

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

### BACKGROUND PAPER

*This document supplements PS10(PM) and PS10(PM) PLS*

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## 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)<sup>1</sup>
- 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 study<sup>2</sup> being conducted by the National Drug and Alcohol Research Centre at UNSW Sydney 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% 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.

## The substances<sup>3</sup>

**Cannabis** (from Latin, meaning hemp)

- Various preparations derived from the plant *Cannabis sativa*
- Synonyms: marijuana (USA), dope, draw, ganja, grass, pot, puff, smoke, toke, 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.

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<sup>1</sup> Note: USA data; some from more than a decade ago

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

<sup>3</sup> From Mather 2005, Mather et al 2013, RCP 2005, APM4e

- 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
  - delta<sup>9</sup>-tetrahydrocannabinol (THC)
  - cannabidiol (CBD)
  - cannabinol (CBN)<sup>4</sup>

### Preparations currently available

#### A. Medical extracts from *Cannabis sativata*:

- nabiximols (Sativex®)
  - oromucosal spray
  - 2.7mg THC and 2.5mg CBD per 100µl
  - max 16 sprays per day
  - indications:
    - adjunctive treatment for the symptomatic relief of neuropathic pain in patients with multiple sclerosis (Canada)
    - adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain (Canada)
    - spasticity in multiple sclerosis (Australia, UK, EU)
- 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)

#### 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

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<sup>4</sup> CBD and CBN have not been adequately evaluated in treatment of pain

## Pharmacology

Some pharmacokinetic considerations:

Transpulmonary (inhaled)

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

Oral (and transmucosal)

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

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."

## Guidance

### TGA guidance

In December 2017 the Therapeutics Goods Administration (TGA) of the Australian Government Department of Health published "**Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia**". <https://www.tga.gov.au/node/732373>

This authoritative document arose out of a systematic review, commissioned by the Department of Health, by a team from the University of New South Wales, University of Sydney and University of Queensland under the coordination of the National Drug and Alcohol Centre (NDARC), which was tasked to assess the available evidence for the use of medicinal cannabis in chronic non-cancer pain (Stockings et al, 2018) and four other settings (palliative care, epilepsy, chemotherapy-induced nausea and vomiting, and multiple sclerosis).

The Recommendations in the TGA guidance document are as follows:

- A comprehensive sociopsychobiomedical assessment of the patient with CNCP is appropriate.
- The use of medications, including medicinal cannabis, is not the core component of therapy for CNCP;
- Patient education is a critical component of therapy for CNCP, particularly with respect to expectations of drug therapy.
- There is a need for larger trials of sufficient quality, size and duration to examine the safety and efficacy of medicinal cannabis use in CNCP. (p. 3)
- In the absence of strong evidence for dosing and specific preparations of cannabis or cannabinoids in the treatment of CNCP, it is recommended that any treating physician who elects to initiate cannabinoid therapy should assess response to treatment, effectiveness and adverse effects after 1 month. This is best achieved as part of a research project or clinical audit. (p. 14)

### IASP guidance (2021)

International Association for the Study of Pain presidential task force on cannabis and cannabinoid analgesia position statement (Pain 2021;162(7)(Supp 1):S1-S2)

In 2021, the IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia Reviews published a series of papers on this topic (see 2021 Addendum).

The overall conclusion of this task force is:

Reviews of preclinical research and clinical safety and efficacy of cannabis and cannabinoids for pain relief have identified important research gaps. Due to the lack of high-quality clinical

evidence, the International Association for the Study of Pain (IASP) does not currently endorse general use of cannabis and cannabinoids for pain relief. International Association for the Study of Pain recognizes the pressing need for preclinical and clinical studies to fill the research gap, and for education on this topic.

### **Choosing Wisely recommendation (Australia), 2021**

#### Recommendation 6<sup>5</sup>

Do not prescribe currently available medicinal cannabis products to treat chronic non-cancer pain (CNCP) unless part of a registered clinical trial.

#### The evidence

##### **Current literature (2018)**

**1. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, Murnion B, Farrell M, Weier M, Degenhardt L. Cannabis and cannabinoids for the treatment of people with chronic non- cancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain 2018; 159(10):1932-1954.**

This rigorous, comprehensive review identified 104 studies (n = 9958 participants), comprising 47 randomised controlled trials (24 parallel, 23 cross-over) and 57 observational studies. Diagnostic groups included "neuropathic<sup>6</sup> pain" (48 studies), "fibromyalgia" (7), MS<sup>7</sup>-related pain (13), and "mixed or undefined CNCP" (29).

The most commonly studied outcomes were pain intensity (100 studies), adverse events (81) and withdrawals (71). Fewer studies reported on physical functioning (52), emotional functioning (43), and patient's global impression of change (24). Only two studies in which pain was the primary indication reported on all six outcomes.

Pain was the primary indication in 76 studies and a secondary indication in 28 studies. Of the 104 included studies, four (n = 47 participants) examined cannabinoids as a first-line therapy, and 87 examined cannabinoids as a second-line therapy in addition to existing medication regimens. In nearly all RCT studies, patients were required to be on a stable dose of current medication before commencement of the trial. The most commonly studied cannabinoid was nabiximols, followed by *Cannabis sativa*.

The main findings regarding pain included:

- Across all CNCP conditions, cannabinoids were more likely than placebo to produce a 30% reduction in pain (OR 1.46, 95%CI 1.16-1.84) . The NNTB<sup>8</sup> was 24 (95% CI 15 to 61).
- There was no significant evidence that cannabinoids reduced pain by 50% compared to placebo (OR 1.43, 95% CI 0.97-2.11)
- Cannabinoids overall were associated with a larger reduction in pain intensity than placebo (SMD -0.14, 95%CI -0.20 to -0.08). This was calculated to be a reduction of about 3mm (95%CI -5 to -1) on a 0-100mm VAS.

CNCP patients who received a cannabinoid had twice the odds of withdrawing from a trial for any reason than patients who received placebo, and 3.5 times the odds of withdrawing because of adverse events. Similarly CNCP patients who received a cannabinoid had 2.3 times the odds of

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<sup>5</sup> How the recommendation was made: FPM conducted a poll of the fellowship to assess support for a Choosing Wisely recommendation regarding the role of medicinal cannabis in chronic non-cancer pain treatment. The proposal, which was very similar to the final wording of the recommendation, was supported by 79% of the fellows who responded (more than 25% of the active fellowship). The final wording of the recommendation was iterated with the Representative Panel of Choosing Wisely.

<sup>6</sup> No distinction made between the pre- and post-2011 definitions of "neuropathic pain"

<sup>7</sup> MS: multiple sclerosis

<sup>8</sup> NNTB: number needed to treat to benefit

experiencing an adverse event compared to placebo. The NNTH<sup>9</sup> for any adverse event was 6 (95%CI 5 to 8).

There were no significant impacts upon physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change.

The authors concluded: "It appears unlikely that cannabinoids are highly effective medicines for CNCP."

### Earlier literature

In the literature that preceded the publication of the TGA Guidance document, there are several reviews on which opinion and advocacy were based. These are summarised here for completeness.

#### 2017

#### **2. National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press.**

This document concluded, "There is substantial evidence that cannabis is an effective treatment for chronic pain in adults." [CONCLUSION 4-1 (page 4-2)] This was based largely on Whiting et al (2015), as the authors commented:

"The rigorous screening approach used by Whiting et al. (2015) led to the identification of 28 randomized trials in patients with chronic pain (2,454 participants). Twenty-two of these trials evaluated plant-derived cannabinoids (nabiximols, 13 trials; plant flower that was smoked or vaporized, 5 trials; THC oramucosal spray, 3 trials; and oral THC, 1 trial) while five trials evaluated synthetic THC (i.e., nabilone). All but one of the selected primary trials used a placebo control, while the remaining trial used an active comparator (amitriptyline). The medical condition underlying the chronic pain was most often related to a neuropathy (17 trials); other conditions included cancer pain, multiple sclerosis, rheumatoid arthritis, musculoskeletal issues, and chemotherapy-induced pain. Analyses across seven trials that evaluated nabiximols and one that evaluated the effects of inhaled cannabis suggested that plant-derived cannabinoids increase the odds for improvement of pain by approximately 40 percent versus the control condition (odds ratio [OR] 1.41, 95% confidence interval [CI] = 0.99–2.00; 8 trials). The effects did not differ significantly across pain conditions, although it was not clear that there was adequate statistical power to test for such differences." (P. 4-3)

#### **3. Nugent SM, Morasco BJ, O'Neil ME, Michele Freeman, M, Low, A, Kondo K, Elven C, Zakher B, Motu'apuaka M, Paynter R, Kansagara D. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. Ann Intern Med 2017;10.7326/M17-0155.**

This review identified 30 RCTs and 3 cohort studies. Of the 13 trials on "neuropathic pain", only 4 post-dated the 2011 change in definition, of which 3 used vaporised or smoked THC. In these 4 trials, NNTHs varied from 8.7 (for nabiximols in peripheral neuropathy) to 2.3 (for 6.7%THC in spinal cord injury). Ten trials were only or predominantly in patients with MS: there was "insufficient evidence to characterize the effects of cannabis on pain in patients with MS because of the small number of methodologically rigorous studies, inconsistent findings across studies, lack of long-term outcomes, and small number of patients included in the trials".

The authors concluded: "Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects".

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<sup>9</sup> NNTH: number needed to treat to harm

## **2016**

### **4. Barnes MP, Barnes JC. Cannabis: The Evidence for Medical Use. Northumberland, Tyne & Wear NHS Foundation Trust, May 2016**

This is a non-critical narrative review of the literature, grouped by agent: nabilone, dronabinol, nabiximols and smoked cannabis. The authors "...amalgamated the studies of chronic pain and neuropathic pain as there appears to be no difference in efficacy between these two modalities" (p. 22).

The authors concluded (p. 33):

"This is a difficult literature to summarise as a number of different formulations have been used and a number of different types of pain have been studied. The authors are also aware of the considerable literature in terms of anecdotal reports, case studies, questionnaires and uncontrolled trials that have also showed efficacy in various types of pain with various formulations.

However, nabilone, dronabinol, nabiximols and smoked marijuana have all been shown to be efficacious to varying extents in a variety of pain settings in good quality studies. We conclude that there is **good** evidence for efficacy of cannabis for pain relief in various formulations and in a number of settings." (Emphasis in original)

## **2015**

### **5. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidtkofer S, Westwood M, Kleijnen J. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. JAMA 2015; 313:2456-2473.**

Until recently this review was the main source of reference. The authors identified 28 studies in chronic pain, involving 2,454 patients in heterogeneous groups, ranging from "neuropathic" pain<sup>10</sup> (12 studies), cancer pain (3 studies), diabetic peripheral neuropathy (3 studies), fibromyalgia (2 studies) and HIV-associated peripheral neuropathy (2 studies). Seventeen studies were considered to be a high risk of bias; 2 were at low risk and 9 were of uncertain risk. Thirteen studies were of nabiximols, 4 studies were of smoked THC, 3 for THC oromucosal spray, 5 of nabilone, 2 of dronabinol; all but one were placebo-controlled.

Overall, "The average number of patients who reported a reduction in pain of at least 30% was greater with cannabinoids than with placebo (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials". In 6 trials of nabiximols, the weighted mean difference in pain on a 0-10 NRS was -0.46 [95% CI, -0.80 to -0.11] (in favour of the cannabinoid).

The authors concluded: "There was moderate quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity... Cannabinoids were associated with an increased risk of short-term AEs".<sup>11</sup>

### **6. Boychuk DG, Goddard G, Mauro G, et al. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache. 2015; 29:7-14.**

This review identified 24 studies of "chronic neuropathic pain" but 11 were excluded for various quality reasons. Five of the 13 included studies (published between 2003 and 2013) were of nabiximols, 5 of smoked or vaporised cannabis, 1 of dronabinol, 1 of nabilone, with a total of 771 subjects.

The authors found:

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<sup>10</sup> See footnote 5

<sup>11</sup> From this study, Stockings et al (2018) calculated NNTB for 30% pain reduction of 22 and for 50% pain reduction 26. These indices do not support the conclusion of Whiting and colleagues.

"The quasi-totality of the high-quality studies included in the present systematic review suggests that cannabinoids provide significant pain reduction in both the short term and longer term, without significant side effects..." and noted that "Nine out of 13 studies clearly stated a NNT ranging from 2 to 4, with no differences among type of cannabinoids". Furthermore, "... the present systematic review found very few risks related to the use of cannabinoid compounds in the treatment of chronic neuropathic pain. The vast majority of adverse events listed were considered minor in nature".

**7. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician 2015; 61:e372-81.**

This review examined 6 RCTs (n=226 patients) of nonsynthetic smoked or vaporised cannabinoids, mainly in "neuropathic" pain, as adjuncts to other drugs including opioids and anticonvulsants. All studies were of short duration (<5 days) and were limited by problems with masking, variability in dosing and strength of THC and lack of functional outcomes. Only 3 of the 6 studies reported a "clinically meaningful pain reduction", defined as a decrease of 2 points on a 0-to10 numerical pain rating or a 30% improvement in pain intensity. Neurocognitive adverse effects were common but "well tolerated".

The authors concluded: "Generalizing the use of medical marijuana to all CNCP conditions does not appear to be supported by existing evidence".

**Prior to 2015**

**8a. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol 2011; 72:735-44.**

This paper reviewed 18 trials published between 2003 and 2010, involving 766 patients. Of these trials, 4 were of smoked cannabis in "neuropathic" pain<sup>12</sup>, 7 of oromucosal preparations in mixed pain populations, 4 of nabilone in mixed pain populations, and 2 of dronabinol in mixed pain populations, all placebo-controlled. In 15 trials, a "significant analgesic effect" of the cannabinoid was noted.

**8b. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol 2015DOI 10.1007/s11481-015-9600-6.**

These same authors identified another 11 trials published between 2010 and 2014, with 1185 patients. Two trials were of smoked cannabis in "neuropathic" pain, 4 of nabiximols in "neuropathic" pain and 4 of nabilone in mixed pain populations; control groups were variable. In 7 trials there were "significant analgesic effects" of cannabinoids.

The authors concluded overall (8a and 8b): "...there are a total of 22 of 29 RCTs demonstrating that cannabinoids demonstrate a modest analgesic effect and are safe in the management of chronic pain."

**9. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JLR. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009; 8:1353-68.**

This review identified 18 double-blind randomised controlled trials of sufficient quality that compared any cannabis preparation to placebo among subjects with chronic pain. There was marked variability in study design, methodology and analysis, the last especially with respect to reporting of outcomes. The efficacy analysis (VAS) found a standardised mean difference of -0.61 [95%CI: -0.84 to -0.37] (in favour of cannabinoid). A high risk of harms was found: for alteration of perception OR was 4.5 [95%CI: 3.0 to 6.7] and NNH 7 [6-9]; for altered cognitive function, OR was 4.5 [95%CI: 2.4 to 8.4] and NNH 8 [6-12].

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<sup>12</sup> Pre-2011 definition



## **2021 addendum**

In 2021, the IASP Presidential Taskforce on Cannabis and Cannabinoid Analgesia published a supplement in PAIN [Voll 162(7)(Supp 1)], containing the following contributions:

- IASP Presidential Task Force on Cannabis and Cannabinoid Analgesia  
International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia position statement  
Pain 2021;162(7)(Supp 1):S1-S2
- Finn DP, Simon Haroutounian S, Hohmann AG, Krane E, Soliman N, Rice ASC.  
Cannabinoids, the endocannabinoid system, and pain: a review of preclinical studies  
Pain 2021;162(7)(Supp 1):S5-25
- Fisher E, R. Moore RA, Fogarty AE, Finn DP, Finnerup NB, Gilron I, Haroutounian S, Krane E, Rice ASC, Rowbotham M, Wallace M, Eccleston C  
Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials  
Pain 2021;162(7)(Supp 1):S45-S66
- Moore RA, Fisher E, Finn DP, Finnerup NB, Gilron I, Haroutounian S, Krane E, Rice ASC, Rowbotham M, Wallace M, Eccleston C  
Cannabinoids, cannabis, and cannabis-based medicines for pain management: an overview of systematic reviews  
Pain 2021;162(7)(Supp 1):S67-S79
- Mohiuddin M, Blyth FM, Degenhardt L, Di Fortid M, Eccleston C, Haroutounian S, Moore RA, Rice ASC, Wallace M, Park R, Gilron I.  
General risks of harm with cannabinoids, cannabis, and cannabis-based medicine possibly relevant to patients receiving these for pain management: an overview of systematic reviews  
Pain 2021;162(7)(Supp 1):S80-S96
- Haroutounian S, Gilron I, Belton J, Degenhardt L, Di Forti M, Finn DP, Fogarty A, Kalso E, Krane E, Moore RA, Rowbotham M, Wallace M, Rice ASC.  
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International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia: research agenda on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management  
Pain 2021;162(7)(Supp 1):S117-S124

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