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INVITED REVIEW

Understanding the evidence for medical cannabis and cannabis-based medicines for the treatment of chronic non-cancer pain

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Abstract

The use of medical cannabis and cannabis-based medicines has received increasing interest in recent years; with a corresponding surge in the number of studies and reviews conducted in the field. Despite this growth in evidence, the findings and conclusions of these studies have been inconsistent. In this paper, we outline the current evidence for medical cannabis and cannabis-based medicines in the treatment and management of chronic non-cancer pain. We discuss limitations of the current evidence, including limitations of randomised control trials in the field, limits on generalisability of previous findings and common issues such as problems with measurements of dose and type of cannabinoids. We discuss future directions for medicinal cannabinoid research, including addressing limitations in trial design; developing frameworks to monitor for use disorder and other unintended outcomes; and considering endpoints other than 30% or 50% reductions in pain severity.

Keywords Cannabis · Chronic pain · Medical cannabis · Cannabis-based medicines

Introduction

Interest in cannabinoids for the treatment of chronic non-cancer pain (CNCP) has increased substantially in recent years. Rapid changes in legislation mean that cannabinoids are increasingly accessible; and treatment of chronic pain is the most commonly cited reason for accessing medicinal cannabinoid products in the United States (US) [1]. Hopes that cannabinoids may help curb the opioid epidemic in the US have piqued the interest of policy makers, researchers, clinicians and patients alike. Consequently, there has been a recent proliferation of controlled and uncontrolled trials examining the efficacy of cannabinoids for chronic pain conditions. With that, there has also been a number of recent reviews examining the evidence for cannabis in chronic pain, though conclusions have been conflicting [2], with some reviews reporting moderate to large effects [1, 3], while others have reported minimal [4–7]. Here, we provide a summary of the current body of evidence to use in CNCP, separately for the major pain conditions for which evidence is available, limitations of the current evidence and suggest future directions in our understanding of the effectiveness of cannabinoids for CNCP. Based on the terminology suggested by Hauser et al. [8], we use the following terms throughout, 'medical cannabinoids' as an umbrella term and refers to the all plant-derived and synthetic derivatives; 'medical cannabis' refers to the use of cannabis plants and plant material, such as buds, leaves or full plant extracts (such as cannabis sativa, THC and or CBD extract) for medical reasons and 'cannabis-based medicines', are registered medicinal extracts with defined sand standardised THC and THC/CBD content (such as nabiximols and nabilone).

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Evidence found in the reviews

Any chronic pain

There have been a number of high-profile reviews that have reported that there is 'moderate' [3] and 'substantial' [1] evidence for the efficacy of medical cannabinoids in the treatment of chronic pain. The 2017 National Academies of Science, Engineering and Medicine (NASEM) report [1] on "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research" concluded that there is "substantial evidence that cannabis is an effective treatment for chronic pain in adults" (p. 90) [1]. Evidence for this conclusion was based heavily on a 2015 review led by Whiting et al. [3] which reported there is "moderate evidence" for medical cannabinoids for the treatment of chronic pain. The overall conclusions of the NASEM and Whiting reviews indicated that there is evidence for the effectiveness of medical cannabinoids for all chronic pain conditions, despite both reviews largely only considering evidence from patients with neuropathic pain (see Table 1). The 2017 NASEM review only included two additional studies to the 2015 Whiting review, both of which comprised participants with neuropathic pain. Further, the review by Whiting et al. [3] has since been criticised as having a "bias towards a positive evaluation of cannabis products" [9] and for interpreting the results as statistically significant despite estimates crossing the line of no effect. Additionally, another recent review by Aviram and Samuelly-Leichtag [6] also states that cannabis-based medicines might be effective for chronic pain management, even though the authors acknowledge this is mainly based on limited evidence for neuropathic pain patients. It is concerning that there have been some broad recommendations for the use of medical cannabinoids in CNCP based on studies of specific conditions, primarily neuropathic pain. Of concern, the reviews by Whiting et al. [3] and Aviram and Samuelly-Leichtag [6], and the review of reviews by Allan et al. [10] also included studies for cancer pain in their analysis. Combining different chronic pain conditions can be problematic. Although both cancer and CNCP can include nociceptive and neuropathic pain, the development, course and persistence of CNCP are inherently different form that of cancer pain and treatments for each should be evaluated separately. Given there are important differences in the aetiology of pain conditions, to understand the potential

Table 1 Summary of the evidence for cannabinoids in the treatment of CNCP

References	Separate estimates for different cannabinoids	Separate estimates for different CNCP types	RCT and observational evidence	IMMPACT guidelines?	*n* studies (participants)	Conclusion
Whiting et al. [3]	Yes	No	RCT only	No	28 (22,454)	Moderate quality evidence that cannabinoids are beneficial for CNCP
National Academies of Science report [1]	No	No	RCT only	No	Review of reviews mainly based on Whiting (2015 with an additional 3 studies of neuropathic pain)	There is substantial evidence that cannabis is an effective treatment for chronic pain in adults
Aviriam et al. [6]	No	Yes	RCT only	No	43 (2437)	Might be effective for neuropathic pain
Nugent et al. [13]	No	Yes	Yes	No	27 (3281)	Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain
Mücke et al. [31]	Yes	Yes—only neuropathic	RCT only	Yes	16 (1750)	Any benefit of cannabinoids outweighed by harms
Stockings et al. [15]	Yes	Yes	Yes	Yes	104 (9958)	Unlikely that cannabinoids are highly effective medicines for CNCP

benefit of cannabinoids in CNCP, it is crucial to examine the evidence for specific pain conditions, where evidence is available, as concluded by Deshpande et al. [11] "Generalizing the use of medical marijuana to all CNCP conditions does not appear to be supported by existing evidence. Clinicians should exercise caution when prescribing medical marijuana for patients, especially in those with non-neuropathic CNCP" (p. e372) [11]. Below we focus on the evidence of for specific CNCP pain conditions, where evidence is available.

Neuropathic pain

Neuropathic pain, that is pain caused by a lesion or disease of the somatosensory nervous system [12], has been the most rigorously studied pain condition in trials of medicinal cannabinoids [3, 13, 14]. A number of reviews of the evidence for medicinal cannabinoids for neuropathic pain have been published, some of which report moderate to large reductions in pain [1, 3], while others have reported minimal benefit and risk of potential harms [4, 6, 7]. A recent review [5] found that in randomised controlled trials (RCTs), medicinal cannabinoids were superior to placebo in producing a 30% reduction in pain and a reduction in pain scores as measured on continuous numeric or visual analogue scale (VAS) for people with neuropathic pain conditions, but these effects were modest: number needed to treat for benefit (NNTB) for one person to achieve a 30% reduction in pain was 27 (38.5% response in treatment versus 33.0% response in placebo), and change in pain scores was equivalent to a reduction of 4 mm on a 0–100 mm VAS. Cannabinoids were not significantly different to placebo in producing a 50% reduction in pain. Observational evidence was largely consistent, but study quality has been poor overall. Importantly, patients using cannabinoids were two to three times more likely to experience adverse events (primarily dizziness, drowsiness, confusion and low mood) and were more likely to withdraw from treatment than people receiving placebo. It is also important to note that the majority of studies have tested nabiximols (trade name Sativex), which delivers a combined dose of tetrahydrocannabinol (THC) and cannabidiol (CBD), with little evidence for other types of cannabis-based medicines or medical cannabis in neuropathic pain.

In a recent Cochrane review examining the efficacy of cannabis-based medicines for chronic neuropathic pain in adults, Mücke and colleagues [7] report a NNTB of 20 for 50% or greater reduction in pain, suggesting a similar efficacy and profile of cannabinoids for pain as reported in the review by Stockings et al. [5].

Most of the evidence to date on the effectiveness of cannabis-based medicine for CNCP has been from studies of neuropathic pain. In a recent review of reviews, Allan et al. [10] concluded that there is uncertainty whether cannabinoids improve pain, though if they do, it is most likely to be neuropathic pain and the benefit is likely minimal. Based on this evidence, recent guidelines in Canada [15] and Europe [8] recommend cannabis-based medicines be used only in patients whose conditions are refractory to standard medical therapies and as a third-line therapy. Medical cannabis, in both guidelines, is only to be used when trials of cannabis-based medicines are ineffective.

Multiple sclerosis-related pain

Pain arising from multiple sclerosis (MS) may either be caused by damage to the nervous system (i.e. MS-related neuropathic pain) or may be due to musculoskeletal pain associated with spasms. Medicinal cannabinoids for MS-related pain have received substantial attention in recent years: a recent overview of systematic reviews [16] identified 11 systematic reviews of the evidence for medicinal cannabinoids in MS-related pain, drawing on 32 studies, 10 of which were moderate to high quality RCTs. Of the seven reviews examining medicinal cannabinoids for pain in MS, two concluded that THC or nabiximols (THC:CBD) are likely effective in reducing pain or painful spasms in MS, one review reported no significant effect, and four reviews cited insufficient evidence or mixed findings [16]. In the systematic review by Stockings et al. [5], cannabinoids produced significant but modest reductions in pain scores relative to placebo for MS-related neuropathic pain (equivalent to a reduction of 4.3 mm on a 0–100 VAS) but not for MS-related musculoskeletal pain. No differences between cannabinoids and placebo were found for 30% or 50% reduction in pain among people with MS; however, only two studies examined these outcomes. As with neuropathic pain, patients using cannabinoids were two to three times more likely to experience adverse events or to withdraw from treatment than those using placebo. It is possible that medicinal cannabinoids may play a role in the treatment of pain among people with MS; however, the number of high-quality studies to date has been small. It is also difficult to isolate the potential benefit on pain symptoms alone, as cannabinoids may also alleviate other symptoms of MS, including muscular spasticity (which can be painful), sleep, and quality of life. Further, there have been concerns that cannabinoids may impair cognitive function among people with MS who have pre-existing cognitive dysfunction [16]. These factors need to be considered when determining the overall suitability of cannabinoids in managing MS-related pain.

Visceral pain

Visceral pain is pain that occurs in the trunk of the body, including the heart, lungs, abdominal and pelvic organs, and includes conditions such as pancreatitis, gallstones, pelvic pain and gastrointestinal conditions such as inflammatory bowel disease, ulcerative colitis and Crohn's disease. While there is a growing literature exploring the potential therapeutic mechanisms of medicinal cannabinoids in visceral pain [17] and demonstrating that people with visceral pain are more likely to use medical cannabis to manage their pain [18], there are currently too few clinical trials to provide a meaningful conclusion regarding their efficacy in managing visceral pain. Two RCTs comprising just 98 patients with chronic abdominal pain after surgery or chronic pancreatitis [19, 20] were identified in a recent review of cannabis for CNCP conditions [5], with meta-analysis indicating that medicinal cannabinoids had no significant impact on pain scores. Interest in this field in increasing and a number of clinical trials examining cannabis for visceral pain are underway which will soon be synthesised in a planned Cochrane review [21].

Other pain

Other pain conditions that have been considered potential targets for medicinal cannabis treatment include fibromyalgia, rheumatoid arthritis and musculoskeletal pain conditions of the back and neck; however, the number of studies is currently too few, and samples sizes are insufficient to draw meaningful conclusions. In a recent Cochrane review, two small RCTs (comprising $n = 32$ and 40 participants) examined nabilone for fibromyalgia [22], however, neither study measured 30 nor 50% reduction in pain. While one of the studies noted improvements in pain scores, anxiety and health-related quality of life [23], no statistically significant effect was found, and review authors concluded that there is currently no convincing evidence that nabilone is of value in treating pain among people with fibromyalgia [14]. One small RCT ($n = 58$) examining nabiximols relative to placebo for pain relief among people with rheumatoid arthritis reported a significant reduction in pain scores among patients receiving nabiximols, however, study quality was low, thus caution is warranted in interpreting trial findings [24]. Finally, one small RCT ($n = 30$) examining nabilone versus placebo for people with musculoskeletal pain conditions [25] [predominantly spinal pain (cervical syndrome), lower back pain (lumbalgia), and thoracic syndrome] reported that nabilone was superior to placebo in achieving reductions in overall pain intensity, however, most findings were borderline non-significant, and replication with larger samples is needed. We identified no trials specifically examining the efficacy of cannabinoids for migraine-related pain.

Harms A recent review of medicinal cannabinoids for neuropathic pain by Mücke et al. found that the Number Needed To Harm (NNTH) was three for nervous system disorders (95% CI 2–6), based on nine studies with 1304 patients and 10 for psychiatric disorders (95% CI 7–16) among nine studies with 1314 participants. Stockings et al. [5] reported that the estimated pooled rate of all-cause adeverse events was 81.2% among people receiving cannabinoids, compared with 66.2% of those receiving placebo; and the NNTH was 6 (95% CI 5–8). Importantly, patients using cannabinoids were two to three times more likely to experience adverse events (primarily dizziness, drowsiness, confusion and low mood) and were more likely to withdraw from treatment than people receiving placebo [5]. Allan et al. [10] also found that the NNTH for psychiatric adverse events was 9, sedation 5, dysphoria 8 and disorientation and confusion 15. In the review by Nugent et al. [13], they found consistent evidence between cannabis use (specifically related to THC content) and the development of psychotic symptoms. Allan et al. [10] concluded that the most consistent effects for medicinal cannabis are adverse events which are also likely to be underestimated as many studies enrol patients with a prior cannabis use history, rather than cannabis naïve individuals. In the comprehensive systematic review of all RCT and observational studies by Stockings et al. [5], only 3% of studies ($n = 104$) reported that patients were cannabis naïve at study entrance. Experienced users are less likely to experience adverse events as they are preselected as resistant, have developed tolerance and may like some adverse events such as 'feeling high' [10]. The review by Mucke et al. concluded that the potential benefits of cannabis-based medicine in chronic neuropathic pain in adults might be outweighed by their potential harms.

Cannabinoid type In a recent review of 104 clinical trials and observational studies on the use of medical cannabis and cannabis-based medicines for CNCP [5], 42 studies were based on medical cannabis (cannabis sativa, THC and or CBD extract), and 59 were based on cannabis-based medicines (e.g. 24 studies for nabiximols, 18 for dronabinol and 17 studies for nabilone). As cannabis contains over 100 distinct cannabinoid constituents and THC and CBD concentrations can vary considerably, it is difficult in studies of medical cannabis to determine the most beneficial dose and type. Both the Canadian [15] and European [8] guidelines for use of medicinal cannabinoids recommend the use cannabis-based medicines first (i.e. nabilone or nabiximols) before the use of medical cannabis. Although some reviews have aimed to examine the evidence for different cannabinoids separately [3, 5, 7], others have grouped the cannabinoids together [6, 13, 26]

which makes guidelines and recommendations difficult to determine.

Limitations of current evidence

This section provides an overview of the limitations of previous evidence of the effectiveness of cannabinoids in CNCP.

Limitations of evidence from RCT's

With the exception of the reviews by Stockings et al. [5] and Hauser et al. [2], most reviews of the evidence for cannabinoids in chronic pain have focused solely on findings from RCTs. Although RCT's are the Gold Standard in determining efficacy, there are a number of issues that need to be considered when evaluating the generalisability of the evidence.

In an attempt to control for variables that may influence treatment outcomes, RCTs typically exclude people with complex physical and mental health comorbidities and people with a history of substance use disorders, which comprise a substantial number of people living with CNCP [27–30]. Previous research has found that people living with CNCP often experience multiple pain and other health conditions, have poorer overall physical health and have also experience high rates of childhood abuse and neglect. People living with CNCP also experience elevated rates of depression and anxiety, suicidal behaviours and a notable proportion have a history of substance use disorder. A recent Cochrane review examining the evidence for cannabis-based medicines for neuropathic pain found the majority (10 out of 16 included studies) explicitly stated that they excluded people with a history of substance use [31]. To understand the overall effectiveness of medicinal cannabinoids in CNCP, we need to understand the impact they may have on people with complex comorbidities.

Second, most RCT's are of limited duration (i.e. median of 8 weeks in the review by Stockings et al.) [5]. Given that CNCP is a chronic long-term condition, the examination of the appropriateness of long-term use of cannabinoids in CNCP is lacking, in terms of both treatment efficacy and safety. Importantly, the review by Stockings et al. [5] found that reductions in pain intensity were largest for 1-day studies, and smaller or non-significant in studies of 13 weeks duration or longer, providing some initial suggestion that the effectiveness of cannabinoids for CNCP may diminish over time. This finding is consistent with the findings of a recent systematic review of systematic reviews [10] that large or longer duration studies were less likely to find an effect of cannabis-based medicines on pain.

Third, current evidence is limited due to small sample sizes in trials conducted to date. A recent Cochrane review for cannabis-based medicine in neuropathic pain found that 9 of the 16 studies were at high risk of bias due to small sample size. The review by Stocking et al. [5] found that for some estimates, effect sizes were notably larger in studies with <30 participants per treatment arm compared to studies of $100+$ per arm, however, these estimates fell within overlapping bounds of uncertainty. There is a growing body of evidence indicating that effect estimates tend to be larger in studies with small sample sizes [32], and as such, caution should be taken when interpreting outcomes based on studies with small sample sizes. Well-conducted, large RCTs comprising at least 100 participants per treatment arm should be considered a priority in this space.

There are also concerns regarding the quality of evidence to date. There is a paucity of high-quality studies on which evidence-based decisions can reasonably be made. Of the 104 studies included in the review by Stockings et al. [5], (which included observational studies) only 15 studies were graded as high according to an adapted version of the standard Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool on study methodology. Forty-three were graded as moderate, 24 graded as low and 22 studies were graded as very low. Further, the authors also reported that most parallel and crossover RCT's were rated as having an unclear risk of bias across all domains as all required information were not reported or could not be obtained from the authors of the studies. Several studies in the review were rated as a high risk of bias because of selective reporting or other biases, such as omission of data and CIs, changes in selection of the primary endpoint, or a failure to take account of within-subject effects in crossover studies [5].

Finally, it is possible that publication bias exists, whereby authors are more likely to publish studies with positive findings. Mücke et al. [7] reported they found three-industry sponsored studies with negative results that had not been fully published and a further three studies were the results unknown despite the study authors attempting to gain the results. Other reviews [6] have not included unpublished studies and may have overestimated the evidence for cannabis-based medicines in CNCP [33].

Lack of studies on main pain conditions

The Global Burden of Disease 2016 study found back pain was the leading cause of non-fatal health burden globally (as measured by years of life lived with disability, YLDs), followed by migraines [34], with neck pain and other musculoskeletal problems among the top ten causes of non-fatal health burden. Not surprisingly then, "severe pain" is the most commonly cited reason for accessing medicinal

cannabis in the US [1]. Despite the substantial variation in pain conditions experienced by people seeking medicinal cannabinoids, most of the clinical evidence to date has been based specifically on studies of participants with neuropathic pain. There is scant, low quality evidence on cannabinoids used for fibromyalgia or visceral pain, and very few studies of cannabinoids' use in the most common and burdensome CNCP conditions, namely, back/neck problems, migraines and arthritides. While some reviews have extended the findings of studies conducted among people with neuropathic pain to apply to CNCP overall, it is important to acknowledge that there is a lack of studies for the most common pain conditions for which people commonly report using cannabis to manage. Future studies focusing on these most common pain conditions should become a priority.

Cannabinoid dose and type

Lynch et al. [35] argue that it is ill-advised to treat all cannabinoids the same and that the term 'medical marijuana' often groups together all compounds and formulations. In fact, there are very important pharmacokinetic differences between modes of delivery (e.g. oral versus inhaled), differences in cannabinoid profiles (e.g. the presence of CBD in different amounts), and source of cannabinoid (plant-based complex botanicals versus synthetic single molecules). Distinctions must be made when citing these studies to ensure that the conclusions are not drawn more widely than is justified. Among the evidence that is currently available, cannabis dose is often poorly recorded. Often only a maximum recommended dose is reported and data on participants' actual cannabinoid consumption are seldom provided, thus it is difficult to make strong recommendations on doses that are maximally effective and safe. Medical cannabis products vary in strength and formulation and the optimal dose range in pain is yet to be determined, and may be affected by a range of factors, including tolerance with long-term use. In recent Canadian [15] and European [8] guidelines, both recommended the use of pharmaceutically developed products (such as nabiximols and nabilone) and recommend against the use of medical marijuana (specifically smoked cannabis), as the evidence for smoked cannabis is likely to have a very high risk of bias and long-term consequences are unknown. To improve recommendations around type and dosing future trials, specific trial designs, including adaptive trial designs [36] utilising products with known dosages, to explore optimal dosing in different populations to provide appropriate guidelines. Research in this area is difficult due to the current legal status of cannabis and cannabinoids in a number of countries. Although U.S states may decide to legalise cannabis, it has not been legalised at the federal level making research into the use of cannabis for medicinal purposes difficult.

As mentioned above, another important issue is that a large proportion of participants that have participated in the research to date are unlikely to be cannabis naïve and therefore are more likely to have a better chance of having better outcomes and less chance of adverse events. The severity and number of adverse events is most likely to be greater than reported and more likely to occur in cannabis naïve patients. It is important that future studies document whether participants are cannabis naïve and should focus on the safety profile of cannabis-based medicines among people who are cannabis naïve.

Most studies included cannabinoids as an adjunctive therapy

Most studies used a placebo comparator and added cannabinoids to stable doses of analgesics, NSAIDS and anti-spasticity drugs, thus the evidence for cannabinoid use in CNCP is largely around cannabinoids as adjuvant medicines, as is common in other RCT's, with other centrally acting pain drugs. Often multiple analgesics were used, which varied between groups, and the ways they were used was not consistently reported. Most studies held doses of other analgesic medications constant, though some studies documented changes in breakthrough medication or adjunctive analgesia [5]. To really understand the effect of cannabinoids in people with CNCP, placebo-controlled trials involving patients with no other medication are warranted.

Lack of evidence of the effectiveness of cannabinoids in other important CNCP outcomes

Pain is considered by leading clinicians and researchers to be only one of a range of core outcomes that must be considered evaluating interventions for CNCP [37]. Other outcomes include physical functioning, emotional functioning and participants (or their carers') ratings of improvement. To date, however, there have been few studies or reviews that have examined these other important outcome domains in CNCP. Research examining the efficacy of cannabinoids in managing pain has often focussed on pure changes in pain scores (e.g. scores on a numerical or visual rating scale), whereas increasingly the pain field is moving towards more global measures of functioning, and quality of life [38]. Two recent reviews [5, 31] examined the impact of cannabinoids on these other outcomes found although there may be evidence for a reduction in sleep problems, psychological distress and patient rating of improvement, this was based on low quality evidence and more research is needed in this area before conclusive recommendation can be made. As the field increasingly focuses on functional improvements, in addition

to considering potential effects of cannabinoids on quality of life and sleep, different conclusions about the effectiveness of cannabinoids may arise. Some of these outcomes may also be more clinically meaningful than reductions in pain scores for patients with chronic disabling pain who experience substantial impairment in their daily functioning.

There is also the possibility that cannabis does not reduce pain severity per se but may help a person living with CNCP tolerate the pain more effectively [39]. It is important that future research begins to focus not only on pain, but that we have high-quality placebo-controlled trials that examine a range of outcomes including effect on sleep, patient's ratings of improvement and distress associated with pain. In a recent study [40], patient reports indicated cannabis provided 7/10 effectiveness in reducing their pain (on a scale of 0–10 where 10 was 'completely effective'), suggesting patients perceived that the cannabis was effective on their pain. This finding came even though patients who reported cannabis use had greater pain scores and that there were no long-term associations between cannabis and pain severity or interference. Patient reports of perceived benefit should be considered in future research alongside 'pure' measures of pain severity.

Future directions

There are a growing number of controlled trials examining the efficacy of cannabinoids in managing CNCP, many with important limitations as discussed above. To advance the field, future trials may consider the following recommendations to improve the quality and applicability of the evidence.

Issues with blinding

Few studies with cannabinoids in pain have addressed limitations with the lack of blinding resulting from the psychoactive effects of THC [41]. Wilsey et al. suggest to address this limitation future studies could consider strategies such as the use of active placebos with similar side effect profiles to cannabinoids. One such example was the successful use of amitriptyline in a study of fibromyalgia, with blinding demonstrated to be preserved as participants estimation of the condition they received being less than 50% (i.e. no better than random chance) [42]. Other proposed strategies include measuring patients' beliefs about the efficacy of the treatment allocations and controlling for this in analyses, and reporting on the effectiveness of the blinding procedures [41]. Such approaches may address the powerful expectancy effects that can contribute to bias in clinical trial results [43]. There is arguably no 'gold standard' analgesic, with limitations surrounding the use of all analgesics. However, the use of active (and psychoactive placebo) controls will help to reduce bias and help to determine if cannabinoids offer additional benefits over existing medications.

The emergence of cannabis use disorders and developing precaution frameworks

Given the already rapid rates at which cannabinoids are becoming increasingly available in many countries, future research should determine the most appropriate ways to assess for the emergence of cannabis use disorders. Cannabinoid use disorders are one of the most prevalent substance use disorders in the general population, estimated at 5.4% in the Australian general population and 6.3% in the US [44, 45]. Among those who use cannabis, rates of dependence are around one in ten [46]. Substance use disorders are identified among people with chronic pain at higher rates than the general population, with a systematic review reporting the lifetime prevalence of a substance use disorder ranged from 16 to 74% [47]. Given this, and the known dependence liability of cannabinoids, it would be prudent to establish frameworks to address this risk proactively and put appropriate management strategies in place for patients. In addition, designing studies with a sufficiently long follow-up period, and including in both RCTs and patient registries standardised measures for use disorders related to cannabis-based medicines will inform often cannabis use disorders emerges and the likely consequences for patients with pain. This would allow a better understanding of these phenomena, and any likely adverse effects for patients using cannabinoids for pain. Recommended frameworks for monitoring these outcomes with opioids provide a good starting point, with suggestions to monitor for substance use disorder outcomes including the use of validated screening tools to assess risks, and collecting routine urine drug screens to detect other substance use [48] being equally applicable to cannabinoids. The experience with prescribed opioids has demonstrated that failure to adequately appreciate and address risk with dependence or use disorders can have devastating consequences. It is inevitable that with the increasing use of cannabinoids for pain we will see some patients develop dependence. Although the likelihood of fatal overdose with cannabinoids is extremely low, the lessons learned from the rapid expansion of opioids, where dependence liability was not only underestimated, but was also not routinely monitored for, can be put into play here. We now have frameworks to monitor for emerging dependence with prescribed opioids [49]. Implementing similar universal precaution frameworks with cannabinoids is one strategy to consider.

With changing legislation leading to growing acceptance of cannabinoids and reduced risk perceptions around its use [50, 51], it is likely that—whether the evidence demonstrates effectiveness—more patients will be interested in trialling

them. Pharmacovigilance in this area will be important to identify any emerging signals of harm. Monitoring for unintended consequences of therapeutic use of cannabinoids will be an area of ongoing interest. Globally, there are a wide range of legal frameworks for therapeutic cannabinoid products. Greater opportunities for monitoring for such consequences exist in countries with legal frameworks to prescribe medicinal cannabinoids, and particularly where registries of prescriptions and patient are utilised [52]. Given that medical cannabis is often supplied outside therapeutic channels even when used for pain, capturing adverse drug reactions associated with therapeutic use may be more challenging than with traditional pharmaceutical drug supply, but this will be important in developing our understanding of which patients benefit and which patients might be most susceptible to side effects.

Potential "opioid-sparing" effects

When considering potential population level benefits of cannabinoids, the potential for cannabinoids to reduce reliance on high dose opioids, and consequently reduce opioid-related overdose and mortality, is an area of both clinical and public health interest. Pre-clinical evidence certainly supports this possibility [53], and ecological [54–57] and epidemiological [58–61] studies also suggest that this is possible [62], though not all studies find cannabis use is associated with reduced opioid use [40]. The evidence base suggesting that cannabinoids may reduce opioid consumption and related mortality is not without its limitations [62]. Few studies have controlled for other interventions that reduce opioid-related mortality (e.g. opioid dependence treatment availability). Epidemiological studies have been limited by their design and recruitment strategies [62]. To date, despite promising pre-clinical and ecological evidence, no well-conducted clinical trials that address these limitations and can demonstrate clear causality have confirmed the potential for cannabinoids to reduce opioid use or harms [53]. Whether cannabinoids represent a potential strategy to help patients taper off prescribed opioids or support the use of lower total doses of opioids would be an area of immense clinical and public health interest.

Fragmented models of care

Unique challenges may arise from the fragmented medical care that may emerge as cannabinoids are prescribed by a separate 'cannabis doctor' and 'cannabis dispensary' in some countries, for example in the United States [63], with proposals for similar models in Australia. Some legal frameworks, such as in operation in many countries in Europe [52], prohibit these models and may facilitate greater communications between healthcare professionals.

These models of care mean that the same health professionals (or retailers in the case of cannabis dispensaries) do not manage the rest of a patient's care or medications. Being able to incorporate therapeutic use of cannabinoids into a patient's medical records may help to identify adverse drug reactions or interactions and also estimate potential benefits from cannabinoids where administrative datasets are used to examine long-term outcomes. These actions are not possible where cannabinoids are supplied outside the mainstream health system, and the lack of information may be of detriment to individual patient care and slow the development of the broader knowledge base relating to benefits and harms.

Finally, it is important to note that many guidelines suggest that for the management of CNCP a multidisciplinary approach with an emphasis on non-drug techniques is best [64–66]. Non-pharmacotherapy options include patient education, cognitive behavioural therapy, physical therapy, surgery and other non-invasive procedures. If medicines are to be used, management of CNCP should not rely on pharmacological therapy alone and a combination of pharmacological and non-pharmacological should be continued. As research and interest of the role of medicinal cannabinoids increases, it is crucial that patients are aware of other treatments that may assist in the management of their pain.

Conclusion

Cannabinoids may offer important advances in a range of areas of medicine, yet currently the evidence in many areas is in its infancy. Despite this, CNCP is now the most commonly cited reason for accessing medicinal cannabis. There are a number of limitations that need to be addressed to advance the field. Public perception around the efficacy of cannabinoids for pain so far are not consistent with evidence [67]. It will be important to ensure that patient expectations are appropriately managed, particularly where there are large out of pocket expenses for these medications. Further, potential side effects may limit utility, particularly among older adults where the prevalence of chronic pain is highest.

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Compliance with ethical standards

Conflict of interest SN has been an investigator on untied investigator-driven educational grants funded by Indivior and Reckitt-Benckiser and has had travel costs covered and honoraria paid to her institution to provide training on identification and management of codeine de-

pendence by Indivior. GC has been an investigator on untied investigator driven educational grants from Reckitt-Benckiser. ES declares no conflicts of interest.

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