“Medicinal Cannabinoids” and MS

MS Society

31.10.19

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Multiple Sclerosis - & Pain

- A chronic neuroinflammatory disease of the central nervous system.
- affects 2.3 – 2.5 million people worldwide
- leading non-traumatic cause of neurologic disability in young adults
- Characterised pathologically by demyelinating plaques of both grey & white matter, representing loss of both myelin sheath & supporting oligodendrocytes
- clinical course varies, with relapsing-remitting multiple sclerosis (RRMS) accounting for approximately 85% of cases
- Common clinical features include spasticity/painful spasms, weakness, sensory disturbances, ataxia, tremor, optic neuritis, opthalmoplegias, fatigue, dysphagia
- Pain affects around two thirds of people with MS, including headache (43%), central neuropathic pain in the arms or legs (26%), back pain (20%), painful spasms (15%), and trigeminal neuralgia (3.8%)
- Another review:
  - High prevalence of chronic pain: 29 – 80%
  - Point prevalence of pain (any type): 50%
  - Pain in the last month: 75%
- Anecdotal reports that MS patients have symptomatic relief (spasticity & pain) after smoking cannabis → research into cannabinoids to manage symptoms.
- Research now: also potential for cannabinoids to slow disease progression

Nielsen S et al: "The use of cannabis and cannabinoids in treating symptoms of multiple sclerosis: a systematic review of reviews"; *Current Neurology & Neuroscience Reports*; February 2018, 18:8

Cannabinoids in MS-Related Pain & Spasticity: 1

"Recent high quality reviews find cannabinoids may have modest effects in MS for pain or spasticity"

- 2 reviews of medium quality: evidence that THC & THC:CBD/nabiximols were efficacious or probably efficacious in reducing MS pain or painful spasm. "Effect sizes are generally small … only modest effects may be expected"
- One recent high quality review (Whiting, *JAMA* 2015) concluded: sufficient evidence to support the clinical use of nabiximols, THC/CBD capsules, nabilone, and dronabinol in treating symptoms of multiple sclerosis – all have THC (not CBD alone)
- But other reviews concluded: insufficient evidence, or mixed findings
- Evidence of efficacy inconclusive in other symptoms (e.g. bladder control, ataxia, tremor)

Rice J, Cameron M: "Cannabinoids for Treatment of MS Symptoms: State of the Evidence"; *Current Neurology & Neuroscience Reports*; August 2018, 18:50

Cannabinoids in MS-Related Pain & Spasticity: 2

"The medical use of cannabinoids remains controversial. While cannabinoids have been studied for a variety of neurologic disorders, there is strongest evidence to indicate benefits in treatment of spasticity and neuropathic pain in multiple sclerosis."

- "Although the best dose for an individual remains uncertain, most participants in the studies discussed in this paper used between 20 & 40 mg of THC a day in divided doses." (ie, again, **NOT** CBD)
- No studies have examined inhaled cannabis in MS

Adverse events (AE):

- generally more common in those using cannabinoids,
- "serious AE were rare", & cannabinoids "generally well-tolerated".
- "Cannabis use does appear to be associated with increased risk of certain adverse events including psychosis, cardiovascular diseases, & cannabinoid hyperemesis syndrome" (chronic, generally daily, cannabis use, cyclic episodes of nausea & vomiting, & hot bathing)

"High-quality scientific methods & standards need to be applied to the study of cannabis & cannabinoids to fully understand their potential for medical use."

Strong Recommendations – 1st-Line

	Dose (mg/day)	NNT
• **Tricyclic ADs**	25-150	3.6

Nortriptyline (fewer side-effects than amitriptyline)

• **Gabapentin**	1200-3600	7.2
• **Pregabalin**	300-600	7.7
• **Duloxetine**	60-120	6.4 *(not funded)*
• **Venlafaxine**	150-225	6.4

Ie, 3 classes of 1st-line pharmacotherapy for NP:

- TCAs, gabapentinoids, SNRIs

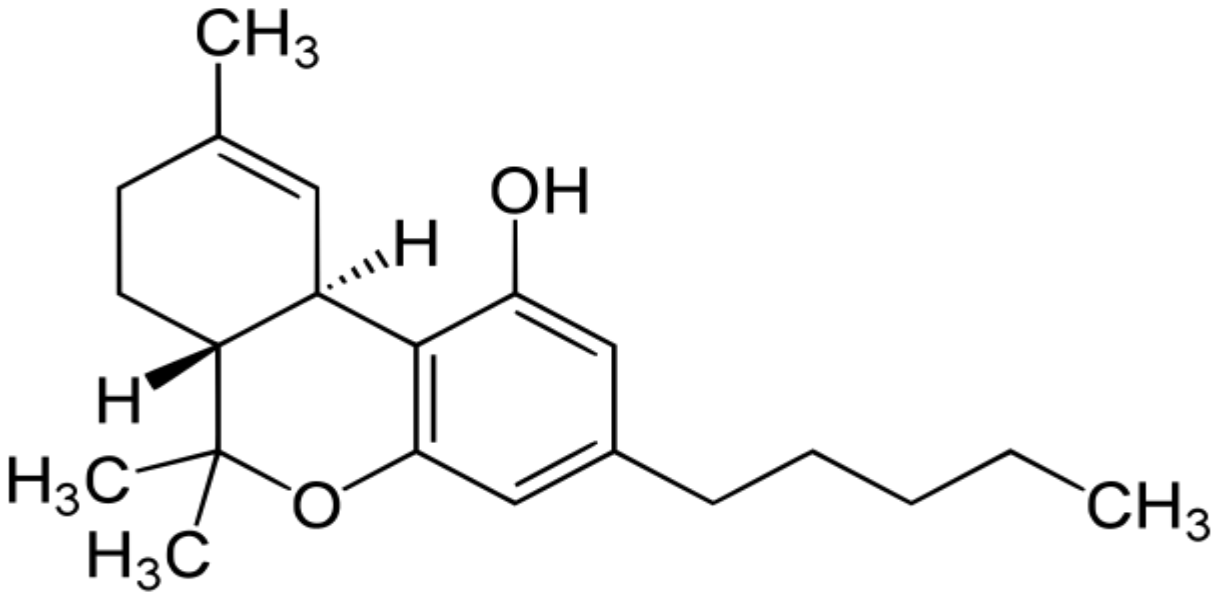
(Finnerup NB et al: "Pharmacotherapy for neuropathic pain in adults: a systematic review & meta-analysis". *Lancet Neurol*, Feb 2015; 162–73)

NB: for Central NP: evidence for duloxetine (60 mg/d for MS-related neuropathic pain – *? venlafaxine?*), pregabalin (SCI pain), lamotrigine (SCI, CPSP), amitriptyline (CPSP) (Watson JC, Sandroni P: "Central Neuropathic Pain Syndromes"; *Mayo Clin Proc*. 2016; 91(3): 372-385)

History of "Medicinal Cannabis"

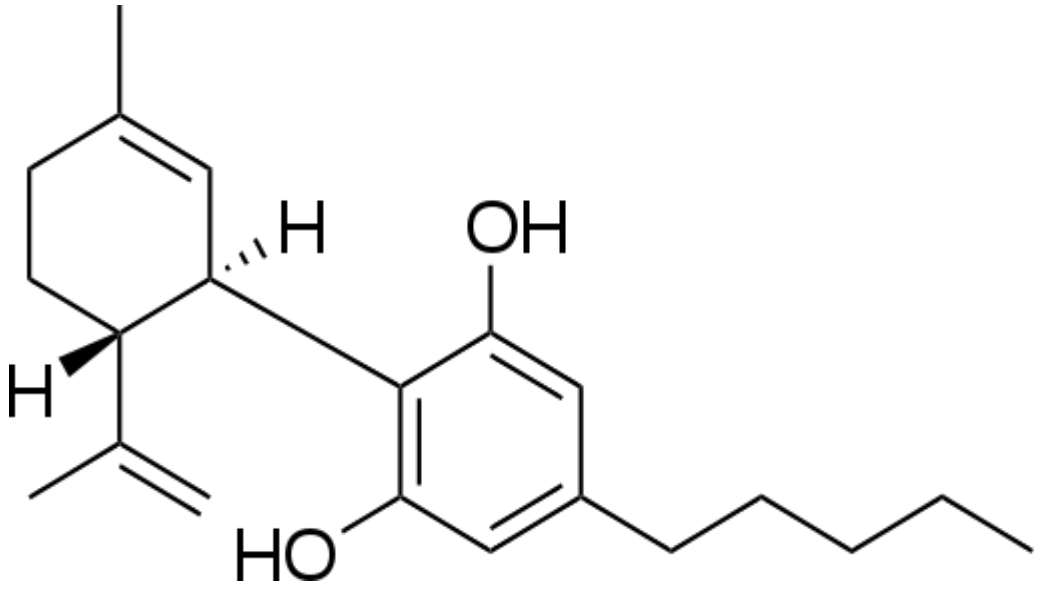
- **ca. 6,000 years BCE** (early Holocene): Archaeological evidence of cannabis use in East Asia and Europe
- **6th century BCE**: Earliest written records of human cannabis use
- **Mid-19th century**: European colonial expansion into Africa and Asia → cannabis use in Europe – eg, for tetanus, seizures, mental illness
- **1851**: cannabis included in 3rd edition of *Pharmacopoeia of the United States* (USP).
- **1916**: U.S. Pharmacopoeial Convention: how to prepare extracts and tinctures of dried cannabis flowers for analgesic, hypnotic, and anticonvulsant use.
- **Early 1900s**: Concerns → cannabis outlawed in several states
- **1937 (Marihuana Tax Act)**: Concerns → Federal prohibition .
- **1942** – the American Medical Association removed cannabis from the 12th edition of *U.S. Pharmacopeia*

Δ9-THC (Tetrahydrocannabinol)



Δ9-THC – partial CB1-R agonist → intoxicant/hallucinogenic

CBD (Cannabidiol)



Very low affinity for CB1 & CB2 receptors

→ lacks the cannabis-like intoxicating properties of Δ9-THC

→ traditionally considered non-psychoactive.

CBD Actions

- Anti-oxidant & anti-inflammatory properties may explain its potential neuroprotective actions →
- Potential / theoretical role in neurology: epilepsy & seizures, psychosis, anxiety, MS, movement disorders (eg, Huntington's, Motor Neurone Disease)
- 2013 – FDA allowed investigational studies of Epidiolex®, a pharmaceutical grade concentrated CBD oil (>98 % CBD).

CBD in Paediatric Epilepsies – 3 x RCTs (1)

1. Devinsky O et al: "Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome"; *NEJM*, 376 (**25.5.17**):

   (Dravet Syndrome, a rare genetic complex childhood epilepsy → drug-resistant seizures, intellectual disability, high mortality

- → **decreased monthly seizures: 12.4 to 5.9**;
- → seizure-free rate 5% (vs 0% placebo)
- Common AE's: anorexia, vomiting, diarrhoea → appreciable dropout
- Editorial (*NEJM*, 25.5.17): "*beginning of solid evidence for the use of cannabinoids in epilepsy. It requires replication … After an era dominated by anecdote, & obfuscated by medicolegal issues & emotionally infused debate, more scientific studies are under way. Much more research is needed to understand the basic science, benefits, & risks of cannabinoids in epilepsy*."
- Churchill: "*This is not the end. This is not the beginning of the end. But it is, perhaps, the end of the beginning*"

CBD in Paediatric Epilepsies – 3 x RCT (2)

2. Thiele EA et al: "Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome: a randomised, double-blind, placebo-controlled phase 3 trial"; *Lancet*, (**17.3.18**);

- **44% (vs 22%) median reduction in monthly drop seizure frequency**
- AE's: 86% (CBD) vs 69% (placebo); most mild-moderate (diarrhoea, somnolence, pyrexia, decreased appetite, vomiting) → 14% (CBD) vs 1% (placebo) withdrew

3. Devinsky O et al: "Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome"; *NEJM*, 378 (**17.5.18**).

- **42% (20mg/kg CBD), 37% (10mg CBD), vs 17% (placebo) median reduction in monthly drop seizure frequency**
- AE's: somnolence, decreased appetite, diarrhoea; more frequent in 20mg group. 6 (20mg) vs 1 (10mg) withdrew.

→

CBD in Paediatric Epilepsies – 3 x RCT (3)

- **25 June 2018**: US Food and Drug Administration (FDA) approved Epidiolex (CBD), the first cannabis-derived treatment, for 2 epilepsy syndromes, Lennox-Gastaut and Dravet Syndrome.

→ FDA: "Show us the Evidence" vs Conspiracy

2 x Synthetic THCs (oral caps) US FDA approved for:

- Chemotherapy associated nausea & vomiting
- Appetite stimulation in AIDS-related wasting syndrome:
  - Dronabinol (Synthetic Δ9-THC)
  - Nabilone (Synthetic Δ9-THC analogue)

Nabiximols (Sativex):

- approved in > 16 countries, incl NZ, but not USA
- Each mL contains 2.7 mg THC & 2.5 mg CBD

Finnerup NB et al: "Pharmacotherapy for neuropathic pain in adults: a systematic review & meta-analysis". *Lancet Neurol*, Feb 2015; 162–73

Recommendations against use:

(Negative Trials &/or Safety Concerns)

Weak recommendation against use:

- **Cannabinoids**

Why? "***negative results, potential misuse, diversion, & long-term mental health risks***"

Review, *Ann Int Med*, 5.9.2017

Neuropathic Pain

- **13 RCTs** examined the effects of cannabis based preparations on central or peripheral neuropathic pain related to various health conditions →
- "**low strength evidence that cannabis may alleviate neuropathic pain in some patients** …
- "Across 9 studies, intervention patients were more likely to report at least 30% improvement in pain (risk ratio, 1.43) …
- "Most studies were small, few reported outcomes beyond 2 to 3 weeks, and none reported long-term outcomes."

Nugent SM et al: "The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review"; *Ann Intern Med.* doi:10.7326/M17-0155; 5 Sept 2017.

Review, *Ann Int Med*, 5.9.2017

Overall Results

(27 chronic pain trials)

- **Low strength evidence that cannabis alleviates neuropathic pain,**
- **Insufficient evidence in other pain populations.**

Harms

(11 systematic reviews, 32 primary studies): **Increased risk for:**

- **motor vehicle accidents,**
- **psychotic symptoms,**
- **short-term cognitive impairment.**

Conclusion

- **"Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain**.
- "Limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects."

Nugent SM et al: "The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review"; *Ann Intern Med.* doi:10.7326/M17-0155; 5 Sept 2017.

Editorial, *Ann Int Med*, 5.9.2017

- *"systematic reviews highlight an **alarming lack of high-quality data** from which to draw firm conclusions about the efficacy of cannabis for these conditions, for which cannabis is both sanctioned and commonly used."*
- *"limited, low-strength evidence that cannabis alleviates neuropathic pain, and insufficient evidence for other types of pain."*
- *"These conclusions seem at odds with the fact that pain is one of the most common medical conditions for which cannabis is used and approved in many states. So, **why the discrepancy?**"*

"Cannabis for Pain and Posttraumatic Stress Disorder: More Consensus Than Controversy or Vice Versa?" Ed. *Ann Int Med*, 5.9.2017

Conclusions

- *"Most available studies are small, have methodological pitfalls, and are of relatively short duration."*

- Little high-quality evidence from which to draw firm conclusions about the efficacy of cannabis and cannabinoid products for treating pain.

"Cannabis for Pain and Posttraumatic Stress Disorder: More Consensus Than Controversy or Vice Versa?" Ed. *Ann Int Med*, 5.9.17

Cochrane Review, 2018: "Cannabis-Based Medicines for Chronic Neuropathic Pain in Adults" 1

- 50% or greater pain relief: 21% (vs placebo 17%): NNTB = 20
- 30% or greater pain relief: 39% (vs placebo 33%)
- 10% (vs 5%) withdrew from trial due to AE's.
- "May increase nervous system adverse events" (61%) vs placebo (29%). NNTH = 3
- "Psychiatric disorders" in 17% using cannabis-based medicines (vs 5% on placebo). NNTH = 10

Cochrane Review 2018: "Cannabis-Based Medicines for Chronic Neuropathic Pain in Adults" 2

- "potential benefits of cannabis-based medicine in chronic neuropathic pain might be outweighed by their potential harms.
- "The quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant co-morbidities from the studies, together with their small sample sizes."

"Cannabis & Cannabinoids for the Treatment of People with Chronic Non-Cancer Pain Conditions: a Systematic Review & Meta-Analysis of Controlled & Observational Studies"; Stockings E et al: *Pain* October 2018

- 91 publications with 104 studies were eligible (n = 9958 participants), including
  - 47 RCTs
  - 57 observational studies.
- **Neuropathic pain – 48 studies**
- Fibromyalgia – 7 studies
- Rheumatoid arthritis – 1 study
- 48 – other CNCP (**13 MS-related pain**, 6 visceral pain, & 29 samples with mixed or undefined CNCP)

"Cannabis & Cannabinoids for the Treatment of People with Chronic Non-Cancer Pain Conditions: a Systematic Review & Meta-Analysis of Controlled & Observational Studies"; Stockings E et al: *Pain* October 2018

- **30% reduction in pain = 29.0% (cannabinoids) vs 26% (placebo)**
- significant effect for cannabinoids, number needed to treat to benefit **(NNTB): 24**
- **50% reduction in pain**, 18.2% vs. 14.4%; **not a significant difference**
- Change in pain from cannabinoids equivalent to **3mm on a 100mm visual analogue scale** greater than placebo

"Cannabis & Cannabinoids for the Treatment of People with Chronic Non-Cancer Pain Conditions: a Systematic Review & Meta-Analysis of Controlled & Observational Studies"; Stockings E et al: *Pain* October 2018

- all-cause **AEs = 81% (vs. 66%)**
- number needed to treat to harm **(NNTH): 6**
- No significant effect on physical functioning,
- Low-quality evidence of improved sleep, and patient global impression of change.
- **Evidence for effectiveness of cannabinoids in CNCP is limited.**
- NNTB are high, and NNTH low, with limited impact on other domains.
- **"It appears unlikely that cannabinoids are highly effective medicines for CNCP."**

“Cannabis & Cannabinoids for the Treatment of People with Chronic Non-Cancer Pain Conditions: a Systematic Review & Meta-Analysis of Controlled & Observational Studies”; Stockings E et al: *Pain* October 2018

“Their findings are largely consistent with the recent Cochrane review of cannabinoids for neuropathic pain, indicating that these medicines are unlikely to be effective in the treatment of pain”

"Cannabis & Cannabinoids for the Treatment of People with Chronic Non-Cancer Pain Conditions: a Systematic Review & Meta-Analysis of Controlled & Observational Studies"; Stockings E et al: *Pain* October 2018

- most higher-quality RCT evidence was for neuropathic pain & MS-related pain
- scant, low-quality evidence on cannabinoids for fibromyalgia or visceral pain, & very few studies of cannabinoids in the most common and burdensome CNCP conditions, ie back/neck pain, migraines, arthritis.
- → the conclusions of this review primarily relate to nabiximols for neuropathic or MS-related pain.

CONCLUSIONS of recent reviews

1. Weak evidence for efficacy in neuropathic pain
2. No or insufficient evidence of efficacy in:
   - Chronic musculoskeletal pain
   - Headache disorders
   - Chronic visceral pain
   - Cancer pain
3. Few and low quality studies, providing insufficient evidence to gain FDA approval
4. Issue of side effects

Whence the pressure for "medicinal cannabis"?

"Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia" TGA, December 2017

Recommendations

- The use of **medications**, including medicinal cannabis, **is not the core component of therapy for chronic pain**;
- **Patient education** is critical, particularly regarding **expectations of drug therapy**;
- Need larger trials of sufficient quality, size & duration to examine the safety and efficacy of medicinal cannabis use in CNCP.

October 2018 UK Statements

(October 2018 *Pain* review, and 2018 Cochrane review on cannabinoids in neuropathic pain)

4 separate British guidelines on "medicinal cannabinoids" published, October 2018 –

1. British Pain Society,
2. NHS,
3. Faculty of Pain Medicine (RCA)
4. Royal College of Physicians.

All agreed:

- Evidence not there yet for routine use of cannabinoids in clinical practice
- Lack of effective pharmaceuticals for chronic pain → need better & more robust studies on the potential of cannabinoids in chronic pain
- Clinical use of pharmaceutical grade cannabinoids, not smoked plants
- If evidence does accrue of the safety & efficacy of cannabinoids for chronic pain, it's clinical availability must be expedited for clinical use.
- Need for an interdisciplinary biopsychosocial approach to the management of chronic pain, rather than trying to rely on a purely biomedical approach.

FPMANZCA
Statement on “Medicinal Cannabis”, in Chronic Non-Cancer Pain, 2019

- FPM adheres to the principle that substances intended for therapeutic purposes be fully characterised chemically, pharmacologically and toxicologically to be eligible for registration by regulatory authorities (Therapeutic Goods Administration in Australia; Medsafe in New Zealand).
- The sociopsychobiomedical framework that informs the assessment and management of people with chronic non-cancer pain requires active engagement of patients in a multimodal management program,
- recognises the adverse effects that may be associated with polypharmacy in general, and cannabinoids in particular.

FPMANZCA
Statement on "Medicinal Cannabis", in Chronic Non-Cancer Pain, 2019

- FPM is very concerned about the adverse event profile in cannabis users, especially the young, including impaired lungfunction, psychotic symptoms & disorders, & cognitive impairment.
- "***At the present time, the scientific evidence for the efficacy of cannabinoids in the management of people with chronic non-cancer pain is insufficient to justify endorsement of their clinical use***."

Misuse of Drugs (Medicinal Cannabis) Amendment Act came into effect, Dec 2018

Intention: improve access to medicinal cannabis:

- Based on fairness, quality & safety, & compassion.
- Cannabinoids are to be made to a quality standard

1. those requiring palliation have an exception, & statutory defence to the charge of possession or use of illicit cannabis (NB – what is "*palliation*"?)
2. quality standards for medicinal cannabis products & production
3. Only tetrahydrocannabinols and related psychoactive substances will be controlled drugs. CBD & other non-psychoactive cannabinoids will not be controlled.

Current NZ Legislation 1 - CBD

- Psychoactive substances (eg THC) must not exceed 2% of the total cannabinoids.
- No longer a class B1 controlled drug under the Misuse of Drugs Act 1975
- Now a prescription medicine under the Medicines Act 1981
- MOH approval not required to prescribe, supply or administer a CBD product for medical purposes
- Can be prescribed for up to 3 months

Current NZ Legislation 2 - nabiximols

- Sativex (each mL contains 2.7 mg THC & 2.5 mg CBD) – a Class B1 controlled drug → MOH approval required before most can be prescribed, supplied or administered (regulation 22, Misuse of Drugs Regulations 1977)
- Exception – MOH approval not required for Sativex as add-on treatment for moderate - severe **multiple sclerosis related spasticity, endorsed by a neurologist**
- Unapproved use: an application can be made to the Ministry of Health to prescribe Sativex for patients with other medical conditions, endorsed by a relevant specialist to the condition being treated. Patients must have first trialled, or have contraindications to, approved medicines typically used for the treatment of their condition.

Guardian Weekly, 22.2.2019, p 31

- *"Cannabis and psychodelics are non-addictive. They have been used as medicines since the beginning of human history. I think our meetings were quite influential in persuading important people of that fact."*

(Amanda Feilding, Lady Neidpath, Countess of Wemyss & March, of the Beckley Foundation)

"The global burden of disease attributable to alcohol & drug use in 195 countries & territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study, 2016"; *Lancet Psychiatry* 5 (December 2018); 987–1012

Globally (in 2016)

1. Alcohol use disorder: 100 million cases (1321 cases per 100 000)
2. Opioid use disorder: 26·8 million (353 cases per 100 000)
3. **Cannabis use disorder**: 22 million (290 cases per 100 000)

"The global burden of disease attributable to alcohol & drug use in 195 countries & territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study, 2016"; *Lancet Psychiatry* 5 (December 2018); 987–1012

Australasia in 2016 :

1. Alcohol use disorder: 384,400 cases (1305 per 100 000)
2. **Cannabis use disorder**: 204,400 (290 cases per 100 000) (2nd highest, behind Nth America) → NZ (4.8 million) → 14,000 CUD in NZ; 375,000 in Christchurch → 1,100 CUD in Christchurch
3. Opioid use disorders: 123,500 (415 cases per 100 000)