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RAPID RECOMMENDATIONS

Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline

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ABSTRACT

CLINICAL QUESTION

What is the role of medical cannabis or cannabinoids for people living with chronic pain due to cancer or non-cancer causes?

CURRENT PRACTICE

Chronic pain is common and distressing and associated with considerable socioeconomic burden globally. Medical cannabis is increasingly used to manage chronic pain, particularly in jurisdictions that have enacted policies to reduce use of opioids; however, existing guideline recommendations are inconsistent, and cannabis remains illegal for therapeutic use in many countries.

RECOMMENDATION

The guideline expert panel issued a weak recommendation to offer a trial of non-inhaled medical cannabis or cannabinoids, in addition to standard care and management (if not sufficient), for people living with chronic cancer or non-cancer pain.

HOW THIS GUIDELINE WAS CREATED

An international guideline development panel including patients, clinicians with content expertise, and methodologists produced this recommendation in adherence with standards for trustworthy guidelines using the GRADE approach. The MAGIC Evidence Ecosystem Foundation (MAGIC) provided methodological support. The panel applied an individual patient perspective.

THE EVIDENCE

This recommendation is informed by a linked series of four systematic reviews summarising the current body of evidence for benefits and harms, as well as patient values and preferences, regarding medical cannabis or cannabinoids for chronic pain.

UNDERSTANDING THE RECOMMENDATION

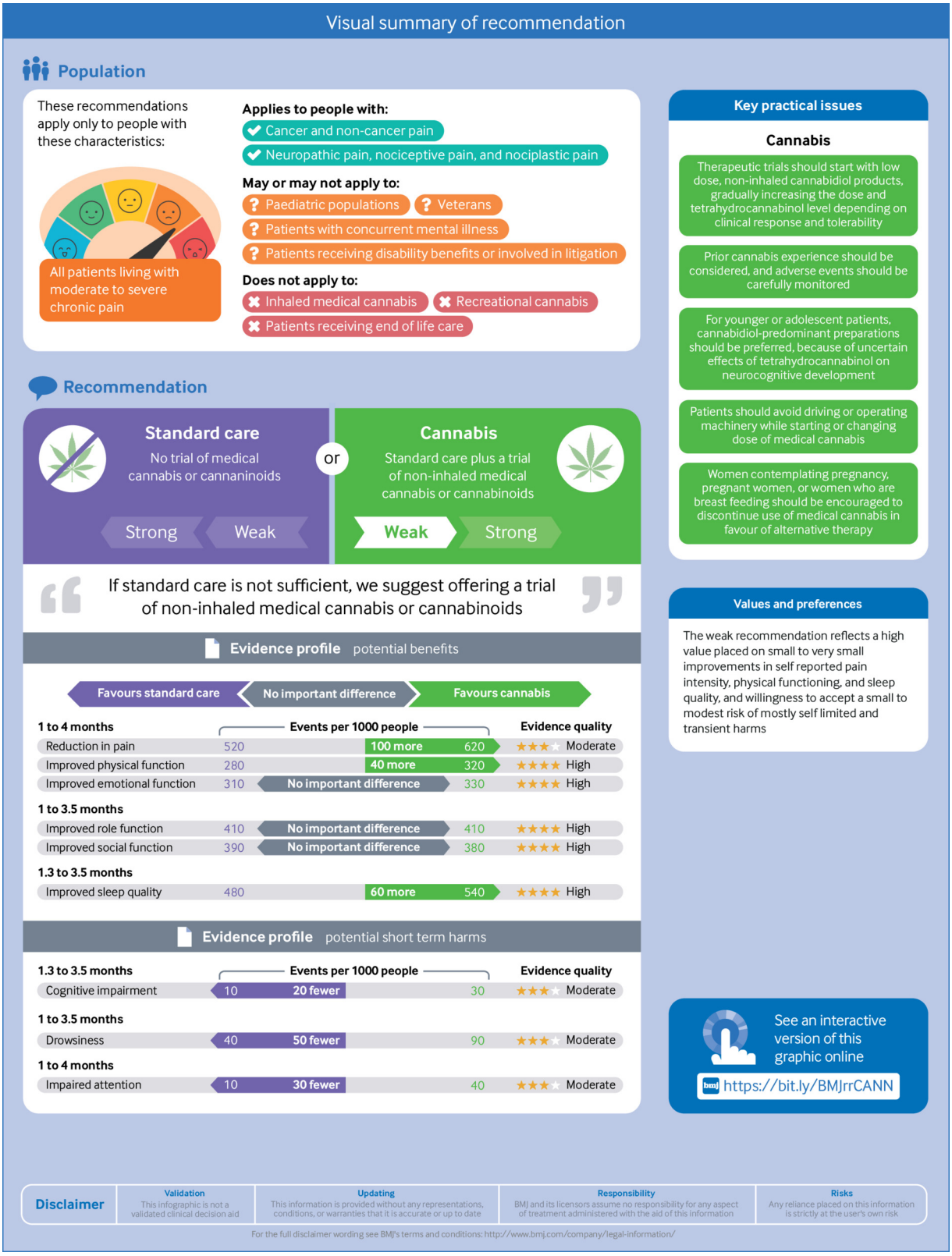
The recommendation is weak because of the close balance between benefits and harms of medical cannabis for chronic pain. It reflects a high value placed on small to very small improvements in self reported pain intensity, physical functioning, and sleep quality, and willingness to accept a small to modest risk of mostly self limited and transient harms. Shared decision making is required to ensure patients make choices that reflect their values and personal context. Further research is warranted and may alter this recommendation.

The increasing legalisation of medical cannabis globally, escalating use by patients, lack of training in the use of medical cannabis or cannabinoids during formal medical education, and inconsistent guidance from professional associations and federal agencies have led to confusion regarding the role of medical cannabis in the management of chronic pain.

In this guideline we have sought to address this confusion by asking what is the optimal, evidence based use of medical cannabis or cannabinoids for chronic pain (box 1).

The guideline panel developed this recommendation based on a series of linked systematic reviews[19-22] and use of the GRADE approach and standards for trustworthy guidelines. Box 2 includes all of the articles linked in this *BMJ* Rapid Recommendation package. The infographic provides the recommendation together with an overview of the absolute benefits and harms of medical cannabis or cannabinoids for chronic pain in the standard GRADE format. Clinicians and their patients can find consultation decision aids to facilitate shared decision making in MAGICapp.

This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (http://magicproject.org/) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (https://app.magicapp.org), in multilayered formats for all devices. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.



Box 1: Overview of chronic pain and medical cannabis or cannabinoids

What is chronic pain and who is affected?

Pain that persists or recurs for three months or more is defined as chronic.[1] Approximately 20% of the population in North America,[2] Australia,[3] and Europe[4] report chronic pain; 10-14% report moderate to severe pain in the UK.[5] Chronic pain is more common among women,[6] elderly people,[7] veterans,[8] indigenous populations,[9] and the socioeconomically disadvantaged.[10] The prevalence of chronic pain of any type among middle and low income countries reaches 33%.[10]

What effect does medical cannabis or cannabinoids have on chronic pain?

Cannabinoids are thought to affect pain through various pathways, including the endocannabinoid system, which has receptors in the central nervous system, periphery, immune and hematologic systems. Cannabis contains over 100 cannabinoids; the 2 most studied of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC inhibits glutamate and 5-hydroxytryptamine release and increases dopamine secretion. CBD enhances adenosine receptor signalling, and decreases reactive oxygen species, tumour necrosis factor, and T cell proliferation, without the psychoactive effects of THC.[11] The multifaceted analgesic and anti-inflammatory properties of cannabinoids may positively influence the perception of pain across different conditions.

What about opioids?

Opioids are prescribed for 1 in 3 people living with chronic pain[12]; but increasing recognition of the harms associated with long term opioid use[13] and greater appreciation for their, at best, modest benefits[14] have generated enthusiasm for alternatives, including medical cannabis.[15] In the US, 36 of 50 states and the District of Columbia have legalised cannabis for medical use,[16 17] and some US states have passed laws encouraging cannabis as a substitute for opioids when managing chronic pain.[18]

Box 2: Linked articles in this *BMJ* Rapid Recommendation cluster

- Busse JW, Vankrunkelsven P, Zeng L, et al. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. *BMJ* 2021;374:n2040
  - Summary of the results from the Rapid Recommendation process
- Wang L, Hong PJ, May C, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. *BMJ* 2021;374:n1034. doi:10.1136/bmj.n1034
  - Review of randomised trials that assessed medical cannabis or cannabinoids for chronic pain
- Zeraatkar D, Cooper MA, Agarwal A, et al. Long-term and serious harms of medical cannabis or cannabinoids for chronic pain: a systematic review of non-randomised studies. *medRxiv* 2021 doi:10.1101/2021.05.27.21257921
  - Review of observational studies exploring long term harms associated with use of medical cannabis or cannabinoids for chronic pain
- Zeng L, Lytvyn L, Wang X, et al. Values and preferences towards medical cannabis or cannabinoids among patients with chronic pain: a mixed methods systematic review. *BMJ Open* 2021;0:e050831. doi:10.1136/bmjopen-2021-050831
  - Review of studies exploring patients' values and preferences regarding use of medical cannabis or cannabinoids for chronic pain.
- Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open* 2021;11:e047717. doi:10.1136/bmjopen-2020-047717
  - Review of evidence assessing the impact of medical cannabis or cannabinoids when added to opioids among patients living with chronic pain.
- MAGICapp (https://app.magicapp.org/#/guideline/jMMYPj)
  - Expanded version of the results with a multilayered recommendation, evidence summaries, and decision aids for use on all electronic devices

Current practice

Although increasingly prescribed or authorised, medicinal cannabis or cannabinoids for chronic pain remains contentious for many physicians because of the suspected or known dangers associated with cannabis use.[23 24] Some have criticised the substitution of one addictive substance (opioids) for another with uncertain benefit (cannabis).[25] In 2018, the vice-president of medical professionalism for the Canadian Medical Association advised that medicinal cannabis should be phased out of practice altogether[26]; however, surveys show that physicians want more education and guidance around use of medical cannabis or cannabinoids as a potential pain management therapeutic.[27 28]

Clinical practice guidelines have emerged to address this knowledge gap, but with inconsistent recommendations (table 1). The most recent guideline, from the National Institute for Health Care and Excellence (NICE), made strong recommendations against the use of medical cannabis for chronic pain outside of clinical trials.[32] Legal action has subsequently been approved against NICE over concerns that their recommendations are overly restrictive and will prevent reasonable access to medical cannabis.[33] Current guidelines have important limitations, including limited or absent involvement of patients, failure to consider patient values and preferences to inform recommendations, inadequate consideration and management of financial and intellectual conflicts of interest in panels, selected review of the evidence, and excessive use of strong recommendations in the face of low certainty or absent evidence.[34]

Table 1 | Current guidance for medical cannabis or cannabinoids and chronic pain

Guideline	Recommendations
Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline (2016)[29]	• Clinicians may follow specific state regulations that allow access to medical cannabis or cannabinoids for patients with chronic pain after a consideration of the potential benefits and harms of the available formulations. (Evidence-based; benefits outweigh harms; evidence quality intermediate; strength of recommendation moderate)
European Pain Federation position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management (2018)[30]	• The quantity and quality of evidence are such that cannabis-based medicines may be reasonably considered for chronic neuropathic pain. • For all other chronic pain conditions (cancer, non-neuropathic noncancer pain), the use of cannabis-based medicines should be regarded as an individual therapeutic trial.
Simplified guideline for prescribing medical cannabinoids in primary care (2018)[31]	• Strong recommendations against medical cannabis for headaches, rheumatologic conditions (including osteoarthritis and back pain), or as 1st or 2nd line therapy for chronic neuropathic pain. • Weak recommendation for medical cannabis for refractory neuropathic pain. • Strong recommendation against medical cannabis as 1st or 2nd line therapy for palliative cancer pain. • Weak recommendation for medical cannabis for refractory palliative cancer pain.
NICE guideline: Cannabis-based medicinal products (2019)[32]	• Do not offer the following to manage chronic pain in adults: nabilone, dronabinol, THC (delta-9-tetrahydrocannabinol), a combination of cannabidiol (CBD) with THC. • Do not offer CBD to manage chronic pain in adults unless as part of a clinical trial.

Individuals using cannabis without authorisation from a physician typically consume inhaled forms (that is, smoked or vapourised) with high concentrations of the psychotropic cannabinoid delta-9-tetrahydrocannabinol (THC) and endorse both therapeutic and recreational use. In a Canadian cohort study of 709 community adult users of cannabis in 2018, 80% of those reporting medical use also acknowledged recreational use.[35] The use of a recreational substance for therapeutic benefit has raised concerns both regarding the underlying motives of patients seeking medical cannabis and the potential for diversion.[36]

The evidence

The linked systematic review reports the effects of medical cannabis or cannabinoids, typically when added to standard care, in people living with chronic pain resulting from cancer or non-cancer causes.[19] Table 2 gives an overview of the number and types of patients included, the formulations of cannabis and cannabinoids administered, the method of administration, and study funding among randomised trials exploring the benefits and harms of medical cannabis or cannabinoids for management of chronic pain.

Table 2 | Characteristics of 32 eligible randomised clinical trials included in systematic review of medical cannabis for chronic pain

	Values
Patient characteristics	**Median (range across trials)**
No of patients enrolled*	71 (20–657)
Length of follow-up (days and months)	50 days (28–154), (~2 months (1–5))
Mean age (years)†	53 (33–83)
Gender (% women)†	60 (0–100)
Trial characteristics	**No of trials; No of patients**
Types of chronic pain represented	Chronic non-cancer pain (28 trials; 3812 patients): Neuropathic (11 trials; 1665 patients) Nociceptive (2 trials; 378 patients) Nociplastic (5 trials; 230 patients) Medication overuse headache (1 trial; 60 patients) Spasticity related (7 trials; 1399 patients) Mixed types (2 trials; 80 patients) Chronic cancer pain, non-palliative (4 trials; 1362 patients)
Type of cannabis	Phytocannabinoids (17 trials)[37–52] Synthetics (10 trials)[51 53–61] Endocannabinoids (5 trials)[62–66]
Type of cannabinoid(s) administered	THC and CBD (15 trials)[37 39–49 52 67] THC (10 trials)[38 53 55–61 67] CBD/CBDV (3 trials)[50 54 67] PEA (5 trials)[62–66]
Mode of administration	Oral capsule (16 trials)[38 51–53 55–61 63–67] Oral spray (13 trials)[37 39–49] Sublingual drops (1 trial)[62] Transdermal cream (2 trials)[50 54]
Funding source	Industry funded (21 trials) No industry funding (6 trials) Not reported (5 trials)

THC=tetrahydrocannabinol; CBD=cannabidiol; CBDV=cannabidivarin; PEA=palmitoylethanolamide.

* Crossover trials were analysed as parallel trials by doubling the sample size.

† Among 31 studies, as one trial did not report age or gender information for enrolled patients.

Guided by current surveys and guidance on outcome assessment,[68 69] the panel identified eight patient-important outcomes needed to inform their recommendation: (1) pain relief, (2) physical functioning, (3) emotional functioning, (4) role functioning, (5) social functioning, (6) sleep quality, (7) opioid substitution, and (8) adverse events.

When considering the adverse events reported among eligible trials, the panel prioritised (in order of importance): cognitive impairment, vomiting, impaired attention, drowsiness, dizziness, nausea, and diarrhoea.

Regarding long term harms, the panel was provided with evidence regarding the risk of cannabis dependence, motor vehicle accident causing injury, falls, suicidal ideation, and suicide associated with medical cannabis or cannabinoid use for chronic pain.

How this recommendation was created

Our international panel included general practitioners, a physical medicine and rehabilitation physician, internists, a paediatrician, a paediatric anaesthesiologist, pharmacists, physicians specialising in pain management, clinical pharmacologists, a chiropractor, a rheumatologist, methodologists, and people living with chronic pain (including a veteran). The panel decided the scope of the recommendation and the outcomes that are most important to patients. Parallel teams conducted systematic reviews on the benefits and harms of medical cannabis or cannabinoids, long term harms of medical cannabis or cannabinoids, the impact of providing medical cannabis or cannabinoids on opioid substitution, and a systematic search for evidence about patients' values and preferences (box 2; appendix 1 on bmj.com). The panel met virtually to discuss this evidence and formulate a recommendation. No panel member had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (see appendix 2 on bmj.com). These considerations may be particularly important regarding medical cannabis, as a recent investigation uncovered links between commercial organisations and patient groups and individuals lobbying for increased access to cannabis for medical use.[112 113]

The panel followed the *BMJ* Rapid Recommendations procedures for creating trustworthy recommendations,[114] including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 3 on bmj.com).[115] The panel considered the balance of benefits, harms, and burdens of medical cannabis, the certainty of the evidence for each outcome, typical and expected variations in patient values and preferences, and acceptability.[116]

Understanding the recommendation

The panel made a weak recommendation to offer a trial of non-inhaled medical cannabis or cannabinoids, in addition to standard care and management (if not sufficient to manage pain symptoms), for people living with chronic cancer or non-cancer pain. Strong recommendations indicate that all or almost all fully informed patients would choose the recommended course of action. Weak recommendations reflect the uncertainty in typical patients' preferences, as well as the likely wide variability in preferences between patients.[70 71]

Who does it apply to?

The recommendation applies to adults and children living with moderate to severe chronic pain regardless of pain mechanism—neuropathic pain (resulting from injury to the somatosensory nervous system, such as diabetic neuropathy); nociceptive pain (injury to non-neural tissues producing noxious stimulus, such as osteoarthritis); and nociplastic pain (pain arising from altered nociception despite no clear evidence of tissue damage, such as fibromyalgia)[72]—as well as cancer related chronic pain. The panel is confident that the recommendation applies to people with different subtypes of pain as the linked systematic review contained

adequate representation from such groups and settings, and, after applying optimal methodology,[73] we found no evidence of credible subgroup effects across clinical subtypes of chronic pain. Chronic pain may result from a specific lesion, but in some cases the cause is unspecified.[74] Moreover, many people living with chronic pain present with mixed pain—a combination of nociceptive, neuropathic, and/or nociplastic features.[75 76]

No trial eligible for our systematic review explored the effect of inhaled forms of medical cannabis or enrolled patients in palliative care. Our recommendation does not apply to smoked or vapourised forms of cannabis, cannabis provided for recreational purposes, or patients receiving end-of-life care. Moreover, inhaling cannabis is associated with adverse pulmonary events[77] that oral and topical administrations avoid.

Trials eligible for our reviews largely excluded chronic pain patients with concurrent mental illness, or those receiving disability benefits or involved in litigation, and did not report the representation of veterans; the generalisability of our recommendation to these populations is therefore uncertain. The median of the mean age among eligible randomised trials we reviewed was 53; a separate review has concluded that, in general, cannabinoid based medicines are safe and acceptable in older adults.[78]

Patients recruited among eligible trials were adults. However, the panel (which included a general paediatrician and a paediatric anaesthesiologist) could see no reason why the expected benefits would be systematically different among adolescents and emerging adults. Regarding potential harms, the panel noted the evidence for an association between use of cannabis and adverse neurocognitive effects,[79] including acute psychotic episodes.[80] However, the literature reporting this association has solely focused on recreational use of cannabis, in particular on high doses of inhaled THC,[73 81] which would not be administered for therapeutic purposes. Neither our review of randomised trials[19] nor observational studies[20] identified evidence for an association between medical cannabis or cannabinoids and early onset psychosis, but these studies were restricted to adult patients.

Indirect evidence from paediatric populations with epilepsy managed with medical cannabis offers some safety information. A 2020 systematic review of medical cannabis and cannabinoids for paediatric epilepsy found four randomised and 31 non-randomised studies that explored benefits and harms.[82] All the randomised trials were considered low risk of bias, whereas the observational studies were at high risk of bias, primarily due to lack of a control group and unblinded outcome assessment. Most studies administered cannabidiol (CBD), often at very high doses (up to 50 mg/kg per day), and three studies provided combination products (CBD and THC). Treatment duration ranged from 10 days to 146 weeks, and no randomised trial followed patients for more than 14 weeks. Two studies that captured emergency department visits found no association between such visits and use of medical cannabis (very low certainty evidence).

In light of current direct and indirect evidence, and because our recommendation applies solely to medical non-inhaled cannabis or cannabinoids, the panel felt the suggestion to consider a trial of medical cannabis or cannabinoids for chronic pain could also apply to younger patients. However, while there is some evidence supporting the safety of CBD in children,[82] the safety profile of THC is less certain and the potential for adverse neurocognitive effects should be considered when deciding whether to trial medical cannabis products containing THC.

The evidence suggested the possibility of a subgroup effect, with medical cannabis or cannabinoids showing larger benefits for chronic non-cancer pain and little or no benefit for chronic cancer pain; however, there were few trials informing this subgroup analysis, the analysis of effect was between rather than within trials, and tests of interaction were non-significant (suggesting that chance was a likely explanation).[19] As such, the subgroup effect was deemed of very low credibility[83] and thus did not affect our recommendation.

Absolute benefits and harms

The infographic explains our recommendation and provides an overview of the absolute benefits and harms of medical cannabis or cannabinoids for chronic pain (GRADE Summary of Findings). Estimates of baseline risk for effects come from the control arms of trials eligible for review.

The panel was confident that non-inhaled medical cannabis or cannabinoids:

- Result in a small increase in the proportion of people living with chronic pain experiencing an important improvement in pain and sleep quality (high and moderate certainty evidence, respectively)
- Result in a very small increase in the proportion of people living with chronic pain experiencing an important improvement in physical function (high certainty evidence)
- Do not improve emotional functioning, role functioning, or social functioning (high certainty evidence)
- Result in a small to very small increase in the proportion of people living with chronic pain experiencing cognitive impairment, vomiting, drowsiness, impaired attention, and nausea, and a moderate increase in the proportion of individuals experiencing dizziness that increased with longer follow-up (GRADE moderate to high certainty evidence).

It is unlikely that new information will change interpretation for outcomes that are high to moderate certainty of evidence.

The panel was less confident about:

- Whether use of medical cannabis or cannabinoids resulted in reduced use of opioids (GRADE very low certainty evidence)
- Whether the use of medical cannabis or cannabinoids was associated with increased risk of cannabis dependence, road traffic accident causing injury, falls, suicidal ideation or suicide, and other potential serious harms (GRADE very low certainty evidence).

Values and preferences

The systematic search for empirical data on patients' values and preferences related to medical cannabis or cannabinoids for chronic pain identified 15 studies of adults with both cancer and non-cancer chronic pain (appendix 1 on bmj.com).

We found moderate to high certainty evidence that:

- People living with chronic pain have greater preference for medical cannabis products with a balanced ratio of THC:CBD or high CBD products, and not for high THC products
- Use of medical cannabis or cannabinoids is influenced by both positive (such as support from friends and family) and negative social consequences (such as stigma surrounding cannabis use, disapproval from healthcare providers)

- Concerns about medical cannabis or cannabinoids included adverse drug effects, addiction, tolerance, losing control or unusual behaviour, and these are related to unwillingness to use cannabis
- Some patients feel that the cost of medical cannabis or cannabinoids is too high, while some report that legalisation has improved access and positively influenced their decision to pursue medical cannabis for symptom relief.

We found low to very-low certainty evidence that:

- Patients had varying levels of willingness to use medical cannabis or cannabinoids and most patients who used medical cannabis products reported positive attitudes towards its use
- Patients with a history of substance use preferred medical cannabis or cannabinoids over prescription opioids
- Patients were motivated to use medical cannabis or cannabinoids to reduce use of prescription medication and felt that it was safer than opioids.

Our weak recommendation in favour of a trial of medical cannabis or cannabinoids reflects a high value placed on small to very small improvements in self reported pain intensity, physical functioning, and sleep quality, and a willingness to accept a very small to modest risk of mostly self limited and transient harms. All panel members agreed on the strength of the recommendation (weak); all but two panel members (20 of 22) agreed with the direction of the recommendation.

The panel, including patient partners, believes that there is great variability in how much reduction in pain severity, improvement in physical functioning, or sleep quality each patient would consider important. Patients who place a high value in improving these symptoms by any amount (for example, patients with lower tolerance to pain or those with severe symptoms) are more likely to pursue a trial of medical cannabis or cannabinoids. For example, a 1 in 10 chance of experiencing important pain relief may be insufficient to justify a trial of medical cannabis if patients are achieving reasonable results with their current management and if the unlikely, but possible, development of cognitive impairment or impaired attention would preclude their ability to function at work or at home. Alternately, patients experiencing problematic pain despite optimisation of non-cannabis management, which is a prevalent condition, or who wish to explore the potential for opioid substitution may be willing to consider a trial of medical cannabis or cannabinoids.

Practical issues and other considerations

Box 3 outlines the key practical issues for patients and clinicians discussing a trial of medical cannabis or cannabinoids for chronic pain, which are also accessible along with the evidence as decision aids to support shared decision making in MAGICapp.[71]

Medical cannabis or cannabinoids are legally available in: Argentina,[84] Australia,[85] Barbados,[86] Bermuda,[87] Brazil,[85] Canada,[88] Chile,[88] Colombia,[88] Croatia,[89] Czech Republic,[89] Denmark,[89] Ecuador,[90] Estonia (with a permit),[89] Finland,[89] Germany,[89] Ghana (only for products with <0.3% THC),[91] Israel,[88] Italy,[88] Jamaica,[88] Lebanon,[92] Lesotho,[91] Malta,[89] Mexico,[93] the Netherlands,[88] New Zealand,[94] Peru,[95] the Philippines,[96] Saint Vincent and the Grenadines,[97] San Marino,[98] South Africa,[91] South Korea,[99] Sri Lanka,[100] Switzerland,[88] Thailand,[88] the United Kingdom,[88] United States (not at the federal level, but in 36 states and the District of Columbia),[17 101] Uruguay,[88] Vanuatu,[102] Zambia and Zimbabwe.[91]

As of 2018, nabiximols (a cannabis extract consisting of THC and CBD) have been available in all European Union member states except for Bulgaria, Cyprus, Greece, Hungary, Latvia, Romania, and Slovakia. For example, nabiximols are available in Austria, Belgium, France, Ireland, Lithuania, Luxembourg, Malta, Poland, Portugal, Slovenia, and Spain.[89] Nabiximols are also available in Turkey.[103]

Box 3: Key practical issues

Medication routine

- Therapeutic trials should start with low dose, non-inhaled cannabidiol (CBD) products, gradually increasing the dose and THC level depending on clinical response and tolerability (such as starting at a dose of 5 mg CBD twice daily and increasing by 10 mg every 2-3 days to a maximum daily dose of 40 mg). If response is unsatisfactory, clinicians may consider adding 1-2.5mg THC per day and titrating 1-2.5 mg every 2-7 days to a maximum of 40 mg/day.
- Prior cannabis experience should be considered, and adverse event monitoring should be carefully conducted.
- For younger or adolescent patients, CBD-predominant preparations should be preferred because of uncertain effects of THC on neurocognitive development.

Administration

- Our evidence synthesis was largely informed by oral preparations of medical cannabis or cannabinoids, including sprays, tablets, and oil drops administered sublingually. Our recommendation does not apply to inhaled forms of cannabis, which entails pulmonary exposure to particulate matter and toxins.

Adverse effects

- Serious adverse events are unlikely with medical cannabis or cannabinoids, and patients cannot fatally overdose. Dizziness is the most common non-serious adverse event with medical cannabis treatment.

Pregnancy and nursing

- Evidence regarding adverse effects of medical cannabis or cannabinoids use during pregnancy or breastfeeding is inconclusive: pregnant women or women contemplating pregnancy should be encouraged to discontinue use of medical cannabis in favour of alternative therapy. Cannabis use during breastfeeding should be discouraged.

Travel and driving

- Avoid driving or operating machinery while starting or changing doses of medical cannabis or cannabinoids.

Once a trial of medical cannabis has been initiated, unexperienced cannabis users should be reviewed at least every month until a stable dose is achieved; experienced users can be reviewed after three months. If benefits are non-sufficient or problematic adverse events are reported, clinicians may elect to return to a previously tolerated dose, increase CBD or reduce THC dose, or change the route of administration. Cannabis should be discontinued if, despite these strategies, patients continue to experience problematic side effects, a maximum dose is achieved without important benefits, or patients are diverting cannabis or develop a cannabis use disorder. If management with medical cannabis is successful, patients should be followed up (for example, every 3-6 months) after a stable dose is achieved.[104 105]

In the absence of approved products and monographs, efforts are under way to offer pragmatic dosing and administration guidance to clinicians who wish to initiate trials of medical cannabis or cannabinoids with their patients. Following preliminary guidance,[105] an industry-led international consensus panel has promoted dosing strategies that involve starting with low doses of oral products (oils,

soft gels) that are CBD-predominant and then gradually increasing dose and THC level depending on clinical response and tolerability (for example, starting at a dose of 5 mg CBD twice daily and increasing by 10 mg every 2-3 days to a maximum daily dose of 40 mg).[104] If response is unsatisfactory, clinicians may consider adding 1-2.5 mg THC per day and titrating 1-2.5 mg every 2-7 days to a maximum of 40 mg/day.[106] Prior cannabis experience should be considered, and adverse event monitoring should be carefully conducted. CBD-predominant preparations should be preferred for younger or adolescent patients because of uncertain effects of THC on neurocognitive development.

Dosing should be individualised and informed by titration, after starting at the lowest plausible therapeutic dose. For example, daily oral doses range from 2.5 mg to 40 mg for dronabinol, from 0.2 mg to 6 mg/day for nabilone, from 1 to 16 oral sprays for nabiximols (dronabinol/cannabidiol), and from 5 to 20 mg/kg/day for Epidiolex (an oil based extract of cannabis containing 98% CBD). Upper limits of dosages may vary between countries. Topical preparations theoretically require lower doses and stay local, therefore reducing harms associated with ingested forms of cannabis; however, commercial products typically lack pharmacokinetic data establishing their ability to cross the aqueous layer and remain localised.[107 108]

The opioid sparing effects of medical cannabis for chronic pain remain uncertain due to very low certainty evidence.[22] Clinicians may, however, consider medical cannabis as part of an approach to help facilitate opioid tapering among consenting patients. Importantly, forced opioid tapering is ineffective and may cause harm.[109 110]

Advertised content of medical cannabis products may not be accurate. One US analysis of 84 products found that 26% contained less CBD than labelled, which could negate any potential clinical effect.[111] Furthermore, with the exception of Epidiolex and Sativex, non-synthetic cannabinoids lack a drug identification number and cannot be prescribed by physicians, only authorised.

The bioavailability of oral preparations of medical cannabis or cannabinoids ranges from 13% to 19% and can take up to four hours to reach peak concentrations.[107] Dronabinol, THC, and CBD are metabolised in the liver, via cytochromes P450 (CYP) 2C9 and CYP3A, and about a third of the molecules and metabolites are eliminated in the urine (remaining metabolites are eliminated in the faeces). Several metabolites of THC are considered psychoactive. The elimination half-life of dronabinol ranges from 25 to 36 hours, and its main metabolite (11-hydroxy-delta-9-tetrahydrocannabinol) is 44-59 hours; the half-life of CBD is 56-61 hours. The effects of medical cannabis or cannabinoids may be enhanced in patients with renal or liver impairment.

Costs and resources

The panel focused on the perspectives of people living with chronic pain rather than those of society or payers when formulating their recommendation. As identified in our review of patient values and preferences, both legal availability of medical cannabis or cannabinoids and costs are likely to influence decision making.

Uncertainties for future research

Key research questions to inform decision makers and future guidelines include:

- Are there systematic differences in treatment effects of medical cannabis or cannabinoids for chronic cancer pain versus chronic non-cancer pain and for nociceptive versus neuropathic versus nociplastic pain?
- Are there systematic differences in treatment effects of different formulations and types of medical cannabis or cannabinoids, including CBD, CBD:THC, THC, and PEA?
- Does medical cannabis or cannabinoids reduce opioid use for chronic pain?
- Are the effects of medical cannabis or cannabinoids consistent among adolescents and young adults with chronic pain?
- What is the optimal dose, formulation, and method of administration of medical cannabis or cannabinoids for chronic pain?
- What are the benefits and harms of inhaled medical cannabis?
- What are the benefits and harms of prolonged medical cannabis or cannabinoid use?

How patients were involved in the creation of this article:

Three people with lived and living experience of chronic pain were members of the guideline panel. These members were involved throughout the process of guideline development, particularly with respect to identifying important outcomes and informing the discussion on values and preferences. Our patient partners agreed that while small reductions in pain severity and small to very small improvements in physical functioning and sleep quality were important to them, these values may not be shared by all patients; they expected moderate to great variability in how much importance other patients would place on small reductions in pain. These panel members participated in teleconferences and email discussions and met all authorship criteria.

Education in practice

- How do you currently approach giving pain management advice for patients living with chronic pain? Do you consider offering a trial of medical cannabis or cannabinoids?
- The recommendation for medical cannabis or cannabinoids is weak, and patient's preferences are likely to vary as to whether they wish to pursue a trial of therapy. What information could you share with your patients to help them reach a decision?
- Chronic pain is common in many clinical settings. How might you share this guideline recommendation with colleagues to facilitate their learning about current best evidence?
- Having read the article, can you think of one thing you have learned which might alter how you consult with patients living with chronic pain?
- How often do you practice shared decision making for such preference-sensitive decisions?

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Infographic: Summary of recommendation and evidence

Appendix 1: Studies eligible for systematic review of patients' values and preferences

Appendix 2: Full list of authors' declarations of interests

Appendix 3: Methodology for development of *BMJ* Rapid Recommendations

Appendix 4: All electronic multilayered information available on the MAGICapp