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Cannabis-based medicines for prevention of postoperative nausea and vomiting in adults (Protocol).
Cochrane Database of Systematic Reviews 2022, Issue 2. Art. No.: CD014567.
DOI: [10.1002/14651858.CD014567](https://doi.org/10.1002/14651858.CD014567).

www.cochranelibrary.com

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[Intervention Protocol]

Cannabis-based medicines for prevention of postoperative nausea and vomiting in adults

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Editorial group: Cochrane Anaesthesia Group.

Publication status and date: New, published in Issue 2, 2022.

Citation: Stojanova J, Pérez-Bracchiglione J, Erridge S, Madrid E, Caracci B, Klabunde R, Franco JVA. Cannabis-based medicines for prevention of postoperative nausea and vomiting in adults (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 2. Art. No.: CD014567. DOI: [10.1002/14651858.CD014567](https://doi.org/10.1002/14651858.CD014567).

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and safety of cannabis-based medicines, compared to placebo or an alternative treatment strategy, for preventing nausea and vomiting during the postoperative period among adults undergoing elective surgery.

BACKGROUND

Description of the condition

Postoperative nausea and vomiting (PONV) following surgery and general anaesthesia are important self-reported outcomes (Macario 1999). They occur in up to 30% of people during the postoperative period without the co-administration of antiemetics (Kranke 2011). The incidence rises to 80% in people at high-risk (Kovac 2013). The pathophysiology of PONV is complex, involving both peripheral and central receptors. The ‘functional vomiting centre’, commonly known as the ‘vomiting centre’, is activated by projections from the chemoreceptor trigger zone, cortical structures, gastrointestinal vagal afferents, and the vestibular system (Cao 2017; Horn 2014; Wiesmann 2015). Specific stimuli that hijack these pathways in the perioperative period, include surgical trauma and inflammation, inhalational anaesthetics, opioids, and altered gastrointestinal motility (Horn 2014). Anaesthetic technique has a key role in the occurrence of PONV. Nitrous oxide results in an increased likelihood of severe nausea and vomiting in the presence of other risk factors (Sun 2015). There is supporting evidence that the reduction in volatile anaesthetic use, with either regional anaesthesia or total intravenous anaesthesia, also reduces severe PONV (Tramèr 1997; Wiesmann 2015; Ziemann-Gimmel 2014).

PONV result in a substantial burden on quality of life for people undergoing surgery. It also increases utilisation of healthcare resources, as it is associated with prolonged recovery stay and hospital admission, readmission for ongoing nausea and vomiting following discharge, and increased healthcare costs (Gan 2014; Kranke 2011; Parra-Sanchez 2012; Wiesmann 2015). PONV can also cause serious adverse effects (aspiration of vomitus, electrolyte imbalances and dehydration, wound dehiscence, herniations, and reactive haemorrhage); however, these are uncommon (Cao 2017). Administration of perioperative antiemetics can reduce the incidence and severity of PONV, although they are not without their limitations, side effects, and associated costs (Wiesmann 2015). In addition to typical antiemetics, dexamethasone is widely used for prophylaxis; however, the implications of corticosteroid use in the postoperative environment on wound healing and glucose control are currently unclear (Polderman 2018). A Cochrane Review compared the efficacy and safety of different prophylactic antiemetics in a network meta-analysis (Weibel 2020). It includes pharmacological agents with direct antiemetic activity, but does not include cannabis-based medicines. Alternative therapies, such as aromatherapy or acupuncture, have been trialled for treatment and prevention of PONV, respectively. While aromatherapy has not been demonstrated to provide any benefit beyond placebo, acupuncture with stimulation of the PC-6 acupoint has been shown to have similar efficacy to traditional antiemetics (Hines 2018; Lee 2015).

Description of the intervention

Over one hundred compounds with human protein receptor targets have been derived from the cannabis plant (Russo 2017).

(-)-*trans*- Δ^9 -tetrahydrocannabinol (THC) is one of the most widely studied cannabinoids, as it typically forms a heavy component of recreational cannabis use, and has pharmacological targets both within and outside the endocannabinoid system (Russo 2017). Dronabinol is a synthetic isomer of THC, and as a result, has similar chemical properties (Russo 2017).

THC is a partial agonist of the cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors (Pacher 2006). Their activation can modulate THC's actions as an anti-nociceptive and anti-inflammatory agent (Russo 2017). Extensive data on THC's side effect profile are derived from its use as a recreational drug rather than clinical use. Nevertheless, THC is known to have potent effects on appetite stimulation, generating euphoria, and causing a dry mouth (Russo 2006).

Cannabidiol (CBD) is the most abundant phytocannabinoid, which acts primarily outside the endocannabinoid system (Russo 2017). As such, it lacks the euphoric effects of THC and other more potent agonists of CB1 and CB2. It appears to act through different mechanisms to THC, such as adenosine signalling and serotonin channels, to produce anti-inflammatory and antiemetic effects (Mechoulam 2007). CBD exhibits a well-tolerated side effect profile. Notably, it has been shown to modulate the effects of both THC and the endocannabinoid system itself. Consequently, cannabis-based medicines can exhibit varying side effect profiles, depending on the levels of both THC and CBD (Li 2019; Russo 2006). Other compounds found within the cannabis plant, such as other cannabinoids, terpenes, and flavonoids, may affect the therapeutic properties and side effects of non-synthetic cannabis-based medicines.

Cannabis-based medicines are approved for limited and very specific indications, and approval and availability vary between countries. A survey by the European Pain Federation highlighted that cannabis-based medicines are not approved or available locally in many European countries (Krcovski-Skvarc 2018). THC/CBD oromucosal spray was approved in 21 European countries and Israel. Dronabinol and nabilone were both approved in Austria, Germany, Ireland, and Serbia; dronabinol was approved in Croatia and Denmark, while nabilone was approved in the United Kingdom. Twelve countries indicated there was no agent available locally, and 11 were not represented, as some members did not respond, or the countries were not member chapters of the Federation. Dronabinol and nabilone are approved by the United States Food and Drug Administration (FDA) for refractory nausea and vomiting associated with cancer chemotherapy, and dronabinol is also licensed for the treatment of anorexia associated with weight loss in people with AIDS (Whiting 2015).

A number of formulations of cannabis-based medicines are available. These including oral capsules (CBD, THC, CBD/THC combinations, dronabinol, nabilone), oromucosal spray (CBD, THC, CBD/THC combinations), and vaporised or smoked (cannabis, THC (Whiting 2015)). We anticipate that oral capsules or oromucosal sprays are the most likely modes of administration in the surgical setting.

Several recent systematic reviews have found more adverse events with cannabis-based medicines in the context of various, primarily chronic, indications (Aviram 2017; Mücke 2018; Whiting 2015). Mücke and colleagues evaluated cannabis-based medicines for chronic neuropathic pain, and found that greater participant withdrawal occurred with cannabis-based medicines compared to placebo. Further, nervous system adverse events and psychiatric disorders were more frequent with these medicines. Serious adverse events were not found to differ (Mücke 2018). In the context of numerous pain indications, including postoperative pain, chronic non-cancer pain, and cancer pain, Aviram 2017 found adverse events most notably affected the central nervous and gastrointestinal systems. Gastrointestinal adverse

events occurred more frequently with oral and oromucosal formulations compared to inhaled formulations. A frequently cited review evaluated cannabis-based medicines in multiple chronic indications, the most common of which were nausea and vomiting due to chemotherapy, chronic pain, and spasticity due to multiple sclerosis or paraplegia (Whiting 2015). Adverse events were reported in 62 of 79 included studies. The authors initially conducted a meta-regression and stratified analysis for findings related to any adverse event, and found no evidence of differences due to type of cannabinoid, study design, indication, comparator, or duration of follow-up. They then combined reports for further analyses of the adverse events. There was an increased risk of short-term adverse events with cannabinoids, including any adverse events, serious adverse events, withdrawals due to adverse events, and numerous specific adverse events. Common adverse events included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination. The authors noted that for studies evaluating multiple doses, the highest dose was chosen to represent the 'worst-case scenario'.

While concerns about adverse events may influence the decision to use cannabis-based medicines more widely, the contexts are complex, and do not represent the relatively short-term postoperative period. Further, it is difficult to mask the feeling these medicines might produce, thus, incomplete blinding could constitute a limitation to adverse event estimates, especially those that are subjective (Aviram 2017).

Abdallah and colleagues evaluated cannabinoids for acute post-surgical pain management and included 12 studies, four of which were observational designs, judged to be of good quality with the Newcastle-Ottawa scale. The most commonly reported adverse events across studies were blurred vision, change of mood, dizziness, drowsiness, dry mouth, hallucinations, headaches, hypotension, and nausea; however, only hypotension occurred more frequently in cannabinoid-treated participants compared to those treated with the control (odds ratio (OR) 3.24, 95% confidence interval (CI) 1.12 to 9.36; Abdallah 2020). Effect estimates for a number of adverse events exhibited a high degree of heterogeneity, notably for dizziness and drowsiness.

How the intervention might work

The endocannabinoid system comprises specific cannabinoid receptors and neurotransmitters, and is involved in the regulation of numerous physiological processes, the detail of which are only partially elucidated (Di Marzo 2015). Cannabinoids block both acute and delayed emesis, primarily mediated by CB1 receptors (Sharkey 2014). Administration of CB1 receptor antagonists causes nausea and vomiting (Darmani 2001; Kipnes 2010).

The antiemetic properties of cannabis have been extensively reviewed (Sharkey 2014). The antiemetic capacity of individual phytocannabinoids and synthetic cannabinoids have been evaluated in a variety of models of nausea and vomiting. This includes THC and synthetic analogues (Darmani 2001), and THC's precursor, tetrahydrocannabinolic acid, which exhibits greater potency (Rock 2013). Precursor cannabidiolic acid (CBDA) also prevents vomiting better than CBD in preventing vomiting, within a specific dose range (Bolognini 2013). Synergy has been demonstrated with the use of combinations of sub-threshold doses of THC, CBD, and CBDA (Rock 2015).

Cannabis-based medicines have a long history of use for the treatment of nausea and vomiting in cancer patients receiving chemotherapy. A Cochrane Review concluded that cannabinoids may be useful for treating refractory chemotherapy-induced nausea and vomiting (Smith 2015). The 23 included trials were conducted between 1975 and 1991, and the review authors noted that chemotherapy and antiemetic strategies across studies likely did not reflect best practices at the time of publishing.

Why it is important to do this review

PONV are significant outcomes in the postoperative period due to their frequency, clinical impact, and effect on the person's satisfaction (Macario 1999). Despite the availability of multiple prophylactic antiemetic strategies, PONV remain an important clinical challenge. Therefore, it is important to determine new prophylactic strategies to improve a person's outcomes as alternatives to existing antiemetics, or to complement multi-modal approaches. A recent rapid review, evaluating nabilone for nausea, identified a single randomised controlled trial that compared it to placebo for preventing PONV (Ho 2019). Although this review suggests a limited number of primary studies on the topic, it specifically focused on nabilone.

Although cannabis-based medicines are rarely used in clinical practice, recent investigation into public perceptions suggest that participants would accept them in mainstream medicine. In the context of acute postoperative pain, participants reported they would be willing to try cannabis-based medicines, with 81% stating they believe they would be effective (Khelemsky 2017). A UK population study reported that 76% of participants would take cannabis-based medicines if prescribed (Public Perceptions to Cannabis). Further, recent legislative changes to facilitate access to cannabis-based medicines for specific indications globally have stimulated research efforts (Pacula 2017). Therefore, we anticipate emerging evidence and results from ongoing studies that address the use of cannabis-based medicines to prevent PONV.

OBJECTIVES

To assess the efficacy and safety of cannabis-based medicines, compared to placebo or an alternative treatment strategy, for preventing nausea and vomiting during the postoperative period among adults undergoing elective surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) comparing synthetic or plant-derived cannabis-based medicines against either placebo or active agents for the prevention of postoperative nausea and vomiting (PONV). We will also include RCTs that evaluate the efficacy of cannabis-based medicines for other indications related to surgical prophylaxis, and report postoperative nausea or vomiting as secondary, exploratory, or safety outcomes.

We will exclude quasi-experimental studies. We will exclude cross-over or cluster-randomized controlled trials. We do not expect to find trials of these designs, given the clinical context. For the former, two separate instances of surgery are required to take place, and therefore, would complicate study execution.

For cluster-randomised trials, participants in a cluster often respond similarly, and data from individuals cannot be assumed to be independent, thus requiring analysis that takes this into consideration. We foresee it is unlikely that cluster-randomised trials would be undertaken, as the usual benefits of this design, namely evaluating group effects or avoiding contamination, would not apply. It is unlikely that cluster randomisation would be applied for convenience, as it is straightforward to apply the intervention and ensure blinding in a traditional parallel design.

We will not restrict study selection based on language or publication status (full publication, abstract, or unpublished data).

Types of participants

We will consider all studies that include adults (aged ≥ 18 years) who underwent any elective (non-emergency) surgical procedure under general anaesthesia.

Types of interventions

We will include studies evaluating the efficacy of any form of plant-derived and synthetic cannabis-based medicines for the prevention of PONV, including studies that use any dosage and method of administration, compared to no treatment, placebo, or an alternative antiemetic. We will accept any type of co-intervention when provided similarly in the experimental and control groups. We will include studies in which the intervention was administered before the onset of postoperative nausea or vomiting, and exclude studies administering the intervention continuously throughout the postoperative period. We will also exclude studies in which the intervention might have been administered prior to hospitalisation for surgery.

Types of outcome measures

Primary outcomes

1. Postoperative vomiting: number of participants with at least one discrete episode in an observation period of 0 to 24 hours $\pm$ 6 hours following surgery
2. Postoperative nausea: number of participants with at least one discrete episode reported subjectively, or as a study-defined threshold on a continuous scale, in an observation period of 0 to 24 hours $\pm$ 6 hours following surgery. Studies reporting only the combined end point of PONV will be considered as nausea only.
3. Any adverse events, as defined by the authors: number of participants with at least one event in the observation period (up to seven days following surgery).

Secondary outcomes

1. Early postoperative vomiting (0 to 2 hours following surgery)
2. Early postoperative nausea (0 to 2 hours following surgery)
3. Any serious adverse events reported, as defined by the authors, including death, admission to high-dependency unit, or postoperative cardiac or respiratory complication: number of participants with at least one serious event in the observation period (up to seven days)
4. Acute psychosis and acute confusional state (delirium): number of participants with at least one event in the observation period (up to seven days)
5. Psychological adverse events potentially related to the intervention, including psychological high and

euphoria: number of participants with at least one event in the observation period (up to seven days)

6. Cardiovascular adverse events including hypotension and tachycardia: number of participants with at least one event in the observation period (up to seven days)
7. Quality of surgical recovery assessed by any means, determined within seven days post-surgery. We expect assessment by scales, such as the Quality of Recovery Questionnaires (9-, 15- and 40-item versions) and the Post-operative Quality Recovery Scale (Bowyer 2014; Myles 2016; Royse 2010).
8. Use of any medication to treat nausea and vomiting: number of participants treated in an observation period of 0 to 24 hours $\pm$ 6 hours following surgery
9. Severity of PONV occurring within 24 hours postoperatively, assessed by a validated scale, such as the PONV Intensity Scale long form (Wengritzky 2010), or simplified version (Myles 2012)

Search methods for identification of studies

Electronic searches

We will identify RCTs by performing a search as described in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2021). We will not restrict on language, publication year, or publication status and we will search for relevant systematic reviews on the same topic.

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; latest Issue);
- MEDLINE Ovid SP (1946 to date of search);
- Embase Ovid SP (1974 to date of search);
- Web of Science (1945 to date of search);
- Scopus (2004 to date of search).

A draft search strategy for MEDLINE is presented in [Appendix 1](#), and will be appropriately modified for other databases.

Searching other resources

We will manually search bibliographic references and citations of primary studies and relevant reviews for further references to trials that meet our inclusion criteria. We will also search:

- ClinicalTrials.gov (www.clinicaltrials.gov);
- The World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/);
- ISRCTN (www.isrctn.com/);
- Open Grey for grey literature (opengrey.eu/); and
- Google Scholar (scholar.google.com/)

We will search for errata or retractions from included studies in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Retraction Watch Database (<http://retractiondatabase.org>).

We plan to identify ongoing studies and those awaiting publication by performing a search in clinical trial databases prior to concluding the review.

When necessary, we will contact trial authors for additional information.

Data collection and analysis

Selection of studies

We will use Covidence, an online software for review management, to undertake the study selection process ([Covidence](#)). Two review authors (of JS, SE, JPB, RK, BC) will independently screen search results (titles and abstracts) to identify potentially relevant studies for full-text evaluation. Two authors (of JS, SE, JPB, RK, BC) will independently investigate the full text of all potentially relevant records, will map records to studies, and will classify studies as included, excluded, awaiting classification, or ongoing. We will resolve any discrepancies through consensus, or consult a third review author (EM or JF). We will document reasons for exclusion. We will present an adapted PRISMA flow diagram showing the process of study selection ([Page 2021](#)).

Data extraction and management

The study team will design a standardised data collection form for data extraction in sufficient detail to populate comprehensive Characteristics of studies and risk of bias tables. We will use the same form to extract outcome data for meta-analyses, and eventual subgroup analyses. We will pilot the form before we agree on the final version (current draft in [Appendix 2](#)). We will use Covidence software for data extraction, with data fields based on the final version of the form ([Covidence](#)).

Four review authors (of JS, SE, JPB, RK, BC) will independently extract data, using the final version of the form; two review authors will extract data from each included study. Conflicts will be resolved by discussion and consensus between the pair of review authors involved, and a third review author will be consulted for disagreements (EM or JF). We will contact study authors when there are missing data, or we need further clarification about the data.

We will extract the following study characteristics:

- Identification of the study: reference(s) of all reports linked to the same study (e.g. duplicated references), as well as other secondary sources of relevant data (e.g. online supplements, or registered trials). We will record study duration, design, setting (hospital-based or ambulatory), country, number of centres (i.e. single or multicentre), location, and period of study.
- Participants: eligibility criteria (as stated by study authors), demographic data (age, sex, ethnicity), relevant clinical baseline data (clinical condition, prior use of cannabis, type of surgery, body mass index, smoking status, comorbidities), data related to the operation, and preoperative risks of PONV. We will also record number of randomised participants, dropouts, and number of participants who were finally analysed.
- Intervention: detailed description of the intervention (cannabis-based medicines, plant-derived or synthetic, of any formulation), dosage, route of administration, administration schedule, and co-medications, when appropriate
- Control group: detailed description of the control group and the corresponding category of comparison: 1) no intervention, sham, or placebo; 2) treatment with other intervention for PONV, and possibly 3) comparisons of two different forms of cannabis-based interventions, if appropriate
- Outcomes: we will record all details about the primary and secondary outcomes of interest, including how they were measured and reported, specifying the instrument of measure,

and time point(s) reported. We will extract data on all relevant results: crude number of events or rates, mean values or mean change from baseline and its standard deviation (SD), and population analysed in each study arm.

- Risk of bias: details on method of treatment allocation and concealment, blinding of the intervention and the outcome assessor, dropouts (number, distribution, and reasons), and study population of analysis. We will compare the outcomes in the published reports to outcomes initially reported in protocols or pre-trial registry entries, to assess the risk of selective reporting bias.
- Funding and any potential conflicts of interest, either disclosed or undisclosed. We will attempt to contact authors of the original trials to request further details when necessary.

One review author (JS) will transfer data to Review Manager Web (RevMan Web ([Review Manager Web 2020](#))). Another author will verify data entry by comparing the source data and the data in RevMan Web (JPB).

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of included studies using the RoB 2 tool ([Higgins 2021b](#); [Sterne 2019](#)). The RoB 2 tool includes five domains, which each include up to seven signalling questions, to ensure that all aspects that may influence risk are considered. The domains of RoB 2 are:

- Risk of bias arising from the randomisation process
- Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
- Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
- Missing outcome data
- Risk of bias in the measurement of the outcome
- Risk of bias in the selection of the reported result

We will assess the risk of bias of RCTs using the RoB 2 tool for the following outcomes:

1. Postoperative vomiting: number of participants with at least one discrete episode in an observation period of 0 to 24 hours $\pm$ 6 hours following surgery
2. Postoperative nausea: number of participants with at least one discrete episode reported subjectively, or as a study-defined threshold on a continuous scale, in an observation period of 0 to 24 hours $\pm$ 6 hours following surgery
3. Any adverse events, as defined by the authors: the number of participants with at least one event in the observation period (up to seven days following surgery)

We will consider the effect of interest to be the effect of assignment to the interventions at baseline, regardless of whether the interventions were received as intended (the intention-to-treat effect).

Two review authors (of JS, SE, JPB, RK, BC) will independently determine the design characteristics relating to each domain, and will enter them into the RoB 2 tool, reaching judgements per domain, based on the tool's algorithm. Conflicts will be resolved by discussion and consensus, or by consultation with the author team

as required. When reporting is unclear, we will contact investigators or the study sponsor to clarify key features.

We will base the overall risk of bias judgement on the five domains: we will categorise studies with all domains assessed as low risk at low risk, and categorise those with any domains assessed as high risk, at high risk. If we assess multiple domains as having some concerns, we may classify the overall judgement at high risk, if they indicate lower confidence in the result. If we need to override judgements proposed by the RoB 2 tool, we will provide a justification.

We will create a risk of bias table to present our assessment, and provide detail for each judgement for transparency and reproducibility. Where assessments are based on unpublished data or correspondence with study investigators, we will provide a footnote with the table. We will also present risk of bias appraisals within the forest plots, alongside the effect estimates for individual studies included in the analysis.

Whenever considering treatment effects across studies, we will take into account the risk of bias for the studies contributing to that outcome.

We will use the RoB 2 Excel tool to record and manage our RoB 2 assessments, processes, and final judgments, available at www.riskofbias.info/ (Sterne 2019). We will make the data available on an [online data repository](#). We will present consensus decisions for the signalling questions as supplemental data.

Measures of treatment effect

We will express dichotomous data for each arm of a study as a proportion or risk, and the treatment effect as a risk ratio (RR) with 95% confidence interval (CIs).

We will express pooled continuous data for each arm as a mean and SD, and treatment effect as mean difference (MD) if outcomes are measured the same way across trials. We will assume that final values for differences in the mean will, on average, be the same as differences in mean change scores (Higgins 2021a). For continuous variables, when different instruments or scales were used across studies, we will combine MDs and analyse using the standardised mean difference (SMD). We will analyse continuous outcomes as mean change from baseline. For studies that report baseline and end point data, we will calculate the SD of the mean change from baseline, based on reported CIs, and use these values in the analysis (Higgins 2021a). For studies with insufficient information to calculate SDs (e.g. studies that present results in graphs or only end point mean values), we will present their results separately.

Unit of analysis issues

If we find studies with more than two intervention groups, we will initially determine whether all comparisons are relevant to the review, and exclude those that are not. In the event more than one comparison is relevant, we will consider combining groups in which different cannabis-related interventions were applied. In the event that we are able to conduct meta-analyses for different types of cannabis-related interventions, we will split the comparator group into two or more groups, as appropriate (Higgins 2021c).

Dealing with missing data

We will endeavour to contact trial authors or sponsors of included studies to request missing data. When we are unable to obtain them, we will attempt to calculate missing standard deviations or correlation coefficients using available data (Altman 2005).

If possible, we will calculate missing SDs using other data from the trial, such as CIs, using the RevMan Web calculator (Review Manager Web 2020). When this is not possible, and missing data are thought to introduce serious bias, we will conduct a sensitivity analysis to explore the impact of including such studies in the overall assessment (see [Sensitivity analysis](#)).

If data remain unavailable, we will conduct an available case analysis by excluding data points that are unavailable.

If results from scales are reported as medians, we will contact study authors, and if unable to determine the mean, estimate it based on formulas that consider the sample size (Hozo 2005; Weir 2018), following the guidance from the *Cochrane Handbook* (Deeks 2021).

Assessment of heterogeneity

We will assess clinical heterogeneity by reviewing the interventions across studies, and the clinicopathological characteristics of included participants to assess for substantial differences, as described below.

We will visually inspect forest plots to consider the direction and magnitude of effects and the degree of overlap between CIs. We will also use the χ^2 test and the I^2 statistic to assess statistical heterogeneity. The threshold value for the χ^2 test we plan to use is $P < 0.10$. We will use the I^2 statistic to quantify heterogeneity not attributable to chance among the trials in each analysis, but acknowledge that there is substantial uncertainty in the value of I^2 , when the number of studies included is small. We will follow the following recommendations for thresholds (Deeks 2021):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100%: may represent considerable heterogeneity.

If we identify substantial and considerable heterogeneity, we will report it and explore possible causes, using prespecified subgroup analysis (see [Subgroup analysis and investigation of heterogeneity](#)). Ultimately, we may decide that a meta-analysis should be avoided (Deeks 2021).

Assessment of reporting biases

We will assess reporting bias by comparing outcomes prespecified in pre-trial registry entries or protocols (where available) to outcomes reported in final manuscripts. If registry entries or protocols are unavailable, we will assess reporting bias by comparing outcomes specified in the methods section to those reported in the results section.

If we are able to pool more than 10 trials in the meta-analyses for an outcome, we will create and examine a funnel plot as a means to explore possible small study biases. If funnel plot asymmetry is detected, for dichotomous outcomes, we will test asymmetry with

the Harbord test ([Harbord 2006](#)). For continuous outcomes, we will use the regression asymmetry test ([Egger 1997](#)).

Data synthesis

We will undertake meta-analyses to pool data only when it is meaningful to do so (i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense ([Deeks 2021](#))). If considerable clinical heterogeneity exists between studies, we will summarise effect estimates across studies, and present these in a structured table of results ([McKenzie 2021](#)). We will use the statistical software in RevMan Web to conduct our meta-analyses ([Review Manager Web 2020](#)).

We will assess intervention effects with both random-effects meta-analyses ([DerSimonian 1986](#)), and fixed-effect meta-analyses ([Demets 1987](#)). We will use the more conservative point estimate of the two. If the two estimates are similar, we will use the estimate with the widest CI.

For studies with no events in one or more arms, and studies with no events in either arm, we will calculate using 0.5 in the place of zero. We will choose a statistical method for meta-analyses of odds ratios considering comparator group risk, the probable size of the treatment effect, and balance in the numbers of experimental and comparator groups, following the guidance from the *Cochrane Handbook* ([Higgins 2021a](#)), and a recently proposed framework for choosing an appropriate synthesis method ([Xu 2021](#)).

Subgroup analysis and investigation of heterogeneity

If data permit, we plan to carry out the following exploratory subgroup analyses for each outcome:

- by type of specific cannabis-based medicine of a similar formulation and dose range
- type of elective surgery

We may conduct meta-regression analyses to evaluate dose-response effects if we find two or more studies in which participants were randomised to one of two doses within the same study, or we observe a consistent relationship across similar studies. We are mindful not to draw conclusions about the absence of an effect in this scenario, given that these analyses typically lack power to detect true effects. We will consider dose-response effects as a possible explanation for heterogeneity ([Higgins 2021a](#)).

Sensitivity analysis

We will include all trials in overall analyses, but we will conduct a sensitivity analysis excluding trials exhibiting a high risk of bias. If results are similar, we will base our primary conclusions on the overall analysis. If they differ, we will base our primary conclusions only on trials exhibiting a low risk of bias. We will also perform a set of sensitivity analyses to explore the impact of imputing missing data.

To assess the potential impact of missing data for dichotomous outcomes, we will perform the following sensitivity analyses when assessing each dichotomous outcome:

- ‘Best-worst-case’ scenario: we will assume all lost to follow-up participants in the experimental group had a favourable result in each of the outcomes, and participants lost to follow-up in the control group had a negative result.

- ‘Worst-best-case’ scenario: we will assume all participants lost to follow-up in the experimental group had a negative result in each of the outcomes, and participants lost to follow-up in the control group had a favourable result.

To assess the potential impact of missing SDs for continuous outcomes, we will conduct the following sensitivity analysis:

- Where SDs are missing, and it is not possible to calculate them, we will impute SDs from trials with similar populations and a low risk of bias. If we do not find such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings (SoF) table for the following outcomes:

1. Postoperative vomiting: number of participants with at least one discrete episode in an observation period of 0 to 24 hours $\pm$ 6 hours following surgery
2. Postoperative nausea: number of participants with at least one discrete episode reported subjectively, or as a study-defined threshold on a continuous scale, in an observation period of 0 to 24 hours $\pm$ 6 hours following surgery
3. Any adverse events, as defined by the authors: number of participants with at least one event in the observation period (up to seven days following surgery)
4. Any serious adverse events: number of participants with at least one serious event in the observation period (up to seven days following surgery)
5. Cardiovascular adverse events including hypotension and tachycardia: number of participants with at least one event in the observation period (up to seven days following surgery)

A template SoF table is presented in [Appendix 3](#) ([Schünemann 2021](#)). Each table will include the effect size (RR, pooled MD, or SMD, as appropriate), number of participants and studies, the certainty of the evidence, and notable comments.

We will use the GRADE approach to assess the certainty of the body of evidence (overall risk of bias, consistency of effect, indirectness, imprecision, and publication bias) for each of the prespecified outcomes, and will produce SoF tables using GRADEpro software ([GRADEpro; Guyatt 2008](#)).

We will justify our decisions to downgrade the certainty of the evidence from studies for a given outcome in footnotes. Two of three review authors (JS, JPB, RK) will independently make these judgements, and we will resolve disagreements by discussion, or involving a third review author (EM or JF). We will incorporate the GRADE judgements about the certainty of the evidence in our reporting of the results.

We plan to extract data, format comparisons in data tables, and prepare a summary of findings table to be discussed prior to writing the results and conclusions of our review.

ACKNOWLEDGEMENTS

The authors would like to thank Stefi Weibel (Content Editor), Xing Jie (Statistical Editor), Winfried Hauser, Maximilian Schaeffer,

and Rune Frederiksen (Peer Reviewers), Janne Vendt (Information Specialist), Teo Quay and Vernon Hedge (Managing Editors), and Andrew Smith (Co-ordinating Editor) for their help and editorial advice during the preparation of this protocol.

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APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) ALL

- 1 Medical Marijuana/
- 2 Cannabis/
- 3 exp Cannabinoids/
- 4 cannabi*.mp.
- 5 mari?uan*.mp.
- 6 ganja.mp.
- 7 ganjas.mp.
- 8 nabilo*.mp.
- 9 CBD.mp.
- 10 DMH-11C.mp.
- 11 tetrahydrocannab*.mp.
- 12 THC.mp.
- 13 dexanabinol.mp.
- 14 ajulemic.mp.
- 15 dronabinol.mp.
- 16 nabiximol*.mp.
- 17 sativex.mp.
- 18 endocannabi*.mp.
- 19 levonantradol.mp.
- 20 (faah and (inhibitor or hydrolase)).mp.
- 21 PF-04457845.mp.
- 22 fatty acid am?d hydrolase.mp.
- 23 cannador.mp.
- 24 benzopyranoperidine.mp.
- 25 nabitan.mp.

26 nabutam.mp.

27 SP-106.mp.

28 marinol.mp.

29 Cesamet.mp.

30 Canemes.mp.

31 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

32 "Postoperative Nausea and Vomiting"/

33 ponv.mp.

34 (surg* or operat* or perioperat* or peroperat* or intraoperat* or postoperat* or an?ssthe*).mp.

35 exp Surgical Procedures, Operative/ or exp Specialties, Surgical/ or perioperative care/ or intraoperative care/ or exp perioperative period/ or exp intraoperative period/ or surgery.fs. or exp Anesthesia/

36 32 or 33 or 34 or 35

37 31 and 36

38 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)

39 37 and 38

Appendix 2. Draft Data Collection Form

CARG 1000: Cannabis-based medicines for prevention of postoperative nausea and vomiting in adults

Study identification

Name (1st author) – year of publication

Acronym

Title (paper)

Reference

NCT

Secondary papers linked to this study

Eligibility criteria

	YES	NO
1. Type of study:		
Randomized or quasi-randomized trial?		
1. Participants:		
Undergone any elective (non-emergency) surgical procedure?		
Procedure performed under general anaesthesia?		
Adults? (aged ≥ 18 years)		
1. Intervention:		
Plant-derived or synthetic cannabis-based medicine?		
1. Outcomes:		
Any of:		
a. Postoperative nausea (in PACU or during admission)		
b. Postoperative vomiting (in PACU or during admission)		
c. PONV severity determined by any scale		
d. Use of antiemetics		
1. Included?		
a. Pending		
<i>If pending, comment:</i>		

To be included, all answers should be YES.

Study population (baseline characteristics)

	Cannabis-based medicine	Comparator
Age (year), mean		
Sex (%)		
Type of surgery (%)		
Gynaecological		
Laparoscopic		

(Continued)

Breast

Urological

Orthopaedic

Other

Length of operation (min), mean

Pre-op risk score for PONV (score), mean

(e.g. Apfel risk factors) – specify

Prophylactic antiemetics

Mean (SD)

None

1

>1

Intervention (description)

Copy and paste the text where full description of the intervention is provided

If the study has ≥ 1 experimental group, specify details for each group (copy and paste this same table).

Details

Name of product used

Active principle(s) (where appropriate)

Dose and administration scheme

Route of administration

Comparison: control group

Copy and paste the text where full description of the control group is provided

Type of control group:

Comparison 1

Not specified (control)

No intervention (standard care)

Placebo or sham intervention

Comparison 2

Other active treatment (specify)

Outcomes measured by the study

Name the outcome, measure, and time point(s) (specify the end point)

Primary outcome(s)

Clinicaltrials.gov

Reported in the paper

Secondary outcome(s)

Clinicaltrials.gov

Reported in the paper

(Continued)

Study design

Copy and paste the text where full description of the inclusion/exclusion criteria is provided

Country

Unicentre vs multicentre

Number of study arms

Study population – total randomised (N)

Period of recruitment

Follow-up (length of the study)

Short-term (admission)

Long-term (outcomes beyond admission)

Funding

Design: parallel groups/other (specify)

Sample size:

- Based on outcome?
- Assumed rate in the control group?
- Expected difference to be detected?

RISK OF BIAS

Dimension	Judgement	Description
	High / low / some concerns	(copy-paste)
Risk of bias arising from the randomisation process		
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		

(Continued)

Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Missing outcome data

Risk of bias in measurement of the outcome

Risk of bias in selection of the reported result

Total number (N, %)

Distribution (balance)

Reasons reported

Population of analysis: intention-to-treat (ITT), per protocol, ITT modified

Imputation of missing values

Sensitivity analysis

Overall risk of bias:

Results (outcomes data): Binary data

For each study group, extract number of events (**n**), total number randomised (**Nr**), and number of analysed (**Na**), and at the end point (TF).

- Example: 4/48/46

If no **crude data** are provided (results are presented only in a Figure or a Graph), specify.

If crude data are obtained from a different source (e.g. supplement online), specify.

Outcome:

Time point:

Experimental			Control		
n	Nr	Na	n	Nr	Na
TF					

Was a subgroup analysis performed in the study for this outcome? Which variables were assessed?

Results (outcomes data): Continuous data

For each study group, extract the mean, the standard deviation (SD) or 95% confidence interval (95CI), total number randomised (**Nr**), and number of analysed (**Na**), at baseline (**T0**) and at the end point (TF).

- Example: (TF) 8(2.1)/48/46

If median and interquartile range are provided instead of mean and SD, specify.

If there is an additional long-term assessment beyond the end point, extract data (TL).

If no **crude data** are provided (results are presented only in a Figure or a Graph), specify.

If crude data are obtained from a different source (e.g. supplement online), specify.

Outcome:

Time point:

Experimental				Control			
mean	SD	Nr	Na	mean	SD	Nr	Na
T0							
TF							

Was a subgroup analysis performed in the study for this outcome? Which variables were assessed?

Appendix 3. Draft summary of findings table

Table XX Summary of findings table - draft

Patient or population: adults undergoing elective surgery

Setting: hospital

Intervention: synthetic or plant-derived cannabis-based medicines

Comparison: placebo or active agents

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	...of par- ticipants (studies)	Certain- ty of the evidence (GRADE)	Comments
	Risk with control	Risk with in- tervention				
Postoperative vomiting						
Postoperative nausea						
Any adverse events						
Any serious adverse events						
Cardiovascular adverse events						

CONTRIBUTIONS OF AUTHORS

Jana Stojanova (JS), Javier Pérez Bracchiglione (JPB), Juan Franco (JF), Eva Madrid (EM), Bruno Caracci (BC), Simon Erridge (SE), and Rachel Klabunde (RK) authored the protocol.

JS developed the search strategy, together with Janne Vendt (Cochrane Information Specialist)

Conceiving the review: SE

Designing the review: SE, JS

Co-ordinating the review: JS

Undertaking manual searches: JS, JPB, RK

Screening search results: JS, JPB, RK, BC, SE

Organizing retrieval of papers: JS, JPB, RK

Cannabis-based medicines for prevention of postoperative nausea and vomiting in adults (Protocol)

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Screening retrieved papers against inclusion criteria: JS, JPB, RK

Appraising quality of papers: JS, JPB, RK

Abstracting data from papers: JS, JPB, RK

Writing to authors of papers for additional information: JS, JPB, RK

Providing additional data about papers: JS, JPB, RK

Obtaining and screening data on unpublished studies: JS, JPB, RK

Data management for the review: JS, JPB, RK, SE

Entering data into RevMan Web: JS

RevMan Web statistical data: JS, JPB, RK

Other statistical analysis, not using RevMan Web: JS, JPB, RK

Double entry of data: JS, JPB, RK

Interpretation of data: JS, JPB, RK, EM, JF, SE, BC

Statistical inferences: JS, JPB, RK, EM, JF

Writing the review: JS, JPB, RK, EM, JF, SE, BC

Providing guidance on the review: SE, BC, JF

Securing funding for the review: N/A

Performing previous work that was the foundation for the present study: N/A

Guarantor for the review (one author): EM

Person responsible for reading and checking review before submission: EM

DECLARATIONS OF INTEREST

JS, JPB, RK, BC, JF, EM, SE: none known; SE is a clinical research fellow at the Department of Surgery and Cancer, Imperial College London. A research collaboration exists between Imperial College London and Emmac Life Sciences (European-based medicinal cannabis company); no members of the authorship group have received direct financial benefit from the collaboration between Emmac Life Sciences and Imperial. SE has performed paid consultancy work to advise Sapphire Medical Clinics.

SOURCES OF SUPPORT

Internal sources

- Interdisciplinary Centre for Health Studies (CIESAL), Chile
Centre for Research, Development and Innovation financed by Universidad de Valparaíso

External sources

- No sources of support provided