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Medical cannabis for the treatment of insomnia (Protocol)

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[Intervention Protocol]

Medical cannabis for the treatment of insomnia

Lucia B Varela[1,2], Camila Micaela Escobar Liquitay[1], Samanta Díaz Menai[1], Luis Garegnani[1]

[1]Universidad Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. [2]Department of Neurology, Italian Hospital of Buenos Aires, Buenos Aires, Argentina

Contact: Lucia B Varela, lucia.varela@hospitalitaliano.org.ar.

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ABSTRACT

Objectives

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

To assess the effects of medical cannabis on adults with insomnia.

BACKGROUND

Description of the condition

Insomnia involves difficulty initiating or maintaining sleep with associated daytime consequences, not due to environmental factors or inadequate sleep opportunities, as defined by the *International Classification of Sleep Disorders, Third Edition* (*ICSD-3*). Chronic insomnia persists for at least three months, with symptoms occurring at least three times per week, while short-term insomnia lasts less than three months [1]. Insomnia is the most prevalent sleep disorder, with approximately 6% to 10% of the population meeting the criteria for insomnia; up to 25% of adults being dissatisfied with their sleep; and up to 10% to 15% experiencing insomnia symptoms severe enough to cause daytime distress or impairments. Insomnia prevalence increases with age and is twice as prevalent in women as in men [2, 3]. It often presents independently or alongside other medical or psychiatric conditions such as chronic pain, fibromyalgia, cancer, major depression, or substance misuse. It is characterised by dissatisfaction with sleep quality or duration, difficulty falling asleep, waking up at night or too early in the morning, or non-restorative sleep, leading to daytime fatigue, low energy, cognition issues, and mood disturbances [2, 4].

Despite its high prevalence and burden, insomnia often remains unrecognised and untreated, being a major public health issue due to the associated increased risk for medical (e.g. hypertension), psychiatric (e.g. depression), and occupational (e.g. absenteeism) morbidity and mortality [2]**.** Treatment should be initiated promptly when individuals report sleep disturbances, particularly if these complaints are severe enough to meet the criteria for an insomnia disorder [4]. Treatment options include non-pharmacological therapies, such as cognitive behavioural therapy for insomnia (CBTi) and sleep hygiene education, which are first-line treatments with reported improvement in approximately 60% of patients [5]. Pharmacological therapies include antidepressants (e.g. amitriptyline, trazodone), benzodiazepine receptor agonists (e.g. flurazepam, eszopiclone), and antipsychotics (e.g. quetiapine, olanzapine) [2].

Description of the intervention and how it might work

Cannabis is a genus of flowering plants in the Cannabaceae family, with three recognised species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. These plants, commonly known as marijuana, have been used for millennia for their pain-relieving properties and effects on appetite, sleep, and mood [6]. *Cannabis* contains various compounds, including tetrahydrocannabinol (THC) and cannabidiol (CBD), which are thought to have effects on sleep by modulating the endocannabinoid system [7].

Medical cannabis (MC) is emerging as an alternative treatment option for insomnia. The therapeutic potential of MC is primarily attributed to its interaction with the endocannabinoid system, which is ubiquitous in the animal kingdom and plays a role in maintaining physiological balance [7]. The endocannabinoid system includes cannabinoid receptors and ligands in the peripheral and central nervous systems and other tissues like bones and the immune system [8, 9]. It is involved in various physiological functions, including antinociception, cognition, memory, endocrine function, nausea and vomiting, inflammation, immune recognition, and, notably, sleep [7].

MC products can be categorised into defined cannabinoids such as plant-derived THC or CBD; and herbal cannabis, resins, and extracts, like oils or tinctures with specific contents of THC or CBD, along with other active ingredients (phytocannabinoids other than CBD/THC, such as terpenes and flavonoids) [7]. Recently, MC has gained attention for its reported benefits in improving sleep quality. In clinical settings, MC is primarily administered through oral preparations, including sprays, tablets, and oil drops taken sublingually [10].

However, the use of MC for chronic insomnia and other conditions remains contentious. Many physicians express concerns about the potential risks associated with cannabis use, such as cognitive impairment, dependency, and psychomotor effects [5]. This scepticism is compounded by the lack of robust clinical evidence and guidelines supporting the efficacy and safety of MC for insomnia [11, 12]. Despite these concerns, the use of MC for insomnia is being explored through various research trials, aiming to provide evidence of its effectiveness and safety profile.

Why it is important to do this review

Addressing insomnia is crucial, as it affects 6% to 10% of the adult population, with a higher prevalence in older adults and those with medical or psychiatric conditions [2, 12]. Insomnia significantly impacts individual health and quality of life, and imposes a heavy burden on healthcare systems through increased emergency and office visits, prescription drug costs, and indirect costs like work absenteeism and reduced productivity [12]. Additionally, insomnia is associated with anxiety or depression, as well as lack of impulse control, substance abuse, hypertension, heart failure, and pain, among other conditions [2].

Conventional treatments for insomnia, while effective, often come with adverse effects such as dependence, tolerance, and cognitive impairment, which limit their long-term use [5]. This has led to a growing interest in alternative treatments, including MC. Studies show that MC can potentially improve sleep quality, with some reports highlighting its benefits [5, 8, 9]. However, its use remains controversial due to legal and safety concerns, and the lack of robust evidence supporting its efficacy and safety for insomnia [5, 10].

This question is especially topical given the increasing legalisation and prescriptions of MC worldwide. Although not yet included in the American guideline for managing insomnia [12], and identified as an area lacking sufficient evidence in the European guideline [11], the use of MC for insomnia has become increasingly intriguing in recent years [7]. This interest has prompted the development of several research trials aimed at exploring its potential benefits [2, 4, 7]. Addressing the efficacy and safety of MC for insomnia is critical for patients seeking alternatives to conventional treatments, healthcare professionals aiming to provide effective care, and policymakers tasked with regulating its use [2, 4, 7].

OBJECTIVES

To assess the effects of medical cannabis on adults with insomnia.

METHODS

We will follow the Methodological Expectations for Cochrane Intervention Reviews (MECIR) when conducting the review [13], and PRISMA 2020 for the reporting [14].

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), cross-over trials, and cluster-RCTs, following the guidelines in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [15]. We will exclude quasi-RCTs, following the algorithm outlined in Chapter 24 of the *Cochrane Handbook* [16], due to the availability of RCTs that address our research questions. We define quasi-RCTs as any quantitative study that uses inappropriate strategies of allocating units to intervention groups [16].

Types of participants

We will include adults (older than 18 years old) with a diagnosis of insomnia, using a standardised diagnostic system such as the *Diagnostic and Statistical Manual of Mental Disorders* [17], or the *International Classification of Sleep Disorders* [1]. We will include all participants irrespective of insomnia type (primary insomnia; insomnia associated with comorbid conditions) or duration (chronic or acute insomnia).

If we identify studies in which only a subset of participants is relevant to this review, we will include these studies if data are available separately for the relevant subset, or if more than 80% of participants meet the inclusion criteria.

Types of interventions

We will include studies comparing MC versus placebo or non-MC drugs in people with insomnia.

We plan to investigate the following comparisons of intervention versus comparator.

Intervention

MC such as the following.

- Licenced medical drugs:
  - plant-based cannabinoids (combined THC and CBD (nabiximols (Sativex)) or oral CBD only (Epidiolex));
  - synthetic cannabinoids (nabilone (Cesamet or Canemes) or dronabinol (Marinol or Syndros), both synthetic THC).
- Magistral preparations of cannabis plant derivatives:
  - plant-derived THC or plant-derived CBD;
  - herbal cannabis, resins, and extracts with a defined content of THC or CBD (or both), together with other active ingredients (phytocannabinoids other than CBD/THC, such as terpenes and flavonoids).

We will include these interventions administered at any dose, at any combination or by any route.

Although the distinction between medical and recreational cannabis is primarily regulatory rather than pharmacological, for this review, we define medical cannabis as any cannabis-derived product used for therapeutic purposes [18]. This includes all the interventions described previously.

We will exclude experimental and unregistered drugs, including cannabis receptor antagonists and negative allosteric modulators like rimonabant, as well as modulators that enhance endocannabinoid system activity, such as fatty acid amide hydrolase inhibitors, and synthetic cannabis like levonantradol.

Comparator

- Placebo
- Benzodiazepine receptor agonists: zopiclone, eszopiclone, zolpidem, zaleplone
- Benzodiazepines: short-, intermediate- or long-acting such as diazepam, flunitrazepam, flurazepam, lormetazepam, nitrazepam, triazolam
- Melatonin receptor agonist: fast-release melatonin, ramelteon or prolonged-release melatonin
- Antidepressants: amitriptyline, doxepin, mirtazapine, trazadone
- Antipsychotics: levomepromazine, quetiapine, olanzapine, chlorprothixene, melperone, pipamperone, prothipendyl

We will include comparisons of any drugs that allow for double-blind treatment. We will consider treatments administered in an outpatient setting in any formulation. We will include co-interventions, provided they are not part of the randomised treatment and are comparable in both the intervention and comparator groups, to establish a fair comparison. If a study includes multiple arms, we will include any arm that meets the inclusion criteria for this review.

Outcome measures

We will not exclude a study if it fails to report more than one of our critical or important outcome measures of interest. We will only exclude studies if none of our outcomes of interest is measured, and provided there is evidence to support this (e.g. contact with trial authors, access to the original protocol, etc.).

We will consider all types of measurement including subjective measures (such as participant-reported sleep measures, as well as different types of scores (change from baseline scores, double-blind average scores)) and objective measures (e.g. polysomnography).

Critical outcomes

- Quality of sleep/satisfaction with sleep: measured by the validated scale Pittsburgh Sleep Quality Index (PSQI), a 24-item self-report measure of sleep quality, where poor sleep is a global score > 5, or any other validated tool chosen by the study authors such as the Insomnia Severity Index (ISI), a 7-item rating validated used to assess the patient's perception of insomnia [19], or the Leeds Sleep Evaluation Questionnaire (LSEQ), 10 self-rating 100-millimetre-line analogue questions concerned with aspects of sleep and early morning behaviour [20, 21]. We will analyse the data as continuous data, with the primary measure being the mean change in score from baseline. Additionally, in the case of sufficient information, we will analyse the data dichotomously to assess whether a significant improvement has occurred.
- Total Sleep Time (TST): defined as the total time (in minutes) a person spends sleeping during the in-bed interval and calculated as time in bed minus Sleep Onset Latency and minus Wake After Sleep Onset [21]. It reflects both sleep onset and maintenance effects within a single variable [22]. We will analyse the data as continuous data, with the primary measure being the mean change in score from baseline. Additionally, in the case of

sufficient information, we will analyse the data dichotomously to assess whether a significant improvement has occurred.

- Adverse events: assessed as the frequency of any type of unfavourable symptoms that occurred during the study. It includes symptoms such as somnolence, dizziness, motor or cognitive impairment, euphoria, disorientation, paranoia, hyperemesis, acute respiratory distress syndrome, and any other adverse events reported by the study authors [23].

Important outcomes

- Sleep Onset Latency (SOL): defined as the length of time (in minutes) from lights-out until sleep onset. We will include this, as it is a key indicator of sleep efficiency and the effectiveness of treatments for insomnia. It is measured in minutes using in-laboratory overnight polysomnography or as defined by the study authors. We will analyse the data as continuous data, with the primary measure being the mean change in score from baseline. Additionally, in the case of sufficient information, we will analyse the data dichotomously to assess whether a significant improvement has occurred.
- Wake After Sleep Onset (WASO): defined as the length of time (in minutes) a person remains awake after the onset of sleep until the final awakening. It reflects sleep quality and is crucial for assessing sleep continuity. It is measured in minutes using in-laboratory overnight polysomnography or as defined by the authors. We will analyse the data as continuous data, with the primary measure being the mean change in score from baseline. Additionally, in the case of sufficient information, we will analyse the data dichotomously to assess whether a significant improvement has occurred.
- Daytime functioning: defined as the state of vigilance the day after taking MC. It will be assessed by the Epworth Sleepiness Scale (ESS), a self-administered questionnaire that provides a measurement of the person's general level of daytime sleepiness [24], or by any other validated tool defined by the study authors such as an 11-point Likert scale (0 to 10); the Stanford Sleepiness Scale (SSS), which assesses the level of sleepiness during the day, whereby higher scores are related to a higher degree of sleepiness [25]; or the E Digit Symbol Substitution Task, which assesses attention, working memory, and visuospatial function [26]. They show the impact of treatment on daytime functionality and overall well-being. We will analyse the data as continuous data, with the primary measure being the mean change in score from baseline. Additionally, in the case of sufficient information, we will analyse the data dichotomously to assess whether a significant improvement has occurred.
- Withdrawal symptoms: assessed as the frequency of any symptoms experienced when discontinuing the treatment due to the placebo run-out period or that had already appeared during treatment but deteriorated during the placebo run-out interval. Withdrawal symptoms are crucial for evaluating dependency and the long-term safety of MC treatment.
- Quality of life: assessed by the validated scale EQ-5D or any other validated tool defined by the study authors. The minimal clinically important difference (MCID) for the EQ-5D will range from 0.08 to 0.12 [27]. The established minimum clinical follow-up will be 90 days. We will analyse the data as continuous data, with the primary measure being the mean change in score from baseline. Additionally, in the case of sufficient information, we will analyse the data dichotomously to assess whether a significant improvement has occurred.

If a study reports several scales for a given outcome, we will select the most appropriate and relevant scale (PSQI for quality of sleep/satisfaction with sleep, ESS for daytime functioning, and EQ-5D for quality of life), following the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Table 9.3.c, MECIR Box 3.2.d) [28].

Timing of outcome measurement

We will categorise outcomes into two sets of time points:

- short-term intervention (defined as 0- to 12-week intervention);
- long-term intervention (defined as longer than 12-week intervention).

When multiple results are reported for a given outcome, we will include the longest follow-up period in each category.

Search methods for identification of studies

Electronic searches

We will search the following sources from the inception of each database to the date of search with no restrictions on the language of publication:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE (Ovid MEDLINE ALL from 1946);
- Embase (Ovid; from 1974);
- Global Index Medicus (globalindexmedicus.net/es/);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int/).

The details of the search strategies can be found in Supplementary material 1.

Searching other resources

We will search the following grey literature sources:

- La Referencia (www.lareferencia.info/);
- MedRxiv (www.medrxiv.org/);
- OpenGrey (opengrey.eu/).

In addition, we will examine the reference lists of relevant trials to identify further published, unpublished, ongoing, or planned trials. We will also contact the authors of the included studies to obtain additional information on the retrieved studies and to determine whether we may have missed any further studies.

As we approach the publication date, we will update our MEDLINE (Ovid) and Embase (Ovid) searches to identify any withdrawals, errors, or corrections in the included studies. We will also search Retraction Watch (retractionwatch.com).

Data collection and analysis

Selection of studies

We will use Covidence software for study selection [29]. Two review authors (LBV and SD) will independently screen the titles and abstracts of references identified by the searches. Any disagreements between review authors will be resolved with input from a third review author (LG). We will obtain full-text copies of all potentially relevant reports. The same two review authors (LBV and SD) will independently screen the full-text studies and record reasons for the exclusion of excluded studies. Any disagreements between review authors will be resolved with input from a third review author (LG) if needed. If we cannot resolve a disagreement, we will categorise the study as awaiting classification and contact the study authors for clarification.

We will present a PRISMA flow diagram to show the process of study selection [14]. We will list all articles excluded after full-text assessment in the 'Characteristics of excluded studies' table along with the reasons for their exclusion [14].

Data extraction and management

For studies that fulfil our inclusion criteria, two review authors (LBV and SD) will independently extract key information on participants, interventions, and comparators using a data extraction form that will be piloted beforehand. The review authors will not be blinded to journals or institutions. Any disagreements between review authors will be resolved by discussion or with input from a third review author (LG) if needed.

One review author (LBV) will enter the data into RevMan [30]. Two other review authors (LG and SD) will check and transfer study data into the analyses.

We will extract the following data from the reports.

- Methods:
  - Study design: study dates (start date to end date; if dates are not available, we will report this) and study settings and country, language of publication, and study identifier
- Participants:
  - Inclusion and exclusion criteria
  - Participant details, baseline demographics (mean age, age range, gender, diagnosis criteria used for insomnia, inclusion criteria and exclusion criteria)
  - Numbers of participants in each treatment group with outcome events
- Interventions and comparisons, according to the Template for Intervention Description and Replication (TIDieR) checklist [31, 32]:
  - Name of the intervention
  - Why: rationale, theory, or goal of the elements essential to the intervention
  - What: physical or informational materials used in the intervention, procedures, activities, or processes used in the intervention
  - Who provided: expertise, background, and specific training given
  - How: describe modes of delivery
  - Where: describe the location where the intervention occurred, including infrastructure and features
  - When/how much: the number of times the intervention was delivered over a period of time
  - Tailoring: describe if personalisation or adaptations were planned
  - Modifications: during the course of the study
  - How well: measurements of adherence or fidelity
- Outcomes:
  - Definitions of relevant outcomes, method and timing of outcome measurement, as well as any subgroups relevant to the review
- Study funding sources
- Declarations of interest, by primary investigators

We will report these data in the 'Characteristics of included studies' table and summarise them in Table 1.

We will contact authors of all included studies to enquire whether they are willing to answer questions regarding their studies and document these communications. We will seek relevant missing information on the study from the primary study authors if required.

Dealing with duplicates and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximise the information yield by collating all available data, and we will use the most complete data set, aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included trials (such as trial registry information) as secondary references under the study ID of the included study. We will also list duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded trials (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trial registers

If data from included studies are available as study results in clinical trial registers such as ClinicalTrials.gov or similar sources, we will make full use of this information and extract the data. If there is also a full publication of the study, we will collate and critically appraise all available data. If the published and unpublished data do not match, we will ask the study authors for clarification. If we receive no response, we will report the discrepancies in the full review. If an included study is labelled as completed in a clinical trial register but no additional information (study results, publication, or both) is available, we will categorise this study as awaiting classification.

Risk of bias assessment in included studies

Two review authors (LBV and SD) will independently assess the risk of bias for the outcomes listed in the Certainty of the evidence assessment section using the Cochrane RoB 2 tool [33, 34], at the latest reported follow-up. For all outcomes, the effect of interest will be the effect of assignment to the intervention (intention-to-treat) [28]. Any disagreements will be resolved by consulting a third review author (LG). If adequate risk of bias information is unavailable from the publications, trial protocols, clinical study

reports, or other sources, we will contact the study authors for more details.

We will assess the risk of bias for all RoB 2 domains and judge each domain as having low risk of bias, some concerns, or high risk of bias, using the responses to the signalling questions and algorithms within the RoB 2 tool. Domains include:

- bias arising from the randomisation process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome;
- bias in selection of the reported result.

The tool algorithm will be used to reach an overall risk of bias for each outcome. We will quote evidence to support our judgements in the risk of bias table, and, if we disagree with a judgement recommended by the algorithm, will include an explicit statement as to why. We will manage our risk of bias assessments using the RoB 2 Excel tool [33, 34]. All these data will be publicly available as supplementary material in a public repository.

For cluster-RCTs, we will use the RoB 2 tool and add a domain specifically for cluster-RCTs from the archived version of the tool (bias arising from the timing of identification and recruitment of participants), available at www.riskofbias.info/, with its corresponding signalling questions. We will follow the guidance in the *Cochrane Handbook* (Section 23.1.2 and Table 23.1.a) [15].

For cross-over RCTs, we will use the RoB 2 tool and add a domain specifically for cross-over RCTs from the archived version of the tool, available at www.riskofbias.info/, with its corresponding signalling questions. We will follow the guidance in the *Cochrane Handbook* (Section 23.2.3) [15].

Measures of treatment effect

We will express dichotomous data (e.g. participants with adverse events) as a risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcomes (e.g. WASO, SOL), we will estimate the intervention effect using the mean difference (MD) with 95% CIs. When data are pooled from studies that use different instruments to measure the same outcome, we will calculate standardised mean differences (SMDs) with 95% CIs. We will enter data presented as a scale with a consistent direction of effect, and multiply the SMD by a standard deviation (SD) that is representative of the pooled studies (e.g. the SD from a well-known scale used by several of the studies included in the analysis on which the result was based). We will undertake meta-analyses only when this is meaningful (i.e. when the treatments, participants, and underlying clinical question are similar enough for pooling to make sense). We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

We will take into account the level at which randomisation occurred and multiple observations for the same outcome. If more than one comparison from the same study is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison, or appropriately reduce the sample size so that the same participants do not contribute data to the meta-analysis more than once (splitting the shared group into two or more groups). Although the latter approach offers some solutions for adjusting the precision of the comparison, it does not account for correlation arising from the inclusion of the same set of participants in multiple comparisons [28]. The unit of analysis will be the participants with insomnia.

For cluster-RCTs, we will consider the cluster as the unit of analysis, not the individual participant, in order to avoid unit of analysis errors, as stated in Section 23.1.1 of the *Cochrane Handbook* [15]. If the effect measure for the cluster is not determined by appropriate methods in the included studies, we will multiply the standard error of the effect estimate (from an analysis ignoring clustering) by the square root of the design effect, calculated using an intracluster (or intraclass) correlation coefficient (ICC) of 0.02, following the guidance in Sections 23.1.4 and 23.1.5 of the *Cochrane Handbook* [15].

For cross-over RCTs, we will extract and use within-participant differences where available, using a paired t-test. We will request this information from the study authors as needed. If it is not available, we will attempt to calculate these values using appropriate statistical methods. If necessary, we will impute the within-participant correlation using reasonable estimates from the literature and conduct sensitivity analyses to assess its impact. If paired data are unavailable and cannot be estimated, we will analyse only the first period, treating the study as a parallel design.

Dealing with missing data

If possible, we will obtain missing data from the authors of the included studies. We will carefully evaluate important numerical data, such as screening, randomly assigned participants, and intention-to-treat, as-treated, and per-protocol populations in our risk of bias assessments. We will investigate attrition rates (e.g. dropouts, losses to follow-up, and withdrawals) and critically appraise issues concerning missing data and the use of imputation methods (e.g. 'last observation carried forward'). We will analyse available data only. When this is not possible, and when missing data are deemed to introduce significant bias, we will explore the impact of including such studies in the overall assessment of results through a sensitivity analysis.

Reporting bias assessment

We will undertake extensive literature searching without restrictions on publication date or language to limit reporting bias. We will use study protocols and trial registrations to assess studies for selective reporting. If we include 10 studies or more per comparison and outcome, we will use funnel plots to assess small-study effects. There may be several explanations for funnel plot asymmetry, including true heterogeneity of effect concerning study size, poor methodological design (and hence bias of small studies), and selective non-reporting [35]. We will therefore interpret the results carefully [36].

Synthesis methods

We will complete all syntheses within RevMan [30]. We plan to undertake a meta-analysis only if we judge the participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure a result that is clinically meaningful. We will primarily summarise data using a random-effects model [37]. We will interpret random-effects meta-analyses with due consideration for the whole distribution of effects, and present a CI. We will

perform statistical analyses according to the guidelines presented in the *Cochrane Handbook* [38]. We will perform subgroup analyses using the methodology described by Deeks and colleagues, as recommended in Section 10.11.3 of the *Cochrane Handbook* [38].

If meta-analysis is not possible, we will summarise the results narratively according to Synthesis Without Meta-analysis (SWiM) guidelines, instead of a pooled statistical synthesis, following Chapter 12 of the *Cochrane Handbook* [39].

Investigation of heterogeneity and subgroup analysis

We will visually examine the variability in point estimates and the overlap in CIs. We will use the I^2 statistic to estimate the degree of heterogeneity present among the trials in each analysis [40]. If we identify substantial unexplained heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis. In the event of substantial clinical or methodological heterogeneity, we will not report study results as the pooled effect estimate in a meta-analysis.

We will use this rough guide to interpret the I^2 value, as outlined in Chapter 10 of the *Cochrane Handbook* [38]:

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

We will avoid using absolute cutoff values, but will interpret the I^2 in relation to (a) the size and direction of effects, and (b) the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI for I^2).

We expect the following characteristics to introduce clinical heterogeneity, for which we plan to carry out subgroup analyses, including an investigation of interactions [41].

- Subgroups of intervention based on the type of MC administered.
- Men versus women, considering trials conducted on one gender exclusively or with over 80% of participants representing a specific gender to establish the subgroups.
- Type of insomnia (primary insomnia or insomnia associated with comorbid conditions).
- Insomnia duration (chronic or acute insomnia).
- Age: younger than 65 years old versus older than 65 years old.

We will use the formal test for subgroup interactions in RevMan [30], acknowledging its limitations due to its observational nature and low power to detect differences with fewer than 10 studies per category [28].

Equity-related assessment

We will explore health inequities through three characteristics defined by PROGRESS-Plus: gender/sex, age, and personal characteristics associated with discrimination (such as oncologic patients, psychiatric patients, etc.) [42].

Insomnia is significantly more prevalent in women than in men, with women being twice as likely to suffer from the condition. By evaluating the effectiveness of MC for insomnia, the review will provide insights that can help tailor interventions specifically for women, thereby addressing a significant health disparity. In addition to this, the prevalence of insomnia increases with age. Despite its high prevalence, insomnia in older adults often remains underdiagnosed and undertreated. This review aims to highlight effective treatments for older adults, ensuring that this vulnerable population receives appropriate care. Finally, patients with chronic health conditions face higher rates of insomnia and barriers to accessing effective treatment. By including data from diverse populations and considering factors like comorbid conditions, the review will address the specific needs of these groups and promote more equitable health care [2, 4].

Sensitivity analysis

We plan to perform the following sensitivity analyses for critical outcomes:

- excluding studies with cluster randomisation;
- excluding cross-over studies;
- removing studies with an overall high risk of bias.

Certainty of the evidence assessment

We will present the overall certainty of the evidence for each outcome specified below according to the GRADE approach, which considers issues related to internal validity (overall risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results). Two review authors (LBV and SD) will independently rate the certainty of the evidence for each outcome. Any disagreements will be resolved by discussion or in consultation with a third review author (LG).

We will present a summary of the evidence in a summary of findings table, which will provide key information about the best estimate of the magnitude of effect, in relative terms and absolute differences, for each relevant comparison of alternative management strategies; the numbers of participants and studies addressing each important outcome; and a rating of overall confidence in effect estimates for each outcome. We will create the summary of findings table using the methods described in the *Cochrane Handbook* [43], employing RevMan and GRADEpro GDT software [30, 44, 45].

If meta-analysis is not possible, we will present the results in a narrative format in the summary of findings table. We will justify all decisions to downgrade the certainty of the evidence by using informative footnotes and GRADE guidelines for informative statements [46].

We will create a summary of findings table for the following comparisons and outcomes at the longest reported follow-up.

Comparisons

- MC versus placebo
- MC versus benzodiazepine receptor agonists
- MC versus benzodiazepines

Outcomes

- Quality of sleep/satisfaction with sleep
- TST
- Adverse events

- Daytime functioning
- Quality of life

Consumer involvement

Consumers will not be involved in this review due to limited resources.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016216.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

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Contributions of authors

All review authors read and approved the final draft of the protocol.

LBV concepted the review and searched studies for the Background section.

LBV, SD, CE, and LG drafted the protocol.

LG co-ordinated the review.

CE and LBV developed the search strategy.

Declarations of interest

LBV: no commercial or non-commercial conflicts of interest relevant to this review

CE: no commercial or non-commercial conflicts of interest relevant to this review

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  No external sources of support were received.

Registration and protocol

Cochrane approved the proposal for this review in July 2024.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

Notes

Published notes in RevMan are for editor use only. Authors should leave this section blank.

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ADDITIONAL TABLES

Table 1. Table 1: Overview of included studies and synthesis

Study name (year) country	Study design	Intervention details	Population (sample size: intervention/control)	Outcomes with available data (synthesis method/metric)	Outcome measures	Outcome time point	Method of synthesis	**Overall risk of bias**