The efficacy and safety of medicinal cannabis in adult populations: An evidence review

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Research. Evidence. Action.

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Abbreviations

Abbreviation	Explanation
ADHD	attention deficit hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immune deficiency syndrome
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CBD	cannabidiol
CBDV	cannabidivarin
CD4	cluster of differentiation 4
COPD	chronic obstructive pulmonary disease
CT-3	1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid
DARE	Database of Abstracts of Reviews of Effects
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HRB	Health Research Board
JBI	Joanna Briggs Institute
LILACS	Latin American and Caribbean Health Sciences Literature
MeSH	Medical Subject Headings
NHS	National Health Service
PICO	population, intervention, comparison, and outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	post-traumatic stress disorder
RCT	randomised controlled trial
SciELO	Scientific Electronic Library Online
THC	tetrahydrocannabinol
THC:CBD	tetrahydrocannabinol and cannabidiol combined
UK	United Kingdom
vs.	versus

Glossary of terms

Term	Explanation
active control	Active control (or active comparator) means that an already known, effective treatment (rather than a placebo) is being compared with an experimental treatment.
agonist	An agonist is a chemical that can bind to and activate a receptor to produce a biological response.
cannabidiol	Cannabidiol (CBD) is a natural cannabinoid chemical found in the *Cannabis* plant. It is not a psychoactive chemical and so does not change functions of the nervous system, and does not result in alterations in perception, mood, consciousness, cognition, or behaviour.
cannabinoid(s)	'Cannabinoids' is the name given to a type of chemical found in the *Cannabis* plant or similar chemicals found in the body (see 'endocannabinoids') or similar chemicals synthesised in a laboratory (see 'synthetic cannabinoids').
cannabinoid receptors	Cannabinoid receptors, located throughout the body, are part of the endocannabinoid system (see 'endocannabinoid system') and mediate the central (brain and spinal cord) and peripheral (outside the brain and spinal cord) actions of cannabinoids. To date, two receptors have been discovered, which are named cannabinoid receptor 1 and cannabinoid receptor 2.
Cannabis	*Cannabis* is a genus of flowering plants in the family Cannabaceae originating in Asia. There are three recognised species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis contains more than 100 cannabinoids, such as tetrahydrocannabinol (THC) and CBD.
cohort study	A cohort study is a form of longitudinal (analytic observational) epidemiological study in which a group of subjects, called a cohort, is followed over a period of time, and data relating to predetermined exposures and outcomes are collected on two or more occasions over this time period. The incidence (new cases) of the outcome(s) of interest is calculated in the exposed people and compared with the incidence in the non-exposed people. This comparison of

Term	Explanation
	incidence is known as relative risk. The data for the cohort can be collected either by following the participants into the future (prospective study) or by asking them about their past (retrospective study). However, retrospective cohort studies are limited by recall bias. One of the indicators of a high-quality cohort study is a loss to follow-up rate of less than 20%. Cohort studies contribute to causality or disease aetiology and provide, at most, moderate-quality evidence.
control	A control is used when completing an experiment to test an element or intervention. The control is the element that remains unchanged or unaffected by other variables. A control is the point of comparison against which other test results are measured.
double-blind	A double-blind study is one in which neither the participants nor the experimenter knows which experimental group the participant belongs to (e.g. whether the participant is receiving a placebo or an active treatment).
endocannabinoids	Endocannabinoids are a subtype of cannabinoids that are found naturally occurring in the body.
endocannabinoid system	The endocannabinoid system is the name given to the biological system comprising endocannabinoids; the proteins that synthesise/degrade endocannabinoids; and the cannabinoid receptors.
marijuana use	Marijuana (another name for cannabis) use refers to using cannabis (usually for recreational purposes) by smoking, inhaling, or eating.
medical cannabis/marijuana medicinal cannabis/marijuana	Medical or medicinal cannabis or marijuana is a broad term for cannabis-based medicine that is used to relieve symptoms of certain conditions. It is a general term that covers both authorised or licensed medicines produced by pharmaceutical companies, and unlicensed cannabis-based products for medical use.
Medical Cannabis Access Programme	The Medical Cannabis Access Programme is a programme in Ireland enacted in June 2019 that facilitates access to cannabis-based products for medical use in line with legislation and with the clinical guidance for the scheme. The programme makes it possible for a medical specialist to prescribe a cannabis-based treatment for a

Term	Explanation
	patient when the patient has failed to respond to standard treatments.
overlap	Overlap between systematic reviews occurs when a single primary study is included in more than one systematic review evaluating the same outcome. For example, Review A and Review B both synthesise evidence on THC for ameliorating depression, and both include Primary Study C. It is important to understand the degree of overlap between reviews, because a large number of reviews on a topic may give an inaccurate impression of the size of the body of evidence if many of the reviews are not independent but are based on the same relatively small number of primary studies. It is possible to calculate the degree of overlap between reviews (known as the corrected covered area).
phytocannabinoids	Phytocannabinoids are a subtype of cannabinoid that are found only in the *Cannabis* plant. The most widely known and studied phytocannabinoids are THC and CBD.
placebo	'Placebo' is the name given to a substance which has no pharmacological effect but is administered as a control in testing the efficacy of a pharmacologically active preparation. Common placebos include inert tablets (sugar pills) or inert injections (sterile water or saline) which are designed to look and feel like the active substance being tested but do not contain any active ingredients.
randomised controlled trial	A randomised controlled trial (RCT) is an analytic interventional epidemiological study in which subjects are randomly assigned to one of at least two groups. The first group is the experimental group, which receives the intervention of interest, and the other group is the comparison or control group, which receives an alternative treatment (current conventional therapy or a placebo). The two groups are then followed up on to see if there are any differences between them with respect to the outcome(s) of interest. The results of the trial compare the incidence of success in the intervention group with that in the control group to assess the effectiveness of the intervention. RCTs are the most stringent study design for

Term	Explanation
	evaluating the effect of an intervention on an outcome.
RCT – crossover design	A crossover design RCT is a specific type of RCT where a researcher assesses two or more interventions and the effect of the interventions are measured on the same individuals at different time points. It can also be described as participants receiving a sequence of interventions. For example, a researcher wishes to compare the efficacy of drug A and drug B to treat high blood pressure. They recruit 100 participants and randomly allocate 50 to receive drug A (group 1) and 50 to receive drug B (group 2). At first, participants in group 1 receive drug A for 2 weeks and those in group 2 receive drug B for 2 weeks. After that there will be a 'wash-out' period of, say, 4 weeks, during which the participants receive no drug (this is to allow the body to clear out any remaining traces of drug A). Then, group 1 takes drug B for 2 weeks and group 2 takes drug A for 2 weeks (crossover of drugs). The researcher measures the outcome (high blood pressure) twice: first after group 1 takes drug A and again after group 1 takes drug B, and vice versa for group 2.
RCT – parallel design	A parallel design RCT is a type of RCT where the participants are randomly allocated to one of two treatment groups and all of the participants in each group only receive one treatment for the entirety of the study. The researcher measures and compares the outcomes in the two groups at the end of the study.
synthetic cannabinoids	Synthetic cannabinoids are a subtype of cannabinoids that are artificially designed in a laboratory to mimic and bind to the same receptors as naturally occurring cannabinoids (either phytocannabinoids or endocannabinoids). Synthetic cannabinoids may be prepared to alleviate symptoms of a health condition, or sold as mind-altering recreational drugs.
tetrahydrocannabinol	Tetrahydrocannabinol (THC) is the main psychoactive cannabinoid found in the *Cannabis* plant. The term 'THC' usually refers to the delta-9-THC isomer. It is a psychoactive chemical and so it changes the functions of the nervous system, and

Term	Explanation
	may result in alterations in perception, mood, consciousness, cognition, or behaviour.
usual care	The standard treatment that a study participant would be expected to receive in the ordinary course of normal practice. An experimental study may compare outcomes between an experimental group, which receives the intervention of interest, and a usual care group, which receives the standard care that would be provided if no experiment were being undertaken.

Executive summary

Purpose

This evidence review, examining the efficacy and safety of medicinal cannabis for a range of conditions, aims to support the 2022 review of the Medical Cannabis Access Programme in Ireland. The synthesis will also inform Department of Health responses to communications concerning the prescribing of cannabis-based products, and inform the Department's position on the suitability of cannabis-based products for various clinical indications.

Review questions

- Question 1: What is the evidence for the clinical efficacy of medicinal cannabis in the treatment of the conditions/clinical indications of interest among adults?
- Question 2: What is the evidence for the safety of medicinal cannabis in the treatment of the conditions/clinical indications of interest among adults?

Methods

This evidence review comprises an overview of reviews (umbrella review). The methods used in this review are divided into five stages: identifying research evidence; screening of search results; data extraction; quality assessment; and synthesis. From a terminology viewpoint, we use the term 'medicinal cannabis' rather than 'medical cannabis' in this evidence review for consistency, as an umbrella term to include both pharmaceutical cannabis-based medicines and cannabis plant and its preparations used for medical purposes. We acknowledge the varied understandings of these and other terms used to describe cannabis-based products for medical use, as well as the diversity of opinions as to which terms are most appropriate.

Identifying research evidence

A search strategy was developed to identify all publications related to both of our research questions. In June 2022, comprehensive searches were conducted of 7 bibliographic databases (MEDLINE, Embase, CINAHL Complete, SocINDEX with Full Text, PsycINFO, SciELO (Scientific Electronic Library Online, and LILACS (Latin American and Caribbean Health Sciences Literature), as well as 10 review resources, 3 preprint resources, 3 search engines, 1 open access resource aggregator, and 1 topic-specific website. These searches were supplemented by citation chaining; reference chasing; and follow-up of protocols, conference abstracts, posters, and umbrella reviews identified from the literature searches in January 2023. Follow-up searches in four resources (Ovid MEDLINE, Epistemonikos, the Cochrane Library, and Google Scholar) were conducted in January 2023 to identify any new research that had been published since June 2022 when the initial searches had been conducted.

Screening of search results

Screening was carried out in EPPI-Reviewer Web. Screening was carried out as a double-blind multistage process. Double-screening at title and abstract level was conducted by four independent reviewers working in two teams of two. Conflicts in screening decisions were resolved by discussion among the four reviewers. Full-text screening was conducted by two reviewers. In addition to standard screening exclusion criteria (study design, intervention, age, date, etc.), exclusion criteria also included inadequate literature search and inadequate risk of bias/quality assessment.

Data extraction

Data were extracted from each review using an amended version of the Joanna Briggs Institute data extraction form. The extracted data included citation details, review objectives, participants, setting, interventions, comparators, search information, study date range, number of primary studies, study design, risk of bias tool used, risk of bias assessment, analysis methods, outcomes assessed, and results by outcome. Data extraction for each included systematic review was carried out by one of three reviewers and validated by another for accuracy and comprehensiveness.

Quality assessment

Quality assessment was conducted in two stages. The first stage involved assessing the methodological quality of each individual systematic review meeting the pre-set inclusion criteria. Methodological quality, examining study design and conduct, was assessed using a modified version of the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2 instrument, and methodological quality was scored as high, moderate, low, or critically low.

The second stage involved assessing the quality or certainty of evidence for each outcome by intervention reported across all included systematic reviews. The certainty of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, and was scored as high, moderate, low, or very low.

Both quality assessment stages were conducted independently by three reviewers, and all assessments were validated by one other reviewer for accuracy.

Synthesis

Descriptive data on review characteristics were documented in tables. For each included review, the extracted data are presented in two formats: a high-level summary in the main report, taking account of the quality of evidence; and detailed structured summaries in Appendix F. Primary outcomes identified in the included reviews are presented in the main report. Data on any secondary outcomes are included in the structured extractions in the report appendices.

To reflect the research questions, data on primary outcomes were synthesised under ‘efficacy’ and ‘safety’ headings. Under the efficacy heading, separate syntheses were conducted for reviews investigating specific and mixed health conditions to provide insight into the efficacy of cannabinoids by health condition or symptom. Under the safety heading, data from all included studies were synthesised to provide an in-depth account of adverse events associated with the use of cannabinoids across a broad range of health conditions. To account for the variations in mechanisms of action/beneficial properties associated with distinct cannabinoid types, outcomes were categorised by cannabinoid type (e.g. cannabis, tetrahydrocannabinol (THC), tetrahydrocannabinol and cannabidiol combined (THC:CBD), or cannabidiol (CBD)) compared with comparator type (e.g. placebo, active control, or usual care) under both efficacy and safety headings.

Findings

Initial searches of databases and registers identified 25,888 records, of which 11,252 were duplicates, leaving 14,636 records for title and abstract screening. During title and abstract screening, 14,244 records were excluded, leaving 392 records for full-text screening. A total of 352 records were excluded at the full-text screening stage, leaving 40 records for extraction. An additional 7 articles were identified for extraction through supplemental searches, resulting in a total of 47 included papers.

Of these 47 reviews, 26 assessed the efficacy of cannabinoids/cannabis for relieving symptoms of specific health conditions, including cancer, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), inflammatory bowel disease, mental health and neuropsychological conditions,

palliative care, rheumatic diseases and fibromyalgia, spinal cord injury, and multiple sclerosis. Four of these systematic reviews assessed the efficacy of cannabinoids/cannabis for relieving symptoms of specific conditions in older adults. A range of primary outcomes were assessed in these reviews, including pain, sleep, quality of life, and relief of specific symptoms related to each health condition. The remaining 21 reviews investigated the efficacy and safety of cannabinoids/cannabis in a mix of populations and conditions; primary outcomes included pain, quality of life, muscle spasticity, cachexia (severe weight and muscle mass loss), sleep, mental health/well-being, and overall function/disability. Across both specific and mixed health conditions, 14 reviews synthesised evidence on the safety and tolerability of cannabinoids/cannabis as a primary outcome. A synopsis of the key findings is presented in this Executive summary, more detailed information is included in Section 3 of the main report, and a standardised summary of each review is presented in Appendix F.

Efficacy in specific health conditions

Cancer

- Six systematic reviews reported evidence on the efficacy of medicinal cannabis among adults with cancer.
- Three systematic reviews found no significant difference in **pain-related outcomes** for THC:CBD groups compared with the control groups, and these outcomes were graded as having a very low to moderate certainty of evidence.
- In contrast with previous systematic reviews, there was low certainty of evidence in one systematic review reporting significant improvement in **patient-perceived global improvement** in pain associated with cancer for THC:CBD compared with placebo groups.
- One review reported that there was significant improvement in **nausea and vomiting** associated with chemotherapy in the THC group compared with the placebo group; however, there was no difference between the THC group and the anti-emetics group in the same review. The outcomes related to relief of nausea and vomiting were graded as having a very low to moderate certainty of evidence.
- Two systematic reviews synthesised evidence of low to very low certainty on **weight loss/gain** and **appetite** associated with cancer; neither reported significant improvements in the THC compared with placebo groups or in the THC:CBD compared with megestrol acetate (an appetite stimulant) groups.
- One systematic review synthesised evidence on **dietary intake outcomes** associated with cancer in the THC group compared with the placebo group. There were mixed findings in relation to increased protein and carbohydrate intake, and no significant increase in total calories, fat, or iron intake. All outcomes with respect to dietary intake were graded as having a very low certainty of evidence.

HIV/AIDS

- One systematic review found no evidence to determine the effect of cannabinoid and cannabis products on **mortality and morbidity** associated with HIV/AIDS.

Conditions in older adults

- We found four systematic reviews examining medicinal cannabis for outcomes related to conditions in older adults, including Parkinson's disease, Alzheimer's disease, dementia, chronic obstructive pulmonary disease (COPD), and neoplasms.

- There is very low-certainty evidence for improvements in agitation, cognitive function in dementia, and tremor in Parkinson's disease in the THC compared with placebo groups.
- However, no significant benefit of medicinal cannabis was observed for breathlessness in COPD, nausea and vomiting associated with neoplasms, or pain in Parkinson's disease (very low-certainty evidence).

Inflammatory bowel disease

- Two systematic reviews synthesised evidence on inflammatory bowel disease.
- Findings indicated no significant difference in the incidence of **clinical remission** in ulcerative colitis or Crohn's disease among cannabis and CBD groups compared with placebo groups (very low-certainty evidence).

Mental health and neuropsychological conditions

- The findings and certainty of evidence from the six systematic reviews on medicinal cannabis in relation to mental health and neuropsychological conditions vary quite widely.
- There was no significant difference in **psychosis symptoms** in the CBD groups compared with the placebo or amisulpride (an antipsychotic medication) groups in two reviews, with outcomes graded as having low- to very low-certainty evidence. There was very low-certainty evidence of a significant worsening of cognitive function and symptoms of psychosis in schizophrenia in the THC compared with placebo groups in one systematic review.
- Mixed evidence, based on three systematic reviews, was synthesised on symptoms related to **anxiety disorders**. Compared with placebo, significant improvements were reported for mixed cannabinoids and cannabis, THC, and CBD for generalised anxiety disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder, respectively. All outcomes were graded as having a low or very low certainty of evidence. Cannabis was reported to have no significant effect on obsessive-compulsive disorder symptoms compared with placebo in one systematic review (very low-certainty evidence). One systematic review reported a significant improvement in anxiety symptoms for the mixed cannabinoid and THC group compared with the placebo group, but no significant difference in the CBD group compared with the placebo group, nor in the THC group compared with the ibuprofen group (very low certainty of evidence).
- One systematic review reported no significant difference between the medicinal cannabis/cannabinoid group and the placebo group for outcomes related to **mood disorders** (low to very low certainty of evidence). Two reviews reported a significant improvement in weight gain in patients with anorexia nervosa for the THC group compared with the placebo group (very low-certainty evidence), but no significant difference in the cannabis group compared with the diazepam group (also very low-certainty evidence).
- Two systematic reviews reported mixed findings for withdrawal symptoms related to **cannabis use disorder, opioid use disorder, and tobacco use disorder** (moderate to very low certainty of evidence).
- Two systematic reviews reported no significant difference between the THC:CBD group and the placebo group for **attention deficit hyperactivity disorder (ADHD) symptoms** (very low-certainty evidence).

- One systematic review reported mixed evidence related to the efficacy of THC products compared with placebo for tic severity and/or frequency in **Tourette's syndrome** (very low-certainty evidence).

Palliative care

- One systematic review reported on the use of medicinal cannabis in the context of palliative care.
- The review found no significant difference between medicinal cannabis and placebo for most primary outcomes in palliative care, including relief of some symptoms associated with the management of cancer, HIV, and Alzheimer's disease (low or very low certainty of evidence).
- However, a significant improvement was reported for the THC group compared with the placebo group in weight gain in HIV and Alzheimer's disease, and appetite in HIV (low or very low certainty of evidence).
- Compared with placebo, there was a significantly increased likelihood of a 30% or greater reduction in cancer-related pain in the mixed cannabinoid group.

Rheumatic diseases and fibromyalgia

- There is generally limited and inconsistent evidence on outcomes of low or very low certainty, based on the findings of two systematic reviews, indicating the relative benefit of medicinal cannabis compared with placebo for some outcomes related to rheumatic diseases and fibromyalgia, including fibromyalgia, rheumatoid arthritis, and chronic therapy-resistant pain caused by the skeletal and locomotor system.
- Cannabinoids (nabiximols, nabilone) were observed to produce improvements in some (but not all) measures of pain, sleep, and quality of life.

Spinal cord injury

- One systematic review reported a significant improvement in pain intensity in spinal cord injuries in the THC group compared with the placebo group (very low-certainty evidence).
- However, no significant difference was reported in the THC group compared with the diphenhydramine (a sedative and antihistamine) group or the THC:CBD group compared with the placebo group (very low-certainty evidence).

Multiple sclerosis

- Two systematic reviews reported on the efficacy of medicinal cannabis in multiple sclerosis, and the outcomes were graded as having moderate- to very low-certainty evidence.
- Compared with placebo, one review reported no significant improvement in observer-rated **spasticity** after using cannabis extract, THC:CBD, or THC, or in subjective spasticity after using THC. Two systematic reviews reported a significant improvement in subjective spasticity using mixed cannabinoids, cannabis extract, or THC:CBD compared with using a placebo. One systematic review reported a significant likelihood of a 30% or greater reduction in spasticity in the THC:CBD group compared with the placebo group.
- Two systematic reviews reported significant improvements in **pain** outcomes in the cannabis extract, THC (nabilone only), and mixed cannabinoids groups compared with the placebo groups. However, one systematic review reported no significant difference in the THC:CBD and THC groups compared with the placebo group. The pain outcomes were graded as having low- to very low-quality evidence.

- In relation to **bladder dysfunction**, one systematic review reported no significant difference in the THC and THC:CBD groups, but significant improvement in the mixed cannabinoids group, compared with the placebo group.
- One review reported no significant difference in **health-related quality of life**, but a significant difference in **patient-rated global impressions of change** for improvement in spasticity in the mixed cannabinoids group compared with the placebo group.

Efficacy in mixed health conditions

Reviews on populations with mixed health conditions synthesised evidence on pain (15 reviews), quality of life (3 reviews), spasticity (2 reviews), cachexia (1 review), sleep (2 reviews), mental health/well-being (1 review), and overall function and disability (1 review).

Pain

- Overall, there is conflicting evidence on the efficacy of mixed cannabinoids for reducing **pain intensity** across diverse cannabinoid interventions and their varied comparator types, and the outcomes are based on moderate- to very low-certainty evidence in 12 systematic reviews.
  - Evidence comparing mixed cannabinoids with placebo indicated a significant improvement in three systematic reviews (low- to very low-certainty evidence) but no significant difference in one review (low-certainty evidence).
  - However, one systematic review reported a significant improvement for pain intensity in the mixed cannabinoid group compared with the mixed control group (high-certainty evidence), although the mechanism of action cannot be ascertained due to mixed cannabinoid types.
  - Overall, three reviews showed a significant improvement in pain intensity in the cannabis group compared with various control groups, including placebo and mixed control groups (low- to very low-certainty evidence), but no difference between the cannabis group and the usual care group (low-certainty evidence).
  - Moving on to specific cannabinoid types, the evidence on pain intensity indicates potential benefits of THC:CBD compared with placebo in four reviews (high- to very low-certainty evidence).
  - However, evidence of reduced pain intensity in the THC:CBD group compared with the placebo group is mixed in one systematic review, and no significant difference was reported in one systematic review (both very low-certainty evidence).
  - Six systematic reviews compared THC groups and placebo groups; four reviews reported a significant improvement in the THC groups (low- to very low-certainty evidence), one systematic review had mixed findings (very low-certainty evidence), and one systematic review found no significant difference between the THC group and the placebo group (very low-certainty evidence).
  - Evidence comparing THC with active/mixed controls reported no significant difference between groups in four systematic reviews (moderate- to very low-certainty evidence), while one systematic review reported a significant improvement in the THC group compared with the active control group (very low-certainty evidence).
  - Evidence on the efficacy of CBD compared with placebo was conflicting and inconclusive in three systematic reviews (all very low-certainty evidence).

  - One systematic review reported no significant difference between the group receiving cannabidivarin (CBDV) and the group receiving cannabinoid 1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3; also referred to as ajulemic acid) compared with the placebo group (very low-certainty evidence).

- Outcome evidence synthesised in seven systematic reviews on the likelihood of medicinal cannabis achieving greater than a **30% reduction in pain** ranged from moderate to very low certainty.
  - One systematic review indicated a significant improvement in the mixed cannabinoids and cannabis group compared with the placebo group (very low-certainty evidence), and three systematic reviews reported a significant reduction in pain in the cannabis group compared with the placebo group (moderate- to very low-certainty evidence).
  - Three systematic reviews reported no significant difference in pain reduction between the THC:CBD group and the placebo group (low- to very low-certainty evidence), while one systematic review reported a significant improvement in pain reduction in the THC:CBD group compared with the placebo group (low-certainty evidence).
  - One systematic review reported a significant likelihood of greater than a 30% reduction in pain in the group using THC compared with a combined placebo and codeine control group (very low-certainty evidence).
  - Two reviews reported mixed evidence in THC compared with placebo groups.
  - One review reported a significant improvement in THC compared with placebo groups (very low-certainty evidence), but one review reported no significant difference between groups (low-certainty evidence).
- Outcome evidence synthesised from five systematic reviews on the likelihood of medicinal cannabis achieving greater than a **50% reduction in pain** ranged from low to very low certainty.
  - One systematic review reported a significant likelihood of a 50% reduction in pain in the cannabinoids and cannabis group compared with the placebo group (very low-certainty evidence), and another reported a significant likelihood of a 50% reduction in pain in the cannabinoid group compared with the placebo group (low-certainty evidence).
  - Three systematic reviews compared THC:CBD groups with placebo groups; one review reported a significant improvement in the THC:CBD group compared with the placebo group (very low-certainty evidence), and two reviews reported no significant difference between the THC:CBD group and the placebo group (low- to very low-certainty evidence).
  - No significant difference in the likelihood of a 50% reduction in pain was reported between the THC group and the comparator group in two systematic reviews (both very low-certainty evidence).
- In relation to **patients' global impressions of pain**, outcome evidence from two systematic reviews ranged from low to very low certainty.
  - Two reviews reported a significant improvement in patients' global impressions of pain in mixed cannabinoid, THC:CBD, and THC groups compared with placebo groups.
- One systematic review reported no significant difference in **morphine consumption** (as a proxy for adequacy of pain relief) in the THC group compared with the placebo group (very low-certainty evidence).

- Three systematic reviews reported no significant difference in **quality of life** outcomes in mixed cannabinoid, THC:CBD, and THC groups compared with placebo or mixed control groups (low- to very low-certainty evidence). One systematic review reported a significant improvement in quality of life in the THC group compared with the placebo group (low-certainty evidence).

Spasticity

- Medicinal cannabis and **spasticity intensity** was measured in two systematic reviews. One systematic review reported no significant difference in spasticity intensity between the THC:CBD group and the placebo group (low-certainty evidence), while the other systematic review reported mixed evidence on the efficacy of mixed cannabinoids compared with a placebo (very low-certainty evidence).
- In relation to the likelihood of **greater than a 30% reduction in spasticity**, one systematic review reported no significant difference in outcomes between the THC:CBD group and the placebo group (very low-certainty evidence).
- In contrast, this systematic review reported significant improvements in **observer-rated spasticity** in the THC:CBD group compared with the placebo group, and in the THC-only group compared with the placebo group (low- to very low-certainty evidence).
- The second systematic review reported no significant difference in **spasm frequency or severity** in the mixed cannabinoid and cannabis group compared with the placebo group (very low-certainty evidence).
- Apart from observer-rated spasticity in one systematic review, there was no significant difference between cannabinoid and comparator groups across the synthesised evidence. All spasticity outcomes were judged as having a low to very low certainty of evidence.

Cachexia

- One systematic review synthesised evidence on cachexia outcomes.
- The systematic review reported no significant difference in **appetite** in the mixed cannabinoid group compared with the placebo group (low-certainty evidence).
- The review also reported no significant difference in **weight loss/gain** in the THC group compared with the mixed control group (very low-certainty evidence).

Sleep

- Two systematic reviews indicated significant improvements in **sleep quality** in the cannabinoid and cannabis group compared with the placebo group (moderate- to high-certainty evidence), but no significant difference in sleep quality between the THC group and the placebo group (very low-certainty evidence).
- One systematic review reported a significant improvement in **sleep disturbance** for the mixed cannabinoid group and the THC group when compared with the placebo group and the active control group, respectively (low-certainty evidence).
- This systematic review also indicated no significant improvement in **nightmares associated with PTSD** and significantly reduced **sleepiness** in the THC group compared with the placebo group (very low-certainty evidence), as well as a significant reduction in **insomnia** but no significant difference in **sleep interruptions** in the THC group compared with the active control groups (very low-certainty evidence).

- One systematic review reported a significantly higher likelihood of daytime somnolence (drowsiness or a strong desire to fall asleep) in the mixed cannabinoid group compared with the placebo group (high-certainty evidence).
- Evidence-based outcomes synthesised on sleep quality ranged from high to very low certainty.

Mental health/well-being

- One systematic review reported no significant difference in **mental health outcomes** between the mixed cannabinoid group and the mixed control group, between the THC:CBD group and the placebo group, and between the THC-only group and the placebo group.
- All mental health outcomes were judged as having a low certainty of evidence.

Overall function or disability

- The evidence synthesised on overall function or disability outcomes was graded as being of low to very low certainty.
- One systematic review found no significant difference in **overall function or disability** between the cannabis group compared with the usual care group (very low-certainty evidence), and between the THC group compared with the active control group (very low-certainty evidence).
- This systematic review reported a significant improvement in **overall function or disability** for the THC-only and the THC:CBD groups compared with the placebo group (low-certainty evidence).

Safety and tolerability

Specific adverse events: Nervous system adverse events

- Five systematic reviews synthesised evidence on specific adverse events categorised as nervous system adverse events.
- Two of these seven systematic reviews synthesised evidence on the outcome of **dizziness**, and were judged to have moderate- to very low-certainty evidence. One systematic review reported no significant difference in dizziness between the cannabis group and the usual care group (very low-certainty evidence), or between the THC group and the mixed control group (very low-certainty evidence). Both systematic reviews reported a significantly higher likelihood of dizziness in the THC group compared with the placebo group (moderate- to very low-certainty evidence), and in the THC:CBD group compared with the placebo group (very low-certainty evidence).
- Three systematic reviews reported a significantly increased likelihood of **sedation** in the medicinal cannabis group compared with the comparator groups. One systematic review reported a significantly higher likelihood of sedation in the cannabis group compared with the usual care group (very low-certainty evidence) and in the THC:CBD group compared with the placebo group (low-certainty evidence). Three systematic reviews reported a significantly higher likelihood of sedation in the THC group compared with the placebo and mixed control groups (moderate- to very low-certainty evidence).
- One systematic review reported a significantly increased likelihood of **drowsiness** in the nabilone group (but not in the dronabinol group) compared with the placebo group (very low-certainty evidence).
- Two systematic reviews reported a significantly increased likelihood of **dry mouth** in the THC group compared with the placebo group (moderate- to very low-certainty evidence). In contrast, one

systematic review indicated no significant difference in dry mouth between the THC group and the active control group (very low-certainty evidence).

- One review reported significantly lower likelihood of **impotence** in dronabinol compared with active control (megestrol acetate) (very low-certainty evidence).
- One systematic review reported a significantly higher likelihood of **headache** in the THC (dronabinol or nabilone) group compared with the placebo group (low- to very low-certainty evidence).
- One systematic review reported no significant difference in **fatigue** in the THC group compared with the placebo and mixed control groups (moderate-certainty evidence).
- Three reviews reported evidence on **any nervous system disorder** (low- to very low-certainty evidence). One review reported a significantly increased likelihood of any nervous system disorder in the mixed cannabinoid group compared with the placebo group (low-certainty evidence). The second review reported no significant difference in the THC:CBD group or the THC-only group compared with the placebo group (very low-certainty evidence). The third review reported no significant difference between THC and placebo groups (very low-certainty).

Specific adverse events: Nervous system adverse events

- Three systematic reviews synthesised evidence on specific adverse events categorised as gastrointestinal system adverse events.
- One systematic review reported a significantly increased likelihood of **nausea** in the cannabis group compared with the usual care group (very low-certainty evidence). This systematic review also reported a significantly increased likelihood of nausea in the THC:CBD group compared with the placebo group (low-certainty evidence). Two systematic reviews reported no significant difference in nausea in the THC group compared with the placebo group (moderate-certainty evidence).
- One review synthesised evidence on **any gastrointestinal disorder**, and it reported no significant difference between the THC group and the placebo group (very low-certainty evidence).

Specific adverse events: Psychiatric system disorder adverse events

- Two reviews reported no significant difference in the occurrence of **any psychiatric system disorder adverse events** in the cannabis group compared with the usual care group or in the THC group compared with the placebo group (very low-certainty evidence).

Specific adverse events: Any specific adverse events

- Three systematic reviews reported no significant difference in the incidence of **any specific adverse events** in the THC:CBD, THC-only, or CBD-only groups compared with placebo groups or THC compared with megestrol acetate groups (very low-certainty evidence). Two systematic reviews reported incidence data on any specific adverse event; as no comparative statistics were reported, we cannot comment on the significance of these findings.

Serious adverse events

- Six systematic reviews synthesised evidence on serious adverse events (low- to very low-certainty evidence).
- Overall, one systematic review found a significant **risk of serious adverse events** in the cannabis group compared with the usual care group (low-certainty evidence), but two systematic reviews found no significant risk in the THC:CBD or THC-only groups compared with the placebo group (low-

to very low-certainty evidence). Three systematic reviews reported incidence data on serious adverse events, as no comparative statistics were reported we cannot comment on the significance of these findings.

- In relation to **mortality** outcomes, two systematic reviews reported no significant risk of death in the THC:CBD or THC-only groups compared with placebo groups (low- to very low-certainty evidence).

Tolerability

- Seven systematic reviews investigated tolerability measured by **withdrawals due to adverse events** (low- to very low-certainty evidence). It is important to note that in this context, "withdrawals due to adverse events" refers to participants choosing to stop participating in a study due to their experience of adverse events (in either intervention or comparator groups), not symptoms of withdrawal that may occur when a person stops taking a drug.
- One systematic review reported a significantly increased likelihood of withdrawals due to adverse events in the cannabis group compared with the usual care group (very low-certainty evidence).
- Similarly, one systematic review reported a significantly increased likelihood of withdrawals due to adverse events in the mixed cannabinoid and cannabis group compared with the placebo group (low-certainty evidence).
- Four systematic reviews reported mixed findings on withdrawals due to adverse events in the THC:CBD groups compared with the placebo groups (low- to very low-certainty evidence). One systematic review reported a significantly increased likelihood in withdrawals due to adverse events in the THC:CBD group compared with the placebo group, while one systematic review reported no significant difference between the THC:CBD group and the placebo group (low- to very low-certainty evidence). Another systematic review comparing the THC:CBD group with the placebo group reported s significantly increased likelihood of withdrawals due to adverse events in a meta-analysis of adults with neuropathic pain (low-certainty evidence); however, this same review reported no significant difference in withdrawals due to adverse events in a meta-analysis of adults with cancer (low-certainty evidence). One systematic review reported incidence data on the THC:CBD group compared with the placebo group; as no comparative statistics were reported, we cannot comment on the significance of these findings.

Conclusions

This overview of 47 systematic reviews on the efficacy and safety of medicinal cannabis for a wide range of health conditions/clinical indications has generally revealed a fragmented body of research and a low degree of certainty in the evidence for most outcomes. The methodological quality, following a systematic quality assessment of the included systematic reviews, is generally very low.

While some evidence was found to support the use of medicinal cannabis for some indications for which it has traditionally been recommended, such as nausea and vomiting in cancer and spasticity in multiple sclerosis, findings for most other outcomes were inconsistent at best, including for anxiety and pain in conditions such as cancer, rheumatic diseases and fibromyalgia, and multiple sclerosis. The evidence for neuropathic pain was promising: moderate- to high-certainty evidence indicated a significant benefit of cannabis, mixed cannabinoids, and THC:CBD, although some moderate-certainty evidence indicated no significant benefit of THC.

Although serious adverse events do not appear to be common, evidence was found for a significantly higher likelihood of some specific adverse events associated with medicinal cannabis (including dizziness,

dry mouth, sedation, and headache). However, no difference in likelihood was reported for other adverse events, including fatigue. Mixed evidence was reported on the likelihood of drowsiness, nausea, and any psychiatric disorder adverse events.

Our findings align with the findings of other overviews of reviews, as they also reported a general lack of quality in primary studies and systematic reviews, which makes it very difficult to draw well-founded conclusions about the relative benefits (or lack thereof) of medicinal cannabis for any given health condition or clinical indication. The certainty of the evidence for most outcomes is generally low (24% of total outcomes) or very low (64% of total outcomes), meaning that findings from future research are likely to change the conclusions we have drawn. A majority of the evidence compares medicinal cannabis with placebo, not with active comparators that reflect up-to-date treatment options. It is important to note that our findings refer only to adult populations and conclusions should not be transferred to children or adolescents.

Further high-quality, adequately powered randomised controlled trial research is needed; in the meantime, conclusions may only be drawn narrowly, if at all, with respect to the particular type of cannabis treatment in the specific patient groups and clinical indications studied in a given analysis, and a number of authors of other overviews of reviews recommend that if medicinal cannabis is to be prescribed to a patient, it should, like any drug, be carefully tailored to the individual's circumstances and closely monitored for clinical response and adverse events.

1 Introduction

1.1 Background

Cannabis, also known as marijuana, is a derivative of the Indian hemp plant *Cannabis sativa* (*C. sativa*). Cannabis has a long history of recreational and medicinal use in human populations [1], and the first evidence of therapeutic cannabis use dates back thousands of years [2]. The Irish physician William O'Shaughnessy is credited with introducing cannabis as a treatment option in western medicine in the 1800s after researching potential medicinal properties of a range of indigenous plants in India [3]. Various constituents of the *Cannabis* plant, including the leaves, flowers, seeds, stalks, and resin glands, have been used as food, fuel, and medicine throughout history [4].

Cannabis contains compounds called cannabinoids, which are a group of more than 100 oxygen-containing aromatic hydrocarbons [5,6]. Cannabinoids are grouped into three distinct subtypes:

1. Plant-derived cannabinoids (phytocannabinoids) are compounds found only in the *Cannabis* plant.
2. Endogenous cannabinoids (endocannabinoids) are cannabinoids that naturally occur in the body.
3. Synthetic cannabinoids are artificially designed molecules that mimic naturally occurring cannabinoids and are used predominantly for scientific research and medicines.

To date, many phytocannabinoids have been discovered in the *Cannabis* plant and characterised, with the most well-known being tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a psychoactive cannabinoid that results in euphoria and the sensation of 'feeling high' after ingestion; this has led to both plant-derived and synthetic THC-containing cannabinoids being used in recreational settings and the potential for misuse. CBD is a non-psychoactive cannabinoid. THC and CBD are the most abundant and extensively studied cannabinoids found in the *Cannabis* plant. A large body of literature exists that has investigated THC's and CBD's potential as neuroprotective [7], anti-inflammatory [8], antioxidant [9], and anti-excitotoxic [10] compounds. Indeed, other phytocannabinoids that are less studied (such as tetrahydrocannabivarin, tetrahydrocannabinolic acid, cannabidivarin, and cannabigerol, to name a few) have also been linked to potential therapeutic value. Therefore, research is warranted to investigate a range of cannabinoids and cannabis extracts in order to describe their pharmacological functions, their physiological behaviours, and their therapeutic potentials.

1.2 Medicinal cannabis

From a terminology viewpoint, the Health Research Board (HRB) generally uses the term 'medicinal cannabis' rather than 'medical cannabis' in this evidence review for consistency, as an umbrella term to include both pharmaceutical cannabis-based medicines and cannabis plant and its preparations used for medical purposes. We acknowledge the varied understandings of these and other terms used to describe cannabis-based products for medical use, as well as the diversity of opinions as to which terms are most appropriate.

1.2.1 Mechanism of action

There currently exists a large body of scientific literature that investigates the potential therapeutic properties of cannabinoids. The potential to use cannabis and cannabinoids as medicines is due to their ability to have physiological functions in the human body, although the mechanism of action of phytocannabinoids has not yet been fully elucidated [11]. Within humans, there exists the endocannabinoid system, which is the name given to the receptors to which cannabinoids can bind (these are called cannabinoid receptors 1 and 2) and the enzymes that regulate the expression of

endocannabinoids (such as fatty acid amide hydrolase and monoacylglycerol lipase). To date, two cannabinoid receptors have been discovered. Cannabinoid receptor 1 is located predominantly in the central nervous system [12](olfactory bulb, hippocampus, basal ganglia, cerebellum, cerebral cortex, septum, amygdala, hypothalamus, and parts of the brainstem and the dorsal horn of spinal cord) [13], and cannabinoid receptor 2 is expressed mainly on immune cells [14]. However, the expression of cannabinoid receptors is very widespread throughout the body and they have been detected in many organs and cell types outside of the central nervous system and immune cells such as the spleen, thymus, cardiovascular system, gastrointestinal tract, liver, adipose tissue, bone, and reproductive system [14,15]. The endocannabinoid system plays a part in the modulation of various physiological functions particularly in the central nervous system and has a role in maintaining homeostasis in the body in addition to the regulation of immune response, inflammation, and pain [16,17]. However, it is important to note that not all cannabinoids can activate or inhibit these receptors. For example, THC can bind to both cannabinoid receptors 1 and 2; however, CBD has low binding affinity to both of these receptors.

Other receptors/mechanisms exist beyond the endocannabinoid system that allow cannabinoids to elicit their function, such as transient receptor potential channels, ion channels, various signalling pathways found in the body and some G-protein coupled receptors [18–20]. The two most studied endocannabinoids are *N*-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). 2-AG is a full agonist (an agonist is a chemical that activates a receptor to produce a biological response) for cannabinoid receptors 1 and 2, whereas AEA, also known as anandamide, is a partial agonist for both cannabinoid receptors 1 and 2 [21–23].

1.2.2 Available cannabis-based therapies

The receptors and subsequent pathways activated by cannabinoids vary based on which receptor is activated, and this leads to physiological effects on pain, appetite, and mood, as well as many other effects on the body [24]. This has led to the development of several cannabis-based medicines (see Table 1).

Dronabinol and **nabilone** (see Table 1) are two approved cannabis-based medicines that were developed in the 1980s and 1990s and are prescribed for the management of nausea in patients receiving chemotherapy [25] and as an appetite stimulant for patients with acquired immune deficiency syndrome (AIDS) [26]. Dronabinol and nabilone are both synthetic forms of THC and are taken orally as capsules or liquids. In some German-speaking countries, the term dronabinol is also used for plant-derived or semi-synthetic THC.

Additionally, there are cannabis-based medicines approved for use in patients that are based on cannabinoids found naturally in the *Cannabis* plant. **Epidiolex** (or Epidyolex in the European Union) (see Table 1) is a plant-derived, highly purified CBD oral solution approved for the management of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex in the United States of America (USA), and as an add-on therapy to clobazam for Dravet syndrome and Lennox-Gastaut syndrome in the European Union [27].

Another plant-based cannabinoid medicine approved for therapeutic uses is **Sativex** (see Table 1), which contains an almost equal concentration of THC and CBD, is administered orally as an ethanolic spray, and is prescribed for people with multiple sclerosis with moderate to severe spasticity and, in some countries, for neuropathic pain [28]. In terms of potential psychoactivity, Sativex has been reported to be generally well tolerated and does not produce the 'feeling high' effect in most users that THC can usually produce [29].

The four approved pharmaceutical-grade cannabinoid preparations described in the previous paragraphs contain known and controlled amounts of THC and/or CBD. Other **unlicensed cannabis products** are also available, which have not gone through recommended or regulated pharmaceutical good manufacturing practice and quality assurance. These contain varied concentrations of THC and CBD, thereby making it very difficult to determine the effects of exposure to such products [30].

Table 1 List of cannabis-based medications, route of administration, and associated indications

Drug name	Active ingredients	Administration	Indications
Dronabinol	Synthetic THC	Oral (capsule)	1. Anorexia associated with AIDS 2. Nausea and vomiting associated with chemotherapy
Nabilone	Synthetic THC mimic	Oral (capsule)	Nausea and vomiting associated with chemotherapy
Sativex	THC:CBD (plant-derived)	Oromucosal spray	Spasticity associated with multiple sclerosis
Epidiolex	CBD (plant-derived)	Oral solution	Seizures associated with Lennox-Gastaut syndrome or Dravet syndrome
Whole plant extract	Mixed cannabinoids	Mixed administration (oral, spray, oil)	Not established
Whole plant (herbal cannabis/marijuana)	Mixed cannabinoids	Mixed administration (smoked, vaporised, edibles)	Not established

It is worth noting that therapeutic cannabis and associated extracts can have varying levels of THC and CBD concentrations, in addition to a range of other potentially therapeutic cannabinoids and constituents of the plant (cannflavins, terpenes, etc.). There are certain disorders or disease conditions where the ratio of THC to CBD is critical. For example, a high-CBD, low-THC formulation may be more beneficial for anxiety-related disorders, as CBD has anxiolytic properties [31]. Conversely, high-THC, low-CBD formulations are preferred when attempting to increase appetite in patients with AIDS due to the appetite stimulatory effects of THC, which CBD does not possess [32]. Additionally, the whole *Cannabis* plant or whole plant extract has been explored as a therapeutic option. This is due to the 'entourage effect', which is the idea that the potential beneficial therapeutic value of the *Cannabis* plant is due to the combination of many compounds working together to give the desired effect; that is, that the cannabinoids, terpenes, cannflavins, and other components of the plant all work together to give the patient the desired effect [33].

Medicinal cannabis can be administered in a variety of ways, including: smoking; consuming a capsule or tablet orally; eating food containing cannabis extract; absorbing oil or a lozenge oromucosally or sublingually; inhaling a vapour; or administering topically, rectally, or intravenously [34,35]. The most common method of administration is smoking and inhaling the combusting plant material. However, smoking is associated with impairment and abuse potential [34], in addition to the variability in individual smoking dynamics and differences in the cannabinoid composition of cannabis. Therefore, smoking cannabis is not a recommended route of administration for therapeutic preparations [36].

The oral route of administration is the most common choice for the therapeutic application of medicinal cannabis. This route overcomes many of the drawbacks of smoking or inhaling as it enables the control of the exact dose of cannabinoid(s) and maintains a stable serum concentration of the active ingredient over time, whereas smoking or inhaling leads to a fast peak in serum concentration of cannabinoids (the active ingredient), which decreases rapidly and cannot be sustained over time. Choosing the correct dose of orally administered cannabinoids can be difficult due to their initial metabolism in the liver; therefore, other routes that aim to avoid liver metabolism have been explored, such as oromucosal sprays (Sativex), which allow for a more consistent and titratable (i.e. adjustable) dose [37].

Research on the use of medicinal cannabis is limited due to the complexity of gaining access to the quantity, quality, and type of cannabis product necessary to address specific research questions. As governments around the world ease their regulations around cannabis access for research and medical treatments, reliable studies examining the therapeutic potential of medicinal cannabis for a range of disorders are needed in order to give policy-makers, clinicians, scientists, and patients the best possible evidence on which to base decisions around medicinal cannabis use. There is a need for rigorous, well-designed, and sufficiently statistically powered clinical trials investigating the therapeutic potential of medicinal cannabis and patient response [38].

1.2.3 Medicinal cannabis access around the world

The debate around medicinal cannabis and its derivatives is a controversial subject among clinicians and scientists; nevertheless, several governments have authorised the use of medicinal cannabis and its associated products.

Israel introduced medicinal cannabis reform in 1992, and soon after became a centre for scientific research and development of cannabis varieties. Israel created a subsidiary of the Ministry of Heath called the Israeli Agency on Medical Cannabis [39,40], which has the power to grant licences for cannabis cultivation, extraction, packaging, and distribution. In addition, it is responsible for allowing special clinicians to prescribe cannabis to patients suffering from severe pain, chemotherapy-induced nausea and vomiting, inflammatory bowel diseases, post-traumatic stress disorder (PTSD), and refractory epilepsy after conventional treatment options have been exhausted [41,42].

In 1996, California became the first state in the USA to legalise medicinal cannabis, sparking a trend that spread to a majority of states by 2016. As of early 2023, there are 47 states that have legislation allowing medicinal cannabis use in some form [43,44]. Medicinal cannabis access and use in the USA is restricted by geographical location and socioeconomic status, as not all private health insurers cover medicinal cannabis. These state regulations differ and range from only allowing acquisition of pharmaceutical medicinal cannabis to allowing cultivation of cannabis for personal use [45]. The health conditions that qualify for medicinal cannabis vary from state to state, as some states allow clinicians to use their own discretion when prescribing/recommending medicinal cannabis, while other states only allow prescriptions under a limited set of conditions [46].

Canada regulated the medical use of cannabis in 2001, and legalised recreational use in 2018. Health Canada enacted the Marihuana Medical Access Regulations in 2001, which were designed to enable access to cannabis for the relief of pain, nausea, and other symptoms related to serious, chronic, or terminal illness, where conventional symptom management approaches had failed [47,48]. Individual healthcare practitioners have the discretion to determine whether a patient should be treated with medicinal cannabis. Access is not limited to patients presenting with particular conditions. However, many provincial and territorial medical licensing bodies have published their own medicinal cannabis guidance for healthcare professionals. The new Cannabis Regulations introduced within the Cannabis Act in 2018 removed personal storage limits for patients, allowing all Canadian adults to store as much

cannabis as they want at home for personal use (adults may carry limited quantities of cannabis on their person in public places) [49–51]. As of early 2023, there is no dedicated register that monitors outcomes for patients receiving medicinal cannabis in Canada. Health Canada's post-market surveillance programme, the Canada Vigilance Program, collects and assesses reports of suspected adverse reactions to health products marketed in Canada [52]. Cannabis-based products are included in this remit. As of 2021, herbal medicinal cannabis (as distinct from licensed pharmaceutical cannabinoids available on a prescription basis (nabiximols and nabilone)) does not yet have its own drug identification number and is therefore not subject to the same financial coverage as prescription medications. However, some private insurance plans cover the cost of medicinal cannabis, as do a number of federal and provincial/territorial social assistance programmes. Indeed, medicinal cannabis can be claimed as a medical expense on income tax returns in Canada, providing some financial relief for patients [53]. There are some social assistance programmes that reimburse patients for the cost of medicinal cannabis, and others on a provincial level where those in financial need, those with disabilities, and those requiring long-term care are reimbursed.

In Italy, clinicians have been allowed to prescribe cannabis products, including synthetic cannabinoids, for therapeutic use since 1998 [54]. Access to medicinal cannabis is allowed and the Ministry of Health grants permits for cultivation for scientific and research purposes, in addition to authorising the production, manufacture, sale, export, transport, and purchase of medicinal cannabis. Currently, Italy allows plant-based cannabis medicines in addition to dronabinol, nabilone, and Sativex when conventional and standard therapies prove ineffective for chronic pain, multiple sclerosis, spinal cord injury, nausea from chemotherapy, AIDS symptoms, cachexia, and anorexia nervosa. Access is through prescription from a registered clinician [55,56].

In the Netherlands, the medical use of cannabis was legalised in 2003, and the government created the *Bureau voor Medicinale Cannabis*, or Office of Medicinal Cannabis. Patients can obtain medicinal cannabis, as well as pharmaceutical and non-pharmaceutical cannabis formulations, by prescription only. Medicinal cannabis is recommended in the Netherlands predominantly for chronic neuropathic pain, spasms and pain associated with multiple sclerosis, poor appetite or nausea and vomiting related to cancer or human immunodeficiency virus (HIV)/AIDS, therapy-resistant glaucoma, and Tourette's syndrome [57,58].

In Germany, a law that passed in 2017 allows medicinal cannabis to be included in the basic range of medications that health insurers must cover under certain restricted circumstances. Germany set up a national Cannabis Agency (*Cannabisagentur*) to oversee the new regulations [59,60]. According to a 2021 survey of physicians who prescribe medicinal cannabis in Germany, the most frequent reason for prescribing was for pain (73%), followed by spasticity (10%) and anorexia/wasting (6%). Dronabinol was most frequently prescribed (65%), followed by *Cannabis* flower (18%), Sativex (13%), cannabis extract (4%), and nabilone (0.3%) [61].

In 2018, Denmark introduced a medicinal cannabis pilot programme, allowing for the manufacturing and dispensing of cannabis products that had not undergone the usual clinical trials and authorisation processes [62]. There are two authorised medicines containing cannabis available in Denmark: Epidiolex and Sativex. Additionally, the Danish Medicines Agency has granted permits for two medicines containing synthetic cannabinoids: dronabinol and nabilone. Doctors may apply for a compassionate use permit to prescribe manufactured medicines that are not authorised for sale or dispensing in Denmark but that are available in other countries for use by a specific patient, or for a general permit for administration to a group of patients with a specific condition [63]. Access to cannabis-based products is not limited to patients presenting with particular conditions; however, in its guidelines for doctors, the Danish Medicines Agency provides a list of patient groups and clinical indications that could be considered for

cannabis-based products, and states that doctors should not, in principle, prescribe cannabis-based products outside these indications and should only prescribe such products when conventional symptom management approaches have proven insufficient [64]. At present, there is no dedicated register that monitors outcomes for patients receiving medicinal cannabis in Denmark. Doctors are obligated to report all suspected adverse reactions involving medicinal cannabis to the Danish Medicines Agency. Doctors can apply to the Danish Medicines Agency for reimbursement for individual patients for authorised medicines, for medicines accessed through a compassionate use permit/dispensing permit, and for magistral preparations (medicinal products prepared in a pharmacy for an individual patient in accordance with a prescription form). A special reimbursement scheme was established for products covered by the medicinal cannabis pilot programme, whereby patients can be reimbursed for 50% of the cost of cannabis-based products.

In 2018, the United Kingdom (UK) rescheduled cannabis within the Misuse of Drugs Regulations 2001 from Schedule 1 (considered to have little or no therapeutic value) to Schedule 2 (can be legally possessed only by those who hold a prescription) [65]. The only way to access medicinal cannabis in the UK is through prescription, either privately or through the National Health Service (NHS). Only specialists are permitted to prescribe unlicensed cannabis-based products for medical use. Individual specialist doctors have discretion to determine whether a patient should be treated with medicinal cannabis and can offer unlicensed products to a patient with special needs that are unmet by conventional licensed medicines. Access is, in principle, not limited to patients presenting with named conditions. Three cannabis-based medicines have been approved in the UK as licensed medicines for administration to patients with specific conditions; these are Epidiolex, nabilone, and Sativex [66]. Unlicensed cannabis-based products for medicinal use are also available on a prescription basis from specialist doctors, after all existing licensed and off-label medicine options have been exhausted. The NHS Patient Registry for Cannabis-Based Products was established in order to collect a uniform dataset for NHS patients who have been prescribed licensed or unlicensed cannabis-based products for medicinal use for any indication, in order to track the health impacts associated with the use of such products over time. In addition, there are also some private and independent registries [67]. Anyone, including healthcare professionals or members of the public, can report side effects and adverse events related to medicinal cannabis to the Medicines and Healthcare products Regulatory Agency. At the level of local NHS trusts, medicine management committees decide whether to allow licensed cannabis-based medicines and unlicensed cannabis-based products for medicinal use to be prescribed and funded at particular NHS hospitals. This has led to inconsistencies across hospitals and the existence of a ‘postcode lottery’ for access to both licensed cannabis-based medicines (such as Sativex (nabiximols)) and unlicensed cannabis-based products for medicinal use under the NHS.

In Australia, medicinal cannabis use is legal following the passing of the Narcotic Drugs Amendment Act 2016. In 2019, additional laws were passed which allow personal use and cultivation [68–71]. The Office of Drug Control, under the Australian Department of Health and Aged Care, controls the issuing of licenses to growers and regulates medicinal cannabis crops. Clinicians may offer medicinal cannabis products to patients after notifying the Office of Drug Control and obtaining permission from the federal government. In 2018, New Zealand enacted the Misuse of Drugs (Medicinal Cannabis) Amendment Act 2018 [72]; however, recreational use legislation is still pending. The New Zealand Government Inquiry into Mental Health and Addiction has strongly recommended the decriminalisation of drug use in general [73].

Latin America is considered the world leader in the promotion and adoption of policies allowing access to medicinal cannabis [40]. Uruguay was a pioneer in this regard, as it was an early adopter of completely legalising the cannabis market for scientific research, medicinal cannabis, and industrial and recreational use. However, access to pharmaceutical-grade medicinal cannabis is only possible through submission of

an application to the Ministry of Public Health and, if accepted, the price remains high. In Chile, patients can access medicinal cannabis with a prescription [74]. Elsewhere in Latin America, Colombia has also made progress with medicinal cannabis regulations, whereby the national government retains control over the market and grants licences to private groups for production, manufacturing, exporting, transformation, and research [75,76]. There is also legislation and access to medicinal cannabis programmes in Argentina, Bolivia, Brazil, Jamaica, Mexico, and Peru.

Asian countries continue to have restrictive drug policies, and many countries, such as Cambodia, Japan, Nepal, Pakistan, and Vietnam, still prohibit the use of medicinal cannabis [40,77]. In the Philippines, some progress has been made towards medicinal cannabis reform: in September 2016, the House of Representatives approved the Compassionate Medical Cannabis Act, which allows patients who have prior authorisation from a doctor to access medicinal cannabis in specialised treatment centres [78,79]. However, the proposal did not pass in the senate, and access is still prohibited as of early 2023 [77]. Elsewhere in Asia, there has been some development in terms of medicinal cannabis regulation. In 2019, Thailand approved the use of medicinal cannabis for research and for treating patients [80]. In India, since 2022, cannabis has been permitted for medical and research purposes only [81].

1.3 Policy context in Ireland

In January 2017, the Health Products Regulatory Authority, at the request of the Minister for Health, convened an expert working group to review the potential medical use of cannabis. The outcome of this review was a report titled *Cannabis for Medical Use: A Scientific Review* [82].

The Health Products Regulatory Authority advised that any programme to make cannabis available for medical purposes should recognise patient need but also be evidence based. It advised that access to cannabis should be permitted under a controlled access programme for the treatment of patients with one of three stated conditions who have failed to respond to all other previous treatments, namely:

1. Spasticity associated with multiple sclerosis resistant to all standard therapies and interventions while under expert medical supervision
2. Intractable nausea and vomiting associated with chemotherapy, despite the use of standard anti-emetic regimens while under expert medical supervision, and
3. Severe, refractory (treatment-resistant) epilepsy that has failed to respond to standard anticonvulsant medications while under expert medical supervision.

This recommendation was made on the basis that there was “at least modest evidence that cannabis may be effective” for these conditions [82] p66. Clinical guidelines for the medical use of cannabis were published in 2019 [83]. The legislation to establish the Medical Cannabis Access Programme was also enacted that year. The Medical Cannabis Access Programme was added to the Health Service Executive National Service Plan 2021, and is currently operated by the Primary Care Reimbursement Service.

The Department of Health has received many representations and communications seeking to expand the Medical Cannabis Access Programme’s scope to include other conditions, including chronic pain, fibromyalgia, anxiety, and endometriosis, among others. There is significant media, political, and public interest in this topic.

1.3.1 Policy considerations

There exists a clear need for transparent and evidence-based protocols to be in place for clinicians in order for them to prescribe optimal treatment plans for their patients. Development of Ireland’s Medical Cannabis Access Programme has aided clinicians and patients alike in accessing medicinal cannabis for

specific conditions. There are three main areas for policy-makers to consider when introducing medicinal cannabis regulations: easily accessible and evidence-based prescribing guidelines and support for clinicians, an effective and easily accessed system for monitoring outcomes and safety at a national level, and sufficient funding mechanisms and equity of access.

In Canada and Denmark, professional associations have raised concerns that the existing systems in those countries place doctors in a difficult position: doctors have been given authority to prescribe cannabis-based therapies in the context of substantial demand from the general public, but there is an absence of training, clear clinical guidance, or evidence to support prescribing for most clinical conditions [84–86]. In the UK, concerns about medicolegal liability and an insufficient evidence base to support prescribing unlicensed products have led to a situation where very few prescriptions are being issued and public funding for prescriptions varies by area of residence [87].

The correct systems need to be in place to adequately monitor outcomes and safety when prescribing medicinal cannabis. National-level voluntary reporting systems for safety outcomes (side effects and adverse events) associated with medicinal cannabis are well established in Canada and the UK, as these are incorporated into existing monitoring systems for all medicines and medical devices. In other countries, such as Denmark, a dedicated reporting system for medicinal cannabis has been established. However, these types of reporting systems rely on spontaneous and voluntary reporting rather than on systematic monitoring, and adverse events may be under-reported or selectively reported. National-level monitoring systems for outcomes associated with medicinal cannabis more generally are lacking, with registries more likely to be established and managed by private industry. Funding models (including reimbursement schemes, public health insurance, private health insurance, means-testing, and upfront out-of-pocket payments) vary internationally, and equity of access to both licensed and unlicensed products is a key challenge and a limiting factor for prescribing medicinal cannabis.

1.4 Purpose of this review

This evidence review, examining the efficacy and safety of medicinal cannabis for a range of conditions, has been prepared by the HRB Evidence Centre with the aim of supporting the 2022 review of the Medical Cannabis Access Programme, including decisions on what conditions should be included in the Medical Cannabis Access Programme. The synthesis will also be used to respond to the many communications the Department of Health receives each year on the prescribing of cannabis-based products, and will support the Department's position as to what clinical indications are suitable for access to cannabis-based products.

1.5 Review questions

1. What is the evidence for the clinical efficacy of medicinal cannabis in the treatment of the conditions/clinical indications of interest among adults?
2. What is the evidence for the safety of medicinal cannabis in the treatment of the conditions/clinical indications of interest among adults?

The conditions of interest included but were not limited to:

- Inflammatory disorders, including endometriosis
- Sleep disorders
- Parkinson's disease
- Anxiety

- Depression
- Severe refractory epilepsy

The clinical indications of interest included but were not limited to:

- Chronic pain
- Cancer-related pain and appetite-related symptoms
- Appetite-related symptoms due to HIV/AIDS
- Spasticity associated with multiple sclerosis
- Nausea/vomiting associated with chemotherapy

The above conditions/clinical indications were selected through discussion with the Department of Health and specified in the review protocol. Other conditions/clinical indications were included in the review if they were found in the literature.

2 Methods

2.1 Review design

This evidence review comprises an overview of reviews (umbrella review).

We chose an overview of reviews for two reasons. First, our scoping searches indicated that the literature is already populated with a number of systematic reviews that are relevant to our review questions. The available reviews vary in design and conduct, and comprise both Cochrane and non-Cochrane reviews. Therefore, it would be inappropriate to undertake an original systematic review while ignoring the existing evidence base in systematic reviews. According to Aromataris *et al.,* "if current, multiple, good quality, systematic reviews exist about a given topic or question, any reviewer should reconsider the need to conduct yet another review addressing the same issue. Rather, these [existing reviews] may be the basis to conduct an Umbrella Review [overview of reviews] and summarise or synthesise the findings of systematic reviews already available" [88] p365.

Second, to inform policy decisions around the scope of the Medical Cannabis Access Programme in Ireland, the Department of Health requires information about the efficacy and safety of medicinal cannabis for symptom management in a very wide range of conditions/clinical indications. The efficiencies offered by our selected approach allow for this review to cover the full scope of conditions of interest, which would not be possible with a traditional systematic review in the available time.

2.1.1 Definition of an overview of reviews

There have been numerous attempts to define the parameters of an overview of reviews. However, a recent consensus has emerged to agree on the key elements. The definition of 'overview of reviews', as cited in Gates *et al.* [89] and developed by the Cochrane Collaboration [90], comprises five key elements. An overview of reviews:

1. Contains a clearly formulated objective designed to answer a specific research question, typically about a healthcare intervention
2. Intends to search for and include only systematic reviews (with or without meta-analyses)
3. Uses explicit and reproducible methods to identify multiple systematic reviews that meet the overview of reviews' inclusion criteria, and to assess the quality/risk of bias of these systematic reviews
4. Intends to collect, analyse, and present the following data from included systematic reviews: descriptive characteristics of the systematic reviews and their included primary studies; risk of bias of primary studies; quantitative outcome data; and certainty of evidence for predefined, clinically important outcomes, and
5. Discusses findings as they relate to the purpose, objective(s), and specific research question(s) of the overview of reviews, including a summary of the main results, the overall completeness and applicability of the evidence, the quality of the evidence, potential biases in the overview process, and agreements and/or disagreements with other studies and/or reviews.

2.1.2 Overview of reviews as an evidence-based product for policy-makers

Overviews of reviews have become feasible mainly due to the increasing volume of systematic reviews that are published on a regular basis in many subject areas. It is estimated that between 11 and 22 systematic reviews are produced daily; according to Aromataris *et al.*, "The number of systematic reviews published to accommodate the demands of evidence-informed decision-making has increased markedly

over the past two decades. One estimate [in 2015] suggests that 11 systematic reviews are published every day" [91] p133. According to Hunt *et al.*, it was estimated that around 22 new systematic reviews were published every day in 2018 [92].

According to Gates *et al.*:

> It is estimated that 8,000 systematic reviews were published in 2014, more than three times the annual publication rate recorded in 2004. Around the turn of the century overviews of reviews, which compile data from multiple systematic reviews, emerged to deal with the growing volume of published systematic reviews. By taking advantage of existing syntheses, overviews of reviews can create efficiencies and answer broader research questions. [89] p2

Systematic reviews are a recognised evidence-based product and are often used by policy-makers in their deliberations and decision-making. As systematic reviews are the exclusive unit of analysis in overviews of reviews, this means that overviews of reviews can contribute to evidence-based policy-making. According to Aromataris *et al.*, "With the ever-increasing number of systematic reviews published daily, umbrella reviews [overviews of reviews] have a clear role in evidence-based healthcare and evidence-informed decision-making" [91] p139.

2.1.3 Purpose of overviews of reviews

According to Aromataris *et al.*:

> The principal reason for the conduct of an umbrella review [overview of reviews] is to summarize the evidence from multiple research syntheses…. Umbrella reviews are conducted to provide an overall examination of the body of information that is available for a given topic, and to compare and contrast the results of published systematic reviews. The wide picture obtainable from the conduct of an umbrella review is ideal to highlight whether the evidence base around a topic is consistent or contradictory, and to explore the reasons for the findings. Furthermore, an umbrella review allows ready assessment of whether review authors addressing similar review questions independently observe similar results and arrive at generally similar conclusions. [91] p133

According to McKenzie and Brennan:

> The purposes of overviews include (but are not limited to) mapping the available evidence, examining the effects of different interventions for the same condition or population, examining the effects of the same intervention for different conditions or populations (also referred to as multiple-indication reviews) or examining reasons for discordance of findings and conclusions across reviews. Overviews are more suited to some purposes than others, and careful consideration of whether they are the appropriate type of review (overview of systematic reviews or systematic review of primary studies) is required. [93] p1

2.1.4 Our overall methodological approach to undertaking this work

We based our methodological approach on the guidance published by Gates *et al.* on anticipating and addressing the main challenges posed for reviewers when embarking on an overview of reviews [89].

Each step involved in designing and implementing an overview of reviews requires careful consideration by reviewers. Decisions taken should be based on evidence, as such decisions will ultimately affect the credibility of the findings. According to McKenzie and Brennan, "The choice of methods used in overviews may affect the trustworthiness of the findings, coverage of the evidence, and usability and usefulness of

the overview, amongst other outcomes. Decisions as to which methods to use are best informed by methods research, along with theoretical considerations" [93] p2–3.

2.1.5 Inclusion of non-Cochrane systematic reviews

According to Gates *et al.*:

> The decision about whether to only include Cochrane systematic reviews or to also include non-Cochrane systematic reviews can be a balance between ensuring quality and coverage of all-important interventions. Although some non-Cochrane reviews can be of poorer methodological quality and have less detailed reporting, Cochrane reviews alone may not cover all relevant interventions or be adequately up to date. If authors choose to include both Cochrane and non-Cochrane systematic reviews, it is likely that they will need to deal with primary study overlap. However, this may occur even if only Cochrane systematic reviews are included. [89] p15

We have used the decision tool developed by Pollock *et al.* to inform our decisions on including non-Cochrane reviews in our overview of reviews [94]. This decision tool contains four questions:

1. Do Cochrane systematic reviews likely examine all relevant intervention comparisons and available data?
2. Do the Cochrane systematic reviews overlap?
3. Do the non-Cochrane systematic reviews overlap?
4. Are researchers prepared and able to avoid double-counting outcome data from overlapping systematic reviews by ensuring that each primary study's outcome data are extracted from overlapping systematic reviews only once?

Guidance is provided to help researchers answer each question, and empirical evidence is provided regarding the advantages, disadvantages, and potential trade-offs of the different inclusion decisions.

We have included both Cochrane and non-Cochrane reviews in this overview of reviews in order to better capture research on a broad scope of health outcomes and conditions, as required by the review questions.

2.2 Protocol and reporting guidelines

A full protocol was prepared for this review, which was registered in advance on PROSPERO (reference number: CRD42022384405) [95]. The review is reported in accordance with the Preferred Reporting Items for Overviews of Reviews (PRIOR) guidelines; please see Appendix A for the PRIOR checklist [96].

2.3 Eligibility criteria

Eligibility criteria for this review are outlined in Table 2, including population, intervention, comparison, and outcome (PICO) inclusion criteria.

Regarding population, the scope of this overview of reviews was limited to adult patients only, as considerations for adolescent and paediatric patients present different complexities and access may be channelled through separate systems and healthcare providers. Syntheses of data from paediatric patients aged 12 years and under were excluded. Syntheses from systematic reviews with mixed adult and adolescent (aged 13–17 years) patients were excluded if adolescents made up 20% or more of the sample.

Regarding outcomes, misuse or diversion of prescribed products were not included under adverse events and were not examined in this review. We believe that a review of primarily randomised controlled trials

(RCTs), in which supply of medicinal cannabis is tightly controlled and follow-up is generally only short- or medium-term, will not capture these outcomes as effectively as other study designs (e.g. patient registries). Therefore, we have chosen not to explore these outcomes, rather than present only a narrow and potentially unrepresentative slice of data on misuse or diversion.

The outcomes listed were intentionally wide-ranging so as not to exclude any relevant outcomes that may be examined in the literature; for the same reason, the conditions/clinical indications of interest were considered in advance but not specified in our eligibility criteria or in our search terms. As characterised by Lunny *et al.*, "Overviews of systematic reviews synthesise the results of multiple systematic reviews. Overviews are typically broader in scope than systematic reviews and may examine different interventions for the same condition, the same intervention for different conditions, or the same intervention for the same condition but focusing on different outcomes" [97] p2.

Regarding study design, we followed the definition of a systematic review specified by Page *et al.* in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement: "a review that uses explicit, systematic methods to collate and synthesise findings of studies that address a clearly formulated question" [98] p3.

Regarding date, the date range of 2010–2023 was chosen in order to capture systematic reviews from approximately the last 12 years. Based on expert guidance, we expected that this would yield primary research conducted in the last 30 years [99], which comprehensively covers the period since the first medical cannabis access programmes were launched.

Regarding language, only English-language reviews were included in the final analysis. The databases searched (see Section 2.4.3 and Appendix B) index primarily English-language material. No language limit was used in the search strategy. Relevant reviews in non-English languages were excluded during full-text screening and are listed among the excluded studies in Appendix C.

Table 2 Eligibility criteria

Domain	Inclusion	Exclusion
Population	Adult patients (aged 18 years and over) Adolescent patients (aged 13–17 years), provided that they comprise no more than 20% of the sample	Paediatric patients (aged 12 years and under) Populations of unspecified age Animals
Intervention	Cannabis-based medicinal products containing natural or synthetic CBD or THC or CBD or THC derivatives	Cannabis for recreational use Cannabis for medicinal use without prescription/medical supervision Systematic reviews including interventions not focused on cannabis-based medicinal products
Comparator	Other cannabis-based medicinal products/doses/regimens Placebo Any relevant alternative treatment Usual/standard care No treatment	Systematic reviews of studies with no comparator
Outcome	Reduction in relevant symptoms Changes in quality of life Relevant adverse events Withdrawal/complications	Patient satisfaction
Study design	Systematic reviews of RCTs and/or prospective longitudinal cohort studies	Systematic reviews of non-randomised trials

Domain	Inclusion	Exclusion
		Systematic reviews based on searches of only one bibliographic database Systematic reviews that do not present a full search strategy Systematic reviews without a quality assessment/risk of bias assessment of their included studies, or systematic reviews that used an inappropriate tool for assessment Systematic reviews of descriptive epidemiological studies or case-control studies Systematic reviews in which it is not possible to extract data based on outcomes of interest, or systematic reviews in which it is not possible to extract data based on study designs of interest Narrative (non-systematic) reviews Primary studies
Date	2010 to January 2023	Pre-2010
Language	English	Non-English languages

2.4 Identifying research evidence

2.4.1 Approach to searching

A broad search approach was employed for this overview of reviews, in line with guidance by Aromataris and Munn [99]. The search was designed with the aim of prioritising sensitivity (capturing as much relevant material as possible, at the cost of including irrelevant material) over specificity (capturing only relevant research, at the cost of excluding some relevant material). The expected capture of large amounts of irrelevant research was to be managed using a multiple-stage double-blind screening process, relying on the researchers' ability to recognise relevant research even with general or unclear indexed terminology. The use of citation chaining/reference chasing and searches for grey literature or non-traditionally published research (that is, research published outside of the indexed journal article format, such as reports, preprints, or review protocols) would supplement the searches of databases.

Cooper *et al.* (2018) suggest that a specific definition of a comprehensive search has not yet been agreed in the current guidance [100], but it was expected that using searches of databases, grey literature sources, and reference/citation/protocol chasing would satisfy the general requirements of a comprehensive literature search. An English-language limit was used in this review. This naturally imposes a limit on the comprehensiveness of the research captured; however, the time frame of the project and the language abilities of the authors did not allow for inclusion of non-English results. The risk of misinterpreting research results while using an automated translator was a concern, given the variability of the terminology used across this field.

In the *JBI Manual for Evidence Synthesis*, Aromataris and Munn note that the inclusion of reviews published in the previous 5–10 years will be likely to capture primary research published in the previous 30 years [99]. For this reason, an initial date limit of 2010–2022 was used for the searches carried out in 2022. This date limit was then extended to the current year for the follow-up searches in January 2023,

for a date range of 2010–2023. Using these dates as search limits was expected to capture the majority of the body of research published since the first medicinal cannabis access programmes were introduced. Searches were carried out by the information specialist (CL), in consultation with the review team.

2.4.2 Literature search concepts

The primary concept of the literature search was cannabis (any nomenclature) and this concept was limited by a study design concept: that of reviews (see Figure 1). The search did not seek to only capture research referring to medicinal cannabis in the searchable fields, as research on medicinal uses of cannabis may not refer specifically to medicinal marijuana/cannabis. Similarly, the search did not focus only on systematic reviews, but included any type of review. The reasoning for this was that a wide range of terminology is used for the publication type 'systematic review', and that some reviews may be called 'systematic' but would more accurately be considered literature reviews or evidence summaries. Similarly, a review may not include the word 'systematic' in its metadata or searchable fields but could still be a systematic review. The appropriateness of including a review could be more accurately examined within the results screening process.

As the purpose of this review was to examine the efficacy and safety of medicinal cannabis in adult populations for the management of any condition or clinical indication, the scope of the literature was left deliberately wide. No specific conditions or clinical indications were included in the search, as this could limit the search. A number of conditions and clinical indications for which medicinal cannabis has been used were noted by the Department of Health as being of particular interest (including inflammatory disorders, sleep disorders, Parkinson's disease, anxiety, depression, severe refractory epilepsy, chronic pain, pain- or appetite-related symptoms due to cancer, appetite-related symptoms due to HIV/AIDS, spasticity associated with multiple sclerosis, and nausea/vomiting associated with chemotherapy). It was, however, expected that there may be other conditions for which medicinal cannabis has been used outside of this list noted by the Department of Health, and narrowing the search to only these concepts would miss other unlisted conditions or clinical indications.

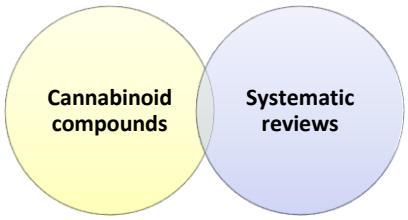

Figure 1 Overview of reviews literature search concepts

2.4.3 Information sources

To capture as much relevant research as possible, comprehensive searches were conducted of 7 bibliographic databases (MEDLINE, Embase, CINAHL Complete, SocINDEX with Full Text, PsycINFO, SciELO (Scientific Electronic Library Online, and LILACS (Latin American and Caribbean Health Sciences Literature), as well as 10 review resources, 3 preprint resources, 3 search engines, 1 open access resource aggregator, and 1 topic-specific website. The databases selected for the literature search were intended to cover as wide a range of aspects of the topic as possible in the time frame available. These included medical, nursing, sociology, and psychology bibliographic databases; databases including non-English research; databases and resources specifically covering reviews (systematic or otherwise); preprint servers; search engines; and research aggregators.

Clinical databases searched included Ovid MEDLINE, Ovid Embase, Ovid PsycINFO, EBSCO CINAHL Complete, and SocINDEX. Databases emphasising non-English research included LILACS (Latin American and Caribbean Health Sciences Literature) and SciELO (Scientific Electronic Library Online). Databases and resources focusing on publishing or indexing reviews included the Cochrane Library (Wiley), the Campbell Library, Epistemonikos, the Agency for Healthcare Research and Quality (AHRQ) Systematic Review Data Repository (SRDR), the Database of Abstracts of Reviews of Effects (DARE), the Database of Promoting Health Effectiveness Reviews (DoPHER), Joanna Briggs Institute (JBI) Evidence Synthesis journal, McMaster University's Health Evidence database, and the International HTA Database. PROSPERO was included as a resource for review protocols in the main searches (rather than as a supplemental search) so that the results could be screened early in the process, as were the Google Scholar, Bielefeld Academic Search Engine (BASE), and DuckDuckGo search engines. Core.ac.uk (the open access research aggregator managed by Jisc and the Open University) was also used, as it can capture reports on a wide range of topics published in non-traditional routes. Preprint servers were also included in the search (Osf.io, Research Square, and medRxiv/bioRxiv). A topic-specific website was included in the search – that of the International Alliance for Cannabinoid Medicines (IACM), however, it was expected that search engines would also capture material from other topic-specific websites. See Appendix B for more details on the searches.

The resources used for follow-up searches as part of the supplemental search process included Ovid MEDLINE, the Wiley Cochrane Library, Epistemonikos, and short searches in Google Scholar. This stage of searching also included reference and citation chasing (using the reviews that were included at the initial full-text screening stage) as well as protocols identified from the initial screening process. Some of the initially included reviews were subsequently excluded following deeper reading or during data extraction. See Section 2.4.6 for further details on supplemental search methods and Appendix B for search strategies.

2.4.4 Search terminology

Search terminology was based around the primary search concept of cannabis and a limit/hedge of publication type (reviews). Where controlled vocabulary was available (e.g. Medical Subject Headings (MeSH)), relevant terms were included in the search. For all searches, keywords/'free terms' were used. There is some variation in what terminology and phrasing was possible for different search resources, as some search resources do not allow for complex searching.

Scoping searches for relevant terminology were carried out in Ovid MEDLINE. The online tool PubReMiner and the standalone MeSH Browser were used to source relevant MeSH terms [101,102]. The initial search was constructed in Ovid MEDLINE using a combination of MeSH terms and keywords.

The terminology was not restricted to medicinal cannabis alone, as research may not refer specifically to medicinal cannabis in the indexed fields. After scoping search development work, some cannabis keywords were linked with therapeutic terms (using the Boolean operator 'AND' rather than phrase searches) in order to reduce the amount of purely chemical and non-clinical research returned by keyword searching. This was not done for MeSH index terms. The type of terminology was as broad as possible and included variations of terms such as 'cannabis', 'marijuana', 'THC', and 'CBD', as well as proprietary terms and some slang terms for these agents. Truncation was used (e.g. 'cannabin*' or 'cannabid*') in order to capture all variations of the root word. The initial search was carried out in Ovid MEDLINE, and was translated for use in other databases. Controlled vocabulary was used if it was available (e.g. MeSH terms for MEDLINE and the Wiley Cochrane Library).

There is a range of terminology for cannabis (medicinal or otherwise) that would be of use in this overview. As many of these terms were included as were captured in the scoping searches and other

search resources; however, this list was not exhaustive. There may be other terms and abbreviations (including misspelled terms) that could have captured relevant work. However, all efforts were made to run as broad a search as possible. Some examples of the variations in terminology (including colloquial terms and proprietary terms, where identified) are listed below:

> "Marijuana/Marihuana"; "Cannabis/cannabis"; "Cannabinoids"; "Exocannabinoids"; "Phytocannabinoids"; "Cannabidiol"; "Cannabinol"; "CBD", "THC", "THCVS"; "Tetrahydrocannabinol"; "C. indica"; "C. sativa"; "C. ruderalis"; "Cannabaceae"; "Dronabinol"; "Marinol"; "Syndros"; "Nabiximols"; "Sativex"; "Tetrabinex"; "Nabidiolex"; "GW 1000-02"; "GW-1000-02"; "GW 1000"; "SAB 378"; "Nabilone"; "Cesamet"; "Canemes"; "Epidiolex"; "Epidyolex"; "Dexanabinol"; "HU-211"; "cannabicyclol"; "cannabichromene"; "cannabigerol"; "Tilray Oral Solution"; "Bedrobinol"; "Transvamix"; "VER-01"; "Bedrocan"; "Bediol"; "Bedica"; "Bedrolite"; "Aurora Sedamen Softgels"; "Namisol"; "CannEpil"; "hemp"; "hash"; "hashish"; "ganja"; "bhang"; "weed"; "joint"; "Maconha"; "dagga"; "marihuaanat"; "marihuwana"; "marigwana"; "mariuana"; "tshuaj maj"; "marihuana"; "marijuana"; "11-OH-THC" or "11-Hydroxy-THC"; "11-Hydroxy-delta9-tetrahydrocannabinol"; "11-Hydroxyhexahydrocannabinol"; "11-OH-delta9-THC"; "11-Hydroxycannabinol (11-OH-CBN)"; "delta-1-Tetrahydrocannabinol"; "delta(1)-Tetrahydrocannabinol"; "delta1-tetrahydrocannabinol"; "1-tetrahydrocannabinol"; "delta(1)-THC"; "delta1-THC" or "1-THC"; "delta-8-tetrahydrocannabinol"; "delta(8)-tetrahydrocannabinol"; "delta8-tetrahydrocannabinol"; "8-tetrahydrocannabinol"; "delta(8)-THC"; "delta8-THC"; "8-THC"; "delta-9-tetrahydrocannabinol"; "delta(9)-Tetrahydrocannabinol"; "delta9-tetrahydrocannabinol"; "9-tetrahydrocannabinol"; "delta(9)-THC"; "delta9-THC"; "Delta-9-THC"; "9-THC"; "(–)-trans-Δ9-tetrahydrocannabinol".

For database searches, comprehensive search terms were used. For resources with more limited search functions (for example, where Boolean searches or use of multiple terms were not effective or possible), more restricted searches with fewer terms were carried out. A full description of the searches, including the specific search terms used and how they were combined, is given in Appendix B.

2.4.5 Search limiters

The primary study limiter for this search was study design; for an overview of reviews, the unit of study is systematic reviews. To this end, a block of search terms relating to systematic reviews was included in the search where possible – not all search resources allow for this type of complex searching, and some resources only included reviews so that a study design limiter was not required. A date limit of 2010–2022 was imposed for searches carried out in 2022, and 2010–2023 for searches carried out in 2023. Only English-language reviews were eligible for inclusion in this overview of reviews. The searches did not limit results by language, but non-English-language research was excluded in the screening process. For the primary search topic (medicinal cannabis), controlled vocabulary terms were not limited.

Some general keywords relating to cannabis returned huge numbers of results that were irrelevant to this overview. Therefore, after testing, the search level was retained at the 'multipurpose' search or '.mp.' level for the Ovid,databases used in the search. However, a wide range of terms relating to therapy (also searched at '.mp.' level) were added to the primary search terms. This was in order to exclude the large numbers of papers dealing with chemical analysis, *Cannabis* growing, drug development, and other such topics that did not meet the PICO inclusion criteria. Some of the terms used returned many confounding results as they have several meanings (e.g. 'weed' or 'joint'), and these were also searched in combination with terms relating to therapy, so as to return research on therapeutic or clinical aspects of the topic. Many of the acronyms/abbreviations searched also have several meanings and, given the very large number of search results, these were also limited by exclusion of the non-relevant terms (e.g. 'CBD' also returned many results related to 'cortical bone density' and 'common bile duct'). In testing the exclusion

of these terms as keywords, it was found that cannabis research carried out using such terms was also captured by the MeSH terms for cannabis, meaning that their exclusion did not exclude relevant research, as far as could be ascertained.

2.4.6 Supplemental searching

To supplement the primary searches, citation chaining – which comprises 'reference chasing', citation chasing, and follow-up of protocols, conference abstracts, posters, and overviews of reviews – was carried out on 14–15 January 2023. Once the initial full-text screening of results was carried out, 53 reviews were considered for inclusion (this number was later reduced on further examination of the reviews). The reference lists/bibliographies of these 53 reviews were extracted using Dimensions (the database by Digital Science) and AnyStyle.io [103,104]. As this process is not completely without error, the extracted lists were compared with the published reference lists in these reviews, and amendments were made as required. Citations of the 53 reviews were extracted using Google Scholar. These citations included duplications, incomplete citations, and fragments of references.

In the screening process, an exclusion category was used for potentially relevant review protocols, conference abstracts, and posters. According to the inclusion criteria, these publication types were not to be included and could not be considered as complete reviews as they do not contain sufficient detail such as search strategies, quality assessments etc. However, they could point to a more complete published version of the review they outline and so could be included in the supplemental searches and followed up to capture any relevant reviews associated with them. These potentially relevant protocols and other study types were therefore included for follow-up and screened as part of the supplemental search process.

Follow-up searches in four resources (Ovid MEDLINE, Epistemonikos, the Cochrane Library, and Google Scholar) were also carried out in January 2023. These supplemental searches and follow-up of references captured 8,516 results, deduplicated to 5,571 results.

Some searches traditionally regarded as 'grey literature' searching, such as search engines and protocol searches, were included within the main searches for ease of screening. It was thus not necessary to carry out these searches separately as part of the supplemental searching process.

2.4.7 Search dates

Scoping searches on the topic were carried out in May 2022 prior to the formal searches. Formal searches of bibliographic databases and other resources were carried out in June 2022. Supplemental searches (follow-up of references, citations, protocols, conference abstracts, and other relevant material, in addition to searches of Ovid MEDLINE, the Cochrane Library, Epistemonikos, and Google Scholar) were carried out in January 2023.

2.4.8 Search data management

Zotero (version 6.0.8) was used to store and manage bibliographic data for this project [105]. Search results were exported to Zotero from the relevant databases and resources and were screened in EPPI-Reviewer Web [106]. At the full-text stage of screening, PDFs of the relevant papers were uploaded to EPPI-Reviewer Web. Screening at the title and abstract stage was performed using the Priority Screening tool in EPPI-Reviewer Web, which assisted in managing the large number of records to be screened. At all other stages of screening, Comparison mode or Normal mode screening (non-Priority screening) was used.

2.5 Screening of search results

A multistage screening process was used to screen the results of literature searches. This included double-blind screening at the title and abstract and the full-text stages. Multiple screens of results were conducted at each stage (e.g. two title and abstract screening stages). An overview of the results for each stage is presented in the PRISMA flow chart in Figure 3 (see Section 3.1), and full details of each stage are given in Appendix B.

2.5.1 Screening on title and abstract

The first stage of screening was to remove duplicates from the initial search results (N=25,888). A total of 11,252 duplicates were removed (Stage 1 of the screening process in Appendix B). This process was done in Zotero.

Stage 2 of the screening process, requiring several steps, involved screening the titles and abstracts of the 14,636 records from Stage 1. This was a multistage process, where the deduplicated results of the primary searches were screened on title and abstract, deduplicated, screened again on title and abstract, and then deduplicated again. Title and abstract screening was carried out by four screeners (KL, OC, DP, CL) in a double-blind process using the comparison screening mechanism provided by EPPI-Reviewer Web.

The codes used for title/abstract screening were:

- Include on title and abstract
- Exclude on study design
- Exclude on relevant protocol/conference abstract/poster
- Exclude on intervention
- Exclude on age
- Exclude on date
- Exclude on language (in scope)
- Exclude on language (out of scope), and
- Exclude on duplicate.

Full details, including tables of inclusion and exclusion results, are provided in the screening section of Appendix B.

Papers excluded on language were screened separately into 'Language out of scope' and 'Language in scope' because, while it was beyond the remit of this project to examine non-English-language papers, it was of interest to note any relevant non-English-language work and to acknowledge the existence of a body of work on the topic in languages other than English.

A code for 'Exclude on in scope: protocol/conference abstract/poster' was used so that any such work could be tracked in the supplemental search process. For example, where a protocol was screened as potentially being relevant with respect to the PICO of this overview of reviews at the title and abstract screening stage, it would be followed up in the supplemental search process.

An 'Exclude on duplicate' code was used in the first stage of title and abstract screening (Stage 2a) but, on discussion, it was found to be more effective to carry out screening for duplicates outside of the double-screening process by examining the final list of records included for similarities. Within the double-screening process, it is possible to miss duplicates if one of the duplicate records is distributed to one set of screeners, and the other duplicated record is distributed to the other group.

The Priority Screening mode of EPPI-Reviewer Web was employed for Stage 2a of screening. With this mode of screening, a graph of the numbers of included and excluded records is recorded. The EPPI-Reviewer Web system learns to recognise relevant records from the information provided in the titles and abstracts of the records (for example, the system recognises terms relating to study design, intervention, or age). The codes used for this iteration of Priority Screening were:

- Include on title and abstract
- Exclude on study design
- Exclude on study design: in-scope protocol/conference abstract/poster
- Exclude on intervention, and
- Exclude on age.

The mode of reconciliation of discrepant decisions used for this project was 'Reconciliation mode: Multiple: auto complete (include/exclude level)'. Reconciliation was carried out regularly throughout this screening process. For items differing by type of exclude code (e.g. 'Exclude on study type' compared with 'Exclude on intervention'), no comparative reconciliation was necessary. EPPI-Reviewer Web recorded these as disagreements that could be reconciled by a single exclude code – the lead researcher's (KL's) code was used for this level of reconciliation. For records where the code differed at the include/exclude level, agreement was reached between team members by re-examining and discussing the records in question and the available information. Where not enough information was available to make a definitive decision, the record was retained for the next stage of screening.

Figure 2 presents the screening progress through Stage 2a, in a screenshot of the EPPI-Reviewer Web Screening Progress graph which tracks screening progress. Pointers have been added to the screenshot by the authors to show where plateaus occurred. In brief, at the point at which approximately 8,000 records had been screened, a plateau can be seen in the graph. This indicates the point beyond which the number of records included as relevant had not increased. When the plateau was clearly consistent as a pattern, the team decided to discontinue the double-screening process and to continue the process using a single-screening mode.

When we had reached 4,831 items screened, the number of included items began to plateau. (This is of course not visible at that point, and we needed to continue screening as the plateau is visible in retrospect only). Between 4,861 and 7,822 items screened, the number of included items increased very gradually from 586 to 594 included items. At 7,897 items screened, we had included 613 items. Between 7,897 and 9,026 items screened, we did not find any further items to include. By 9,080 items screened, we had included 1 more item (614 included items). At the point where we had screened and reconciled 11,661 items (2,581 further items screened from the last included item), we had included only 3 further items (617 included items). We changed to single screening at this point (12 September 2022) and did not find any further includes up to the end point at 14,636 items screened, resulting in 617 included items.

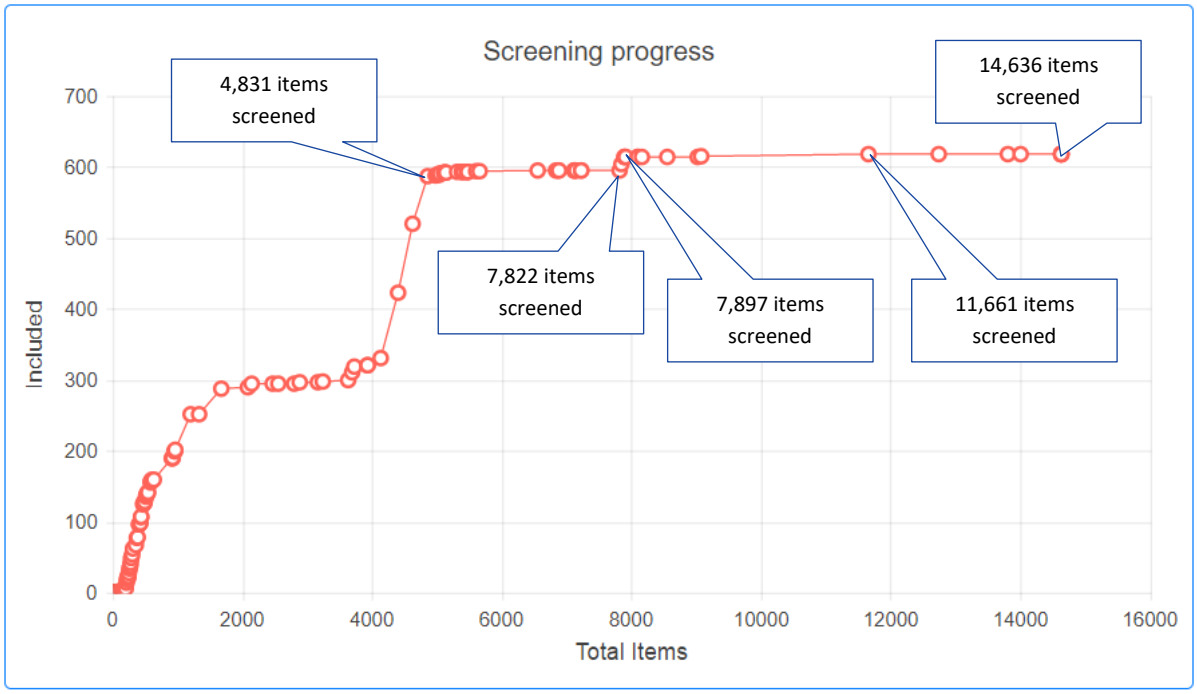

Figure 2 Title and abstract screening progress graph

2.5.2 Screening on full text (Stages 3a/3b/3c)

After title and abstract screening was completed, 392 citations were selected as matching the review inclusion criteria. The complete records (full-text published versions, in addition to any supplemental material/separate appendices) were then sourced by the information specialist (CL) and uploaded to EPPI-Reviewer Web for screening. Double-blinded, full-text screening was carried out in multiple stages by two researchers (KL and OC). Priority screening was not used for the full-text screening process. Arbitration assistance was given by the information specialist (CL) where screening verdicts were discrepant.

Stage 3a included exclusion codes relating to search methods and design items in the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2 appraisal tool [107], as reviews not meeting these standards (e.g. reviews that did not report search strategies or risk of bias assessments) would not be of sufficient quality to include in the overview of reviews. The inclusion and exclusion codes used for the first stage of full-text screening (Stage 3a) were:

- Include on full-text screening
- Subcategory: Include (double-blinded)
- Subcategory: Include (mixed blinding)
- Subcategory: Include (no blinding)
- Exclude on intervention
- Exclude on outcome
- Exclude on methods: no/inadequate quality assessment/risk of bias assessment
- Exclude on methods: no search strategy reported
- Exclude on methods: searched fewer than two databases
- Exclude on methods: no supplemental search reported

- Exclude on methods: review contains unextractable studies
- Exclude on study design: general
- Exclude on study design: empty review (i.e. review that found no relevant studies)
- Exclude on study design: relevant umbrella review (overview of reviews)
- Exclude on study design: in-scope protocol/conference abstract/poster
- Exclude on age
- Exclude on language
- Exclude on date, and
- Exclude on duplicate.

At Stage 3a of screening, 119 citations were included and 273 were excluded. Full details of the breakdown of results for each code are available in Appendix B. Once the set of citations that met the review inclusion criteria were selected, these were again screened (Stage 3b) by two researchers (KL and AT), which involved close reading of the full-text papers. The citations included from Stage 3a were divided based on blinding status into systematic reviews that included primary studies with double-blinding, mixed blinding, and no blinding; we did this because, at the time of screening, we were considering synthesising the findings of reviews that included only double-blinded studies separately from other reviews, in order to carry out a comparative analysis. Ultimately, we chose another framework for organising our synthesis that allowed for more precise reporting on outcomes related to specific health conditions. The screening codes used were:

- Include
- Exclude on methods: no/inadequate quality assessment/risk of bias assessment
- Exclude on intervention
- Exclude on outcome
- Exclude on methods: review contains unextractable studies
- Exclude on methods: no/inadequate search strategy reported
- Exclude on methods: searched fewer than two databases
- Exclude on methods: no supplemental search reported
- Exclude on study design: general
- Exclude on age
- Exclude on age and no/inadequate search strategy
- Exclude on age and review not cannabis-specific
- Exclude on non-cannabis-specific review
- Exclude on review not cannabis-specific and no/inadequate search strategy, and
- Exclude on age, no/inadequate search strategy, and review not cannabis-specific.

The term ‘inadequate search strategy’ refers to the custom of naming some databases and referring to a small selection of keywords as an entire search strategy. This description of a search strategy is not

adequate to understand what the search process involved, to assess what range of relevant research the search could have examined, or to reproduce the search.

From the Stage 3b screening, 53 citations appeared to match the inclusion criteria, and 66 citations were excluded. On close examination and discussion of the results included from this stage of screening, it was deemed useful to carry out a final stage of screening (Stage 3c) as some questions had arisen about aspects of the included reviews that would bear reassessment. To this end, the included reviews from Stage 3b were included in a final stage of screening, which used these codes:

- Include
- Exclude on methods: review contains unextractable studies
- Exclude on not cannabis-specific
- Exclude on methods: no/inadequate search strategy reported
- Exclude on study design, and
- Exclude on intervention.

The final number of full-text systematic review papers included from this round of screening was 40, as 13 citations were excluded. The PRISMA flow chart in Figure 3 (see Section 3.1) presents an overview of the stages of screening and the numbers of papers included and excluded at each stage.

2.5.3 Screening of supplemental search records

The supplemental searches (as described in Section 2.4.6) resulted in 8,477 citations. These were screened in Zotero (Stage 4) for the exclusion of duplicates by the information specialist (CL), which resulted in a set of 5,571 citations. A preliminary round of screening (using codes similar to those described for title and abstract screening, but with the addition of an exclusion code for any of the 40 reviews that were already included from the screening of primary search results) was then carried out by the information specialist (CL). Double-screening was not carried out at this stage, as it was expected that the majority of the results to be screened would have already been screened in Stages 1–3. The title and abstract screening codes used were:

- Include
- Exclude on already included reviews
- Exclude on date
- Exclude on study design
- Exclude on intervention
- Exclude on age
- Exclude on study design: in-scope protocol/conference abstract/poster
- Exclude on language (in scope)
- Exclude on language (out of scope)
- Exclude on duplicate, and
- Exclude on non-cannabis-specific review

From this screening process, 5,514 citations were excluded and 57 citations were included for further consideration. The full texts of these citations were sourced by the information specialist (CL).

The lead researcher (KL) then screened these citations using these codes:

- Include
- Exclude on already included reviews
- Exclude on study design
- Exclude on intervention
- Exclude on intervention: population
- Exclude on methods: no/inadequate search reported
- Exclude on methods: no/inadequate risk of bias assessment reported
- Exclude on methods: review contains unextractable studies
- Exclude on age
- Exclude on age and no/inadequate search strategy reported
- Exclude on age and no/inadequate risk of bias assessment reported
- Exclude on no/inadequate search reported and no/inadequate risk of bias assessment reported
- Exclude on age, no/inadequate search strategy reported, and no/inadequate risk of bias assessment reported
- Exclude on non-cannabis-specific review
- Exclude on date
- Exclude on outcome
- Exclude as unavailable paper, and
- Exclude on duplicate.

From the 57 citations screened, 7 were included and 50 were excluded. These results were then incorporated into the data extraction process (see Section 2.6).

2.5.4 Screening flow

The flow of information (i.e. citation numbers and sources) through the search and screening processes is illustrated in the PRISMA flow chart in Figure 3 (see Section 3.1).

2.6 Data extraction

We used an amended version of the JBI data extraction form [108] (see Appendix D) for systematic reviews and research syntheses in order to extract data from each included systematic review. The extracted data included: citation details, objectives of the review, participants, setting, interventions, comparators, search information, study date range, number of primary studies, study design, risk of bias tool used, risk of bias assessment (including publication bias), analysis methods, outcomes assessed, and results by outcome. Our amendments to the tool included additional notes (in order to ensure that all reviewers undertaking extraction made decisions using the same parameters), as well as additional items

for extraction to capture data required for quality assessment (see Section 2.7) and for calculation of overlap (see Section 2.8.3).

Data extraction for each included systematic review was carried out by one of three reviewers and validated by another for accuracy and comprehensiveness.

Data were extracted at the level of the included systematic reviews only, not at the level of the primary studies included therein. Following expert guidance, extraction and presentation of data were limited to the findings presented by the included systematic reviews; while primary studies included in the systematic reviews were occasionally retrieved to check the accuracy of extraction by systematic review authors where necessary, no additional data were extracted directly from the primary studies [108].

2.7 Quality assessment

The AMSTAR 2 instrument was used to assess the quality and risk of bias of each included systematic review [107]. The AMSTAR 2 instrument has been used in one previous HRB evidence review [109] and allows for the appraisal of systematic reviews of both randomised and non-randomised studies of healthcare interventions, which makes it highly appropriate for this review.

Two reviewers independently applied the instrument to each included systematic review. Discrepancies in scores were resolved through discussion.

The AMSTAR 2 instrument contains 16 items, and the original text of the items was used [107]. However, having piloted the tool and used it in a previous HRB evidence review [109], we have made a number of adjustments. These adjustments are not intended to alter the items, but merely to provide more explicit guidance and to ensure that all reviewers made decisions using the same parameters. There changes are as follows:

- The scoring of items 1, 4, and 8 was adjusted in order to provide consistent and more stringent judgement of the parameters being scrutinised.
- For items 1–4, 8, 9, and 11–16, we added text to further explain and clarify what is required for each parameter.

The adapted instrument is included in Appendix E.

Shea *et al.* [107] recommend defining critical domains before beginning appraisal of a systematic review; these are domains in which the identification of weaknesses should undermine confidence in the results of the review. According to Shea *et al.*, "responses to AMSTAR 2 items should not be used to derive an overall score. We accept that an overall score may disguise important weaknesses that should diminish confidence in the results of a systematic review, and we recommend that users adopt the rating process based on identification of critical domains, or some variation based on these principles" [107] p6.

In the absence of clear definitions from Shea *et al.*, we regard a **critical domain** as a fundamental characteristic of a study design that is essential for its validity (e.g. adequate randomisation in an RCT, no excessive loss to follow-up in a cohort study). We regard a **critical flaw** as a weakness or failing in a critical domain. We regard a **non-critical weakness** as a weakness or failing in a non-critical domain. We regard a **fatal flaw** as a failing in a critical domain that renders the study ineligible for inclusion in this overview of reviews (see exclusion criteria in Table 2).

Shea *et al.* suggest seven critical domains in the AMSTAR 2 instrument that reviewers may use to identify important weaknesses or flaws in systematic reviews [107]. However, reviewers can change some of these domains depending on the focus of their overview. Reflecting our exclusion criteria (see Table 2), we excluded reviews that did not meet the criteria in domains 2 (adequacy of the literature search) and 4

(risk of bias of individual studies included in the review). We have identified eight rather than seven critical domains (see Appendix E for selected domains and justifications).

We also allocated each included systematic review a confidence rating using the schema from Shea *et al.*, shown in Table 3 [107].

Table 3 Rating overall confidence in the results of individual systematic reviews

Score	Criteria
High	No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
Moderate	More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
Low	One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
Critically low	More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
*Downgrade	*Multiple non-critical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence

Source: Shea *et al.*, 2017 [107]

2.8 Synthesis

2.8.1 Collecting and presenting data on characteristics of included reviews

As described in Section 2.6, we used the JBI data extraction form for systematic reviews and research syntheses [108] (see Appendix D) in order to extract review characteristics data from each included systematic review. Data extraction was carried out by one reviewer and validated by another.

Descriptive data on the review characteristics were documented in tabular form. For each included systematic review, we present the extracted data in two formats: a high-level summary taking account of the quality of evidence, presented in the main report, and a detailed structured summary, presented in the appendices to the main report. PICO and other study characteristics were extracted and presented in the appendices to demonstrate to the reader why each study was included.

The main report also presents information on the overlap of primary papers evaluating the same intervention for the same outcomes across one or more systematic reviews using the Pieper *et al.* corrected covered area method [110] (see Section 2.8.3).

2.8.2 Collecting, analysing, and presenting outcome data

Gates *et al.* [89] describe a number of challenges in synthesising findings from multiple systematic reviews, including heterogeneity of outcome measures, procedural variation at the level of individual systematic reviews, multiple comparisons, discordant results, and contrasting conclusions across different systematic reviews.

The outcomes specified a priori were intentionally wide-ranging in order to ensure that evidence on any relevant outcomes of the conditions/clinical indications of interest was captured. As characterised by Lunny *et al.*, "Overviews of systematic reviews synthesise the results of multiple systematic reviews.

Overviews are typically broader in scope than systematic reviews and may examine different interventions for the same condition, the same intervention for different conditions, or the same intervention for the same condition but focusing on different outcomes" [97] p2.

As described in Section 2.6, we used the JBI data extraction form for systematic reviews and research syntheses [108] in order to extract outcome data from each included systematic review. We extracted and compiled all findings pertaining to efficacy and safety from each included review. Findings for primary outcomes from the reviews are presented in the main report. Findings for secondary outcomes are presented in the extraction forms for individual reviews (see Appendix F).

Findings for outcomes related to efficacy (e.g. reduction in relevant symptoms, changes in quality of life) and safety (e.g. relevant adverse events, withdrawals/complications) are presented separately, in accordance with the two research questions (see Section 1.5). Under the efficacy heading, each review was categorised as focusing on specific health conditions (i.e. a review that synthesises evidence for the use of medicinal cannabis for a particular health condition, such as cancer or HIV/AIDS) or on mixed health conditions (i.e. a review that synthesises evidence for the use of medicinal cannabis for a given outcome across a range of health conditions).

We then synthesised the findings from reviews on specific health conditions and mixed health conditions separately. It was more precise to describe the effect of medicinal cannabis on symptoms of specific health conditions, and it was generally not possible to extract data on specific health conditions from the reviews on mixed health conditions; these therefore had to be analysed in an aggregated format as presented by the systematic review authors.

2.8.3 Overlapping reviews

Overlap occurs between systematic reviews when a single primary study is included in more than one systematic review evaluating the same outcome. For example, Review A and Review B both synthesise evidence on THC for ameliorating depression, and both include Primary Study C. It is important to understand the degree of overlap between reviews, because a large number of reviews on a topic may give an inaccurate impression of the size or consensus of the body of evidence if many of the reviews are based on the same relatively small number of primary studies.

To address the issue of overlapping systematic reviews in this overview of reviews, we calculated the corrected covered area as a measure of overlap. This approach is recommended by Pieper *et al.* [110], who contend that "all producers of overviews should analyse the overlaps and report their analysis. Reporting should be done even if the amount of overlap is small and unlikely to have an impact on the conclusion. Otherwise, consumers will not know whether there is no meaningful overlap or if the authors simply did not [take] account of it. Consequently, overlaps should be reported by default" [110] p374–375.

For each outcome, the corrected covered area is calculated as follows:

$$Corrected\ covered\ area = \frac{N - r}{r \times c - r}$$

where *N* is the number of included primary publications (including double counting) in the evidence synthesis, *r* is the number of unique primary publications, and *c* is the number of reviews.

2.8.3.1 Worked example of overlap calculation

For example, Review A and Review B both synthesise evidence for THC products compared with placebo for pain relief in multiple sclerosis. Review A includes Primary Study 1 and Primary Study 2. Review B includes Primary Study 2, Primary Study 3, and Primary Study 4.

N = number of included primary publications (including double counting) = 5

r = number of unique primary publications = 4

c = number of reviews = 2

$$Corrected\ covered\ area = \frac{N - r}{r \times c - r} = \frac{5 - 4}{4 \times 2 - 4} = \frac{1}{4} = 0.25$$

The overlap between Review A and Review B is thereby calculated to be 25%.

2.8.3.2 Application of overlap calculation for reviews on specific health conditions and mixed health conditions

We used the overlap calculation slightly differently depending on the nature of the interventions and outcomes examined in the included systematic reviews. Our three approaches and corresponding examples are listed below.

1. **The effect of a single class of cannabis products (nabiximols, CBD, or THC) on a specific symptom for a specific health condition:**

For example, Review A and Review B both synthesise evidence for THC products compared with placebo for pain relief in multiple sclerosis. Review A includes Primary Study 1 and Primary Study 2. Review B includes Primary Study 2, Primary Study 3, and Primary Study 4. The overlap between Review A and Review B is calculated to be 25%.

2. **The effect of two or more classes of cannabis products (nabiximols, CBD, and/or THC) on a specific symptom for a specific health condition:**

For example, Review A synthesises evidence for CBD products compared with placebo for relief of nausea associated with chemotherapy. Review B synthesises evidence for a mixed range of cannabis products, including nabiximols, CBD, and THC products, compared with placebo for nausea in cancer. Review A includes Primary Study 1, Primary Study 2, and Primary Study 3, all on CBD. Review B includes Primary Study 1 and Primary Study 3, both on CBD, as well as Primary Study 4 on nabiximols, and Primary Study 5 and Primary Study 6, both on THC products.

Although the interventions do not perfectly match across the two reviews (the scope of Review A being narrower than that of Review B), it is important to clarify that the sets of evidence discussed in the two reviews are not completely independent; they both concern types of cannabis products and examine the same outcome (relief of nausea associated with cancer/chemotherapy), and as such are combined together to quantify the degree of that overlap. The overlap between Review A (CBD) and Review B (mixed cannabinoids) is calculated to be 33%.

3. **The effect of two or more classes of cannabis products (nabiximols, CBD, and/or THC) on a specific symptom for mixed health conditions:**

For example, Review A, Review B, Review C, and Review D each synthesise evidence for a range of medicinal cannabis products for pain relief across a range of health conditions. It is not possible to meaningfully explore overlaps for specific products and pain relief in each of the specific health conditions, as these are mixed in all of the reviews (e.g. studies of pain relief in cancer, HIV/AIDS, and multiple sclerosis are all examined in a single analysis). Therefore, we calculated an overlap statistic for all of the reviews examining the effect of cannabis products on pain relief in general. Review A, Review B, Review C, and Review D include Primary Study 3, Primary Study 5, Primary Study 5, and Primary Study 6,

respectively. There are 10 unique primary studies included across all four reviews; therefore, the overlap among reviews on pain relief across a range of health conditions is calculated to be 30%.

2.8.4 Assessing the certainty of evidence of outcome data

2.8.4.1 The Grading of Recommendations, Assessment, Development and Evaluation approach

The *Cochrane Handbook for Systematic Reviews of Interventions* recommends using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for assessing certainty (or quality) of a body of evidence [111]. While the AMSTAR 2 instrument described in Section 2.7 rates the **methodological quality** of individual systematic reviews, the GRADE approach is used to rate the **quality of the body of evidence** for each outcome across all studies. To illustrate the distinction, a systematic review can be of high methodological quality (e.g. with a comprehensive search, rigorous data extraction, and appropriate synthesis techniques) but identify only low- or very low-quality evidence for the outcomes of interest (e.g. a lack of RCTs, studies with small sample sizes, or outcome evidence from a single trial).

Under the GRADE system, the initial certainty of the evidence is determined based on study design, with RCTs providing a high degree of certainty and observational studies providing a lower degree of certainty. The level of certainty is then adjusted upwards or downwards based on a number of factors. Ultimately, a body of evidence related to an outcome receives one of four grades (high, moderate, low, or very low), reflecting the level of confidence we may have that the true effect of the intervention (medicinal cannabis) on the outcome (e.g. pain) is similar to (or substantially different from) the estimate of the effect presented in the systematic review(s), and that the findings of future trials and systematic reviews will be the same or similar.

The definitions of the four certainty of evidence grades are outlined in Table 4.

Table 4 Certainty of evidence grades

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

Source: Schünemann *et al.*, 2013 [112]

2.8.4.2 Challenges of applying GRADE to overviews of reviews

The GRADE approach has been traditionally applied to rating the quality or certainty of evidence in single systematic reviews, primarily reviews that include a meta-analysis. However, there is a lack of consensus on how best to apply a GRADE assessment when undertaking an overview of reviews. The following extract from Gates *et al.* elaborates these difficulties [89]:

> It may not be possible or appropriate to simply extract existing GRADE appraisals from the included systematic reviews. The reviews might not include GRADE appraisals for the outcomes or populations of interest or be missing details on each of the GRADE considerations. Different

> systematic reviews with the same studies that have made different decisions about handling data (analysis) and appraising study quality may come to different GRADE conclusions, especially related to the study limitations, consistency, and precision domains. Different [assessors] across systematic reviews could come to different conclusions, due to the subjectivity of the GRADE approach. If re-doing the GRADE for each systematic review, authors are likely to encounter difficulty due to an absence of guidance on how to apply GRADE in the context of an overview, incomplete reporting at the level of the systematic review, and a lack of familiarity with the contributing primary studies. [89] p16

These difficulties notwithstanding, the HRB believes that it is important to assess the quality of evidence in this overview of reviews, given the intended purpose of the review to inform decision-making by the Department of Health in relation to the scope of Ireland's Medical Cannabis Access Programme. As previously noted, GRADE is the framework recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* for facilitating the transparency rating of evidence quality. However, following a 2016 study attempting to apply GRADE in an overview of reviews, Pollock *et al.* concluded that "Within our overview, reviewers found that current GRADE guidance was insufficient to make reliable and consistent judgments" [113] p106.

In an effort to overcome some of these challenges to applying GRADE in an overview of reviews, Pollock *et al.* developed a modified algorithm to grade the quality of evidence in their overview [113]. Our approach to applying GRADE was based on this algorithm. We applied the modified algorithm to all reviews included in our overview of reviews. If individual included reviews had applied the original GRADE assessment, we refrained from using these assessments; this is because we wanted to avoid re-reporting potential conflicting uses of the original instrument by different review teams. Additionally, the original instrument is comparatively more subjective than the more objective modified algorithm, and we wanted to avoid mixing the GRADE assessments of the systematic review authors and the HRB.

2.8.4.3 Pollock *et al.*'s modified GRADE algorithm

Pollock *et al.*'s algorithm for applying GRADE to an overview of reviews is based on four criteria [113]:

1. The number of participants within the analysis considering imprecision based on sample size and confidence intervals around outcomes of interest
2. The risk of bias within the trials contributing participants to the analysis with respect to randomisation and blinding
3. The statistical inconsistency or heterogeneity within the analysis, as determined by I^2, and
4. The methodological quality of the review as determined by the selection of critical factors from the quality assessment tool. These can be adapted depending on the subject matter of the review [113].

As recommended by Pollock *et al.*, we identified five additional critical factors from our quality assessment tool (AMSTAR 2) to include in our GRADE assessment, in order to ensure that all of the AMSTAR 2 critical domains for this overview of reviews (see Section 2.7 and Appendix E) contributed to the GRADE assessment:

1. Research questions and inclusion criteria for the review include the components of PICO (AMSTAR 2 item 1)
2. Protocol registered before commencement of the review (AMSTAR 2 item 2)
3. Adequacy of the literature search (AMSTAR 2 item 4)
4. Appropriateness of meta-analytical methods (AMSTAR 2 item 11), and

5. Review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis (AMSTAR 2 item 12).

Finally, two further modifications were applied to Pollock *et al*.'s GRADE system. Our GRADE assessment scored risk of bias due to randomisation and risk due to blinding (outcome ascertainment/blinding of outcome assessors) separately. Additionally, any outcome with evidence based on one primary study was automatically rated as very low-certainty evidence. These modifications are modest and do not materially change the principles nominated by Pollock *et al*. [113]. A detailed rationale underlying our choice of critical domains in AMSTAR 2 (and thereby our critical factors in GRADE) is presented in Appendix E.

Each review starts with a ranking of high certainty. The ranking may then be downgraded one or two levels for serious methodological concerns, including: imprecision (based on sample size); risk of bias in randomisation and blinding of outcome assessors (trial quality); inconsistency (heterogeneity); appropriateness of the research question (AMSTAR 2 item 1); a priori research design (AMSTAR 2 item 2); comprehensive literature search (AMSTAR 2 item 4); appropriateness of meta-analytical methods (AMSTAR 2 item 11); and assessment of risk of bias in meta-analytical methods (AMSTAR 2 item 12).

Table 5 provides a full account of how the GRADE algorithm was applied in this overview of reviews.

Table 5 Formula for applying GRADE level of evidence to reviews included in this overview of reviews using modified Pollock et al. algorithm

	IMPRECISION (BASED ON SAMPLE SIZE)	RISK OF BIAS (TRIAL QUALITY)	INCONSISTENCY	RISK OF BIAS (REVIEW QUALITY)	STUDY DESIGN
	Adequate number of participants included in the pooled analysis	Proportion of study participants included in the pooled analysis from primary trials or studies judged to have low risk of bias for randomisation and blinding of outcome assessors	Statistical heterogeneity or inconsistency (e.g. assessed by I^2 or *Q* statistic)	Responses to five AMSTAR items (1, 2, 4, 11, and 12)	
No downgrade (no serious limitations)	≥200	≥75% of study participants included in the pooled analysis from primary trials or studies judged to have low risk of bias for randomisation and blinding of outcome assessors	I^2 ≤75%	5/5 are all 'yes' on AMSTAR 2	Randomised study design
Downgrade 1 level (serious limitations)	100–199	<75% of study participants included in the pooled analysis from primary trials or studies judged to have low risk of bias for randomisation and blinding of outcome assessors	I^2 >75%	4/5 are 'yes' and 1 is 'partial yes' or 'no' on AMSTAR 2	Non-randomised or cohort study design
Downgrade 2 levels (very serious limitations)	1–99	Not applicable	Not applicable	3/5 are 'yes' and the remainder are 'partial yes' or 'no' on AMSTAR 2	Not applicable
Notes		If risk of bias for individual trials is not reported within the review, we can assume that fewer	If only one trial contributed to the analysis, no downgrade; if I^2 not reported, it		

	IMPRECISION (BASED ON SAMPLE SIZE)	RISK OF BIAS (TRIAL QUALITY)	INCONSISTENCY	RISK OF BIAS (REVIEW QUALITY)	STUDY DESIGN
		than 75% of participants had low risk of bias.	is assumed to be greater than 75%.		

Source: Adapted from Pollock *et al.*, 2016 [113]

The number of downgrades that can be applied using the modified algorithm ranges from 0 to 8 (as risk of bias due to randomisation or due to blinding of outcome assessors may each result in up to one downgrade) and, on this basis, ratings can be applied using the standard GRADE level of evidence. Table 6 displays the system we used to determine the rating of levels of evidence in our overview of reviews. GRADE assessments were carried out only for primary outcomes.

Table 6 Classification of GRADE level of evidence to overview of reviews from number of downgrades determined using the Pollock et al. modified algorithm

GRADE level of evidence	Number of downgrades (derived from objective assessment)
High	Score awarded when 0 downgrades are applied
Moderate	Score awarded when 1 or 2 downgrades are applied
Low	Score awarded when 3 or 4 downgrades are applied
Very low	Score awarded when 5, 6, 7 or 8 downgrades are applied

Source: Adapted from Pollock *et al.*, 2016 [113]

2.8.5 Interpreting outcome data and drawing conclusions

Gates *et al.* [89] describe a number of challenges in synthesising findings from multiple systematic reviews, including heterogeneity of outcome measures, procedural variation at the level of individual systematic reviews, multiple comparisons, discordant results, and contrasting conclusions across different systematic reviews.

To address these challenges, we used the six-item framework proposed by Lunny *et al.* [114] in order to synthesise our interpretations and conclusions. We therefore:

1. Elaborate our interpretation and conclusions
2. Summarise the results from included systematic reviews
3. Assess and report on heterogeneity
4. Assess and report on risk of bias in the reviews
5. Assess and report on overlap of primary studies included in more than one systematic review, and
6. Assess and report on discordant results, interpretations, and conclusions among the included reviews.

2.9 Deviations from protocol

We added a number of additional elements to the JBI data extraction form in order to capture data to be used for the AMSTAR 2 and GRADE assessments and for calculation of corrected covered area. The date range for eligible reviews was also updated to reflect the actual date of our final searches.

The protocol did not specify a priori how we would group reviews or outcomes for the purpose of synthesising them. Once screening was complete, the review team determined that the findings from reviews on specific health conditions and from reviews on mixed health conditions should be synthesised separately. It was more precise to describe the effect of medicinal cannabis on symptoms of specific health conditions, and it was generally not possible to extract data on specific health conditions from the reviews on mixed health conditions; therefore, these had to be analysed in an aggregated format as presented by the systematic review authors.

It was also decided that only findings for primary outcomes (as defined by the included reviews) would be synthesised and presented in the main report. Findings on secondary outcomes are presented in the extraction forms for the individual reviews (see Appendix F). This decision not to compile all relevant data from each included systematic review, as intended in the protocol, was made in the interest of presenting a manageable amount of data on the most critical outcomes. However, all data on primary and secondary efficacy and safety outcomes were extracted, validated, and presented in the extraction forms.

The decision to automatically rate any outcome with evidence from only one trial as very low-certainty evidence was also made during the assessment process, not a priori.

3 Findings

3.1 Search results

Initial searches of databases and registers identified 25,888 records, of which 11,252 were duplicates, leaving 14,636 records for title and abstract screening. During title and abstract screening, 14,244 records were excluded, leaving 392 records for full-text screening. A total of 352 records were excluded at the full-text screening stage, leaving 40 records for extraction. An additional 7 articles were identified for extraction through supplemental searches, resulting in a final search yield of 47 reviews (see Appendix G for a complete list of included reviews). The PRISMA flow chart in Figure 3 outlines the flow of information throughout the searching and screening process.

The amount of detail required to be included in the PRISMA flow chart for accuracy and transparency would have rendered the flow chart difficult to read, especially for accessibility purposes. Each stage of screening had large numbers of exclusion criteria, and each screening stage, including supplemental screening, had multiple steps. For this reason, the PRISMA flow chart gives an overview of the flow of information through the review, and the full details of each stage and all inclusion and exclusion codes are presented in the tables in Appendix B. Studies excluded at the full-text screening stage, with their reason(s) for exclusion, are presented in Appendix C.

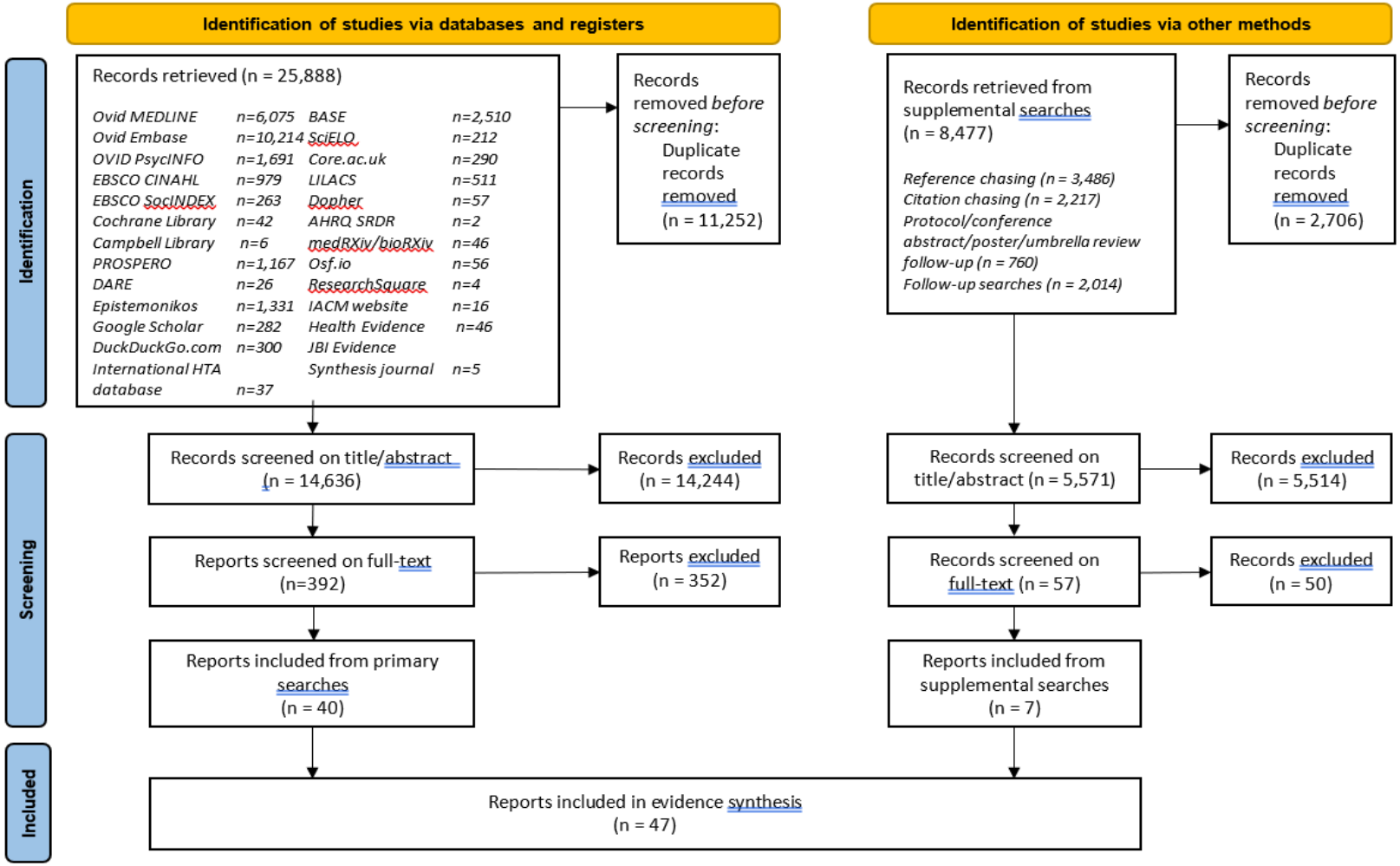

Figure 3 PRISMA flow chart

Source: PRISMA flow chart per Page *et al*, 2020[98]

3.2 Classification of systematic reviews

The findings presented in this chapter are organised under two headings: efficacy and safety. Under the efficacy heading, findings are organised by health condition (specific health conditions or mixed health conditions), then by primary outcomes, and finally by type of cannabinoid and comparator.

Of the 47 included reviews, 26 reviews synthesised research on specific health conditions (cancer; HIV/AIDS; conditions in older adults (e.g. dementia, Parkinson's disease); inflammatory bowel disease; mental health and neuropsychological conditions; palliative care; rheumatic diseases and fibromyalgia; spinal cord injury; and multiple sclerosis). The remaining 21 reviews synthesised research on mixed health conditions. Figure 4 (see Section 3.7.1), Figure 5 (see Section 3.7.1), and Figure 6 (see Section 3.7.3) illustrate the primary outcomes under these headings.

3.3 Synthesis of extracted data

As outlined in Section 2.6, data were initially extracted using a modified JBI data extraction form. For each included review, this extraction form provides a structured summary of the following: review objectives; participants; setting/context; intervention description; search strategy; search results; risk of bias appraisal tools; method of analysis; outcome assessed (both primary and secondary); results/findings; and heterogeneity.

Based on the extraction forms, high-level summaries of the evidence for each intervention for the outcomes of interest were developed in order to facilitate comparison between the interventions presented. The complete high-level summaries are presented in Appendix H. Each high-level summary provides an overview of primary outcomes, intervention and comparator type, intervention duration/follow-up range, and certainty of the evidence. To reflect the structure of the results presented in Section 3.7, high-level summaries are also organised under specific health condition and mixed health condition headings in Appendix H.

3.4 Characteristics of included reviews

A full account of the characteristics of each included review is provided in Appendix I. As per the inclusion criteria, all included reviews synthesised evidence in adult populations. Thirteen reviews did not report full details on age ranges but specified that all primary studies examined adult populations. The remaining 34 reviews reported an overall age range of 22.5–87.0 years, reflecting the variation in health conditions synthesised. Fourteen reviews did not provide details on the gender breakdown of primary studies; gender breakdown across the remaining 33 reviews ranged from 9.2% to 100.0% female participants. Publication dates for the included reviews ranged from 2013 to 2023, with primary study publication dates ranging from 1975 to 2021. Only two reviews aimed to synthesise evidence related to a specific cannabinoid formulation and administration (cannabidiol oil and inhaled cannabis); the remaining reviews aimed to synthesise evidence on a range of cannabinoid/cannabis formulations and administrations. In relation to study design, RCT data were extracted from 45 reviews, prospective cohort data were extracted from 1 review, and a mix of prospective and RCT data were extracted from 1 review. Of the 47 included reviews, 25 did not report in which country the primary studies were based, and details from the remaining 22 reviews are provided in the review characteristics in Appendix I. In relation to funding, 28 reviews did not report on the funding sources of primary studies, and details on the funding sources of the remaining 19 reviews are provided in the review characteristics in Appendix I.

Of the 47 included reviews, 26 reviews synthesised research on efficacy for specific health conditions. Table 7 outlines the specific health conditions and associated primary outcomes across these 26 reviews.

Table 7 Overview of primary efficacy outcomes (specific health conditions)

Health conditions	Primary outcomes	Reviews
Cancer	Pain-related outcomes, global improvement, nausea/vomiting, nutrition-related outcomes	Boland *et al.* (2020) [115] Häuser *et al.* (2019) [116] Noori *et al.* (2021) [117] Razmovski-Naumovski *et al.* (2022) [118] Simon *et al.* (2022) [119] Smith *et al.* (2015) [120]
HIV/AIDS	Mortality, morbidity	Lutge *et al.* (2013) [121]
Conditions in older adults	Agitation, cognitive function in dementia, breathlessness in chronic obstructive pulmonary disease (COPD), general behavioural/psychological symptoms, movement disorder, nausea/vomiting, nutrition-related outcomes, pain-related outcomes, mental health/well-being, sleep-related outcomes	Bosnjak Kuharic *et al.* (2021) [122] Paunescu *et al.* (2020) [123] Urbi *et al.* (2022) [124] van den Elsen *et al.* (2014) [125]
Inflammatory bowel disease	Clinical remission in Crohn's disease, clinical remission in ulcerative colitis	Kafil *et al.* (2018a) [126] Kafil *et al.* (2018b) [127]
Mental health and neuropsychological conditions	Psychotic disorders, anxiety disorders, mood disorders, eating disorders, substance dependence, neurodevelopmental disorders	Bahji *et al.* (2020) [128] Black *et al.* (2019) [129] De Aquino *et al.* (2022) [130] Kopelli *et al.* (2020) [131] McKee *et al.* (2021) [132] Rosager *et al.* (2021) [133]
Palliative care	Pain-related outcomes, nutrition-related outcomes, sleep-related outcomes, mental health/well-being	Mücke *et al.* (2018a) [134]
Rheumatic diseases and fibromyalgia	Pain-related outcomes, global impressions of change, sleep-related outcomes, quality of life	Fitzcharles *et al.* (2016a) [135] Fitzcharles *et al.* (2016b) [136] Walitt *et al.* (2016) [137]
Spinal cord injury	Pain-related outcomes	Thomas *et al.* (2022) [138]
Multiple sclerosis	Spasticity-related outcomes, pain-related outcomes, bladder-related outcomes, quality of life, global impressions of change	Filippini *et al.* (2022) [139] Torres-Moreno *et al.* (2018) [140]

The remaining 21 reviews synthesised research on mixed health condition populations; 20 of these reviews examined efficacy outcomes (see Table 8) while one review examined safety and tolerability outcomes only. As highlighted in Section 2.8.2, it was not possible to separate out primary outcome analysis by health condition in the majority of these reviews. These reviews have instead been synthesised by primary outcome only rather than by health condition.

Table 8: Overview of primary efficacy outcomes (mixed health conditions)

Primary outcomes	Reviews
Pain	Andreae *et al.* (2015) [141] Abdallah *et al.* (2020) [142] Bialas *et al.* (2022) [143] Butler *et al.* (2015) [144] Fisher *et al.* (2021) [145] Giossi *et al.* (2022) [146] Longo *et al.* (2021) [147] McDonagh *et al.* (2022) [148] Meng *et al.* (2017) [149] Mücke *et al.* (2018b) [150] Oordt *et al.* (2021) [151] Price *et al.* (2022) [152] Quintero *et al.* (2022) [153] Sainsbury *et al.* (2021) [154] Votrubec *et al.* (2022) [155]
Quality of life	Belgers *et al.* (2023) [156] Hammond *et al.* (2021) [157] Oordt *et al.* (2021) [151]
Spasticity	da Rovare *et al.* (2017) [158] Oordt *et al.* (2021) [151]
Cachexia	Hammond *et al.* (2021) [157]
Sleep	AminiLari *et al.* (2022) [159] McParland *et al.* (2023) [160]
Mental health/well-being	Belgers *et al.* (2023) [156]
Overall function or disability	McDonagh *et al.* (2022) [148]

Fourteen reviews synthesised research on safety and tolerability for either or mixed specific health conditions (see Table 9).

Table 9 Overview of primary safety and tolerability outcomes

Primary outcomes	Reviews
Nervous system adverse events	Bajtel *et al.* (2022) [161] Bosnjak Kuharic *et al.* (2021) [122] Hammond *et al.* (2021) [157] McDonagh *et al.* (2022) [148] Paunescu *et al.* (2020) [123]
Gastrointestinal system adverse events	Bajtel *et al.* (2022) [161] Bosnjak Kuharic *et al.* (2021) [122] McDonagh *et al.* (2022) [148]
Psychiatric system disorder adverse events	Bosnjak Kuharic *et al.* (2021) [122] McDonagh *et al.* (2022) [148]
Any specific adverse events	Bosnjak Kuharic *et al.* (2021) [122] Hammond *et al.* (2021) [157] Paunescu *et al.* (2020) [123]

Primary outcomes	Reviews
	Quintero *et al.* (2022) [153] Urbi *et al.* (2022) [124] van den Elsen *et al.* (2014) [125]
Serious adverse events	Bosnjak Kuharic *et al.* (2021) [122] Fitzcharles *et al.* (2016b) [136] Häuser *et al.* (2019) [116] McDonagh *et al.* (2022) [148] Mücke *et al.* (2018b) [150] Oordt *et al.* (2021) [151] van den Elsen *et al.* (2014) [125] Walitt *et al.* (2016) [137]
Tolerability (withdrawal due to adverse events)	Bahji *et al.* (2020) [128] Fitzcharles *et al.* (2016b) [136] Häuser *et al.* (2019) [116] McDonagh *et al.* (2022) [148] Mücke *et al.* (2018b) [150] Oordt *et al.* (2021) [151] Paunescu *et al.* (2020) [123] Walitt *et al.* (2016) [137]

3.5 Methodological quality of included reviews

The methodological quality of the included reviews was assessed using the 16-item AMSTAR 2 tool [107]. As highlighted in Section 2.7, we identified eight critical domains; these are domains in which identification of weaknesses should undermine confidence in the results of the review [107]. Our critical domains were the inclusion of PICO components in the research question and inclusion criteria; the availability of a protocol prior to conducting the review; a comprehensive literature search; an appropriate method for assessment of bias; appropriate methods for meta-analysis; consideration of risk of bias in the meta-analysis; discussion of the risk of bias in relation to the quality of the evidence; and discussion of heterogeneity in relation to the quality of evidence.

The methodological quality of the included reviews was varied: 1 review was rated as having high methodological quality (one non-critical flaw was identified); 5 reviews were rated as having moderate methodological quality (more than one non-critical flaw was identified); 9 reviews were rated as having low methodological quality (one critical flaw was identified); and 32 reviews were rated as having critically low methodological quality (more than one critical flaw was identified).

Of our eight critical domains on the AMSTAR 2 tool, reviews were most commonly rated ‘no’ or only ‘partial yes’ for the following: stating that the review methods were established a priori in the protocol (68% of reviews), assessing the potential impact of risk of bias of primary studies on the results of the meta-analysis (51%), and accounting for, or discussing, risk of bias (45%) or heterogeneity (38%) when interpreting or discussing the results of the review. Future systematic reviews may therefore benefit from more fully considering the impact of risk of bias and heterogeneity on their findings and discussing how the interpretation of the findings should take account of these factors. A full account of the AMSTAR 2 assessment for each review is provided in Appendix J.

3.6 Certainty of evidence

The calculated GRADE score for each systematic review included downgrades for inadequate conduct of the review, specifically where the primary studies included in the review had non-randomised designs, unclear or high risk of bias, high heterogeneity, and/or inadequate sample sizes. High-quality reviews adequately addressed each of these areas; moderate-quality reviews received one or two downgrades; low-quality reviews received three or four downgrades; and very low-quality reviews received five or more downgrades. Therefore, the GRADE rating is used as a summary indicator of the quality of the evidence that is presented. It is important to note that the GRADE rating takes account of the methodological quality of a systematic review and its primary studies. The GRADE rating of evidence for the primary outcomes is presented in Section 3.7, and the number of downgrades (and the reason for them) are presented in Appendix K.

In total, evidence was synthesised on 329 outcomes categorised by intervention and comparator type. Under the specific health conditions heading, 163 outcomes (11 with moderate-certainty evidence, 34 with low-certainty evidence, and 118 with very low-certainty evidence) were identified. Under the mixed health conditions heading, 94 outcomes (5 with high-certainty evidence, 9 with moderate-certainty evidence, 29 with low-certainty evidence, and 51 with very low-certainty evidence) were identified. Under the safety and tolerability heading, 71 outcomes (8 with moderate-certainty evidence, 14 with low-certainty evidence, and 49 with very low-certainty evidence) were identified.

3.7 Results

The results section is presented under three main headings: Efficacy in specific health conditions (Section 3.7.1); Efficacy in mixed health conditions (Section 3.7.1); and Safety and tolerability (Section 3.7.3). Findings for primary outcomes identified by the included reviews are presented in detail in these sections. Findings for secondary outcomes are outlined in the extraction forms for individual reviews in Appendix F.

In Section 3.7.1, evidence related to the efficacy of medicinal cannabis (cannabinoids and cannabis) interventions compared with comparator conditions is presented. Specific health conditions include cancer; HIV/AIDS; conditions in older adults (e.g. dementia, Parkinson's disease); inflammatory bowel disease; mental health and neuropsychological conditions; palliative care; rheumatic diseases and fibromyalgia; spinal cord injury; and multiple sclerosis. Primary outcomes for specific health conditions are presented and are broken down by cannabinoid and comparator group types.

In Section 3.7.1, evidence related to the efficacy of medicinal cannabis (cannabinoids and cannabis) interventions compared with comparator conditions is presented. Due to the design of reviews included in this section, it was not possible to separate findings for outcomes by health condition types. Therefore, primary outcomes per mixed health condition population are presented under medicinal cannabis (cannabinoids and/or cannabis) and comparator group types.

In Section 3.7.3, evidence related to the safety and tolerability of medicinal cannabis (cannabinoids and cannabis) interventions compared with comparator conditions is presented. In order to provide a comprehensive overview of adverse events, reviews on both specific and mixed health conditions that synthesise data on safety as a primary outcome have been combined in this section. Safety outcomes in specific and mixed health conditions are presented under medicinal cannabis (cannabinoids and/or cannabis) and comparator group types.

It is important to note at the outset that several reviews provide analysis of mixed cannabinoid types (i.e. cannabis, tetrahydrocannabinol and cannabidiol combined (THC:CBD), THC alone, CBD alone, cannabidivarin (CBDV), and 1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3)). In these cases, review authors synthesised evidence for multiple cannabinoid types together, rather than carrying out separate syntheses for different cannabinoid interventions. As outlined in Section 1.2.1, these

interventions have different mechanisms of action. In many cases, given the design of these reviews, it was not possible to categorise these analyses by cannabinoid type. The limitations associated with grouping different cannabinoid types in the same analyses are discussed in Section 4.3.4.

3.7.1 Efficacy in specific health conditions

In total, 26 systematic reviews assessed outcomes in specific health condition populations or care settings. These included six reviews on cancer [115–120]; one on HIV/AIDS [121]; four on conditions in older adults [122–125]; two on inflammatory bowel disease [126,127]; six on mental health and neuropsychological conditions [128–133]; one on palliative care [134]; three on rheumatic diseases and fibromyalgia [135–137]; one on spinal cord injury [138]; and two on multiple sclerosis [139,140].

The following sections present collated data for the primary outcomes examined by the systematic reviews, organised by condition (e.g. cancer) and by outcome category within each condition (e.g. pain-related outcomes). The secondary outcomes examined by the reviews are also presented for each condition. Finally, a brief summary of the findings on safety outcomes is presented for each condition in order to provide a sense of the sorts of adverse events and tolerability outcomes that may arise for patients with each specific health condition (e.g. patients with cancer, older adults). Figure 4 illustrates the breakdown of conditions and primary outcome categories.

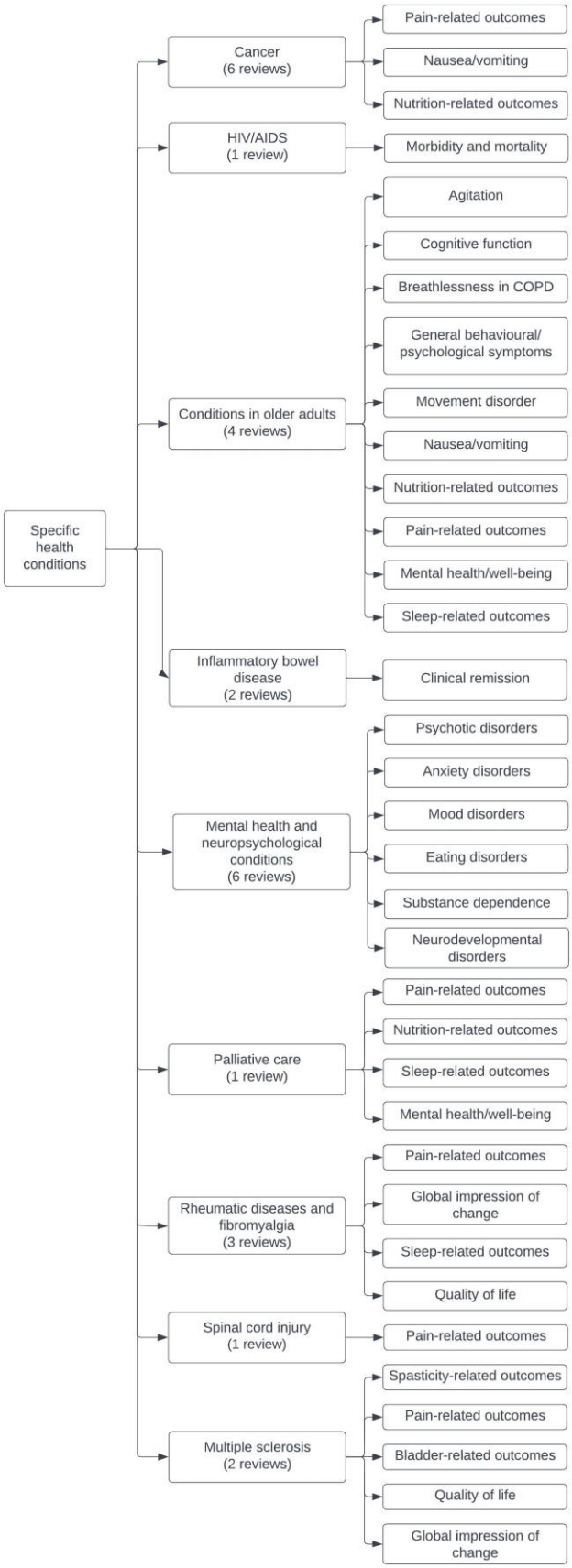

Figure 4 Primary outcomes for efficacy (specific health conditions)

3.7.1.1 Cancer

We identified six systematic reviews that investigated the impact of medicinal cannabis on outcomes related to cancer [115–120]. Three reviews investigated pain-related outcomes [115–117], one review investigated nausea and vomiting [120], and two reviews investigated nutrition-related outcomes [118,119]. The reviews also presented evidence on a range of secondary outcomes and adverse events. Please note that outcomes related to cancer in the context of palliative care were also addressed by the systematic review on palliative care, with some overlap in primary studies (see Section 3.7.1.6).

3.7.1.1.1 Efficacy: Primary outcomes

3.7.1.1.1.1 Pain-related outcomes

Table 10 provides an overview of the primary pain-related outcomes in cancer.

Table 10 Primary pain-related outcomes in cancer

Outcome	Intervention versus (vs.) comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain intensity						
	THC:CBD formulations (Sativex, nabiximols, THC:CBD extract) vs. placebo	1 (5) [115]	Low	No overlap (single review)	Moderate	No significant difference
Pain relief of 50% or greater						
	Nabiximols vs. placebo	1 (4) [116]	Critically low	No overlap (single review)	Low	No significant difference
Combined response (pain relief of 30% or greater and reduced opioid use)						
	Nabiximols vs. placebo	1 (1) [116]	Critically low	No overlap (single review)	Very low	No significant difference
Opioid dose reduction						
	THC:CBD/opioid vs. opioid only	1 (4) [117]	Low	No overlap (single review)	Low	No significant difference
Patient-perceived global improvement of pain						
	Nabiximols vs. placebo	1 (3) [116]	Critically low	No overlap (single review)	Low	Greater improvement with nabiximols

We identified one systematic review on the topic of **pain intensity**. Boland *et al.* (2020) [115] compared the effectiveness of THC:CBD formulations (Sativex, nabiximols, and THC:CBD extract) against placebo, finding evidence indicating no significant difference in pain intensity between THC:CBD formulations and placebo (five RCTs) in a meta-analysis of adults with cancer, with intervention durations ranging from 2 to 9 weeks. The certainty of the evidence was moderate.

We identified one systematic review on the topic of **pain relief of 50% or greater**. Häuser *et al.* (2019) [116] compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference in the likelihood of pain relief of 50% or greater between nabiximols and placebo (four RCTs) in a meta-analysis of adults with moderate to severe cancer-related pain insufficiently relieved by opioids, with intervention durations ranging from 2 to 5 weeks. The certainty of the evidence was low.

We identified one systematic review on the topic of **combined response** (i.e. pain relief of 30% or greater and reduced opioid use). Häuser *et al.* (2019) [116] compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference between nabiximols and placebo in the likelihood of a combined response (one RCT) in adults with cancer-related pain insufficiently relieved by opioids, with an intervention duration of 5 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **opioid dose reduction**. Noori *et al.* (2021) [117] compared the effectiveness of combined THC:CBD and opioid interventions against opioids alone, finding evidence indicating no significant difference in opioid dose reduction between the intervention with THC:CBD and opioids versus the intervention with opioids alone (four RCTs) in a meta-analysis of people living with chronic cancer-related pain, with intervention durations ranging from 2 to 5 weeks. The certainty of the evidence was low.

We identified one systematic review on the topic of **patient-perceived global improvement of pain**. Häuser *et al.* (2019) [116] compared the effectiveness of nabiximols against placebo, finding evidence indicating a significantly improved likelihood of much or very much improved global impression of pain for the intervention with nabiximols compared with placebo (two RCTs) in a meta-analysis of adults with moderate to severe cancer-related pain insufficiently relieved by opioids. One additional RCT with an enriched enrolment randomised withdrawal design (reported separately from the meta-analysis) reported the same findings. Intervention duration was 5 weeks for all included studies. The certainty of the evidence was low.

3.7.1.1.1.2 Nausea/vomiting

Table 11 provides an overview of the primary nausea/vomiting-related outcomes in cancer.

Table 11 Primary nausea/vomiting-related outcomes in cancer

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Absence of nausea						
	THC (nabilone, dronabinol) vs. placebo	1 (2) [120]	Critically low	No overlap (single review)	Low	No significant difference

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	THC (nabilone, dronabinol) vs. anti-emetic	1 (5) [120]	Critically low	No overlap (single review)	Moderate	No significant difference
	THC (dronabinol, nabilone)/anti-emetic vs. anti-emetic only	1 (1) [120]	Critically low	No overlap (single review)	Very low	No significant difference
Absence of vomiting						
	THC (nabilone, dronabinol) vs. placebo	1 (3) [120]	Critically low	No overlap (single review)	Moderate	More likely with THC
	THC (nabilone, dronabinol) vs. anti-emetic	1 (4) [120]	Critically low	No overlap (single review)	Moderate	No significant difference
	THC (dronabinol, nabilone)/anti-emetic vs. anti-emetic only	1 (2) [120]	Critically low	No overlap (single review)	Low	No significant difference
Absence of nausea and vomiting						
	THC (nabilone, dronabinol) vs. placebo	1 (3) [120]	Critically low	No overlap (single review)	Moderate	More likely with THC
	THC (nabilone, dronabinol) vs. anti-emetic	1 (4) [120]	Critically low	No overlap (single review)	Moderate	No significant difference
	THC (dronabinol, nabilone)/anti-emetic vs. anti-emetic only	1 (1) [120]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **absence of nausea**. Smith *et al.* (2015) [120] compared the effectiveness of THC (nabilone, dronabinol) against placebo, finding evidence indicating no significant difference in the likelihood of complete absence of nausea between the THC and placebo groups (two RCTs) in a meta-analysis of adults with cancer, with intervention durations of up to 15 hours. The certainty of the evidence was low. Smith *et al.* (2015) [120] also compared the effectiveness of THC (nabilone, dronabinol) against anti-emetic agents, finding evidence indicating no significant difference in

the likelihood of complete absence of nausea between the THC and anti-emetic groups (five RCTs) in a meta-analysis of adults with cancer, with intervention durations ranging from 1 to 4 days (reported for four RCTs). The certainty of the evidence was moderate. Smith *et al.* (2015) [120] also compared the effectiveness of THC (nabilone, dronabinol) combined with an anti-emetic agent against anti-emetic agents alone, finding evidence indicating no significant difference in the likelihood of complete absence of nausea between the combination THC/anti-emetic and the anti-emetic-only groups (one RCT) in adults with cancer, with treatment administered every 6 hours for an unspecified duration. The certainty of the evidence was very low. The review authors acknowledge that the included studies are generally older (pre-1991) and do not reflect current chemotherapy regimens and newer anti-emetic drugs. Further research is likely to modify the conclusions [120].

We identified one systematic review on the topic of **absence of vomiting**. Smith *et al.* (2015) [120] compared the effectiveness of THC (nabilone, dronabinol) against placebo, finding evidence indicating a greater likelihood of complete absence of vomiting with THC compared with placebo (three RCTs) in a meta-analysis of adults with cancer, with intervention durations of up to 15 hours (reported for two RCTs). The certainty of the evidence was moderate. Smith *et al.* (2015) [120] also compared the effectiveness of THC (nabilone, dronabinol) against anti-emetic agents, finding evidence indicating no significant difference in the likelihood of complete absence of vomiting between the THC and anti-emetic groups (four RCTs) in a meta-analysis of adults with cancer, with intervention durations ranging from 3 to 4 days (reported for three RCTs). The certainty of the evidence was moderate. Smith *et al.* (2015) [120] also compared the effectiveness of THC (nabilone, dronabinol) combined with an anti-emetic agent against anti-emetic agents alone, finding evidence indicating no significant difference in the likelihood of complete absence of vomiting between the combination THC/anti-emetic and the anti-emetic-only groups (two RCTs) in a meta-analysis of adults with cancer, with an intervention duration of up to 24 hours (reported for one RCT). The certainty of the evidence was low. The review authors acknowledge that the included studies are generally older (pre-1991) and do not reflect current chemotherapy regimens and newer anti-emetic drugs. Further research is likely to modify these conclusions [120].

We identified one systematic review on the topic of **absence of both nausea and vomiting**. Smith *et al.* (2015) [120] compared the effectiveness of THC (nabilone, dronabinol) against placebo, finding evidence indicating a greater likelihood of reporting a complete absence of nausea and vomiting with THC compared with placebo (three RCTs) in a meta-analysis of adults with cancer. Intervention duration was clearly reported for only one RCT (3 days). The certainty of the evidence was moderate. Smith *et al.* (2015) [120] also compared the effectiveness of THC (nabilone, dronabinol) against anti-emetic agents, finding evidence indicating no significant difference in the likelihood of complete absence of nausea and vomiting between THC and anti-emetic agents (four RCTs) in a meta-analysis of adults with cancer, with intervention durations ranging from 1 to 3 days (reported for two RCTs). The certainty of the evidence was moderate. Smith *et al.* (2015) [120] also compared the effectiveness of THC (nabilone, dronabinol) combined with an anti-emetic agent against an anti-emetic agent alone, finding evidence indicating no significant difference in the likelihood of complete absence of nausea and vomiting between THC and an anti-emetic in combination versus using anti-emetics alone (one RCT) in adults with cancer, with the intervention administered every 6 hours for an unspecified duration. The certainty of the evidence was very low. The review authors acknowledge that the included studies are generally older (pre-1991) and do not reflect current chemotherapy regimens and newer anti-emetic drugs. Further research is likely to modify these conclusions [120].

3.7.1.1.1.3 Nutrition-related outcomes

Table 12 provides an overview of the primary nutrition-related outcomes in cancer.

Table 12 Primary nutrition-related outcomes in cancer

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Appetite						
	THC (THC, dronabinol, nabilone) vs. placebo	1 (4) [118]	Critically low	75.0% overlap with cannabinoids vs. placebo	Low	No significant difference
	Dronabinol vs. megestrol acetate/dronabinol vs. megestrol acetate	2 (1) [118,119]	Critically low	100.0%	Very low	Greater improvement with megestrol acetate compared with dronabinol; no significant difference between combination treatment and megestrol acetate alone
	Cannabis extract vs. placebo	1 (1) [118]	Critically low	75.0% overlap with cannabinoids vs. placebo	Very low	No significant difference
	Cannabinoids (THC, cannabis extract) vs. placebo	1 (3) [119]	Critically low	75.0% overlap with THC vs. placebo, 75.0% overlap with cannabis extract vs. placebo	Low	No significant difference
Weight						
	THC (dronabinol, nabilone, THC) vs. placebo	2 (3, 1) [118,119]	Critically low	33.3%	Low Very low	No significant difference
	Cannabis extract vs. placebo	1 (1) [118]	Critically low	No overlap (single review)	Very low	No significant difference
	Dronabinol vs. megestrol	2 (1) [118,119]	Critically low	100.0%	Very low	Greater improvement

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	acetate/dronabinol vs. megestrol acetate					with megestrol acetate compared with dronabinol; no significant difference between combination treatment and megestrol acetate alone
Body mass index						
	Nabilone vs. placebo	1 (1) [118]	Critically low	No overlap (single review)	Very low	No significant difference
Caloric intake per day						
	THC (nabilone, dronabinol) vs. placebo	1 (2) [118]	Critically low	No overlap (single review)	Very low	No significant difference
Protein intake per day						
	THC (dronabinol, nabilone) vs. placebo	1 (2) [118]	Critically low	No overlap (single review)	Very low	Mixed findings; some evidence for greater improvement with THC
Carbohydrate intake per day						
	THC (dronabinol, nabilone) vs. placebo	1 (2) [118]	Critically low	No overlap (single review)	Very low	Mixed findings; some evidence for greater improvement with THC
Fats intake per day						

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Nabilone vs. placebo	1 (2) [118]	Critically low	No overlap (single review)	Very low	No significant difference
Iron intake per day						
	Nabilone vs. placebo	1 (1) [118]	Critically low	No overlap (single review)	Very low	No significant difference
Chemosensory perception						
	Dronabinol vs. placebo	1 (1) [118]	Critically low	No overlap (single review)	Very low	Greater improvement with dronabinol
Satiety						
	Dronabinol vs. placebo	1 (1) [118]	Critically low	No overlap (single review)	Very low	Greater improvement with dronabinol

We identified two systematic reviews on the topic of **appetite**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of THC (nabilone, dronabinol, THC) against placebo, finding evidence indicating no significant difference in appetite between THC (nabilone, dronabinol, THC) and placebo (four RCTs, narrative synthesis) in adults with cancer. Intervention durations/evaluations ranged from 3 to 8 weeks, with follow-up reported at 4 weeks for one RCT. The certainty of the evidence was low. Two of the RCTs found that appetite improved from baseline with both nabilone and dronabinol, but that this improvement was not significantly different from that seen in placebo groups. One of the RCTs found a greater improvement in pre-meal appetite with dronabinol compared with placebo. Razmovski-Naumovski *et al.* (2022) [118] also compared the effectiveness of cannabis extract against placebo, finding evidence indicating no significant difference in appetite between cannabis extract and placebo (one RCT) in adults with cancer, with an evaluation period of 6 weeks (intervention duration was not reported). The certainty of the evidence was very low. Simon *et al.* (2022) [119] compared the effectiveness of mixed cannabinoids (THC, cannabis extract) against placebo, finding evidence indicating no significant difference in appetite between mixed cannabinoids and placebo (three RCTs) in a meta-analysis of adults with cancer. The certainty of the evidence was low. The three RCTs in this analysis were also included in the analyses of THC against placebo (75% overlap) and of cannabis extract against placebo (75% overlap) by Razmovski-Naumovski *et al.* (2022). Intervention durations ranged from 18 days to 8 weeks, with follow-ups ranging from 30 days to 8 weeks. The reviews by Razmovski-Naumovski *et al.* (2022) [118] and Simon *et al.* (2022) [119] both compared the effectiveness of dronabinol against megestrol acetate (an appetite stimulant) and of dronabinol in combination with megestrol acetate against megestrol acetate alone. Each found evidence, based on the same single RCT (100% overlap), indicating improved appetite with megestrol acetate compared with dronabinol in adults with cancer. The same RCT found no significant difference between the combination treatment (both megestrol acetate and dronabinol) and megestrol

acetate alone. The intervention duration was not reported. The certainty of the evidence was very low in both reviews.

We identified two systematic reviews on the topic of **weight**. Razmovski-Naumovski *et al.* (2022) [118] and Simon *et al.* (2022) [119] both compared the effectiveness of THC (dronabinol, nabilone, THC) against placebo, finding no significant difference in weight change between THC (dronabinol, nabilone, THC)) and placebo (three RCTs, narrative synthesis, and one RCT, respectively) in adults with cancer. Intervention durations/evaluations ranged from 4 to 8 weeks, and overlap of primary studies between the two reviews was 33.3%. The certainty of the evidence was low [118] and very low [119], respectively. Razmovski-Naumovski *et al.* (2022) [118] also compared the effectiveness of cannabis extract against placebo, finding evidence indicating no significant difference in weight change between cannabis extract and placebo (one RCT) in adults with cancer, with an evaluation period of 6 weeks (intervention duration was not reported). The certainty of the evidence was very low. Razmovski-Naumovski *et al.* (2022) [118] and Simon *et al.* (2022) [119] both compared the effectiveness of dronabinol against megestrol acetate (an appetite stimulant) and of dronabinol in combination with megestrol acetate against megestrol acetate alone. Each found evidence, based on the same single RCT (100% overlap), indicating significantly improved weight gain (both self-reported and physician-reported) with megestrol acetate compared with dronabinol in adults with cancer. The same RCT found no significant difference between the combination treatment (both megestrol acetate and dronabinol) and megestrol acetate alone. The intervention duration was not reported. The certainty of the evidence was very low in both reviews.

We identified one systematic review on the topic of **body mass index**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of nabilone against placebo, finding evidence indicating no significant difference in body mass index between nabilone and placebo groups (one RCT) in adults with cancer, with an evaluation period of 8 weeks (intervention duration was not reported). The certainty of the evidence was very low.

We identified one systematic review on the topic of **caloric intake per day**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of THC (nabilone, dronabinol) against placebo, finding evidence indicating no significant difference in caloric intake per day between THC and placebo groups (two RCTs, narrative synthesis) in adults with cancer, with evaluation periods ranging from 3 to 8 weeks (intervention duration was not reported). The certainty of the evidence was very low.

We identified one systematic review on the topic of **protein intake per day**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of THC (nabilone, dronabinol) against placebo, finding mixed evidence for a significant difference in protein intake per day between the THC and placebo groups (two RCTs, narrative synthesis) in adults with cancer, with one RCT reporting no difference and the second reporting a significant increase in the proportion of calories consumed as protein with dronabinol compared with placebo, although the overall increase in protein intake was not significant. The intervention duration was not reported, but the evaluation period ranged from 3 to 8 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **carbohydrate intake per day**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of THC (nabilone, dronabinol) against placebo, finding mixed evidence for a significant difference in carbohydrate intake per day between THC and placebo (two RCTs, narrative synthesis) in adults with cancer, with one RCT reporting no difference and the second reporting a significant increase in carbohydrate intake with THC compared with placebo. The intervention duration was not reported but the evaluation period ranged from 3 to 8 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **fats intake per day**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of nabilone against placebo, finding evidence indicating no significant difference in fats intake per day between the nabilone and placebo groups (two RCTs, narrative synthesis) in adults with cancer. The intervention duration was not reported but the evaluation period ranged from 3 to 8 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **iron intake per day**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of nabilone against placebo, finding evidence indicating no significant difference in iron intake per day between nabilone and placebo (one RCT) in adults with cancer. The intervention duration was not reported but the evaluation took place for up to 8 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **chemosensory perception** (taste and smell). Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of dronabinol against placebo, finding evidence indicating significant improvements in chemosensory perception with dronabinol compared with placebo (one RCT) in adults with cancer. The intervention duration was not reported but the evaluation took place for up to 3 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **satiety**. Razmovski-Naumovski *et al.* (2022) [118] compared the effectiveness of dronabinol against placebo, finding evidence indicating significant improvements in satiety compared with baseline for dronabinol compared with placebo (one RCT) in adults with cancer. Trial duration was not reported, but the evaluation took place for up to 3 weeks. The certainty of the evidence was very low.

3.7.1.1.2 Efficacy: Secondary outcomes

Three reviews on cancer explored only adverse events and related dropouts as secondary outcomes [115,117,120]. Secondary outcomes explored by the three remaining reviews on cancer included additional pain outcomes (e.g. pain relief of 30% or greater, mean pain intensity) [116], sleep problems [116], daily maintenance and breakthrough opioid dosage [116], performance status (i.e. ability to carry out activities of daily living) [119], and quality of life [118,119]. Please see extraction forms for individual reviews for full information on secondary outcomes (Appendix F).

3.7.1.1.3 Safety

None of the reviews on cancer examined adverse events as primary outcomes, but all six reviews examined them as secondary outcomes [115–120]. Serious adverse events and dropouts due to adverse events were examined as primary outcomes by one review [116].

Adverse events noted included dizziness [115,118], nausea and vomiting [115,117,118], somnolence [115], nervous system effects [116], gastrointestinal effects [116], withdrawal due to lack of efficacy [120] or due to adverse events [116,120], dystonia [120], feeling good [118], feeling 'high' [118,120], sedation [120], drowsiness [118], and cardiac effects [118]. Psychiatric effects included hallucinations [118,120], euphoria [120], paranoia [120], anxiety [120], panic attacks [118], and psychiatric effects generally [116].

Generally, no differences were reported in the frequency of adverse events between cannabinoid intervention and comparator conditions, although the following adverse events were reported by at least one review to be more common in cannabinoid intervention conditions than in comparator conditions, based on meta-analysis: dizziness [115]; somnolence [115]; nervous system effects with clinical harm [116]; gastrointestinal effects without clinical harm [116]; nausea and vomiting [117]; and dropout due to adverse events [116].

Serious adverse events were examined by two reviews and did not appear to differ in frequency between intervention and comparator conditions [116,118].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.1.4 Summary of findings for cancer

The findings and certainty of evidence from the reviews on medicinal cannabis in relation to cancer outcomes vary quite widely. There is evidence of mixed certainty (very low to moderate) based on three systematic reviews generally indicating no significant difference between medicinal cannabis (THC:CBD) and placebo or opioid controls for pain-related outcomes. There is low-certainty evidence based on one systematic review indicating greater improvement in patient-perceived global improvement of pain with nabiximols compared with placebo. There is evidence of mixed certainty (very low to moderate) that THC (nabilone, dronabinol) performs better than placebo in eliminating vomiting only, as well as both nausea and vomiting, but is not superior to anti-emetics. There is evidence of mixed certainty (very low to low) that cannabinoids are no better than placebo in improving appetite, weight, body mass index, caloric intake, fats intake, and iron intake, and very low-certainty evidence that megestrol acetate is superior to dronabinol in improving appetite and weight. There is very low-certainty evidence that THC (dronabinol) is superior to placebo in improving chemosensory perception and satiety, and very low-certainty mixed evidence for a relative benefit of THC (dronabinol, nabilone) compared with placebo for improving protein and carbohydrate intake; however, findings indicating no significant benefit for THC compared with placebo were also identified. The reviews also presented evidence on secondary outcomes, including additional pain outcomes, sleep problems, and quality of life. Adverse events (including dizziness, gastrointestinal effects, somnolence, psychiatric effects, and feeling good or feeling 'high') were noted, but in most cases were not more common in the intervention (cannabinoid) than in the comparator condition.

3.7.1.2 HIV/AIDS

We identified one systematic review that investigated the impact of medicinal cannabis in adults with HIV/AIDS [121]. This review investigated morbidity and mortality in HIV/AIDS and also presented evidence on a range of secondary outcomes and adverse events. Please note that outcomes related to HIV/AIDS in the context of palliative care were also addressed by the systemic review on palliative care (see Section 3.7.1.6).

3.7.1.2.1 Efficacy: Primary outcomes

Table 13 provides an overview of the primary outcomes in HIV/AIDS.

Table 13 Primary outcomes in HIV/AIDS

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Morbidity						
	No evidence found for this outcome	1 [121]	Critically low	Not applicable	No evidence found for this outcome	Not applicable

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Mortality						
	No evidence found for this outcome	1 [121]	Critically low	Not applicable	No evidence found for this outcome	Not applicable

3.7.1.2.1.1 Morbidity and mortality

We identified one systematic review on the topic of **morbidity and mortality**. Lutge *et al.* (2013) [121] found no evidence relating to these outcomes.

3.7.1.2.2 Efficacy: Secondary outcomes

Secondary outcomes explored by the single review on HIV/AIDS included changes in weight, body fat, appetite, caloric intake, nausea and vomiting, performance (e.g. memory and dexterity), peripheral neuropathy, and mood, along with effects on viral load and cluster of differentiation 4 (CD4) cell count (a measure of immune system health) [121]. Please see the extraction forms for individual reviews for full information on secondary outcomes (Appendix F).

3.7.1.2.3 Safety

Adverse events were examined as secondary outcomes by the single review on HIV/AIDS [121].

Adverse events were measured in four of the seven primary studies included in the review [121]. Only one primary study reported adverse events in any group, finding that adverse events were more common in the dronabinol intervention compared with placebo. The nature of the adverse events was not reported. Very low numbers of dropouts due to adverse events were reported; reasons for these dropouts included acute cannabis-induced psychosis, intractable smoking-related cough, mood-altering effects, and sedation.

Serious adverse events were reported for only one primary study, which found that approximately 8% of adverse events reported in the dronabinol condition were serious in nature [121].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.2.4 Summary of findings for HIV/AIDS

We found one review examining medicinal cannabis for outcomes related to HIV/AIDS. The review found no evidence relating to the primary outcomes of interest (morbidity and mortality). The review presented evidence on a range of secondary outcomes, including outcomes related to nutrition, nausea and vomiting, peripheral neuropathy, and mood, along with effects on viral load and CD4 cell count. Adverse events were reported as having occurred in only one of seven primary studies included in the review, and were more common in the cannabinoid (dronabinol) condition compared with placebo. Dropouts due to adverse events were very uncommon. Serious adverse events were reported for only one primary study and represented a small proportion of overall adverse events.

3.7.1.3 Conditions in older adults

We identified four systematic reviews that investigated the impact of medicinal cannabis on symptom management in conditions in older adults. In terms of diagnostic focus, three reviews focused on specific diagnoses (Parkinson's disease [124], Alzheimer's disease [123], and dementia [122]) while one examined a range of indications for medicinal cannabinoids in older subjects [125]. In terms of outcomes, one review investigated agitation [125], one review investigated cognitive function [122], one review investigated breathlessness in chronic obstructive pulmonary disease (COPD) [125], all four reviews investigated general behavioural/psychological symptoms [122–125], two reviews investigated movement disorder [124,125], one review investigated nausea and vomiting [125], one review investigated nutrition-related outcomes [125], one review investigated pain-related outcomes [124], one review investigated mental health/well-being [124], and one review investigated sleep-related outcomes [124]. The reviews also presented evidence on a range of secondary outcomes and adverse events.

We have grouped these reviews together under the heading 'Conditions in older adults' primarily for pragmatic reasons. We acknowledge that the conditions described in these reviews can also affect younger adults; however, we believe that this grouping is useful for illuminating the particular case of medicinal cannabis use among older adults, particularly in relation to safety outcomes. We also acknowledge that not all older adults experience these outcomes (e.g. changes in cognitive function), and so we have endeavoured to specify the condition associated with the outcome wherever possible.

3.7.1.3.1 Efficacy: Primary outcomes

3.7.1.3.1.1 Agitation

Table 14 provides an overview of the primary outcomes related to agitation in Alzheimer's disease.

Table 14 Primary outcomes related to agitation in Alzheimer's disease

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Agitation in Alzheimer's disease (Cohen-Mansfield Agitation Inventory)						
	Dronabinol vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	Greater improvement with dronabinol
Agitation in Alzheimer's disease (nocturnal motor activity)						
	Dronabinol vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low/no evidence presented for this outcome	Outcome was assessed but no statistical analysis was presented due to small sample size

We identified one systematic review on the topic of **agitation in Alzheimer's disease** measured using the Cohen-Mansfield Agitation Inventory. Van den Elsen *et al.* (2014) [125] compared the effectiveness of dronabinol against placebo, finding evidence indicating significant improvements in disturbed behaviour with dronabinol compared with placebo (one RCT) in adults with Alzheimer's disease, with an intervention duration of 42 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **agitation (nocturnal motor activity) in Alzheimer's disease**. Van den Elsen *et al.* (2014) [125] included one RCT that compared the effectiveness of dronabinol against placebo for nocturnal motor activity in adults with Alzheimer's disease; however, the RCT presented no statistical analysis due to the very small sample size (N=2).

3.7.1.3.1.2 Cognitive function

Table 15 provides an overview of the primary outcomes related to cognitive function in dementia.

Table 15 Primary outcomes related to cognitive function in dementia

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Cognitive function in dementia						
	Nabilone vs. placebo	1 (1) [122]	Low	No overlap (single review)	Very low	Small, significant improvement with nabilone compared with placebo

We identified one systematic review on the topic of **cognitive function in dementia**. Bosnjak Kuharic *et al.* (2021) [122] compared the effectiveness of nabilone against placebo, finding evidence indicating a small, significant improvement in global and specific cognitive function with nabilone compared with placebo (one RCT) in adults with dementia, with an evaluation duration of 14 weeks (6 weeks for nabilone intervention period). The certainty of the evidence was very low.

3.7.1.3.1.3 Breathlessness in COPD

Table 16 provides an overview of the primary outcomes related to breathlessness in older adults with COPD.

Table 16 Primary outcomes related to breathlessness in older adults with COPD

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Minute ventilation						
	THC:CBD vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	No significant difference
PetCO2						
	THC:CBD vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	No significant difference

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Visual analogue scale for breathlessness						
	THC:CBD vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of breathlessness in older adults with COPD. Van den Elsen *et al.* (2014) [125] compared the effectiveness of THC:CBD against placebo for older adults with COPD, finding evidence indicating no significant difference in **minute ventilation**, **PetCO2**, or any measure of **visual analogue scale for breathlessness** between THC:CBD and placebo, based on one RCT with an intervention duration of 1 day. The certainty of the evidence was very low.

3.7.1.3.1.4 General behavioural/psychological symptoms

Table 17 provides an overview of the primary outcomes related to general behavioural/psychological symptoms in conditions in older adults.

Table 17 Primary outcomes related to general behavioural/psychological symptoms in conditions in older adults

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Behavioural and psychological symptoms of dementia						
	THC (dronabinol, nabilone, THC, delta-THC (Namisol)) vs. placebo	2 (3, 6) [122,123]	Critically low Low	50%	Very low Moderate	Mixed findings; stronger evidence for no significant difference
Observed affect in Alzheimer's disease (Lawton Observed Affect Scale-Past)						
	Dronabinol vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	Significantly greater benefit with dronabinol
General symptoms of Parkinson's disease (Unified Parkinson's Disease Rating Scale (UPDRS))						
	Mixed cannabinoids (THC:CBD, CBD only) vs. placebo	1 (2) [124]	Critically low	No overlap (single review)	Very low	Marginal worsening with cannabinoids

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
General symptoms of Parkinson's disease (Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS))						
	Nabilone vs. placebo	1 (1) [124]	Critically low	No overlap (single review)	Very low	Less deterioration in non-motor symptoms with nabilone; no differences reported for other subscales

We identified two systematic reviews on the topic of **behavioural and psychological symptoms of dementia**. Paunescu *et al.* (2020) [123] and Bosnjak Kuharic *et al.* (2021) [122] both compared the effectiveness of THC formulations (including dronabinol, nabilone, THC, and delta-THC (Namisol)) against placebo. Overlap between the two reviews was 50%. The findings from the reviews were divergent. Paunescu *et al.* (2020) [123] found mixed evidence for a significant difference in neuropsychiatric symptoms (aggression in dementia) between cannabinoids and placebo (six RCTs, narrative synthesis) in adults with Alzheimer's disease or other types of dementia, with intervention durations ranging from 2 to 14 weeks. Four RCTs reported a significant improvement in aggression with THC (dronabinol, nabilone) compared with placebo. Two other RCTs reported no significant difference between dronabinol and placebo. The certainty of the evidence was very low. Bosnjak Kuharic *et al.* (2021) [122] found no significant difference in behavioural and psychological symptoms of dementia between THC (nabilone, THC, delta-THC (Namisol)) and placebo (three RCTs, all of which were also included in Paunescu *et al.* (2020) [123]) in a meta-analysis of adults with dementia, with intervention durations ranging from 3 to 14 weeks. The certainty of the evidence was moderate.

We identified one systematic review on the topic of **observed affect in Alzheimer's disease**, measured using the Lawton Observed Affect Scale-Past. Van den Elsen *et al.* (2014) [125] compared the effectiveness of dronabinol against placebo, finding evidence indicating significant improvements in observed affect with dronabinol compared with placebo (one RCT) in adults with Alzheimer's disease. Positive affect was similar during the placebo and dronabinol intervention periods, but negative affect decreased over both periods and decreased further during the dronabinol period. Trial duration was 42 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **general symptoms of Parkinson's disease**, measured using two instruments: the UPDRS and the MDS-UPDRS. Urbi *et al.* (2022) [124] compared the effectiveness of mixed cannabinoids (THC:CBD, CBD only) against placebo, finding evidence indicating a marginal worsening of total UPDRS scores with cannabinoids (THC:CBD, CBD only) compared with placebo (two RCTs) in a meta-analysis of adults with Parkinson's disease, with intervention durations ranging from 4 to 6 weeks. The certainty of the evidence was very low. Urbi et al. (2022) [124] also identified one additional RCT that used the **MDS-UPDRS**, which is a revised version of the UPDRS. The two measures cannot be meaningfully combined for pooled analysis. Urbi *et al.* (2022) [124] compared the effectiveness of nabilone against placebo, finding evidence indicating significantly less deterioration in non-motor

symptoms with nabilone compared with placebo (one RCT) in adults with Parkinson's disease; however, no significant differences were found using other subscales examining motor experiences of daily living, motor examination, and motor complications. The intervention duration was 4 weeks, and the certainty of the evidence was very low.

3.7.1.3.1.5 Movement disorder

Table 18 provides an overview of the primary outcomes related to movement disorder in Parkinson's disease.

Table 18 Primary outcomes related to movement disorder in Parkinson's disease

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Levodopa-induced dyskinesia in Parkinson's disease						
	THC:CBD vs. placebo	1 (1) [125]	Critically low	50% overlap with mixed cannabinoids vs. placebo	Very low	No significant difference
	Mixed cannabinoids (THC (nabilone), THC:CBD) vs. placebo	1 (2) [124]	Critically low	50% overlap with THC:CBD vs. placebo	Very low	Mixed findings; greater improvement with nabilone compared with placebo, but no difference between THC:CBD and placebo
Tremor in Parkinson's disease						
	CBD vs. placebo	1 (1) [124]	Critically low	No overlap (single review)	Very low	Greater improvement with CBD

We identified two systematic reviews on the topic of **levodopa-induced dyskinesia in Parkinson's disease** (i.e. involuntary, erratic movements induced by levodopa, a dopamine replacement agent used in the management of symptoms of Parkinson's disease). Van den Elsen *et al.* (2014) [125] compared the effectiveness of THC:CBD against placebo, finding evidence indicating no significant difference in the incidence of levodopa-induced dyskinesia between THC:CBD and placebo (one RCT) in older adults with Parkinson's disease, with an intervention duration of 28 days. The certainty of the evidence was very low. Urbi *et al.* (2022) [124] compared the effectiveness of mixed cannabinoids (THC (nabilone), THC:CBD) against placebo, finding mixed evidence for a significant difference in levodopa-induced dyskinesia between mixed cannabinoids (THC (nabilone), THC:CBD) and placebo (two RCTs, narrative synthesis) in adults with Parkinson's disease, with one RCT reporting no difference (THC:CBD, an intervention duration of 4 weeks, no follow-up period specified) and the second RCT reporting a significant improvement with THC (nabilone) compared with placebo (one-time administration, no follow-up period reported). The

certainty of the evidence was very low. One RCT included in the analysis by van den Elsen *et al.* (2014) [125] was also included in the analysis by Urbi *et al.* (2022) [124]; overlap was 50%.

We identified one systematic review on the topic of **tremor in Parkinson's disease**. Urbi *et al.* (2022) [124] compared the effectiveness of CBD against placebo, finding evidence indicating a decrease of tremor amplitude following a single administration of CBD compared with placebo (one RCT) in adults with Parkinson's disease. The certainty of the evidence was very low.

3.7.1.3.1.6 Nausea/vomiting

Table 19 provides an overview of the primary outcomes related to nausea/vomiting in conditions in older adults.

Table 19 Primary outcomes related to nausea/vomiting in conditions in older adults

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Nausea and vomiting score						
	THC vs. prochlorperazine	1 (1) [125]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **nausea/vomiting**. Van den Elsen *et al.* (2014) [125] compared the effectiveness of THC against prochlorperazine (an anti-sickness medication), finding evidence for no significant difference in chemotherapy-induced nausea and vomiting between THC and prochlorperazine (one RCT) in older adults with a wide variety of neoplasms, with an intervention duration of 1 day. The certainty of the evidence was very low.

3.7.1.3.1.7 Nutrition-related outcomes

Table 20 provides an overview of the primary nutrition-related outcomes in conditions in older adults.

Table 20 Primary nutrition-related outcomes in conditions in older adults

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Global impression of change of appetite and food intake						
	No evidence was presented for this outcome	1 (1) [125]	Critically low	No overlap (single review)	No evidence was presented for this outcome	This outcome was assessed by one included primary study, but no data were presented in the review
Weight in Alzheimer's disease						

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Dronabinol vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	Significantly greater weight gain with dronabinol
Skin fold thickness in Alzheimer's disease						
	Dronabinol vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	No significant difference between dronabinol and placebo, but significant increase from baseline with dronabinol treatment
Caloric intake in Alzheimer's disease						
	Dronabinol vs. placebo	1 (1) [125]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **global impression of change of appetite and food intake**. Van den Elsen *et al.* (2014) [125] included one RCT that reportedly investigated this outcome among older adults with a wide variety of neoplasms; however, the review presented no data from this study for this outcome.

We identified one systematic review on the topic of **weight**. Van den Elsen *et al.* (2014) [125] compared the effectiveness of dronabinol against placebo, finding evidence indicating significantly greater weight gain with dronabinol compared with placebo (one RCT) in adults with Alzheimer's disease, with an intervention duration of 42 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **skin fold thickness**. Van den Elsen *et al.* (2014) [125] compared the effectiveness of dronabinol against placebo, finding evidence indicating that skin fold thickness increased from baseline with dronabinol in adults with Alzheimer's disease, but this increase was not significant compared with placebo (one RCT), with an intervention duration of 42 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **caloric intake**. Van den Elsen *et al.* (2014) [125] compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in caloric intake with dronabinol compared with placebo (one RCT) in adults with Alzheimer's disease, with an intervention duration of 42 days. The certainty of the evidence was very low.

3.7.1.3.1.8 Pain-related outcomes

Table 21 provides an overview of the primary pain-related outcomes in Parkinson's disease.

Table 21 Primary pain-related outcomes in Parkinson's disease

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain intensity in Parkinson's disease						
	Mixed cannabinoids (THC:CBD, THC only) vs. placebo	1 (2) [124]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **pain intensity in Parkinson's disease**. Urbi *et al.* (2022) [124] compared the effectiveness of mixed cannabinoids (THC:CBD, THC only) against placebo, finding evidence indicating no significant difference in pain intensity between mixed cannabinoids (THC:CBD, THC only) and placebo (two RCTs, narrative synthesis) in adults with Parkinson's disease, with an intervention duration of 4 weeks. The certainty of the evidence was very low.

3.7.1.3.1.9 Mental health/well-being

Table 22 provides an overview of the primary outcomes related to mental health/well-being in Parkinson's disease.

Table 22 Primary outcomes related to mental health/well-being in Parkinson's disease

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Anxiety in Parkinson's disease						
	Mixed cannabinoids (CBD, nabilone) vs. placebo	1 (2) [124]	Critically low	No overlap (single review)	Very low	Significantly greater decrease in anxiety with CBD and THC interventions
Quality of life in Parkinson's disease						
	Mixed cannabinoids (THC:CBD, CBD only) vs. placebo	1 (2) [124]	Critically low	No overlap (single review)	Very low	Mixed evidence; no significant difference reported for THC:CBD, but significant improvement with CBD only compared with placebo

We identified one systematic review on the topic of **anxiety in Parkinson's disease**. Urbi *et al.* (2022) [124] compared the effectiveness of mixed cannabinoids (CBD, nabilone) against placebo, finding evidence indicating a decrease in anxiety with CBD (single administration) and with THC (nabilone) compared with placebo (two RCTs, narrative synthesis) in adults with Parkinson's disease. Intervention duration was 4 weeks, and the certainty of the evidence was very low.

We identified one systematic review on the topic of **quality of life in Parkinson's disease**. Urbi *et al.* (2022) [124] compared the effectiveness of mixed cannabinoids (THC:CBD, CBD only) against placebo, finding mixed evidence for a significant difference in quality of life between mixed cannabinoids (THC:CBD, CBD only) and placebo (two RCTs, narrative synthesis) in adults with Parkinson's disease, with one RCT reporting no difference (THC:CBD, intervention duration of 4 weeks) and a second RCT reporting significant improvements with CBD-only treatment compared with placebo (intervention duration of 6 weeks). The certainty of the evidence was very low.

3.7.1.3.1.10 Sleep-related outcomes

Table 23 provides an overview of the primary sleep-related outcomes in Parkinson's disease.

Table 23 Primary sleep-related outcomes in Parkinson's disease

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sleep quality in Parkinson's disease						
	Nabilone vs. placebo	1 (1) [124]	Critically low	No overlap (single review)	Very low	Significantly greater improvement with nabilone

We identified one systematic review on the topic of **sleep quality in Parkinson's disease**. Urbi *et al.* (2022) [124] compared the effectiveness of nabilone against placebo, finding evidence for significantly improved sleep quality with nabilone compared with placebo (one RCT) in adults with Parkinson's disease, with an intervention duration of 4 weeks. The certainty of the evidence was very low.

3.7.1.3.2 Efficacy: Secondary outcomes

Secondary outcomes explored by one review on dementia [122] included agitation/aggression, quality of life, change in functional outcomes, dementia severity, nutritional outcomes, and carer burden. No other reviews reported secondary outcomes. Please see extraction forms for individual reviews for full information on secondary outcomes (Appendix F).

3.7.1.3.3 Safety

Adverse events were examined as primary outcomes by three reviews on conditions in older adults [122,124,125] and as secondary outcomes by one review [123].

Adverse events noted included drowsiness/sedation [122–125], forgetfulness [124], sleep effects (including somnolence, insomnia, and nightmares) [123,124], nervous system effects (including balance and dizziness) [122,123], physiological effects [125], psychological/psychiatric effects [122,125], and gastrointestinal effects [122]. A number of adverse events were reported to be more common in cannabinoid intervention conditions compared with control conditions by at least one review, including sedation/drowsiness [122,123,125] and physiological and psychological adverse events [125]. Urbi *et al.* (2022) [124] reported a higher frequency of adverse events with higher dosing of cannabinoids, particularly with products containing THC.

Regarding **serious adverse events**, two reviews reported that no major safety events/serious adverse events occurred [124,125].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.3.4 Summary of findings for conditions in older adults

We found four reviews examining the effectiveness of medicinal cannabis for outcomes related to conditions in older adults. There is some evidence of mixed certainty (almost exclusively very low) for improvements in behavioural and psychological symptoms of dementia, Alzheimer's disease, and Parkinson's disease with cannabinoids, as well as for movement disorder, anxiety, quality of life, and sleep quality in Parkinson's disease, and weight gain in Alzheimer's disease. However, no significant benefit of cannabinoids was observed for breathlessness in COPD, for nausea and vomiting in older adults receiving chemotherapy, or for pain in Parkinson's disease. One review on dementia presented evidence on secondary outcomes, including agitation/aggression, quality of life, change in functional outcomes, dementia severity, nutritional outcomes, and carer burden. Adverse events (including drowsiness/sedation, sleep effects, nervous system effects, and gastrointestinal effects) were noted, and sedation was noted to be more common with cannabinoid interventions than with placebo.

3.7.1.4 Inflammatory bowel disease

We identified two systematic reviews that investigated the impact of medicinal cannabis on outcomes related to inflammatory bowel disease [126,127]. One review investigated clinical remission rates in Crohn's disease [126] and the other review investigated clinical remission rates in ulcerative colitis [127]. The reviews also presented evidence on a range of secondary outcomes and adverse events.

3.7.1.4.1 Efficacy: Primary outcomes

Table 24 provides an overview of the primary outcomes in inflammatory bowel disease.

Table 24 Primary outcomes in inflammatory bowel disease

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Clinical remission in Crohn's disease						
	THC (cannabis cigarette) vs. placebo	1 (1) [126]	Low	No overlap (single review)	Very low	No significant difference
	CBD (cannabis oil 5%) vs. placebo	1 (1) [127]	Low	No overlap (single review)	Very low	No significant difference
Clinical remission in ulcerative colitis						
	CBD vs. placebo	1 (1) [127]	Moderate	No overlap (single review)	Very low	No significant difference

3.7.1.4.1.1 Clinical remission

We identified one systematic review on the topic of **clinical remission in Crohn's disease**. Kafil *et al.* (2018a) [126] found evidence indicating no significant difference between THC (cannabis cigarette) and placebo (one RCT) in adults with Crohn's disease. The certainty of the evidence was very low. Kafil *et al.* (2018a) also found evidence indicating no significant difference between CBD (cannabis oil 5%) and placebo (one RCT) in adults with Crohn's disease. The certainty of the evidence was very low. In each case, trial duration was 16 weeks (8 weeks for the intervention, 8 weeks for the placebo) with an additional follow-up after 2 weeks.

We identified one systematic review on the topic of **clinical remission in ulcerative colitis**. Kafil *et al.* (2018b) [127] compared the effectiveness of CBD against placebo, finding evidence indicating no significant difference between CBD and placebo (one RCT) in adults with ulcerative colitis, with an intervention duration of 10 weeks. The certainty of the evidence was very low.

3.7.1.4.2 Efficacy: Secondary outcomes

Secondary outcomes explored by the two reviews on inflammatory bowel disease included clinical response [126,127], C-reactive protein [126,127], quality of life [126,127], and bowel symptoms [127]. Please see extraction forms for individual reviews for full information on secondary outcomes (Appendix F).

3.7.1.4.3 Safety

Neither of the reviews on inflammatory bowel disease examined adverse events as primary outcomes, but both reviews examined adverse events as secondary outcomes [126,127].

Adverse events noted included sleepiness/somnolence [126,127], nausea [126,127], vomiting [127], cognitive symptoms (e.g. difficulty with concentration, confusion) [126,127], headache [127], dizziness [126,127], fatigue [127], and dry mouth [127]. They were reported to be generally mild or moderate in severity [126,127] and were more common in the intervention conditions [126,127]. Withdrawals from the primary studies due to adverse events were no more common in the intervention conditions compared with the control conditions [127].

Serious adverse events noted included worsening of clinical condition and did not appear to differ between the intervention and comparator conditions [126,127].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.4.4 Summary of findings for inflammatory bowel disease

There is very low-certainty evidence based on two systematic reviews generally indicating no significant difference between medicinal cannabis and placebo for primary outcomes related to inflammatory bowel disease, namely clinical remission in ulcerative colitis and in Crohn's disease. The reviews presented evidence on secondary outcomes, including clinical response, C-reactive protein, quality of life, and bowel symptoms. Adverse events (including sleepiness, nausea, cognitive symptoms (e.g. difficulty with concentration, confusion), dizziness, and dry mouth) were reported to be generally mild or moderate in severity and were more common in the intervention conditions.

3.7.1.5 Mental health and neuropsychological conditions

We identified six systematic reviews that investigated the impact of medicinal cannabis on outcomes related to mental health and neuropsychological conditions. In terms of diagnostic focus, four reviews focused on specific diagnoses (namely schizophrenia and other psychoses [131], anxiety disorders [128], anorexia nervosa [133], and opioid dependence [130]), while two reviews examined a range of mental health and neuropsychological conditions [129,132]. In terms of outcomes, three reviews investigated outcomes related to psychotic disorders [129,131,132], three reviews investigated outcomes related to

anxiety [128,129,132], one review investigated outcomes related to mood disorders [129], two reviews investigated outcomes related to eating disorders [132,133], two reviews investigated outcomes related to substance dependence [130,132], and two reviews investigated outcomes related to neurodevelopmental disorders [129,132]. The reviews also presented evidence on a range of secondary outcomes and adverse events.

3.7.1.5.1 Efficacy: Primary outcomes

3.7.1.5.1.1 Psychotic disorders

Table 25 provides an overview of the primary outcomes related to psychotic disorders.

Table 25 Primary outcomes related to psychotic disorders in mental health and neuropsychological conditions

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Remission from psychotic disorders						
	No evidence found for this outcome	1 [129]	Critically low	Not applicable	No evidence found for this outcome	No evidence found for this outcome
Positive symptoms of psychosis						
	THC vs. placebo	1 (1) [129]	Critically low	No overlap (single review)	Very low	No significant difference
	CBD vs. placebo	1 (2) [129]	Critically low	No overlap (single review)	Low	No significant difference
	CBD vs. amisulpride	1 (1) [129]	Critically low	No overlap (single review)	Very low	No significant difference
Negative symptoms of psychosis						
	THC vs. placebo	1 (1) [129]	Critically low	No overlap (single review)	Very low	Significant worsening with THC
	CBD vs. placebo	1 (2) [129]	Critically low	No overlap (single review)	Low	No significant difference
	CBD vs. amisulpride	1 (1) [129]	Critically low	No overlap (single review)	Very low	No significant difference
Total symptoms of psychosis/schizophrenia						
	CBD vs. placebo	3 (2) [129,131,132]	Critically low	100%	Low (2) Very low (1)	No significant difference

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	CBD vs. amisulpride	3 (1) [129,131,132]	Critically low	100%	Very low	No significant difference
	THC vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significant short-term worsening with THC
Cognitive function in schizophrenia						
	CBD vs. placebo	2 (2, 1) [131,132]	Critically low	50%	Very low	No significant difference
	THC vs. placebo	1 [132]	Critically low	No overlap (single review)	Very low	Significant short-term worsening with THC

We identified one systematic review on the topic of **remission from psychotic disorders** (i.e. the patient no longer meets diagnostic criteria following treatment). Black *et al.* (2019) [129] found no evidence for this outcome.

We found one systematic review on the topic of **positive symptoms of psychosis** (i.e. changes in behaviour or thoughts, such as hallucinations, delusions, movement disorders, confused thoughts, and disorganised speech). Black *et al.* (2019) [129] compared the effectiveness of THC against placebo, finding evidence indicating no significant difference in positive symptoms of psychosis between intravenous THC and placebo (one RCT) in adults, with an intervention duration of 3 weeks [129]. The certainty of the evidence was very low. Black *et al.* (2019) [129] also compared the effectiveness of CBD against placebo, finding evidence indicating no significant difference in positive symptoms of psychosis between CBD and placebo (two RCTs) in a meta-analysis of adults, with an intervention duration of 6 weeks. The certainty of the evidence was low. Black *et al.* (2019) [129] also compared the effectiveness of CBD against amisulpride (an antipsychotic medication), finding evidence indicating no significant difference in positive symptoms of psychosis between CBD and the active comparator (amisulpride) (one RCT) in adults, with an intervention duration of 4 weeks. The certainty of the evidence was very low.

We found one systematic review on the topic of **negative symptoms of psychosis** (i.e. withdrawal of the patient from the world around them, with loss of pleasure, emotion, expressiveness, and interest in social interaction). Black *et al.* (2019) [129] compared the effectiveness of THC against placebo, finding evidence indicating significant worsening of negative symptoms of psychosis with intravenous THC compared with placebo (one RCT) in adults, with an intervention duration of 3 weeks. The certainty of the evidence was very low. Black *et al.* (2019) [129] also compared the effectiveness of CBD against placebo, finding evidence indicating no significant difference in negative symptoms of psychosis between CBD and placebo (two RCTs) in a meta-analysis of adults, with an intervention duration of 6 weeks. The certainty of the evidence was low. Black *et al.* (2019) [129] also compared the effectiveness of CBD against amisulpride, finding evidence indicating no significant difference in negative symptoms of psychosis between CBD and the active comparator (amisulpride) (one RCT) in adults, with an intervention duration of 4 weeks. The certainty of the evidence was very low.

We found three systematic reviews on the topic of **total symptoms of psychosis/schizophrenia**. Black *et al.* (2019) [129], Kopelli *et al.* (2020) [131], and McKee *et al.* (2021) [132] all compared the effectiveness of CBD against placebo, all based on the same two RCTs (100% overlap). Black *et al.* (2019) [129] and Kopelli *et al.* (2020) [131] reported evidence indicating no significant difference in total symptoms of psychosis/schizophrenia between CBD and placebo (two RCTs) in a meta-analysis of adults with schizophrenia or related psychotic disorders. The certainty of the evidence was low. McKee *et al.* (2021) [132], in a narrative synthesis of the same two RCTs, reported evidence indicating that one RCT found no significant difference between CBD and placebo, while the other RCT reported a statistically but not clinically significant difference favouring CBD. The certainty of the evidence was very low. Black *et al.* (2019) [129], Kopelli *et al.* (2020) [131], and McKee *et al.* (2021) [132] also all compared the effectiveness of CBD against amisulpride, all based on the same single RCT (100% overlap). All three reviews reported evidence indicating no significant difference in improvement in positive/negative psychotic symptomatology between CBD and amisulpride (one RCT) in adults with schizophrenia, with an intervention duration of 4 weeks. The certainty of the evidence was very low. McKee *et al.* (2021) [132] also compared the effectiveness of THC against placebo, finding evidence indicating short-term worsening of positive and negative symptoms of schizophrenia with THC compared with placebo (one RCT) in adults with schizophrenia, with THC administered on 3 test days, each separated by at least 7 days. The certainty of the evidence was very low.

We found two systematic reviews on the topic of **cognitive function in schizophrenia**. Kopelli *et al.* (2020) [131] and McKee *et al.* (2021) [132] both compared the effectiveness of CBD against placebo (50% overlap of primary studies), finding evidence indicating no significant difference in cognitive function between CBD and placebo (two RCTs) in a meta-analysis of adults with schizophrenia or related psychotic disorders, with an intervention duration of 6 weeks. The certainty of the evidence was very low. McKee *et al.* (2021) [132] also compared the effectiveness of THC against placebo, finding evidence indicating short-term worsening of cognitive function with THC compared with placebo (one RCT) in adults with schizophrenia, with THC administered on 3 test days, each separated by at least 7 days. The certainty of the evidence was very low.

3.7.1.5.1.2 Anxiety disorders

Table 26 provides an overview of the primary outcomes related to anxiety.

Table 26 Primary outcomes related to anxiety in mental health and neuropsychological conditions

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Remission from anxiety disorder						
	No evidence found for this outcome	1 [129]	Critically low	Not applicable	No evidence found for this outcome	No evidence found for this outcome
Generalised anxiety disorder symptoms						

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Mixed cannabinoids (nabilone, CBD) vs. placebo	1 (3) [128]	Critically low	No overlap (single review)	Low	Significantly greater improvement with cannabinoids
	Medicinal cannabis with varying ratios of THC to CBD	1 (1)[128]	Critically low	No overlap (single review)	Very low	Significant improvement with cannabis
Remission from post-traumatic stress disorder (PTSD)						
	No evidence found for this outcome	1 [129]	Critically low	Not applicable	No evidence found for this outcome	No evidence found for this outcome
PTSD symptoms						
	Nabilone vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significantly greater improvement with nabilone
Social anxiety disorder symptoms						
	CBD vs. placebo	2 (2) [128,132]	Critically low	100%	Very low Low	Significantly greater improvement with CBD
Anxiety symptoms						
	Mixed cannabinoids (THC with or without CBD) vs. placebo	1 (7) [129]	Critically low	No overlap (single review)	Low	Significantly greater improvement with cannabinoids
	Nabilone vs. ibuprofen	1 (1) [129]	Critically low	No overlap (single review)	Very low	No significant difference
	CBD vs. placebo	1 (2) [129]	Critically low	No overlap (single review)	Very low	No significant difference
	Nabilone vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significantly greater improvement with nabilone

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Obsessive-compulsive disorder symptoms						
	High-THC cannabis vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	No significant difference
	Low-THC cannabis vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **remission from anxiety disorder** (i.e. the patient no longer meets diagnostic criteria following treatment). Black *et al.* (2019) [129] found no evidence for this outcome.

We identified one systematic review on the topic of **generalised anxiety disorder symptoms**. Bahji *et al.* (2020) [128] compared the effectiveness of mixed cannabinoids (nabilone, CBD) against placebo, finding evidence indicating significant improvements in anxiety symptoms with cannabinoids compared with placebo groups (three RCTs) in a meta-analysis of adults with generalised anxiety disorder, with intervention durations ranging from 1 to 4 weeks. The certainty of the evidence was low. Bahji *et al.* (2020) [128] also compared the effectiveness of different types of medicinal cannabis with varying ratios of THC to CBD, finding evidence indicating a significant reduction in anxiety symptoms with medicinal cannabis (one open-label RCT) in adults with generalised anxiety disorder, with an intervention duration of 10 months. The certainty of the evidence was very low.

We identified one systematic review on the topic of **remission from PTSD** (i.e. the patient no longer meets diagnostic criteria following treatment). Black *et al.* (2019) [129] found no evidence for this outcome.

We identified one systematic review on the topic of **PTSD symptoms**. McKee *et al.* (2021) [132] compared the effectiveness of nabilone against placebo, finding evidence indicating a significant improvement in PTSD symptoms (recurring and distressing dreams) with nabilone compared with placebo (one RCT) in adults with PTSD, with an intervention duration of 16 weeks. The certainty of the evidence was very low. See Section 3.7.2.5.3 for additional evidence on medicinal cannabis for relief of nightmares in PTSD from reviews of mixed health conditions.

We identified two systematic reviews on the topic of **social anxiety disorder symptoms**. Bahji *et al.* (2020) [128] and McKee *et al.* (2021) [132] both compared the effectiveness of CBD against placebo based on the same two RCTs (100% overlap). They found low- and very low-certainty evidence, respectively, indicating a significantly greater improvement in anxiety symptoms with CBD compared with placebo (two RCTs, narrative synthesis) in adults with social anxiety disorder, with intervention durations of 1 day, or 2 treatment days separated by 7 days. The certainty of the evidence was low in Bahji *et al.* (2020) [128] and very low in McKee *et al.* (2021) [132]; even though the reviews report evidence from the same RCTs, the discrepancy arises from each review assigning different risk of bias scores to the included RCTs.

We identified two systematic reviews on the topic of **anxiety symptoms**. Black *et al.* (2019) [129] compared the effectiveness of mixed cannabinoids (THC with or without CBD) against placebo, finding evidence indicating significantly greater improvements in anxiety symptoms with THC (with or without

CBD) compared with placebo groups (seven RCTs) in a meta-analysis of adults, with intervention durations ranging from 1 day to 12 weeks. The certainty of the evidence was low. Black *et al.* (2019) [129] also compared the effectiveness of nabilone against ibuprofen (an analgesic/nonsteroidal anti-inflammatory drug), finding evidence indicating no significant difference in anxiety symptoms between THC (nabilone) and the active comparator (ibuprofen) (one RCT) in adults, with an intervention duration of 8 weeks. The certainty of the evidence was very low. Black *et al.* (2019) [129] also compared the effectiveness of CBD against placebo, finding evidence indicating no significant difference in anxiety symptoms between CBD and placebo (two RCTs) in a meta-analysis of adults, with an intervention duration of 1 day. The certainty of the evidence was very low. McKee *et al.* (2021) [132] compared the effectiveness of nabilone against placebo, finding evidence indicating a significantly greater improvement in anxiety symptoms with nabilone compared with placebo (one RCT) in adults with an anxiety disorder, with an intervention duration of 28 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **obsessive-compulsive disorder symptoms**. McKee *et al.* (2021) [132] compared the effectiveness of high-THC cannabis against placebo, finding evidence indicating no significant difference in obsessive-compulsive disorder symptomatology between high-THC cannabis and placebo (one RCT) in adults with obsessive-compulsive disorder. Patients administered placebo had lower anxiety scores than those who were administered cannabis. The certainty of the evidence was very low. The intervention was administered on 3 test days. McKee *et al.* (2021) [132] also compared the effectiveness of low-THC cannabis against placebo for the same outcome, finding evidence indicating no significant difference in obsessive-compulsive disorder symptomatology between low-THC cannabis and placebo (one RCT) in adults with obsessive-compulsive disorder. Patients administered placebo had lower anxiety scores than those who were administered cannabis. The certainty of the evidence was very low. The intervention was administered on 3 test days.

3.7.1.5.1.3 Mood disorders

Table 27 provides an overview of the primary outcomes related to mood disorders.

Table 27 Primary outcomes related to mood disorders in mental health and neuropsychological conditions

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Remission from depression						
	No evidence found for this outcome	1 [129]	Critically low	Not applicable	No evidence found for this outcome	No evidence found for this outcome
Depression symptoms						
	Mixed cannabinoids (THC with or without CBD) vs. placebo	1 (12) [129]	Critically low	No overlap (single review)	Low	No significant difference

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Nabilone vs. ibuprofen	1 (1) [129]	Critically low	No overlap (single review)	Very low	No significant difference
	Cannabis (plant) vs. placebo	1 (1) [129]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **remission from depression** (i.e. the patient no longer meets diagnostic criteria following treatment). Black *et al.* (2019) [129] found no evidence for this outcome.

We identified one systematic review on the topic of **depression symptoms**. Black *et al.* (2019) [129] compared the effectiveness of mixed cannabinoids (THC with or without CBD) against placebo, finding evidence indicating no significant difference in depression symptoms between THC (with or without CBD) and placebo (12 RCTs) in a meta-analysis of adults, with intervention durations ranging from 1 day to 156 weeks. The certainty of the evidence was low. Black *et al.* (2019) [129] also compared the effectiveness of nabilone against ibuprofen (an analgesic/nonsteroidal anti-inflammatory drug), finding evidence indicating no significant difference in depression symptoms between THC (nabilone) and the active comparator (ibuprofen) (one RCT) in adults, with an intervention duration of 8 weeks. The certainty of the evidence was very low. Black *et al.* (2019) [129] also compared the effectiveness of cannabis (plant) against placebo, finding evidence indicating no significant difference in depression symptoms between cannabis and placebo (one RCT) in adults, with an intervention duration of 5 days. The certainty of the evidence was very low.

3.7.1.5.1.4 Eating disorders

Table 28 provides an overview of the primary outcomes related to eating disorders.

Table 28 Primary outcomes related to eating disorders in mental health and neuropsychological conditions

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Weight in anorexia nervosa						
	Dronabinol vs. placebo	2 (1) [132,133]	Critically low	100%	Very low	Significantly greater improvement with dronabinol
	Cannabis vs. diazepam	1 (1) [133]	Critically low	No overlap	Very low	No significant difference

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
				(single review)		

We found two systematic reviews on the topic of **weight in anorexia nervosa**. McKee *et al.* (2021) [132] and Rosager *et al.* (2021) [133] both compared the effectiveness of dronabinol against placebo, based on the same single RCT (100% overlap), finding evidence indicating significantly higher weight gain with dronabinol compared with placebo (one RCT) in adults with anorexia nervosa. Trial length was 12 weeks, including 4 weeks of intervention with dronabinol. The certainty of the evidence was very low. Rosager *et al.* (2021) [133] also compared the effectiveness of cannabis against diazepam (a benzodiazepine), finding evidence indicating no significant difference in weight change between cannabis and diazepam (one RCT) in adults with anorexia nervosa, with an intervention duration of 5 weeks. The certainty of the evidence was very low.

3.7.1.5.1.5 Substance dependence

Table 29 provides an overview of the primary outcomes related to substance dependence.

Table 29 Primary outcomes related to substance dependence in mental health and neuropsychological conditions

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Withdrawal symptoms/discomfort in cannabis use disorder						
	Dronabinol vs. placebo (in combination with motivational enhancement/relapse prevention therapy)	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significantly greater improvement with dronabinol
	Dronabinol vs. placebo	1 (2) [132]	Critically low	No overlap (single review)	Very low	No significant difference
	Nabiximols vs. placebo	1 (4) [132]	Critically low	No overlap (single review)	Moderate	No significant difference
Cravings in cannabis use disorder						

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Nabiximols vs. placebo	1 (2) [132]	Critically low	No overlap (single review)	Very low	No significant difference
Treatment retention/abstinence in cannabis use disorder						
	Dronabinol vs. placebo (in combination with motivational enhancement/relapse prevention therapy)	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significantly greater retention with dronabinol
	Nabiximols vs. placebo	1 (3) [132]	Critically low	No overlap (single review)	Low	Mixed findings; no improved retention with nabiximols beyond 3 days after treatment cessation
Cannabis consumption (amounts) in cannabis use disorder						
	Dronabinol vs. placebo (in combination with motivational enhancement/relapse prevention therapy)	1 (1) [132]	Critically low	No overlap (single review)	Very low	No significant difference
	Nabilone vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	No significant difference
	Nabiximols vs. placebo (in combination with cognitive behavioural therapy)	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significantly greater reduction in consumption with nabiximols
Maintenance (reduction in use and reduction in cravings) in cannabis use disorder						

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Dronabinol vs. placebo	1 (3) [132]	Critically low	No overlap (single review)	Very low	Significantly greater with dronabinol
Cravings in opioid use disorder						
	CBD (Epidyolex) vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significantly reduced cravings and anxiety with CBD
Withdrawal symptoms in opioid use disorder/opioid dependence						
	Dronabinol vs. placebo	2 (2, 1) [130,132]	Critically low	50%	Low Very low	Mixed findings; some evidence for significantly greater reduction in withdrawal symptoms with dronabinol
	Dronabinol vs. oxycodone	1 (2) [130]	Critically low	No overlap (single review)	Very low	Significantly greater reduction in withdrawal symptoms with dronabinol
Tobacco use/cravings in tobacco use disorder						
	CBD vs. placebo	1 (1) [132]	Critically low	No overlap (single review)	Very low	Significantly greater reduction in tobacco use with CBD and significantly greater but short-lived reduction in

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect

cravings with CBD

We identified one systematic review on the topic of **withdrawal symptoms/discomfort in cannabis use disorder**. McKee *et al.* (2021) [132] compared the effectiveness of dronabinol against placebo (in combination with motivational enhancement/relapse prevention therapy), finding evidence indicating significantly improved withdrawal symptoms with dronabinol compared with placebo (in combination with motivational enhancement and relapse prevention therapy) (one RCT) in adults with cannabis use disorder, with a trial length of 12 weeks. The certainty of the evidence was very low. McKee *et al.* (2021) [132] also compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in withdrawal discomfort between dronabinol and placebo (two RCTs) in a meta-analysis of adults with cannabis use disorder, with trial length ranging from 40 to 51 days. The certainty of the evidence was very low. McKee *et al.* (2021) [132] also compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference in withdrawal discomfort between nabiximols and placebo (four RCTs) in a meta-analysis of adults with cannabis use disorder. Trial length ranged from 8 to 12 weeks for three studies, with one study reporting a 6-day intervention regimen and a 28-day follow-up period. The certainty of the evidence was moderate.

We identified one systematic review on the topic of **cravings in cannabis use disorder**. McKee *et al.* (2021) [132] compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference in cravings between nabiximols and placebo (two RCTs, narrative synthesis) in adults with cannabis use disorder, with trial lengths ranging from 8 to 12 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **treatment retention/abstinence in cannabis use disorder**. McKee *et al.* (2021) [132] compared the effectiveness of dronabinol against placebo (in combination with motivational enhancement/relapse prevention therapy), finding evidence indicating significantly improved treatment retention after 8 weeks with dronabinol compared with placebo (in combination with motivational enhancement and relapse prevention therapy) (one RCT) in adults with cannabis use disorder. However, this study observed no difference in abstinence between the groups after 2 weeks. Trial length was 12 weeks. The certainty of the evidence was very low. McKee *et al.* (2021) [132] also compared the effectiveness of nabiximols against placebo, finding mixed evidence for a significant difference in treatment retention/abstinence between nabiximols and placebo (three RCTs, narrative synthesis) in adults with cannabis use disorder. Two RCTs reported no difference between groups. The third study reported significantly improved treatment retention with nabiximols compared with placebo; however, the effects were not observed beyond 3 days after cessation of treatment. Trial length was 12 weeks for the two studies reporting null findings, and the study with positive findings reported a 6-day intervention regimen and a 28-day follow-up period. The certainty of the evidence was low.

We identified one systematic review on the topic of **cannabis consumption (amounts) in cannabis use disorder**. McKee *et al.* (2021) [132] compared the effectiveness of dronabinol against placebo (in

combination with motivational enhancement/relapse prevention therapy), finding evidence indicating no significant difference in the amount of cannabis consumed between dronabinol and placebo (in combination with motivational enhancement and relapse prevention therapy) (one RCT) in adults with cannabis use disorder, with a trial length of 12 weeks. The certainty of the evidence was very low. McKee *et al.* (2021) [132] also compared the effectiveness of nabilone against placebo, finding evidence indicating no significant difference in the amount of cannabis consumed between nabilone and placebo (one RCT) in adults with cannabis use disorder, with a trial length of 12 weeks. The certainty of the evidence was very low. McKee *et al.* (2021) [132] also compared the effectiveness of nabiximols against placebo (in combination with cognitive behavioural therapy), finding evidence indicating a significant reduction in the amount of cannabis consumed with nabiximols compared with placebo (in combination with cognitive behavioural therapy) (one RCT) in adults with cannabis use disorder, with a trial length of 12 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **maintenance (reduction in use and reduction in cravings) in cannabis use disorder**. McKee *et al.* (2021) [132] compared the effectiveness of dronabinol against placebo, finding evidence indicating a significant improvement in maintenance with dronabinol compared with placebo (three RCTs, narrative synthesis) in adults with cannabis use disorder. Trial length ranged from 40 to 51 days for two studies, with one study reporting three intervention administration sessions separated by at least 7 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **cravings in opioid use disorder**. McKee *et al.* (2021) [132] compared the effectiveness of CBD (Epidyolex) against placebo, finding evidence indicating significantly reduced cravings and anxiety responses with CBD (Epidyolex) compared with placebo (one RCT) in adults with opioid use disorder, with a trial length of 6 weeks. The certainty of the evidence was very low.

We identified two systematic reviews on the topic of **withdrawal symptoms in opioid use disorder/opioid dependence**. McKee *et al.* (2021) [132] and De Aquino *et al.* (2022) [130] both compared the effectiveness of dronabinol against placebo (50% overlap). McKee *et al.* (2021) [132] found evidence indicating some degree of improved withdrawal symptoms with dronabinol compared with placebo (two RCTs, narrative synthesis) in adults with opioid use disorder, with one RCT reporting improvement and the other reporting weak but short-lived effects. Trial length ranged from 5 to 8 weeks. The certainty of the evidence was low. De Aquino *et al.* (2022) [130] found very low-certainty evidence indicating a significant reduction in opioid withdrawal symptoms with dronabinol compared with placebo (one RCT, which was also included in McKee *et al.* (2021) [132]) in adults with opioid dependence, with a trial length of 5 weeks (intervention duration of 8 days). The certainty of the evidence was very low. De Aquino *et al.* (2022) [130] also compared the effectiveness of dronabinol against oxycodone (a semi-synthetic opioid), finding evidence indicating a significantly greater reduction in opioid withdrawal symptoms with oxycodone compared with dronabinol (two RCTs using the same dataset; narrative synthesis) in adults with opioid dependence, with an intervention duration of 5 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **tobacco use/cravings in tobacco use disorder**. McKee *et al.* (2021) [132] compared the effectiveness of CBD against placebo, finding evidence indicating a significant reduction in cigarettes smoked in the CBD compared with placebo groups (one RCT) in adults with tobacco use disorder. Nicotine cravings fell significantly during the treatment phase, but this was not maintained at follow-up. The intervention was administered on 2 days, separated by 1 week, and with a 21-day follow-up. The certainty of the evidence was very low.

3.7.1.5.1.6 Neurodevelopmental disorders

Table 30 provides an overview of the primary outcomes related to neurodevelopmental disorders.

Table 30 Primary outcomes related to neurodevelopmental disorders in mental health and neuropsychological conditions

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Attention deficit hyperactivity disorder (ADHD) symptoms						
	THC:CBD (nabiximols) vs. placebo	2 (1) [129,132]	Critically low	100%	Very low	No significant difference
Tic severity in Tourette's syndrome						
	THC/dronabinol vs. placebo	2 (2, 2) [129,132]	Critically low	33%	Very low	Mixed findings; some evidence for a significant reduction in tic severity and frequency with dronabinol

We identified two systematic reviews on the topic of **ADHD symptoms**. Black *et al.* (2019) [129] and McKee *et al.* (2021) [132] both compared the effectiveness of THC:CBD (nabiximols) against placebo, based on the same single RCT (100% overlap), finding evidence indicating no significant difference in ADHD symptoms (cognitive performance and activity levels) between nabiximols and placebo (one RCT) in adults with ADHD, with an intervention duration of 6 weeks. The certainty of the evidence was very low.

We identified two systematic reviews on the topic of **tic severity in Tourette's syndrome**. Black *et al.* (2019) [129] and McKee *et al.* (2021) [132] both compared the effectiveness of THC (described as THC or dronabinol) against placebo (33% overlap), with inconsistent findings. Black *et al.* (2019) [129] found evidence indicating no significant difference in tic severity between THC and placebo (two RCTs) in a meta-analysis of adults with Tourette's syndrome, with intervention durations ranging from 1 day to 6 weeks. McKee *et al.* (2021) [132] found evidence indicating a significant improvement in global tic scores, and in tic frequency and severity, with dronabinol compared with placebo (two RCTs, narrative synthesis) in adults with Tourette's syndrome, with a trial length ranging from 4 to 6 weeks. The certainty of the evidence was very low in both reviews.

3.7.1.5.2 Efficacy: Secondary outcomes

Five reviews of mental health and neuropsychological conditions explored **secondary outcomes**. Two reviews explored only adverse events as secondary outcomes [128,130]. Secondary outcomes explored by three other reviews included global functioning [129], quality of life [129], patient and caregiver impressions of change [129], weight gain [131], prolactin increase [131], response to treatment [131], positive and negative symptoms of psychosis [131], and physical activity in the context of anorexia nervosa [133]. Please see the extraction forms for individual reviews for full information on secondary outcomes (Appendix F).

3.7.1.5.3 Safety

Five reviews examined safety outcomes as secondary outcomes in mental health and neuropsychological conditions [128–131,133]. One review examined discontinuation due to adverse events as a primary outcome [128].

One review (meta-analysis) found that **adverse events** were more likely in THC:CBD and CBD conditions compared with placebo conditions [129]. Another review (meta-analysis) found that adverse events were no more likely in CBD conditions compared with placebo in the context of schizophrenia [131].

One review (meta-analysis) found that **withdrawals due to adverse events** were more likely in THC:CBD conditions compared with placebo conditions, but that there was no difference between the CBD and placebo conditions [129].

Regarding **specific adverse events**, one review (meta-analysis) found that sedation, sexual side effects, and weight gain were no more likely in CBD conditions compared with placebo in the context of schizophrenia [131]. In one review, increased heart rates, tachycardia, and anxiogenic effects were more common with dronabinol compared with placebo, particularly at higher doses [130]. Another review reported that dry mouth, dry eyes, headaches, presyncope, and drowsiness were more common with nabilone than with placebo [128]. A review on anorexia nervosa reported that somatisation, interpersonal sensitivity, sleep disturbance, increased systolic blood pressure, and decreased diastolic blood pressure were more common with cannabis compared with diazepam (a benzodiazepine) [133].

One review (meta-analysis) found that **serious adverse events** were no more likely in THC:CBD conditions and in CBD-only conditions compared with placebo conditions [129].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.5.4 Summary of findings for mental health and neuropsychological conditions

The findings and certainty of evidence from the reviews on medicinal cannabis in relation to mental health and neuropsychological conditions vary quite widely. There is evidence of mixed certainty (low or very low) based on three systematic reviews generally indicating no significant difference between cannabinoids and placebo or active control (amisulpride) for outcomes related to psychotic disorders, and some very low-certainty evidence for a detrimental effect on symptoms of psychosis and on cognitive function in schizophrenia for THC compared with placebo. There is mixed evidence of mixed certainty (low or very low), based on three systematic reviews, indicating a possible relative benefit of cannabinoids and cannabis compared with placebo for some anxiety outcomes, including symptoms of generalised anxiety disorder, PTSD, and social anxiety disorder, but not for obsessive-compulsive disorder. However, findings indicating no significant benefit for these anxiety outcomes were also identified. There is evidence of mixed certainty (low to very low) based on one systematic review indicating no significant difference between cannabinoids/medicinal cannabis and placebo for outcomes related to mood disorders. There is very low-certainty evidence based on two systematic reviews indicating the relative benefit of THC (dronabinol) compared with placebo for weight gain in anorexia nervosa; however, there was no significant difference between cannabis and diazepam for this outcome. There is mixed evidence of mixed certainty (very low to moderate) based on two systematic reviews indicating a possible relative benefit of cannabinoids compared with placebo for some outcomes related to cannabis use disorder, opioid use disorder, and tobacco use disorder; however, findings indicating no significant benefit were also identified. There is very low-certainty evidence based on two systematic reviews indicating no significant difference between THC:CBD (nabiximols) and placebo for ADHD symptoms. There is very low-certainty mixed evidence based on two systematic reviews indicating a possible relative benefit of THC (dronabinol) compared with placebo for tic severity and frequency in Tourette's syndrome; however, findings indicating no significant benefit were also identified. The reviews presented evidence on

secondary outcomes, including global functioning, quality of life, and patient and caregiver impressions of change, among others. Adverse events and withdrawals from primary studies due to adverse events were reported to be more likely in THC:CBD conditions compared with placebo conditions; however, the findings on adverse events in CBD conditions were mixed. Sedation, sexual side effects, cardiac effects, dry mouth, headaches, drowsiness, and sleep disturbances, among others, were reported in the cannabinoid conditions.

3.7.1.6 Palliative care

We identified one systematic review that investigated the impact of medicinal cannabis on outcomes in palliative care, including outcomes in cancer, HIV, and Alzheimer's disease [134]. The review investigated outcomes related to pain, nutrition, sleep, and mental health/well-being, and also presented evidence on a range of secondary outcomes and adverse events. Please note that outcomes related to cancer and HIV in the context of palliative care were also addressed by the systematic reviews on cancer and HIV, with some overlap in primary studies (see Sections 3.7.1.1 and 3.7.1.2, respectively).

3.7.1.6.1 Efficacy: Primary outcomes

3.7.1.6.1.1 Pain-related outcomes

Table 31 provides an overview of the primary pain-related outcomes in palliative care.

Table 31 Primary pain-related outcomes in palliative care

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain reduction of 30% or greater in cancer						
	Cannabinoids (THC:CBD spray, THC extract) vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Low	More likely with cannabinoids

We identified one systematic review on the topic of **pain reduction of 30% or greater in cancer**. Mücke *et al.* (2018a) [134] compared the effectiveness of mixed cannabinoids (THC:CBD spray, THC extract) against placebo, finding evidence indicating a significantly greater likelihood of pain reduction of 30% or greater with cannabinoids compared with placebo (one RCT) in adults with cancer, with intervention duration ranging from 16 days to 9 weeks. The certainty of the evidence was low.

3.7.1.6.1.2 Nutrition-related outcomes

Table 32 provides an overview of the primary nutrition-related outcomes in palliative care.

Table 32 Primary nutrition-related outcomes in palliative care

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Body weight change in cancer						
	Cannabinoids vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Very low	No significant difference
	Dronabinol vs. megestrol acetate	1 (1) [134]	Critically low	No overlap (single review)	Very low	Greater weight gain with megestrol acetate
Caloric intake in cancer						
	Dronabinol vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Very low	No significant difference
Appetite in cancer						
	Cannabis/cannabinoids vs. placebo	1 (3) [134]	Critically low	No overlap (single review)	Very low	No significant difference
	Dronabinol vs. megestrol acetate	1 (1) [134]	Critically low	No overlap (single review)	Very low	Greater appetite improvement with megestrol acetate
Nausea and vomiting in cancer						
	Mixed cannabinoids (THC only, THC:CBD) vs. placebo	1 (2) [134]	Critically low	No overlap (single review)	Low	No significant difference
Body weight change in HIV						
	Cannabis/cannabinoids vs. placebo	1 (2) [134]	Critically low	No overlap (single review)	Low	No significant difference
	Dronabinol vs. megestrol acetate	1 (1) [134]	Critically low	No overlap (single review)	Very low	Greater weight gain with megestrol acetate
	Herbal cannabis vs. dronabinol	1 (1) [134]	Critically low	No overlap	Very low	Greater weight gain with herbal cannabis

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
				(single review)		
Appetite in HIV						
	Dronabinol vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Very low	Greater appetite improvement with dronabinol
Nausea and vomiting in HIV						
	Dronabinol vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Very low	No significant difference
	Dronabinol vs. megestrol acetate	1 (1) [134]	Critically low	No overlap (single review)	Very low	No significant difference
Body weight change in Alzheimer's disease						
	Dronabinol vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Very low	Greater weight gain with dronabinol
Caloric intake in Alzheimer's disease						
	Dronabinol vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **body weight change in cancer**. Mücke *et al.* (2018a) [134] compared the effectiveness of cannabinoids against placebo, finding evidence indicating no significant difference in weight gain between cannabinoids and placebo (one RCT) in adults with cancer, with an intervention duration of 6 weeks. The certainty of the evidence was very low. Mücke *et al.* (2018a) [134] also compared the effectiveness of dronabinol against megestrol acetate (an appetite stimulant), finding evidence indicating significantly greater weight gain with megestrol acetate compared with dronabinol (one RCT) in adults with cancer, with intervention duration ranging from 57 to 80 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **caloric intake in cancer**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in caloric intake between dronabinol and placebo (one RCT) in adults with cancer, with an intervention duration of 22 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **appetite in cancer**. Mücke *et al.* (2018a) [134] compared the effectiveness of cannabis/cannabinoids against placebo, finding evidence indicating no

significant difference in appetite between cannabis/cannabinoids and placebo (three RCTs) in a meta-analysis of adults with cancer, with intervention durations ranging from 16 days to 6 weeks. The certainty of the evidence was very low. Mücke *et al.* (2018a) [134] also compared the effectiveness of dronabinol against megestrol acetate, finding evidence indicating a significantly greater improvement in appetite with megestrol acetate compared with dronabinol (one RCT) in adults with cancer, with intervention duration ranging from 57 to 80 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **nausea and vomiting in cancer**. Mücke *et al.* (2018a) [134] compared the effectiveness of mixed cannabinoids (THC only, THC:CBD) against placebo, finding evidence indicating no significant difference in nausea and vomiting between cannabinoids (THC:CBD, THC extract) and placebo (two RCTs) in a meta-analysis of adults with cancer, with an intervention duration of 16 weeks. The certainty of the evidence was low.

We identified one systematic review on the topic of **body weight change in HIV**. Mücke *et al.* (2018a) [134] compared the effectiveness of cannabis/cannabinoids against placebo, finding evidence indicating no significant difference in weight gain between cannabis/cannabinoids (dronabinol, cannabis) and placebo (two RCTs) in a meta-analysis of adults with HIV, with intervention durations ranging from 3 to 6 weeks. The certainty of the evidence was low. Mücke *et al.* (2018a) [134] also compared the effectiveness of dronabinol against megestrol acetate, finding evidence indicating significantly greater weight gain with megestrol acetate compared with dronabinol (one RCT) in adults with HIV, with an intervention duration of 12 weeks. The certainty of the evidence was very low. Mücke *et al.* (2018a) [134] also compared the effectiveness of herbal cannabis against dronabinol, finding evidence indicating significantly greater weight gain with herbal cannabis compared with dronabinol (one RCT) in adults with HIV, with an intervention duration of 3 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **appetite in HIV**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against placebo, finding evidence indicating significantly increased appetite with dronabinol compared with placebo (one RCT) in adults with HIV, with an intervention duration of 6 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **nausea and vomiting in HIV**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in nausea and vomiting between dronabinol and placebo (one RCT) in adults with HIV, with an intervention duration of 6 weeks. The certainty of the evidence was very low. Mücke *et al.* (2018a) [134] also compared the effectiveness of dronabinol against megestrol acetate, finding evidence indicating no significant difference in nausea and vomiting between dronabinol and megestrol acetate (one RCT) in adults with HIV, with an intervention duration of 12 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **body weight change in Alzheimer's disease**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against placebo, finding evidence indicating significantly greater weight gain with dronabinol compared with placebo (one RCT) in adults with Alzheimer's disease, with an intervention duration of 6 weeks per intervention period. The certainty of the evidence was very low.

We identified one systematic review on the topic of **caloric intake in Alzheimer's disease**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in caloric intake between dronabinol and placebo (one RCT) in adults with Alzheimer's disease, with an intervention duration of 6 weeks per intervention period. The certainty of the evidence was very low.

3.7.1.6.1.3 Sleep-related outcomes

Table 33 provides an overview of the primary sleep-related outcomes in palliative care.

Table 33 Primary sleep-related outcomes in palliative care

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sleeping dysfunction in cancer						
	Cannabinoids (dronabinol, THC:CBD spray) vs. placebo	1 (2) [134]	Critically low	No overlap (single review)	Very low	No significant difference
Fatigue						
	No evidence found for this outcome	1 [134]	Critically low	No overlap (single review)	Not applicable	Not applicable

We identified one systematic review on the topic of **sleeping dysfunction in cancer**. Mücke *et al.* (2018a) [134] compared the effectiveness of cannabinoids (dronabinol, THC:CBD spray) against placebo, finding evidence indicating no significant difference in sleeping dysfunction between cannabinoids (dronabinol, THC:CBD spray) and placebo (two RCTs) in a meta-analysis of adults with cancer, with intervention durations ranging from 16 to 22 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **fatigue**. Mücke *et al.* (2018a) [134] found no evidence relating to this outcome.

3.7.1.6.1.4 Mental health/well-being

Table 34 provides an overview of the outcomes related to mental health/well-being in palliative care.

Table 34 Primary outcomes related to mental health/well-being in palliative care

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Depressive mood in HIV						
	Dronabinol vs. megestrol acetate	1 (1) [134]	Critically low	No overlap (single review)	Very low	No significant difference
Health-related quality of life in cancer						
	Dronabinol vs. megestrol acetate	1 (1) [134]	Critically low	No overlap	Very low	Greater health-related quality of life improvement

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
				(single review)		with megestrol acetate
Health-related quality of life in HIV						
	Dronabinol vs. megestrol acetate	1 (1) [134]	Critically low	No overlap (single review)	Very low	No significant difference
Negative affect in Alzheimer's disease						
	Dronabinol vs. placebo	1 (1) [134]	Critically low	No overlap (single review)	Very low	Greater reduction in negative affect with dronabinol

We identified one systematic review on the topic of **depressive mood in HIV**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against megestrol acetate (an appetite stimulant), finding evidence indicating no significant difference in depressive mood between dronabinol and megestrol acetate (one RCT) in adults with HIV, with an intervention duration of 12 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **health-related quality of life in cancer**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against megestrol acetate, finding evidence indicating significantly improved health-related quality of life with megestrol acetate compared with dronabinol (one RCT) in adults with cancer, with intervention duration ranging from 57 to 80 days. The certainty of the evidence was very low.

We identified one systematic review on the topic of **health-related quality of life in HIV**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against megestrol acetate, finding evidence indicating no significant difference in health-related quality of life between dronabinol and megestrol acetate (one RCT) in adults with HIV, with an intervention duration of 12 weeks. The certainty of the evidence was very low.

We identified one systematic review on the topic of **negative affect in Alzheimer's disease**. Mücke *et al.* (2018a) [134] compared the effectiveness of dronabinol against placebo, finding evidence indicating a significantly greater reduction in negative affect with dronabinol compared with placebo (one RCT) in adults with Alzheimer's disease, with an intervention duration of 6 weeks. The certainty of the evidence was very low.

3.7.1.6.2 Efficacy: Secondary outcomes

The single review on palliative care did not specify any secondary outcomes in terms of efficacy [134].

3.7.1.6.3 Safety

Tolerability and safety were examined as secondary outcomes by the single review on palliative care [134].

Tolerability was assessed by dropouts [134]. Across all conditions, dropouts were significantly more common in mixed cannabinoid/cannabis groups compared with placebo groups (six RCTs, meta-analysis). Significantly fewer dropouts were reported in the megestrol acetate (an appetite stimulant) condition compared with the dronabinol condition among cancer populations in one RCT, but no difference was reported among HIV populations in another RCT. There was no significant difference in the frequency of dropouts between the herbal cannabis and plant-derived THC conditions in one RCT.

Safety was assessed by serious adverse events [134]. Across all conditions, serious adverse events were significantly more common in mixed cannabinoid/cannabis groups compared with placebo groups (six RCTs, meta-analysis). There was no significant difference in the frequency of adverse events between dronabinol and megestrol acetate conditions in two RCTs (narrative synthesis). There were no serious adverse events in either the herbal cannabis or the plant-derived THC conditions in another RCT.

Data were also synthesised through meta-analysis on a number of individual adverse events, including sleep disorder, dizziness, and mental health effects. No significant difference in frequency was reported between cannabinoid and comparator conditions [134].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.6.4 Summary of findings for palliative care

There is evidence of mixed certainty (low or very low) based on one systematic review generally indicating no significant difference between medicinal cannabis and placebo for primary outcomes in palliative care, including outcomes in cancer, HIV, and Alzheimer's disease. A relative benefit of cannabinoids compared with placebo was observed for pain reduction in cancer, appetite in HIV, and negative affect in Alzheimer's disease. Standard therapy with megestrol acetate was noted to be more effective than THC (dronabinol) in one RCT for some nutrition-related outcomes in cancer and HIV, and for health-related quality of life in cancer. Serious adverse events and dropouts were more common in the cannabis/cannabinoid intervention conditions when pooled across all conditions.

3.7.1.7 Rheumatic diseases and fibromyalgia

We identified three systematic reviews that investigated the impact of medicinal cannabis on outcomes related to rheumatic diseases and fibromyalgia [135–137], including fibromyalgia [135–137], rheumatoid arthritis [135,136], and chronic therapy-resistant pain caused by the skeletal and locomotor system [136]. We included studies on fibromyalgia in this category, reflecting how the reviews we included categorised this condition, although we acknowledge that fibromyalgia is not straightforwardly categorised as a rheumatic condition. All three reviews investigated outcomes related to pain [135–137], two of the reviews investigated global impressions of change [136,137], one review investigated sleep-related outcomes [135], and one review investigated quality of life [135]. The reviews also presented evidence on a range of secondary outcomes and adverse events.

3.7.1.7.1 Efficacy: Primary outcomes

3.7.1.7.1.1 Pain-related outcomes

Table 35 provides an overview of the primary pain-related outcomes in rheumatic diseases and fibromyalgia.

Table 35 Primary pain-related outcomes in rheumatic diseases and fibromyalgia

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain intensity						
	Nabiximols vs. placebo	1 (1) [135]	Low	No overlap (single review)	Very low	No significant difference
	Nabilone vs. placebo	2 (2, 2) [135,136]	Low Critically low	50%	Very low	Mixed findings; some evidence for greater improvement with nabilone
	Nabilone vs. amitriptyline	2 (1) [135,136]	Low Critically low	100%	Very low	No significant difference
Morning pain on movement						
	Nabiximols vs. placebo	1 (1) [135]	Low	No overlap (single review)	Very low	Greater improvement with nabiximols
Morning pain at rest						
	THC:CBD (nabiximols) vs. placebo	2 (1) [135,136]	Low Critically low	100%	Very low	Greater improvement with nabiximols
Pain reduction of 50% or greater						
	No evidence found for this outcome	1 [136]	Critically low	No overlap (single review)	No evidence found for this outcome	No evidence found for this outcome
Pain reduction of 50% or greater in fibromyalgia						
	No evidence found for this outcome	1 [137]	High	No overlap (single review)	No evidence found for this outcome	No evidence found for this outcome

We identified two systematic reviews on the topic of **pain intensity**. Fitzcharles *et al.* (2016a) [135] compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference in pain intensity between nabiximols and placebo (one RCT) in adults with rheumatic disease, with an intervention duration of 5 weeks. The certainty of the evidence was very low. Fitzcharles *et al.* (2016a) [135] and Fitzcharles *et al.* (2016b) [136] both compared the effectiveness of nabilone against placebo. Overlap between the two reviews was 50%. The reviews found mixed evidence for a significant difference in pain intensity between nabilone and placebo (two RCTs, narrative synthesis) in adults with

rheumatic disease, with one RCT reporting no difference and the second reporting a significant improvement in pain intensity with nabilone compared with placebo. Trial duration was 4 weeks per intervention period, and one study had a 16-week follow-up period. The certainty of the evidence was very low in both reviews. Fitzcharles *et al.* (2016a) [135] and Fitzcharles *et al.* (2016b) [136] also both compared the effectiveness of nabilone against amitriptyline (a tricyclic antidepressant). Each found evidence, based on the same single RCT (100% overlap), indicating no significant difference in pain intensity between nabilone and amitriptyline (one RCT) in adults with rheumatic disease, with an intervention duration of 2 weeks per intervention period. The certainty of the evidence was very low in both reviews.

We identified one systematic review on the topic of **morning pain on movement**. Fitzcharles *et al.* (2016a) [135] compared the effectiveness of nabiximols against placebo, finding evidence indicating significant improvements in morning pain on movement with nabiximols compared with placebo (one RCT) in adults with rheumatic disease, with an intervention duration of 5 weeks. The certainty of the evidence was very low.

We identified two systematic reviews on the topic of **morning pain at rest**. Fitzcharles *et al.* (2016a) [135] and Fitzcharles *et al.* (2016b) [136] both compared the effectiveness of nabiximols against placebo. Each found evidence, based on the same single RCT (100% overlap), indicating significant improvements in morning pain at rest with nabiximols compared with placebo (one RCT) in adults with rheumatic disease, with an intervention duration of 5 weeks. The certainty of the evidence was very low in both reviews.

We identified one systematic review on the topic of **pain reduction of 50% or greater**. Fitzcharles *et al.* (2016b) [136] found no evidence relating to this outcome.

We identified one systematic review on the topic of **pain reduction of 50% or greater in fibromyalgia**. Walitt *et al.* (2016) [137] found no evidence relating to this outcome.

3.7.1.7.1.2 Global impression of change

Table 36 provides an overview of the primary outcomes related to global impression of change in rheumatic diseases and fibromyalgia.

Table 36 Primary outcomes related to global impression of change in rheumatic diseases and fibromyalgia

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Patient global impression of change						
	No evidence found for this outcome	2 [136,137]	Critically low High	Not applicable	No evidence found for this outcome	No evidence found for this outcome

We identified two systematic reviews on the topic of **patient global impression of change**. Neither Fitzcharles *et al.* (2016b) [136] nor Walitt *et al.* (2016) [137] found evidence relating to this outcome.

3.7.1.7.1.3 Sleep-related outcomes

Table 37 provides an overview of the primary sleep-related outcomes in rheumatic diseases and fibromyalgia.

Table 37 Primary sleep-related outcomes in rheumatic diseases and fibromyalgia

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sleep quality						
	Nabiximols vs. placebo	1 (1) [135]	Low	No overlap (single review)	Very low	Greater improvement with nabiximols
	Nabilone vs. amitriptyline	1 (1) [135]	Low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **sleep quality.** Fitzcharles *et al.* (2016a) [135] compared the effectiveness of nabiximols against placebo, finding evidence indicating significant improvements in sleep quality with nabiximols compared with placebo (one RCT) in adults with rheumatic disease, with an intervention duration of 5 weeks. The certainty of the evidence was very low. Fitzcharles *et al.* (2016a) [135] also compared the effectiveness of nabilone against amitriptyline (a tricyclic antidepressant), finding evidence indicating no significant difference in sleep quality between nabilone and amitriptyline (one RCT) in adults with rheumatic disease; both groups reported significant improvements in sleep quality, but only a marginal advantage was reported for the nabilone group on one of two metrics. Trial duration was 2 weeks per intervention period. The certainty of the evidence was very low.

3.7.1.7.1.4 Quality of life

Table 38 provides an overview of the primary outcomes related to quality of life in rheumatic diseases and fibromyalgia.

Table 38 Primary outcomes related to quality of life in rheumatic diseases and fibromyalgia

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Quality of life						
	Nabilone vs. placebo	1 (1) [135]	Low	No overlap (single review)	Very low	Greater improvement with nabilone
	Nabilone vs. amitriptyline	1 (1) [135]	Low	No overlap (single review)	Very low	No significant difference

We identified one systematic review on the topic of **quality of life**. Fitzcharles *et al.* (2016a) [135] compared the effectiveness of nabilone against placebo, finding evidence indicating a significant improvement in quality of life with nabilone compared with placebo (one RCT) in adults with rheumatic disease, with an intervention duration of 8 weeks. The certainty of the evidence was very low. Fitzcharles *et al.* (2016a) [135] also compared the effectiveness of nabilone against amitriptyline (a tricyclic antidepressant), finding evidence indicating no significant difference in quality of life between nabilone and amitriptyline (one RCT) in adults with rheumatic disease, with an intervention duration of 2 weeks per intervention period. The certainty of the evidence was very low.

3.7.1.7.2 Efficacy: Secondary outcomes

Secondary outcomes explored by the three reviews on rheumatic diseases and fibromyalgia included measures of disability (disease activity) [135–137]; additional measures of pain- [137] and sleep-related outcomes [136,137]; depression and anxiety [136,137]; and health-related quality of life [136,137]. Please see extraction forms for individual reviews for full information on secondary outcomes (Appendix F).

3.7.1.7.3 Safety

Among the three systematic reviews on rheumatic diseases and fibromyalgia, adverse events were examined as primary outcomes by one review [136] and as secondary outcomes by two reviews [135,137]. Serious adverse events and withdrawal from primary studies due to adverse events were examined as primary outcomes by two reviews [136,137].

Adverse events noted included dizziness, dry mouth, light-headedness, nausea, falls, drowsiness, vertigo, and ataxia, all of which were reported to be more common with cannabinoid (nabiximols, nabilone) treatment compared with placebo or an active comparator [135,136]. Other adverse events noted included confusion, poor concentration, headache, dysphoria, euphoria, and constipation, which were reported to be less common in cannabinoid intervention conditions than in placebo conditions [135]. The frequency of withdrawals from primary studies due to adverse events was similar in the cannabinoid intervention and placebo conditions [135,137].

Serious adverse events were also noted. Two reviews reported no adverse events [135,137] and one review [136] reported very low rates of adverse events (<4%), for which there was no significant difference in the frequency between cannabinoid/cannabis and comparator conditions.

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.7.4 Summary of findings for rheumatic diseases and fibromyalgia

There is generally limited and inconsistent evidence (of low or very low certainty), based on two systematic reviews, indicating a relative benefit of medicinal cannabis compared with placebo for some outcomes related to rheumatic diseases and fibromyalgia, including fibromyalgia, rheumatoid arthritis, and chronic therapy-resistant pain caused by the skeletal and locomotor system. Cannabinoids (nabiximols, nabilone) were observed to produce improvements in some (but not all) measures of pain, sleep, and quality of life. Some adverse events, but not serious adverse events, were reported to be more common in the cannabinoid/cannabis intervention conditions compared with placebo conditions, including dizziness, dry mouth, light-headedness, nausea, and drowsiness, among others.

3.7.1.8 Spinal cord injury

We identified one systematic review [138] that examined the impact of medicinal cannabis on outcomes related to spinal cord injury, investigating pain-related outcomes and also presenting evidence on a range of adverse events.

3.7.1.8.1 Efficacy: Primary outcomes

Table 39 provides an overview of the primary outcomes in spinal cord injury.

Table 39 Primary outcomes in spinal cord injury

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain intensity						
	THC vs. placebo	1 (1) [138]	Critically low	No overlap (single review)	Very low	Significantly greater pain relief with both low and high THC doses compared with placebo
	Nabiximols (THC:CBD) vs. placebo	1 (1) [138]	Critically low	No overlap (single review)	Very low	No significant difference
	Dronabinol vs. diphenhydramine	1 (1) [138]	Critically low	No overlap (single review)	Very low	No significant difference

3.7.1.8.1.1 Pain-related outcomes

We identified one systematic review on the topic of **pain intensity**. Thomas *et al.* (2022) [138] compared the effectiveness of both low and high THC doses against placebo, finding evidence indicating a significant improvement in pain intensity with both low and high THC doses compared with placebo (one RCT) in adults with spinal cord injury. Interventions were administered on single treatment days with minimum 3-day wash-out periods between testing days, and no follow-up period was reported. The certainty of the evidence was very low. Thomas *et al.* (2022) [138] also compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference in pain intensity between nabiximols and placebo (one RCT) in adults with spinal cord injury, with intervention durations ranging from 21 to 30 days. The certainty of the evidence was very low. Thomas *et al.* (2022) [138] also compared the effectiveness of dronabinol against diphenhydramine (a sedative and antihistamine), finding evidence indicating no significant difference in pain intensity between dronabinol and diphenhydramine (one RCT) in adults with spinal cord injury, with an intervention duration of 56 days per intervention period. The certainty of the evidence was very low.

3.7.1.8.2 Efficacy: Secondary outcomes

The single review [138] on spinal cord injury did not specify any secondary efficacy outcomes; therefore, we have regarded all reported efficacy outcomes as primary outcomes.

3.7.1.8.3 Safety

Adverse events were examined as secondary outcomes by the single review on spinal cord injury [138].

Adverse events noted included dry mouth, constipation, fatigue, drowsiness/somnolence, confusion, and paranoia, and were observed across intervention and comparator conditions. None of the included RCTs statistically assessed differences in the frequency of adverse events between the intervention and comparator conditions [138].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.8.4 Summary of findings for spinal cord injury

There is very low-certainty evidence based on one systematic review indicating the relative benefit of both low and high THC doses compared with placebo for pain related to spinal cord injury, but generally finding no significant difference between nabiximols and placebo or between dronabinol and diphenhydramine for pain related to spinal cord injury. Adverse events (including dry mouth, constipation, fatigue, drowsiness/somnolence, confusion, and paranoia) were reported across both intervention and comparator conditions.

3.7.1.9 Multiple sclerosis

We identified two systematic reviews that investigated the impact of medicinal cannabis on outcomes related to multiple sclerosis [139,140]. Both reviews investigated outcomes related to spasticity and pain, whereas bladder dysfunction [140], quality of life [139], and global impression of change [139] were each investigated by one review. The reviews also presented evidence on a range of secondary outcomes and adverse events.

3.7.1.9.1 Efficacy: Primary outcomes

3.7.1.9.1.1 Spasticity-related outcomes

Table 40 provides an overview of the primary spasticity-related outcomes in multiple sclerosis.

Table 40 Primary spasticity-related outcomes in multiple sclerosis

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Observer-rated spasticity (Ashworth Scale)						
	Cannabis extract vs. placebo	1 (4) [140]	Critically low	No overlap (single review)	Moderate	No significant difference
	Nabiximols vs. placebo	1 (8) [140]	Critically low	No overlap (single review)	Low	No significant difference
	Dronabinol vs. placebo	1 (3) [140]	Critically low	No overlap (single review)	Moderate	No significant difference
Subjective spasticity						
	Cannabis extract vs. placebo	1 (3) [140]	Critically low	No overlap with mixed cannabinoids vs. placebo	Low	Greater reduction with cannabis extract

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Nabiximols vs. placebo	1 (9) [140]	Critically low	33.3% overlap with mixed cannabinoids vs. placebo	Low	Greater reduction with nabiximols
	Dronabinol vs. placebo	1 (3) [140]	Critically low	No overlap with mixed cannabinoids vs. placebo	Low	No significant difference
	Mixed cannabinoids (THC:CBD, THC only) vs. placebo	1 (7) [139]	Low	33.3% overlap with nabiximols vs. placebo	Low	Greater reduction with mixed cannabinoids
Spasticity reduction of 30% or greater						
	THC:CBD vs. placebo	1 (5) [139]	Low	No overlap (single review)	Low	Greater reduction with cannabinoids

We identified one systematic review on the topic of **observer-rated spasticity** (measured using instruments such as the Ashworth Scale). Torres-Moreno *et al.* (2018) [140] compared the effectiveness of cannabis extract against placebo, finding evidence indicating no significant difference in observer-rated spasticity between cannabis extract and placebo (four RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 4 to 20 weeks. The certainty of the evidence was moderate. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference in observer-rated spasticity between nabiximols and placebo (eight RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 6 to 50 weeks. The certainty of the evidence was low. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in observer-rated spasticity between dronabinol and placebo (three RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 15 to 20 weeks. The certainty of the evidence was moderate.

We identified two systematic reviews on the topic of **subjective spasticity**. Torres-Moreno *et al.* (2018) [140] compared the effectiveness of cannabis extract against placebo, finding evidence indicating a significant improvement in subjective spasticity with cannabis extract compared with placebo (three RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 14 to 15 weeks. The certainty of the evidence was low. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of nabiximols against placebo, finding evidence indicating a significant improvement in subjective spasticity with nabiximols compared with placebo (nine RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 6 to 50 weeks. The certainty of the evidence was low. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in subjective spasticity between dronabinol

and placebo (three RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 15 weeks to 3 years. The certainty of the evidence was low. Filippini *et al.* (2022) [139] compared the effectiveness of mixed cannabinoids (THC:CBD, THC only) against placebo, finding evidence indicating a significantly greater reduction in subjective spasticity with mixed cannabinoids compared with placebo (seven RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 4 to 14 weeks. The certainty of the evidence was low. There was 33.3% overlap between the RCTs included in this analysis and the RCTs comparing nabiximols against placebo that were included in the analysis by Torres-Moreno *et al.* (2018) [140].

We identified one systematic review on the topic of **spasticity reduction of 30% or greater**. Filippini *et al.* (2022) [139] compared the effectiveness of THC:CBD against placebo, finding evidence indicating a significantly greater likelihood of spasticity reduction of 30% or greater with THC:CBD cannabinoids compared with placebo (five RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 6 to 14 weeks. The certainty of the evidence was low.

3.7.1.9.1.2 Pain-related outcomes

Table 41 provides an overview of the primary pain-related outcomes in multiple sclerosis.

Table 41 Primary pain-related outcomes in multiple sclerosis

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain						
	Cannabis extract vs. placebo	1 (3) [140]	Critically low	10.0% overlap with mixed cannabinoids vs. placebo	Low	Greater reduction with cannabis extract
	Nabiximols vs. placebo	1 (6) [140]	Critically low	7.7% overlap with mixed cannabinoids vs. placebo	Low	No significant difference
	Nabilone vs. placebo	1 (1) [140]	Critically low	No overlap with mixed cannabinoids vs. placebo	Very low	Greater reduction with nabilone
	Dronabinol vs. placebo	1 (4) [140]	Critically low	No overlap with mixed cannabinoids vs. placebo	Low	No significant difference
	Mixed cannabinoids (THC:CBD, THC only) vs. placebo	1 (8) [139]	Low	10.0% overlap with cannabis extract vs. placebo; 7.7% overlap with	Low	Greater reduction with mixed cannabinoids

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
				nabiximols vs. placebo		
Pain relief of 50% or greater						
	Dronabinol vs. placebo	1 (1) [139]	Low	No overlap (single review)	Very low	Improvement more likely with dronabinol

We identified two systematic reviews on the topic of **pain**. Torres-Moreno *et al.* (2018) [140] compared the effectiveness of cannabis extract against placebo, finding evidence indicating a significant improvement in pain with cannabis extract compared with placebo (three RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 14 to 15 weeks. The certainty of the evidence was low. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference between nabiximols and placebo (six RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 5 to 15 weeks. The certainty of the evidence was low. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of nabilone against placebo, finding evidence indicating a significant improvement in pain (borderline statistical significance) with nabilone compared with placebo (one RCT) in adults with multiple sclerosis, with an intervention duration of 9 weeks. The certainty of the evidence was very low. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in pain between dronabinol and placebo (four RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 9 weeks to 3 years. The certainty of the evidence was low. Filippini *et al.* (2022) [139] compared the effectiveness of mixed cannabinoids (THC:CBD, THC only) against placebo, finding evidence indicating significant improvements in neuropathic pain with mixed cannabinoids compared with placebo (eight RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 3 to 16 weeks. The certainty of the evidence was low. This analysis had 10.0% overlap with the primary studies on cannabis extract included in Torres-Moreno *et al.* (2018) [140], and 7.7% overlap with the primary studies on nabiximols included in Torres-Moreno *et al.* (2018) [140].

We identified one systematic review on the topic of **pain relief of 50% or greater**. Filippini *et al.* (2022) [139] compared the effectiveness of dronabinol against placebo, finding evidence indicating a significantly greater likelihood of pain reduction of 50% or greater with dronabinol compared with placebo (one RCT) in adults with multiple sclerosis, with an intervention duration of 3 weeks. The certainty of the evidence was very low.

3.7.1.9.1.3 Bladder-related outcomes

Table 42 provides an overview of the primary bladder-related outcomes in multiple sclerosis.

Table 42 Primary bladder-related outcomes in multiple sclerosis

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Bladder dysfunction						
	Cannabis extract vs. placebo	1 (3) [140]	Critically low	No overlap (single review)	Moderate	Greater improvement with cannabis extract
	Nabiximols vs. placebo	1 (4) [140]	Critically low	No overlap (single review)	Low	No significant difference
	Dronabinol vs. placebo	1 (3) [140]	Critically low	No overlap (single review)	Low	No significant difference

We identified one systematic review on the topic of **bladder dysfunction**. Torres-Moreno *et al.* (2018) [140] compared the effectiveness of cannabis extract against placebo, finding evidence indicating a significant improvement in bladder dysfunction with cannabis extract compared with placebo (three RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 4 to 15 weeks. The certainty of the evidence was moderate. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of nabiximols against placebo, finding evidence indicating no significant difference in bladder dysfunction between nabiximols and placebo (four RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 6 to 15 weeks. The certainty of the evidence was low. Torres-Moreno *et al.* (2018) [140] also compared the effectiveness of dronabinol against placebo, finding evidence indicating no significant difference in bladder dysfunction between dronabinol and placebo (three RCTs) in a meta-analysis of adults with multiple sclerosis, with intervention durations ranging from 15 weeks to 3 years. The certainty of the evidence was low.

3.7.1.9.1.4 Quality of life

Table 43 provides an overview of the primary outcomes related to quality of life in multiple sclerosis.

Table 43 Primary outcomes related to quality of life in multiple sclerosis

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Health-related quality of life						
	Mixed cannabinoids (THC:CBD, THC only) vs. placebo	1 (8) [139]	Low	No overlap (single review)	Low	No significant difference

We identified one systematic review on the topic of **health-related quality of life**. Filippini *et al.* (2022) [139] compared the effectiveness of mixed cannabinoids (THC:CBD, THC only) against placebo, finding evidence indicating no significant difference in health-related quality of life between mixed cannabinoids and placebo (eight RCTs) in adults with multiple sclerosis, with intervention durations ranging from 3 weeks to 36 months. The certainty of the evidence was low.

3.7.1.9.1.5 Global impression of change

Table 44 provides an overview of the primary outcomes related to global impression of change in sclerosis.

Table 44 Primary outcomes related to global impression of change in multiple sclerosis

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Patient-rated global impression of change						
	Mixed cannabinoids (THC:CBD, THC only) vs. placebo	1 (8) [139]	Low	No overlap (single review)	Low	Greater improvement with mixed cannabinoids

We identified one systematic review on the topic of **patient-rated global impression of change**. Filippini *et al.* (2022) [139] compared the effectiveness of mixed cannabinoids (THC:CBD, THC only) against placebo, finding evidence indicating a significant improvement in patient-rated global impression of change with cannabinoids compared with placebo (eight RCTs) in adults with multiple sclerosis, with intervention durations ranging from 4 to 50 weeks. The certainty of the evidence was low.

3.7.1.9.2 Efficacy: Secondary outcomes

One review on multiple sclerosis explored **secondary outcomes**. The secondary outcomes explored by Filippini *et al.* (2022) [139] included specific aspects of quality of life (e.g. physical functioning, social functioning, vitality), activities of daily living, carer global impression of change, muscle spasms and tremor, and use of analgesics [139]. Torres-Moreno *et al.* (2018) [140] did not explore any secondary outcomes. Please see extraction forms for individual reviews for full information on secondary outcomes (Appendix F).

3.7.1.9.3 Safety

Adverse events were examined as secondary outcomes by both reviews on multiple sclerosis [139,140].

Adverse events noted included dizziness or vertigo [139], dry mouth [139], feeling drunk [139], impaired balance or ataxia [139], memory impairment [139], somnolence [139], nervous system effects [139], and psychiatric effects [139], all of which were reported as being more common in cannabinoid intervention conditions compared with placebo conditions. Fatigue was reported as an adverse event in both reviews, although only Filippini *et al.* (2022) [139] found evidence that this was more common with cannabinoid interventions than in placebo groups. Filippini *et al.* (2022) [139] reported no significant difference between cannabinoid interventions and placebo conditions in the frequency of drug tolerance, depression, or anxiety, and reported that sleep quality was improved with nabiximols compared with placebo.

Both reviews (meta-analyses) found that withdrawals from primary studies due to adverse events were more frequent in cannabis/cannabinoid intervention groups compared with placebo groups [139,140].

Serious adverse events were also noted. Neither review specified the nature of the serious adverse events, although Torres-Moreno *et al.* (2018) defined serious adverse events as "death or threat to a patient's life or functioning" [140] p7. Both reviews reported no significant difference in the frequency of serious adverse events between cannabinoid/cannabis and placebo conditions [139,140].

Please see extraction forms for individual reviews for full information on safety outcomes (Appendix F).

3.7.1.9.4 Summary of findings for multiple sclerosis

There is some evidence of mixed certainty (very low to moderate) based on two systematic reviews indicating the relative benefit of medicinal cannabis compared with placebo for some outcomes related to multiple sclerosis. Cannabinoids (THC:CBD, nabiximols, and THC only) and cannabis extract were observed to produce improvements in subjective spasticity but not in observer-rated spasticity, as well as in some (but not all) measures of pain, bladder dysfunction, and patient-rated global impression of change. Adverse events, but not serious adverse events, were reported to be more common in the cannabinoid/cannabis intervention conditions compared with placebo groups.

3.7.2 Efficacy in mixed health conditions

In total, 20 reviews assessed efficacy as a primary outcome in mixed health condition populations. Efficacy was assessed in relation to pain [141–155], quality of life [151,156,157], spasticity [151,158], cachexia [157], sleep [159,160], mental health/well-being [156], and overall function or disability [148]. The remainder of this section presents evidence on these outcomes. Where applicable, each outcome has been divided into relevant subheadings. Figure 5 illustrates the breakdown of the identified outcomes into relevant subheadings.

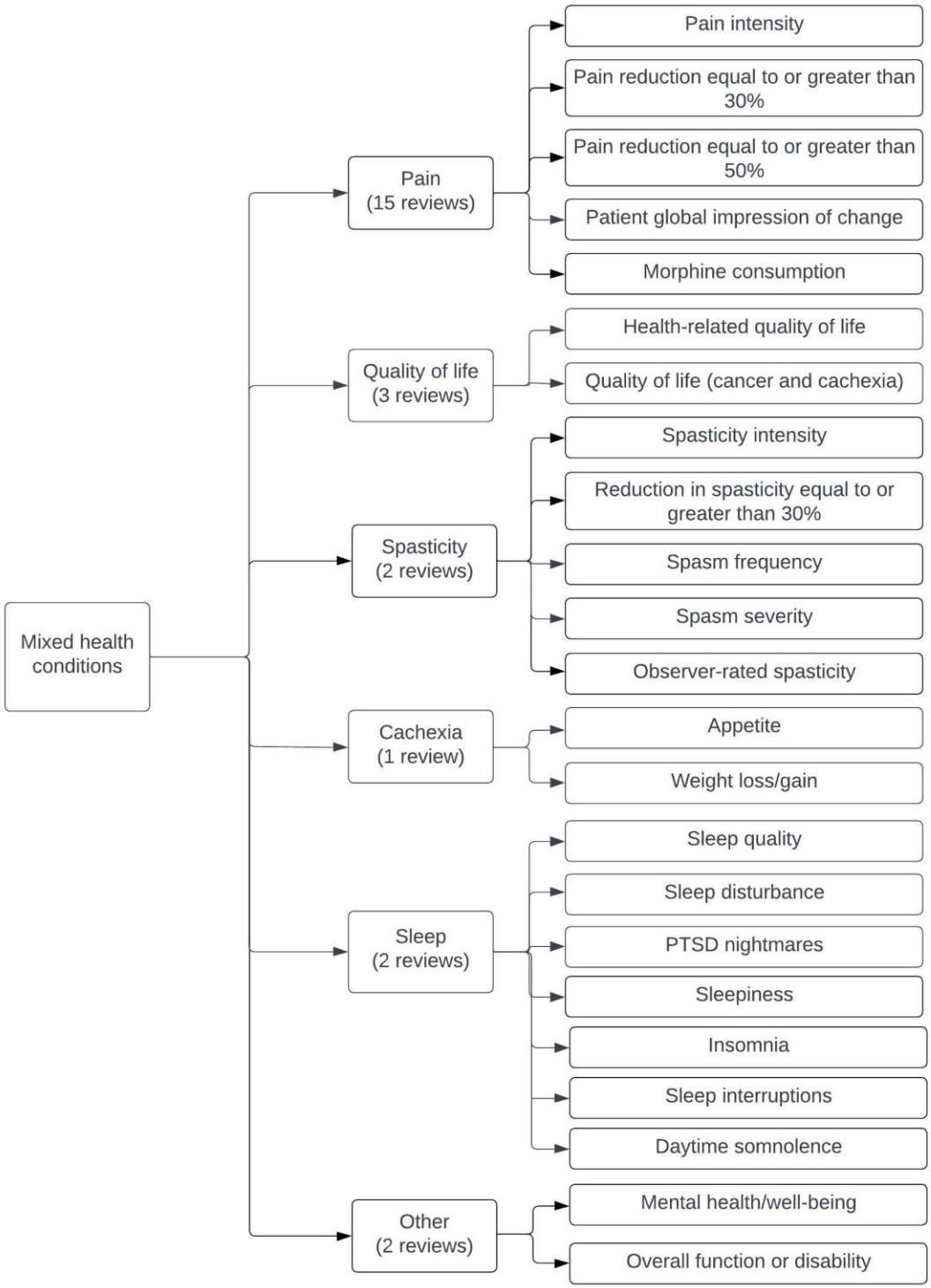

Figure 5 Primary outcomes for efficacy (mixed health conditions)

3.7.2.1 Pain

Fifteen reviews investigated pain-related outcomes as a primary outcome in adult populations with mixed health conditions [141–155]. Pain intensity was investigated in 12 reviews [142–144,146–149,151–155]. Pain reduction equal to or greater than 30% was investigated in six reviews [141,143–145,148,151]. Pain reduction equal to or greater than 50% was investigated in four reviews [143,145,150,151]. Two reviews

presented outcomes related to patient global impression of change of pain [144,150]. One review synthesised evidence related to morphine consumption as an analgesic [142].

3.7.2.1.1 Pain intensity

A summary of the evidence on pain intensity is presented in Table 45.

Table 45 Pain intensity outcomes (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain intensity						
	Mixed cannabinoids and cannabis vs. placebo	3 (6, 10, 6) [143,147,154]	Critically low	2.38%	2 very low 1 low	Significant improvement in mixed cannabinoid and cannabis groups (2 reviews) Mixed findings (1 review)
	Mixed cannabinoids vs. placebo	2 (6, 2) [146,148]	Critically low	14.29%	Low	Significant improvement in mixed cannabinoids group (1 review) No significant difference (1 review)
	Mixed cannabinoids vs. mixed controls	1 (10) [149]	Moderate	No overlap (single review)	High	Significant improvement in mixed cannabinoids group
	Cannabis vs. placebo	2 (1, 2) [152,154]	Critically low	0.00%	1 very low 1 low	Significant improvement in cannabis group
	Cannabis vs. usual care	1 (3) [148]	Critically low	No overlap (single review)	Low	Mixed findings
	THC:CBD vs. placebo	5 (reporting	1 moderate	36.36%	3 very low 1 low	Significant improvement in

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
		6 outcomes) (3, 7, 6, 1, 7, 5) [144,148,149,151,154]	4 critically low		1 moderate 1 high	THC:CBD group (3 reviews) Mixed findings (1 review) No significant difference (1 review)
	THC vs. placebo	6 (2, 6, 1, 1, 1, 2) [142,148,149,151,154,155]	1 moderate 5 critically low	3.33%	1 low 5 very low	Significant improvement in THC group (4 reviews) Mixed findings (1 review) No significant difference (1 review)
	THC vs. mixed controls	1 (3) [149]	Moderate	No overlap (single review)	Moderate	No significant difference
	THC vs. active controls	4 (reporting 5 outcomes) (1, 3, 1, 2) [146–148,152]	Critically low	13.33%	Very low	Significant improvement in THC group (1 review) No significant difference (4 reviews)
	CBD vs. placebo	3 (1, 1, 1) [153–155]	Critically low	11.11%	Very low	Significant improvement in CBD group (1 review) Mixed findings (1 review)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
						No significant difference (1 review)
	CBDV vs. placebo	2 (1) [148,154]	Critically low	No overlap (single review)	Very low	No significant difference (1 review) Insufficient information (1 review)
	CT-3 vs. placebo	1 (1) [154]	Critically low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 6.69%.

Mixed cannabinoid products compared with placebo

Two systematic reviews [146,148] synthesised evidence on pain intensity in mixed cannabinoid products compared with placebo. There was 14.3% overlap of primary studies.

In one review [148], low-certainty evidence indicated a significant improvement in pain intensity in extracted products with high ratios of THC to CBD compared with placebo groups comprising adult populations with fibromyalgia and multiple sclerosis (two RCTs, meta-analysis). Intervention durations ranged from 8 to 12 weeks; no follow-up was reported.

In the other review [146], low-certainty evidence indicated no significant difference in pain intensity between mixed cannabinoids and placebo groups of adults experiencing chronic pain (six RCTs, meta-analysis). Trial durations ranged from 2 days to 8 weeks; no follow-up was reported.

Mixed cannabinoids and cannabis products compared with placebo

Three systematic reviews synthesised evidence on pain intensity in mixed cannabinoids and cannabis products compared with placebo groups [143,147,154]. There was 2.4% overlap of the primary studies included in the three systematic reviews.

In one review [143], very low-certainty evidence indicated significant improvement in pain intensity in the medicinal cannabis compared with placebo groups comprising adult populations with various health conditions (six prospective cohort studies). Trial durations ranged from 6 to 12 months; no follow-up was reported.

In one review [154], low-certainty evidence indicated a significant improvement in pain intensity in the mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with chronic neuropathic pain (six RCTs, meta-analysis). Intervention durations ranged from four 4-hour sessions to 14 days, and no follow-up was reported.

In the final review [147], very low-certainty evidence indicated mixed findings in pain intensity between the mixed cannabinoids and placebo groups comprising adult populations with various health conditions (10 RCTs, narrative synthesis). Five studies reported no significant improvement in the mixed cannabinoids compared with placebo groups, and five RCTs reported no significant difference between the mixed cannabinoids and cannabis compared with placebo groups. Trial durations ranged from 1 to 18 weeks, and no follow-up was reported.

Mixed cannabinoid products compared with mixed controls

One systematic review [149] synthesised evidence on pain intensity in mixed cannabinoid products compared with mixed controls (placebo, dihydrocodeine). High-certainty evidence indicated a significant improvement in pain intensity in the mixed cannabinoids compared with mixed control groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (10 RCTs, meta-analysis). The review authors also conducted subgroup analyses by pain type (peripheral and central neuropathic pain). The subgroup analysis of neuropathic pain indicated a significant improvement in the mixed cannabinoids compared with placebo groups (five RCTs, subgroup analysis, high-certainty evidence). In contrast, the subgroup analysis of peripheral pain indicated no significant difference between the mixed cannabinoids and placebo groups (four RCTs, subgroup analysis, moderate-certainty evidence). Trial durations ranged from 2 to 14 weeks, and no follow-up period was specified.

Cannabis products compared with placebo

Two systematic reviews synthesised evidence [152,154] on pain intensity in cannabis products compared with placebo. There was no overlap of primary studies between these reviews.

In one review [154], low-certainty evidence indicated significant improvement in pain intensity in the THC compared with placebo groups comprising adult populations with chronic neuropathic pain (two RCTs, meta-analysis). Intervention durations ranged from three 150-minute sessions to 14 weeks; no follow-up was reported.

In one review [152], very low-certainty evidence indicated significant improvement in pain intensity in cannabis compared with placebo groups comprising adult populations with spinal cord injury and multiple sclerosis (one RCT, narrative synthesis). Intervention duration was three eight-hour sessions; follow-up was one, two and three-hour post-intervention.

Cannabis products compared with usual care

One systematic review [148] synthesised evidence on pain intensity indicating mixed finding in cannabis compared with usual care groups in a population of adults with various health conditions (chronic, non-cancer pain, neuropathic pain, musculoskeletal pain) (three prospective cohort studies, narrative review). Low-certainty evidence indicated mixed findings. Two prospective cohort studies reported no significant difference, one prospective cohort study reported significant improvement in cannabis compared with usual care. Treatment duration ranged from 12 weeks to 4 years, no follow-up was reported.

THC:CBD products compared with placebo

Five systematic reviews [144,148,149,151,154] synthesised evidence on pain intensity in THC:CBD products compared with placebo. There was 36.36% overlap of primary studies.

In one review [149], high-certainty evidence indicated significantly improved pain intensity in the THC:CBD (nabiximols) compared with placebo groups comprising adult populations with various health

conditions experiencing chronic neuropathic pain (six RCTs, meta-analysis). Trial durations ranged from 2 to 14 weeks, and no follow-up period was specified.

In one review [148], low-certainty evidence indicated a significant improvement in pain intensity in extracted products with comparable compared with placebo groups comprising adults with various health conditions experiencing chronic pain (seven RCTs, meta-analysis). Intervention durations ranged from 4 to 15 weeks, and no follow-up was reported.

In one review [154], moderate-certainty evidence indicated a significant improvement in pain intensity in the THC:CBD compared with placebo groups comprising adult populations with chronic neuropathic pain (five RCTs, meta-analysis). Intervention durations ranged from 2 to 14 weeks, and no follow-up was reported.

In one review [151], very low-certainty evidence indicated mixed findings on the efficacy of THC:CBD spray compared with placebo in pain intensity in a narrative review (seven RCTs) of adults with various health conditions. In six RCTs, no significant difference was reported between the THC:CBD and placebo groups (cancer, neuropathic pain). One RCT reported a significant improvement in the THC:CBD group for musculoskeletal pain in a population of adults with rheumatoid arthritis. Trial durations ranged from 3 to 14 weeks, and follow-up was conducted at the end of the intervention.

In contrast with the other reviews, one review [144] reported very low-certainty evidence indicating no significant improvement in pain intensity in THC:CBD compared with placebo groups comprising adult populations with various health conditions (multiple sclerosis, allodynia) (three RCTs, meta-analysis). This review also reported a second analysis of RCTs investigating neuropathic pain; low-certainty evidence found a significant improvement in pain intensity in nabiximols compared with placebo groups comprising adult populations with neuropathic pain (four RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks; no follow-up was reported.

THC products compared with placebo

Six systematic reviews [142,148,149,151,154,155] synthesised evidence on pain intensity in cannabis products (THC) compared with placebo. There was 3.3% overlap of primary studies between the reviews.

One review [148] reported low-certainty evidence of a significant improvement in pain intensity in synthetic products with high ratios of THC to CBD compared with placebo groups comprising adult populations experiencing chronic pain in various health conditions (six RCTs, meta-analysis). Intervention durations ranged from 4 to 16 weeks.

In one review [151], very low-certainty evidence indicated a significant improvement in pain intensity in the THC (dronabinol) compared with placebo groups comprising an adult population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 16 weeks, and follow-up was conducted at the end of treatment.

In one review [149], very low-certainty evidence indicated a significant improvement in pain intensity in the dronabinol compared with placebo groups comprising an adult population experiencing central neuropathic pain (one RCT, narrative synthesis). Trial duration was 3 weeks, with follow-up at the end of the intervention.

In one review [154], very low-certainty evidence indicated a significant improvement in the dronabinol compared with placebo groups comprising an adult population experiencing chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 21 days, and no follow-up was reported.

In one review [142], very low-certainty evidence indicated mixed findings in THC products compared with placebo. In a narrative review (two RCTs), one RCT reported no significant difference between the THC

and placebo groups, whereas the other RCT reported significantly higher pain in the nabilone compared with placebo groups. Intervention durations ranged from 24 to 48 hours post-operation; no follow-up was reported.

In the final review [155], very low-certainty evidence indicated no significant improvement in pain intensity in the THC (nabilone and intravenous THC) compared with placebo groups comprising adult populations experiencing orofacial pain (two RCTs, narrative synthesis). Trial duration was not reported clearly; however, the review authors reported follow-up every 7 days during the intervention and 28 days after the intervention in one RCT; and at the intervention midpoint, 30 minutes, 24 hours, and 1 month post-intervention in the other RCT.

THC products compared with mixed controls

One systematic review [149] synthesised evidence on pain intensity in THC products compared with mixed controls (placebo, dihydrocodeine). Moderate-certainty evidence indicated no significant difference in pain intensity between the THC (nabilone) compared with mixed control (placebo and dihydrocodeine) groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (three RCTs, meta-analysis). Trial durations ranged from 5 to 9 weeks, and no follow-up period was specified.

THC products compared with active controls

Four systematic reviews [146–148,152] synthesised evidence on pain intensity in THC products compared with active control groups. There was 13.3% overlap of primary studies between the reviews.

Very low-certainty evidence from one review [147] reported no significant difference in pain intensity between mixed cannabinoid and active control groups (amitriptyline (a tricyclic antidepressant), diazepam (a benzodiazepine), diphenhydramine (a sedative and antihistamine)) comprising adult populations with various health conditions (three RCTs, narrative synthesis). Trial durations ranged from 16 days to 18 weeks; no follow-up was reported.

Very low-certainty evidence from one review [146] reported no significant improvement in pain intensity in the THC compared with amitriptyline (a tricyclic antidepressant) groups comprising an adult population experiencing orofacial pain (one RCT, narrative synthesis). Trial duration was 10 weeks, and no follow-up period was reported.

Very low-certainty evidence from one review [152] reported no significant difference in pain intensity in the THC compared with active control groups (diphenhydramine (a sedative and antihistamine) and mannitol (a diuretic medication)) comprising an adult population with spinal cord injury (two RCTs, narrative synthesis). Trial duration was 4 weeks, and follow-up was at the end of the intervention in one RCT. Trial duration was not clearly reported in the other RCT, however authors reported follow-up 14 days after the intervention.

Very low-certainty evidence from one review [148] reported a significant improvement in the THC (nabilone) compared with gabapentin (an anticonvulsant medication) groups comprising an adult population with neuropathic pain (one prospective cohort study, narrative synthesis). No significant difference was reported between the cannabinoid-only group and the combined cannabinoid and gabapentin group. Trial duration was 6 months, and no follow-up was reported.

CBD products compared with placebo

Three systematic reviews [153–155] synthesised evidence on pain intensity in CBD products compared with placebo. There was 11.1% overlap of primary studies between the reviews.

Very low-certainty evidence [155] reported a significant improvement in pain intensity in the CBD compared with placebo groups comprising an adult population experiencing orofacial pain (one RCT, narrative synthesis). Trial duration was not reported clearly; however, the review authors reported a follow-up 14 days after the intervention.

Very low-certainty evidence [153] reported mixed evidence for improvement in pain intensity between the CBD oil and placebo groups comprising an adult population with neuropathic pain (one RCT, narrative synthesis). This study reported a significant decrease in intense cold sensations in favour of CBD oil compared with placebo; however, this study also reported a significant decrease in sharp and itchy sensations in favour of placebo compared with CBD oil. Trial duration was 4 weeks, and no follow-up was reported.

Very low-certainty evidence [154] reported no significant difference between the CBD and placebo groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 2 weeks, and no follow-up was reported.

Cannabidivarin products compared with placebo

Two reviews [148,154] synthesised evidence on pain intensity in cannabidivarin (CBDV) products compared with placebo. There was 100% overlap of primary studies between the reviews.

Very low-certainty evidence [154] reported no significant difference between the CBDV and placebo groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported.

The other review [148] reported insufficient evidence to draw conclusion on the efficacy of CBDV compared with placebo groups.

CT-3 compared with placebo

One review [154] synthesised evidence on pain intensity in 1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3) products compared with placebo. Very low-certainty evidence indicated no significant difference between the CT-3 and placebo groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 1 week, and no follow-up was reported.

3.7.2.1.2 Pain reduction equal to or greater than 30%

A summary of the evidence on pain reduction equal to or greater than 30% is presented in Table 46.

Table 46 Pain reduction equal to or greater than 30% (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain reduction equal to or greater than 30%						
	Mixed cannabinoids and cannabis vs. placebo	1 (6) [143]	Critically low	No overlap (single review)	Very low	Significant improvement in mixed cannabinoids and cannabis group

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Cannabis vs. placebo	2 (reporting 3 outcomes) (5, 2, 1) [141,145]	1 moderate 1 low	14.29%	2 moderate 1 very low	Significant improvement in cannabis group
	THC:CBD vs. placebo	4 (3, 6, 4, 4) [144,145,148,151]	1 low 3 critically low	47.62%	3 low 1 very low	Significant improvement in THC:CBD group (1 review) No significant difference (3 reviews)
	THC vs. placebo	2 (2, 1) [145,148]	1 low 1 critically low	0.00%	1 low 1 very low	Significant improvement in THC group (1 review) No significant difference (1 review)
	THC vs. placebo/codeine	1 (1) [145]	Low	No overlap (single review)	Very low	Significant improvement in THC group

Note: Overall overlap was 8.80%.

Mixed cannabinoids and cannabis products compared with placebo

One systematic review [143] synthesised evidence for pain reduction equal to or greater than 30% as a primary outcome in mixed cannabinoid and cannabis products compared with placebo. Very low-certainty evidence indicated a significant improvement in the mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with various health conditions (six prospective cohort studies, meta-analysis). Trial durations ranged from 6 to 12 months, and no follow-up was reported.

Cannabis products compared with placebo

Two systematic reviews [141,145] synthesised evidence for pain reduction equal to or greater than 30% as a primary outcome in cannabis products compared with placebo. There was 14.3% overlap of primary studies between the reviews.

One review reported moderate-certainty evidence [141] indicating significant improvement in the THC (inhaled *Cannabis sativa*) compared with placebo groups comprising adult populations with neuropathic

pain (five RCTs, meta-analysis). Intervention durations ranged from 2 hours to 5 weeks; additional details on follow-up were unclear.

One review reported moderate-certainty evidence [145] indicating significant improvement in pain in the cannabis compared with placebo groups comprising adult populations with chronic pain (neuropathic pain, neuropathic pain after injury) (two RCTs, meta-analysis). Trial durations ranged from 18 to 24 hours, and no follow-up was reported. This review also reported very low-certainty evidence indicating a significant improvement in pain in the cannabis compared with placebo groups comprising an adult population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 12 weeks, and no follow-up was reported.

THC:CBD products compared with placebo

Four systematic reviews [144,145,148,151] synthesised evidence for pain reduction equal to or greater than 30% as a primary outcome in THC:CBD products compared with placebo. There was 47.6% overlap of primary studies between the reviews.

One review reported low-certainty evidence [145] indicating a significant improvement in pain in nabiximols compared with placebo groups comprising adult populations with chronic pain (cancer, multiple sclerosis, neuropathic pain, allodynia) (six RCTs, meta-analysis). Trial durations ranged from 2 to 15 weeks, and no follow-up was reported.

One review reported low-certainty evidence [144] indicating no significant improvement in pain in nabiximols compared with placebo groups comprising adult populations with various health conditions (multiple sclerosis, diabetic neuropathy, allodynia) (three RCTs, meta-analysis). Trial durations ranged from 5 to 14 weeks; no follow-up was reported.

One review reported low-certainty evidence [148] reported no significant difference between comparable THC:CBD products and placebo groups comprising adult populations with chronic, non-cancer pain (four RCTs, meta-analysis). Intervention durations ranged from 5 to 15 weeks, and no follow-up was reported.

One review reported very low-certainty evidence [151] reported no significant difference in reducing pain by ≥30% between THC:CBD spray and placebo groups comprising adult populations with various health conditions (four RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks, and follow-up was conducted at the end of treatment.

THC products compared with placebo

Two systematic reviews [145,148] synthesised evidence for pain reduction equal to or greater than 30% as a primary outcome in THC products compared with placebo. There was no overlap of primary studies between these reviews.

One systematic review reported very low-certainty evidence [148] indicating significant improvement in whole products with a high ratio of THC to CBD compared with placebo groups comprising an adult population with diabetic neuropathy pain (one RCT, narrative synthesis). Trial duration was 5 weeks; no follow-up was reported.

One review reported low-certainty evidence [145] indicating no significant difference between THC and placebo groups comprising adult populations with chronic pain (multiple sclerosis, cancer) (two RCTs, meta-analysis). Intervention durations ranged from 2 weeks to 3 years, and no follow-up was reported.

THC products compared with placebo/codeine

One systematic review [145] synthesised evidence for pain reduction equal to or greater than 30% as a primary outcome in THC products compared with placebo/codeine. Very low-certainty evidence indicated a significant improvement in pain in the THC congener compared with placebo/codeine groups

comprising an adult population with cancer (one RCT, narrative synthesis). Trial duration was 5 days; no follow-up was reported.

3.7.2.1.3 Pain reduction equal to or greater than 50%

A summary of the evidence on pain reduction equal to or greater than 50% is presented in Table 47.

Table 47 Pain reduction equal to or greater than 50% (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Pain reduction equal to or greater than 50%						
	Mixed cannabinoids vs. placebo	1 (6) [150]	Low	No overlap (single review)	Low	Significant improvement in mixed cannabinoids group
	Mixed cannabinoids and cannabis vs. placebo	1 (8) [143]	Critically low	No overlap (single review)	Very low	Significant improvement in mixed cannabinoids and cannabis group
	THC:CBD vs. placebo	3 (2, 1, 4) [145,150,151]	2 low 1 critically low	37.5%	1 low 2 very low	Significant improvement in THC:CBD group (1 review) No significant difference (2 reviews)
	THC vs. placebo	1 (1) [150]	Low	No overlap (single review)	Very low	No significant difference
	THC products vs. mixed controls	1 (2) [145]	Low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 11.11%.

Mixed cannabinoids and cannabis products compared with placebo

One review [143] synthesised evidence on pain reduction equal to or greater than 50% as a primary outcome in mixed cannabinoids and cannabis compared with placebo. Very low-certainty evidence

indicated a significant improvement in the mixed cannabinoids and cannabis compared with placebo groups comprising adult populations with various health conditions (six prospective cohort studies, meta-analysis). Trial durations ranged from 6 to 12 months; no follow-up was reported.

Mixed cannabinoid products compared with placebo

One review [150] synthesised evidence on pain reduction equal to or greater than 50% as a primary outcome in mixed cannabinoids compared with placebo. Low-certainty evidence indicated a significant improvement in mixed cannabinoids compared with placebo groups (eight RCTs, meta-analysis) comprising adults with chronic neuropathic pain. The review authors note that this difference was not clinically significant. Trial durations ranged from 2 to 14 weeks, and no follow-up was reported.

THC:CBD products compared with placebo

Three systematic reviews [145,150,151] synthesised evidence on pain reduction equal to or greater than 50% as a primary outcome in THC:CBD products compared with placebo. There was 37.5% overlap of primary studies between these reviews.

One review reported very low-certainty evidence [150] of a significant improvement in the THC:CBD compared with placebo groups comprising an adult population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 4 weeks; no follow-up was reported.

One systematic review reported low-certainty evidence [145] indicating no significant difference between the THC:CBD and placebo groups comprising adult populations with chronic pain (two RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks, and no follow-up was reported.

One review reported very low-certainty evidence [151] indicating no significant difference in pain reduction equal to or greater than 50% between THC:CBD spray and placebo groups comprising adult populations with various health conditions (four RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks, and follow-up was carried out at the end of treatment.

THC products compared with placebo

One systematic review [150] synthesised evidence on pain reduction equal to or greater than 50% as a primary outcome in THC products compared with placebo. Very low-certainty evidence indicated no significant difference in nabilone compared with placebo groups comprising an adult population with diabetic neuropathy (one RCT, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported.

THC products compared with mixed controls

One review [145] synthesised evidence on pain reduction equal to or greater than 50% as a primary outcome in THC products compared with mixed controls. Very low-certainty evidence indicated no significant differences between the THC and codeine/placebo groups comprising adult populations with cancer (two RCTs, meta-analysis). Trial duration was 5 days; no follow-up was reported.

3.7.2.1.4 Patient global impression of change of pain

A summary of evidence on patient global impression of change of pain is presented in Table 48.

Table 48 Patient global impression of change outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Patient global impression of change of pain						
	Mixed cannabinoids vs. placebo	1 (2) [144]	Critically low	No overlap (single review)	Very low	Significant improvement in mixed cannabinoid groups
	THC:CBD vs. placebo	1 (6) [150]	Low	No overlap (single review)	Low	Significant improvement in THC:CBD groups
	THC vs. placebo	1 (1) [150]	Low	No overlap (single review)	Very low	Significant improvement in THC groups

Note: Overall overlap was 12.5%.

Mixed cannabinoid products compared with placebo

One review [144] synthesised evidence on patient global impression of change of pain as a primary outcome in mixed cannabinoid products compared with placebo. Very low-certainty evidence indicated a significant improvement in the mixed cannabinoid (nabiximols, nabilone) compared with placebo groups (two RCTs, meta-analysis) comprising adult populations with multiple sclerosis. Trial durations ranged from 4 to 9 weeks, and no follow-up was reported.

THC:CBD products compared with placebo

One review [150] synthesised evidence on patient global impression of change of pain as a primary outcome in THC:CBD products compared with placebo. Low-certainty evidence indicated a statistically significant improvement in the THC:CBD compared with placebo groups comprising adult populations experiencing chronic neuropathic pain (six RCTs, meta-analysis). The review authors note that this difference was not clinically significant. Trial durations ranged from 3 to 15 weeks, and no follow-up was reported.

THC products compared with placebo

One review [150] synthesised evidence on patient global impression of change of pain as a primary outcome in THC products compared with placebo. Very low-certainty evidence indicated a significant improvement in the THC (nabilone) compared with placebo groups comprising an adult population with diabetic neuropathy (one RCT, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported.

3.7.2.1.5 Morphine consumption

A summary of the evidence on morphine consumption is presented in Table 49.

Table 49 Morphine consumption outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Morphine consumption						
	THC vs. placebo	1 (2) [142]	Critically low	No overlap (single review)	Very low	No significant difference

THC products compared with placebo

One systematic review [142] synthesised evidence on morphine consumption as a primary outcome in THC products compared with placebo. Very low-certainty evidence indicated no significant difference in cumulative oral morphine equivalent consumption at 24 hours postoperatively between the THC and control groups (two RCTs, narrative synthesis). Trial durations ranged from 24 to 48 hours post-operation, and no follow-up was reported.

3.7.2.1.6 Summary

Overall, there is mixed evidence on the efficacy of cannabinoids on pain intensity, ranging from moderate to very low certainty. Three reviews [143,147,154] reported a significant improvement for mixed cannabinoids and cannabis compared with placebo groups (low- to very low-certainty evidence). Two reviews [146,148] reported contrasting evidence on the efficacy of mixed cannabinoids compared with placebo (low-certainty evidence). When mixed cannabinoids were compared with mixed controls, one review [149] indicated a significant improvement in mixed cannabinoids compared with mixed controls (high-certainty evidence). Two reviews [152,154] indicated a significant improvement in pain intensity in the cannabis compared with placebo groups (low- to very low-certainty evidence), while one review [148] reported no significant difference between the cannabis and usual care groups (low-certainty evidence).

In the THC:CBD compared with placebo groups, three reviews [148,149,154] indicated a significant improvement in pain intensity for the THC:CBD groups (high- to very low-certainty evidence), and two reviews [144,151] reported mixed findings (very low-certainty evidence). In THC compared with placebo groups, four systematic reviews [148,149,151,154] reported a significant improvement in the THC groups (moderate- to very low-certainty evidence), one review [142] reported mixed findings (low-certainty evidence), and one review [155] reported no significant difference (very low-certainty evidence). One review [149] that compared THC with mixed controls reported moderate-certainty evidence indicating no significant difference between THC and dihydrocodeine/placebo groups. Four reviews [146–148,152] compared THC with active controls only, and found no significant difference between the groups (very low-certainty evidence). Three reviews compared CBD with placebo (very low-certainty evidence). Very low-certainty evidence in these reviews reported a significant improvement in the CBD group [155], mixed findings [153], and no significant difference [154]. Reviews comparing CBDV [148,154] and CT-3 [154] indicated no significant difference when compared with placebo.

Evidence synthesised on the likelihood of a 30% or greater reduction in pain ranged from moderate to very low certainty. One review indicated a significant improvement in mixed cannabinoids and cannabis products compared with placebo (very low-certainty evidence) [143]. Two reviews [141,145] reported a

significant improvement in the cannabis compared with placebo groups (moderate- to very low-certainty evidence). Three reviews [144,148,151] reported no significant difference between the THC:CBD and placebo groups (low-certainty evidence), and one review [145] reported a significant likelihood of improvement in the THC:CBD group (very low-certainty evidence). One review [145] indicated a significant likelihood of improvement in the THC compared with placebo/codeine groups (very low-certainty evidence). Two reviews [141, 139] reported mixed evidence in THC compared with placebo groups. One review [141] reported very low-certainty evidence indicating significant improvement in THC compared with placebo groups comprising adults with diabetic neuropathy, but one review [139] reported low-certainty evidence indicating no significant difference between groups of adults with chronic pain.

Evidence synthesised on the likelihood of a 50% or greater reduction in pain ranged from low to very low certainty. One review [143] reported a significant likelihood of at least a 50% reduction in pain in the mixed cannabinoids and cannabis compared with placebo groups (very low-certainty evidence). Two reviews reported mixed evidence in the THC:CBD compared with placebo groups. One review [150] reported a significant likelihood of a greater than 50% reduction in pain in the THC:CBD group (very low-certainty evidence), and two reviews [145,151] reported no significant difference between the THC:CBD and placebo groups (low- and very low-certainty evidence, respectively). One review [150] reported no significant difference between the THC and placebo groups (very low-certainty evidence). One review [145] reported no significant difference in the THC compared with mixed control groups (very low-certainty evidence).

In relation to patient global impression of pain outcomes, evidence ranged from low to very low certainty. Two reviews reported a significant improvement in patient global impression of change of pain in the mixed cannabinoid [144], THC:CBD [150], and THC [150] compared with placebo groups.

One review [142] reported no significant difference in morphine consumption in the THC compared with placebo groups (very low-certainty evidence).

3.7.2.2 Quality of life

Three reviews investigated quality of life as a primary outcome. Two reviews [151,156] investigated health-related quality of life, a multidimensional self-reported outcome representing the person's perception of the effect of illness and treatment on the physical, psychological, and social aspects of life. One review [157] synthesised quality of life evidence across scales specific to cancer and cachexia.

3.7.2.2.1 Health-related quality of life

A summary of evidence on health-related quality of life is presented in Table 50.

Table 50 Health-related quality of life outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Health-related quality of life						
	Mixed cannabinoids	1 (13) [156]	Critically low	No overlap	Low	No significant difference

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	vs. mixed controls			(single review)		
	THC:CBD vs. placebo	2 (4, 5) [151,156]	Critically low	0%	1 moderate 1 low	No significant difference
	THC vs. placebo	1 (1) [151]	Critically low	No overlap (single review)	Very low	No significant difference
	THC vs. mixed controls	1 (6) [156]	Critically low	No overlap (single review)	Low	No significant difference

Note: Overall overlap was 15.28%.

Mixed cannabinoid products compared with mixed controls (megestrol acetate, placebo)

One review [156] synthesised evidence on health-related quality of life in mixed cannabinoids compared with mixed controls. There is low-certainty evidence indicating no significant difference in health-related quality of life between mixed cannabinoid and mixed control groups (megestrol acetate (an appetite stimulant), placebo) comprising adult populations with cancer and central nervous system disorders (13 RCTs, meta-analysis). Intervention durations ranged from 2 to 14 weeks, and no follow-up period was specified.

THC:CBD products compared with placebo

Two reviews [151,156] synthesised evidence on health-related quality of life in THC:CBD products compared with placebo. There was no overlap of primary studies included in the two systematic reviews.

One review [156] reported moderate-certainty evidence indicating no significant difference in health-related quality of life in the THC:CBD compared with placebo groups comprising adult populations with cancer and central nervous system disorders (five RCTs, meta-analysis). Intervention durations ranged from 6 to 12 weeks; no follow-up period was specified.

Similarly, in the second review [151], low-certainty evidence indicated no significant difference in quality of life in the THC:CBD compared with placebo groups in a narrative review (four RCTs) of adults with multiple sclerosis and allodynia. Trial durations ranged from 4 to 14 weeks with follow-up at the end of treatment.

THC products compared with placebo

One review [151] reported very low-certainty evidence indicating no significant difference in quality of life in the THC (dronabinol) compared with placebo groups comprising an adult population with allodynia experiencing neuropathic pain (one RCT, narrative synthesis). Trial duration was 4 weeks with follow-up at the end of treatment.

THC products compared with mixed controls (megestrol acetate, placebo)

One review [156] synthesised evidence on health-related quality of life in THC products compared with mixed controls (megestrol acetate (an appetite stimulant), placebo). There is low-certainty evidence indicating no significant difference in health-related quality of life between the THC and mixed control groups comprising adult populations with cancer and central nervous system disorders (six RCTs, meta-analysis). Intervention durations ranged from 2 weeks to 80 days, and no follow-up period was specified.

3.7.2.2.2 Quality of life (cancer and cachexia)

A summary of the evidence on quality of life in cancer and cachexia is presented in Table 51.

Table 51 Quality of life (cancer and cachexia) outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Quality of life (cancer and cachexia)						
	Mixed cannabinoids vs. mixed controls	1 (3) [157]	Critically low	No overlap (single review)	Low	No significant difference

Mixed cannabinoids compared with mixed controls

One systematic review [157] synthesised evidence on quality of life in cancer and cachexia for mixed cannabinoids versus mixed controls (placebo, megestrol acetate (an appetite stimulant)). There is low-certainty evidence indicating no significant difference in quality of life between mixed cannabinoid and mixed control groups (three RCTs, meta-analysis) comprising adult populations with cancer and HIV. Intervention durations ranged from 4 to 8 weeks, and no follow-up period was specified.

3.7.2.2.3 Summary

Overall, three systematic reviews synthesised evidence on quality-of-life-related outcomes. Two systematic reviews [151,156] reported on health-related quality of life. In relation to health-related quality of life, evidence indicated no significant difference in mixed cannabinoids compared with mixed control groups (low certainty) [156], THC:CBD products compared with placebo (moderate and low certainty) [151,156], and THC products compared with mixed controls (low certainty) [156]. One review [151] indicated a significant improvement in the THC compared with placebo groups. In relation to quality-of-life measures specific to cancer and cachexia, one review [157] reported no significant difference in mixed cannabinoids compared with mixed controls (low certainty).

3.7.2.3 Spasticity

3.7.2.3.1 Spasticity intensity

A summary of the evidence on spasticity intensity is presented in Table 52.

Table 52 Spasticity intensity outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Spasticity intensity						
	Mixed cannabinoids and cannabis vs. placebo	1 (7) [158]	Critically low	No overlap (single review)	Low	No significant difference
	THC:CBD vs. placebo	1 (2) [151]	Critically low	No overlap (single review)	Very low	Mixed evidence

Note: Overall overlap was 0%.

Mixed cannabinoids and cannabis products compared with placebo

One review [158] synthesised evidence on spasticity intensity as a primary outcome in mixed cannabinoids and cannabis compared with placebo groups. Low-certainty evidence indicated no significant difference between mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with spasticity (seven RCTs, meta-analysis). Trial durations ranged from 2 to 10 weeks, and no follow-up was reported.

THC:CBD products compared with placebo

One review [151] synthesised evidence on spasticity intensity as a primary outcome in THC:CBD products compared with placebo. Very low-certainty evidence indicated mixed findings for adult populations with multiple sclerosis (two RCTs, narrative synthesis). One RCT reported no significant difference between THC:CBD and placebo groups, while the other RCT reported a significant improvement in the THC:CBD compared with placebo groups. Trial durations ranged from 6 to 14 weeks, and follow-up was conducted at the end of treatment.

3.7.2.3.2 Reduction in spasticity equal to or greater than 30%

A summary of the evidence on reduction in spasticity equal to or greater than 30% is presented in Table 53.

Table 53 Reduction in spasticity equal to or greater than 30% (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Reduction in spasticity equal to or greater than 30%						
	THC:CBD vs. placebo	1 (2) [151]	Critically low	No overlap	Very low	No significant difference

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
				(single review)		

THC:CBD products compared with placebo

One systematic review [151] synthesised evidence of reduction in spasticity equal to or greater than 30% as a primary outcome in THC:CBD products compared with placebo groups. Very low-certainty evidence indicated no significant difference between the THC:CBD spray and placebo groups comprising adult populations with multiple sclerosis (two RCTs, meta-analysis). Trial durations ranged from 6 to 14 weeks, and follow-up was conducted at the end of treatment.

3.7.2.3.3 Spasm frequency

A summary of the evidence on spasm frequency is presented in Table 54.

Table 54 Spasm frequency outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Spasm frequency						
	Mixed cannabinoids and cannabis vs. placebo	1 (6) [158]	Critically low	No overlap (single review)	Very low	No significant difference

Mixed cannabinoids and cannabis products compared with placebo

One review [158] synthesised evidence on spasm frequency as a primary outcome in mixed cannabinoids and cannabis compared with placebo groups. Very low-certainty evidence indicated no significant difference between mixed cannabinoids and cannabis compared with placebo groups comprising adult populations with spasticity (six RCTs, meta-analysis). Trial durations ranged from 3 to 10 weeks, and no follow-up was reported.

3.7.2.3.4 Spasm severity

A summary of the evidence on spasm severity is presented in Table 55.

Table 55 Spasm severity outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Spasm severity						
	Mixed cannabinoids and cannabis vs. placebo	1 (3) [158]	Critically low	No overlap (single review)	Very low	No significant difference

Mixed cannabinoids and cannabis products compared with placebo

One review [158] synthesised evidence on spasm severity as a primary outcome in mixed cannabinoids and cannabis compared with placebo groups. Very low-certainty evidence indicated no significant difference between mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with spasticity (three RCTs, meta-analysis). Intervention durations ranged from 7 to 10 weeks, and no follow-up was reported.

3.7.2.3.5 Observer-rated spasticity

A summary of the evidence on observer-rated spasticity is presented in Table 56.

Table 56 Observer-rated spasticity outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Observer-rated spasticity						
	THC:CBD vs. placebo	1 (2) [151]	Critically low	No overlap (single review)	Low	Significant improvement in THC:CBD group
	THC vs. placebo	1 (1) [151]	Critically low	No overlap (single review)	Very low	Significant improvement in THC group

Note: Overall overlap was 0%.

THC:CBD products compared with placebo

One review [151] synthesised evidence on observer-rated spasticity as a primary outcome in THC:CBD products compared with placebo groups. Low-certainty evidence indicated a significant improvement in observer-rated spasticity for the THC:CBD groups comprising adult populations with various health

conditions (amyotrophic lateral sclerosis, multiple sclerosis) (two RCTs, narrative synthesis). Trial durations ranged from 2 to 4 weeks, and follow-up was conducted at the end of treatment.

THC products compared with placebo

One review [151] synthesised evidence on observer-rated spasticity as a primary outcome in THC products compared with placebo groups. Very low-certainty evidence indicated a significant improvement in observer-rated spasticity in THC (dronabinol) compared with placebo groups comprising an adult population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 8 weeks, and follow-up was conducted at the end of treatment and again at 12 months.

3.7.2.3.6 Summary

Evidence on spasticity intensity was synthesised in two reviews, with one review indicating no significant difference between mixed cannabinoids and cannabis compared with placebo (low-certainty evidence) [158] and the other review indicating mixed evidence on the efficacy of THC:CBD compared with placebo on spasticity intensity [151]. In relation to the likelihood of a greater than 30% reduction in spasticity, one review [151] reported no significant difference between THC:CBD and placebo groups. One review [158] reported no significant difference in spasm frequency or severity in the mixed cannabinoids and cannabis compared with placebo groups. One review [151] reported significant improvements in observer-rated spasticity in the THC:CBD compared with placebo groups and in the THC compared with placebo groups. With the exception of observer-rated spasticity, there was no significant difference between cannabinoids and comparator groups across the synthesised evidence (low- to very low-certainty evidence).

3.7.2.4 Cachexia

One review [157] investigated cachexia (defined as a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass) as a primary outcome. This review synthesised evidence on appetite and weight gain/loss in a mixed population of adults with cancer and HIV.

3.7.2.4.1 Appetite

A summary of the evidence on appetite in cachexia is presented in Table 57.

Table 57 Appetite in cachexia outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Appetite						
	Mixed cannabinoids vs. placebo	1 (2) [157]	Critically low	No overlap (single review)	Low	No significant difference

Mixed cannabinoids compared with placebo

One review found low-certainty evidence [157] indicating no significant difference in appetite between mixed cannabinoid and placebo groups comprising adult populations with cancer associated cachexia

(two RCTs, meta-analysis). Intervention durations ranged from 4 to 6 weeks, and no follow-up period was specified.

3.7.2.4.2 Weight loss/gain

A summary of the evidence on weight loss/gain in cachexia is presented in Table 58.

Table 58 Weight loss/gain in cachexia outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Weight loss/gain						
	THC vs. mixed controls	1 (2) [157]	Critically low	No overlap (single review)	Very low	No significant difference

THC products compared with mixed controls

One review found very low-certainty evidence [157] indicating no significant difference in weight changes between THC (dronabinol, nabilone) and mixed control groups (megestrol acetate (an appetite stimulant) and placebo) comprising adult populations with cancer and HIV (two RCTs, meta-analysis). Intervention durations ranged from 8 to 12 weeks, and no follow-up period was specified.

3.7.2.4.3 Summary

One review [157] synthesised evidence on cachexia-related outcomes. The synthesised evidence indicated no significant difference in appetite (low-certainty evidence) in mixed cannabinoid compared with placebo groups, and no significant difference in weight loss/gain in THC compared with mixed control groups (very low-certainty evidence).

3.7.2.5 Sleep

Two reviews investigated sleep as a primary outcome. The following sleep-related outcomes were investigated: sleep quality [159,160], sleep disturbance, PTSD nightmares, sleepiness, insomnia, sleep interruptions [159], and daytime somnolence [160] in adult populations with various health conditions.

3.7.2.5.1 Sleep quality

A summary of the evidence on sleep quality is presented in Table 59.

Table 59 Sleep quality outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sleep quality						

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	Mixed cannabinoids and cannabis vs. placebo	2 (16, 6) [159,160]	1 critically low 1 moderate	23.5%	1 moderate 1 high	Significant improvement in mixed cannabinoid and cannabis groups
	THC vs. placebo	1 (1) [159]	Critically low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 15.28%.

Mixed cannabinoids and cannabis compared with placebo

Two reviews [159,160] synthesised evidence on sleep quality for mixed cannabinoid and cannabis products compared with placebo. There was 23.5% overlap of primary studies included in the two systematic reviews.

In one review [159], there was moderate-certainty evidence indicating a significant improvement in sleep quality in the mixed cannabinoids and cannabis compared with placebo groups comprising adult populations with various health conditions (16 RCTs, meta-analysis). Trial durations were reported as follow-ups ranging from 14 to 98 days.

In the other review [160], high-certainty evidence indicated significantly improved sleep quality in the cannabinoid and cannabis compared with placebo groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (six RCTs, meta-analysis). Trial durations ranged from 2 to 15 weeks, and no follow-up period was specified.

THC products compared with placebo

There was very low-certainty evidence from one review [159] indicating no significant difference in sleep quality between the THC (nabilone) and placebo groups comprising an adult population undergoing radiotherapy for head and neck carcinomas (one RCT, narrative synthesis). Intervention duration/follow-up was 70 days.

3.7.2.5.2 Sleep disturbance

A summary of the evidence on sleep disturbance is presented in Table 60.

Table 60 Sleep disturbance outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sleep disturbance						
	Mixed cannabinoids vs. placebo	1 (16) [159]	Critically low	No overlap (single review)	Low	Significant improvement in mixed cannabinoid group
	THC vs. active controls	1 (1) [159]	Critically low	No overlap (single review)	Very low	Significant improvement in THC group

Note: Overall overlap was 0%.

Mixed cannabinoids compared with placebo

One review [159] synthesised evidence on sleep disturbance for mixed cannabinoid products compared with placebo. Low-certainty evidence indicated a significant improvement in sleep disturbance in the mixed cannabinoid compared with placebo groups of adult populations with cancer and non-cancer-related health conditions (16 RCTs, meta-analysis). Trial durations were reported as follow-ups ranging from 14 to 84 days. Subgroup analysis by cancer and non-cancer-related health condition groups remained significant in both groups (moderate-certainty evidence).

THC products compared with active controls

One review [159] synthesised evidence on sleep disturbance for THC products compared with active controls. Very low-certainty evidence found significant improvements in sleep disturbance in THC products compared with diazepam (a benzodiazepine) groups comprising an adult population with anorexia nervosa (one RCT, narrative synthesis). Intervention duration/follow-up was 28 days.

3.7.2.5.3 PTSD nightmares

A summary of evidence on PTSD nightmares is presented in Table 61. See Section 3.7.1.5.1.2 for additional evidence on medicinal cannabis for PTSD from reviews of specific health conditions (mental health and neuropsychological conditions).

Table 61 PTSD nightmares outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
PTSD nightmares						
	THC vs. placebo	1 (1) [159]	Critically low	No overlap (single review)	Very low	No significant difference

THC products compared with placebo

One review [159] synthesised evidence on PTSD nightmares for THC products compared with placebo. Very low-certainty evidence indicated no significant difference in PTSD nightmares between the THC (nabilone) and placebo groups among an adult population undergoing radiotherapy for head and neck carcinomas (one RCT, narrative synthesis). Intervention duration/follow-up was 14 days.

3.7.2.5.4 Sleepiness

A summary of the evidence on sleepiness is presented in Table 62.

Table 62 Sleepiness outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sleepiness						
	THC vs. placebo	1 (1) [159]	Critically low	No overlap (single review)	Very low	Significant improvement in THC group

THC products compared with placebo

One review [159] synthesised evidence on sleepiness for THC products compared with placebo. Very low-certainty evidence indicated significantly reduced sleepiness in the THC (dronabinol) compared with placebo groups comprising an adult population with moderate obstructive sleep apnoea (one RCT, narrative synthesis). Intervention duration/follow-up was 42 days.

3.7.2.5.5 Insomnia

A summary of the evidence on insomnia is presented in Table 63.

Table 63 Insomnia outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Insomnia						
	THC vs. active control	1 (1) [159]	Critically low	No overlap (single review)	Very low	Significant improvement in THC group

THC products compared with active control

One review [159] synthesised evidence on insomnia for THC products compared with active control groups. Very low-certainty evidence indicated significantly improved insomnia in the THC (nabilone) compared with active control (amitriptyline (a tricyclic antidepressant)) groups comprising an adult population with fibromyalgia (one RCT, narrative synthesis). Intervention duration/follow-up was 14 days.

3.7.2.5.6 Sleep interruptions

A summary of the evidence on sleep interruptions is presented in Table 64.

Table 64 Sleep interruption outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sleep interruptions						
	THC vs. active control	1 (1) [159]	Critically low	No overlap (single review)	Very low	No significant difference

THC products compared with active control

One review [159] synthesised evidence on sleep interruptions for THC products compared with active control groups. Very low-certainty evidence found no significant difference between the THC (nabilone) and active control (dihydrocodeine) groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Intervention duration/follow-up was 42 days.

3.7.2.5.7 Daytime somnolence

A summary of evidence on daytime somnolence is presented in Table 65.

Table 65 Daytime somnolence outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Daytime somnolence						
	Mixed cannabinoids vs. placebo	1 (6) [160]	Moderate	No overlap (single review)	High	Significantly increased likelihood in mixed cannabinoid group

Mixed cannabinoids compared with placebo

One review [160] synthesised evidence on daytime somnolence for mixed cannabinoid products compared with placebo. High-certainty evidence found a significantly higher likelihood of daytime somnolence in the mixed cannabinoids compared with placebo groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (six RCTs, meta-analysis). Trial durations ranged from 2 to 15 weeks, and no follow-up period was specified.

3.7.2.5.8 Summary

Evidence synthesised on sleep quality ranged from high to very low certainty. Two reviews [159,160] indicated a significant improvement in sleep quality for the mixed cannabinoids and cannabis compared with placebo groups (moderate- and high-certainty evidence), but no significant difference was reported between the THC and placebo groups (very low-certainty evidence) [159]. One review [159] reported a significant improvement in sleep disturbance for mixed cannabinoid and THC products when compared with placebo (low- and very low-certainty evidence, respectively). This review also indicated no significant improvement in PTSD nightmares, as well as significantly reduced sleepiness, in the THC compared with placebo groups (very low-certainty evidence), in addition to a significant improvement in insomnia and no significant difference in sleep interruptions in the THC compared with amitriptyline and dihydrocodeine groups, respectively (very low-certainty evidence). One review [160] reported a significantly higher likelihood of daytime somnolence in the mixed cannabinoids compared with placebo groups (high-certainty evidence).

3.7.2.6 Mental health/well-being

3.7.2.6.1 Mental health/well-being

One review [156] investigated mental health/well-being as a primary outcome. In this review, mental health/well-being was defined as any outcome measuring psychological functioning, emotional functioning, mood, anxiety, depression, or mental health. A summary of evidence on mental health/well-being is presented in Table 66.

Table 66 Mental health/well-being outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Mental health/well-being						
	Mixed cannabinoids vs. mixed controls	1 (13) [156]	Critically low	No overlap (single review)	Low	No significant difference
	THC:CBD vs. placebo	1 (5) [156]	Critically low	No overlap (single review)	Low	No significant difference
	THC vs. placebo	1 (6) [156]	Critically low	No overlap (single review)	Low	No significant difference

Note: Overlap exists between analyses conducted on the intervention group in this single review. Overall overlap was 34.62%.

Mixed cannabinoid products compared with mixed controls

One systematic review [156] synthesised evidence on mental health/well-being as a primary outcome for mixed cannabinoid products compared with mixed control groups. There is low-certainty evidence indicating no significant difference in mental health/well-being between mixed cannabinoids and mixed controls (placebo and megestrol acetate (an appetite stimulant)) comprising adult populations with cancer and central nervous system disorders (13 RCTs, meta-analysis). Intervention durations ranged from 2 weeks to 36 months, and no follow-up period was specified.

THC:CBD products compared with placebo

One systematic review [156] synthesised evidence on mental health/well-being as a primary outcome for THC:CBD products compared with placebo groups. There is low-certainty evidence indicating no significant difference in mental health/well-being between the THC:CBD and placebo groups comprising adult populations with cancer and central nervous system disorders (five RCTs, meta-analysis). Intervention durations ranged from 5 to 12 weeks; no follow-up period was specified.

THC products compared with placebo

One systematic review [156] synthesised evidence on mental health/well-being as a primary outcome for THC products compared with placebo groups. There is low-certainty evidence indicating no significant difference in mental health/well-being between THC and placebo groups comprising adult populations with cancer and central nervous system disorders (six RCTs, meta-analysis). Intervention durations ranged from 2 months; no follow-up period was specified.

3.7.2.6.2 Summary

One review [156] reported low-certainty evidence on mental health/well-being outcomes, indicating no significant difference between mixed cannabinoids and mixed control groups, THC:CBD and placebo groups, and THC and placebo groups in relation to mental health/well-being outcomes.

3.7.2.7 Overall function or disability

3.7.2.7.1 Overall function or disability

A summary of the evidence on overall function or disability is presented in Table 67.

Table 67 Overall function or disability outcome (mixed health condition population)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Overall function or disability						
	Cannabis vs. usual care	1 (1) [148]	Critically low	No overlap (single review)	Very low	No significant difference
	THC:CBD vs. placebo	1 (reporting 2 outcomes) (6, 1) [148]	Critically low	No overlap (single review)	1 low 1 very low	Significant improvement in THC:CBD group
	THC vs. placebo	1 (2) [148]	Critically low	No overlap (single review)	Low	No significant difference
	THC vs. active controls	1 (1) [148]	Critically low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 0%.

Cannabis products compared with usual care

One systematic review [148] synthesised evidence on overall function or disability as a primary outcome for cannabis products compared with usual care groups. Very low-certainty evidence indicated no significant difference in overall function or disability in the cannabis compared with usual care groups comprising adults with neuropathic pain (one prospective cohort study, narrative synthesis). Trial duration was 6 months, and no follow-up was reported.

THC:CBD products compared with placebo

One systematic review [148] synthesised evidence on overall function or disability as a primary outcome for THC:CBD products compared with placebo groups. The review found low-certainty evidence of a

significant improvement in overall function or disability in products with comparable ratios of THC to CBD compared with placebo groups comprising adult populations with chronic, non-cancer pain (six RCTs, meta-analysis). Intervention durations ranged from 5 to 15 weeks; no follow-up was reported.

The same review [148] also reported very low-certainty evidence of a significant improvement in overall function or disability for extracted products with high ratios of THC to CBD compared with placebo groups comprising an adult population with fibromyalgia (one RCT, narrative synthesis). Trial duration was 8 weeks, and no follow-up was reported.

THC products compared with placebo

One systematic review [148] synthesised evidence on overall function or disability as a primary outcome for THC products compared with placebo groups. Low-certainty evidence found no significant difference in overall function or disability between products with a high THC:CBD ratio and placebo groups comprising adult populations with chronic, non-cancer pain (multiple sclerosis, diabetic neuropathy) (two RCTs, meta-analysis). Intervention durations ranged from 5 to 9 weeks; no follow-up was reported.

THC products compared with active controls

One systematic review [148] synthesised evidence on overall function or disability as a primary outcome for THC products compared with active control groups comprising adults with neuropathic pain. Very low-certainty evidence indicated no significant difference in THC compared with gabapentin (an anticonvulsant medication) groups or THC compared with combined THC and gabapentin groups (one prospective cohort study, narrative synthesis). Trial duration was 6 months, and no follow-up was reported.

3.7.2.7.2 Summary

The evidence synthesised on overall function or disability was low to very low certainty. One review [148] indicated no significant difference between cannabis compared with usual care, and between THC compared with active control groups, on overall function or disability. The same review reported a significant improvement in overall function or disability for both THC and THC:CBD compared with placebo groups.

3.7.3 Safety and tolerability

In this section, evidence has been combined for both specific and mixed health condition reviews to provide a general overview of safety and tolerability associated with the use of cannabinoids or cannabis products. Evidence has been organised under three headings: specific adverse events (safety), serious adverse events (safety), and withdrawals from primary studies due to adverse events (tolerability).

Specific adverse events are defined as unfavourable changes in health that occur during treatment or within a specified period following treatment [162]. In this overview of reviews, specific adverse events can be categorised as nervous system disorders (e.g. dizziness, somnolence, headache), psychiatric system disorders (e.g. confused state, paranoia, psychosis, substance dependence), and gastrointestinal system disorders (e.g. nausea, vomiting, constipation) according to the Medical Dictionary for Regulatory Activities (MedDRA) classification system [163,164].

In contrast to specific adverse events, which can range from mild to severe, serious adverse events are defined as adverse events that result in death, require either inpatient hospitalisation or the prolongation of hospitalisation, are life-threatening, result in a persistent or significant disability/incapacity, or result in a congenital anomaly or birth defect [162].

In total, 44 reviews (25 reviews on specific health conditions and 19 reviews on mixed health conditions) synthesised data on adverse events. Fourteen reviews synthesised safety and tolerability as a primary

outcome; these findings are presented in Sections 3.7.3.1, 3.7.3.2, and 3.7.3.3. Thirty-one additional reviews collected and/or synthesised data on safety and/or tolerability as a secondary outcome; this information is outlined in the extraction forms for individual reviews in Appendix F.

Five reviews [122,123,148,157,161] synthesised evidence on adverse events categorised as nervous system disorders. Three reviews [122,148,161] synthesised evidence on adverse events categorised as gastrointestinal disorders. Two reviews [122,148] synthesised evidence on adverse events categorised as psychiatric system disorders. Six reviews [122–125,153,157] presented findings on any specific adverse events. Eight reviews [116,122,125,136,137,148,150,151] synthesised evidence on serious adverse events. Eight reviews [116,123,128,136,137,148,150,151] synthesised evidence on tolerability. Figure 6 illustrates the breakdown of safety and tolerability outcomes.

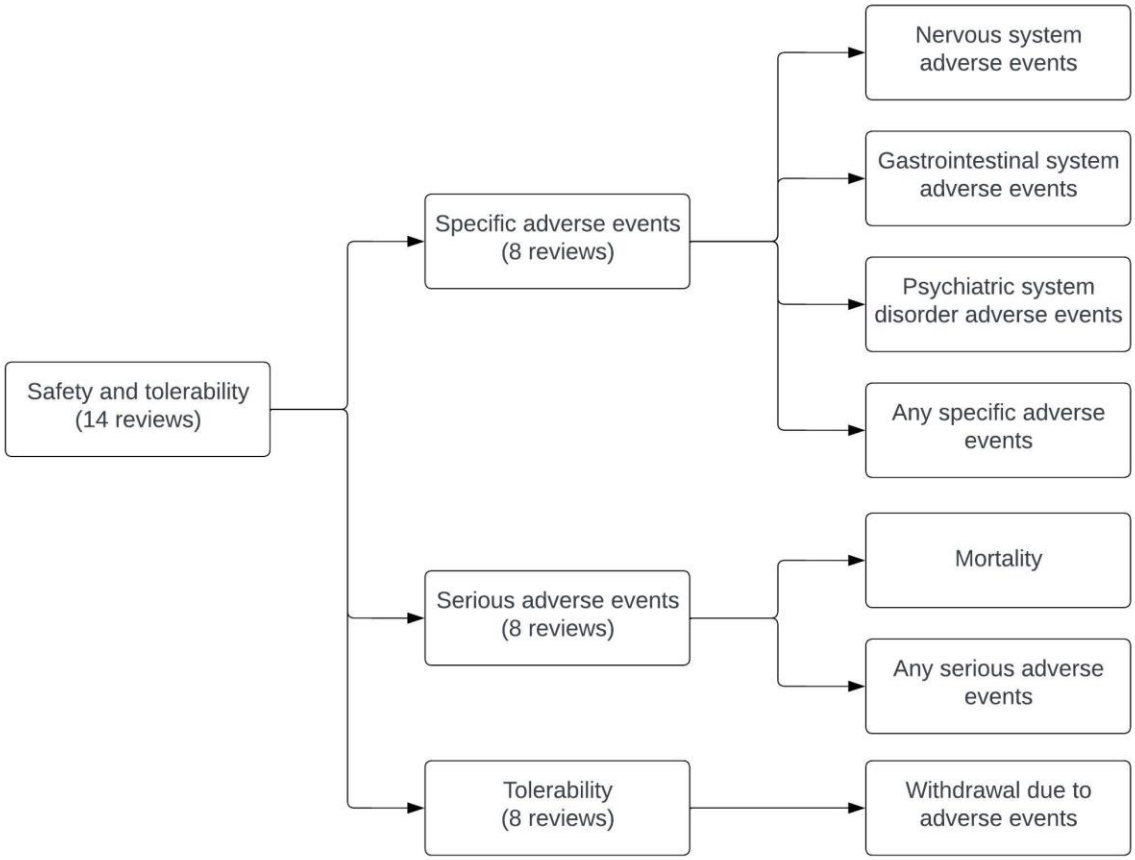

Figure 6 Primary outcomes for safety and tolerability

3.7.3.1 Specific adverse events (safety)

3.7.3.1.1 Nervous system adverse events

Five reviews [122,123,148,157,161] synthesised evidence on adverse events categorised as nervous system disorders. Two reviews [148,161] synthesised evidence on dizziness. Three reviews [122,123,148] synthesised evidence on sedation. One review [161] synthesised evidence on dry mouth, drowsiness, and headache. One review [161] investigated fatigue. One review reported on impotence in male participants [157]. Two reviews [122,157] synthesised evidence on nervous system disorders more generally.

3.7.3.1.1.1 Dizziness

A summary of the evidence on nervous system adverse events related to dizziness is presented in Table 68.

Table 68 Nervous system adverse events related to dizziness

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Dizziness						
	Cannabis vs. usual care	1 (1) [148]	Critically low	No overlap (single review)	Very low	No significant difference
	THC:CBD vs. placebo	1 (6) [148]	Critically low	No overlap (single review)	Very low	Significantly higher likelihood in THC:CBD group
	THC vs. placebo	2 (reporting 3 outcomes) (3, 3, 8) [148,161]	Critically low	7.69%	1 very low 2 moderate	Significantly higher likelihood in THC group
	THC vs. mixed controls (placebo and gabapentin)	1 (1) [148]	Critically low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 7.69%.

Cannabis products compared with usual care

One review [148] synthesised evidence on dizziness as a primary outcome for cannabis products compared with usual care groups. Very low-certainty evidence indicated no significant difference between the cannabis and usual care groups (one prospective cohort study, narrative synthesis) comprising an adult population with chronic, non-cancer pain. Trial duration was 13 months, and no follow-up was reported.

THC:CBD products compared with placebo

One review [148] synthesised evidence on dizziness as a primary outcome for THC:CBD products compared with placebo groups. Very low-certainty evidence indicated a significantly increased likelihood of dizziness in the THC:CBD compared with placebo groups (six RCTs, meta-analysis) comprising adult populations with mixed health conditions (cancer, rheumatoid arthritis, multiple sclerosis, neuropathic pain). Trial durations ranged from 4 to 15 weeks; no follow-up was reported.

THC products compared with placebo

Two systematic reviews [148,161] synthesised evidence on dizziness as a primary outcome for THC products compared with placebo. There was 7.7% overlap of primary studies between the reviews.

One review [161] reported very low-certainty evidence indicating a significantly increased likelihood of dizziness in the THC (nabilone) compared with placebo groups (three RCTs, meta-analysis) comprising adult populations with mixed health conditions (dementia, pain) experiencing neuropathic pain. Trial durations ranged from three sessions to 14 weeks, and no follow-up was reported.

The same review [161] reported moderate-certainty evidence indicating a significantly increased likelihood of dizziness in the THC (dronabinol) compared with placebo groups (eight RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people, dementia, irritable bowel syndrome). Trial durations ranged from 2 days to 16 weeks; no follow-up was reported.

One review [148] reported moderate-certainty evidence indicating a significantly increased likelihood of dizziness in the THC compared with placebo groups (three RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, visceral pain). Subgroup analysis was conducted by cannabinoid type (synthetic, extract). There was a significantly increased likelihood of dizziness in the THC compared with placebo groups in both subgroup analyses. Trial durations ranged from 7 to 16 weeks; no follow-up was reported.

THC products compared with mixed controls (placebo and gabapentin)

One systematic review [148] synthesised evidence on dizziness as a primary outcome for THC products compared with mixed control groups. Very low-certainty evidence indicated no significant difference between the THC and placebo/gabapentin (an anticonvulsant medication) groups (one prospective cohort study, narrative review) comprising an adult population with mixed neuropathic pain. Trial duration was 6 months, and no follow-up was reported.

3.7.3.1.1.2 Sedation

A summary of the evidence on nervous system adverse events related to sedation is presented in Table 69.

Table 69 Nervous system adverse events related to sedation

Outcome	Intervention vs. comparator	Number of systematic reviews	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Sedation						
	Cannabis vs. usual care	1 (1) [148]	Critically low	No overlap (single review)	Very low	Significantly higher likelihood in cannabis
	THC:CBD vs. placebo	1 (6) [148]	Critically low	No overlap (single review)	Low	Significantly higher likelihood in THC:CBD
	THC vs. placebo	3 (1, 1, 3) [122,123,148]	2 critically low 1 low	12.5%	1 low 1 moderate 1 very low	Significantly higher likelihood in THC

Outcome	Intervention vs. comparator	Number of systematic reviews	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
	THC vs. mixed controls (placebo and gabapentin)	1 (1) [148]	Critically low	No overlap (single review)	Very low	Significantly lower likelihood in THC

Note: Overall overlap was 4.17%.

Cannabis products compared with usual care

One systematic review [148] synthesised evidence on sedation as a primary outcome for cannabis products compared with usual care. Very low-certainty evidence indicated a significantly increased likelihood of sedation in the cannabis compared with usual care groups (one prospective cohort study, narrative synthesis) comprising an adult population with chronic, non-cancer pain. Trial duration was 13 months, and no follow-up was reported.

THC:CBD products compared with placebo

One systematic review [148] synthesised evidence on sedation as a primary outcome for THC:CBD products compared with placebo groups. Low-certainty evidence indicated a significantly increased likelihood of sedation in the THC:CBD compared with placebo groups (six RCTs, meta-analysis) comprising adult populations with mixed health conditions (cancer, rheumatoid arthritis, multiple sclerosis, neuropathic pain). Trial durations ranged from 4 to 16 weeks, and no follow-up was reported.

THC products compared with placebo

Three systematic reviews [122,123,148] synthesised evidence on sedation as a primary outcome for THC products compared with placebo. There was 12.5% overlap of primary studies between the three reviews.

One review [148] reported moderate-certainty evidence indicating a significantly increased likelihood of sedation in the THC compared with placebo groups (three RCTs, meta-analysis) comprising adult populations with mixed health conditions (visceral pain, fibromyalgia, multiple sclerosis). Trial durations ranged from 4 to 16 weeks; no follow-up was reported.

The second review [122] reported very low-certainty evidence finding a significantly increased likelihood of sedation in the THC compared with placebo groups comprising an adult population with dementia (one RCT, narrative review). Trial duration was 14 weeks, and no follow-up was reported.

The third review [123] reported very low-certainty evidence of a significantly increased likelihood of sedation in the THC compared with placebo groups comprising an adult population with dementia (one RCT, narrative review). Trial duration was 14 weeks, and no follow-up was reported.

THC products compared with mixed controls (placebo and gabapentin)

One systematic review [148] synthesised evidence on sedation as a primary outcome for THC products compared with mixed controls (gabapentin (an anticonvulsant medication), placebo). Very low-certainty evidence indicated a significantly lower likelihood of sedation in the THC compared with gabapentin and placebo groups (one prospective cohort study, narrative review) comprising an adult population with mixed neuropathic pain. Intervention duration was 6 months; no follow-up was reported.

3.7.3.1.1.3 Drowsiness

A summary of the evidence on nervous system adverse events related to drowsiness is presented in Table 70.

Table 70 Nervous system adverse events related to drowsiness

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Drowsiness						
	THC vs. placebo	1 (reporting 2 outcomes) (3, 3) [161]	Critically low	No overlap (single review)	Very low	Significantly higher likelihood in nabilone No significant difference in dronabinol

THC products compared with placebo

One systematic review [161] synthesised evidence on drowsiness as a primary outcome for THC products compared with placebo groups. This systematic review conducted two meta-analyses on THC products (nabilone, dronabinol). There was no overlap of primary studies between the analyses.

The meta-analysis on nabilone reported very low-certainty evidence indicating a significantly increased likelihood of drowsiness in the nabilone compared with placebo groups (three RCTs, meta-analysis) comprising adult populations with mixed health conditions (spasticity-related pain, fibromyalgia, spinal cord injury). Trial durations ranged from 4 to 10 weeks, and no follow-up was reported.

The meta-analysis on dronabinol reported very low-certainty evidence indicating no significant difference in drowsiness between the dronabinol and placebo groups (three RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people). Trial durations ranged from 2 days to 6 weeks; no follow-up was reported.

3.7.3.1.1.4 Dry mouth

A summary of evidence on nervous system adverse events related to dry mouth is presented in Table 71.

Table 71 Nervous system adverse events related to dry mouth

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Dry mouth						
	THC vs. placebo	1 (reporting	Critically low	No overlap	1 very low 1 moderate	Significantly increased

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
		2 outcomes) (4, 6) [161]		(single review)		likelihood in THC (nabilone and dronabinol)

THC products compared with placebo

One systematic review [161] synthesised evidence on dry mouth as a primary outcome for THC products compared with placebo groups. This systematic review conducted two meta-analyses on THC products (nabilone, dronabinol). There was no overlap of primary studies between the meta-analyses.

The meta-analysis on nabilone reported very low-certainty evidence indicating a significantly increased likelihood of dry mouth in the THC (nabilone) compared with placebo groups (four RCTs, meta-analysis) comprising adult populations with mixed health conditions (spasticity-related pain, fibromyalgia, spinal cord injury). Trial durations ranged from three sessions to 8 weeks; no follow-up was reported.

The meta-analysis on dronabinol [161] reported moderate-certainty evidence indicating a significantly increased likelihood of dry mouth in the THC (dronabinol) compared with placebo groups (six RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people, dementia). Trial durations ranged from 2 days to 16 weeks, and no follow-up was reported.

3.7.3.1.1.5 Headache

A summary of the evidence on nervous system adverse events related to headache is presented in Table 72.

Table 72 Nervous system adverse events related to headache

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Headache						
	THC vs. placebo	1 (reporting 2 outcomes) (4, 9) [161]	Critically low	No overlap (single review)	1 very low 1 low	Significantly increased likelihood in THC (nabilone and dronabinol)

THC products compared with placebo

One systematic review [161] synthesised evidence on headache as a primary outcome for THC products compared with placebo groups. This systematic review conducted two meta-analyses on THC products (nabilone, dronabinol). There was no overlap of primary studies between the meta-analyses.

The meta-analysis on nabilone reported very low-certainty evidence indicating a significantly increased likelihood of headache in the nabilone compared with placebo groups (four RCTs, meta-analysis) comprising adult populations with mixed health conditions (spasticity-related pain, fibromyalgia, spinal cord injury). Trial durations ranged from three sessions to 8 weeks, and no follow-up was reported.

The meta-analysis on dronabinol reported low-certainty evidence indicating a significantly increased likelihood of headache in the dronabinol compared with placebo groups (nine RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people, dementia, irritable bowel syndrome, cancer, pain). Trial durations ranged from 2 days to 16 weeks; no follow-up was reported.

3.7.3.1.1.6 Fatigue

A summary of the evidence on nervous system adverse events related to fatigue is presented in Table 73.

Table 73 Nervous system adverse events related to fatigue

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Fatigue						
	THC vs. placebo	1 (4) [161]	Critically low	No overlap (single review)	Moderate	No significant difference

THC products compared with placebo

One systematic review [161] synthesised evidence on fatigue as a primary outcome for THC products compared with placebo groups. Moderate-certainty evidence indicated no significant difference in the likelihood of fatigue in the THC (dronabinol) compared with placebo groups (four RCTs, meta-analysis) comprising adult populations with mixed health conditions (pain, multiple sclerosis, dementia). Trial durations ranged from 3 to 16 weeks, and no follow-up was reported.

3.7.3.1.1.7 Impotence

A summary of evidence on impotence adverse events is presented in Table 74.

Table 74 Nervous system adverse events related to impotence

Outcome	Intervention/ comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Impotence						
	THC vs. megestrol acetate	1 (1) [157]	Critically low	No overlap (single review)	Very low	Significantly increased likelihood in megestrol acetate

THC products compared with active control

One systematic review [157] synthesised evidence on impotence as a primary outcome in THC products compared with active control groups. Very low-certainty evidence indicated significantly lower likelihood of impotence in dronabinol compared with active control (megestrol acetate (an appetite stimulant)) groups consisting of male adults with cancer associated cachexia (one RCT, narrative review). Treatment duration was 4 weeks, and no follow-up was reported.

3.7.3.1.1.8 Any nervous system disorder

A summary of evidence on any nervous system disorder adverse events is presented in Table 75.

Table 75 Any nervous system disorder adverse events

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Any nervous system disorder adverse events						
	THC vs. placebo	2 (1, 1) [122,157]	1 low 1 critically low	0.00%	Very low	No significant difference

Note: Overall overlap was 0%.

THC compared with placebo

Two systematic reviews [122,157] synthesised evidence on any nervous system disorder adverse events as a primary outcome for THC compared with placebo groups. There was 0% overlap of primary studies.

One systematic review [122] reported very low-certainty evidence of no significant difference between the THC and placebo groups comprising an adult population with dementia (one RCT, narrative review). Trial duration was 3 weeks, and no follow-up was reported.

One systematic review [157] reported very low certainty evidence indicating significantly increased likelihood in THC (dronabinol) compared with placebo groups consisting of an adult population with AIDS (one RCT, narrative review). Trial duration was 6 weeks, and no follow-up was reported.

3.7.3.1.1.9 Summary

Two reviews [148,161] synthesised moderate- to very low-certainty evidence on dizziness as a primary outcome. One review [148] reported no significant difference in the likelihood of dizziness between cannabis and usual care groups, or between THC products and mixed control groups. This re[118,150]view also reported a significantly higher likelihood of dizziness in the THC:CBD compared with placebo groups. Evidence synthesised comparing THC with placebo groups [148,161] also indicated a significantly increased likelihood of dizziness in the THC group.

Moderate- to very low-certainty evidence indicated a significantly increased likelihood of sedation in cannabinoid and cannabis groups versus comparator groups [122,123,148]. One review [148] reported a significantly increased likelihood of sedation in the cannabis compared with usual care groups, in the THC:CBD compared with placebo groups, and in the THC compared with mixed control groups. A significantly increased likelihood of sedation in the THC compared with placebo groups was also reported in two reviews [122,123].

One review [161] reported findings related to drowsiness in THC compared with placebo groups. The review reported a significantly increased likelihood of drowsiness in the nabilone (but not dronabinol) compared with placebo groups (very low-certainty evidence). One review reported moderate- to very low-certainty evidence [161] indicating a significantly increased likelihood of dry mouth in the THC (nabilone, dronabinol) compared with placebo groups.

One review found low- to very low-certainty evidence [161] of a significantly higher likelihood of headache in the THC (dronabinol, nabilone) compared with placebo groups. This review [161] also reported no significant difference in the likelihood of fatigue between THC (dronabinol) and placebo groups (moderate-certainty evidence). One additional review reported very low-certainty evidence [157] of significantly lower likelihood of impotence in dronabinol compared with active control (megestrol acetate) groups consisting of male adults with cancer associated cachexia.

Two reviews reported very low-certainty evidence on any nervous system disorder as a primary outcome. One review reported significantly increased likelihood in THC compared with placebo [157], however another review reported no significant difference between THC and placebo groups [122].

3.7.3.1.2 Gastrointestinal system adverse events

Three reviews [122,148,161] synthesised evidence on adverse events categorised as gastrointestinal disorders. Nausea was investigated in two reviews [148,161]. One review [122] synthesised evidence on adverse events under a general gastrointestinal heading (i.e. any gastrointestinal disorder adverse events).

3.7.3.1.2.1 Nausea

A summary of the evidence on gastrointestinal system adverse events related to nausea is presented in Table 76.

Table 76 Gastrointestinal system adverse events related to nausea

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Nausea						
	Cannabis vs. usual care	1 (1) [148]	Critically low	No overlap (single review)	Very low	Significantly increased likelihood in cannabis
	THC:CBD vs. placebo	1 (6) [148]	Critically low	No overlap (single review)	Low	Significantly increased likelihood in THC:CBD
	THC vs. placebo	2 (2, 5) [148,161]	Critically low	16.67%	Moderate	No significant difference

Note: Overall overlap was 7.69%.

Cannabis products compared with usual care

One systematic review [148] synthesised evidence on nausea as a primary outcome for cannabis compared with usual care groups. Very low-certainty evidence indicated a significantly increased likelihood of nausea in the cannabis compared with usual care groups (one prospective cohort study, narrative synthesis) comprising an adult population with chronic, non-cancer pain. Trial duration was 13 months, and no follow-up was reported.

THC:CBD products compared with placebo

One systematic review [148] synthesised evidence on nausea as a primary outcome for THC:CBD compared with placebo groups. Low-certainty evidence indicated a significantly increased likelihood of nausea in the THC:CBD compared with placebo groups (six RCTs, meta-analysis) comprising adult populations with mixed health conditions (cancer, rheumatoid arthritis, multiple sclerosis, neuropathic pain). Trial durations ranged from 4 to 16 weeks; no follow-up was reported.

THC products compared with placebo

Two systematic reviews [148,161] synthesised evidence on nausea as a primary outcome for THC compared with placebo groups. There was 16.7% overlap of primary studies between the reviews.

One review [161] reported moderate-certainty evidence indicating no significant difference in the likelihood of nausea between the THC (dronabinol) and placebo groups (five RCTs, meta-analysis) comprising adult populations with mixed health conditions (pain, multiple sclerosis, gastrointestinal transit and postprandial satiation, older people). Trial durations ranged from 2 days to 16 weeks; no follow-up was reported.

The second systematic review [148] reported moderate-certainty evidence indicating no significant difference in the likelihood of nausea between the THC and placebo groups (two RCTs, meta-analysis)

comprising adult populations with mixed health conditions (visceral pain, multiple sclerosis). Trial durations ranged from 7 to 16 weeks, and no follow-up was reported.

3.7.3.1.2.2 Any gastrointestinal system adverse events

A summary of the evidence on any gastrointestinal system adverse events is presented in Table 77.

Table 77 Any gastrointestinal system adverse events

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Any gastrointestinal system adverse events						
	THC vs. placebo	1 (1) [122]	Critically low	No overlap (single review)	Very low	No significant difference

THC products compared with placebo

One review [122] synthesised evidence broadly relating to any gastrointestinal system adverse events. Very low-certainty evidence indicated no significant difference in the likelihood of any gastrointestinal adverse events between the THC and placebo groups comprising an adult population with dementia (one RCT, narrative review). Trial duration was 3 weeks, and no follow-up was reported.

3.7.3.1.2.3 Summary

Three reviews [122,148,161] synthesised evidence on adverse events categorised as gastrointestinal disorders as primary outcomes. One review [148] reported very low-certainty evidence indicating a significantly increased likelihood of nausea in cannabis compared with usual care groups. This review also reported low-certainty evidence of a significantly increased likelihood of nausea in the THC:CBD compared with placebo groups. Two reviews [148,161] reported moderate-certainty evidence indicating no significant difference in the likelihood of nausea in the THC compared with placebo groups. One review [122] synthesised very low-certainty evidence indicating no significant difference in the likelihood of any gastrointestinal system adverse events between the THC and placebo groups.

3.7.3.1.3 Psychiatric system disorder adverse events

Two reviews [122,148] synthesised adverse events under a general psychiatric system disorder heading (i.e. any psychiatric disorder). A summary of the evidence on any psychiatric system disorder adverse event is presented in Table 78.

Table 78 Any psychiatric system disorder adverse events

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Any psychiatric system disorder adverse events						
	Cannabis vs. usual care	1 (1) [148]	Critically low	No overlap (single review)	Very low	No significant difference
	THC vs. placebo	1 (1) [122]	Low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 0%.

Cannabis products compared with usual care

One review [148] synthesised evidence on psychiatric system disorder adverse events as a primary outcome for cannabis compared with usual care. The review reported very low-certainty evidence indicating no significant difference in the likelihood of psychiatric system disorder adverse events in the cannabis compared with usual care groups comprising an adult population with chronic, non-cancer pain (one prospective cohort study, narrative synthesis). Trial duration was 13 months, and no follow-up was reported.

THC products compared with placebo

One systematic review [122] synthesised evidence on psychiatric system disorder adverse events as a primary outcome for THC compared with placebo. Very low-certainty evidence found no significant difference in the likelihood of psychiatric system disorder adverse events between the THC and placebo groups comprising an adult population with dementia (one RCT, narrative review). Trial duration was 3 weeks; no follow-up was reported.

Summary

Two reviews reported very low-certainty evidence on any psychiatric system disorder adverse events as a primary outcome. No significant difference in the likelihood of psychiatric system disorder adverse events was reported in cannabis compared with usual care groups [148] or in THC compared with placebo groups [122].

3.7.3.1.4 Any specific adverse events

Five reviews [122–124,150,153] presented findings on any specific adverse events associated with cannabinoid products. A summary of the evidence on any specific adverse events is presented in Table 79.

Table 79 Any specific adverse events

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Any specific adverse events						
	Mixed cannabinoid vs. mixed control	1 (4) [125]	Critically low	No overlap (single review)	Low	Inferential statistics not reported (1 review)
	THC:CBD vs. placebo	2 (1, 1) [124,157]	Critically low	0.00%	Very low	No significant difference
	THC vs. placebo	4 [122–124,157]	3 critically low 1 low	7.41%	2 low 2 very low	No significant difference (3 reviews) Inferential statistics not reported (1 review)
	CBD vs. placebo	2 (2, 1) [124,153]	Critically low	0.00%	Very low	No significant difference (1 review) No adverse events reported (1 review)

Note: Overall overlap was 2.94%.

Mixed cannabinoid products compared with mixed control

One systematic review [125] on any specific adverse events as a primary outcome in mixed cannabinoid products compared with mixed control groups. Low-certainty evidence indicated 266 adverse events in cannabinoid compared with 133 adverse events in mixed control groups (placebo and prochlorperazine) groups consisting of older adults with various health conditions (cancer, dementia, Parkinson's Disease, COPD) (four RCTs, narrative synthesis). Treatment duration was 1 day to 6 weeks, and no follow-up was reported. Authors did not report inferential statistics, therefore we cannot comment on the significance of these findings.

THC:CBD products compared with placebo

Two systematic reviews [124,157] synthesised evidence on any specific adverse events as a primary outcome in THC:CBD products compared with placebo groups. There was 0% overlap of primary studies between the two reviews.

One systematic review [124] reported very low-certainty evidence indicating no significant difference between the THC:CBD (cannador) and placebo groups comprising adult populations with Parkinson's disease (one RCT, narrative synthesis). Trial duration was 4 weeks; no follow-up was reported.

One systematic review [157] reported very low certainty evidence indicating no significant difference between THC:CBD (cannabis extract) and placebo groups consisting of adults with cancer associated cachexia (one RCT, narrative review). Treatment duration was 6 weeks; no follow-up was reported.

THC products compared with placebo

Four systematic reviews [122–124,157] synthesised evidence on adverse events generally as a primary outcome in THC products compared with placebo. There was 7.41% overlap of primary studies between the four reviews.

One review [123] reported very low-certainty evidence indicating no significant difference between the THC and placebo groups comprising adult populations with dementia (two RCTs, narrative synthesis). Trial durations ranged from 3 to 12 weeks; no follow-up was reported.

One review [124] reported very low-certainty evidence indicating no significant difference between the THC (nabilone) and placebo groups comprising adult populations with Parkinson's disease (two RCTs, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported.

One review [157] reported low-certainty evidence indicated no significant difference between THC and placebo groups comprising adult populations with various health conditions (AIDS, cancer) (three RCTs, narrative review). Treatment duration was 6 to 8 weeks, and no follow-up was reported.

The final review [122] reported 160 individual adverse events in THC groups (nabilone, Namisol, dronabinol) compared with 131 individual adverse events in placebo groups comprising adult populations with dementia (four RCTs, narrative synthesis, low-certainty evidence). Trial durations ranged from 3 to 14 weeks, and no follow-up was reported. The review authors did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

THC products compared with active control

One systematic review [157] synthesised evidence on adverse events generally as a primary outcome. This review reported low-certainty evidence indicating no significant difference between THC and active control (megestrol acetate (an appetite stimulant)) groups comprising adult populations with various health conditions (HIV, cancer) (two RCTs, narrative review). Treatment duration was 4–12 weeks, no follow-up was reported.

CBD products compared with placebo

Two systematic reviews [124,153] synthesised evidence on adverse events generally as a primary outcome in CBD products compared with placebo. There was 0% overlap of primary studies between the two reviews.

One review [153] synthesised evidence on any adverse events as a primary outcome in CBD products compared with placebo groups. It reported very low-certainty evidence of no adverse events in either the CBD or placebo groups (one RCT, narrative synthesis) comprising adults with back pain. Trial duration was 4 weeks, and no follow-up was reported.

The other review [124] reported very low-certainty evidence indicating no significant difference between the CBD capsule and placebo groups comprising adult populations with Parkinson's disease (two RCTs, narrative synthesis). Trial duration was 4 weeks; no follow-up was reported.

Summary

One review [122] reported 160 individual adverse events in THC groups compared with 131 individual adverse events in placebo groups comprising adult populations with dementia (low-certainty evidence). Another review [125] reported 266 adverse events in cannabinoid compared with 133 adverse events in mixed control groups (placebo and prochlorperazine) (low-certainty evidence). Inferential statistics were

not reported in either review, so the significance of these findings is unclear. Three reviews reported very low-certainty evidence indicating no significant difference in the THC:CBD compared with placebo groups [124], the THC compared with placebo groups [123,124], THC compared with megestrol acetate [157], or the CBD compared with placebo groups [124]. One review reported no adverse events in either the CBD or placebo groups [153].

3.7.3.2 Serious adverse events (safety)

Two reviews [122,151] synthesised evidence on mortality outcomes in RCTs comparing cannabinoid and placebo groups. Six reviews [116,125,136,137,148,150] presented findings on any serious adverse events associated with cannabinoid products.

3.7.3.2.1 Mortality

A summary of the evidence on serious adverse events related to mortality is presented in Table 80.

Table 80 Serious adverse events related to mortality

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Mortality						
	THC:CBD vs. placebo	1 (reporting 3 outcomes) (2, 2, 1) [151]	Critically low	No overlap (single review)	1 low 1 very low	No significant difference (1 outcome) No deaths reported (2 outcomes)
	THC vs. placebo	2 (2, 1) [122,151]	1 critically low 1 low	0%	Very low	No significant difference (1 review) No deaths reported (1 review)

Note: Overall overlap was 0%.

THC:CBD products compared with placebo

One systematic review [151] synthesised evidence on mortality as a primary outcome in THC:CBD products compared with placebo groups. This systematic review conducted one meta-analysis and two narrative reviews. There was no overlap of primary studies between the analyses.

The review found low-certainty evidence indicating no significant difference in mortality between the THC:CBD and placebo groups (two RCTs, meta-analysis) comprising adult populations with cancer. Trial duration was 3 weeks; no follow-up was reported.

Low-certainty evidence indicated no deaths across THC:CBD spray and placebo groups in a narrative review (two RCTs) of adults with multiple sclerosis or allodynia. Treatment duration was 3 weeks, and follow-up was end of treatment.

The review also found very low-certainty evidence reporting no deaths across THC:CBD spray and placebo groups (one RCT, narrative synthesis) comprising an adult population with rheumatoid arthritis. Trial duration was 3 weeks, and follow-up was conducted at the end of treatment.

THC products compared with placebo

Two reviews [122,151] synthesised evidence on mortality as a primary outcome in THC products compared with placebo groups. There was 0% overlap of primary studies between the two reviews.

One review [151] reported very low-certainty evidence indicating no deaths in either the THC or placebo groups (one RCT, narrative synthesis) comprising an adult population with multiple sclerosis. Trial duration was 16 weeks, and no follow-up was reported.

The other review [122] reported very low-certainty evidence indicating no significant difference in mortality across the THC (nabilone and dronabinol) and placebo groups comprising adult populations with dementia (two RCTs, meta-analysis). Trial durations ranged from 12 to 14 weeks; no follow-up was reported.

3.7.3.2.2 Any serious adverse events

A summary of the evidence on any serious adverse events is presented in Table 81.

Table 81 Any serious adverse events

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Any serious adverse events						
	Mixed cannabinoids vs. placebo	1 (4) [125]	Critically low	No overlap (single review)	Very low	Inferential statistics not reported
	Mixed cannabinoids and cannabis vs. placebo	1 (13) [150]	Low	No overlap (single review)	Low	No significant difference
	Cannabis vs. usual care	1 (1) [148]	Critically low	No overlap (single review)	Very low	Significantly increased likelihood in cannabis
	THC:CBD vs. placebo	2 (reporting 3 outcomes)	Critically low	0%	2 low 1 very low	No significant difference (1

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
		(4, 1, 1) [116,136]				review, 2 outcomes) Inferential statistics not reported (1 review)
	THC vs. placebo	2 (1, 1) [136,137]	1 critically low 1 high	0%	Very low	Inferential statistics not reported
	THC vs. active control	2 (1) [136,137]	1 critically low 1 high	100%	Very low	No serious adverse events reported
	THC vs. mixed controls (placebo and gabapentin)	1 (1) [148]	Critically low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 1.48%.

Mixed cannabinoid products compared with placebo

One systematic review [125] synthesised evidence on any serious adverse events in mixed cannabinoids compared with placebo. Very low-certainty evidence reporting one serious adverse event (grand mal seizure) in cannabinoid compared with no serious adverse events in placebo groups comprising older adults with various health conditions (dementia, Parkinson's Disease, COPD) (four RCTs, narrative synthesis). Treatment duration was 1 day to 6 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.

Mixed cannabinoids and cannabis products compared with placebo

One systematic review [150] synthesised evidence on any serious adverse events in mixed cannabinoid and cannabis compared with placebo groups. Low-certainty evidence indicated no significant difference in the likelihood of any serious adverse events between mixed cannabinoids and cannabis compared with placebo groups (13 RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, spinal cord injury, cancer, diabetes, HIV, plexus injury, pain). Trial durations ranged from 2 to 15 weeks, and no follow-up was reported.

Cannabis products compared with usual care

One systematic review [148] synthesised evidence on any serious adverse events for cannabis compared with usual care. Very low-certainty evidence indicated a significantly increased likelihood of any serious adverse events in the cannabis compared with usual care groups (one prospective cohort study, narrative

synthesis) comprising an adult population with chronic, non-cancer pain. Trial duration was 13 months, and no follow-up was reported.

THC:CBD products compared with placebo

Two reviews [116,136] synthesised evidence on any serious adverse events as a primary outcome in THC:CBD compared with placebo groups. There was 0% overlap of primary studies between the reviews.

One review [116] reported low-certainty evidence indicating no significant difference in the likelihood of any serious adverse events between the THC:CBD and placebo groups comprising adult populations with cancer (four RCTs, meta-analysis). Trial durations ranged from 2 to 5 weeks; no follow-up was reported. This review also reported very low-certainty evidence indicating no significant difference between the THC:CBD and placebo groups comprising an adult population with cancer (one enriched enrolment withdrawal trial, narrative review). Trial duration was 5 weeks, and no follow-up was reported.

The other review [136] reported 0% prevalence of any serious adverse events in the THC:CBD group compared with 2% in the placebo group comprising an adult population with rheumatic diseases (one RCT, narrative synthesis, very low-certainty evidence). Trial duration was 5 weeks and no follow-up was reported. The review authors did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

THC products compared with placebo

Two reviews [136,137] synthesised evidence on serious adverse events as a primary outcome in THC compared with placebo groups. There was 0% overlap of primary studies between these reviews.

One review [136] reported 3.3% prevalence of any serious adverse events in the THC (nabilone) group compared with 0% in the placebo group comprising an adult population with rheumatic diseases (one RCT, narrative synthesis, very low-certainty evidence). Trial duration was 4 weeks, and no follow-up was reported. The review authors did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

One review [137] reported 0% prevalence of any serious adverse events in either the THC (nabilone) or placebo groups comprising an adult population with rheumatic diseases (one RCT, narrative synthesis, very low-certainty evidence). Trial duration was 4 weeks; no follow-up was reported.

THC products compared with active control

Two reviews [136,137] synthesised evidence on any serious adverse events as a primary outcome in THC compared with active control groups. There was 100% overlap of primary studies, as both reviews reported findings from a narrative synthesis relating to the same single RCT.

Both reviews [136,137] reported 0% prevalence of any serious adverse events in either the THC (nabilone) or active control (amitriptyline (a tricyclic antidepressant)) groups comprising an adult population with rheumatic diseases (one RCT, narrative synthesis, very low-certainty evidence). Trial duration was 2 weeks, and no follow-up was reported.

THC products compared with mixed controls (placebo and gabapentin)

One systematic review [148] synthesised evidence on serious adverse events for THC compared with mixed controls. Very low-certainty evidence indicated no significant difference between the THC and gabapentin (an anticonvulsant medication)/placebo groups (one prospective cohort study, narrative review) comprising an adult population with mixed neuropathic pain. Intervention duration was 6 months, and no follow-up was reported.

3.7.3.2.3 Summary

In relation to mortality outcomes, two reviews [122,151] reported low- to very low-certainty evidence indicating no significant difference in mortality for the THC:CBD or THC compared with placebo groups. Five reviews [116,125,136,137,148] synthesised low- to very low-certainty evidence on the likelihood of any serious adverse events. One review [148] reported a significantly increased likelihood of serious adverse events in the cannabis compared with usual care groups. Two reviews reported no significant difference in the likelihood of any serious adverse events for the THC:CBD compared with placebo groups [116] or for the THC compared with mixed control groups [148]. Three reviews reported the prevalence of serious adverse events in the mixed cannabinoid compared with placebo groups (1 event vs. 0 event) [125], the THC compared with placebo groups (0.0% vs. 0.0% [137]; 3.3% vs. 0.0% [136]), and in the THC compared with active control groups (0.0% vs. 0.0% for both reviews) [136,137]. Inferential statistics were not reported in these reviews, so the significance of these findings is unclear.

3.7.3.3 Tolerability

Seven reviews [116,123,136,137,148,150,151] synthesised evidence investigating withdrawals from primary studies due to adverse events (i.e. tolerability) as a primary outcome. An additional review [128] also aimed to synthesise data on tolerability as a primary outcome; however, no findings were reported by the authors of that review. It is important to note that in this context, "withdrawals due to adverse events" refers to participants choosing to stop participating in a study due to their experience of adverse events (in either intervention or comparator groups), not symptoms of withdrawal that may occur when a person stops taking a drug.

3.7.3.3.1 Withdrawal due to adverse events

A summary of the evidence on withdrawal due to adverse events is presented in Table 82. One additional review [128] searched for evidence on this outcome as a primary outcome, but reported no findings.

Table 82 Withdrawal due to adverse events

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
Withdrawal due to adverse events						
	Cannabis vs. usual care	1 (1) [148]	Critically low	No overlap (single review)	Very low	Significantly increased likelihood in cannabis
	Mixed cannabinoids and cannabis vs. placebo	1 (13) [150]	Low	No overlap (single review)	Low	Significantly increased likelihood in mixed cannabinoids and cannabis
	THC:CBD vs. placebo	4 (reporting 6 outcomes) (4, 1, 1, 5,	Critically low	25.93%	2 low 4 very low	Significantly increased likelihood in THC:CBD (3 reviews)

Outcome	Intervention vs. comparator	Number of systematic reviews (number of included studies)	AMSTAR 2 quality of reviews	Overlap of primary studies	GRADE certainty of evidence	Direction of effect
		4, 2) [116,136,148,151]				No significant difference (2 reviews) Inferential statistics not reported (1 review)
	THC vs. placebo	5 (1, 1, 1, 5, 1) [123,136,137,148,151]	1 high 4 critically low	12.50%	1 moderate 4 very low	No significant difference (1 review) Inferential statistics not reported (4 reviews)
	THC vs. active control	2 (1) [136,137]	Critically low	100.00%	Very low	Inferential statistics not reported (2 reviews)
	THC vs. mixed controls	1 (1) [148]	Critically low	No overlap (single review)	Very low	No significant difference

Note: Overall overlap was 9.88%.

Mixed cannabinoids and cannabis products compared with placebo

One systematic review [150] synthesised evidence on withdrawals due to adverse events as a primary outcome for mixed cannabinoids and cannabis products compared with placebo. It found low-certainty evidence of an increased prevalence of withdrawals in the mixed cannabinoids and cannabis compared with placebo groups (13 RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, spinal cord injury, cancer, diabetes, peripheral and central pain, HIV, plexus injury). Trial durations ranged from 2 to 15 weeks; no follow-up was reported.

Cannabis products compared with usual care

One systematic review [148] synthesised evidence on withdrawals from primary studies due to adverse events as a primary outcome for cannabis compared with usual care. Very low-certainty evidence found an increased prevalence of withdrawals from primary studies due to adverse events in the cannabis compared with usual care groups comprising an adult population with chronic, non-cancer pain (one prospective cohort study, narrative synthesis). Trial duration was 13 months, and no follow-up was reported.

THC:CBD products compared with placebo

Four reviews [116,136,148,151] synthesised evidence on withdrawals due to adverse events as a primary outcome for THC:CBD products compared with placebo. There was 25.9% overlap of primary studies between these reviews.

One review [151] reported very low-certainty evidence indicating a significantly increased likelihood of withdrawals due to adverse events in the THC:CBD compared with placebo groups (four RCTs, meta-analysis) comprising adult populations with mixed health conditions (multiple sclerosis, allodynia) experiencing neuropathic pain. Trial durations ranged from 4 to 14 weeks; no follow-up was reported.

One review [116] reported low-certainty evidence indicating a significantly increased likelihood of withdrawals due to adverse events in the THC:CBD compared with placebo groups comprising adult populations with cancer (four RCTs, meta-analysis). Trial durations ranged from 2 to 5 weeks, and no follow-up was reported. This review also reported very low-certainty evidence indicating a significantly increased likelihood of withdrawals in the THC:CBD compared with placebo groups comprising an adult population with cancer (one enriched enrolment withdrawal trial, narrative review). Trial duration was 5 weeks, and no follow-up was reported.

One review [148] reported low-certainty evidence of no significant difference in withdrawals between the THC:CBD compared with placebo groups (five RCTs, meta-analysis) comprising adults with mixed health conditions (rheumatoid arthritis, multiple sclerosis, neuropathic pain). Trial durations ranged from 5 to 15 weeks; no follow-up was reported.

One review [151] reported very low-certainty evidence indicating no significant difference in the likelihood of withdrawals between THC:CBD compared with placebo groups (two RCTs, meta-analysis) comprising adult populations with cancer. Trial duration was 3 weeks, and no follow-up was reported.

One review [136] reported a 0% prevalence of withdrawals in the THC:CBD group compared with 11% in the placebo group comprising an adult population with rheumatic diseases (one RCT, narrative synthesis, very low-certainty evidence). Trial duration was 5 weeks, and no follow-up was reported. The review authors did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

THC products compared with placebo

Five reviews [123,136,137,148,151] synthesised evidence on withdrawals due to adverse events as a primary outcome for THC products compared with placebo. There was 11.11% overlap of primary studies.

One review [123] reported one withdrawal in the THC group and one withdrawal in the placebo group in a sample of adults with dementia (one RCT, narrative synthesis, very low-certainty evidence). Trial duration was 12 weeks, and no follow-up was reported. The review authors did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

Another review [148] reported moderate-certainty evidence indicating no significant difference between THC and placebo groups in a meta-analysis (five RCTs) of adults with mixed health conditions (fibromyalgia, multiple sclerosis, visceral pain). Subgroup analysis was conducted by cannabinoid type (synthetic, extract). No significant difference was found in synthetic THC compared with placebo (four RCTs, subgroup analysis, moderate-certainty evidence); however, significantly increased likelihood was reported in THC extract compared with placebo groups (one RCT, subgroup analysis, very low-certainty evidence). Trial duration was 4 to 16 weeks, and no follow-up was reported.

One review [151] reported very low-certainty evidence on the withdrawal of 9.7% of participants due to adverse events in the treatment (THC) arm compared with 0.9% in the placebo arm in a narrative review

of adults with multiple sclerosis (one RCT, narrative synthesis). The review authors did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

Two reviews [136,137] reported the findings of narrative syntheses relating to the same single RCT. They reported very low-certainty evidence of a 15% withdrawal rate in the THC (nabilone) group compared with a 0% withdrawal rate in the placebo group comprising an adult population with rheumatic diseases (one RCT, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported. The authors of these two reviews did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

THC products compared with active control

Two reviews [136,137] synthesised evidence on withdrawals due to adverse events as a primary outcome for THC products compared with active control. There was 100% overlap of primary studies, as both reviews report findings of a narrative synthesis relating to the same RCT.

Both reviews [136,137] reported a 3% withdrawal rate in the THC (nabilone) group compared with a 0% withdrawal rate in the active control (amitriptyline (a tricyclic antidepressant)) group comprising an adult population with rheumatic diseases (one RCT, narrative synthesis, very low-certainty evidence). Trial duration was 2 weeks, and no follow-up was reported. The authors of these two reviews did not report inferential statistics; therefore, we cannot comment on the significance of these findings.

THC products compared with mixed controls (placebo and gabapentin)

One systematic review [148] synthesised evidence on withdrawals due to adverse events as a primary outcome for THC products compared with mixed controls (placebo and gabapentin (an anticonvulsant medication)). Very low-certainty evidence found no significant difference between the THC and gabapentin groups or between the THC group and the combined placebo/gabapentin group comprising an adult population with mixed neuropathic pain (one prospective cohort study, narrative synthesis). Trial duration was 6 months, and no follow-up was reported.

Summary

Seven reviews [116,123,136,137,148,150,151] reported moderate- to very low-certainty evidence investigating withdrawals due to adverse events as a primary outcome. An additional review [128] also aimed to synthesise data on tolerability as a primary outcome; however, no findings were reported by the authors of that review.

One review [148] reported a significantly increased likelihood of withdrawals from primary studies due to adverse events in cannabis compared with usual care groups. Similarly, one review [150] reported a significantly increased likelihood of withdrawals in mixed cannabinoids and cannabis compared with placebo groups.

Four reviews reported low- to very low-certainty mixed evidence on tolerability in THC:CBD compared with placebo groups. One review [116] reported a significantly increased likelihood of withdrawals in the THC:CBD compared with placebo groups, whereas one review [148] reported no significant difference between groups. Another review [151] comparing THC:CBD with placebo reported a significantly increased likelihood of withdrawals in the THC:CBD compared with placebo groups in a meta-analysis of adults with neuropathic pain; however, this same review reported no significant difference between groups in a meta-analysis of adults with cancer. One review [136] reported a 0% incidence of withdrawals in the THC:CBD group compared with an 11% prevalence in the placebo group; however, no inferential statistics were reported, so the significance of these findings is unclear.

Moderate- to very low-certainty evidence was reported on the tolerability of THC compared with placebo in five reviews. One review [148] reported no significant difference in withdrawals in the THC compared

with placebo groups. The remaining reviews comparing THC with placebo reported incidence data; as no inferential statistics were reported, the significance of these findings is unknown. One review reported one withdrawal in both the THC and placebo groups [123], one review reported a 9.7% withdrawal rate in the THC group compared with a 0.9% withdrawal rate in the placebo group [151], and the final two reviews reported a 15% withdrawal rate in the THC group compared with a 0% withdrawal rate in the placebo group based on one RCT [136,137].

Two reviews [136,137] reported very low-certainty evidence, based on the findings from one RCT, of a 3% withdrawal rate in the THC group compared with a 0% withdrawal rate in the active control (amitriptyline) group. One review [148] reported very low-certainty evidence indicating no significant difference in the likelihood of withdrawal between the THC compared with the mixed control (gabapentin and placebo) groups.

4 Discussion

4.1 Summary of findings

4.1.1 Efficacy in specific health conditions

4.1.1.1 Cancer

The findings and certainty of evidence from the reviews on medicinal cannabis in relation to cancer outcomes vary quite widely. There is evidence of mixed certainty (very low to moderate) based on three systematic reviews generally indicating no significant difference between medicinal cannabis (THC:CBD) and placebo or opioid controls for pain-related outcomes. There is low-certainty evidence based on one systematic review indicating greater improvement in patient-perceived global improvement of painwith nabiximols compared with placebo. There is evidence of mixed certainty (very low to moderate) that THC (nabilone, dronabinol) performs better than placebo in eliminating vomiting only, as well as both nausea and vomiting, but is not superior to anti-emetics. There is evidence of mixed certainty (very low to low) that cannabinoids are no better than placebo in improving appetite, weight, body mass index, caloric intake, fats intake, and iron intake, and very low-certainty evidence that megestrol acetate is superior to dronabinol in improving appetite and weight. There is very low-certainty evidence that THC (dronabinol) is superior to placebo in improving chemosensory perception and satiety, and very low-certainty mixed evidence for a relative benefit of THC (dronabinol, nabilone) compared with placebo for improving protein and carbohydrate intake; however, findings indicating no significant benefit for THC compared with placebo were also identified. The reviews also presented evidence on secondary outcomes, including additional pain outcomes, sleep problems, and quality of life. Adverse events (including dizziness, gastrointestinal effects, somnolence, psychiatric effects, and feeling good or feeling 'high') were noted, but in most cases were not more common in the intervention (cannabinoid) than in the comparator condition.

4.1.1.2 HIV/AIDS

We found one review examining medicinal cannabis for outcomes related to HIV/AIDS. The review found no evidence relating to the primary outcomes of interest (morbidity and mortality). The review presented evidence on a range of secondary outcomes, including outcomes related to nutrition, nausea and vomiting, peripheral neuropathy, and mood, along with effects on viral load and CD4 cell count. Adverse events were reported as having occurred in only one of seven primary studies included in the review, and were more common in the cannabinoid (dronabinol) condition compared with placebo. Dropouts due to adverse events were very uncommon. Serious adverse events were reported for only one primary study and represented a small proportion of overall adverse events.

4.1.1.3 Conditions in older adults

We found four reviews examining the effectiveness of medicinal cannabis for outcomes related to conditions in older adults. There is some evidence of mixed certainty (almost exclusively very low) for improvements in behavioural and psychological symptoms of dementia, Alzheimer's disease, and Parkinson's disease with cannabinoids, as well as for movement disorder, anxiety, quality of life, and sleep quality in Parkinson's disease, and weight gain in Alzheimer's disease. However, no significant benefit of cannabinoids was observed for breathlessness in COPD, for nausea and vomiting in older adults receiving chemotherapy, or for pain in Parkinson's disease. One review on dementia presented evidence on secondary outcomes, including agitation/aggression, quality of life, change in functional outcomes, dementia severity, nutritional outcomes, and carer burden. Adverse events (including drowsiness/sedation, sleep effects, nervous system effects, and gastrointestinal effects) were noted, and sedation was noted to be more common with cannabinoid interventions than with placebo.

4.1.1.4 Inflammatory bowel disease

There is very low-certainty evidence based on two systematic reviews generally indicating no significant difference between medicinal cannabis and placebo for primary outcomes related to inflammatory bowel disease, namely clinical remission in ulcerative colitis and in Crohn's disease. The reviews presented evidence on secondary outcomes, including clinical response, C-reactive protein, quality of life, and bowel symptoms. Adverse events (including sleepiness, nausea, cognitive symptoms (e.g. difficulty with concentration, confusion), dizziness, and dry mouth) were reported to be generally mild or moderate in severity and were more common in the intervention conditions.

4.1.1.5 Mental health and neuropsychological conditions

The findings and certainty of evidence from the reviews on medicinal cannabis in relation to mental health and neuropsychological conditions vary quite widely. There is evidence of mixed certainty (low or very low) based on three systematic reviews generally indicating no significant difference between cannabinoids and placebo or active control (amisulpride) for outcomes related to psychotic disorders, and some very low-certainty evidence for a detrimental effect on symptoms of psychosis and on cognitive function in schizophrenia for THC compared with placebo. There is mixed evidence of mixed certainty (low or very low), based on three systematic reviews, indicating a possible relative benefit of cannabinoids and cannabis compared with placebo for some anxiety outcomes, including symptoms of generalised anxiety disorder, PTSD, and social anxiety disorder, but not for obsessive-compulsive disorder. However, findings indicating no significant benefit for these anxiety outcomes were also identified. There is evidence of mixed certainty (low to very low) based on one systematic review indicating no significant difference between cannabinoids/medicinal cannabis and placebo for outcomes related to mood disorders. There is very low-certainty evidence based on two systematic reviews indicating the relative benefit of THC (dronabinol) compared with placebo for weight gain in anorexia nervosa; however, there was no significant difference between cannabis and diazepam for this outcome. There is mixed evidence of mixed certainty (very low to moderate) based on two systematic reviews indicating a possible relative benefit of cannabinoids compared with placebo for some outcomes related to cannabis use disorder, opioid use disorder, and tobacco use disorder; however, findings indicating no significant benefit were also identified. There is very low-certainty evidence based on two systematic reviews indicating no significant difference between THC:CBD (nabiximols) and placebo for ADHD symptoms. There is very low-certainty mixed evidence based on two systematic reviews indicating a possible relative benefit of THC (dronabinol) compared with placebo for tic severity and frequency in Tourette's syndrome; however, findings indicating no significant benefit were also identified. The reviews presented evidence on secondary outcomes, including global functioning, quality of life, and patient and caregiver impressions of

change, among others. Adverse events and withdrawals from primary studies due to adverse events were reported to be more likely in THC:CBD conditions compared with placebo conditions; however, the findings on adverse events in CBD conditions were mixed. Sedation, sexual side effects, cardiac effects, dry mouth, headaches, drowsiness, and sleep disturbances, among others, were reported in the cannabinoid conditions.

4.1.1.6 Palliative care

There is evidence of mixed certainty (low or very low) based on one systematic review generally indicating no significant difference between medicinal cannabis and placebo for primary outcomes in palliative care, including outcomes in cancer, HIV, and Alzheimer's disease. A relative benefit of cannabinoids compared with placebo was observed for pain reduction in cancer, appetite in HIV, and negative affect in Alzheimer's disease. Standard therapy with megestrol acetate was noted to be more effective than THC (dronabinol) in one RCT for some nutrition-related outcomes in cancer and HIV, and for health-related quality of life in cancer. Serious adverse events and dropouts were more common in the cannabis/cannabinoid intervention conditions when pooled across all conditions.

4.1.1.7 Rheumatic diseases and fibromyalgia

There is generally limited and inconsistent evidence (of low or very low certainty), based on two systematic reviews, indicating a relative benefit of medicinal cannabis compared with placebo for some outcomes related to rheumatic diseases and fibromyalgia, including fibromyalgia, rheumatoid arthritis, and chronic therapy-resistant pain caused by the skeletal and locomotor system. Cannabinoids (nabiximols, nabilone) were observed to produce improvements in some (but not all) measures of pain, sleep, and quality of life. Some adverse events, but not serious adverse events, were reported to be more common in the cannabinoid/cannabis intervention conditions compared with placebo conditions, including dizziness, dry mouth, light-headedness, nausea, and drowsiness, among others.

4.1.1.8 Spinal cord injury

There is very low-certainty evidence based on one systematic review indicating the relative benefit of both low and high THC doses compared with placebo for pain related to spinal cord injury, but generally finding no significant difference between nabiximols and placebo or between dronabinol and diphenhydramine for pain related to spinal cord injury. Adverse events (including dry mouth, constipation, fatigue, drowsiness/somnolence, confusion, and paranoia) were reported across both intervention and comparator conditions.

4.1.1.9 Multiple sclerosis

There is some evidence of mixed certainty (very low to moderate) based on two systematic reviews indicating the relative benefit of medicinal cannabis compared with placebo for some outcomes related to multiple sclerosis. Cannabinoids (THC:CBD, nabiximols, and THC only) and cannabis extract were observed to produce improvements in subjective spasticity but not in observer-rated spasticity, as well as in some (but not all) measures of pain, bladder dysfunction, and patient-rated global impression of change. Adverse events, but not serious adverse events, were reported to be more common in the cannabinoid/cannabis intervention conditions compared with placebo groups.

4.1.2 Efficacy in mixed health conditions

4.1.2.1 Pain

Overall, there is mixed evidence on the efficacy of cannabinoids on pain intensity, ranging from moderate to very low certainty across diverse cannabinoid and comparator types. Low- to very low-certainty

evidence from three reviews [143,147,154] comparing mixed cannabinoids and cannabis with placebo indicated a significant improvement for mixed cannabinoids and cannabis compared with placebo, but another review (low-certainty evidence) found no significant difference [146]. However, one review with high-certainty evidence reported a significant improvement in mixed cannabinoids compared with mixed controls [149], although the mechanism of action cannot be ascertained due to mixed cannabinoid types. Overall, low- to very low-certainty evidence showed a significant improvement in the cannabis compared with placebo groups [152,154] , but mixed findings between the cannabis and usual care groups (low-certainty evidence) [148].

Moving on to specific cannabinoid types, stronger evidence indicates potential benefits of THC:CBD compared with placebo (high- to very low-certainty evidence) [148,149,154]; however, evidence was mixed in two reviews [144,151]. Similarly, stronger evidence indicated a significant improvement in pain intensity in THC compared with placebo groups (moderate- to very low-certainty evidence) [148,149,151,154], but two reviews reported mixed [142] and non-significant [155] findings (very low-certainty evidence). In contrast with significant findings for THC compared with placebo groups, all reviews comparing THC with active/mixed controls reported no significant difference between groups (moderate- to very low-certainty evidence) [146–149,152]. Evidence on the efficacy of CBD compared with placebo was inconclusive and of very low certainty; three reviews reported a significant improvement in the CBD compared with placebo group [155], mixed findings [153], and no significant difference between groups [154]. Reviews comparing CBDV [148,154] and 1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3) [154] indicated no significant difference when compared with placebo.

Evidence synthesised on the likelihood of a 30% or greater reduction in pain ranged from moderate to very low certainty. One review [143] indicated a significant improvement in mixed cannabinoids and cannabis compared with placebo (very low-certainty evidence). Two reviews [141,145] reported a significant improvement in the cannabis compared with placebo groups (moderate- to very low-certainty evidence). Three reviews [144,148,151] reported no significant difference between the THC:CBD and placebo groups (low-certainty evidence), and one review [145] reported a significant likelihood of improvement in the THC:CBD group (very low-certainty evidence). One review [145] indicated a significant likelihood of improvement in the THC compared with placebo/codeine groups (very low-certainty evidence). One review [141] reported very low-certainty evidence indicating significant improvement in THC compared with placebo groups comprising adults with diabetic neuropathy, but one review [139] reported low-certainty evidence indicating no significant difference between groups of adults with chronic pain.

Evidence synthesised on the likelihood of a 50% or greater reduction in pain ranged from low to very low certainty. One review [143] reported a significant likelihood of at least a 50% reduction in pain in the mixed cannabinoids and cannabis compared with placebo groups (very low-certainty evidence). Two reviews reported mixed evidence in the THC:CBD compared with placebo groups. One review [150] reported a significant likelihood of a greater than 50% reduction in pain in the THC:CBD group (very low-certainty evidence), and two reviews [145,151] reported no significant difference between the THC:CBD and placebo groups (low- and very low-certainty evidence, respectively). One review [150] reported no significant difference between the THC and placebo groups (very low-certainty evidence). One review [145] reported no significant difference in the THC compared with mixed control groups (very low-certainty evidence).

In relation to patient global impression of pain outcomes, evidence ranged from low to very low certainty. Two reviews reported significant improvement in patient global impression of change of pain in the mixed cannabinoid [144], THC:CBD [150], and THC [150] compared with placebo groups.

One review [142] reported no significant difference in morphine consumption in the THC compared with placebo groups (very low-certainty evidence).

4.1.2.2 Quality of life

Three systematic reviews synthesised evidence on quality-of-life-related outcomes. Two systematic reviews reported on health-related quality of life. In relation to health-related quality of life, evidence indicated no significant difference in mixed cannabinoids compared with placebo (low-certainty evidence) [156], THC:CBD products compared with placebo (moderate- and very low-certainty evidence) [151,156], and THC products compared with mixed controls (low-certainty evidence) [156]. One review [151] indicated a significant improvement in the THC compared with placebo groups. In relation to quality-of-life measures specific to cancer and cachexia, one review [157] reported no significant difference in mixed cannabinoids compared with mixed controls.

4.1.2.3 Spasticity

Evidence on spasticity intensity was synthesised in two reviews, with one review indicating no significant difference between mixed cannabinoids and cannabis compared with placebo (low-certainty evidence) [158] and the other review indicating mixed evidence on the efficacy of THC:CBD compared with placebo on spasticity intensity [151]. In relation to the likelihood of a greater than 30% reduction in spasticity, one review [151] reported no significant difference between the THC:CBD and placebo groups. One review [158] reported no significant difference in spasm frequency or severity in the mixed cannabinoids and cannabis compared with placebo groups. One review [151] reported significant improvements in observer-rated spasticity in the THC:CBD compared with placebo groups and in the THC compared with placebo groups. With the exception of observer-rated spasticity, there was no significant difference between cannabinoids and comparator groups across the synthesised evidence (low- to very low-certainty evidence).

4.1.2.4 Cachexia

One review [157] synthesised evidence on cachexia-related outcomes. The synthesised evidence indicated no significant difference in appetite (low-certainty evidence) in mixed cannabinoid compared with placebo groups, and no significant difference in weight loss/gain in THC products compared with mixed control groups (very low-certainty evidence).

4.1.2.5 Sleep

Evidence synthesised on sleep quality ranged from high to very low certainty. Two reviews [159,160] indicated a significant improvement in sleep quality for the mixed cannabinoids and cannabis compared with placebo groups (moderate- and high-certainty evidence), but no significant difference was reported between the THC and placebo groups (very low-certainty evidence) [159]. One review [159] reported a significant improvement in sleep disturbance for mixed cannabinoid and THC products when compared with placebo (low- and very low-certainty evidence, respectively). This review also indicated no significant improvement in PTSD nightmares, as well as significantly reduced sleepiness, in the THC compared with placebo groups (very low-certainty evidence), in addition to a significant improvement in insomnia and no significant difference in sleep interruptions in the THC compared with amitriptyline and dihydrocodeine groups, respectively (very low-certainty evidence). One review [160] reported a significantly higher likelihood of daytime somnolence in the mixed cannabinoids compared with placebo groups (high-certainty evidence).

4.1.2.6 Mental health/well-being

One review [156] reported low-certainty evidence on mental health/well-being outcomes, indicating no significant difference between the mixed cannabinoids and mixed control groups, THC:CBD and placebo groups, and THC and placebo groups in relation to mental health/well-being outcomes.

4.1.2.7 Overall function or disability

The evidence synthesised on overall function or disability was low to very low certainty. One review [148] indicated no significant difference between cannabis compared with usual care, and between THC compared with active control groups, on overall function or disability. This review reported a significant improvement in overall function or disability for both THC and THC:CBD compared with placebo groups.

4.1.3 Safety and tolerability

4.1.3.1 Specific adverse events (safety)

4.1.3.1.1 Nervous system adverse events

Five reviews [122,123,148,157,161] synthesised evidence on adverse events categorised as nervous system disorders. Two reviews [148,161] synthesised moderate- to very low-certainty evidence on dizziness as a primary outcome. One review [148] reported no significant difference in the likelihood of dizziness between cannabis and usual care groups, or between THC products and mixed control groups. This review also reported a significantly higher likelihood of dizziness in the THC:CBD compared with placebo groups. Evidence synthesised comparing THC with placebo groups [148,161] also indicated a significantly increased likelihood of dizziness in the THC group.

Moderate- to very low-certainty evidence [122,123,148] indicated a significantly increased likelihood of sedation in cannabinoid and cannabis groups versus comparator groups. One review [148] reported a significantly increased likelihood of sedation in the cannabis compared with usual care groups, in the THC:CBD compared with placebo groups, and in the THC compared with mixed control groups. A significantly increased likelihood of sedation in the THC compared with placebo groups was also reported in three reviews [122,123,148].

One review [161] reported findings related to drowsiness in the THC compared with placebo groups. There was a significantly increased likelihood of drowsiness in the nabilone (but not dronabinol) compared with placebo groups (very low-certainty evidence). This review also reported moderate- to very low-certainty evidence indicating a significantly increased likelihood of dry mouth in the THC (nabilone, dronabinol) compared with placebo groups.

One review found low- to very low-certainty evidence [161] of a significantly higher likelihood of headache in the THC (dronabinol, nabilone) compared with placebo groups. This review also reported no significant difference in the likelihood of fatigue between THC (dronabinol) and placebo groups (moderate-certainty evidence). One additional review reported very low-certainty evidence of significantly lower likelihood of impotence in dronabinol compared with active control (megestrol acetate) groups consisting of male adults with cancer associated cachexia [157].

Two reviews reported low- to very low-certainty evidence on any nervous system disorder as a primary outcome. One review reported significantly increased likelihood in THC compared with placebo [157], however another review reported no significant difference between THC and placebo groups [122].

4.1.3.1.2 Gastrointestinal system adverse events

Three reviews [122,148,161] synthesised evidence on adverse events categorised as gastrointestinal disorders as primary outcomes. One review [148] reported very low-certainty evidence indicating a significantly increased likelihood of nausea in cannabis compared with usual care groups. This review also

reported low-certainty evidence indicating a significantly increased likelihood of nausea in the THC:CBD compared with placebo groups. Two reviews [148,161] reported moderate-certainty evidence indicating no significant difference in the likelihood of nausea in THC compared with placebo groups. One review [122] synthesised very low-certainty evidence indicating no significant difference in the likelihood of any gastrointestinal system adverse events between THC and placebo groups.

4.1.3.1.3 Psychiatric system disorder adverse events

Two reviews reported very low-certainty evidence on any psychiatric system disorder adverse events as a primary outcome. No significant difference in the likelihood of psychiatric system disorder adverse events was reported in cannabis compared with usual care groups [148] or in THC compared with placebo groups [122].

4.1.3.1.4 Any specific adverse events

One review [122] reported 160 individual adverse events in THC groups compared with 131 individual adverse events in placebo groups comprising adult populations with dementia; however, no inferential statistics were reported (low-certainty evidence). Another review [125] reported 266 adverse events in cannabinoid compared with 133 adverse events in mixed control groups (placebo and prochlorperazine) (low-certainty evidence). Inferential statistics were not reported in either review, so the significance of these findings is unclear. Two reviews reported very low-certainty evidence indicating no significant difference in the THC:CBD compared with placebo groups [124,157], the THC compared with placebo groups [123,124,157], THC compared with megestrol acetate [157], or the CBD compared with placebo groups [124]. One review reported no adverse events in either the CBD or placebo groups [153].

4.1.3.2 Serious adverse events (safety)

In relation to mortality outcomes, two reviews [122,151] reported low- to very low-certainty evidence indicating no significant difference in mortality for the THC:CBD or THC compared with placebo groups. Six reviews [116,125,136,137,148,150] synthesised low- to very low-certainty evidence on the likelihood of any serious adverse events. One review [125] reported one serious adverse event (grand mal seizure) in mixed cannabinoids compared with no serious adverse events in placebo groups, however no inferential statistics were reported so the significance of these findings is unclear. One review [148] reported a significantly increased likelihood of serious adverse events in the cannabis compared with usual care groups. Two reviews reported no significant difference in the likelihood of any serious adverse events for the THC:CBD compared with placebo groups [116] or for the THC compared with mixed control groups [148]. Two reviews [136,137] reported the prevalence of serious adverse events in the THC compared with placebo groups (0.0% vs. 0.0% [137]; 3.3% vs. 0.0% [136]) and in the THC compared with active control groups (0% vs. 0% for both reviews); inferential statistics were not reported in either review, so the significance of these findings is unclear.

4.1.3.3 Tolerability

Seven reviews [116,123,136,137,148,150,151] reported moderate- to very low-certainty evidence investigating withdrawals due to adverse events as a primary outcome. It is important to note that in this context, “withdrawals due to adverse events” refers to participants choosing to stop participating in a study due to their experience of adverse events (in either intervention or comparator groups), not symptoms of withdrawal that may occur when a person stops taking a drug.

One review [148] reported a significantly increased likelihood of withdrawals from primary studies due to adverse events in cannabis compared with usual care groups. Similarly, one review [150] reported a significantly increased likelihood of withdrawals in mixed cannabinoids and cannabis compared with placebo groups.

Four reviews reported low- to very low-certainty mixed evidence on tolerability in THC:CBD compared with placebo groups. One review [116] reported a significantly increased likelihood of withdrawals in the THC:CBD compared with placebo groups, whereas two reviews [148,150] reported no significant difference between groups. Another review [151] comparing THC:CBD with placebo reported a significantly increased likelihood of withdrawals in the THC:CBD compared with placebo groups in a meta-analysis of adults with neuropathic pain; however, this same review reported no significant difference between groups in a meta-analysis of adults with cancer. One review [136] reported a 0% incidence of withdrawals in the THC:CBD group compared with an 11% prevalence in the placebo group. However, no inferential statistics were reported, so the significance of these findings is unclear.

Moderate- to very low-certainty evidence was reported on the tolerability in THC compared with placebo groups in five reviews. One review [148] reported no significant difference in withdrawals in the THC compared with placebo groups. The remaining reviews comparing THC with placebo reported incidence data; as no inferential statistics were reported, the significance of these findings is unknown. One review [123] reported one withdrawal in both the THC and placebo groups, one review [151] reported a 9.7% withdrawal rate in the THC group compared with a 0.9% withdrawal rate in the placebo group, and the final two reviews [136,137] reported a 15% withdrawal rate in the THC group compared with a 0% withdrawal rate in the placebo group based on one RCT.

Two reviews [136,137] reported very low-certainty evidence, based on the findings from one RCT, of a 3% withdrawal rate in the THC group compared with a 0% withdrawal rate in the active control (amitriptyline) group. One review [148] reported very low-certainty evidence indicating no significant difference in the likelihood of withdrawal in the THC compared with the mixed control (gabapentin and placebo) groups.

4.2 Comparison with other overviews of reviews

4.2.1 Efficacy in specific health conditions

4.2.1.1 Cancer

Our findings on medicinal cannabis for outcomes related to cancer are broadly in line with findings from other overviews of reviews on the topic.

Overviews of reviews by Allan *et al.* (2018) [165], Riera *et al.* (2022) [11], Tafelski *et al.* (2016) [166], and Schussel *et al.* (2018) [167] all found evidence of relative benefits for cannabinoids compared with placebo or conventional anti-emetics for chemotherapy-induced nausea and vomiting. Additionally, Bywood and McMillan (2021) [168] found that there was weak and very weak evidence to support the use of cannabinoids in managing vomiting and nausea, respectively, in cancer. Tafelski *et al.* (2016) [166] noted that there was insufficient evidence on cannabinoids relative to newer anti-emetics, including 5-HT3 antagonists and neurokonin-1 (NK-1) receptor antagonists. Similarly, our review found evidence that THC outperformed placebo in the management of vomiting only, as well as both vomiting and nausea, in cancer, but we have noted that the primary studies in our included reviews are generally rather old and do not account for modern anti-emetics. Vila Silván *et al.* [169] are known to have conducted an additional relevant umbrella review published in 2022, but it was not possible to source the full text; the review is noted here for reference only.

Regarding cancer-related pain, a scoping review by Pratt *et al.* (2019) [170] found limited evidence supporting the use of cannabinoids. However, Häuser *et al.* (2017) [171] found insufficient evidence to support the use of cannabinoids, and Häuser *et al.* (2018) [172] consistently found no benefit of cannabinoids over placebo. Our review generally found no significant difference between cannabinoids and controls for pain in cancer. Divergent findings between reviews may be due to variations in inclusion

criteria (and therefore included studies), particularly in relation to study duration, and in the analysis of risks and benefits [172].

Vila Silván *et al.* [169] are known to have conducted an additional relevant umbrella review published in 2022, but it was not possible to source the full text; the review is noted here for reference only.

Please see Section 4.2.1.6 for additional findings on cancer outcomes in the context of palliative care.

4.2.1.2 HIV/AIDS

We identified no overviews of reviews examining the same primary outcomes in HIV/AIDS as those examined in our review. Please see Section 4.2.1.6 for findings on HIV/AIDS outcomes in the context of palliative care.

4.2.1.3 Conditions in older adults

A scoping review of systematic reviews, RCTs, and non-randomised studies of medicinal and non-medicinal cannabis use by Wolfe *et al.* (2023) [173] found inconsistent results for specific health conditions among adults aged 50 years and over, including Alzheimer's disease and Parkinson's disease. There was mixed evidence for possible benefits in relation to agitation/aggression, cognitive functioning, neuropsychiatric symptoms, sleep, and mental well-being; however, studies finding no significant difference between cannabinoid interventions and controls were also identified. This is broadly in line with our findings; we found limited evidence for improvements in these domains with cannabinoids, but the certainty of the evidence was generally very low. Wolfe *et al.* [173] also noted that older adults may be at higher risk of adverse events associated with cannabis use, including mental health issues and substance misuse, and that the risk/benefit ratio is not clear.

4.2.1.4 Inflammatory bowel disease

Häuser *et al.* (2017) [171], in a review of systematic reviews of RCTs and prospective cohort studies, found insufficient evidence for positive effects of cannabinoid interventions on ulcerative colitis or Crohn's disease. This reflects our findings of no significant benefit for remission rates for these conditions.

4.2.1.5 Mental health and neuropsychological conditions

Bywood and McMillan (2021) [168] found weak evidence leaning towards no significant benefit of cannabinoids for PTSD, depression, psychiatric disorders, or substance use disorders, but noted that the evidence was insufficient to draw firm conclusions. Bywood and McMillan stated that the primary studies in their review were of poor quality with high risk of bias, factors that "preclude meaningful comparative analysis" [168] p32.

Like Bywood and McMillan, we found no evidence to support cannabinoids as a therapy for psychosis or depression; however, we did find very low-certainty evidence in favour of cannabinoids in the management of sleep disturbances in PTSD, as well as some mixed evidence for the benefits of cannabis in relation to opioid dependence. Bywood and McMillan's findings do not align fully with our own; however, we concur that the evidence is generally of very low quality. As above, variations in inclusion criteria and risk-benefit analyses may explain the differences in findings across reviews.

Our findings on PTSD were supported by the overview of reviews by Farrell and Premji (2021) [174]; however, the evidence presented by Farrell and Premji was a single open-label study (which found benefits for nightmare reduction in PTSD) and is therefore not directly comparable to our own review.

4.2.1.6 Palliative care

Häuser *et al.* (2017) [171] found insufficient evidence to support medicinal cannabis as a symptom management approach for chronic pain related to cancer; for loss of appetite; or for nausea and vomiting in advanced disease stages of cancer or HIV/AIDS. Häuser *et al.* stated that prescribing guidelines for medicinal cannabis could not be supported based on this evidence and that cannabinoid use in palliative medicine should be regarded as individual therapeutic trials in most cases.

This reflects the mixed evidence found in our review for the use of cannabinoids in palliative care. We found only limited evidence of a beneficial effect of cannabinoids as a symptom management approach for cancer-related pain and for appetite loss in HIV, and did not find evidence to support cannabinoids for appetite/weight gain in cancer, for nausea and vomiting in HIV or cancer, or for health-related quality of life in HIV or cancer. However, our overview of systematic reviews of cancer generally (not specific to palliative care settings) did find some evidence for the efficacy of THC in reducing nausea and vomiting in cancer (see Section 4.2.1.1).

4.2.1.7 Rheumatic diseases and fibromyalgia

An overview of reviews by Allan *et al.* (2018) and a scoping review by Pratt *et al.* (2019) [165,170] both reported inconsistent findings for the use of cannabinoids in treating rheumatologic and fibromyalgia-related pain, while two reviews by Häuser *et al.* (2017) [171] and Häuser *et al.* (2018) [172] found insufficient evidence to support their use. This aligns with our findings of limited and inconsistent evidence of low or very low certainty indicating a relative benefit of cannabinoids for some (but not all) pain-related outcomes in rheumatic diseases and fibromyalgia.

4.2.1.8 Spinal cord injury

We identified no overviews of reviews examining the same primary outcomes for spinal cord injury as were examined in our review.

4.2.1.9 Multiple sclerosis

Allan *et al.* (2018) and Nielsen *et al.* (2018) [165,169,175] reported limited or low-certainty evidence on the benefits of cannabinoids for spasticity in multiple sclerosis. This is reflective of our own findings that there is low- to moderate-certainty evidence that cannabinoids perform better than placebo in reducing subjective (but not observer-rated) spasticity. Vila Silván *et al.* [169] are known to have conducted an additional relevant umbrella review published in 2022, but it was not possible to source the full text; the review is noted here for reference only.

Findings on pain in multiple sclerosis were divergent across four reviews: Nielsen *et al.* (2018) [175] reported possible or probable benefits for pain in multiple sclerosis; Pratt *et al.* (2019, scoping review) [170] and Häuser *et al.* (2018) [172] both reported inconsistent findings for pain in multiple sclerosis; and Riera *et al.* (2022) [11] found moderate-certainty evidence for no benefit in spasticity-related pain in multiple sclerosis. Similarly, our review found inconsistent evidence of low or very low certainty for the effect of cannabinoids on pain in multiple sclerosis.

4.2.2 Efficacy in mixed health conditions

We found no overviews of reviews that presented evidence on quality of life, cachexia, sleep, mental health/well-being, or overall function or disability across mixed health conditions. Therefore, in this section we provide comparisons to findings from other overviews of reviews of multiple health conditions for pain and spasticity outcomes only.

4.2.2.1 Pain

The evidence identified by our overview of reviews on the efficacy of medicinal cannabis for pain outcomes across mixed health conditions varied widely. Although we identified a number of reviews that found evidence for improvements in pain intensity and reduction in pain by 30% or 50% with mixed cannabinoids, cannabis, THC:CBD, and THC, we also identified reviews finding mixed evidence or evidence of no effect when these interventions were compared with placebo or active controls. Moderate- to high-certainty evidence was presented in four of our included reviews for a beneficial effect of cannabis, mixed cannabinoids, and THC:CBD compared with placebo or control groups for neuropathic pain; however, results finding mixed evidence or no evidence of effect were also identified. Additionally, we found evidence that medicinal cannabis does not significantly reduce morphine consumption compared with placebo (i.e. 'opioid-sparing').

These inconsistent findings are reflected in a number of other recent overviews of reviews. Allan *et al.* (2018) [165] reported inconsistent evidence of low certainty for neurological, rheumatologic, and fibromyalgia-related pain. Bywood and McMillan (2021) reported "equivocal" [168] p15 evidence for relief of chronic, non-cancer pain with cannabinoids, stating that reviews of higher quality reported mixed results with small or non-significant effects. Bywood and McMillan also reported null or inconclusive findings for opioid-sparing effects, in line with our findings. A scoping review by Pratt *et al.* (2019) [170] reported inconsistent findings for chronic, non-cancer pain and pain related to multiple sclerosis, HIV, and rheumatic disease. Riera *et al.* (2022) [11] reported moderate-certainty evidence for no relative benefit of cannabinoid interventions for acute postoperative pain; chronic, non-cancer pain; or spasticity-related pain in multiple sclerosis. Häuser *et al.* (2017) [171] found insufficient evidence to support the use of medicinal cannabis for musculoskeletal pain, rheumatoid arthritis, and cancer-related pain, but did find support for the use of nabiximols for neuropathic pain in some studies with generally small sample sizes and short durations. Häuser *et al.* (2018) [172] reported inconsistent findings for neuropathic pain. Vila Silván *et al.* [169] are known to have conducted an additional relevant umbrella review published in 2022, but it was not possible to source the full text; the review is noted here for reference only.

An overview of reviews by Moore *et al.* (2021) [176] assessed the quality of existing review literature on the use of cannabis, cannabinoids, and medicinal cannabis for pain management, and found that most reviews are lacking in quality and cannot provide a basis for decision-making. Moore *et al.* state:

> To the extent that any conclusions can be drawn from existing systematic reviews, they can only be made with respect to the types of cannabinoid, cannabis, and [cannabis-based medicine] investigated to date, in the specific patient groups and pain types studied…. What we have is a body of work that tells us little about whether any particular cannabinoid or cannabis-based treatment tested to date, at a particular dose and route of administration, given to someone with a particular form of pain could lead to a particular degree of pain reduction (at least 50% pain intensity reduction or reduction of pain to just mild). Low-quality reviews do no more than suggest there may be, whereas the highest quality say probably not. [176] pS73, S76

4.2.2.2 Spasticity

In this review, we report generally no significant difference between medicinal cannabis and placebo in spasticity-related outcomes (with the exception of observer-rated spasticity) across mixed health conditions (multiple sclerosis and amyotrophic lateral sclerosis) based on low- or very low-certainty evidence. Allan *et al.* (2018) [165] reported somewhat different conclusions, finding limited evidence for the benefits of cannabinoids for spasticity, primarily in multiple sclerosis and paraplegia. This is reflected in our findings on spasticity in multiple sclerosis from the reviews on multiple sclerosis specifically, rather than from those on mixed health conditions.

4.2.3 Safety and tolerability

4.2.3.1 Specific adverse events

We found some evidence for a significantly higher likelihood of some specific adverse events associated with medicinal cannabis (dizziness, dry mouth, sedation, headache). However, no difference in likelihood of fatigue compared with placebo and lower likelihood of impotence compared with megestrol acetate was reported. We also reported mixed evidence on the likelihood of drowsiness, any gastrointestinal system adverse events, and any psychiatric disorder adverse events.

Our findings do not clearly align with the findings of other overviews of reviews; both Mohiuddin *et al.* (2021) [177] and Allan *et al.* (2018) [165] reported that cannabis use or cannabinoid interventions were associated with an increased risk of adverse events. A number of other overviews of reviews commented only on whether particular types of adverse events were reported, without comment on relative risks, including somnolence, dizziness, dry mouth, nausea, and adverse events of the central nervous and gastrointestinal systems [168,170]. Bywood and McMillan (2021) [168] noted that adverse events tended to be mild and transient and that inconsistency of reporting meant that adverse events were likely to be under-reported. Bywood and McMillan also noted that some adverse events may interfere with accurate measurement of efficacy outcomes (for example, feeling 'high' or euphoric interfering with measurement of pain). As above, variations in inclusion criteria and risk-benefit analyses may explain the differences in findings across reviews.

4.2.3.2 Serious adverse events

Of the seven reviews we included that reported on serious adverse events, only one reported a significantly greater risk of serious adverse events in a cannabinoid condition (in this case, cannabis) compared with placebo or control condition (low- to very low-certainty evidence), with the remainder reporting no difference in risk. This aligns with the findings of Bywood and McMillan (2021) [168], who found that serious adverse events were not more common in cannabinoid compared with placebo conditions. Our findings also align with those of a review on the general risks of cannabis, cannabinoids, and cannabis-based medicines by Mohiuddin *et al.* (2021) [177], which found that cannabis use was not associated with an increased risk of serious adverse events.

4.2.3.3 Tolerability

We report low- to very low-certainty evidence that withdrawals from primary studies due to adverse events may be more common in cannabinoid/cannabis interventions compared with placebo; however, findings across our included reviews were highly mixed. This contrasts with the review by Allan *et al.* (2018) [165], which found high-certainty evidence that adverse events were significantly more common with cannabinoids, even when compared with other active interventions.

4.3 Strengths and limitations

4.3.1 Research design

We chose an overview of reviews design for two reasons: to appropriately acknowledge and take advantage of the large number of existing systematic reviews on medicinal cannabis, and to allow us to cover the full scope of conditions of interest, which would not have been possible with a traditional systematic review in the available time. Methods for overviews of reviews are continually evolving, and we have consulted best-practice guidance provided by thought leaders in this area in order to develop our approach, tailoring our methods where necessary to take account of the particular needs and challenges of the literature on medicinal cannabis.

In our synthesis, we have presented information on the direction of effect but not the strength of effect at the level of individual reviews. We acknowledge that information may be important for drawing more focused conclusions. Subsequently, a detailed summary of pooled estimate and effects sizes reported in each of the 47 included systematic reviews is included in Appendix F.

While our review was conducted in accordance with best-practice guidance for overviews of reviews, it is vulnerable to some of the disadvantages inherent to this form of synthesis. Most significantly, the validity of any overview of reviews depends on the quality of the included systematic reviews, and while we have endeavoured to screen out poor-quality work (see Section 2.3: Eligibility criteria), weaknesses within the body of evidence as a whole cannot be overcome by overviews of reviews. There may be errors in the extraction of data from primary studies that were difficult to detect, or there may be inconsistencies between reviews (such as with the two reviews [128,132] examining social anxiety symptoms, which assigned different risk of bias ratings to the same primary studies; see Section 3.7.1.5.1.2). Additionally, the authors of an overview of reviews are separated from the original research by an extra layer of abstraction, and so important nuances of methodology or interpretation from the original research may be diluted or obfuscated in the findings of an overview of reviews.

4.3.2 Scope

A limitation of the literature search was the lack of non-English-language databases and resources included in the search. The exclusion of non-English-language papers was necessary, as the members of the review team do not have the necessary skills to translate or interpret complex and technical material in other languages, and the time frame of this review, together with competing work commitments, did not allow for the professional translation of papers. Based on previous experience, the review team determined that the use of software such as Google Translate would not be adequate for detailed extraction and synthesis of these papers, particularly in an area such as medicinal cannabis with wide-ranging and inconsistent terminology used to define interventions. However, we are aware that a considerable amount of primary research has been carried out on this topic in languages other than English. In Appendix C, we have noted the number of records excluded on the basis of language at each stage of screening, and we have listed the citations of records excluded on the basis of language at the full-text screening stage, so that the scope of this research can be recorded and credited and serve as a resource for future review authors. (However, it is not certain that any or all of these reviews would have met our inclusion criteria had we included non-English-language material.) Eleven reviews were excluded at full-text screening on the basis of language: one in Polish, two in Portuguese, four in German, and four in Spanish. With the exception of Latin American and Caribbean Health Sciences Literature (LILACS), the majority of the databases we searched primarily collate English-language evidence, and it is expected that using a wider range of non-English-language databases or regional databases would capture considerably more of this body of work.

We also limited our search to systematic reviews published since 2010 (i.e. in the last 13 years). Based on expert guidance, we expected that this would yield primary research conducted in the last 30 years [99], which comprehensively covers the period since the first medicinal cannabis access programmes were launched. This allowed us to cover a comprehensive range of literature while keeping our volume of records more manageable.

Medicinal cannabis is frequently used for the management of some forms of epilepsy; however, evidence on the efficacy and safety of medicinal cannabis for epilepsy is not represented in our included reviews. Although our search returned several reviews on the topic of epilepsy, all of these reviews included studies of paediatric populations and were therefore excluded from our overview of reviews (see Section 2.3 for eligibility criteria). Readers who wish to learn more about the evidence for medicinal cannabis in

the management of epilepsy are invited to consult the comprehensive 2018 review by Stockings *et al.* [178], which found that pharmaceutical-grade CBD as adjuvant therapy in paediatric-onset drug-resistant epilepsy may reduce seizure frequency, although minor adverse events were relatively common. Stockings *et al.* also noted that the existing RCT evidence, at the time of writing their review, was mostly focused on paediatric populations with rare and severe forms of epilepsy [178].

Our eligibility criteria specified that only systematic reviews of RCTs and/or prospective cohort studies (or reviews from which data on only these study types could be meaningfully extracted) were included. We made this choice because RCTs are regarded as the gold standard trial methodology for evaluating the effectiveness of interventions, and RCTs and prospective cohort studies offer the strongest evidence for causality. This is one strength of this evidence review. However, we acknowledge that there exists a very large body of evidence on medicinal cannabis from observational studies and that discourse around the merits of patient-reported outcomes is ongoing [179]. Observational studies are limited in what they can tell us about efficacy and causality, but they can tell us more than RCTs about subjective patient experiences and about patients with rare health conditions or significant comorbidities (who are often ineligible for inclusion in RCTs). Where their findings diverge from those of RCTs and patients report therapeutic benefits, these patterns of evidence should be further investigated and, where appropriate, incorporated into decision-making [179]. In particular, while intervention duration in the RCTs included in this review was generally on the order of weeks, observational studies (and open-label extensions of RCTs, some of which are described in our review) can gather data over longer periods of time, which is particularly valuable for assessing long-term tolerability, as well as incidence of adverse events and misuse/diversion. Our focus on study designs that provide strong evidence for causality means that these additional sources of evidence were excluded from this review, and our conclusions on safety may therefore paint an incomplete picture of the available data on adverse events.

Hall and Hoch (2023)[180] discuss the nuances of the question of research design, highlighting the necessity to minimise double standards in assessing the adverse and beneficial effects of cannabis and the need for triangulation of evidence from a variety of study designs, each with their own strengths and weaknesses:

> "Evidence for medical uses of cannabis should be provided by randomized controlled clinical trials. These study designs reduce the plausibility of alternative explanations of patient improvements seen in uncontrolled studies, such as placebo effects and variations in the severity of a chronic illness or disorder over time... The evidence from clinical trials should be supplemented by well-controlled observational studies that assess whether the benefits in clinical trials reliably translate into routine clinical practice in more representative samples of patients than those participating in clinical trials. Observational studies should not, however, be accepted as sufficient evidence to justify the widespread medical use of cannabis, or indeed any other drug, because of the major inferential problems in interpreting such data... Research on the harms of cannabis use will primarily come from observational epidemiological studies, because ethical issues preclude experimental studies of the harms of regular and long-term cannabis use in humans."

4.3.3 Search

We are confident that the search underpinning this evidence review is robust and comprehensive. We did not specify particular outcomes or health conditions in our search terms in order to capture as wide a range of outcomes and conditions as possible in our search, and we carried out substantial supplementary searches using a variety of strategies in order to minimise the risk of missed reviews. The search strategies were designed, piloted, and refined by an experienced information specialist, and a team of

four screened the titles and abstracts of more than 20,000 unique records in a multistage, double-blind screening process. All seven reviews that were identified for inclusion through supplemental searches were published in 2022, suggesting that these were not captured by our primary searches only because they had not yet been published/indexed.

The body of primary research and systematic review work on the topic of medicinal cannabis is growing very rapidly. This is evidenced by the distribution of reviews per year of publication in the reviews included in our overview of reviews: more than 50% (24/47, 51.1%) of the included reviews were published between 2021 and 2023. The searches we carried out were as comprehensive as possible within the time frame available and the most recent searches were carried out in January 2023. However, more recent reviews may not be picked up by even the most recent searches. Revisiting the topic in the near future may prove fruitful in allowing the capture of new reviews.

4.3.4 Quality of evidence

In designing our eligibility criteria, we aimed to limit the inclusion of systematic reviews with serious shortcomings by excluding reviews with inadequate coverage of bibliographic databases, inadequate descriptions of search methods, and inadequate appraisal of methodological quality/risk of bias of included primary studies (see Section 2.3). However, as reported in Section 0, the methodological quality of many of the systematic reviews included in this review is lower than desired. Only 6 of the 47 included reviews were rated as having methodological quality better than low; 9 reviews were rated as having low methodological quality and 32 reviews were rated as having critically low methodological quality.

The methodological quality of the primary studies included in the systematic reviews also appears to be relatively poor in some respects. For our Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment, we assessed whether the primary studies that contributed to the evidence for a given outcome in a systematic review were at risk of bias for randomisation or blinding of outcome assessors, and whether the sample sizes were adequately large. The certainty of the evidence was downgraded in a majority of cases due to a high risk of bias for randomisation (56% of outcomes), a high risk of bias for blinding of outcome assessors (65% of outcomes), and inadequate sample size (62% of outcomes) (see Appendix K for full GRADE assessments).

The low methodological quality of the systematic reviews on medicinal cannabis contributed in large part to the low certainty of evidence, as determined using GRADE, for many of the outcomes. For the majority of outcomes in this overview of reviews, the certainty of the evidence was low or very low. This means that the quality of the body of evidence for these outcomes is poor, and that we have limited confidence that the estimated effect of the interventions under examination is close to the true effect. This is a reflection of the relatively poor quality of the existing research that makes up the body of evidence for medicinal cannabis.

While most evidence in this review is of low or very low certainty, 34 outcomes were scored as having moderate- to high-certainty evidence across 9 reviews. This evidence was mainly related to mixed health condition populations in the areas of pain, quality of life, sleep, and adverse events. Four reviews reported moderate-certainty evidence relating to nausea and vomiting in cancer, behavioural and psychological symptoms in older populations, withdrawal symptoms in cannabis use disorder, and spasticity- and bladder-related symptoms in multiple sclerosis.

Moderate- to high-certainty evidence indicated a beneficial effect of medicinal cannabis compared with placebo or controls for the following outcomes: neuropathic pain (cannabis, mixed cannabinoids, and THC:CBD, but not THC) [141,145,149,154], sleep quality in mixed health conditions (mixed cannabinoids) [159,160], nausea and vomiting in cancer (THC) [120], observer-rated spasticity in multiple sclerosis (THC)

[140], and bladder-related dysfunction in multiple sclerosis (cannabis extract) [140]. Moderate-certainty evidence was reported for no significant effect on health-related quality of life in patients with cancer and central nervous system disorders (THC:CBD) [156] and withdrawal symptoms in cannabis use disorder (THC:CBD) [132]. In relation to safety outcomes, one review reported moderate-certainty evidence highlighting a significantly increased likelihood of dizziness and dry mouth, but no significant difference in the likelihood of fatigue or nausea, in dronabinol compared with placebo groups [161]. Finally, one review reported moderate-certainty evidence of no significant difference in withdrawals from primary studies due to adverse events in mixed cannabinoid and cannabis compared with placebo groups [148].

The body of evidence for medicinal cannabis summarised in this evidence review may be described as fragmented. For many outcomes, particularly those in specific populations (e.g. the effectiveness of CBD for reducing pain intensity in multiple sclerosis), evidence is drawn from only one systematic review that itself only included a small number of RCTs – fewer than three RCTs in approximately 68% of outcomes. Where more than one systematic review addresses the same outcome, overlap is generally high, with the same RCTs being counted in multiple systematic reviews, potentially contributing to an illusion of a stronger, deeper body of evidence than actually exists. This is in part due to the very fragmented nature of the evidence. Cannabis is very chemically complex, and a large range of products have been examined in the literature. Studies examining the impact of products containing only THC, only CBD, a combination of both THC and CBD, whole-plant herbal cannabis, or a mixed selection of these products cannot be meaningfully combined into a single analysis and must be considered separately. This has the effect of fragmenting the evidence and making it difficult to say with confidence whether any one, or all, of these medicinal cannabis options may be effective for a given outcome. At the same time, analyses that combine multiple types of cannabis products obscure the effectiveness of each product and do not provide strong evidence that might guide prescribing. Furthermore, a majority of the evidence compares medicinal cannabis with placebo, not with active comparators that reflect up-to-date treatment options, and authors do not always clearly discuss whether the medicinal cannabis treatment is being provided as an add-on to usual care. The evidence for each product in each context is generally thinner on the ground than the high volume of commentary and rapid pace of new publications on medicinal cannabis might suggest.

4.4 Future research

As mentioned in Section 4.3.3, the body of primary research and systematic review work on the topic of medicinal cannabis is growing very rapidly. Revisiting this topic in the near future may prove fruitful in allowing the capture of new reviews and evidence, which might in turn help to clarify what is, at present, a fragmented picture and bolster the certainty of the evidence on the benefits (or lack thereof) of medicinal cannabis in specific contexts.

In relation to specific conditions, as mentioned in Section 4.3.2, while the use of medicinal cannabis in the management of epilepsy has been studied quite extensively in paediatric populations, we found no systematic reviews synthesising evidence on the use of medicinal cannabis in the management of epilepsy specifically in only adult populations. The authors of one systematic review that examined nausea and vomiting in cancer as a primary outcome [120] noted that the studies included in their review were generally older (pre-1991) and did not reflect current chemotherapy regimens and newer anti-emetic drugs. This is an important avenue for future research to clarify the relative benefits of medicinal cannabis, if any, compared with standard modern therapies. For now, in this context, the clinical validity of the findings on nausea and vomiting in cancer may be regarded as very limited.

In addition to variations in mechanisms of action associated with distinct types of cannabinoids, there are also variations in the benefits and risks associated with administration routes (i.e. oral, oromucosal,

transdermal, inhalation by vaporising or smoking). Additional analyses or subgroup analyses based on administration route may be a useful avenue for future research, particularly given the known risks associated with smoking.

We concur with the recommendations of Häuser *et al.* [181] for methodological improvements in future research, including recommendations for subgroup analyses to elucidate efficacy according to pain mechanisms; studies with active comparators rather than placebo, which would be more ethically feasible and also allow assessment of comparative efficacy and safety; studies with different treatment arms to define the optimal ratio of THC and CBD for the condition/indication of interest; studies with sufficiently large samples to ensure adequate power and mitigate the effects of attrition; built-in stopping rules after an adequate trial of therapy so that participants who do not experience pain relief can pursue other treatments; reporting the details of the assessment of adverse events.

4.5 Conclusions

This overview of 47 reviews on the efficacy and safety of medicinal cannabis for a wide range of health conditions/clinical indications has generally revealed a fragmented body of research and a low degree of certainty in the evidence for most outcomes. The methodological quality of the included systematic reviews is generally very low.

Although our review questions were framed around the efficacy and safety of medicinal cannabis for the treatment of the health conditions/clinical indications of interest, the research we found is arguably more accurately described as being concerned with symptom management rather than with curative care or treatment, per se.

While some evidence was found to support the use of medicinal cannabis for some indications for which it has traditionally been recommended, such as vomiting in cancer and spasticity in multiple sclerosis, findings for most other outcomes were inconsistent at best, including for anxiety and pain in cancer, rheumatic diseases and fibromyalgia, multiple sclerosis, and other health conditions. The evidence for neuropathic pain was promising: moderate- to high-certainty evidence indicated a significant benefit of cannabis, mixed cannabinoids, and THC:CBD, although some moderate-certainty evidence indicated no significant benefit of THC.

Although serious adverse events do not appear to be common, evidence was found for a significantly higher likelihood of some specific adverse events associated with medicinal cannabis (including dizziness, dry mouth, sedation, and headache). However, no difference in likelihood was reported for other adverse events, including fatigue, insomnia, and vertigo. Mixed evidence was reported on the likelihood of drowsiness, nausea, and psychiatric system adverse events.

Our findings align with the findings of other overviews of reviews, as they also reported a general lack of quality in primary studies and systematic reviews, which makes it very difficult to draw well-founded conclusions about the relative benefits (or lack thereof) of medicinal cannabis for any given health condition or clinical indication. The certainty of the evidence for most outcomes is generally low (24% of total outcomes) or very low (64% of total outcomes), meaning that findings from future research are likely to change the conclusions we have drawn. A majority of the evidence compares medicinal cannabis with placebo, not with active comparators that reflect up-to-date treatment options. It is important to note that our findings refer only to adult populations and conclusions should not be transferred to children or adolescents.

Further high-quality, adequately powered RCT research is needed; in the meantime, conclusions may only be drawn narrowly, if at all, with respect to the particular type of cannabis treatment in the specific patient groups and clinical indications studied in a given analysis, and a number of authors of reviews of

medicinal cannabis recommend that if medicinal cannabis is to be prescribed to a patient, it should be carefully tailored to the individual's circumstances and closely monitored for clinical response and adverse events.

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Appendix A Preferred Reporting Items for Overviews of Reviews (PRIOR) checklist

Please see supplementary Appendices document

Appendix B Search strategies

Please see supplementary Appendices document

Appendix C Excluded reviews

Please see supplementary Appendices document

Appendix D HRB-adapted Joanna Briggs Institute data extraction form

Please see supplementary Appendices document

Appendix E HRB-adapted AMSTAR 2 instrument

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Appendix F Data extraction for included reviews

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Appendix G Included reviews

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Appendix H High-level summaries of included reviews

Please see supplementary Appendices document

Appendix I Review characteristics of included reviews

Please see supplementary Appendices document

Appendix J Quality assessment findings of included reviews

Please see supplementary Appendices document

Appendix K Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessments of included reviews

Please see supplementary Appendices document