Pain management: an update on the emerging use of cannabis

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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 Assessment

- **Who is the person?**
  - Developmental history, medical and 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 (infection, #, Ca, etc)*

- **What is the impact?**
  - potential for fear-avoidance behavior to limit recovery

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

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

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

pain score or comfort level?

An approach to pain management

- **Manage from a socio-psycho-biological perspective**
- Patient education
  - include family, medical team → for perception

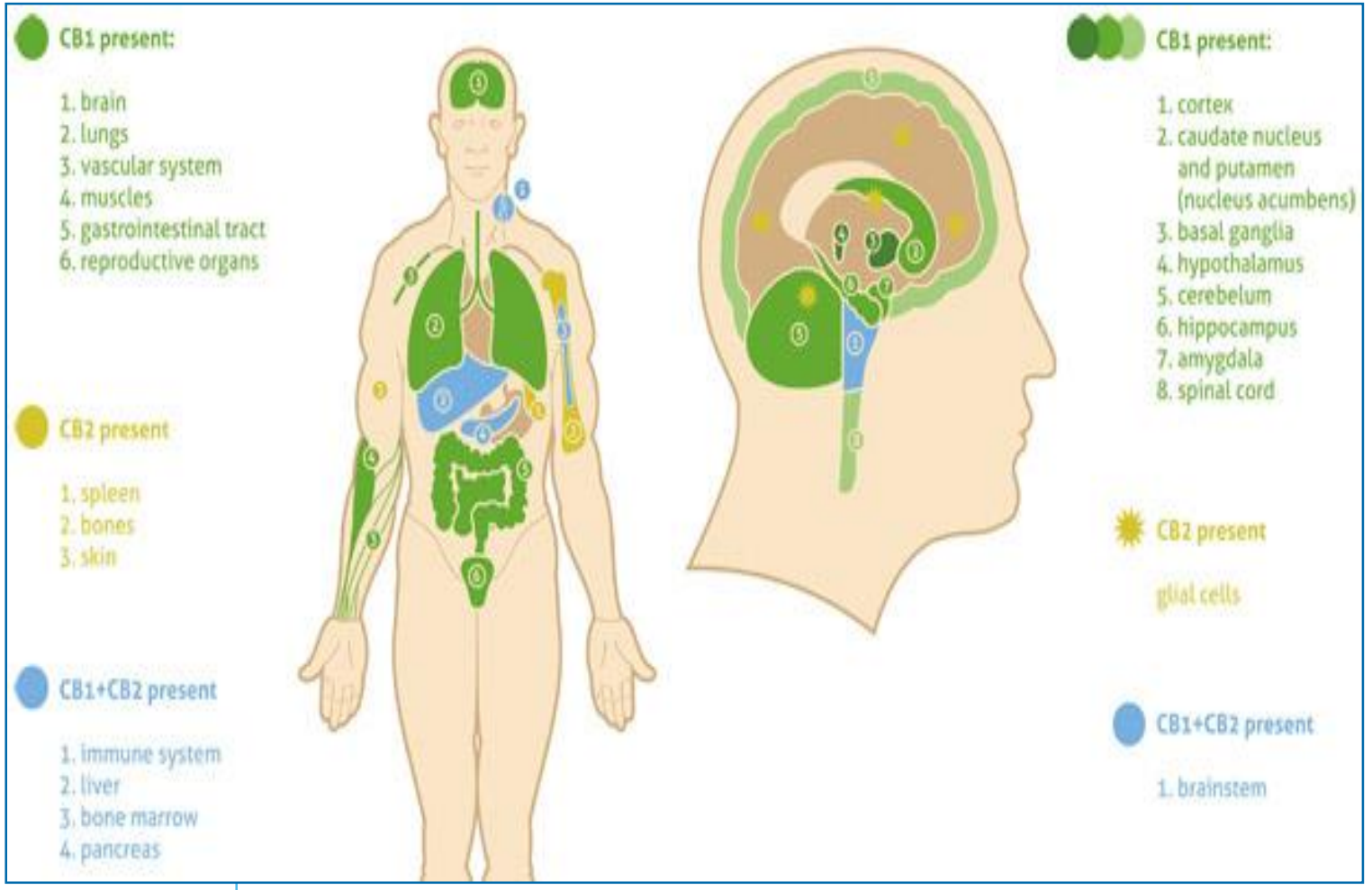
- Pharmacological
  - opioids, clonidine, LA's → for nociceptive pain
  - NSAIDS, biologicals, anti-oxidants → for inflammation
  - blocks/LA's, ketamine, Mg, clonidine, TCAD/SNRI, GBP → for neuropathic, sensitisation
    - ? medical cannabis → for ? perception

- 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)

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

- Delta-9-Tetrahydrocannabinol
  - partial agonist CB1, CB2
  - psychomimetic
    - anxiety
  - analgesia
  - sedation
  - appetite/hyperemesis
  - dependency
  - withdrawal syndrome

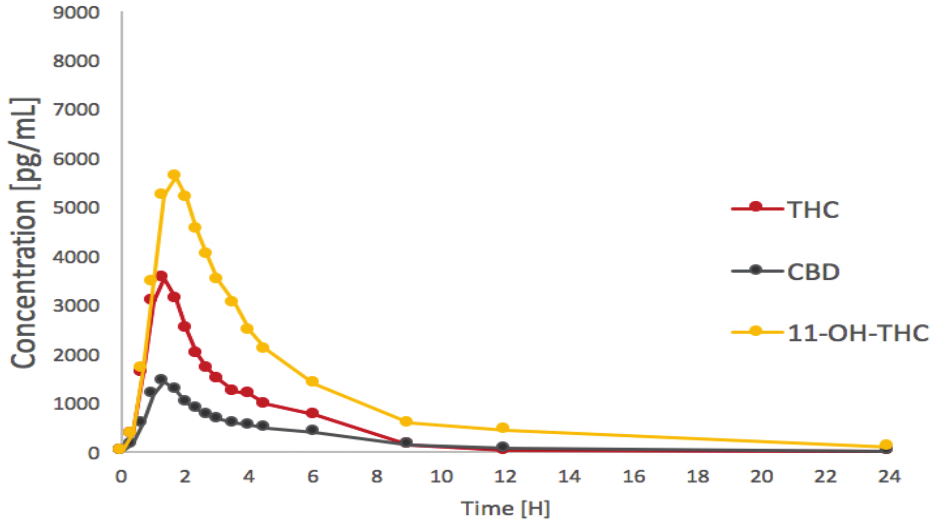
- Cannabidiol
  - interacts with array of other receptors and enzymes
  - anti-inflammatory
  - anxiolytic
  - anti-epileptic
  - anti-psychotic
  - anti-emetic
  - ? analgesic/anti-hyperalgesic
    - animal neuropathic pain
  - modifies THC toxicity

Henderson L. *AJGP* 2021; 50: 724

Pharmacology

- Phytocannabinoids
  - >100 strains cannabis: *sativa, indica main* species for MC
  - >100 cannabinoids, >300 other compounds, terpenes, flavinoids
- Variable content 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



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
- recent meta-analysis/systematic review
  - small effect, short duration studies
    - Johal H. *Clin Med Insights: Arth MSK* 2020; 13: 1
  - low quality studies, 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

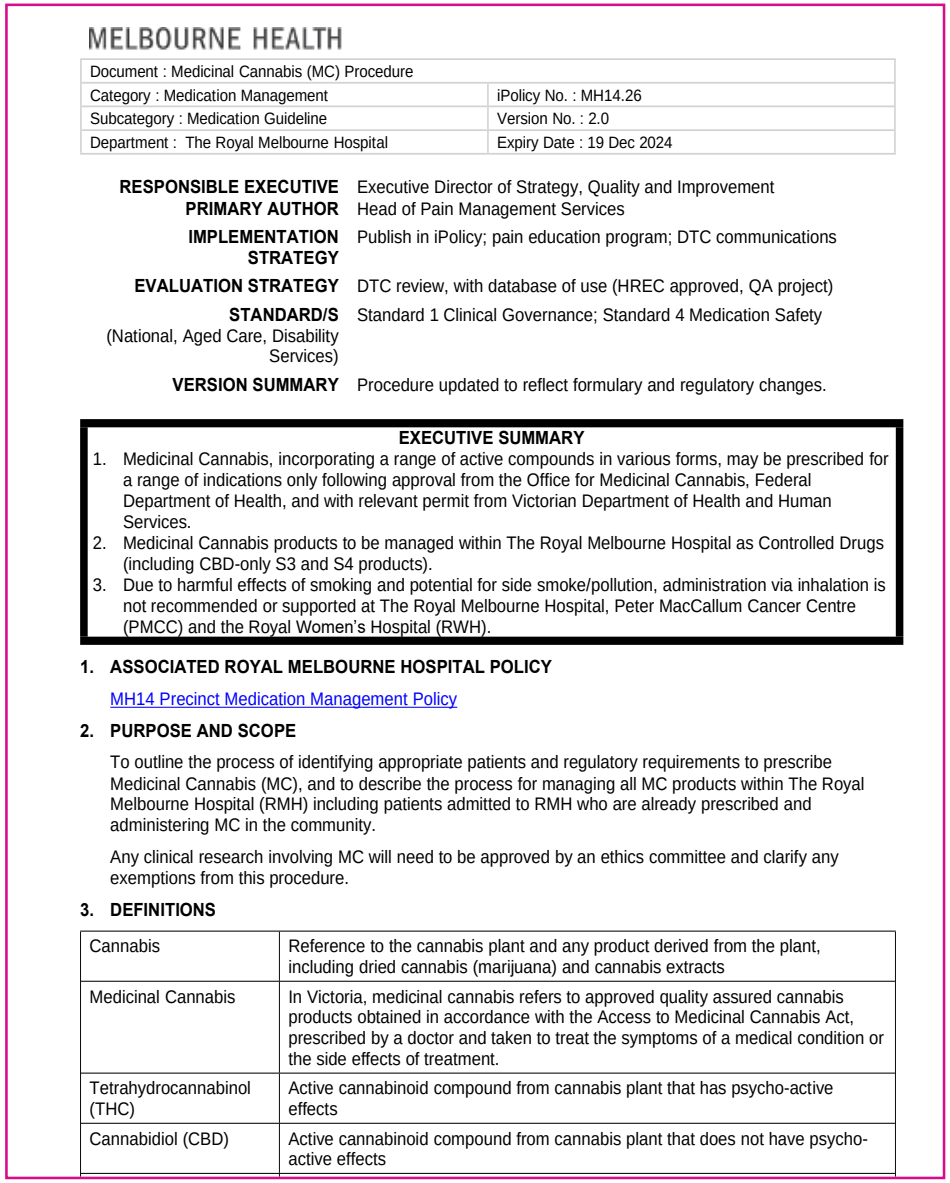
Table 4
Adverse events associated with cannabis-based medicines.

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			✓

Medical Cannabis

- Policy at RMH since 2018
  - No inhalational
  - No $ support, except via IPU/DTC consideration
  - Oral preparation to be prescribed on drug chart
    - self provided, managed as S8
  - Not for acute pain
    - rarely may be instigated for chronic pain/distress or Ca as inpatient

- Outpatient prescribing via pain clinic
  - Authorised prescriber system
  - 2 Dr's, consent process
    - Goal setting
    - Outcome measures
      - Now PROMIS-29



MELBOURNE HEALTH

Document : Medicinal Cannabis (MC) Procedure	
Category : Medication Management	iPolicy No. : MH14.26
Subcategory : Medication Guideline	Version No. : 2.0
Department : The Royal Melbourne Hospital	Expiry Date : 19 Dec 2024

RESPONSIBLE EXECUTIVE Executive Director of Strategy, Quality and Improvement
PRIMARY AUTHOR Head of Pain Management Services
IMPLEMENTATION STRATEGY Publish in iPolicy; pain education program; DTC communications
EVALUATION STRATEGY DTC review, with database of use (HREC approved, QA project)
STANDARD/S (National, Aged Care, Disability Services) Standard 1 Clinical Governance; Standard 4 Medication Safety
VERSION SUMMARY Procedure updated to reflect formulary and regulatory changes.

EXECUTIVE SUMMARY

1. Medicinal Cannabis, 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 products to be managed within The Royal Melbourne Hospital as Controlled Drugs (including CBD-only S3 and S4 products).
3. Due to harmful effects of smoking and potential for side smoke/pollution, administration via inhalation is not recommended or supported at The Royal Melbourne Hospital, Peter MacCallum Cancer Centre (PMCC) and the Royal Women's Hospital (RWH).

1. ASSOCIATED ROYAL MELBOURNE HOSPITAL POLICY

MH14 Precinct Medication Management Policy

2. PURPOSE AND SCOPE

To outline the process of identifying appropriate patients and regulatory requirements to prescribe Medicinal Cannabis (MC), and to describe the process for managing all MC products within The Royal Melbourne Hospital (RMH) including patients admitted to RMH who are already prescribed and administering MC in the community.

Any clinical research involving MC will need to be approved by an ethics committee and clarify any exemptions from this procedure.

3. DEFINITIONS

Cannabis	Reference to the cannabis plant and any product derived from the plant, including dried cannabis (marijuana) and cannabis extracts
Medicinal Cannabis	In Victoria, medicinal cannabis refers to approved quality assured cannabis products obtained in accordance with the Access to Medicinal Cannabis Act, prescribed by a doctor and taken to treat the symptoms of a medical condition or the side effects of treatment.
Tetrahydrocannabinol (THC)	Active cannabinoid compound from cannabis plant that has psycho-active effects
Cannabidiol (CBD)	Active cannabinoid compound from cannabis plant that does not have psycho-active effects

Policy changes

- TGA: >170,000 permits
  - *Sativex* and *Epidyolex* on ARTG
  - CBD only up to 150 mg approved for S3
    - no products yet considered/listed
  - SAS-B, Authorised prescriber program
- DHHS Victoria
  - THC on *safescript* (S8), CBD only not (S4)
  - need for permit for THC products under review
- RMH
  - selected products for formulary application, EPIC listing
  - TGA, HREC reporting
  - Consultation service: alternate units may prescribe

CONSENT FOR THERAPEUTIC TRIAL OF MEDICINAL CANNABIS PRODUCT

Patient Name: _____ RMH UR: _____

_____ (clinician) and I have discussed my present condition:

_____

and possible treatment options, including the potential role of MEDICINAL CANNABIS.

I am aware that:

1) There have been few well-designed clinical trials using medicinal cannabis, therefore there is limited evidence on its success in treating different medical conditions. https://www.tga.gov.au/sites/default/files/medicinal-cannabis-consumers-factsheet.pdf
2) There is a range of possible side effects including:
   - nausea and vomiting, appetite increase or decrease, dry mouth, diarrhea
   - fatigue, sedation, dizziness, confusion
   - feelings of euphoria or depression, hallucinations, psychosis or cognitive distortion
3) There is a risk of developing cannabis dependency and or addiction, with potential for agitation or other withdrawal symptoms if stopped suddenly
4) Potential interactions with other medications you are taking, causing high or low levels, including with anti-coagulants, epilepsy medications, other sedative or analgesics
5) Medicinal cannabis is a **trial only** and may not provide benefit even though the treatment is carried out with due professional care; my doctor may not commit to ongoing prescribing based on their assessment of potential risks and limited benefit
6) It is an offence to drive a motor vehicle whilst impaired by any substance or prescription medication, including medicinal cannabis containing significant amount of THC https://www.vicroads.vic.gov.au/safety-and-road-rules/driver-safety/drugs-and-alcohol/medicinal-cannabis-and-driving
7) There is a significant cost: Medicinal Cannabis is not subsidised by Royal Melbourne Hospital or Pharmaceutical Benefits Scheme (PBS)
8) I will be expected to complete routine pain specific questionnaires regularly to assess the effectiveness of medicinal cannabis and outcomes which may be used for quality assurance purposes at Royal Melbourne Hospital (with Ethics committee approval)

I give consent to a therapeutic trial of MEDICINAL CANNABIS and understand the risks explained above.
TGA Patient Information Provided

Signature of Patient_____ Date: _____/_____/20___

Print Name of Patient _____

Consenting Clinician Name and Discipline_____.

Medical Cannabis at RMH

- 4.5 yrs: primarily via RMH chronic pain services clinics
  - 106 assessed: 76 (72%) prescribed after screening/consent
    - 26 ongoing (34%): eg CBD 25-100 mg bd, THC 2.5-10 mg bd
    - 8 deaths, nil relating to cannabis
    - 1 haematoma (associated with apixaban)
    - 1 psychosis episode: self escalated with opioid/benzo dependence
- Drug interactions: THC ↑ C1A2; CBD ↓ C2D6, 3A4,5,7
  - Anticoagulants, psychoactives, oxycodone

- Indications
  - MS: anxiety, pain, spasticity
  - Chronic mixed pain (nociceptive, neuropathic, sensitisation)
    - EB, neurofibromatosis, spina bifida
  - Post Ca: head and neck, pelvic clearance
  - Neuropathic pain: HIV, DPN, shingles
  - Movement disorders: RLS, Parkinsons, stiff person syndrome
  - No visceral pain conditions

- Ceased due to lack of benefit, cost, driving, cognitive effects

HREC QA

N=10, 12 mths
8 improved on BPI severity, interference
4 of 5 lowered opioid dose
reduced HCU in 8
5 improved on DASS, 2 worse
no changes on PCS, PSEQ

to add sleep measure, GAS

ASRA Pain Medicine consensus guidelines on the management of the perioperative patient on cannabis and cannabinoids

Shah S. *Reg Anesth Pain Med* 2023; 48: 97-117

- Preop screening for use, CVS-respiratory risks
  - Inhalational cannabis increase AMI risk, resp complications
- May increase pain experience
  - Unclear if should taper, change opioid requirements
- May change anaesthesia requirements: acute toxicity (↓) vs chronic use (↑)
- Withdrawl syndrome risk in those >1.5 gm/d inh, >20 mg/d THC po
  - GBP 1200 mg/d suggested

- Limited evidence in relation to oral MC
  - Combined THC/CBD may reduce pain, not opioid use
  - CBD only may limit changes to BBB, ? less delirium

Cannabis and opioids

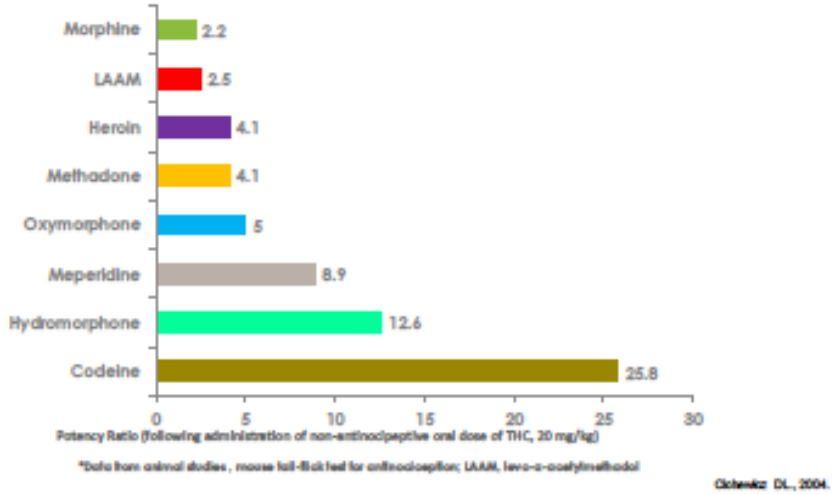
- Reduced deaths in US states with access reversed over time
  - Shover C. *PNAS* 2019; 116(26)
  - ? reduced opioid misuse
    - Wendelboe A. *JPCRR* 2019; 6: 268

- 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

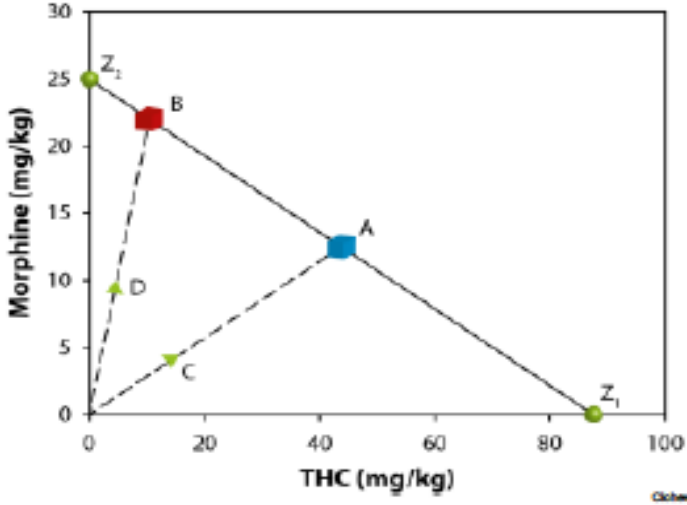
- Systematic review: 9 studies, reduced opioids in CNCP
  - high risk of bias, no causal inference
    - Okusanya O. *Syst Rev* 2020; 9: 167

- 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
  - 3-5 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

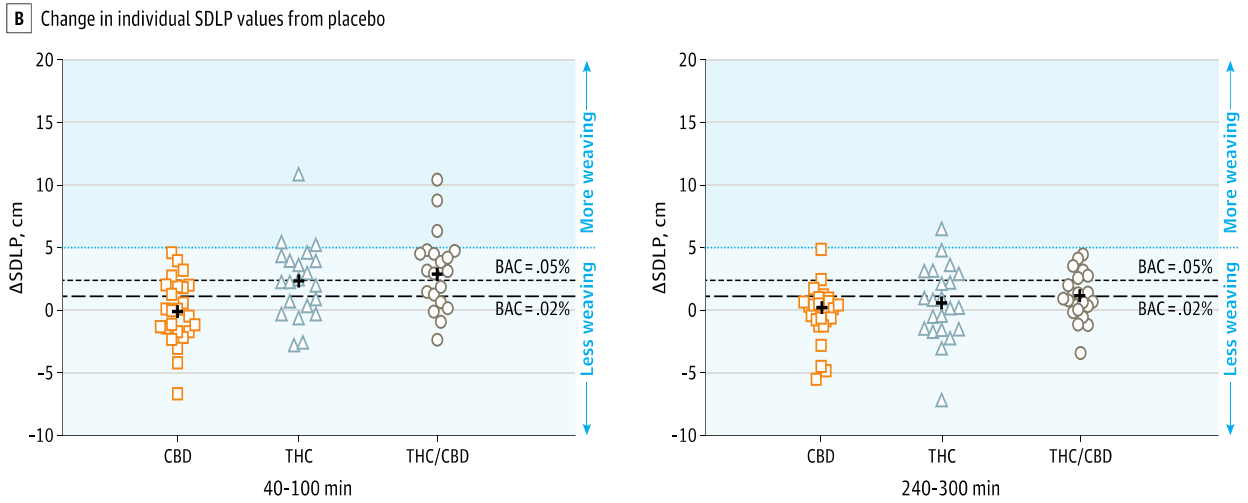
- Prospective cohort reported safety at 1 yr
    - Ware M. *J Pain* 2015; 16: 1233
  - psychiatric disorders/reactivation
  - ? brain development (use <25 yr, cognitive effects)
    - D’Souza D. *JAMA* 2015; 313: 2431

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

Driving and cannabis

- RCT vaporized THC, CBD, balanced product
  - Within participants, ave dose 13.75 mg THC/CBD
  - 100 kms at 90 km/hr, lane variability
  - CBD only equal to placebo
  - Peak effect 40-100 mins, CBD did not protect (worse?)
    - THC increase SDLP by cm (18 to 21)
    - Mild impairment on cognitive tests: digit substitution
      - Arkell T. *JAMA* 2020; 324: 2177

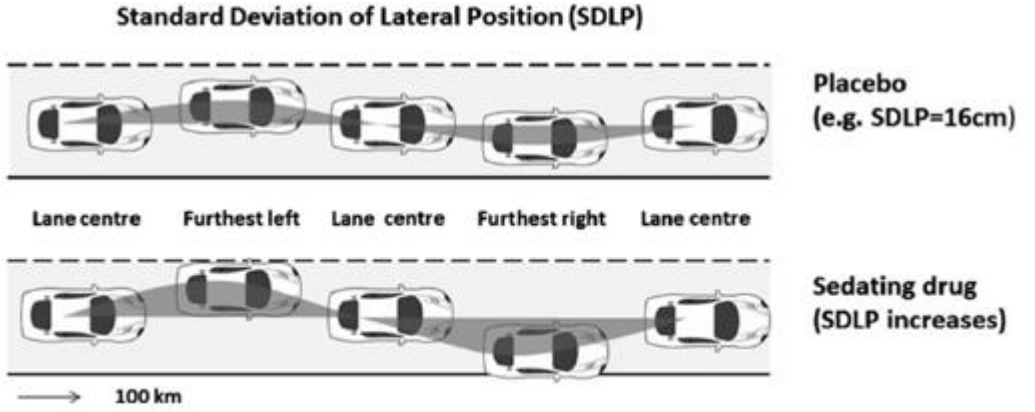


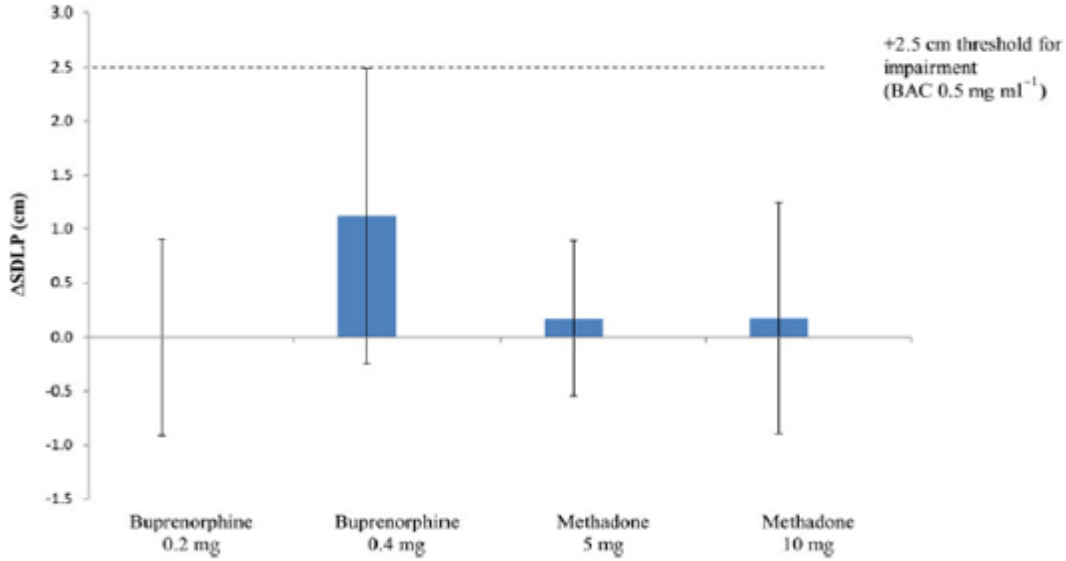
- CBD effects unanswered, as high dose associated with less anxiety, changes in cognitive function
  - Combination THC/CBD may be increased impairment compared to THC alone
    - Rubin R. *JAMA* 2020; 324: 2145

- Cannabis associated with increase in lateral variability and reduced driving speed
  - Similar to low alcohol concentration
  - Combination with alcohol greater effect than either drug alone
    - Simmons S. *Addiction* 2022; 117: 1843

Opioids and driving

- Review suggest not associated with MVA
  - Fishbain D. *J Pain Palliat Care Pharmacother* 2002; 16: 9
- however subsequent statistical analysis suggests 2-10x risk MVA if on opioids
  - Schultz H. 2012 DRUID project, EMCDDA
- Acute opioid in volunteers
  - low dose methadone, buprenorphine
    - high variability, sleepiness
  - dose related impact on driving skills
    - less than alcohol 0.05 threshold
      - Stand M *Br J Clin Phamracol* 2019; 85: 442
  - chronic pain cohort on opioids
    - no significant changes but variable
      - Schumacher M. *Psychopharmacology* 2017; 234: 989
- FPM-UK note legal changes re impairment, 2015
  - meth/morphine quoted, including concentration
  - consider dose, >200mg OMED concerns, other sedatives
  - document discussion with patient
- SA guidelines
  - variability, dose change issues
    - Mailis-Gagnon *Clin J Pain* 2012; 2: 542





Opioids and driving

- Review identified opioid effects of sedation and cognitive impairment
  - Heterogeneity, bias, small studies of concern
  - Context important: illicit, recent initiation, other psychoactives
  - Personal risk factors include age, experience
    - Cameron-Burr K. *J Medical Toxicology* 2021; 17: 289
- 20 of 29 in experimental studies concluded opioids impair psychomotor function with driving impact
  - Small samples sizes, but dose-response relationship
- All studies on illicit use favour impact on driving performance
  - Population factors also influence e.g. young male
- 29 studies on prescription opioids: 15 concluded psychomotor impairment
  - Stable, chronic dosing with no other risk factors do not appear to have increased risk
- 9 of 14 studies on forensic studies concluded impact on driving function
  - Polydrug use major risk factor

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