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Evidence Report for the Use of Medicinal Cannabinoids in the Management of Chronic Non-Cancer Pain in Veterans

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Contents

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Independent Review Committee

Following best practice, DVA established an Independent Review Committee to provide impartial and expert advice to improve the quality and enhance the legitimacy of the guidance. Contributors: Associate Professor Doctor Vicki Kotsirilos AM (Chair), Mr Scott Jeffrey JP (Member; Veteran), Doctor Maxwell Qu (Member), Associate Professor Michael Vagg (Member).

Guideline Development Group

A multidisciplinary Guideline Development Group provided expert clinical input and community perspectives. Members contributed expertise across veteran health, chronic pain, psychiatry, general medicine, addiction medicine and cannabinoid therapeutics, along with lived experience from the veteran and chronic pain communities. Contributors: Professor Robert Ali AO, Ainslie Cahill AM, Professor Nicola Fear, Dr Ian Gardner, Associate Professor Bridin Murnion, Lara Shallard, Dr Hester Wilson

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Glossary

Term	Definition
Adverse events	Any unfavourable or harmful medical outcome occurring *during or after* using an intervention
Adjunctive therapy	A supplementary treatment used alongside a primary intervention to improve outcomes
Comorbidities	The presence of 2 or more health conditions occurring simultaneously in an individual
Control group	Participants in a study who do not receive the intervention being tested, serving as a comparison
Intervention	An action, treatment, or policy applied to individuals or groups to produce a desired effect
Intervention group	Participants in a study who receive the intervention being evaluated
Observational studies	A study in which the investigators do not seek to intervene, and simply observe the course of events. Changes or differences in one characteristic (e.g. whether or not people received the intervention of interest) are studied in relation to changes or differences in other characteristics
Placebo	An inactive substance or procedure given to participants to compare against an active treatment, often used to blind participants in trials
Randomised controlled trial (RCT)	An experimental study design where participants are randomly allocated to intervention or control groups to compare outcomes
Synthesis of evidence	The systematic process of collecting and combining findings from multiple studies to draw comprehensive conclusions
Temporal relationship	The sequence in time between an exposure and an outcome, showing whether the exposure occurred before the outcome
Titration	Gradually increasing the dose of a medication over time until the desired result is achieved without significant side effects

Executive Summary

Purpose

This report provides a synthesis of evidence to inform best practices for the initiation, monitoring and deprescribing of medicinal cannabinoids in the management of chronic non-cancer pain (CNCP) among veterans. The purpose of this report is to support the development of clinical guidance and client education materials that support healthcare providers, veterans and the broader medical community when considering the use of medicinal cannabinoids as part of a chronic pain management plan.

Methods

A two-pronged approach was used to identify relevant literature. First, a systematic review of peer-reviewed published literature was conducted, with a focus on identifying studies evaluating the safety and effectiveness of cannabinoids in managing the symptoms of CNCP. The review prioritised high-quality evidence from randomised controlled trials (RCTs), with lower quality studies (e.g., observational studies) referenced only where evidence was lacking. To support the translation of findings to the unique clinical and contextual factors relevant to veterans, veteran-specific studies are identified and highlighted where possible. Second, a search for international clinical guidelines and guidance documents relating to the initiation, monitoring, and deprescribing of medicinal cannabinoids were identified. The key recommendations and underlying evidence from these guidance documents were extracted and synthesised in a narrative summary.

Findings

There is evidence to suggest specific cannabinoids, particularly products including delta-9-tetrahydrocannabinol (THC), may be beneficial in the therapeutic management of CNCP, whereas cannabidiol (CBD) alone was not associated with a reduction in pain-related symptoms. In most cases, these findings are based on a small number of studies, and with all cannabinoids showing evidence of poorer treatment safety and treatment retention.

Conclusion

Evidence indicates that medicinal cannabinoids, particularly THC-containing products, may provide benefit for some people with CNCP, however treatment effects were modest and adverse events are common. Reflecting this uncertain risk-benefit balance, several leading pain organisations do not currently recommend cannabinoids for chronic pain management, citing insufficient or low-certainty evidence of benefit. Guidance on initiation, monitoring, and deprescribing are available internationally, but approaches are not standardised and require careful consideration.

Background and project overview

Current clinical guidance documents for Australian prescribers of cannabinoids are becoming dated given the rapid expansion of research and academic interest in cannabinoids as a pain management option. Furthermore, there are no domestic or international clinical guidelines available to support prescribers who wish to treat veterans with cannabinoids for chronic non-cancer pain (CNCP). There is an urgent need for clinical resources to guide veteran healthcare providers in the therapeutic use of cannabinoids to ensure veterans with CNCP receive treatment that aligns with the right care for their overall health needs.

This report presents the findings from identifying and synthesising the best available scientific evidence and guidance on the initiation, monitoring and deprescribing of cannabinoid products when treating veterans with CNCP. It examines the evidence base for delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in particular, alone or in combination, for CNCP for which cannabinoids have been advocated or commonly prescribed with a focus on high-quality assessments.

The evidence search used a two-part strategy. First, a systematic review of peer-reviewed studies examining the safety and effectiveness of cannabinoids for CNCP was conducted (see **Section One**), with priority given to randomised controlled trials (RCTs). Lower-quality evidence was considered only when higher quality studies were unavailable. To support the translation of findings to the unique clinical and contextual factors relevant to veterans, veteran-specific studies were identified and highlighted where possible.

Second, international clinical guidelines and guidance documents relating to the initiation, monitoring and deprescribing of medicinal cannabinoids were identified (see **Sections Two-Four**). The findings are structured around clinical questions of highest relevance to veteran healthcare providers, helping ensure veterans with CNCP receive treatment that aligns with the right care for their overall health needs. Contextual considerations, such as harms, benefits and patient values, have

also been factored into the evidence synthesis. Extracted guidance and evidence were narratively summarised.

This evidence report will inform the development of medicinal cannabinoid clinical guidance. Guidance will be linked to evidence via summary tables and be synthesised into accessible client education materials for veterans experiencing CNCP

Section One: Safety and effectiveness

To date, previous reviews have described limited evidence for the effectiveness of medicinal cannabinoids in treating CNCP symptoms (Cásedas et al., 2024; Johal et al., 2020; Mlost et al., 2020; Nugent et al., 2017). However, in recent years, there has been a notable increase in the number of studies being published in this area. To ensure the development of clinical guidance is informed and reflective of contemporary evidence, an updated review, synthesis and analysis of the literature on the safety and effectiveness of cannabinoids in the treatment of CNCP was conducted.

For the purposes of this review, chronic pain was defined as any pain lasting 3 months or longer, including (but not limited to) the following conditions and diagnoses: neuropathic pain, neuralgia, arthritis, fibromyalgia, multiple sclerosis, Crohn's disease, and spinal cord injury. Methods for the present review are provided at the end of this report (see **Appendix 1.1**).

Results of systematic review

Overall, 86 publications (including 115 individual studies) relevant to the safety and effectiveness of cannabinoids in the treatment of CNCP were identified from the peer-reviewed literature; this included 79 RCT publications. Most RCTs (80%) had analgesia as the primary indication, with the next most common indication being spasticity (14%). Among RCTs, participants were mostly middle-aged adults, and 65% female. Publications were primarily conducted in Europe (53%) and Northern America (43%). RCTs most often examined pharmaceutical grade products – primarily THC or a combined CBD and THC product. Most studies examined treatments administered orally, examined treatment effectiveness over prolonged periods of assessment (i.e., >24 hours) and used a placebo or non-exposed comparator. Very few studies compared the cannabinoid with an active comparator (see **Appendix 1.2**).

The outcome-related findings derived from the systematic review are summarised below:

- **THC (CBD<2%)** showed evidence of a positive effect on pain scores and physical functioning. The clearest pain signals were for visceral pain, non-MS neuropathic pain, and fibromyalgia, though heterogeneity was high. No significant overall effect on PGIC or pain reduction thresholds was found.
- **Balanced products (CBD ≥40% and <60%)** showed a positive effect on select pain outcomes - specifically, likelihood of achieving 50% pain reduction (particularly for non-MS neuropathic pain) and, with more uncertainty, 30% pain reduction. They also showed the most consistent positive effect on PGIC. No significant effect on pain scores overall, sleep, or physical functioning was found.
- **CBD products (≥98%)** were associated with a negative effect on the likelihood of achieving 50% pain reduction and on PGIC, with patients less likely to report global improvement compared to placebo. No significant effect on pain scores or 30% pain reduction was found overall.
- **All cannabinoid types** were associated with greater study withdrawals for any reason compared to placebo. THC-dominant (CBD<2%) and balanced (CBD ≥40% and <60%) products were additionally associated with greater withdrawals due to adverse events. THC-dominant products (CBD<2%) were also associated with higher rates of any adverse events and treatment emergent adverse events. No cannabinoid type was associated with a significant increase in serious adverse events.
- Cannabis sativa showed significant pain score reductions and improved likelihood of 30% pain reduction for non-MS neuropathic pain, and improved PGIC change scores for the same condition. Evidence across other outcomes was insufficient to draw conclusions.
- There is considerable variability in the range of doses administered in clinical trials:
    - Dosing varied substantially across studies and was reported using different metrics, including milligram doses, percentage THC/CBD content, and formulation-specific measures, limiting direct comparability (see **Appendix 4** for further details on dosage).

- For **CBD-predominant products**, the most frequently used doses clustered around 40 to 100 mg/day, with a broader range from approximately 10 mg/day to 400 mg/day.
- For **balanced THC: CBD products**, the most common doses were around 20 to 25 mg/day of THC and 20 to 25 mg/day of CBD, with reported ranges extending from approximately 5 mg/day up to 120 mg/day for each cannabinoid.
- For **THC-predominant products**, the most frequently used doses were approximately 10 to 20 mg/day THC, with a wider range from approximately 0.5 mg/day to 60 mg/day, although most studies were concentrated at the lower end of this range.

No RCTs were located that specifically focused on the use of cannabinoids for chronic non-cancer pain in veteran populations. Given the complex bidirectional interaction between psychosocial factors in chronic pain and the psychoactive effects of cannabinoids, we planned to stratify effects for mental health comorbidities and social factors. Unfortunately, most included RCTs did not report results in sufficient detail to allow meaningful effect stratification. However, the high prevalence of mental health conditions among people with CNCP means the unadjusted estimates are likely generalisable to the veteran population. Observational studies of veterans with CNCP have found that people using cannabinoids are not more likely than those who do not use them to report better health outcomes (Enkema et al., 2022; Mannes et al., 2023).

Summary

- Most studies show that some THC-containing medicinal cannabinoid products can reduce certain types of chronic pain, particularly nerve-related pain.
- Products that contain both THC and CBD may also improve pain and sleep in some people.
- CBD-only products do not appear to reduce chronic pain in most cases.

- All cannabinoid products were more likely than placebo to cause side effects or lead people to stop treatment.
- It is important to note that average effect sizes across trials were generally small, and thresholds for what constitutes a clinically meaningful benefit are not consistently defined across studies or patient groups.
- The doses used in clinical trials were generally lower than those currently prescribed in Australia.
- No high-quality trials have specifically studied veterans. Observational studies in veterans have not shown clear improvements in overall health outcomes.

Section Two: Initiation

A targeted literature review and narrative synthesis were undertaken to identify international clinical guidelines, academic publications and grey literature relating to the initiation, monitoring, and deprescribing of medicinal cannabinoids. Clinical guidance documents originated from Australia (Queensland Government, 2017; Therapeutic Goods Administration, 2024), New Zealand (Best Practice Advocacy Centre New Zealand, 2022; The Royal Australian and New Zealand College of Psychiatrists, 2024), Canada (Bell et al., 2024; College of Family Physicians of Canada, 2021), the Netherlands (Fleisch & Woodbridge, 2025), and organisations such as the European Pain Federation (Häuser et al., 2018) and The International Association for the Study of Pain (International Association for the Study of Pain, 2021) (see **Appendix 2** for links to guidance documents). The majority of literature was developed within Western, high-income healthcare settings and published in recent years.

When to consider starting medicinal cannabinoids?

Current Australian guidance suggests that medicinal cannabinoids should be considered only when all other evidence-based treatment options have been tried without adequate success (Queensland Government, 2017; Therapeutic Goods Administration, 2024). Guidelines suggest that CNCP should be managed within a biopsychosocial framework, progressing through established therapies before cannabinoids are contemplated (Centre for Effective Practice, 2018). Initial management emphasises non-pharmacological strategies, including individually tailored physical exercise programs and behavioural therapies such as cognitive-behavioural therapy (CBT) and acceptance and commitment therapy (ACT) to improve coping, function, and quality of life (Mazurenko et al., 2025). When medication is required, clinicians may consider paracetamol, short-term non-steroidal anti-inflammatory drugs (NSAIDs), topical agents, selected antidepressants, and gabapentinoids, each used cautiously and through shared decision-making (Turk et al., 2011). Opioids are reserved for carefully selected situations due to limited long-term benefit and increased risks (The Royal Australian College of General Practitioners, 2022). Complementary therapies such as

acupuncture or massage may also be incorporated based on patient preference (Turk et al., 2011). Only after these approaches have been exhausted without sufficient improvement does current guidance support considering medicinal cannabinoids.

This approach aligns with most international guidance, which positions cannabinoids as a third-line or adjunctive therapy rather than a first-line option. Medicinal cannabinoids have not been included as first-line or second-line medications in international guidelines for chronic pain management, including Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations (N. B. Finnerup et al., 2015; Marcianò et al., 2023). For example, Canadian guidelines advise that patients should trial at least 3 other medications for chronic pain before considering cannabinoids, and New Zealand guidance similarly restricts use to cases where conventional treatments are ineffective or not tolerated (Best Practice Advocacy Centre New Zealand, 2022; College of Family Physicians of Canada, 2021). European recommendations, including those from the European Pain Federation and Germany, echo this stance, emphasising that cannabinoids should only be prescribed for chronic pain when standard therapies have failed (Häuser et al., 2018; National Association of Statutory Health Insurance Physicians, 2023). Finally, a BMJ Rapid Recommendation reinforces this position, offering only a weak suggestion to trial non inhaled medical cannabinoids as an adjunct to standard care due to the narrow balance of benefits and harms (Busse et al., 2021).

However, several leading pain organisations take a different position. The UK's National Institute for Health and Care Excellence (NICE) does not recommend cannabinoids for chronic pain management (unless part of a clinical trial), based on a 2019 review that found insufficient evidence of benefit (National Institute for Health and Care Excellence, 2021). The International Association for the Study of Pain (IASP) states there is insufficient evidence to endorse the general use of cannabinoids for pain management (International Association for the Study of Pain, 2021). Furthermore, the Special Interest Group on Neuropathic Pain (NeuPSIG) conducted a systematic review to inform updated neuropathic pain treatment

guidance and gave a recommendation against the use of cannabinoids, concluding that current evidence does not support their efficacy for neuropathic pain (Finnerup et al., 2015; Soliman et al., 2025). The Faculty of Pain Medicine Australia (ANZCA) agrees with the IASP position and does not support the use of cannabinoids for pain, due to the limited and low certainty evidence of benefit (ANZCA, 2022).

Clinicians should be aware of the limitations of the current evidence base. Most clinical trials have compared medicinal cannabinoids with placebo. Evidence directly comparing cannabinoids with other medications for CNCP (such as opioids, NSAIDs, gabapentinoids, or antidepressants) is scarce. Consequently, the clinical decision on when to start medicinal cannabinoids is typically not whether to choose cannabinoids over conventional analgesics, but rather whether cannabinoids offer an acceptable risk-benefit profile for patients who have not achieved adequate pain relief with other treatments. Evidence limitations extend beyond chronic pain. A recent systematic review of RCTs found minimal evidence of benefit for cannabinoids across most mental health and substance use disorders, with increased adverse events (Wilson et al., 2026). Given the prevalence of these comorbidities in individuals with CNCP, these findings may be relevant when assessing initiation.

Pre-treatment discussion points

The Australian Commission on Safety and Quality in Health Care requires physicians to provide accurate and relevant information to patients when obtaining informed consent from the patient, including enough information about their condition, treatment options, the benefits and risks, and alternative options; and consider shorter and longer consequences of taking cannabinoids for the person (NSQHS Standards, 2020). To enable informed decision-making and setting realistic expectations for both the benefits and risks of potential long-term cannabinoid use, the following points have been recommended as points to be discussed prior to initiating treatment:

- CNCP is typically a lifelong condition, implying that the likelihood of any therapeutic management would need to be effective and safe long-term.
- Research shows 1 in 4 people prescribed medicinal cannabinoids may develop cannabis use disorder (CUD) (Dawson et al., 2024). Veterans with chronic non-cancer pain face a particularly elevated risk (Mannes et al., 2023).
- The ongoing financial costs of sustained cannabinoid therapeutic management (Martin et al., 2020).
- Evidence on its effectiveness for CNCP is limited and variable (Stockings et al., 2018).
- Other evidence-based options, including non-pharmacological treatments (NSQHS Standards, 2020).

Pre-treatment assessment

Before prescribing medicinal cannabinoids , clinicians should conduct a comprehensive assessment to ensure patient safety, assess what treatments have been trialled including non-drug approaches, and establish a baseline for monitoring treatment outcomes.

According to Canadian and Australian guidance, the following areas and risk factors should be reviewed (College of Family Physicians of Canada, 2021; The Royal Australian and New Zealand College of Psychiatrists, 2024; The Royal Australian College of General Practitioners, 2019):

- Current medical status e.g., chronic health conditions, medications, pregnancy
- Past medical history e.g., psychiatric conditions, prior use of cannabinoids and other substances
- Family history of mental illness
- Clinical justification e.g., severity of condition and symptoms, documentation of other evidence-based treatments previously tried.

This pre-treatment assessment provides the foundation for understanding a patient's risk profile. The subsequent sections on contraindications and drug

interactions offer further evidence to inform safe and appropriate prescribing. Cannabinoids can have adverse effects on mood and cognition (Nugent et al., 2017), whilst effective pain relief may also yield broader benefits, such as improved sleep and psychosocial functioning. Documenting baseline status is essential for detecting any deterioration during treatment, monitoring treatment response and assessing whether benefits outweigh risks (MacCallum et al., 2021). Recommended screening tools include:

- Mental health: such as the Generalised Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders DSM-5
- Pain: Brief Pain Inventory (BPI)
- Quality of life: Short Form Survey (e.g., SF-12, SF-6D, EQ-5D).

These baseline assessments enable objective evaluation of treatment effectiveness during follow-up and help physicians identify any adverse effects on mental health or cognitive function that may develop during cannabinoid therapy.

Contraindications

International guidelines and position papers emphasise that medicinal cannabinoids should be prescribed with caution, particularly in populations at higher risk of adverse effects (Allan et al., 2018). While evidence is still emerging and the certainty of evidence about some contraindications remains a matter for debate, most guidelines distinguish between absolute (where treatment should not be initiated) and relative (where caution and close monitoring are required) contraindications (see **Table 1**).

Table 1: Absolute and relative contraindications for medicinal cannabinoids

Contraindication	Supporting evidence	Which guidelines include this contraindication
Absolute		
Hypersensitivity to any cannabinoid product	Allergic reactions documented in case reports, with increased adverse reactions (Ocampo & Rans, 2015).	European Pain Federation, Canada, New Zealand

Severe or unstable cardiopulmonary disease	Cannabinoids can increase heart rate and blood pressure; avoid in unstable cardiac patients (Ravi et al., 2018).	Australia, Canada, European Pain Federation, New Zealand, Netherlands
Previous or current personal history of psychiatric disorders	Strong association between cannabinoids and psychosis risk; guidelines advise avoidance (Chesney et al., 2025; Lim et al., 2017; Moore et al., 2007; Nugent et al., 2017; Turna et al., 2017).	Australia, Canada, European Pain Federation, New Zealand, Netherlands
Pregnant or breastfeeding	Some evidence that links cannabinoids to neurodevelopmental harm and negative neonatal outcomes (Grzeskowiak et al., 2020; Jansson et al., 2018).	Australia, Canada, European Pain Federation, New Zealand, Netherlands
Relative		
Current, previous or family history of mood, anxiety or other mental health disorders	Cannabinoids may worsen symptoms; use with caution and monitor closely (Best Practice Advocacy Centre New Zealand, 2022; Turna et al., 2017)	Australia, Canada, European Pain Federation, New Zealand
Young adults	Some evidence that cannabinoids may impact neurodevelopment (Jager & Ramsey, 2008).	European Pain Federation (under 18), Canada (under 25), Netherlands (under 23), New Zealand (under 18)
Severe liver disease	Cannabinoids metabolised in the liver; hepatic (liver) impairment can increase toxicity of cannabinoids (Hézode et al., 2008; Purohit et al., 2010; Zhu & Peltekian, 2019).	Canada, New Zealand
Severe renal disease	Extra monitoring of renal function for those with chronic kidney disease; start at lowest dose (Rein, 2020).	Canada, European Pain Federation, New Zealand
Previous substance misuse or dependence	Elevated risk of cannabis use disorder; guidelines recommend caution (College of Family Physicians of Canada, 2021).	Canada, European Pain Federation, New Zealand
Interaction with other medications	Described below; caution and additional monitoring, with changes in dose or choice of concomitant drugs, required.	
Elderly patients at risk of falls	Cannabinoids can increase dizziness and psychomotor impairment; thorough assessment of risk needed (Minerbi et al., 2019).	Canada, European Pain Federation, New Zealand

Drug interactions

Medicinal cannabinoids can interact with many commonly prescribed medications through the induction or inhibition of Cytochromes P450 family isoenzymes (e.g., antidepressants, antipsychotics, antiepileptics, bipolar disorder medications, opioids; see **Table 2**) thus affecting drug concentration in the body (Ho et al., 2024). Formal drug interaction studies involving medicinal cannabinoids are limited, particularly for Cannabigerol (Ho et al., 2024; MacCallum et al., 2021; Nachnani et al., 2021). Caution should be used when prescribing cannabinoids to patients taking medications with narrow therapeutic indices (e.g., warfarin [increased international normalised ratio and risk of bleeding], clobazam [increased risk of benzodiazepine toxicity], tacrolimus [increased blood concentration of tacrolimus], and methadone [increased blood concentration of methadone]), as cannabinoids can increase their plasma concentrations and lead to serious adverse events (Antoniou et al., 2020; Damkier et al., 2019; Hauser et al., 2016; MacCallum et al., 2021; Madden et al., 2020). Concurrent use with alcohol or other central nervous system depressants should be avoided (Hsu et al., 2025). Cannabinoids can also reduce efficacy of other medications e.g., theophylline, clozapine, and olanzapine (Antoniou et al., 2020).

Table 2: Interactions between cannabinoids and other medications (Antoniou et al., 2020).

Medication type	THC	CBD
CYP3A4 inhibitors [e.g., macrolide antibiotics (clarithromycin and erythromycin only), azole antifungals, HIV protease inhibitors, diltiazem, verapamil, amiodarone]	↑ THC concentration	↑ CBD concentration
CYP3A4 inducers [e.g., rifamycins, efavirenz, nevirapine, St. John's wort, carbamazepine, phenytoin, phenobarbital]	↓ THC concentration	↓ CBD concentration
CYP3A4 substrates [e.g., alprazolam, PDE5 inhibitors (e.g., sildenafil), carbamazepine, HIV protease inhibitors, diltiazem, verapamil, fentanyl,	Currently no effect found	↑ other medication concentration

cyclosporine, tacrolimus, sirolimus, simvastatin, atorvastatin, zopiclone		
CYP2C9 inhibitors [e.g., sulfamethoxazole, amiodarone, metronidazole, fluconazole, voriconazole, valproic acid]	↑ THC concentration	Currently no effect found
CYP2C9 Inducers [e.g., rifamycins, barbiturates, carbamazepine]	↓ THC concentration	Currently no effect found
CYP2C9 Substrates [e.g., warfarin, rosuvastatin, phenytoin]	↑ other medication concentration	↑ other medication concentration
CYP2C19 inhibitors [e.g., cimetidine, omeprazole, esomeprazole, ticlopidine, fluconazole, fluoxetine, isoniazid]	Currently no effect found	Potential interaction
CYP2C19 inducers [e.g., barbiturates, St. John's wort, carbamazepine, rifamycins]	Currently no effect found	↓ CBD concentration
CYP2C19 substrates [e.g., aripiprazole, clopidogrel, citalopram, diazepam, N-desmethylclobazam (nCBZ)]	Currently no effect found	↑ other medication concentration
CYP2B6 substrates [e.g., methadone, selegiline, meperidine]	↑ THC concentration	↑ CBD concentration
CYP1A2 substrates [e.g., clozapine, theophylline, olanzapine]	↑ clearance of other drugs	↑ clearance of other drugs

Evidence regarding concurrent uses of cannabinoids and opioids remains mixed. A cohort study among Australians with CNCP who had been prescribed opioids found no evidence of a temporal relationship between cannabinoid use and pain severity or pain interference, and no evidence that cannabinoid use reduced prescribed opioid use or increased rates of opioid discontinuation (Campbell et al., 2018). A larger systematic review found preclinical and observational studies demonstrated a potential opioid-sparing effect of cannabinoids in the context of analgesia; however, there was no evidence of opioid-sparing effects in high-quality RCTs (Nielsen et al., 2022). Other studies have shown the opposite (Ho et al., 2024). When cannabinoids are added to an opioid regimen, clinicians should monitor closely, and dose-adjust medicines appropriately.

Prescribing regulations

The regulatory framework for prescribing medicinal cannabinoids in Australia was established following the 2016 amendments to the *Narcotic Drugs Act 1967* which enabled controlled clinical access to cannabinoid-based products for therapeutic use (The Royal Australian College of General Practitioners, 2025). Only 2 medicinal cannabinoid products are registered on the Australian Register of Therapeutic Goods:

- **Sativex (nabiximols):** indicated for moderate to severe spasticity associated with multiple sclerosis. Sativex is available from selected pharmacies and is reported to cost between $700 and $800 for a 6–8-week supply (Multiple Sclerosis Australia, 2026).
- **Epidyolex (cannabidiol):** indicated as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients aged 2 years and older. In 2021, Epidyolex was listed on the Pharmaceutical Benefits Scheme (PBS). For patients who meet the PBS eligibility criteria for these conditions, the out-of-pocket cost is capped at approximately $25 per prescription, compared with $1,535.64 without PBS subsidy or Medicare/concession support (Pharmaceutical Benefits Scheme, 2026).

All other medicinal cannabinoid products are unapproved and must be accessed through the Australian Therapeutic Goods Administration authorisation pathways (Therapeutic Goods Administration, 2025). While the types of products and clinical indications are not restricted in legislation, access is influenced by how each product is scheduled under the Poisons Standard, with scheduling and regulatory requirements varying across states and territories. The Royal Australian College of General Practitioners position is that the current prescribing system for medicinal cannabinoids is overly bureaucratic, inconsistent and burdensome, and should be replaced with a streamlined, nationally consistent framework that enables timely access, reduces duplication, and recognises GPs as specialists with appropriate prescribing autonomy (The Royal Australian College of General Practitioners, 2025).

Formulations

Medicinal cannabinoids contain 2 main active components: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the psychoactive component responsible for the "high" associated with cannabinoid use, while CBD does not produce psychoactive effects.

The current systematic review found that THC had efficacy for chronic pain (see **Section One**). When CBD alone is used, results favour placebo, indicating limited therapeutic benefit. However, clinical experience suggests that some patients may report pain relief when using whole-spectrum CBD products.

The psychoactive effects and associated risks of THC warrant a cautious approach. The selection of cannabinoid should be individualised based on careful assessment of each patient's risk-benefit ratio and their willingness to accept the associated risks. Previous recommendations have included to (MacCallum et al., 2021):

- Start with CBD-predominant formulations
- Add THC only if treatment goals are not met with CBD alone
- Use the lowest effective dose of THC to minimise psychoactive effects and other risks.

When these recommendations are considered alongside the evidence from the updated review (see **Section One**), it may be decided that patients would benefit from starting with a balanced combined CBD and THC product with the lowest possible THC dose. In this way, potentially benefiting from cannabinoid therapy while minimising exposure to psychoactive effects and reducing the risk of adverse outcomes, including cannabis use disorder or significant drug interactions.

Routes of administration

Medicinal cannabinoids can be administered through several routes, each with different characteristics, including oral ingestion (e.g., tablets, capsules, and oils), inhalation, and others (including sublingual and topical). Oral administration was the most common route in the included studies (see **Appendix 1.2**); however, further differentiation by specific oral formulation (e.g. oils, capsules, tablets, or

other preparations) was not possible due to limited and inconsistent reporting. Many studies described interventions simply as “oral” without specifying formulation type, and where reported, formulations were heterogeneous and represented by small numbers of studies. This limits the ability to draw conclusions regarding the comparative effectiveness or safety of different oral routes and highlights an important area for future research. Clinical trials examining topical cannabinoids for chronic pain are currently underway (Seevathee et al., 2025); both products and evidence for this route remain limited at present.

When selecting routes of administration, clinicians should take into account the required dosage and the expected onset of action (MacCallum et al., 2021; Martin et al., 2020). Oral ingestion has been recommended as it provides longer-lasting effects and lower harm compared to vaporisation (MacCallum et al., 2021; MacCallum & Russo, 2018). Smoking is not recommended (Hsu et al., 2025).

Starting dosage and titration

The fundamental principle for initiating medicinal cannabinoids is to ‘start low and go slow’ (MacCallum et al., 2021). Dosing and tolerability are highly patient-specific (Penington, 2015). The safe and effective dosage varies among individuals, and a conservative approach minimises adverse effects while identifying the minimum effective dose (MacCallum et al., 2021; Penington, 2015). This principle is consistently endorsed by guidelines in Canada, Australia, New Zealand, and the Netherlands, as well as by the European Pain Federation, which further recommends that the optimal dose is the one that provides clinical benefit without causing intoxication or unacceptable side effects (Best Practice Advocacy Centre New Zealand, 2022; College of Family Physicians of Canada, 2021; Häuser et al., 2018; Ministry of Health, 2021; Therapeutic Goods Administration, 2024).

Example guidance for a starting dose and titration is listed below (Bhaskar et al., 2021; MacCallum et al., 2021):

For Oral Administration:

1. Start with 5 mg CBD oil twice daily
2. Titrate dose by 5 mg CBD every 2-3 days if no adverse events occur and treatment goals are not yet met
3. If CBD alone does not achieve treatment goals, consider adding THC after reassessing the benefit-risk ratio:
    - Start with 1 mg THC and titrate by 1-2.5 mg every 2-7 days
4. Doses above 40 mg/day of THC are rarely required. If this threshold is reached, clinicians should reassess the risk-benefit ratio for the patient

Physicians can adjust the starting dose or titration schedule based on patient characteristics. Regular monitoring for adverse events is essential throughout titration (see section 3 for more information on adverse events). The goal is to find the minimum effective dose that achieves treatment objectives.

Driving

- Adding CBD to THC may exacerbate THC-induced driving impairment (Arkell et al., 2019)
- Driving with any detectable amount of THC (even if it is a medicinal product) in your body system is an offence in most states of Australia, except in Tasmania[1] (Perkins et al., 2021; Tasmanian Government, 2025; Transport Victoria, 2025).
- However, even if it is a medicinal product, driving impairment is the same as non-medicinal cannabinoid product use.
- The NSW Government provides further information to assist medical practitioners advising patients about driving when using medicinal cannabinoids (NSW Ministry of Health, 2022b).

[1] When the product has been obtained and administered in accordance with the Poisons Act 1971, including being prescribed by a health practitioner physically present in Tasmania and dispensed by a pharmacist located in Tasmania.

Treatment plan and consent

A structured treatment plan and informed consent process are critical for safe, effective and ethical prescribing of medicinal cannabinoids. These steps ensure that therapy is clinically justified, risks are managed, and patients are fully informed about potential benefits and limitations. Guidelines across Australia, Canada, and New Zealand consistently recommend that treatment plans include:

- Treatment objectives (e.g., symptom relief, functional improvement)
- Consideration of other more effective or safer therapies
- Dosing strategy (starting dose, titration schedule, maximum dose)
- Risk management plan (monitoring for adverse effects, misuse)
- Drug interactions occurring from the addition of cannabinoids
- Monitoring criteria (clinical review intervals, validated outcome measures)
- Discontinuation strategy (criteria for stopping if ineffective or harmful).

Given the potential risks of cannabinoids and the still developing evidence base, informed consent and a written agreement are recommended to ensure patients understand the treatment rationale, expected benefits, and limitations. The Royal Australian College of General Practitioners has developed a discussion form and informed consent template to support clinicians in documenting these elements and engaging patients in shared decision-making (The Royal Australian College of General Practitioners, 2019). See Appendix 3 for the full recommended patient declaration and consent form.

Summary

- Medicinal cannabinoids are not a first-line treatment for chronic non-cancer pain. It is generally only considered after other treatments have not worked or were not tolerated.
- Most international guidelines recommend cannabinoids only as a third-line or add-on option, and some organisations do not recommend them at all due to limited evidence.

- There is limited evidence directly comparing cannabinoids with other pain medicines, so decisions are usually based on whether potential benefits outweigh the risks for an individual.
- Before starting treatment, a thorough medical and mental health assessment is essential. Cannabinoids are not recommended for people who are pregnant, have a history of psychosis, unstable heart or lung disease, or certain other conditions.
- Cannabinoids can interact with many common medications and may increase side effects or change drug levels.
- Treatment should follow a “start low, go slow” approach, with clear goals and regular monitoring.
- Driving with THC in your system is illegal in most Australian states, even if prescribed.
- Patients should understand the potential risks, costs, and uncertain long-term benefits before starting treatment.

Section Three: Monitoring

Monitoring patients prescribed medicinal cannabinoids requires a structured approach to ensure both efficacy and safety. This section provides evidence on follow-up frequency, assessment of treatment effectiveness, detection and reporting of adverse events, and screening for Cannabis Use Disorder.

Frequency of monitoring

As the majority of clinical trials are short in duration, there is limited evidence to guide decisions on when treatments should be reviewed (Stockings et al., 2018). According to a practical review on medicinal cannabinoid safety, the recommended follow-up frequency depends on 3 key factors: prior cannabinoid use, comorbidities, and the patient's ability to adhere to the treatment plan (MacCallum et al., 2021).

- High-risk patients, including those with significant comorbidities (e.g., cardiovascular disease), older adults, and individuals with a history of mental health conditions, should be reviewed within 2 weeks of initiation.
- Moderate-risk patients, including those with limited prior experience or moderate comorbidities, or those who may struggle with adherence, should have their first follow-up at approximately one month.
- Finally, lower-risk patients, such as those with prior cannabinoid experience, minimal comorbidities, and good adherence potential, can be scheduled for follow-up within 3 months (MacCallum et al., 2021).

This aligns with current practice globally; the European Pain Federation recommends that reassessment should occur within a maximum of 3 months (Häuser et al., 2018). Both Australian and New Zealand guidance advise first reassessment after one month (Best Practice Advocacy Centre New Zealand, 2022; Therapeutic Goods Administration, 2024), while Canadian guidance recommends within 3 months (College of Family Physicians of Canada, 2021).

Patients should be encouraged to record their cannabinoid use (e.g., dosage, route of administration), any adverse effects, and changes in symptoms (MacCallum et al., 2021). This documentation supports accurate monitoring and facilitates

assessment of the risk versus benefit of treatment. In clinical practice, factors such as the patient's response to treatment and any need for dosage adjustments may also necessitate more frequent review.

Monitoring effectiveness

Accurate assessment of symptom change requires the use of validated instruments (MacCallum et al., 2021). One commonly used tool is the Brief Pain Inventory (BPI), a self-report measure that evaluates both pain severity and its interference with daily functioning (Cleeland, 1991). The BPI uses a simple 10-point scale and has demonstrated strong utility as an outcome measure in clinical trials (Arkell et al., 2023; Bell et al., 2024; Evans et al., 2025; O'Brien et al., 2023). The BPI is endorsed in the Canadian clinical practice guidelines as a key assessment tool (College of Family Physicians of Canada, 2021).

Australian guidelines base their monitoring framework on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations, which identify core domains for comprehensive reporting of patient experiences in clinical trials (Turk et al., 2003). These guidelines recommend assessing changes in pain intensity, physical and emotional functioning, and patient ratings of global improvement and satisfaction with treatment (Therapeutic Goods Administration, 2024), however they do not specify which scales or instruments should be used in clinical practice.

Adverse events

Like most medications, medicinal cannabinoids are associated with a range of potential adverse effects. Evidence from systematic reviews and meta-analyses indicates that non-serious adverse events are common, particularly with THC-containing formulations, while serious adverse events are rare (National Academies of Sciences et al., 2017; Wang et al., 2021). The most frequently reported adverse events are summarised in **Table 3** (Kansagara et al., 2025; MacCallum et al., 2021; Mohammed et al., 2024).

Table 3: Adverse events associated with cannabinoids

Adverse events	Most common	Less common	Rare
THC related	Dizziness Dry mouth Anxiety Drowsiness Fatigue Cognitive impairment e.g. attention or balance	Euphoria Blurred vision	Orthostatic hypotension Psychosis or paranoia Depression Ataxia or discoordination Tachycardia Cannabis hyperemesis syndrome
THC & CBD related	Nausea Mild sedation Appetite changes	Headache	
Smoking specific			Cough Phlegm Bronchitis

Systematic reviews and meta-analyses of randomised controlled trials (RCTs) show that adverse events are common among people using cannabinoids for chronic pain, although most are non-serious and serious events are rare. One review found that oral cannabinoid products were associated with increased rates of dizziness, drowsiness, nausea, vomiting, and mild cognitive impairment compared with placebo (Wang et al., 2021). Similar findings were reported in a broader review of RCTs and observational studies, which noted that cannabinoids were linked to more adverse events than placebo, although most were mild and serious harms remained uncommon (Stockings et al., 2018).

Evidence from non-randomised studies suggests that side effects are frequent but usually not severe. One review concluded, based on very low certainty evidence, that around 1 in 4 patients experience at least one adverse event, most often psychiatric symptoms, while serious harms such as cognitive effects, accidents, and withdrawal generally occur in fewer than one in 20 patients (Zeraatkar et al., 2022). Long term observational studies report a similar pattern; for example, one study found that serious adverse events occurred in only a small proportion (3%) of patients (Bialas et al., 2022).

THC-containing products are most strongly associated with side effects, including dizziness, sedation and cognitive impairment, whereas CBD-only formulations generally cause fewer and milder adverse effects (McDonagh et al., 2022). Acute THC intoxication can impair attention and short-term memory, but systematic reviews indicate that long-term cognitive deficits are minimal and likely reversible after abstinence (Scott et al., 2018). Strategies to minimise these effects include starting with a low THC dose and gradual titration, or using a CBD-dominant preparation to help offset THC-related symptoms (Bell et al., 2024).

Long-term safety data for medicinal cannabinoids remain limited. Most evidence on chronic adverse effects derives from recreational cannabinoids use, which is not directly comparable due to differences in regulation, dosing and route of administration. Furthermore, results are mixed due to different study designs, lack of controls and non-comparable populations (College of Family Physicians of Canada, 2021).

Long term harm

While most clinical trials of medicinal cannabinoids are short-term, observational and epidemiological studies of non-medicinal cannabinoid use highlight potential long-term health risks. Better understanding of these harms and long-term efficacy is essential for informed prescribing and monitoring.

Pulmonary

- Moderate evidence indicates that long-term use of smoked cannabinoids is associated with chronic bronchitis symptoms, including cough, mucus, and wheeze (Ghasemiesfe et al., 2018; Tashkin & Roth, 2019).
- Insufficient evidence exists for a causal link between cannabinoids and chronic obstructive pulmonary disease (COPD), asthma, or significant declines in lung function (National Academies of Sciences et al., 2017).

Cardiovascular

- Low to moderate evidence supports acute cardiovascular effects such as tachycardia and palpitations following cannabinoids use across routes of administration (Ravi et al., 2018).
- A recent systematic review and meta-analysis of observational studies reported positive associations between cannabinoid use and major adverse cardiovascular events (MACE), including acute coronary syndrome, stroke and cardiovascular death, however most included studies were cross-sectional and did not distinguish smoked from non-smoked routes of administration (Storck et al., 2025).
- While causality cannot be established, the emerging signal of increased cardiovascular risk warrants caution in individuals with existing cardiovascular disease, and clinicians should routinely enquire about cannabinoid use when assessing unexplained cardiovascular events.

Cancer

- Cannabinoid smoke contains some of the same carcinogens as tobacco, raising concerns about cancer risk (Hoffmann et al., 1975).
- Low evidence suggests no strong association between cannabinoids use and lung, head, or neck cancers (Ghasemiesfe et al., 2019; Zhang et al., 2015), with studies to date not differentiating between different routes of administration.
- Limited evidence indicates a possible link between cannabinoids and testicular germ cell tumours (Ghasemiesfe et al., 2019).

Cognitive

- A systematic review of medicinal cannabinoids (median 52 weeks use) reported memory impairment, confusion and attention problems, but certainty of evidence was very low due to risk of bias (Zeraatkar et al., 2022)
- Long-term heavy use of cannabis has been linked to small cognitive deficits and altered brain activation (particularly working memory) and reduced

hippocampal volume, but effects are generally modest and based on non-causal study design(Gowin et al., 2025; Meier et al., 2022)

- A retrospective cohort of US Veterans found that cannabis use disorder was associated with increased risk of cognitive disorders, with higher risk in those with comorbid traumatic brain injury(Esmaeili et al., 2024). However, this study examined people with cannabis use disorder rather than those using medicinal cannabinoids, so findings may not be directly generalisable.

Psychosis

- Substantial evidence supports an association between cannabinoids use and psychotic disorders, particularly schizophrenia, with the highest risk among frequent and heavy users (Hall & Degenhardt, 2008; Hindley et al., 2020; Lupke et al., 2024; National Academies of Sciences et al., 2017; Zeraatkar et al., 2022).
- Systematic reviews show that more frequent and heavier cannabis use is associated with a greater risk of psychosis (Marconi et al., 2016; Moore et al., 2007).
- However, due to the nature of these studies, observational and reliant on self-report, causality cannot be definitively established.
- Regardless, clinical guidance recommends avoiding THC-containing products in individuals with a personal or family history of psychosis and educating patients about these risks (College of Family Physicians of Canada, 2021).

Cannabis-induced hyperemesis syndrome

- Cannabis-Induced Hyperemesis Syndrome (CHS) is a condition characterised by recurrent cycles of severe nausea, vomiting, and abdominal pain in long-term cannabinoids users (Sorensen et al., 2017). Symptoms typically emerge after months or years of regular use and often persist despite standard antiemetic therapy.
- Current evidence supports cannabinoid cessation as an effective strategy for achieving symptom resolution (Rubio-Tapia et al., 2024). Adjunctive measures such as hot water bathing, topical capsaicin, droperidol or haloperidol,

electrolyte replacement, anti-emetics, dexamethasone and benzodiazepines have demonstrated symptomatic relief in case series and small trials (Richards et al., 2017; Senderovich et al., 2022).

Reporting adverse events

Reporting adverse effects of medicinal cannabinoids is important for improving safety monitoring. A recent scoping review identified 7 regulatory authority databases and 17 registries worldwide for monitoring adverse events related to medicinal cannabinoids (Wang et al., 2024). These systems vary in quality, accessibility and consistency, and the review concluded that there is a critical need for a standardised international monitoring framework to support pharmacovigilance as clinical use expands.

In 2024, Health Canada received 170 adverse event reports for cannabinoids, of which only 40 were linked to legally prescribed products for medicinal purposes (Health Canada, 2025). The most frequently reported adverse events were oropharyngeal (throat and mouth) pain, cough, headache and dyspnoea (shortness of breath). Health Canada's broader adverse event dataset, which also captures non-medicinal use, showed that reports were more often associated with products containing a higher THC:CBD ratio than those with a higher CBD:THC ratio.

In September 2025, the TGA revealed that between July 1, 2022, and June 1, 2025 there had been 615 reports of adverse events associated with medicinal cannabinoids (Marozzi, 2025). In a study analysing these reports, psychiatric disorders were the most frequently reported adverse event category (30.6%), with anxiety, psychotic disorder and paranoia prominent, and over half of cases involving THC-dominant (Category 5) products (Graham et al., 2026). Reporting adverse events to the TGA is mandatory for pharmaceutical companies, but voluntary for health professionals and consumers (Greenbaum et al., 2024).

Reports to the TGA do not confirm causality; they indicate suspicion and contribute to signal detection for emerging safety concerns. The publicly available TGA data do not distinguish adverse events by cannabinoid type. Interpretation is further complicated by the large number of unapproved medicinal cannabinoid products in

Australia, many of which provide inconsistent information on cannabinoid content, dose, or formulation. Wide variation in individual dosing and use patterns adds an additional layer of uncertainty, making it difficult to attribute adverse events to any single factor. However, under-reporting of adverse events is widely acknowledged. Misconceptions, such as the belief that only serious adverse events should be reported and the voluntary nature of reporting by clinicians and consumers, introduces bias (Greenbaum et al., 2024). Improving reporting accuracy, increasing participation, and ensuring timely investigation and regulatory oversight are critical to making adverse event monitoring systems more effective and safeguarding patient safety.

Cannabis use disorder

The Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-5) defines Cannabis Use Disorder (CUD) as *"a problematic pattern of cannabis use leading to clinically significant impairment or distress"* (American Psychiatric Association, 2013). It typically involves symptoms such as cravings, difficulty controlling use, and continued use despite negative consequences. While most research focuses on recreational cannabinoid use (Gottschling et al., 2020), emerging evidence indicates that CUD is also common among people using cannabinoids for medical purposes.

- A systematic review estimated that approximately 22% of cannabinoid users, whether illicit or prescribed, met the criteria for CUD (Leung et al., 2020).
- More recent analyses focusing on prescribed medical cannabinoids report similar or higher rates: a meta-analysis of 10 studies found a pooled prevalence of 25% (95% CI: 18–33%) (Dawson et al., 2024).
    - Narrative synthesis of these studies suggested that risk of CUD was higher with more frequent or heavier use, younger age, and male sex, as well as among individuals with mental health conditions and other substance use disorders. However, these findings were based on a small and heterogeneous evidence base.
- Despite widespread availability of medicinal and recreational cannabinoids in many U.S. states, only a small minority of Veterans receive a diagnosis of

CUD. For example, a large study of Veterans Health Administration patients found CUD prevalence among those with chronic pain increased from about 1.1% to 2.6% between 2005 and 2014, compared to 0.7% to 1.3% among those without chronic pain. While rates have risen among veterans, they remain relatively low overall (Mannes et al., 2023).

In addition to the direct impacts of cannabinoid use, CUD is also associated with poorer mental health outcomes. A large Danish cohort study found that cannabis use disorder was associated with an increased risk of unipolar depression and bipolar disorder (Jefsen et al., 2023). Another Danish cohort study reported that the proportion of schizophrenia cases associated with cannabis use disorder increased from about 2% in the mid-1990s to around 6–8% since 2010. The authors note that this rise is consistent with a possible causal contribution, given increasing use and potency of cannabinoids, but they also emphasise that the study cannot establish causality with certainty (Hjorthøj et al., 2021). Finally, an observational study of US Veteran health data, found an increased prevalence of CUD among veterans with psychiatric disorders (Livne et al., 2024).

Given these findings, current guidelines recommend routine monitoring for CUD symptoms in patients using medical cannabinoids. The Cannabis Use Disorder Identification Test – Revised (CUDIT-R) is an 8-item test that has been recommended to screen for CUD (College of Family Physicians of Canada, 2021; Fleisch & Woodbridge, 2025). If CUD is suspected, clinicians should reassess the treatment indication for cannabinoids, weigh the risks versus benefits, and consider tapering or discontinuation alongside behavioural interventions.

Systematic reviews identify cognitive behavioural therapy and motivational enhancement therapy as the most supported psychological treatments for CUD, with stronger short-term effects when delivered in multi-session formats (Halicka et al., 2025; Le Foll et al., 2024). These approaches aim to strengthen motivation for change and build practical coping, refusal and problem-solving skills to reduce use and prevent relapse (US Department of Veterans Affairs, 2026).

As cessation may be a treatment goal for CUD, sudden discontinuation of cannabinoids can trigger withdrawal symptoms that can be distressing. These effects may be more complex in people with psychiatric comorbidity (Connor et al., 2022). Further details on withdrawal course and management are provided in the next section.

Summary

- Patients using medicinal cannabinoids should be reviewed regularly, especially in the first few weeks. People at higher risk (older age, heart disease, mental health history) should be reviewed sooner.
- Treatment effectiveness should be assessed using validated outcome measures alongside discussion of daily functioning and progress towards individual treatment goals.
- Side effects are common but usually mild. Serious harms are uncommon but can occur, particularly with THC-containing products.
- Evidence regarding long-term harms remains limited. There may be increased risks related to heart health and psychosis in some people.
- Adverse events should be reported to regulators to improve safety monitoring.
- Clinicians should routinely monitor for signs of Cannabis Use Disorder and reassess treatment if concerns arise

Section Four: Deprescribing

Clinical guidelines recommend discontinuing medicinal cannabinoids if:

- The patient experiences no improvement in pain.
- The treatment is not improving quality of life, mood, sleep or function.
- The patient experiences adverse side effects that do not improve.
- The patient shows signs of cannabis use disorder, particularly if escalating the dose of THC.
- The patient experiences any psychotic symptoms (e.g., paranoia, hallucinations), which require immediate intervention and treatment cessation.

Guideline recommendations

When treatment goals are unmet or adverse effects occur, patients should work closely with their clinician to develop a safe discontinuation plan (Fleisch & Woodbridge, 2025). The New Zealand Best Practice Advocacy Centre advises establishing a discontinuation plan that includes a dose reduction schedule, although specific protocols are not detailed (Best Practice Advocacy Centre New Zealand, 2022). Canadian guidelines recommend reassessing the benefit-risk balance and considering structured tapering when harms outweigh benefits (College of Family Physicians of Canada, 2021).

Practical steps for cessation include:

- Reduce the THC dose incrementally (or 'taper'); as with increasing a dose, tapering should be done slowly and in small steps (Bhaskar et al., 2021).
- Switch to lower THC potency, or CBD dominant products before cessation to reduce withdrawal severity (Bahji et al., 2020).
- Pair deprescribing with psychoeducation, coping strategies and discussion of alternative treatments.

Cannabis withdrawal syndrome (CWS)

Cannabis Withdrawal Syndrome (CWS), recognised in the DSM-5, occurs after abrupt cessation or significant reduction of prolonged cannabinoids use and is characterised by symptoms such as irritability, anxiety, insomnia, and decreased appetite (American Psychiatric Association, 2013). Symptoms typically begin within 24–48 hours, peak between days 2–6, and can last up to 2–3 weeks, with some sleep disturbances persisting longer (Connor et al., 2022). A systematic review of 47 studies (that included 23,518 participants) found that cannabinoids withdrawal syndrome occurred in about 47% of regular or dependent cannabinoids users (Bahji et al., 2020). Increased risk factors include daily use and concurrent tobacco, or other substance use disorders. Cannabis withdrawal scales can be used to assess the degree of patient distress or impairment in functioning (Connor et al., 2022). A differential diagnosis is essential to rule out withdrawal from other substances or symptoms of comorbid mental or medical conditions.

Management of CWS

In most cases, CWS is not severe, nor medically dangerous, however it can be distressing to the patient. Planned cessation with gradual tapering is preferred to reduce withdrawal severity and allow monitoring for emerging symptoms (Connor et al., 2022). There are **no** approved pharmacotherapies for cannabis withdrawal; short courses of symptomatic medicines may be used for sleep disturbance, anxiety, headache, abdominal discomfort or nausea, and local guidance recommends limiting these to about 7 days while prioritising non-pharmacological care (see **Table 4**) (NSW Ministry of Health, 2022a). Providing psychoeducation on the expected time course and symptoms, teach craving-coping and sleep strategies, and reinforce hydration, nutrition and physical activity is strongly recommended (Connor et al., 2022). Counselling and psychological interventions can also assist individuals to safely withdraw from cannabinoids (Connor et al., 2022).

Table 4: Symptomatic medications for the management of CWS – suggested by NSW Health (NSW Ministry of Health, 2022a)

Symptom	Medication (up to 7 days duration, as required)
Sleep problems	Benzodiazepines (e.g. diazepam 5-10 mg nocte) or z-drugs (e.g. zolpidem 10-20 mg nocte, zopiclone 7.5-15 mg nocte).
Restlessness, anxiety, irritability	Diazepam (e.g. 5-10 mg BD or TDS PRN) or antipsychotic medication (e.g. olanzapine 2.5-5 mg BD PRN)
Stomach pains	Hyoscine butylbromide (e.g. Buscopan 20 mg TDS PRN)
Physical pain, headaches	Paracetamol, non-steroidal anti-inflammatory agents
Nausea	Metoclopramide, Ondansetron

Summary

- Medicinal cannabinoids should be stopped if they are not improving pain, quality of life, sleep or function, or if side effects are ongoing or severe.
- Treatment must stop immediately if psychotic symptoms occur.
- Stopping treatment should be planned with a clinician and usually involves gradually reducing the THC dose rather than stopping suddenly.
- Withdrawal symptoms can occur, especially after regular use. These symptoms are usually temporary but can be uncomfortable.

Appendix 1: Systematic review

1.1 Methods

Findings in this report are based on a systematic search of individual studies that assess the safety and effectiveness of cannabinoids in treating the symptoms of CNCP. This review builds on a previous systematic review by (Stockings et al., 2018), which included studies published from 1980 to 2017. For the current report, an updated search was conducted to identify studies published between 2017 and 2025. Studies from the previous review were re-screened according to the current eligibility criteria and combined with newly identified studies for analysis.

The primary objectives were to identify the cannabinoids used, including plant and pharmaceutical formulations, and assess their ability to reduce pain intensity. The review also considers tolerability and safety data, as reported by patient study withdrawals and adverse events.

Search strategy and study eligibility

The following databases were searched using corresponding subject headings according to the databases and specialised Ovid thesaurus: MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), and the Cochrane Central Register of Controlled Trials (CENTRAL, Ovid). Similar to the original reviews, the following search strings were used:

1. Cannabis or marijuana or cannabinoids or endocannabinoids or dronabinol or nabilone or marinol or levonantradol or tetrahydrocannabinol or cesamet or delta-9-THC or delta-9-tetrahydrocannabinol or nabiximols or sativex or cannabidiol
2. therapeutic use or drug therapy or analgesics or treatment or intervention
3. terms for chronic pain (as used in our previous reviews): (chronic non-cancer pain.mp. or neuropathic pain.mp. or exp Neuralgia/ or neuropathy.mp. or rheumatoid arthritis.mp. or exp Arthritis, Rheumatoid/ or exp Arthritis/ or arthritis.mp. or fibromyalgia.mp. or exp Fibromyalgia/ or multiple

sclerosis.mp. or exp Multiple Sclerosis/ or Crohn's disease.mp. or exp Crohn Disease/ or upper motor neuron spasticity.mp. or spinal cord injury.mp. or exp Spinal Cord Injuries/ or exp Brachial Plexus/ or brachial plexus avulsion.mp. or chemotherapy induced neuropathic pain.mp. or exp Diabetic Neuropathies/ or diabetic peripheral neuropathy.mp.)

4. In #1 AND #2 AND #3

The updated searches were limited to human studies published since the previous review (2017) to current (2025) for CNCP. Search terms and keywords were tailored to each database through Ovid. UNSW reviewed references from existing Cochrane and other systematic reviews and extracted RCT and observational-level evidence. Searches included English and non-English language literature and authors were contacted for more details, where possible. Potential studies were also identified via a search of clinicaltrials.gov.

Papers describing mechanisms of cannabinoid action, commentaries and clinical overviews that do not present the results of studies were not included in the review. Observational studies were restricted to those with a minimum sample size of 30.

Each study included in the review needed to address at least one of the key outcomes, namely: pain intensity, physical functioning, emotional functioning, participant ratings of global improvement and satisfaction with treatment, and withdrawals from study including due to adverse events (serious and other adverse events).

Included studies examine impacts of cannabinoids on CNCP. As neuropathic pain is a prominent subgroup of pain conditions, data was extracted on the type of neuropathic pain where possible. Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system. At least 80% of the patient population were required to be experiencing neuropathic pain to be included in this subgroup, otherwise, the study was classified as CNCP (mixed).

Data synthesis

Data from each study's primary endpoint or longest available follow-up has been summarised. RCTs and observational studies are summarised separately by cannabinoid type and pain condition. Wherever published data permitted, we pooled continuous outcomes as standardized mean differences (SMDs) with 95% confidence intervals (CIs), and dichotomous outcomes as odds ratios (ORs), using a random effects model. A narrative synthesis is drafted describing study characteristics, populations, interventions, and outcomes.

The following characteristics have been identified as potential sources of heterogeneity and/or clinical importance, these will be explored in subsequent subgroup analyses:

- Fixed dose (pre-determined, quantified amounts e.g., oil via syringe, capsule) vs self-titrated administration (patients control the amount of use e.g., flower)
- Pharmaceutical-grade (with known cannabinoid content) vs raw/whole plant
- Exclusion of participants with (complex) PTSD
- Dose/dose response (limited to studies with an active/placebo comparator)
- Veteran population (yes/no).

1.2 Summary of included studies

eTable 1: Characteristics of included publications (k = 86)

	Non-RCT k (%)	RCT k (%)
Number of publications	7	79
Year of publication		
2000-2009	0 (0)	21 (27)
2010-2019	4 (57)	30 (38)
2020 onwards	3 (43)	28 (35)
Study design		
Cross-over RCT	0 (0)	37 (47)
Parallel RCT	0 (0)	42 (53)
Prospective non-RCT	4 (57)	0 (0)
Retrospective non-RCT	3 (43)	0 (0)
Region		
Northern America	4 (57)	27 (34)
Northern Europe	0 (0)	17 (22)
Oceania	1 (14)	0 (0)
South America	0 (0)	1 (1)
South-eastern Asia	0 (0)	3 (4)
Southern Asia	0 (0)	2 (3)
Southern Europe	0 (0)	3 (4)
Western Asia	0 (0)	3 (4)
Western Europe	2 (29)	15 (19)
Multiple European regions	0 (0)	6 (8)
Multiple Regions	0 (0)	2 (3)
Conflicts of interest declared		
Declared – no conflicts	3 (43)	31 (39)
Declared – potential conflicts	2 (29)	34 (43)
Not declared	2 (29	14 (18)

k, number of publications.

eTable 2: Characteristics of participants and interventions (k = 115)

	Non-RCT k (%)	RCT k (%)
Number of studies/ interventions/ records	7	108
Number of participants	3, 718	9,074
Study size, median (IQR)	38 (24-103)	249 (84-871)
Participants age, mean (SD) years[a]	51.0 (7.4)	53.0 (5.8)
Participants sex, % female[b]	60.1	65.3
Pain condition		
Arthritis	0 (0)	7 (6)
Chronic non-cancer pain (non-specific)	0 (0)	7 (6)
Fibromyalgia	0 (0)	10 (9)
Musculoskeletal pain (MS-related)	0 (0)	8 (7)
Neuropathic pain (chemotherapy-induced)	0 (0)	1 (1)
Neuropathic pain (diabetic)	2 (29)	2 (2)
Neuropathic pain (HIV-related)	0 (0)	1 (1)
Neuropathic pain (MS-related)	1 (14)	15 (14)
Neuropathic pain (non-MS-related)	2 (29)	25 (23)
Neuropathic pain (non-specific)	1 (14)	5 (5)
Other chronic non-cancer pain	0 (0)	15 (14)
Radicular neuropathic pain	0 (0)	1 (1)
Rheumatoid arthritis	0 (0)	1 (1)
Visceral pain	1 (14)	10 (9)
Primary indication for cannabinoid		
Analgesia	7 (100)	86 (80)
Spasticity	0 (0)	15 (14)
Other	0 (0)	7 (6)
Cannabinoid place in therapeutic hierarchy		
Primary	0 (0)	31 (29)
Adjuvant	3 (43)	65 (60)
Unknown	4 (57)	12 (11)
Type cannabinoid		
THC/other cannabinoid product (CBD <2%)	2 (29)	41 (38)
THC/other cannabinoid dominant product (CBD >=2% and <40%)	0 (0)	4 (4)
Balanced medicinal cannabis product (CBD >=40% and <60%)	1 (14)	26 (24)
CBD dominant medicinal cannabis product (CBD >=60% and <98%)	0 (0)	1 (1)
CBD medicinal cannabis product (CBD <=98%)	0 (0)	14 (13)
Agonist of cannabinoid receptor 2 (olorinab)	0 (0)	3 (3)
Cannabis sativa	1 (14)	19 (18)

Unclear	3 (43)	0 (0)
Pharmaceutical grade product[c]		
Yes	3 (29)	79 (73)
No	0 (0)	24 (22)
Not reported	4 (57)	5 (5)
Route of administration		
Oral tablet or capsule	3 (43)	44 (41)
Oromucosal spray	1 (14)	22 (20)
Sublingual	0 (0)	6 (6)
Topical	0 (0)	7 (6)
Vapourised	0 (0)	21 (19)
Smoked	0 (0)	6 (6)
Chewing gum	0 (0)	1 (1)
Multiple or non-specific	3 (43)	1 (1)
Comparator		
Active[d]	2 (29)	9 (8)
Placebo	5 (71)	99 (92)

a. Excluding 13 studies of 4,198 (15.1%) participants that did not report mean age of participants.
b. Excluding 5 studies of 339 (2.7%) participants that did not report sex distribution.
c. A pharmaceutical grade product is a substance produced under Good Manufacturing Practices and met high purity and quality standards.
d. Active comparators include amitriptyline, diazepam, diclofenac, dihydrocodeine, diphenhydramine, gabapentin, hydromorphone, ibuprofen, oral long-acting opioids and oxycodone

1.3 Overview of evidence

The tables below presents structured summaries of the available evidence, organised by IMMPACT outcome domains (e.g., pain intensity, physical function, emotional functioning, and adverse events). The summaries synthesise key findings from the evidence review and are intended to support transparency in the development of the recommendations.

Change in pain scores:

- THC, and combined THC dominant products were more likely than comparators to produce a clinically meaningful improvement (i.e., reduction) in pain scores
- THC was primarily associated with a reduction in pain scores for participants with visceral pain; a smaller improvement was also associated with non-MS-related neuropathic pain, fibromyalgia and musculoskeletal pain
- Overall, CBD products were not associated with a reduction in pain scores.

30% reduction in pain:

- Combined CBD and THC products were associated with a marginally increased likelihood of achieving 30% pain reduction; the evidence for THC-dominant products alone was not statistically significant.

50% reduction in pain:

- Combined CBD and THC preparations were more likely to result in a 50% reduction in pain than their comparators; this benefit was identified among the non-MS neuropathic and other CNCP pain group.
- CBD was associated with fewer 50% reductions in pain, overall and among the non-MS neuropathic pain group.

Improvement in PGIC:

- Combined CBD and THC were associated with an improvement in PGIC. There was evidence of a positive effect of combined CBD and THC for MS- and non-MS-related neuropathic pain.

- CBD only was associated with a worsening of PGIC.

Change in Patient Global Impression of Change (PGIC):

- There was evidence for a change in PGIC scores for combined CBD and THC and cannabis sativa for non-MS related neuropathic pain.

Overall physical and emotional functioning:

- THC was associated with an improvement in physical functioning comparing with placebos. There was no evidence of an effect for combined CBD and THC, or CBD alone. There was no evidence for an association between any cannabinoids and improvement in emotional functioning.

Sleep problems:

- There was limited evidence of an effect of combined CBD and THC on sleep problems overall; a significant reduction in sleep problems was found among participants with fibromyalgia for THC-dominant products.

Treatment retention:

- THC was more likely to result in any adverse events compared to placebo. The evidence for combined CBD and THC, and CBD products was less consistent.

Treatment safety:

- THC, combined CBD and THC, and CBD were more likely to result in any adverse events compared to placebos, but not serious adverse events. THC was more likely to result in treatment emergent adverse events compared to placebo.

Overall, there is evidence to suggest specific cannabinoids, particularly THC-dominant types, may be beneficial in the treatment of CNCP and that CBD was not associated with a reduction in pain-related symptoms. There is limited evidence of the effectiveness of CBD for CNCP. In most cases, these findings are based on a small number of studies, and with all cannabinoids showing evidence of poorer

treatment safety and treatment retention. International clinical guidance documents and expert opinion will be consulted to guide the processes for initiation, monitoring and deprescribing of medicinal cannabinoids. It should be noted that heterogeneity across studies was high for several key outcomes, which limits confidence in the pooled estimates.

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1.4 Summary of treatment effects from meta-analyses of RCTs, by comparator (active or placebo)

	Comparator	K (studies)	N (participants)	Result	I^2 (%)	Favours
				SMD (95% CI)		
Change in pain scores	Active	7	486	−0.25 [−0.90; 0.41]	88.9	Neither
	Placebo	63	6,499	−0.27 [−0.46; −0.09]	79.8	Cannabinoids
				Pooled OR (95% CI)		
30% reduction in pain	Active	-	-	-	-	-
	Placebo	27	5,701	1.28 [0.90; 1.84]	94.6	Neither
50% reduction in pain	Active	-	-	-	-	-
	Placebo	18	2,348	1.03 [0.71; 1.48]	70.1	Neither
Improvement in PGIC	Active	-	-	-	-	-
	Placebo	17	2,841	1.43 [0.98; 2.08]	91	Neither
				SMD (95% CI)		
Change in PGIC scores	Active	-	-	-	-	-
	Placebo	5	349	0.47 [−0.05; 1.00]	79.3	Neither
Overall physical functioning	Active	1	60	−1.85 [−3.88; 0.18]	N/A	Neither
	Placebo	6	1,214	0.43 [−0.15; 1.01]	81.9	Neither
Sleep problems	Active	-	-	-	-	-
	Placebo	14	1,771	−0.11 [−0.32; 0.09]	62.9	Neither
Quality of life	Active	-	-	-	-	-
	Placebo	10	1,494	0.02 [−0.16; 0.20]	61.1	Neither
Overall emotional functioning	Active	-	-	-	-	-
	Placebo	7	360	−0.03 [−0.32; 0.26]	0	Neither
Symptoms of depression	Active	-	-	-	-	-
	Placebo	9	606	0.11 [−0.09; 0.31]	0	Neither
Symptoms of anxiety	Active	-	-	-	-	-
	Placebo	9	606	−0.13 [−0.33; 0.07]	0	Neither
				Pooled OR (95% CI)		
Withdrawal due to any reason	Active	5	444	1.27 [0.74; 2.17]	0	Neither
	Placebo	48	7,385	1.54 [1.30; 1.83]	5.9	Comparators
Withdrawal due to adverse events	Active	1	52	3.00 [0.71; 12.74]	0	Neither
	Placebo	40	5,680	2.68 [1.98; 3.62]	23.2	Comparators
Any adverse event	Active	-	-	-	-	-
	Placebo	17	1,990	1.84 [1.20; 2.84]	52.2	Comparators
Serious adverse event	Active	-	-	-	-	-
	Placebo	11	2,022	0.99 [0.64; 1.51]	0	Neither
Treatment emergent adverse event	Active	-	-	-	-	-
	Placebo	12	2,078	2.08 [1.30; 3.35]	63.8	Comparators

SMD = standardized mean difference. OR = Odds ratio. – denotes no studies.

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1.5 Detailed treatment effects from meta-analyses of RCTs (placebo-controlled) by cannabinoid type, outcome type, and CNCP comparator

eTable 4. Effect sizes for pain-related outcomes

	THC/other cannabinoid (CBD <2%)			THC/other cannabinoid dominant (CBD ≥2% and <40%)			Balanced (CBD ≥40% and <60%)			CBD (CBD ≥98%)			Agonist of cannabinoid receptor 2 (olorinab)			Cannabis sativa		
Change in pain scores	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**
Arthritis	1	0.24 [−0.22; 0.70]	-				1	−0.62 [−1.14; −0.09]	-	3	−1.88 [−5.65; 1.90]	96				1	−0.14 [−0.65; 0.37]	-
Fibromyalgia	1	0.02 [−0.78; 0.81]	-	1	−1.30 [−2.36; −0.24]	-	1	−0.04 [−0.84; 0.76]	-	2	0.26 [−0.01; 0.52]	0						
Musculoskeletal pain (MS-related)	1	−0.08 [−0.28; 0.12]	-	1	−0.36 [−0.60; −0.12]	-	3	0.12 [−0.08; 0.33]	16							1	0.80 [0.27; 1.33]	-
Neuropathic pain (MS-related)	5	−0.23 [−0.55; 0.10]	48				5	−0.29 [−0.58; 0.00]	63	1	0.23 [−0.24; 0.70]	-						
Neuropathic pain (non-MS-related)	6	−0.53 [−1.71; 0.65]	89	1	−1.00 [−1.42; −0.58]	-	8	−0.10 [−0.34; 0.15]	64	3	0.28 [−0.17; 0.73]	48				6	−0.45 [−0.65; −0.24]	0
Neuropathic pain (non-specific)	1	−0.32 [−1.18; 0.55]																
Other CNCP	2	0.19 [−0.61; 0.98]	72	1	−0.26 [−0.90; 0.38]	-	2	0.05 [−0.35; 0.45]	0									
Visceral pain	3	−2.23 [−4.39; −0.06]	95							1	0.06 [−0.43; 0.55]	-	1	−0.23 [−0.56; 0.10]	-			
Overall	20	−0.52 [−1.04; 0.00]	86	4	−0.64 [−1.08; −0.21]	69	20	−0.12 [−0.26; 0.03]	60	10	−0.37 [−1.39; 0.66]	86	1	−0.23 [−0.56; 0.10]		8	−0.23 [−0.56; 0.10]	69
30% reduction in pain	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**
CNCP (non-specific)										1	5.12 [4.25; 6.17]							
Fibromyalgia	1	1.81 [0.46; 7.03]					1	4.29 [1.02; 17.98]		2	0.33 [0.09; 1.26]	72						
Musculoskeletal pain (MS-related)	1	2.09 [0.92; 4.74]														1	2.69 [1.21; 5.99]	
Neuropathic pain (MS-related)	1	0.42 [0.24; 0.74]					3	2.23 [0.70; 7.14]	96	1	0.82 [0.51; 1.33]							

Neuropathic pain (non-MS-related)	2	1.95 [0.14; 28.01]	88				5	1.22 [0.84; 1.77]	32	2	0.36 [0.23; 0.56]	0				1	3.43 [1.03; 11.46]	
Neuropathic pain (non-specific)	1	8.00 [1.00; 63.98]																
Other CNCP	1	1.80 [1.73; 1.88]																
Visceral pain													3	0.97 [0.85; 1.11]	0			
Overall	7	1.53 [0.71; 3.30]	87				9	1.70 [1.02; 2.83]	89	6	0.67 [0.25; 1.77]	98	3	0.97 [0.85; 1.11]	0	2	2.90 [1.49; 5.65]	0
50% reduction in pain	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**
CNCP (non-specific)																		
Fibromyalgia	1	1.17 [0.21; 6.36]					1	1.69 [0.33; 8.76]		2	0.35 [0.06; 1.92]	62						
Musculoskeletal pain (MS-related)																		
Neuropathic pain (MS-related)	2	1.84 [0.19; 17.51]	72				2	1.12 [0.76; 1.65]	0	1	0.59 [0.25; 1.41]							
Neuropathic pain (non-MS-related)	2	1.18 [0.20; 6.88]	48				3	2.04 [1.32; 3.15]	0	2	0.27 [0.07; 1.00]	36						
Neuropathic pain (non-specific)	1	3.71 [0.13; 104.48]																
Other CNCP	1	1.61 [1.54; 1.70]																
Overall	7	1.23 [0.74; 2.05]	56				6	1.49 [1.08; 2.06]	0	5	0.38 [0.23; 0.65]	28						

[a] A higher score indicates greater amount of pain. A dash ('-') indicates there were not studies reporting available effect estimates for the comparison of interest or the statistics analysis is not feasible. k, number of studies; I^2, level of heterogeneity.

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Favors cannabinoid

Favors comparator

eTable 5. Effect sizes for patient global impression of change (PGIC)

	THC/other cannabinoid (CBD <2%)			Balanced (CBD ≥40% and <60%)			CBD (CBD ≥98%)			Cannabis sativa		
Improvement in PGIC	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**
Musculoskeletal pain (MS-related)				1	1.25 [0.84; 1.86]							
Neuropathic pain (MS-related)	2	1.98 [0.21; 18.93]	69	4	1.33 [1.01; 1.76]	0	1	0.36 [0.20; 0.63]				
Neuropathic pain (non-MS-related)	2	6.27 [0.16; 250.69]	83	5	2.03 [1.16; 3.57]	73	1	0.32 [0.16; 0.65]				
Neuropathic pain (non-specific)												
Other CNCP	1	2.71 [2.59; 2.84]										
Overall	5	2.23 [0.88; 5.65]	89	10	1.59 [1.20; 2.11]	54	2	0.34 [0.22; 0.54]	91			
Change in scores	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	I2
Arthritis							1	0.02 [−0.40; 0.45]				
Neuropathic pain (MS-related)	1	−0.54 [−1.36; 0.28]										
Neuropathic pain (non-MS-related)				1	0.71 [0.35; 1.07]					2	0.96 [0.63; 1.30]	0
Overall	1	−0.54 [−1.36; 0.28]		1	0.71 [0.35; 1.07]		1	0.02 [−0.40; 0.45]		2	0.96 [0.63; 1.30]	0

[a] A higher score indicates better in health conditions. A dash ('-') indicates there were not studies reporting available effect estimates for the comparison of interest. k, number of studies; I^2, level of heterogeneity.

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Favors cannabinoid

Favors comparator

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eTable 6. Effect sizes for physical functioning-related outcomes

	THC/other cannabinoid (CBD <2%)			THC/other cannabinoid dominant (CBD ≥2% and <40%)			Balanced (CBD ≥40% and <60%)			CBD (CBD ≥98%)		
Overall physical functioning	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**
Arthritis										2	1.05 [−0.95; 3.04]	95
CNCP (non-specific)	1	0.27 [0.13; 0.41]										
Fibromyalgia				1	0.28 [−0.68; 1.23]					1	−0.13 [−0.41; 0.14]	
Overall	1	0.27 [0.13; 0.41]		1	0.28 [−0.68; 1.23]					3	0.63 [−0.72; 1.98]	92
Sleep problems	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**
Arthritis										1	−0.19 [−0.52; 0.15]	
Fibromyalgia				1	−1.44 [−2.53; −0.36]					1	0.20 [−0.08; 0.48]	
Neuropathic pain (MS-related)	1	0.04 [−0.42; 0.51]					1	0.09 [−0.38; 0.56]		1	0.23 [−0.24; 0.70]	
Neuropathic pain (non-MS-related)	2	−0.26 [−0.96; 0.45]	0				2	−0.07 [−1.59; 1.45]	69	2	0.55 [−2.86; 3.96]	72
Other CNCP	1	−0.33 [−0.47; −0.19]					1	−0.22 [−0.70; 0.25]				
Visceral pain												
Overall	4	−0.24 [−0.49; 0.00]	0	1	−1.44 [−2.53; −0.36]		4	−0.18 [−0.60; 0.24]		5	0.12 [−0.18; 0.42]	63
Quality of life	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**
Fibromyalgia										1	−0.27 [−0.55; 0.01]	
Neuropathic pain (MS-related)	1	−0.30 [−0.76; 0.17]					1	0.13 [−0.34; 0.60]		1	0.07 [−0.40; 0.53]	
Neuropathic pain (non-MS-related)	2	0.24 [−0.48; 0.96]	58				1	−0.14 [−0.65; 0.37]		1	−0.14 [−0.66; 0.38]	
Other CNCP	1	0.32 [0.18; 0.46]										
Visceral pain										1	0.04 [−0.45; 0.53]	
Overall	4	0.13 [−0.23; 0.49]	66				2	0.01 [−0.34; 0.35]	0	4	−0.14 [−0.34; 0.06]	

[a] A higher score indicates better physical functioning. [b] A higher score indicates more sleep problems. [c] A higher score indicates better quality of life.

LEGEND

Favors cannabinoid

Favors comparator

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eTable 7. Effect sizes for emotional functioning related outcomes

	THC/other cannabinoid (CBD <2%)			THC/other cannabinoid dominant (CBD ≥2% and <40%)			Balanced (CBD ≥40% and <60%)			CBD (CBD ≥98%)		
Overall emotional functioning	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**
Arthritis										1	−0.22 [−0.64; 0.21]	
Fibromyalgia	1	−0.08 [−0.88; 0.71]					1	−0.16 [−0.95; 0.64]		1	0.08 [−0.71; 0.88]	
Neuropathic pain (non-MS-related)	1	0.96 [−0.51; 2.43]					1	0.82 [−0.63; 2.27]		1	0.53 [−0.95; 2.01]	
Overall	2	0.25 [−0.70; 1.20]	33				2	0.14 [−0.74; 1.01]	25	3	−0.11 [−0.47; 0.25]	0
Symptoms of depression	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**
Arthritis										1	−0.02 [−0.35; 0.32]	
Fibromyalgia				1	0.54 [−0.43; 1.51]							
Neuropathic pain (MS-related)	1	−0.04 [−0.50; 0.43]					1	0.19 [−0.28; 0.66]		1	0.13 [−0.34; 0.60]	
Neuropathic pain (non-MS-related)	1	1.64 [−0.24; 3.52]					1	1.49 [−0.39; 3.37]		2	0.13 [−1.05; 1.31]	0
Overall	2	0.54 [−1.02; 2.11]	65	1	0.54 [−0.43; 1.51]		2	0.51 [−0.58; 1.60]	42	4	0.04 [−0.23; 0.30]	0
Symptoms of anxiety	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**	**k**	**SMD [95% CI]**	**I2**
Arthritis										1	−0.18 [−0.52; 0.15]	
Fibromyalgia				1	−0.19 [−1.15; 0.76]							
Neuropathic pain (MS-related)	1	−0.34 [−0.81; 0.13]					1	0.09 [−0.38; 0.56]		1	0.01 [−0.46; 0.48]	
Neuropathic pain (non-MS-related)	1	0.23 [−2.04; 2.50]					1	0.04 [−2.23; 2.31]		2	−0.59 [−2.03; 0.85]	
Overall	2	−0.31 [−0.77; 0.14]	0	1	−0.19 [−1.15; 0.76]		2	0.09 [−0.37; 0.55]	0	4	−0.13 [−0.40; 0.14]	0

[a] A higher score indicates better emotional functioning. [b] A higher score indicates more symptoms of depression. [c] A higher score indicates more symptoms of anxiety. A dash ('-') indicates there were not studies reporting available effect estimates for the comparison of interest. k, number of studies, I^2, level of heterogeneity.

LEGEND

Favors cannabinoid

Favors comparator

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eTable 8. Effect sizes for treatment retention

	THC/other cannabinoid (CBD <2%)			THC/other cannabinoid dominant (CBD ≥2% and <40%)			Balanced (CBD ≥40% and <60%)			CBD dominant (CBD ≥60% and <98%)			CBD (CBD ≥98%)			Agonist of cannabinoid receptor 2 (olorinab)		
Withdrawals any reason	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	I2
Arthritis													2	0.87 [0.24; 3.14]	52			
Fibromyalgia	1	3.00 [0.51; 17.74]		1	3.80 [0.13; 107.31								1	1.26 [0.58; 2.71]				
Neuropathic pain (MS-related)	4	2.11 [1.49; 2.98]	0	1	1.78 [0.96; 3.28]		7	1.73 [0.85; 3.54	39				2	0.98 [0.31; 3.09]	0			
Neuropathic pain (non-MS-related)	3	1.20 [0.35; 4.16]	0	1	0.72 [0.15; 3.39]		4	2.13 [1.32; 3.45]	0				5	0.82 [0.32; 2.12]	0			
Other CNCP	2	1.69 [0.73; 3.95]	83				5	2.16 [0.69; 6.79]	0	1	1.22 [0.66; 2.26]		2	1.56 [1.13; 2.15]	0			
Visceral pain	2	2.32 [0.45; 11.95]	49													3	0.79 [0.46; 1.35]	0
Overall	12	1.97 [1.46; 2.67]	13	3	1.61 [0.92; 2.83]	0	16	1.93 [1.40; 2.67]	0	1	1.22 [0.66; 2.26]		12	1.34 [1.03; 1.75]	0	3	0.79 [0.46; 1.35]	0
Withdrawals adverse events	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2
Arthritis							1	0.11 [0.01; 2.25]					2	1.00 [0.09; 10.77]	59			
Fibromyalgia	1	3.35 [0.32; 35.36]		1	1.12 [0.02; 62.73]								1	1.00 [0.34; 2.96]				
Neuropathic pain (MS-related)	6	5.16 [3.04; 8.78]	27	1	2.68 [1.98; 3.62]		7	1.93 [1.09; 3.44]	0				2	0.81 [0.14; 4.51]	0			
Neuropathic pain (non-MS-related)	1	3.45 [0.13; 88.40]		1	0.98 [0.02; 50.37]		6	3.60 [2.18; 5.96]	0				1	5.98 [0.27; 130.33]				
Other CNCP	1	5.77 [3.24; 10.29]					2	3.23 [0.36; 29.01]	12									
Visceral pain	3	4.83 [1.55; 15.07]	0													3	0.78 [0.28; 2.15]	0
Overall	12	5.28 [3.67; 7.59]	0	3	3.37 [1.58; 7.18]	0	16	2.63 [1.82; 3.81]	2				6	1.38 [0.71; 2.67]	0	3	0.78 [0.28; 2.15]	0

A dash ('-') indicates there were not studies reporting available effect estimates for the comparison of interest.
k, number of studies, I^2, level of heterogeneity,

LEGEND

Favors cannabinoid
Favors comparator

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eTable 9. Effect sizes for treatment safety (number of persons experienced adverse events)

	THC/other cannabinoid (CBD <2%)			THC/other cannabinoid dominant (CBD ≥2% and <40%)			Balanced (CBD ≥40% and <60%)			CBD dominant (CBD ≥60% and <98%)			CBD (CBD ≥98%)			Agonist of cannabinoid receptor 2 (olorinab)		
Any adverse event	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**
Arthritis													2	1.24 [0.79; 1.95]	0			
Fibromyalgia													1	1.70 [0.40; 7.32]				
Musculoskeletal pain (MS-related)	1	48.12 [2.86; 808.62]																
Neuropathic pain (non-MS-related)				1	0.98 [0.26; 3.63]								1	5.74 [0.63; 52.23]				
Other CNCP	1	7.22 [2.05; 25.45]					2	0.86 [0.17; 4.35]	0	1	4.03 [1.09; 14.96]		1	4.03 [1.09; 14.96]				
Visceral pain	3	5.24 [1.36; 20.21]	29													3	0.90 [0.61; 1.32]	0
Overall	5	7.20 [3.15; 16.47]	18	1	0.98 [0.26; 3.63]		2	0.86 [0.17; 4.35]	0	1	4.03 [1.09; 14.96]		5	1.50 [1.00; 2.24]	10	3	0.90 [0.61; 1.32]	0
Serious adverse event	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**	**k**	**OR [95% CI]**	**I2**
Arthritis													1	0.94 [0.13; 6.88]				
Fibromyalgia													1	0.23 [0.05; 1.13]				
Neuropathic pain (MS-related)	1	1.79 [0.67; 4.74]					1	0.96 [0.06; 15.77]										
Neuropathic pain (non-MS-related)													1	3.10 [0.12; 78.87]				
Other CNCP	1	0.90 [0.51; 1.57]					1	5.31 [0.25; 114.79]										
Visceral pain	1	0.90 [0.02; 50.24]														3	1.01 [0.10; 9.83]	0
Overall	3	1.11 [0.61; 2.00]	0				2	2.08 [0.26; 16.52]	0				3	0.57 [0.15; 2.23]	20	3	1.01 [0.10; 9.83]	0
Treatment emergent adverse event	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2	k	OR [95% CI]	I2
Neuropathic pain (MS-related)	3	1.78 [0.58; 5.54]	57				3	2.08 [0.57; 7.65]	77									

Neuropathic pain (non-MS-related)									1	1.00 [0.34; 2.97]		
Other CNCP	1	2.43 [1.74; 3.40]			1	15.17 [4.09; 56.25]						
Visceral pain											3	1.35 [0.74; 2.47] 0
Overall	4	2.52 [1.88; 3.38]	37		4	3.24 [0.88; 11.87]	77		1	1.00 [0.34; 2.97]	3	1.35 [0.74; 2.47] 0

[a] Composition of CBD and THC not reported, unable to classified into TGA categories. A dash ('-') indicates there were not studies reporting available effect estimates for the comparison of interest.
k, number of studies, I^2, level of heterogeneity,

LEGEND

Favors cannabinoid

Favors comparator

Appendix 2: Existing guidance

eTable 10. Overview of international guidance and position statements

Country/ Organisation	Title	Year	Link
Australia (Therapeutic Goods Administration)	Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia	2017 (updated 2020 & 2024)	https://www.tga.gov.au/resources/explore-topic/medicinal-cannabis-hub/medicinal-cannabis-guidance-documents/guidance-use-medicinal-cannabis-treatment-chronic-non-cancer-pain-australia
The Royal Australian and New Zealand College of Psychiatrists	Therapeutic use of medicinal cannabis products	2024	https://www.ranzcp.org/getcontentasset/233218fd-068d-4846-875e-3bf319bb5d0a/dfc3d011-8f63-43f6-9ed8-4b444333a1d0/cm-therapeutic-use-of-medicinal-cannabis-products.pdf?language=en-AU
Canada (The College of Family Physicians of Canada)	Guidance in Authorizing Cannabis Products Within Primary Care	2021	https://www.cfpc.ca/CFPC/media/PDF/CFPC-Guidance-in-Cannabis-Within-Primary-Care.pdf
European Pain Federation	European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management	2018	https://pubmed.ncbi.nlm.nih.gov/30074291/
The Netherlands (Bedrocan)	A clinical primer: A guide to the rational use of cannabis based products	2025	https://clinicalprimercannabis.com/wp-content/uploads/2025/03/Clinical-primer.-A-guide-to-the-rational-use-of-cannabis-based-medicines.-Edition-2025.pdf
The International Association for the Study of Pain	International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia position statement	2021	https://www.iasp-pain.org/publications/iasp-news/iasp-position-statement-on-the-use-of-cannabinoids-to-treat-pain/
New Zealand (Best Practice Advocacy Centre)	An overview of medicinal cannabis for health practitioners	2022	https://bpac.org.nz/2022/docs/medicinal-cannabis.pdf

Appendix 3: Patient consent forms

Prescribing medicinal cannabinoid products checklist and consent form developed by the RACGP, accessible here: https://www.racgp.org.au/FSDEDEV/media/documents/RACGP/Position%20statements/Appendix-Medicinal-use-of-cannabis-products.pdf

Appendix 4: Characteristics of cannabinoids used in interventions (115 studies)

eTable 11. Characteristics of interventions

Study	Cannabinoid classification	CBD/THC concentration	Route of administration	Comparator	Duration	Dosage details
Abbasifard 2025(i)	Hemp seed oil	Cannabis sativa	Topical	Placebo	8 weeks	NR
Abbasifard 2025(ii)	Hemp seed oil	Cannabis sativa	Topical	Active: 1% diclofenac gel	8 weeks	NR
Abrams 2007	Plant based cannabis	Cannabis sativa	Smoked	Placebo	1 week	Daily dose: 3.56% THC
Abrams 2020	CBD+THC	Cannabis sativa	Vapourised	Placebo	5 days	Daily dose: 4.4% THC; 4.9% CBD, TID
Almog 2020(i)	THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Vapourised	Placebo	Acute	Daily dose: 0.5mg
Almog 2020(ii)	THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Vapourised	Placebo	Acute	Daily dose: 1.0mg
Ball 2015	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	156 weeks	Daily dose range: 7mg to 28mg
Bassat 2023(i)	CDB + THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Sublingual	Placebo	6 weeks	Maximum daily dose: 5mg THC; 30mg CBD, TID
Bassat 2023(ii)	CDB + THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Sublingual	Placebo	6 weeks	Maximum daily dose: 5mg THC; 30mg CBD, TID
Berman 2004(i)	THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oral spray	Placebo	2 weeks	Maximum daily dose: 129.6mg THC
Berman 2004(ii)	Nabiximols	Cannabis sativa	Oromucosal spray	Placebo	2 weeks	Maximum daily dose 129.6mg THC; 120mg CBD
Bestard 2011	Nabilone	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oral	Active: Gabapentin	6 months	Mean daily dose: 3.02mg ± 1.42mg
Bettstetter 2023	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	7 to 20 days	Mean daily dose: 14.8 mg
Blake 2006	Nabiximols	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oromucosal spray	Placebo	5 weeks	Mean daily dose: 14.58mg THC; 13.5mg CBD
Campbell 2023(i)	Dronabinol	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oral	Placebo	Acute	Daily dose: 10mg

Campbell 2023(ii)	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Active: Hydromorphone 4mg	Acute	Daily dose: 10mg
Carroll 2004	CBD + THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	8 weeks	Lowest daily dose: 5mg THC; 2.5mg CBD
Chang 2023(i)	Olorinab	Agonist of cannabinoid receptor 2 (olorinab)	Oral	Placebo	12 weeks	Daily dose: 10mg TID
Chang 2023(ii)	Olorinab	Agonist of cannabinoid receptor 2 (olorinab)	Oral	Placebo	12 weeks	Daily dose: 25mg TID
Chang 2023(iii)	Olorinab	Agonist of cannabinoid receptor 2 (olorinab)	Oral	Placebo	12 weeks	Daily dose: 50mg TID
Chaves 2020	CDB + THC	THC/other cannabinoid dominant medicinal cannabis product (CBD >=2% and <40%)	Sublingual	Placebo	8 weeks	Mean daily dose: 4.4mg THC; 0.08mg CBD
Chung 2009a	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	4 weeks	NR
Collin 2010	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oral mucosal spray	Placebo	14 weeks	Mean daily dose 22.95mg THC; 21.25mg CBD
Corey-Bloom 2012	Plant based cannabis	Cannabis sativa	Smoked	Placebo	2.5 weeks	Daily dose: 4% THC
D'Andre 2024	CBD	CBD medicinal cannabis product (CBD <=98%)	Topical	Placebo	2 weeks	Daily dose: 4mg, BID
de Vries 2016	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Active: 5 mg/10 mg diazepam	Acute	Daily dose: 8mg
de Vries 2017	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	7 weeks	Daily dose range: 9mg to 24mg
Degenhardt 2015	Plant based cannabis	Unclear	Oral	Placebo	NR	NR
Eibach 2021	Cannabidivarin	CBD medicinal cannabis product (CBD <=98%)	Oral	Placebo	4 weeks	Daily dose: 400mg
Ellis 2009	Plant based cannabis	Cannabis sativa	Smoked	Placebo	9 weeks	Daily dose range: 1% THC to 8% THC
Frank 2008	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Active: Dihydrocodeine	12 weeks	Daily dose range: 0.25mg to 2mg
Gruber 2021	Plant based cannabis	Unclear	Mixed	Placebo	6 months	Variable dosage
GW Pharmaceuticals 2008 (Tesfaye; NCT00710424)	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	14 weeks	Maximum daily dose: 65mg THC; 60mg CBD
GW Pharmaceutic	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	3 weeks	Maximum daily dose: 120mg THC; 120mg CBD

als 2012a (Notcutt; NCT01606176)						
GW Pharmaceuticals 2012b (Berman; NCT01606202)	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	3 weeks	Maximum daily dose: 130mg THC; 120mg CBD
Hagenbach 2007c	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	6 weeks	Daily dose range: 20mg to 60mg
Hansen 2023(i)	THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)		Placebo	7 weeks	Maximum daily dose: 22.5mg, TID
Hansen 2023(ii)	CBD	CBD medicinal cannabis product (CBD <=98%)	Oral	Placebo	7 weeks	Maximum daily dose: 45mg
Hansen 2023(iii)	CBD + THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oral	Placebo	7 weeks	Maximum daily dose: 22.5mg THC; 45mg CBD
Heineman 2022	CBD	CBD medicinal cannabis product (CBD <=98%)	Topical	Placebo	2 weeks	Daily dose: 6.2mg, BID
Karst 2003	CT-3	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	2 weeks	Daily dose range: 40mg to 80mg
Karst 2025	CBD + THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	12 weeks	Maximum daily dose: 32.5mg THC (20mg in one sitting)
Kittithamvongs 2025	CBD + THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Sublingual	Placebo	10 days	Maximum daily dose: 30mg THC; 27.78mg CBD
Langford 2013	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	14 weeks	Mean daily dose 23.76mg THC; 22mg CBD. Maximum daily dose: 32.4mg THC; 30mg CBD
Luplipon 2024	19.23% v/v rhizomes of phlai and cannabis leaf oil	Cannabis sativa	Topical	Active	2 weeks	Daily dose: 1-2 sprays, TID
Lynch 2014	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	14 weeks	Mean daily dose 21.6mg of THC, 20mg of CBD
Malik 2017	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	4 weeks	Daily dose: 5mg, BID
Marinelli 2022	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	4 weeks	Maximum daily dose: 12 sprays

Meuth 2020	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	12 weeks	Maximum daily dose: 12 sprays
Mousavi 2025	CBD	CBD medicinal cannabis product (CBD <=98%)	Sublingual	Placebo	4 weeks	Daily dose: 40mg, BID
Narang 2008(i)	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	1 week	Mean daily dose: 10mg
Narang 2008(ii)	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	1 week	Mean daily dose: 20mg
Novotna 2011	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal	Placebo	12 weeks	Mean daily dose: 22.41mg THC; 20.75mg CBD
Nurmikko 2007	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	5 weeks	Mean daily dose: 29.40mg THC; 27.225mg CBD
Pini 2012	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Active	20 weeks	Mean daily dose: 0.5mg
Pinsger 2006	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	8 weeks	Daily dose range: 0.25mg to 1mg
Pramhas 2023	Cannabidiol	CBD medicinal cannabis product (CBD <=98%)	Oral	Placebo	8 weeks	Daily dose: 200mg, TID
Rasmussen 2025	Plant-derived CBD	CBD medicinal cannabis product (CBD <=98%)	Oral	Placebo	6 months	Daily dose range: 30mg to 50mg
Rintala 2010	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Active	18 weeks	Daily dose range: 5mg to 20mg
Riva 2016	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	6 weeks	NR
Rog 2005	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	5 weeks	Mean daily dose 25.92mg THC; 24mg CBD
Saleska 2022	CBD - variable products	CBD medicinal cannabis product (CBD <=98%)	mixed	Placebo	4 weeks	Variable dosage
Schimrigk 2017	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	16 weeks	Mean daily dose: 12.7mg
Schuster 2024(i)	THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oromucosal spray	Placebo	Acute	Daily dose: 6% THC, 4 puffs
Schuster 2024(ii)	CBD	CBD medicinal cannabis product (CBD <=98%)	Oromucosal spray	Placebo	Acute	Daily dose: 11% CBD, 4 puffs
Schuster 2024(iii)	CBD + THC	CBD dominant medicinal cannabis product (CBD >=60% and <98%)	Oromucosal spray	Placebo	Acute	Daily dose: 6% THC; 11% CBD, 4 puffs
Seevathee 2024	Cannabidiol	THC/other cannabinoid dominant medicinal cannabis product (CBD >=2% and <40%)	Topical	Placebo	12 weeks	Daily dose range: 1 to 6 drops. THC: 3.20 mg/drop; CBD: 0.32 mg/drop; CBN: 0.65 mg/drop

Selvarajah 2010	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	12 weeks	NR
Serpell 2014	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	15 weeks	Mean daily dose 24.03mg of THC, 22.25mg of CBD
Shah 2017	Unclear	Unclear	Multiple - smoking or oral	Placebo	3 weeks	NR
Skrabek 2008	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	8 weeks	Range 0.5mg to 2mg
Svendsen 2004	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	6 weeks	Daily dose range: 2.5mg to max 10mg
Toth 2012	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	5 weeks	Mean daily dose 2.24mg, range 1mg-4mg
Turcotte 2015	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	9 weeks	Daily dose range: 0.5mg - 2mg
Ueberall 2022	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Active	6 months	Daily mean dose: 6.2 sprays
van Amerongen 2017a	THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	4 weeks	Maximum daily dose: 16mg
van Amerongen 2017b	THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	4 weeks	Mean daily dose: 21.75mg daily
van Dam 2024	CBD + THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Vapourised	Active	6 weeks	Daily dose: 9.5mg THC; 12mg CBD, up to 5 times
Van de Donk 2019(i)	THC (Bedrocan)	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Vapourised	Placebo	Acute	Mean daily dose: 22.4mg
Van de Donk 2019(ii)	THC+CBD (Bediol)	Balanced medicinal cannabis product (CBD >=40% and <60%)	Vapourised	Placebo	Acute	Mean daily dose: 13.4mg THC; 17.8mg CBD
Van de Donk 2019(iii)	CBD (Bedrolite)	CBD medicinal cannabis product (CBD <=98%)	Vapourised	Placebo	Acute	Mean daily dose: 18.4mg
van Orten-Luiten 2022	CBD	CBD medicinal cannabis product (CBD <=98%)	chewing gum	Placebo	3 weeks	Maximum daily dose: 300mg
Vela 2022	Cannabidiol	CBD medicinal cannabis product (CBD <=98%)	oral capsule or tablet	Placebo	12 weeks	Daily dose: 10mg, TID
Wade 2003a	THC extract	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Sublingual spray	Placebo	8 weeks	Daily dose range: 2.5mg to 120mg

Wade 2003b(i)	CBD extract	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Vapourised	Placebo	8 weeks	Daily dose range: 2.5mg to 120mg
Wade 2003b(ii)	CBD + THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Vapourised	Placebo	8 weeks	Daily dose range: 2.5mg to 120mg THC; 2.5mg to 120 mg CBD
Wade 2004	Nabiximols	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oromucosal spray	Placebo	6 weeks	Maximum daily dose: 120mg THC; 120mg CBD
Wallace 2015(i)	Plant based cannabis	Cannabis sativa	Vapourised	Placebo	10 weeks	Daily dose: 1% THC
Wallace 2015(ii)	Plant based cannabis	Cannabis sativa	Vapourised	Placebo	10 weeks	Daily dose: 4% THC
Wallace 2015(iii)	Plant based cannabis	Cannabis sativa	Vapourised	Placebo	10 weeks	Daily dose: 7% THC
Wallace 2020(i)	Plant based cannabis	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Vapourised	Placebo	Acute	Daily dose: 4mg
Wallace 2020(ii)	Plant based cannabis	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Vapourised	Placebo	Acute	Daily dose: 16mg
Wallace 2020(iii)	Plant based cannabis	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Vapourised	Placebo	Acute	Daily dose: 28mg
Ware 2010a	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Active	10 weeks	Daily dose range: 0.5mg to 1mg
Ware 2010b(i)	Plant based cannabis	Cannabis sativa	Smoked	Placebo	2.8 weeks	Daily dose: 2.5% THC
Ware 2010b(ii)	Plant based cannabis	Cannabis sativa	Smoked	Placebo	2.8 weeks	Daily dose: 6% THC
Ware 2010b(iii)	Plant based cannabis	Cannabis sativa	Smoked	Placebo	2.8 weeks	Daily dose: 9.4% THC
Ware 2015	herbal cannabis (12.5% THC)	Cannabis sativa	Multiple - smoking, oral, vaporised	Placebo	1 year	Mean daily dose: 2.5g
Weizman 2018	THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	sublingual	Placebo	Acute	Mean daily dose: 15.4mg
Wilsey 2008(i)	Plant based cannabis	Cannabis sativa	Vapourised	Placebo	4 weeks	Daily dose: 3.5% THC
Wilsey 2008(ii)	Plant based cannabis	Cannabis sativa	Vapourised	Placebo	4 weeks	Daily dose: 7% THC
Wilsey 2013(i)	Plant based cannabis	Cannabis sativa	Vapourised	Placebo	2 weeks	Daily dose: 1.29% THC

Wilsey 2013(ii)	Plant based cannabis	Cannabis sativa	Vapourised	Placebo	2 weeks	Daily dose: 3.53% THC
Wilsey 2016(i)	Herbal cannabis	Cannabis sativa	Vapourised	Placebo	2 weeks	Daily dose: THC 2.9%
Wilsey 2016(ii)	Herbal cannabis	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Vaporised	Placebo	2 weeks	Daily dose: 6.7% THC
Wissel 2006	Nabilone	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	8 weeks	Daily dose range: 0.5mg to 1mg
Wong 2011(i)	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	Acute	Daily dose: 2.5mg or 5mg
Wong 2011(ii)	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	Acute	Daily dose: 2.5mg or 5mg
Xu 2020	CBD	CBD medicinal cannabis product (CBD <=98%)	Topical	Placebo	4 weeks	Maximum daily dose: 250mg per 3 fl.oz cream, QID
Zajicek 2003(i)	Dronabinol	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	15 weeks	Daily dose range: 10mg to 25mg
Zajicek 2003(ii)	CBD + THC	Cannabis sativa	Oral	Placebo	15 weeks	Daily dose range: 10mg to 25mg THC; 5mg to 12.5mg CBD
Zajicek 2012	THC	THC/other cannabinoid dominant medicinal cannabis product (CBD >=2% and <40%)	Oral	Placebo	12 weeks	Mean daily dose: 17.1mg
Zubcevic 2023(i)	CBD	CBD medicinal cannabis product (CBD <=98%)	Oral	Placebo	8 weeks	Maximum daily dose: 50mg
Zubcevic 2023(ii)	THC	THC/other cannabinoid medicinal cannabis product (CBD <2%)	Oral	Placebo	8 weeks	Maximum daily dose: 25mg per day
Zubcevic 2023(iii)	CBD+THC	Balanced medicinal cannabis product (CBD >=40% and <60%)	Oral	Placebo	8 weeks	Maximum daily dose: 25mg THC; 50mg CBD

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