



Faculty of Pain Medicine
Australian and New Zealand College of Anaesthetists

Statement on “Medicinal Cannabis” with particular reference to its use in the management of patients with chronic non-cancer pain

1. The Faculty of Pain Medicine (FPM) acknowledges the reality of the widespread, uncontrolled and unlawful use of *cannabis* preparations in the Australian and New Zealand communities.
2. Such use is primarily for recreational purposes.
3. In Australia, there is no regulatory framework for medicinal cannabis or cannabinoid use. In New Zealand, there is a framework for the prescription of nabiximols (Sativex) in multiple sclerosis. Both cannabis possession and use are illegal in both countries.
4. FPM does not take a stance on the issue of decriminalisation of personal use of *cannabis* preparations.
5. FPM considers that calls for the liberalisation of the availability of cannabinoids as medicines are based more on anecdote than on sound clinical science and practice.
6. FPM is very concerned about the adverse event profile in *cannabis* users, especially in young people, including impaired respiratory function, psychotic symptoms and disorders, and cognitive impairment.
7. FPM adheres to the principle that substances intended for therapeutic purposes be fully characterised chemically, pharmacologically and toxicologically.
8. FPM does not support off-label or non-approved prescription of cannabinoid products.

With respect to the use of cannabinoids **in patients with chronic non-cancer pain***:

9. The sociopsychobiomedical conceptual framework that informs the assessment and management of people with chronic non-cancer pain requires active engagement of patients in multimodal management programs, and recognises the adverse effects on this that may be associated with polypharmacy in general and with cannabinoids in particular.
10. FPM does not recognise a need for greater availability of medicines in general and in particular does not endorse the use of cannabinoids in chronic non-cancer pain until such time as a clear therapeutic role for them is identified in the scientific literature.
11. With the possible exception of pain and spasticity in multiple sclerosis, there is little evidence for the effectiveness of cannabinoids in chronic non-cancer pain situations, whether or not the pain attracts the descriptor “neuropathic”.
12. FPM recognises the difficulties inherent in performing trials of any medication in patients with chronic non-cancer pain. Nonetheless FPM believes that trials of cannabinoids are necessary and should be conducted on a coordinated national basis, by highly credentialed persons and within strict parameters.

* Points 9 to 12 do not apply to the management of patients under palliative care.

BACKGROUND NOTES

THE LANDSCAPE

- Worldwide, cannabis is the third most commonly used substance after alcohol and tobacco.
- Unauthorised use of cannabis as a medicine in Australia is widespread (Swift et al, 2005).
- 92% of respondents to the 2012 Illicit Drug Reporting System survey in Australia reported that hydroponic cannabis was “easy” or “very easy” to obtain (Stafford & Burns, 2012).
- In the general population, 4.7% of those aged over 40 years had used cannabis in the past year (Australian Institute of Health and Welfare, 2011).

In populations of pain patients:

- Prevalence of use in chronic pain clinics: 12-15% (Ware et al, 2002, 2003)¹
- Chronic pain is the most common “reason” for patients to report “medical” use of cannabis in the United States (USA) (Dyer 2013) (inverted commas added).

Complexity of chronic pain phenotype

Baseline data from the POINT study² being conducted by the National Drug and Alcohol Research Centre at UNSW Australia have illustrated in more detail the complexity of the phenotype of chronic non-cancer pain (Campbell et al, 2015; Degenhardt et al, 2015).

Findings include:

- Complex clinical profiles were more prevalent among the younger age-groups (‘working’ and ‘nearing retirement’ age groups). These groups reported more mental health problems, more experience of childhood abuse/neglect and lifetime suicidality, and more substance use than the retirement age-group.
- These two groups were also prescribed higher doses of opioids, were more likely to be prescribed codeine as well, and were likely to be taking concurrently prescribed benzodiazepines, antidepressants and antipsychotics.
- Just under half met criteria for current moderate/severe depression, with a substantial minority meeting criteria for
 - current moderate/severe anxiety or agoraphobia
 - lifetime suicidal ideation
 - lifetime alcohol use disorder
- Almost half (43±2%; mean ± 95% CI) of the sample had used cannabis for recreational purposes at some time.
- One in eight (12±2%) of the entire cohort met ICD 10 criteria for lifetime cannabis use disorder
- One in six of the cohort (15±2%) had used cannabis for pain relief.
- A quarter (24±2%) reported that they would use cannabis for pain relief if they had access to it.

1 Note: USA data; some from more than a decade ago.

2 A prospective study in Australia of 1500 patients who have been prescribed opioids for CNCP.

THE SUBSTANCES³

Cannabis (from Latin, meaning hemp)

- Various preparations derived from the plant *Cannabis sativa*.
- Synonyms: marijuana (USA), dope, draw, ganja, grass, pot, puff, smoke, toké, weed. Street names for varieties of cultivated cannabis are: Northern Lights, Haze, Purple Haze, White Widow, Skunk#1, Sensie Star, Orange Bud, Bubblegum, Hindu Kush, Chronic, and Jack Herer.
- Herbal cannabis: leaves and compressed female flower heads of *Cannabis sativa*; also known as weed, grass, ganja, herb, green, thai stick, and bud or bush.
- Resin: compressed tetrahydrocannabinol (THC)-rich bracts from Cannabis plants; also known as hashish, hash, black, blonde palm, rocky, dark rocky, slate, and soapy or soap bar.
- Concentrations of chemical constituents can vary by plant strain and by conditions of growing, storage, harvest and preparation.
- Pharmacological effects may be enhanced by synergies between constituents of cannabis not present in isolated or synthetic cannabinoid pharmaceuticals.
- Standardisation of any plant material, extract or blend for medicinal use is essential, and the chemovar (or chemotype) is the most reliable predictor of medicinal value.

Cannabinoids

- Substances (regardless of chemical structure or whether they are natural or synthetic) that bind to biological receptors and produce the classical spectrum of pharmacological effects demonstrated by extracts of *C. sativa*.
- Principal botanical cannabinoids are
 - delta⁹-tetrahydrocannabinol (THC)
 - cannabidiol (CBD)
 - cannabinol (CBN)⁴

Preparations currently available

A. Medical extracts from *Cannabis sativa*:

- nabiximols (Sativex[®])
 - oromucosal spray
 - 2.7mg THC and 2.5mg CBD per 100µl
 - max 16 sprays per day
 - Indications:
 - chronic neuropathic pain and muscle spasticity in multiple sclerosis (UK, Canada)
 - advanced cancer pain (Canada)
- whole plant extract (Cannador)
 - THC 2.5g and CBD 1.2mg
 - Oral capsule
- standardised plant matter in granular form (produced by Bedrocan BV for the Netherlands Ministry of Health, Welfare and Sport; pharmacy-supplied for vaporisation or tea preparation)
 - THC:CBD 19:1 (Bedrocan),
 - 12:<1 (Bedrobinol),
 - 6:75 (Bediol),
 - 14:< 1 (Bedica)

3 From Mather 2005, Mather et al 2013, RCP 2005, APM4e.

4 CBD and CBN have not been adequately evaluated in treatment of pain.

B. Synthetic cannabinoids:

- dronabinol (Marinol®)
 - synthetic THC
 - oral capsule, 2.5mg, 5mg, 10mg
 - max dose 20mg per day
 - Indications:
 - stimulation of appetite in AIDS-related anorexia and weight loss
 - severe nausea and vomiting associated with cancer chemotherapy
- nabilone (Cesamet®)
 - synthetic THC analogue
 - oral capsule, 0.25mg, 0.5mg, 1mg
 - max dose 6mg per day
 - indications:
 - severe nausea and vomiting associated with cancer chemotherapy

Pharmacology

Some pharmacokinetic considerations:

Transpulmonary (inhaled)

- rapid absorption
- rapid onset of effect
- bioavailability ~18%
- inaccurate dosing
- levels fall within 2h

Oral

- poor absorption
- low bioavailability (<10%)
- difficult to titrate

Transmucosal

- ~oral

Mather 2005: "Any successful future clinical development of cannabinoid pharmacotherapy depends upon a dosage form that is reliable, rapidly titratable to effect, non-smoked, non-injected, and preferably parenteral to avoid hepatic first pass metabolism."

THE EVIDENCE

There are three reviews, of variable quality:

1. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med* 2009; 10:1353-1368.
 - 18 trials; heterogeneous patient groups; questionable quality
 - "... cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms."
2. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain. A systematic review of randomized trials. *Brit J Clin Pharmacol* 2011; 72:735-744.
 - CNCP included: neuropathic pain, fibromyalgia, rheumatoid arthritis, mixed chronic pain
 - 15/18 trials "significant analgesic effect of cannabinoids as compared with placebo"
 - Side-effects "generally well-tolerated"

3. Grotenhermen F, Müller-Vahl K. The therapeutic potential of cannabis and cannabinoids. *Dtsch Arztebl Int* 2012; 109: 495-501.⁵

Perhaps the most reliable overview comes in a commentary from Farrell, Buchbinder & Hall (2014), who put (1) and (2) above into perspective, as well doing their own search. Their conclusions are quoted below, under their arbitrary headings:

Multiple sclerosis (spasticity or neuropathic pain)

Farrell, Buchbinder & Hall (2014): "... the effectiveness of cannabinoids for the treatment of muscle spasticity or neuropathic pain in multiple sclerosis is unclear and any benefit is likely to be modest, while mild to moderate adverse events are common and long term safety has not been established."

Other "neuropathic" pain⁶

Spinal cord injury pain

HIV-associated neuropathy pain

Painful diabetic neuropathy

Farrell, Buchbinder & Hall (2014): "The effectiveness of cannabinoids for the treatment of other neuropathic pain has not been proved."

"Other chronic pain"

Fibromyalgia

Farrell, Buchbinder & Hall (2014): "... the effectiveness of cannabinoids in treating other chronic pain is unclear and any benefit is likely to be modest. Mild to moderate adverse events are often reported and long term safety has not been established."

Cancer pain

Farrell, Buchbinder & Hall (2014): "... the effectiveness of cannabinoids for the treatment of chronic cancer pain remains unclear, although any benefit is likely to be modest. The available evidence indicates a risk of potentially serious adverse effects, including alterations in perception, motor function, and cognitive function."

Safety

"In drug development terms, we have witnessed this complex botanical drug jump straight from phase II to phase IV." (Ware & Desroches, 2014)

Risk factors in cannabis use

- personal or family history of psychosis
- unstable ischaemic heart disease
- pregnancy/breast-feeding
- severe liver or kidney disease
- polypharmacy (especially in the elderly)
- persons < 25y

Most probable adverse effects (Hall & Degenhardt, 2009)

- Cannabis dependence syndrome (around 1/10 users), the main features of which are compulsive use, tolerance of its effects, and withdrawal symptoms. Use may interfere with family, school, and work.
- Chronic bronchitis and impaired respiratory function in regular smokers.

⁵ Quoted in Mather et al 2013: "...a preponderance of favourable controlled trials for treatment of a range of conditions including spasticity resulting from disseminated sclerosis (9 favourable, 3 unfavourable)...chronic neuropathic pain (12 favourable, 2 unfavourable) and other chronic pain (cancer rheumatism, fibromyalgia) (11 favourable, 2 unfavourable)".

⁶ As per IASP 2011 definition.

- Psychotic symptoms and disorders in heavy users, especially those with a history of psychotic symptoms or a family history of these disorders.
- Impaired educational attainment in adolescents who use regularly.
- Subtle cognitive impairment in those who use daily for a decade or more.

Possible adverse effects

- Respiratory cancers.
- Behavioural disorder in children whose mothers used cannabis while pregnant.
- Depressive disorders, mania and suicide
- Increased likelihood in adolescents of using other illicit drugs.

THE “SHOULD” QUESTION CONSIDERED BY THE FACULTY

1. Shipton & Shipton (2014). *Should doctors be allowed to prescribe cannabinoids for pain in Australia and New Zealand?* (New Zealand, Australia)
 - Case to be made for medical cannabinoids to be legally available on a limited basis to patients with specific pain conditions.
 - Cannabinoids should be used only in those patients who might benefit from their use, such as those with neuropathic pain from various causes (including multiple sclerosis).
 - Medical cannabis should be considered only for painful conditions when treatment failure with standard therapy has occurred or where other analgesic medications are not tolerated
2. Farrell, Buchbinder & Hall (2014). *Should doctors prescribe cannabinoids?* (Australia)
 - Doctors are not legally able to prescribe cannabis (the plant product that is smoked) in any jurisdiction as it has not received regulatory approval.
 - Many doctors will be faced with patients using cannabis for complex symptoms of multiple chronic disabling conditions for which there are limited treatment options.
 - Doctors should discuss, in a dispassionate and non-judgmental and supportive manner, the advisability or otherwise of using cannabis to palliate such symptoms.
 - There is no clear evidence for effectiveness in treating pain. Any benefits are likely to be modest, and there is no clear evidence that putative benefits outweigh possible harms.
 - If the product is legally available, then doctors are free to prescribe it for approved indications.
 - If medical use is likely to be long term, patients should be warned that the adverse effects of long term use remain unclear. Patients could also be advised of the adverse effects reported in long term recreational users, such as the development of dependence.
 - Clinicians should avoid taking medicolegal responsibility for non-approved or off-label prescribing.
3. Ware & Desroches (2014). *What does the practicing pain clinician need to know?* (In: Clinical Updates) (USA)
 - “... the response ... that there is ‘not enough information’ is disingenuous at best, and at worst, an abnegation of clinical responsibility.”
 - “It is assumed that practicing clinicians can and will put aside their own biases and prejudices (in any direction) and base their therapeutic decisions on clinical need, known risks and benefits, and the context in which the consultation occurs.”
 - “The medical use of cannabis is not an end in itself; the patient demanding cannabis and refusing to consider options may have motivations other than amelioration of pain and improvement in quality of life.”

- “Careful consideration of cannabis use in pain medicine provides an opportunity to deepen and refine our pain-management toolbox, understand our patients’ needs and wishes, strengthen our relationships, and improve the quality of our care, while we wait for more long-term RCTs to provide more definitive evidence.”
- “...clinicians must be aware of their own knowledge and practice and should be prepared to decline access...”

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