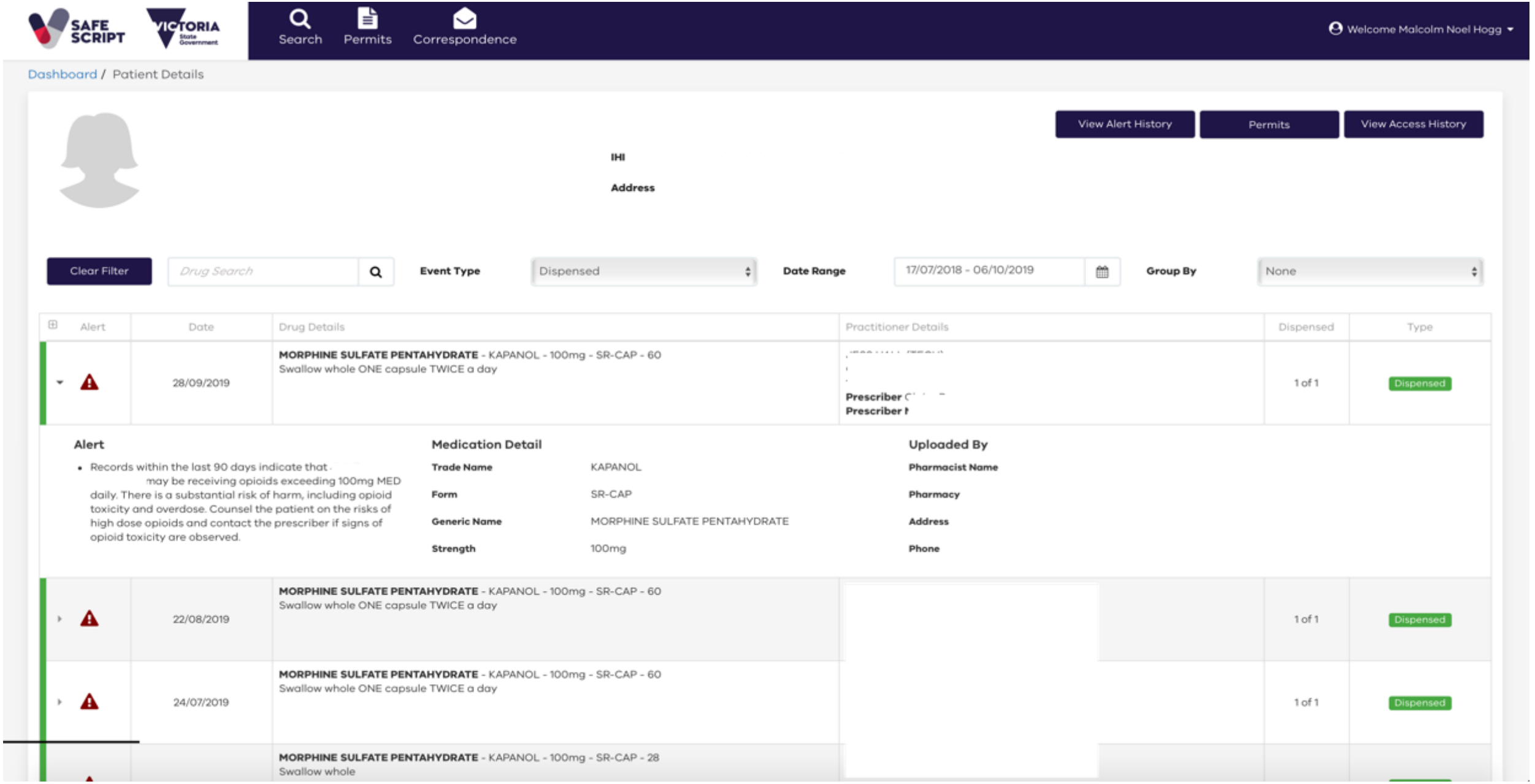
$$P_AO_2 = [F_iO_2 \times (P_B - P_{H_2O})] - \frac{P_aCO_2}{RQ}$$

$$P_AO_2 = 150 - \frac{P_aCO_2}{0.8}$$

If P_aCO_2 ↑, P_AO_2 must ↓



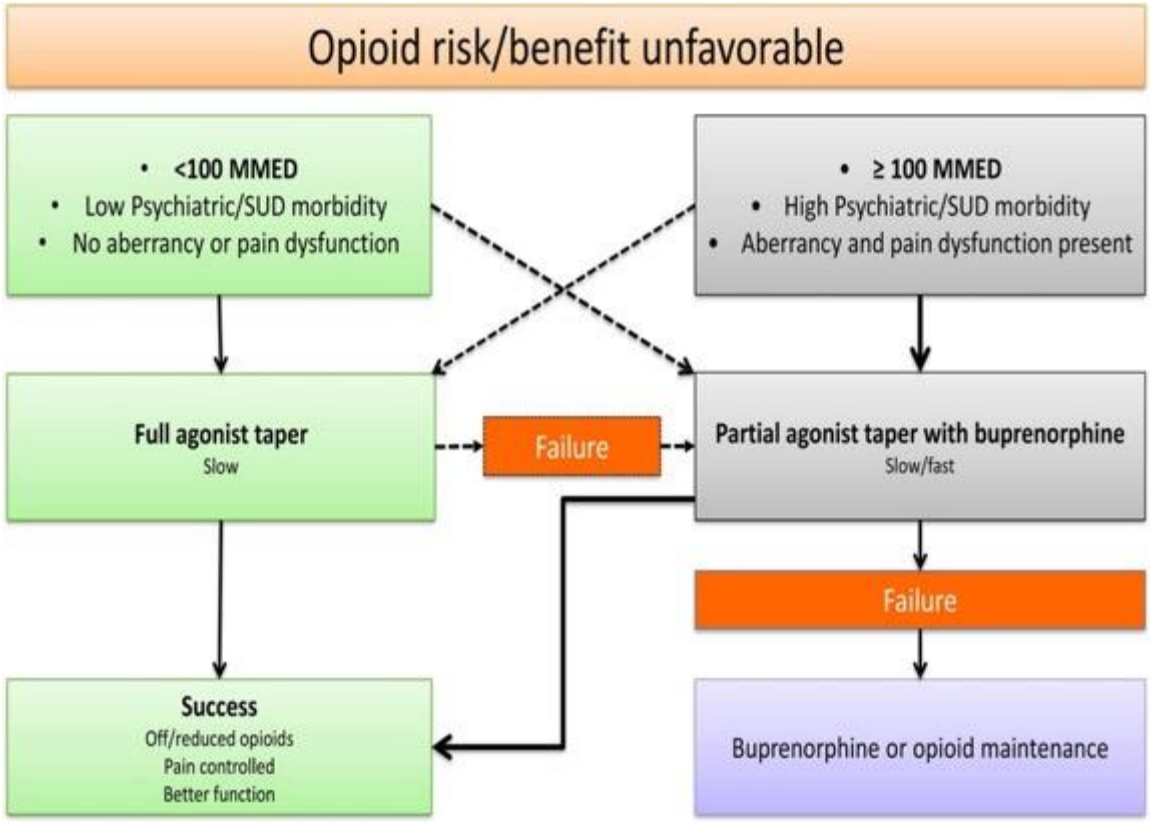
DHHS, Vic, 2019


SAFE SCRIPT
VICTORIA
State Government
Search
Permits
Correspondence
Welcome Malcolm Noel Hogg
Dashboard / Patient Details
View Alert History
Permits
View Access History
IHI
Address
Clear Filter
Drug Search
Event Type
Dispensed
Date Range
17/07/2018 - 06/10/2019
Group By
None
Alert
Date
Drug Details
Practitioner Details
Dispensed
Type
MORPHINE SULFATE PENTAHYDRATE - KAPANOL - 100mg - SR-CAP - 60
Swallow whole ONE capsule TWICE a day
28/09/2019
1 of 1
Dispensed
Prescriber
Alert
Records within the last 90 days indicate that
may be receiving opioids exceeding 100mg MED daily. There is a substantial risk of harm, including opioid toxicity and overdose. Counsel the patient on the risks of high dose opioids and contact the prescriber if signs of opioid toxicity are observed.
Medication Detail
Trade Name
KAPANOL
Form
SR-CAP
Generic Name
MORPHINE SULFATE PENTAHYDRATE
Strength
100mg
Uploaded By
Pharmacist Name
Pharmacy
Address
Phone
MORPHINE SULFATE PENTAHYDRATE - KAPANOL - 100mg - SR-CAP - 60
Swallow whole ONE capsule TWICE a day
22/08/2019
1 of 1
Dispensed
MORPHINE SULFATE PENTAHYDRATE - KAPANOL - 100mg - SR-CAP - 60
Swallow whole ONE capsule TWICE a day
24/07/2019
1 of 1
Dispensed
MORPHINE SULFATE PENTAHYDRATE - KAPANOL - 100mg - SR-CAP - 28
Swallow whole

Adverse outcomes of opioid revision

- Overdose death classification issues
  - any opioid implicated in with death listed yet combo's implicated
  - suicide listing challenged
    - 16% ABS, 28% Vic data (+ 18% unknown)
    - 40-70% mental health condition
      - 15% with chronic pain
  - younger male drug dependent vs older female pain cohort
    - Dwyer J. *Turning Point* 2017

- Risk with opioid wean
  - acute: anxiety, agitation
  - chronic: anhedonia
    - Manhapra A. *Subst Abus* 2018; 39: 152
  - subsequent overdose risk
    - higher mortality rates in retrospective review following cessation
      - O/D rate higher, undefined other death causes
        - James J. J *Gen Intern Med* 2019
  - social stigma
  - service provision issues
    - role for depot buprenorphine



MMED: Milligram morphine equivalent daily; SUD: Substance use disorders

Safety strategies

- Active management approaches
  - rural access/support strategies
    - education/leadership
  - sleep study, dental, HPA review
  - permits, legal, family engagement
  - de-prescribing
    - ? ketamine, ?clonidine
      - Frank J. *Annals Int Med* 2017; 167: 181

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

- Dual/triple diagnosis management plans
  - psychiatry, addiction services poorly accessible to pain services
    - proposal for triple assessment process for DHHS identified patients

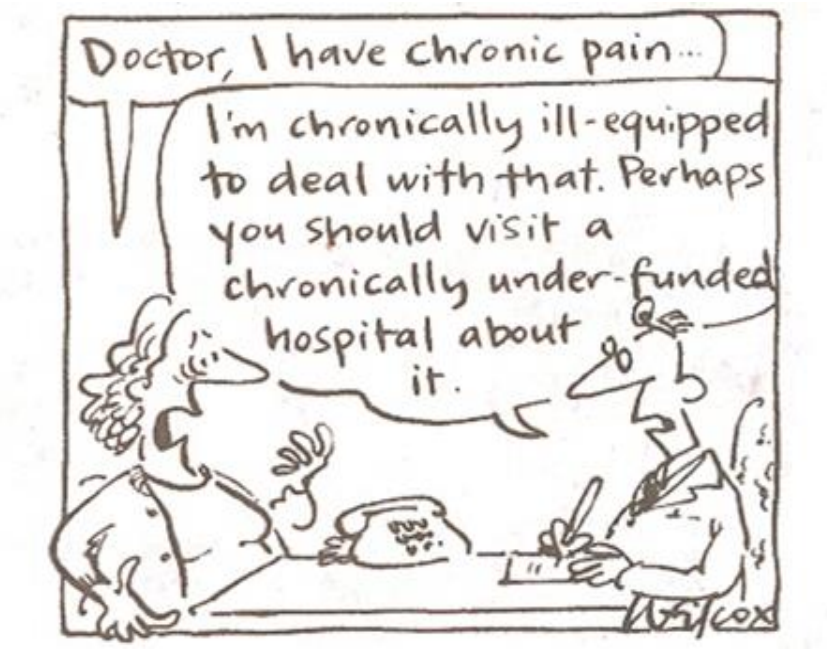
Victorian Opioid Management ECHO

home evaluations downloads zoom guide contact

https://echo.pabn.org.au/ St Vincent's Hospital

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

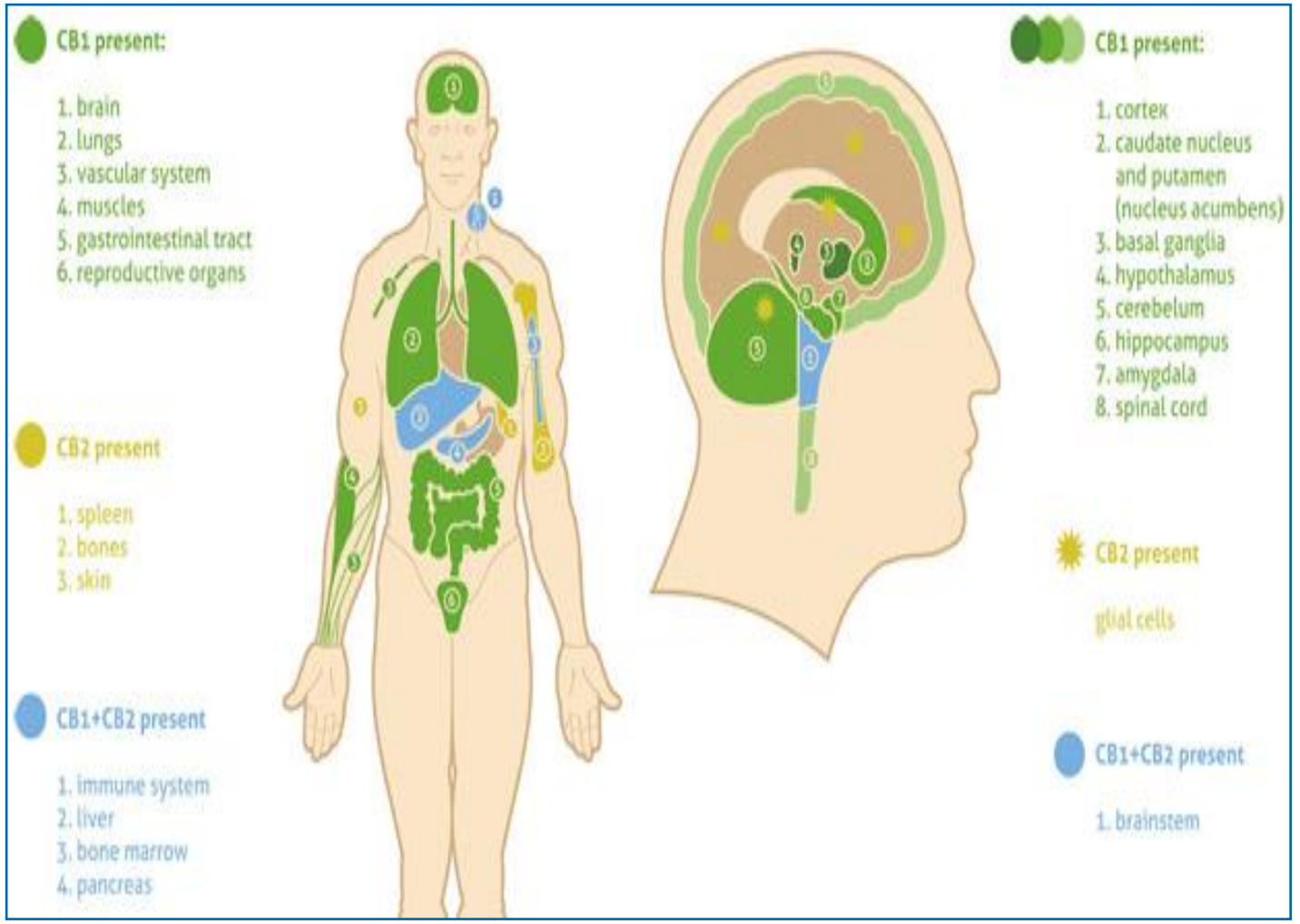


Brain man videos
https://www.youtube.com/watch?v=5KrUL8tOaQs
Tame the beast video
https://www.tamethebeast.org
Pain toolkit
http://www.paintoolkit.org

Endogenous endocannabinoid system

- Homeostatic regulatory system: CB1,2, TRVPV1
  - “relax, eat, sleep, forget, protect”
  - CB1 predominantly CNS, CB2 immune system, including glia

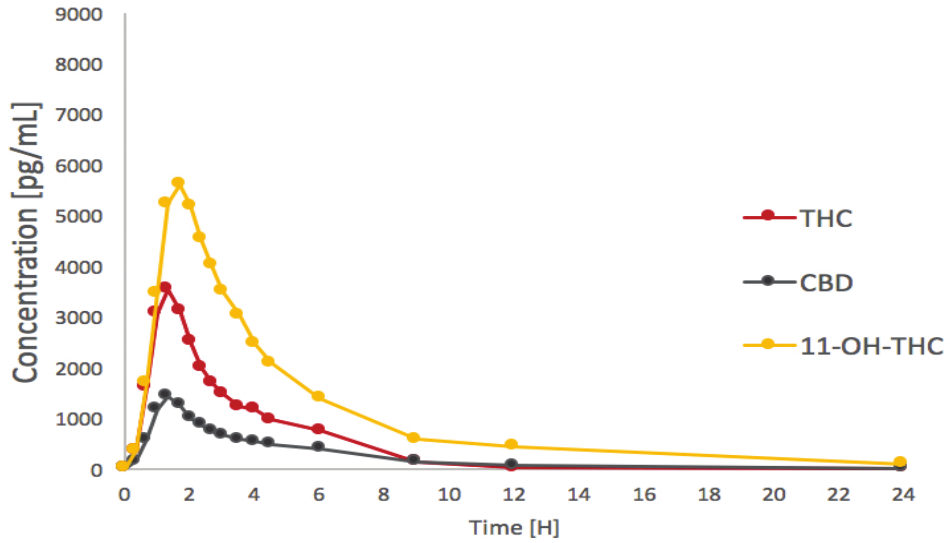
- May be deficient in functional pain states
  - Smith SC. *Neuroendocinology Letters* 2014; 35(3)



Pharmacology

- Phytocannabinoids
  - >100 strains cannabis: *sativa, indica main* species for MC
  - >100 cannabinoids, >300 other compounds, terpenes, flavinoids
- Variable: THC/CBD/CBN (cannabinol)/CBG (cannabigerol)
  - illicit 10-15% THC: 1 gm = 100-150 mg THC
  - lipophilic
- Administration/bioavailability varies
  - inhalation: rapid onset 6-10 mins, 2-4 hr duration, F= 10-50%
  - oral (oil, edibles) slow, 60-180 min onset, longer duration
    - F= 20-30% improved with food/fat
  - oromucosal, topical, PR

Figure 1: Mean Plasma Concentration-Time Plot—Tilray THC/CBD Oral Solution



Pharmacology

- Delta-9-Tetrahydrocannabinol
  - partial agonist CB1, CB2

  - psychomimetic
    - anxiety
  - analgesia
  - sedation
  - appetite/hyperemesis

  - dependency
  - withdrawal syndrome

- Cannabidiol
  - interacts with array of other receptors and enzymes

  - anti-inflammatory
  - anxiolytic
  - anti-epileptic
  - anti-psychotic
  - anti-emetic
  - ? analgesic/antihyperalgesic
    - Animal neuropathic pain

  - modifies THC toxicity

Henderson L. *AJGP* 2021; 50: 724

Pharmacology

- Hepatic metabolism (oxidation)
  - CYP 2C9, 2C19, 3A4; high faecal elimination
  - potential for drug interactions
    - inhibit > induce: eg clobazam, SNRI, anti-coag.
- Dosing: some tolerance to psych effects
  - average illicit use 0.5-1 gm/d
  - “herbal” (europe) 1-3 gm/d oral
  - oro-mucosal 10-30 mg/d each THC + CBD
  - oral oil 5-30 mg/d
  - >100 mg/d CBD common/tolerable when used alone
- CI: pregnancy, lactation, psychosis, cardiac
    - MacCallum CA. *Eur J Int Med 2018; 49: 12*

RESPONSIBLE EXECUTIVE	Medication Safety Executive Sponsor
PRIMARY AUTHOR	Head of Pain Management Services
IMPLEMENTATION STRATEGY	Publish in iPolicy
EVALUATION STRATEGY	DTC review, with database of use (HREC approved, QA project)
STANDARD/S (National, Mental Health, Aged Care, Disability Services)	Standard 1 Clinical Governance; Standard 4 Medication Safety
VERSION SUMMARY	Process for prescribing/accessing Medicinal Cannabis

EXECUTIVE SUMMARY

1. Medicinal Cannabis (MC), incorporating a range of active compounds in various forms, may be prescribed for a range of indications only following approval from the Office for Medicinal Cannabis, Federal Department of Health, and with relevant permit from Victorian Department of Health and Human Services.
2. Medicinal Cannabis (MC) products to be managed within Melbourne Health as Controlled Drugs (including CBD-only S4 products).
3. Due to harmful effects of smoking and potential for side smoke/pollution, administration via inhalation is not recommended or supported at Melbourne Health (includes Royal Melbourne Hospital (RMH), Peter MacCallum Cancer Centre (PMCC) and the Royal Women's Hospital (RWH).

1. **ASSOCIATED MELBOURNE HEALTH POLICY**

MH14 Precinct Medication Management Policy

Cannabis and the pain clinic

- USA/European experience
  - 50% for chronic pain
  - common in older persons
    - 1/3 >60yrs in dutch program
  - high CBD, low THC preferred: less anxiety
    - Brunt T. *J Clin Psychopharmacol* 2014; 34: 344

- 5 trials report older persons
  - may reduce behavioural, anorexia with dementia
  - adverse effects >placebo
  - lack of data in older persons
    - pain in particular
      - Van der Elsen G. *Ageing Research Reviews* 2014; 14: 56

- High patient report of use in multidisciplinary ca care
  - 15-25% regular, high exposure
  - 75% want information
    - Pergam S. *Cancer* 2017; 123:4488

Medical Cannabis

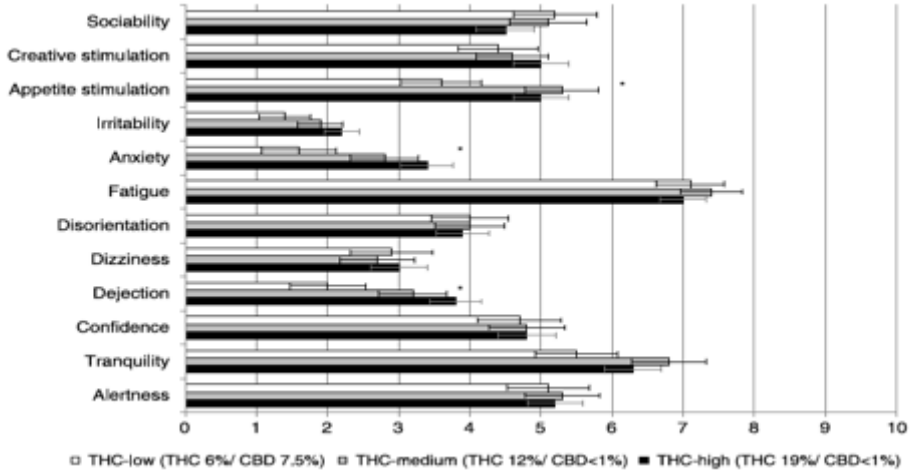
- Oils/oral preferred, combination THC/CBD
  - best for nerve related pain, anxiety, sleep
  - $, driving, but safe
    - e.g. THC 5/CBD20 mg/ml, 0.5-1 ml bd
- Evidence for effectiveness limited/poor
  - 30% pain benefit
  - NNT 24, NNH 6
    - Stockings E. *Pain* 2018; 159: 1932
- meta-analysis/systematic review
  - small effect, short duration studies
    - Johal H. *Clin Med Insights: Arth MSK* 2020; 13: 1
  - low quality, minimal benefit in pain, possible benefit to sleep
    - Fisher E. *Pain* may 2021
- "scientific evidence of efficacy is insufficient to justify use"
  - PM-10 2019
  - IASP 2020

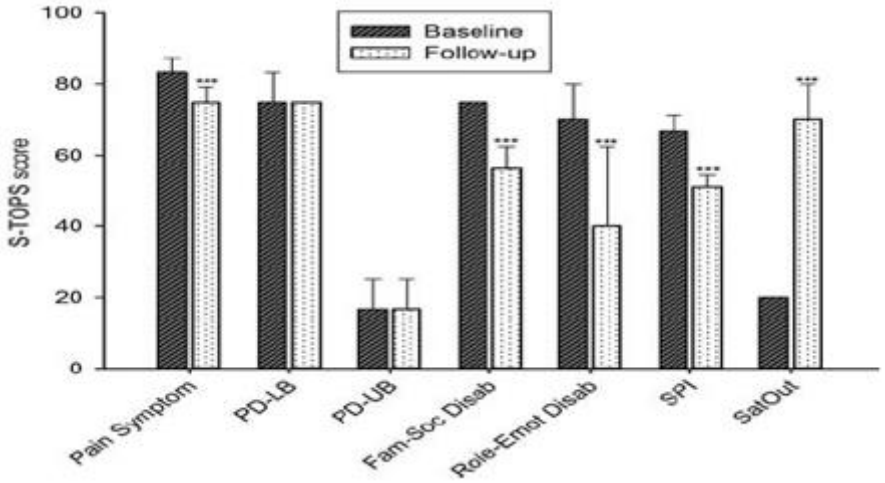
Table 4
Adverse events associated with cannabis-based medicines.

Side effect	Most common	Common	Rare
Drowsiness/fatigue	✓		
Dizziness	✓		
Dry mouth	✓		
Cough, phlegm, bronchitis (Smoking only)	✓		
Anxiety	✓		
Nausea	✓		
Cognitive effects	✓		
Euphoria		✓	
Blurred vision		✓	
Headache		✓	
Orthostatic hypotension			✓
Toxic psychosis/paranoia			✓
Depression			✓
Ataxia/dyscoordination			✓
Tachycardia (after titration)			✓
Cannabis hyperemesis			✓
Diarrhea			✓

Is it pain or is it other benefits?

- Consumer preference for CBD product
  - high satisfaction, pain predominant Ix
  - ↓ anxiety, appetite with high CBD/low THC
    - Brunt T. *J Clin Psychopharm* 2014; 34: 344
- QOL
  - prospective cohort mixed conditions, 1 yr
  - pain ↓, family/emotional function ↑
  - reduced opioid use (44%)
    - Haroutounian S. *Clin J Pain* 2016; 32: 1036
- Human experimental pain
  - no change in SS activation fMRI
    - less functional connectivity
  - reduce pain perception/affect
    - Lotsch J. *Eur J Pain* 2018; 22: 471





Cannabis and opioids

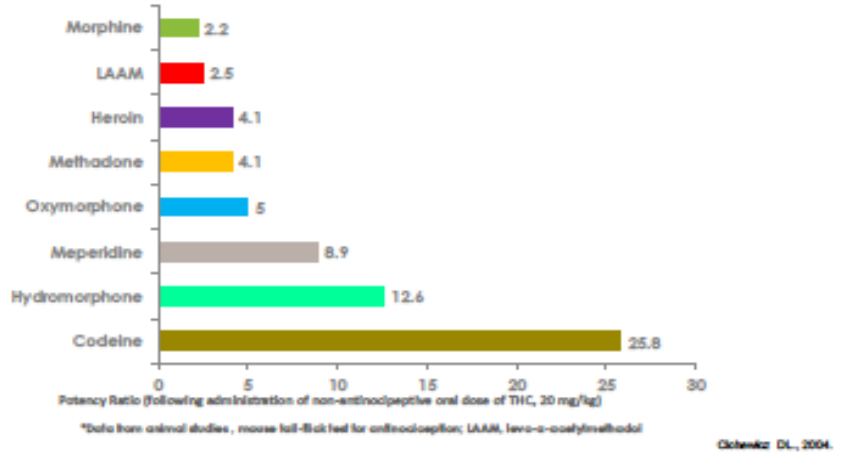
- Reduced deaths in US states with access reversed over time
  - Shover C. *PNAS* 2019; 116(26)
  - ? reduced opioid misuse
    - Wendelboe A. *JPCRR* 2019; 6: 268

- 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

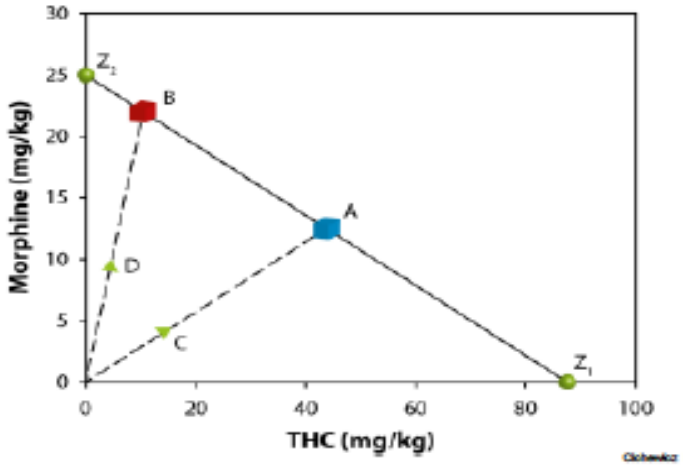
- Systematic review: 9 studies, reduced opioids in CNCP
  - high risk of bias, no causal inference
    - Okusanya O. *Syst Rev* 2020; 9: 167

- 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



Safety concerns

- Driving impairment
  - 2-5 mcg/l reported suggested “legal limit”
    - peak high when inhaled vs oro-mucosal
  - combination with alcohol, opioids
    - Chow R. *Anesth Analg* 2018; june 20

- Dependence +/- addiction reported in 10% users
  - associated withdrawal syndrome
    - potent with synthetic
  - tolerance: increased dose, CB1 down regulation, but level may rise
  - 25% meet criteria problematic use with MC, identified early
    - Ware M. *Psychopharm* 2018; 235: 409

- Prospective cohort reported safety at 1 yr
    - Ware M. *J Pain* 2015; 16: 1233
  - psychiatric disorders/reactivation
  - ? brain development (use <25 yr, cognitive effects)
    - D’Souza D. *JAMA* 2015; 313: 2431

Table 5. Recommendations for Screening for DUIC

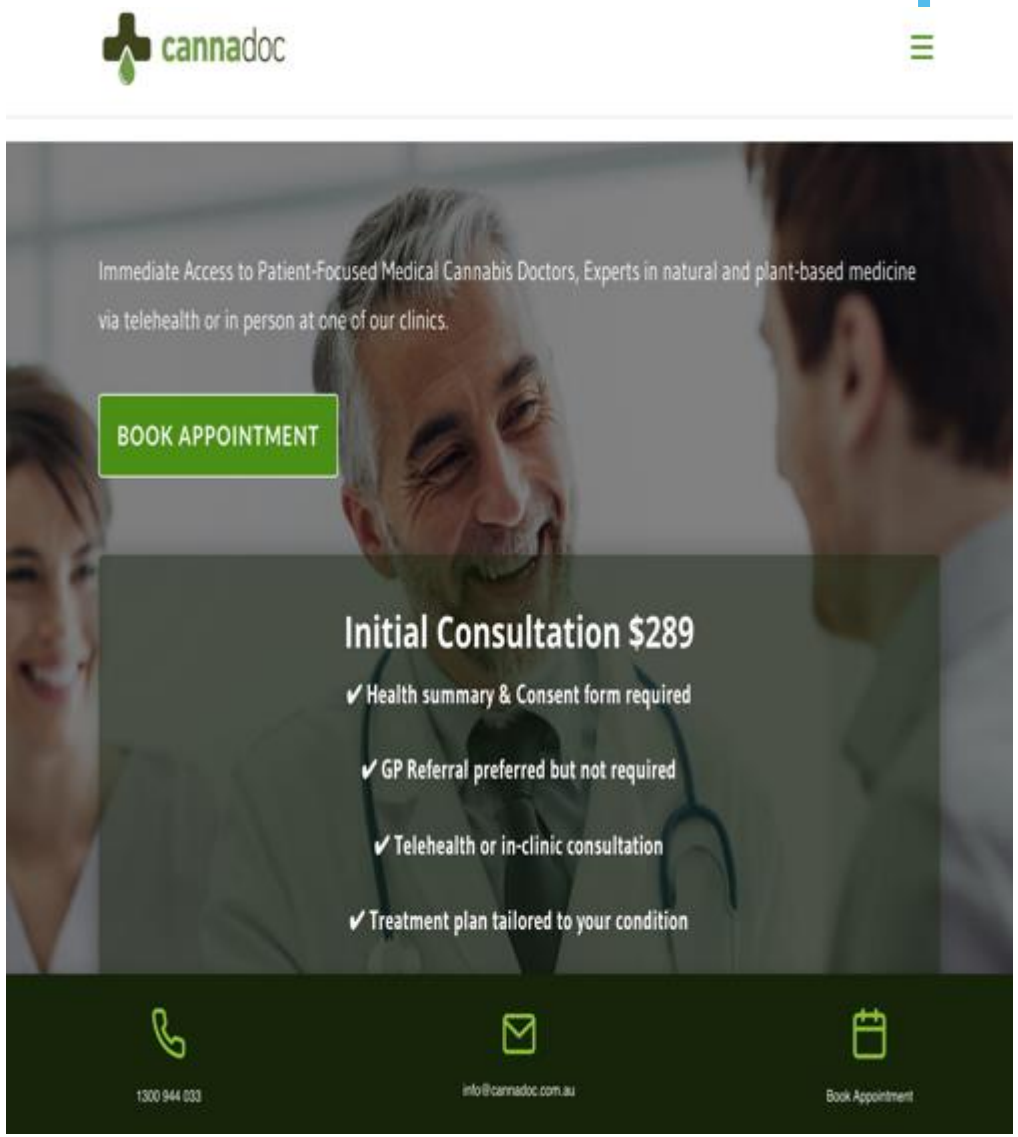
DUIC Screening Method	Implementation
Prescription verification	Utilize local prescription drug monitoring program
Legal	Verify federal versus state law and jurisdiction
Surveillance	Obtain witness accounts, video recording of the event in question
Laboratory assessment	Measure blood levels of THC: THC blood level of <5 µg/L if marijuana is the sole agent, <3 µg/L if alcohol is present
Physical assessment	Administer a field sobriety test, preferably by a Drug Recognition Expert
Cognitive assessment	Test working memory, power of attention, and continuity of attention

Medicinal Cannabis in practice

- Tertiary pain practice in setting of multi-disciplinary team
  - policy development, consultation, HREC
  - TGA approved “purified” products
    - *Tilray, Spectrum, Adaya*

- In practice: post comprehensive medical assessment
  - discuss goals, baseline measures
  - consent process, referring Dr communication, TGA/State/IPU

- Issues
  - avoid high THC levels, cognitive effects: e.g. *Sativex*
  - costs: $5-10/d, 2-3x higher in private
    - commercial cannabis access clinics
    - lack of comprehensive assessments, communication
  - driving, younger persons of concern
  - interactions with anti-coagulants
  - perioperative care
    - maintain or stabilise pre/post op, although may ↑ pain experience
      - Shah, S. *Reg Anesth Pain Med* 2023; 48: 97



RMH Pain Management Service

Cross-Divisional, Dual-Campus Consultative Service
Inpatient & Outpatient Care
Continuum of Care from Acute to Persistent Pain

Acute Pain → Sub-Acute Pain → Persistent Pain

Inpatient Consulting

APS Daily Ward Round & Referrals (24/7 Mobile #6322)
- Consultations (45-65 patients/day)
  - **Perioperative/Trauma**
  - Cancer
  - Medical
- **Specialist Techniques** assessment and follow up
  - PCA/Ketamine infusions/Lignocaine infusions
- **Enhanced Recovery after Surgery (ERAS)** pathways

Sub-Acute Ward Round & Referrals (APS)
- 2-3 x per week
- Ongoing review of patients with:
  - **Complex surgery**
  - **Severe trauma**
  - Opioid stewardship
  - Distress/Anxiety
  - Substance Use Disorders

Persistent Pain Inpatient Consultations (Pain Fellow)
- City Campus and Royal Park Campus
- As required consultations
  - **Complex Post-Surgical Pain**
  - Persistent Pain
  - Cancer Pain/Palliative Care Patients
  - **Interventional Pain Procedure candidates**

Outpatient Clinic

City Campus
- **Acute & Transitional Pain Clinic** (Friday PM)
  - **Pre & Post-Operative Pain Consultations**
  - Discharge follow up from APS
- **CRPS Clinic** (M/W/F)
  - In collaboration with Hand Therapy

Royal Park Campus
- **Sub-Acute Pain Clinic** (Tues PM)
- **Pre & Post-Operative Pain Consultations**
- Urgent Community Referrals

Royal Park Campus Multi-Disciplinary Clinics
- Allied Health Team
  - PT/OT/SW/Clinical psychology
- **Aged Pain Clinic** (Tues AM)
  - Pain Specialists & Geriatricians
- **Persistent Pain Clinic** (Thursday)
  - **Interventional**/Rehabilitation Streams
  - Pain Specialists & Rehab Physicians
  - Addiction Medicine Specialist & Psychiatrist
  - Neurosurgeon (monthly)

Interventional Procedures

Regional Techniques (APS)
- **Rib Fractures**
- Hip Fractures

Interventional Pain Procedures (Pain Specialists)
- Intrathecal/Epidural catheters for cancer/pall care patients

Weekly **Elective Interventional Pain Procedure List**
- Epidural and intra-articular steroid injections
- **Radiofrequency denervation**
- Neurolytic Procedures
- Implantable devices

Session Conclusion

You will receive a post session email within a week which will include slides and resources discussed during this session.

Attendance certificate will be received within 4-6 weeks.

RACGP CPD hours will be uploaded within 30 days.

To attend further education sessions, visit,

https://nwmphn.org.au/resources-events/events/

This session was recorded, and you will be able to view the recording at this link within the next week.

https://nwmphn.org.au/resources-events/resources/

We value your feedback, let us know your thoughts.

Scan this QR code