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CLINICAL PERSPECTIVE

Medicinal cannabis: is current use clinically justified?

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Abstract

Cannabis products are increasingly perceived and advertised as natural and safe treatments for a variety of conditions, including chronic non-cancer pain (CNCP). The number of prescriptions for medicinal cannabis (MC) currently averages >80 000 per month for >1 million Australians. Although over 800 different cannabis products are available to prescribe in Australia, only two are registered on the Australian Register of Therapeutic Goods and approved by the Therapeutic Goods Administration for specific clinical indications. Using treatment for CNCP as an example, evidence of efficacy across nine systematic reviews was inconsistent and/or of low quality and, with the exception of neuropathic pain, was unable to identify patient phenotypes in whom a specific type and dosing of cannabis product can reliably provide sustained symptomatic relief. Professional bodies do not endorse unregulated or first-line use of cannabis for CNCP. Harm from cannabis is under-reported but adverse effects include impaired cognitive function, dizziness, sedation, confusion, psychosis and arrhythmias, potentially more so in older patients. Healthcare professionals must inform patients of the significant limitations of current evidence of efficacy and safety for cannabis use in CNCP and other conditions and resist media and industry pressures for greater access to and prescribing of MC.

Introduction

In recent years, medicinal cannabis (MC) has attracted attention as a potentially safe and effective treatment for a variety of conditions, including chronic non-cancer pain (CNCP), anxiety syndromes, post-traumatic stress syndrome (PTSD) and sleep disorders. Since legalisation for medical purposes in 2016, approximately 1 million Australians now regularly use MC.[1] In tandem, industry manufacturers of MC have grown in numbers, with revenue virtually doubling each year over the past 5 years, with an estimated $402 million in sales in the first 6 months of 2024.[2] Maintaining a balance between access and safety of MC has become a key priority for health regulators across Australia amid fast-growing numbers of prescriptions, emergence of telehealth, online prescribing and direct-to-consumer health services, minimal evidence of efficacy for unapproved indications and rising awareness of incidents of patient harm. This clinical perspective has several aims: to chronicle the rise of MC use and the reasons why; appraise evidence of efficacy of MC using treatment of CNCP as an example, given it accounts for almost half of all approved MC prescriptions[3]; assess risks of harm; and ascertain professional attitudes towards MC prescribing for CNCP.

Brief history of MC de-regulation

The approval process applied by the Therapeutic Goods Administration (TGA) to a registered product, predicated on satisfactory assessments of its quality, efficacy and safety, does not apply to MC.[4] In December 2020, low-dose cannabidiol (CBD) preparations were down-scheduled in the Australian Registry of Therapeutic Goods (ARTG) from 'prescription only' medicines (Schedule 4) to 'over-the-counter' medicines (Schedule 3).[5] There are currently two pathways patients can access MC via the TGA: authorised prescribers (APs), currently >5700

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medical and nurse practitioners,[1] who are registered to prescribe specific MC products directly to a class of patients for specified indications (see below) and who do not have to notify the TGA of each prescription written; and the Special Access Scheme (SAS)-B pathway, which allows access to cannabis on compassionate grounds as a treatment of last resort, without the usual quality and safety checks. This is separate from the (SAS)-A pathway, which is reserved for seriously ill patients. Approvals via the AP pathway reached a new record high in the first half of 2024 (393 111), up 15% from the second half of 2023 (341 803). Approvals via the SAS-B pathway have been climbing slowly upwards, reaching a new peak of 89 422 approvals in the first half of 2024.[3] In total, this represents >80 000 approved prescriptions per month, but which includes multiple prescriptions for the same patient.

Although over 800 different MC products are currently available to prescribe in Australia, only two are registered on the ARTG and subject to TGA pharmacovigilance: Sativex (nabiximols) for spasticity associated with multiple sclerosis; and Epidyolex (CBD) for seizures associated with Dravet and Lennox–Gastaut syndromes.[6] The number of prescriptions for unregistered products has risen exponentially,[7] with >812 000 approvals via the AP pathway,[8] and an additional 447 500 approvals via the SAS-B pathway between July 2016 and July 2023.[9] While the TGA has called for the MC industry to include all their products in the ARTG, no further applications have been received, leaving the TGA to pass responsibility for prescribing unregistered products to practitioners with patient consent. In addition, the TGA, during the COVID-19 pandemic, allowed product sponsors, including overseas manufacturers, to no longer submit a declaration of compliance with Therapeutic Goods Order 93, its standard for quality manufacturing of MC.[10] The caveats are that sponsors must still submit 6-monthly supply reports to the TGA listing the product (brand name) details and quantities supplied in Australia, and that the TGA will still conduct random and targeted monitoring of products. The most recent audit in 2022–2023 was to check whether several cannabis oil products, sold as oils, had been adulterated with delta-8 tetrahydrocannabinol (THC), but no further testing of imported products has been performed since then.

Since adverse event reporting does not apply to unregistered products, this increase in prescribing has not been accompanied by a parallel process for collecting robust data on efficacy or safety of MC products. The TGA does not record or report numbers of patients accessing MC products, only approvals for access.[11] Limited information is available on patient age, gender and indications for MC and, as such, data are only collected and reported for approvals issued via the SAS-B pathway.

Since 2021, the TGA has split MC products into five categories based on how much CBD or THC they contain. Category 5 comprises Schedule 8 products containing >98% THC, products that may render the user euphoric if used inappropriately. Under the SAS-B pathway, Category 5 products are those most commonly prescribed: over 203 000 approvals to May 2024, compared to 81 560 for Category 1 (Schedule 1 drugs), which are high-concentrate CBD-dominant products.[3] Such approvals account for about a quarter of all patients and nearly a third of new patients. Significantly, about a third (45 684) of Category 5 THC approvals were for anxiety treatment, despite the TGA's own guidance stating THC-containing products are 'generally not appropriate' for patients with a 'previous psychotic or concurrent active mood or anxiety disorder'. In October 2022, the TGA conceded there is 'little scrutiny on whether the risk-benefit ratio remains favourable to patients' in using these products and considered various reforms, such as restricting AP numbers, confining prescribers to specific specialists or linking prescribing to practitioners with proven ongoing relationships with patients.[12] None of these reforms has been enacted. Similarly, a joint meeting in February 2024 between the TGA, federal, state and territory health departments, and various health complaints commissions has yet to announce any action plan.

In the meantime, patient access to MC has been further enhanced by their ability to search the internet and find an MC-prescribing clinic offering a prompt initial telehealth consultation, avoiding the need for face-to-face consultation and assessment by a medical or nurse practitioner.[13] 'Vertically integrated' clinics can direct patients to a specific pharmacy or outlet, often having a commercial agreement with the prescriber, and provide a particular brand of MC product that can then be ordered and paid for online and promptly delivered directly to a home address.[14] Even with this, only 30% of users always or sometimes access MC via a prescription.[15]

Currently, MC is not subsidised by the Pharmaceutical Benefits Scheme or any private health insurance fund, and can cost between $250 and $300 a month.[16] In 2023, Australians spent an estimated $448 million purchasing MC and $402 million in just the first 6 months of 2024.[17] Advertising of MC to the public contributes to this expenditure despite being strictly prohibited by the TGA, which, in the past 2 years, has issued infringement notices worth over $1.4 million.[18] Despite this, a recent study of 54 MC clinic websites found nearly half were breaching at least two of the six TGA guidelines

regarding MC promotion and advertising, many using terms such as 'green medicine' or 'plant medicine' to obscure their promotion and making unsubstantiated claims about health benefits of MC.[19]

Appraising evidence of efficacy of medical cannabis: the example of CNCP

Clearly there needs to be a balance between protecting patients from inappropriate and potentially harmful prescribing while maintaining legitimate access to MC in patients where it has demonstrated, or has significant potential for, clinically meaningful benefit with little risk of harm. CNCP, defined as daily pain for longer than 3 months, affects approximately one in five Australian adults[20] and up to one in three children and adolescents.[21] CNCP can be debilitating, with worse health, societal and financial outcomes. In 2018, CNCP cost the Australian economy $139.3 billion in lost productivity, $2.7 billion in out-of-pocket expenses for patients and > $12 billion to the healthcare system.[22] Opioids are commonly prescribed to treat such pain, with a risk of side effects and addiction. Between 2009 and 2014, opioid prescribing increased by 30%,[23] and opioid-induced deaths doubled between 2007 and 2016 from 3.8 to 6.6 deaths per 100 000, with >75% involving pharmaceutical opioids. In response, codeine was up-scheduled in the ARTG by the TGA in 2018 and real-time opioid prescription monitoring was introduced.

It is not surprising that regulators, clinicians and patients have been eager to find more effective and safer agents for treating CNCP in cases where simple analgesics (such as paracetamol) or non-steroidal anti-inflammatory drugs are ineffective, contraindicated or not tolerated. In Table 1, we summarise the results of nine contemporary systematic reviews of clinical trials retrieved from a literature search from January 2018 to May 2024 using 'medicinal cannabis,' 'chronic pain' and synonyms as search terms and rated for quality using the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews (v2)) appraisal tool.[24] These reviews[25–33] mostly comprised randomised controlled trials (RCTs) and, except for one review,[28] were rated as high-quality, and their results for MC are briefly described below.

A 2018 Cochrane review found moderate-quality evidence for the clinically meaningful outcome of ≥30% relief of chronic neuropathic pain.[25] A 2018 review found a 3% absolute increase in the proportion of patients reporting a 30% reduction in CNCP,[26] with larger effects seen in small sample studies, although effects diminished to non-significant levels with longer-duration studies (≥13 weeks). A 2020 review of 33 trials found clinically small reductions in the intensity of neuropathic and non-neuropathic pain.[27] A 2020 review of 29 trials concluded a small benefit from cannabinoids based on low-quality evidence.[28] A 2021 review of 36 RCTs concluded there was low- or very low-quality evidence of benefit, with a duration of >7 days in only six trials.[29] Another 2021 review of 32 RCTs reported moderate certainty evidence for more patients experiencing ≥30% pain reduction from non-inhaled cannabis.[30] A 2022 review of eight RCTs of cannabinoid treatment restricted to several chronic pain conditions found low-quality evidence of little or no benefit.[31] Another 2022 review of 18 RCTs was limited by variation in interventions and insufficient data for some products (including the THC-CBD ratio and purity of extracted products).[32] Finally, a 2023 review that included 16 RCTs showed effects on chronic pain and sleep quality below pre-defined minimal clinically important differences (MCIDs).[33]

Evidence limitations

Individual trials and reviews varied greatly in patient populations, pain phenotypes, efficacy outcomes, choice of cannabis products, dosage and ratios of THC versus CBD and routes of administration (oral, sublingual, inhaled, flower, leaf, tablet, alcohol-based sprays, oil preparations).[34,35] Most trials compared cannabis with inactive placebo rather than active controls receiving standard treatments.[36] Meaningful pain improvements varied greatly, particularly influenced by baseline levels of pain and co-existing clinical conditions.[37] However, small samples (<100), short duration (none >6 months), selective and inconsistent outcome reporting, imprecision, use of visual analogue pain scales (or conversions to a numerical rating scale) where MCIDs were not defined *a priori*, marked heterogeneity in study designs and publication bias towards 'positive' results means it is almost impossible, apart from chronic neuropathic pain, to identify which patients, with which pain syndromes, may meaningfully benefit from a particular cannabinoid administered by a certain route at a particular dose over a defined period of time. After performing a meta-analysis of all randomised studies in CNCP across all MC products in November 2024, the TGA stated that MC was more likely than placebo to produce 30% and 50% reductions in pain scores, while noting that for most studies evidence was of low quality.[38]

Conducting an RCT involving specific dosing of a drug with a hypothesised mechanism of action is difficult when cannabis products have many variable constituents,[39] with some having both synergistic or antagonistic interactions.[40] In contrast to studies

Table 1 Summary of evidence

Reference, year	Study design; No. trials/ studies; No. participants	Cannabis product type; pain syndrome	Quality assessment method; risk of bias for individual studies	Main results for outcome measures	Authors' conclusions	AMSTAR-2 rating of quality
Mucke *et al.*, 2018[25]	16 trials; mixture cannabis versus placebo/active treatment $n = 1750$ Subgroup analyses according to type of cannabis product	Oromucosal spray with plant-derived THC/CBD combination Synthetic cannabinoid Inhaled herbal cannabis Plant-derived THC Chronic neuropathic pain	GRADE system Cochrane RoB tool Low quality ($n = 2$) Moderate quality ($n = 12$) High quality ($n = 2$)	50% pain relief: RD 5% (low-quality evidence); NNTB = 20 30% pain relief: RD 9% (moderate-quality evidence); NNTB = 11 PGIC: RD 9% (very low-quality evidence); NNTB =10 Adverse event: RD 4% increase (moderate-quality evidence); NNTH = 25 CNS adverse events: RD 38% increase (low-quality evidence); NNTH = 3 Psychiatric disorders: RD 10% increase in cannabis (low-quality evidence); NNTH = 10	Beneficial effects of cannabis-based medicines may be outweighed by potential harms	High
Stockinga *et al.*, 2018[26]	104 studies; 47 RCTs; 57 non-RCTs Mixture of cannabis versus placebo/active treatment $n = 9958$ Separate analyses for RCTs and non-RCTs	THC, CBM, THC + CBD combinations, plant-based cannabis, synthetic THC CNCP; neuropathic pain, arthritis, fibromyalgia	GRADE system Cochrane RoB tool for RCTs Cochrane RoB for non-RCTs (ROBINS-1) tool RCTs Low RoB ($n = 15$) Moderate RoB ($n = 31$) High RoB ($n = 1$) Non-RCTs All high RoB	RCTs 30% pain relief: OR, 1.48; RD, 3.9% (moderate-quality evidence); NNTB = 24 PGIC: OR, 1.62; RD, 7.1% (moderate-quality evidence); NNTB = 38 SMD in pain scale: −0.14 (equivalent to 3-mm difference on a 100-mm VAS) (moderate-quality evidence). Adverse events (dizziness, depression, cognitive disturbance, drowsiness, confusion): OR, 2.3; RD, 15.0% increase (moderate-quality evidence); NNTH = 6 Non-RCTs 30% pain relief: OR, 8.80 (very low-quality evidence) 50% pain relief: OR, 5.54 (very low-quality evidence)	Evidence for effectiveness of cannabinoids is limited; seems unlikely they are highly effective medicines for CNCP; NNTB is high and NNTH is low	High

Table 1 *Continued*

Reference, year	Study design; No. trials/ studies; No. participants	Cannabis product type; pain syndrome	Quality assessment method; risk of bias for individual studies	Main results for outcome measures	Authors' conclusions	AMSTAR-2 rating of quality
Wong *et al.*, 2020[27]	43 RCTs 33 RCTs placebo-controlled RCTs; 10 active-controlled RCTs $n = 3444$ Subgroup analyses according to control group and pain type	Inhaled, oral, oromucosal forms of synthetic THC or cannabis extract CNCP; neuropathic pain, fibromyalgia, multiple sclerosis	GRADE system Cochrane RoB tool Low RoB ($n = 4$) High RoB ($n = 17$) Unclear RoB ($n = 22$)	Reduction in mean pain score (scale 0–10) All cannabinoids (all trials) −0.63 (low-quality evidence) All cannabinoids (placebo only) −0.70 (moderate-quality evidence Neuropathic pain −0.74 (moderate-quality evidence) Non-neuropathic pain −0.60 (moderate-quality evidence) Multiple sclerosis pain −0.67 (moderate-quality evidence)	Pain intensity was reduced with cannabinoids but effect sizes were small	High
Johal *et al.*, 2020[28]	36 RCTs $n = 4006$ Stratified analyses according to route and type of cannabinoids and pain type	Inhaled, oral, oromucosal forms of synthetic THC or CBD CNCP; neuropathic pain, fibromyalgia, multiple sclerosis, spinal cord injury	GRADE system Cochrane RoB tool Low RoB ($n = 3$) Moderate RoB ($n = 5$) High RoB ($n = 28$)	MD in pain scale (0–10): 1 day to 6 months: −0.63 (low-quality evidence) 1 day to 2 weeks: −0.54 (moderate-quality evidence) 2–8 weeks: −0.68 (low-quality evidence) 2–6 months: −0.43 (low-quality evidence)	Moderate evidence to support cannabinoids in treating CNCP at 2 weeks. Similar results observed at later time points but confidence in effect is low	Moderate
Fisher *et al.*, 2021[29]	36 RCTs 30 RCTs cannabis versus placebo 6 RCTs cannabis versus other treatments $n = 7217$ Subgroup analyses according to type of cannabinoids, study duration and pain type	Any type of cannabinoid product, natural or synthetic, delivered by any route of administration Acute pain of any type, neuropathic pain, multiple sclerosis, carpal tunnel	GRADE system Cochrane RoB tool Low RoB ($n = 5$) Moderate RoB ($n = 5$) High/uncertain RoB ($n = 26$)	Pain outcomes up to 7 days 30% pain relief: RD 33% in 2 trials (very low-quality evidence); NNTB = 3 Pain outcomes ≥7 days 30% pain relief: RD 6% in 6 trials (very low-quality evidence); NNTB = 16 Adverse events: RD 13% increase in 12 trials (low-quality evidence); NNTH 7	RCT evidence for cannabis products in people with pain is of low to very low quality, and neither supports nor refutes claims of efficacy or safety	High
Wang *et al.*, 2021[30]	32 RCTs 29 RCTS cannabis versus placebo	Oral (17 RCTs), inhaled (13 RCTs) or topically administered (2 RCTs) cannabis product	GRADE system Cochrane RoB tool Low RoB ($n = 4$) Moderate RoB ($n = 16$)	Placebo-controlled trials WMD in pain scale (0–10): −0.50; RD in proportions achieving MCID 1 point: 10%	Moderate to high certainty evidence shows non-inhaled medical cannabis or cannabinoids, compared to	High

Table 1 *Continued*

Reference, year	Study design; No. trials/ studies; No. participants	Cannabis product type; pain syndrome	Quality assessment method; risk of bias for individual studies	Main results for outcome measures	Authors' conclusions	AMSTAR-2 rating of quality
	3 RCTs cannabis versus active control $n = 5174$ Subgroup analyses according to type of cannabinoids and control groups	Any chronic pain lasting ≥1 month 28 RCTs non-cancer pain	High RoB ($n = 12$)	(moderate-quality evidence); NNTB = 10 30% pain relief: RD 7% (moderate-quality evidence); NNTB = 14 WMD in physical functioning scale (0–100): 1.7; RD in proportions achieving MCID 10 points: 4% (high-quality evidence); NNTB = 25 WMD in sleep quality scale (0–10): −0.35; RD in proportions achieving MCID 1 point: 6% (high-quality evidence); NNTB = 16 Adverse events: RD <3 months: 2% increased cognitive impairment; 3% increased vomiting; 5% increased drowsiness; 5% increased nausea; 3% increased impaired attention (moderate-quality evidence); NNTH 20–33 RD in dizziness >3 months: 28% risk increase (high-quality evidence); NNTH 4	placebo, results in a small to very small improvement in pain relief, physical functioning and sleep quality among patients with chronic pain, along with several, mostly transient adverse side effects. No differences were seen in comparisons to active controls	
Giossi *et al.*, 2022[31]	8 RCTs 7 RCTs cannabis versus placebo; 1 RCT cannabis versus active control $n = 240$ No subgroup analyses	Any type and preparation of cannabinoid treatment Studies restricted to patients with chronic primary pain: fibromyalgia, chest or regional pain, irritable bowel syndrome	GRADE system Cochrane RoB 2 tool for RCTs Low RoB ($n = 1$) Moderate RoB ($n = 5$) High RoB ($n = 2$)	MD in pain scale (0–10) with treatment ≥4 weeks: −1.28 (low-quality evidence) for all pain; −0.82 for fibromyalgia (low-quality evidence) OR for adverse events causing discontinuation: 2.15 (low-quality evidence)	Cannabinoid treatment had limited benefit on pain relief, with generally low quality of evidence	High
McDonagh *et al.*, 2022[32]	25 studies 18 placebo-controlled RCTs 7 non-RCTs with concurrent control	Any type of oral, sublingual or topical natural or synthetic cannabis product	Cochrane Back Pain Group version of Cochrane RoB tool	Synthetic products with high THC-to- CBD ratio	Oral synthetic high TBC-to-CBD ratio and sublingual, plant-extracted comparable THC-to-CBD treatments may	High

Table 1 *Continued*

Reference, year	Study design; No. trials/ studies; No. participants	Cannabis product type; pain syndrome	Quality assessment method; risk of bias for individual studies	Main results for outcome measures	Authors' conclusions	AMSTAR-2 rating of quality
	$n = 14\,512$ RCTs $n = 1777$ Subgroup analyses according to THC-to-CBD ratios and type of cannabis-based products	Studies restricted to chronic pain, mostly neuropathic pain; minimum 4 weeks of treatment or follow-up	US Preventive Services Task Force criteria for non-RCTs RCTs Low RoB ($n = 4$) Moderate RoB ($n = 9$) High RoB ($n = 5$) Non-RCTs Moderate RoB ($n = 3$) High RoB ($n = 4$)	MD on pain scale (0–1) −1.15 (moderate-quality evidence based on 6 RCTs) 30% pain relief: RD 47% (very low-quality evidence based on 1 RCT of diabetic neuropathy; $n = 26$); NNTB = 2 Adverse events: RD 9% increase sedation (3 RCTs); 21% increase dizziness (2 RCTs; moderate-quality evidence); NNTH 5–10 Comparable THC-to-CBD ratio natural products MD on pain scale (0–10): −0.54 (moderate quality of evidence based on 7 RCTs) Adverse events: RD 22% increase dizziness; 7% increase sedation; 6% increase nausea (all based on 6 RCTs) (moderate-quality evidence); NNTH 5–16.	be associated with short-term improvements in primarily neuropathic chronic pain, but at increased risk of dizziness and sedation	
Barakji *et al.*, 2023[33]	65 placebo-controlled trials $n = 7017$ Subgroup analyses according to type of cannabinoid and pain type	Any type of oral, sublingual or topical natural or synthetic cannabis product Chronic pain (neuropathic, chronic nociceptive pain), cancer pain, acute pain, fibromyalgia	Cochrane RoB tool Low RoB ($n = 6$) High RoB ($n = 59$)	MD on numerical rating scale (0–10) for chronic pain: −0.43 (low-quality evidence) MD for quality of sleep on rating scale (0–10): −0.42 (very low quality of evidence) Adverse events: RD 14% increase for non-serious events (very low-quality evidence); NNTH 7	Cannabinoids reduce chronic pain and improve quality of sleep but effect sizes are of questionable significance, and harmful effects may outweigh beneficial effects	High

AMSTAR 2, A Measurement Tool to Assess Systematic Reviews (v2); CBD, cannabidiol; CBM, cannabinoid-based medicine; CNCP, chronic non-cancer pain; CNS, central nervous system; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MCID, minimal clinically important difference; MD, mean difference; NNTB, number needed to be treated for benefit; NNTH, number needed to be treated for harm; OR, odds ratio; PGIC, Patient lobal IGmpression of Change; RCT, randomised controlled trial; RD, absolute risk difference; RoB, risk of bias; ROBINS-1, Risk of Bias in Non-randomised Studies - of Interventions; SMD, standardised mean difference; THC, tetrahydrocannabinol; VAS, visual analogue scale; WMD, weighted mean difference.

comparing equipotent dosages of standard treatments such as opioids, doses of cannabinoid products are often poorly recorded or reported as maximum recommended doses, rather than actual consumption.[41] Trials must account for placebo effects, which vary in magnitude, and are influenced by multiple contextual factors including patient suggestibility, how patients receive placebo instructions[42] and how they have been conditioned by repeated trials of active analgesic agents.[43] Tolerable pain thresholds vary between individuals, and positive media reporting, high patient and prescriber expectations of benefit and unmasking in placebo-controlled trials can all accentuate placebo responses.[44] Unfortunately, the lack of stringent evidence requirements for TGA approval and increasing availability and use of MC products likely limit opportunities for researchers to undertake more rigorous research into MC efficacy.[45]

Risk of harms from MC

Reporting of known harms of cannabis treatment in clinical studies is inconsistent,[40] although a systematic review of low-dose CBD studies (<60 mg/day) by the TGA in April 2020 concluded that such preparations had a good safety and tolerability profile.[46] However, adverse events, particularly in older patients with a higher prevalence of arthritis and other causes of CNCP, have included an increased risk of dizziness, sedation,[29] agitation, confusion, memory impairment and psychosis.[30,47] Impaired cognitive function, particularly when driving, is a hazard to both patients and other road users.[48] A recent Danish study revealed an increased risk of new-onset arrhythmia in patients with chronic pain receiving MC.[49] Among chronic MC users, the development of iatrogenic tolerance and dependence with cannabis use disorder affects one in four,[50] leading to escalating use of, or defaulting to, more potent illicit cannabis, which has been noted in one Australian study[51] and a systematic review,[52] with attendant risks of further harms.[53,54] Chronic cannabis use (recreational or medicinal) has been associated with the development of other substance use disorders.[55] There are no studies of long-term adverse effects of MC, and prolonged exposure, especially in vulnerable paediatric populations, is of concern given the potential causal association between teenage use and later onset of schizophrenia.[56] More information is required on MC interactions with other prescription drugs metabolised through the same cytochrome P450 enzyme system, whereby combining MC with warfarin can increase bleeding risk, and with certain antiepileptic drugs can cause excessive sedation.[57]

Inappropriate prescribing also raises safety concerns, such as cannabis clinic doctors prescribing high-THC products to patients with mental health conditions, including past psychotic disorders, without notifying their treating psychiatrist or usual general practitioner (GP).[58] A Queensland early psychosis service observed that five patients referred over 9 months up to July 2023 were receiving prescribed MC, despite four having had a history of psychosis.[59] A survey of 258 Queensland health practitioners in July 2024 (mostly GPs and pharmacists of whom half either prescribed or dispensed MC products)[60] reported 47% as observing frequent inappropriate MC prescribing and 58% observing adverse patient effects.

Whether MC use reduces opioid use or overdose mortality is unclear. Multiple prospective studies have reported increased opioid use in those using MC.[61–63] Studies in the United States comparing opioid use and mortality between states with MC legislation and those without show either no differences[64] or increased mortality rates[65] in the former.

Professional opinions on the use of MC for chronic pain

In Australia, the Royal Australasian College of Physicians in 2018 cautioned against prescribing cannabinoids in the absence of high-quality, replicated research.[66] The Royal Australian College of General Practitioners also advocates for further research into MC safety and effectiveness before endorsing its use in treating CNCP.[67] The Faculty of Pain Management of the Australian and New Zealand College of Anaesthetists in 2021[68] recommended cannabinoid products not be prescribed outside of registered, properly designed RCTs comparing MC with usual pain treatments.[69] A 2024 Royal Australian and New Zealand College of Psychiatrist Clinical Memorandum argued that regulatory changes to improve MC access in both countries had been based not on efficacy evidence but on perceptions of low risk of harm,[70] overlooking the risk of products containing high-potency THC.

Overseas, the International Association for the Study of Pain in 2021 did not endorse MC in treating CNCP, warning of the safety risks from its wider use without high-quality data about effectiveness and toxicity.[71] In the same year, the first multi-national clinical practice guideline issued a weak recommendation to offer a trial of non-inhaled MC or cannabinoids, in addition to standard care, to people with refractory chronic pain.[72] Similarly, the European Pain Federation recommended MC products be considered only as part of a multidisciplinary treatment programme and preferably as adjunctive

medication if recommended first- and second-line therapies proved inadequate or toxic.[73]

Future directions

Well-designed and adequately powered RCTs with long-term follow-up cohort studies are needed to provide robust evidence of sustained efficacy and safety. More *n*-of-1 RCTs able to assess cannabinoid effects at the individual patient level should be conducted,[74] together with research aimed at identifying factors predicting which patients are more likely to derive meaningful pain relief or experience adverse effects from MC.[75] Authoritative professional bodies do not endorse unregulated or first-line use of MC for CNCP, with health practitioners clearly voicing concerns about its increasing use and wanting more guidance on when and how to prescribe it. The TGA advises that a comprehensive sociopsychobiomedical assessment of patients with CNCP is appropriate, that MC should not be seen as the core component of therapy for CNCP, that patient education is a critical component of therapy for CNCP, particularly with respect to expectations of drug therapy, and that larger trials of sufficient quality, size and duration are needed to examine the safety and efficacy of MC use in CNCP.[38]

We are not advocating prohibitionist policies towards MC use and we recognise there is reasonable evidence for using MC for certain indications, such as treating spasticity in multiple sclerosis,[76] neuropathic pain[25] and specific treatment-refractory epilepsies in children.[77] We also concede that, among patients with intractable CNCP not responding to standard treatments, a time-limited trial (around 4 weeks in most cases[34]) of cannabis may be justified, more so in terminally ill patients in whom long-term adverse effects are not a consideration. However, there is no good evidence to date that MC benefits patients with anxiety syndromes or other mental health disorders[78,79] (despite anxiety accounting for more than a quarter of TGA SAS-B approvals),[3] fibromyalgia,[80] PTSD[81] or sleep disorders.[82]

Prescribers must inform patients of the significant limitations of current evidence of efficacy and safety for most conditions associated with current MC use, be aware of contraindications and precautions (older patients, pregnancy, mental health disorders, cognitive impairment, cardiovascular disease) and drug–drug interactions, monitor patients over time and discontinue MC if no benefit is seen or sustained or adverse effects emerge. They must not accede to pecuniary overtures or the findings of questionable studies sponsored or funded solely by the cannabis industry.

The currently unregulated deployment of 'vertically integrated' cannabis telehealth clinics, and lack of any formalised monitoring process for assessing effectiveness or safety of cannabis prescribing, must be reformed. The public perception that cannabis products represent natural and safe treatments for multiple conditions, primed by mainstream and social media, patient testimonials, celebrity endorsements and industry promotions[83] needs to be tempered by government-sponsored public education campaigns, health professional training programmes and more strict regulations regarding access to standardised, good-quality MC products for evidence-based indications, developed in collaboration between the TGA, researchers, prescribing clinicians and patients. Any regulatory framework should provide mechanisms to encourage scientific research, with government agencies both facilitating access to MC and providing financial resources, so that the evidence base for safe and effective use of MC can be enhanced, which, in turn, informs ongoing review of existing regulatory policies. The cannabis industry must address inconsistencies in MC product quality, labelling and safety and implement manufacturing practices that guarantee pharmaceutical-grade products, and be prepared to have these products investigated by independent researchers.

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