Melatonin effects on sleep quality of COVID-19 patients: a protocol for systematic review and meta-analysis of randomised controlled trials with trial sequential analysis

Juan Juan Zhang, Ran Sun, Sha Guo, Hong Zhang

ABSTRACT

Introduction Sleep disturbance is one of the common complaints of patients with COVID-19 infection. Melatonin is a physiological indoleamine involved in circadian rhythm regulation and it is currently used for secondary sleep disorders caused by various diseases. Some clinical randomised controlled trials (RCTs) have obtained a small amount of evidence and controversial results in support of their therapeutic effect on sleep disorders, but no studies have summarised and evaluated RCTs in all current databases to obtain conclusive results. Therefore, the aim of this systematic review and meta-analysis was to determine the efficacy and safety of melatonin in the treatment of sleep disturbances in patients with COVID-19.

Methods and analysis We will search for RCT-type studies of melatonin in the treatment of sleep disturbances in patients with COVID-19. From inception to October 2022 we will be available on PubMed/MEDLINE, Web of Science, Embase, CINAHL, PsycINFO, LILACS, SCOPUS, Cochrane Central Register of Controlled Trials, ICTRP, Wanfang Data, VIP database and CNKI, VIP database, China Biomedical Literature Database to search for eligible studies. There are no language and geographical restrictions. Two authors will independently screen and select eligible studies, assess methodological quality and perform data extraction. Two additional authors will independently extract data from each study. Then, meta-analysis will then be carried out using a fixed-effects or random-effects model, using the mean difference for continuous outcomes and the relative risk for dichotomous outcomes. Risk of bias assessment will be assessed using the Cochrane risk-of-bias tool. Heterogeneity between studies was assessed by Cochrane Q-test and I². The quality of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation methodology. Funnel plots, Begg’s test and Egger’s test will be used to assess the risk of publication bias. Subgroup analysis, data synthesis, meta-analysis and overall incidence of adverse events will be performed using Review Manager V5.4 software and Stata software. Trial sequential analysis will be performed if appropriate.

Ethics and dissemination This study is an extraction review of data from existing studies, and thus it is unnecessary to obtain ethical approval. The results of this systematic review will be published in a peer-reviewed journal.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Control of random errors with trial sequential analysis by calculating the diversity adjusted information size for the outcomes.
⇒ Application of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines for a better quality of meta-analytical results.
⇒ Other strengths include a comprehensive search strategy, predefined subgroup analyses and use of Grading of Recommendations, Assessment, Development and Evaluation methodology to assess certainty of evidence.
⇒ Different measurement tools may not necessarily be assessing the same thing, and the conclusions reached, in that case, may be misleading.

INTRODUCTION

In December of 2019, a massive epidemic of a virus, the new coronavirus, emerged in Wuhan, China, namely SARS-CoV-2.1 2 This virus is highly contagious.3 Since the outbreak, there have been confirmed cases of SARS-CoV-2 infection in more than 200 countries and regions around the world, and until 10 September 2022, over 678 million confirmed cases and over 651 million deaths have been reported worldwide.4 5 6 It was soon discovered by clinicians that suffering from symptoms such as dyspnoea and fever, patients with COVID-19, also experienced sleep disturbances.7 8 9 10 11 12 This study is an extraction review of data from existing studies, and thus it is unnecessary to obtain ethical approval. The results of this study will be published in a peer-reviewed journal.
and subsequent isolation and quarantine lead to sleep disturbances, anxiety and depressive episodes, among others. The novel COVID-19 pandemic has increased the number of patients with insomnia.\(^7\) As we all know, sleep is an essential requirement of good health. Sleep has restorative functions and, in critically ill patients, is thought to improve healing and survival.\(^8\) Patients with COVID-19 are often prescribed drugs that further contribute to sleep deprivation because of particularly to mechanically ventilated patients.\(^9\) For example, benzodiazepines are used for necessary sedation.\(^10\) Sleep problems associated with COVID-19 may include poor sleep quality, lethargy or insomnia. During COVID-19, the estimated global prevalence of sleep disorders was 52.39%.\(^11\) Relevant populations involved include COVID-19 patients (inpatients: 33.3%–84.7%); discharges: (29.5%–40%), healthcare workers (18.4%–84.7%) and the general community (17.65%–81%).\(^12\) A subsequent survey showed that a pooled prevalence of COVID-19-related insomnia of 16.45% in the general population and that in medical staff was 36.52%.\(^13\) Insomnia, difficulty falling asleep or maintaining sleep is associated with multiple negative outcomes, including increased risk of depression, alcohol dependence, hypertension, metabolic syndrome and coronary heart disease.\(^14\) Insufficient sleep, both quantitatively and qualitatively, is a known risk factor for cardiovascular disease, hypertension, vascular disease, metabolic dysfunction and neurocognitive disorders.\(^15\) In addition, insomnia is associated with decreased productivity, increased healthcare utilisation and reduced quality of life.\(^16\)\(^17\)

Melatonin is a natural hormone produced by the pineal gland at night, and its synthesis is characterised by a regular circadian rhythm, reaching peak plasma concentrations at night. It has been used for the past two decades to treat sleep disorders in adults and children.\(^18\) It is a master regulator of sleep and has widespread effects on the central nervous system, affecting the activity of the suprachiasmatic nucleus, including the regulation of the hypothalamus’s biological master clock and sleep onset.\(^19\) In addition to the circadian phase-shifting effects of melatonin, the hormone has direct sleep-promoting effects.\(^20\) It has a variety of uses in sleep medicine for the treatment of insomnia, anxiety and sleep disturbances, among others. The high safety profile of melatonin and its potential anti-SARS-CoV-2 effect make this molecule a drug of choice for the treatment of sleep disorders in patients with COVID-19.\(^21\) We also noted that the effectiveness of melatonin for the recognised indication of primary insomnia was questioned by some guidelines and that the various studies were also heterogeneous in terms of outcome measures, indication statements and formulated advice. According to the retrospective study, only 19.6% of the requirements met the official EMA indication.\(^22\) Furthermore, the most suitable dose ranges and pharmaceutical preparations for melatonin administration are yet to be clearly defined. While it is true that melatonin is a well-known and widely studied medication, it is still important to continue evaluating its safety profile as new research emerges. Even medications that have been on the market for a long time can sometimes have unexpected side effects or interactions with other medications, particularly if they are used in specific populations or at higher dosages. Therefore, it is important to periodically review the safety of established medications like melatonin to ensure their continued safe use by patients. Additionally, given the increasing use of melatonin as a supplement, it is important to assess its safety when used in this context as well. Although melatonin is known to have anti-inflammatory, antioxidant and immunomodulatory functions during bacterial and viral infections, its specific efficacy and safety in sleep quality in patients with novel COVID-19 has not been established. Been extensively studied. Therefore, we decided to conduct a systematic review and meta-analysis of randomised controlled trials (RCTs).

**METHODS**

The retrospective study found that only 19.6% of the requirements met the official EMA indication.\(^26\) Meta-analysis guidelines extension (PRISMA-P) statement design. The protocol is registered with the International Prospective Register of Systematic Reviews.

**Inclusion criteria**

**Types of studies**

We will include all RCTs testing the effect of melatonin or melatonin agonists on sleep quality in patients with COVID-19.

**Exclusions**

Case reports, observational studies, reviews. Studies with non-human participants. Conference abstracts, review papers. Qualitative studies, letters to the editor, policy papers and meta-analyses. Narrative reviews, modelling studies, opinion articles, letters, news, editorials, opinions and articles in other publications that lack raw data and/or methodological details. Studies with duplicate datasets.
Types of participants
Inclusion criteria for the study population will be all COVID-19 patients with sleep problems, regardless of population age, race and educational status.

Type of interventions
Melatonin or melatonin agonists.

Comparisons
Placebo, standard of care, psychological intervention.

Date and language restrictions
Research published in any language from inception to October 2022.

Types of outcomes
Main results
Participant-reported or human-assessed measures of sleep quantity and quality.
Quantity and quality of sleep as measured by PSG, Activity Map, BIS or EEG.

Secondary results
Adverse events (such as nausea, headache or dizziness).

Search strategy
Electronic database search
We will use both free-text terms and Medical Subject Headings (Mesh) in PubMed/MEDLINE, Web of Science, Embase, CINAHL, PsycINFO, LILACS, Google Scholar, SCOPUS, Cochrane Central Register of Controlled Trials, International Clinical Trials Registration Platform (ICTRP), Wanfang Data, VIP Database, China Biomedical Literature Database (CBM) and China National Knowledge Infrastructure (CNKI) to conduct a comprehensive literature search. By including specific keywords relevant to their research topic, such as “melatonin” and “sleep disorders”, the authors aim to retrieve articles directly related to their research objectives. Additionally, by using MeSH terms, they can identify relevant articles even if those articles do not include the exact keywords initially identified. Relevant reviews, meta-analyses and references of included articles will also be searched for additional eligible studies. In addition, the WHO’s COVID-19 global coronavirus disease database literature was searched, along with six preprint repositories: Chinese medical journal net (preprints), chinaxiv (preprints), biorxiv (preprints), medrxiv (preprints), chemrxiv (preprints) and ssrn (preprints). From inception to October 2022, the detailed retrieval strategy of PubMed is described in table 1. According to the characteristics of each database, this search strategy will be adjusted according to the constraints of each database. Boolean logical operators are used to develop searches in searches, and advanced search features of each database are used to change the search syntax.

Searching other resources
Any relevant ongoing or unpublished clinical study will be obtained from the National Institutes of Health (NIH) clinical registry, and the Chinese clinical registry defined. In order to ensure comprehensive coverage, we will also be conducting manual searches on grey literature sources. These sources include a variety of academic

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Search strategy used in PubMed</th>
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<tr>
<td>Number</td>
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<tr>
<td>#1</td>
<td>“COVID-19”OR“COVID19”OR“SARS-CoV-2”OR“2019-nCoV”OR “2019-nCoV disease” OR “COVID 19”OR “2019 novel coronavirus infection” OR “coronavirus” OR “SARS-CoV-2” OR “COVID-19 Pandemic” OR “covid-19” OR “covid19”’ OR “cv19”’ OR “cv-19” OR “cv 19” OR “n-cov” OR ncvv”OR “sars-cov-2” OR “sars-cov2”OR“2019-nrov” OR“SARS-CoV-2” OR “SARS-CoV2” OR “wuhan” AND (virus OR viruses OR viral) OR (covid* AND (virus OR viruses OR viral)) OR “covid-19-related” OR “SARS-CoV-2-related” OR “SARS-CoV2-related” OR “2019-nCoV-related” OR “cv-19-related” OR “n-cov-related”).</td>
</tr>
<tr>
<td>#2</td>
<td>“Sleep” OR “Sleep Medicine” OR “Sleep Disorder” OR “Sleep Disorder” OR “Sleep Problem” OR “Sleep Quality” OR “Insomnia Severity Index” OR “ISI” OR “Insomnia” OR “Circadian Rhythm” OR “insomnia” OR “sleep OR “sleepiness” OR “sleep quality OR (OSA)” OR “obstructive sleep apnoea” OR “obstructive sleep apnea” OR “sleep problem”</td>
</tr>
<tr>
<td>#3</td>
<td>Melatonin”(Title/Abstract)</td>
</tr>
<tr>
<td>#4</td>
<td>#1AND#2AND#3</td>
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<tr>
<td>#5</td>
<td>“Melatonin”*(Title/abstract)</td>
</tr>
<tr>
<td>#6</td>
<td>“Randomized controlled trial” (type of publication) OR “controlled clinical trial” (type of publication) OR “randomized”(title/abstract))OR “placebo”(title/abstract)OR “random”(title/abstract)OR “trial”(title/abstract)OR “group”(title/abstract)</td>
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<tr>
<td>#7</td>
<td>#4AND#5</td>
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<tr>
<td>#8</td>
<td>“Drug therapy”(Title/Abstract)</td>
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<tr>
<td>#9</td>
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<tr>
<td>#10</td>
<td>“human”(Title/Abstract)</td>
</tr>
<tr>
<td>#11</td>
<td>#4AND#7AND#8AND#9AND#10</td>
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</tbody>
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publications such as theses, dissertations, research and committee reports, government reports, conference papers, and ongoing research. These sources are often valuable sources of evidence used in systematic reviews and meta-analyses. In order to improve the comprehensiveness and timeliness of reviews while reducing publication bias, it is important to conduct a thorough search for relevant literature. Grey literature will be searched using Google or Google Scholar, OpenGrey, WONDER and SCOPUS. Another strategy that can be used to find evidence within grey literature is handsearching through conference proceedings and abstracts.

**Study selection and screening**

Two reviewers will independently assess and select titles and abstracts of all retrieved publications according to the inclusion criteria and search strategy, and the retrieved study titles and abstracts will be imported into EndNote V.X5.01. If eligibility cannot be determined from the title or abstract, the full text will be searched. The full text of selected studies will be independently analysed by two additional reviewers. Any disagreements arising during this process will be resolved between reviewers by discussion and consensus by a third member of the study group. We will document the reasons for excluding clinical trials at all stages of review. Reasons and results for selection or exclusion of studies will be reported using the PRISMA flow chart, as shown in **figure 1**.

**Data extraction**

Two authors independently extracted the following data for each included study using standardised data extraction tables:

- **Author information:** first author; year of publication.
- **Information about the study:** study design (PICOS), study location (country).
- **Information on patients in the study:** age, gender, mean age of SD participants; participants, baseline H&Y, baseline Clinical Global Impression-Improvement). Intervention information: The study includes information on the intervention and control groups, such as the dosage and treatment regimen, duration of the study, time since diagnosis, route of administration, outcomes

![Figure 1](http://bmjopen.bmj.com/) The PRISMA flow diagram of studies identified. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
assessed, follow-up time, measurement time, and any adverse effects observed.

Funding types and sources are derived from trial report support and publication status.

### Assessing the risk of bias of included studies

We will use the revised Cochrane ‘Risk of Bias’ tool (RoB 2)\(^2\) to assess study quality, study limitations and potential risk of bias included studies. The Tool for Assessing Risk of Bias in Randomized Trials (RoB Tool) is used to evaluate the risk of bias in randomized trials that assess each significant outcome included in the synthesis. Bias is assessed in five different areas. That is, biases arising from the randomisation process, biases due to deviations from expected interventions, biases due to lack of outcome data, biases in measurement results, biases in the selection of reported outcomes, biases arising from the randomisation process. Three different assessments will be made: high risk, low risk and unclear risk.

### Data synthesis

Data will be statistically analysed using RevMan V.5.4 software (Review Manager, The Cochrane Collaboration, 2020) and STATA software V.15.0 (StataCorp). For dichotomous outcomes in results, ORs and 95% CIs will be extracted/calculated from each study. For continuous stool size results, we will have estimated between-group standardised mean differences (SMDs) and SMDs and their 95% CIs will be measured as effect sizes.

In cases where statistical pooling of meta-analyses was not possible, a narrative synthesis of included studies was performed. The methodological characteristics of the study, subgroup characteristics, test characteristics and the sensitivity and specificity of the tests will also be presented in text and table form. The assessment of the certainty of evidence will take into account the precision of the combined results (ie, the CI, if any), the number of studies and participants, the consistency of effects between studies, the risk of bias of the studies, and whether the results of the studies will be combined with the report. Reports are presented in the same way as tables or graphs to facilitate comparison of similarities and differences in design and results between studies.

### Dealing with missing data

During the data extraction phase, if there are studies with incomplete data, we will attempt to contact the first author of the study by phone, email or post to obtain the necessary information. For example, studies without complete baseline data, or with no OR, or for which OR and 95% CI could not be calculated. If contact with the authors or data were not available, we would assume missing values using last-observation-carry-forward imputation.\(^2\) We will use available case data, not estimates.

### Heterogeneity assessment

Heterogeneity between studies will be assessed by forest plots and Cochran’s Q test (p<0.05 was considered statistically significant) and I\(^2\) values describing the total variation between studies and Cochran’s Q statistic were quantified. According to the Cochrane Handbook, the thresholds for interpreting the I\(^2\) statistic are as follows: 0%–40%, probably not significant; 30%–60%, likely to reflect moderate heterogeneity; 50%–90%, likely to indicate significant heterogeneity; 75%–100%, representing considerable heterogeneity.\(^2\) If the I\(^2\) value is below 50%, a fixed-effects model will be used; otherwise, a random-effects model will be used.

### Subgroup analysis

We planned to perform the following subgroup analyses where possible: melatonin versus melatonin agonist, (1) dose of melatonin/melatonin agonist, (2) age, (3) type of control and (4) risk of bias others). Subgroup analyses were not performed if the number of studies was less than three. If significant differences were found between subgroups (p<0.05 for interaction test), we will report the results for each subgroup separately. We will also formally test subgroup interactions using RevMan V.5.4.

### Sensitivity analysis

We will use a sensitivity analysis to explore the effect of trial risk of bias on the results. Analyses were mainly performed on studies with low risk of RoB 2 assessment or with some issues of bias or other special characteristics. We will also perform sensitivity analyses by sequentially excluding one study at a time to determine the effect of individual studies on the overall estimate and to explore whether the results are stable. We will include studies at high risk of bias in secondary analyses to assess the impact on the results. If there is a significant difference between the impact estimates from the primary analysis and the sensitivity analysis, we will perform an adjusted sensitivity analysis.

### Grading the quality of evidence

To assess the certainty of the evidence included in the systematic review, we will use a methodology developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE)\(^3\) working group of the GRADEpro Guideline Development Tool (https://gradepro.org/). Used to rate the certainty of evidence for each finding in the review as high, medium, low or very low. The assessment included assessing risk of bias, imprecision, inconsistency, indirectness and publication bias.

### Assessment of publication bias

If the total number of studies included in this study exceeds 10, the publication bias of Eggers’ test of funnel plot asymmetry will be checked using the funnel plot in RevMan software.\(^2\) In the case where multiple small studies are included, it is probable that funnel plots will be utilized.

### DISCUSSION

Adequate sleep is necessary for humans to maintain daily functions. When facing the COVID-19 pandemic, sleep

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becomes essential because of its many benefits for mental and physical health. Lack of sleep can impair psychological functioning and decision-making, jeopardise immune response, increase accidents, lead to mood changes, increase medical expenditures and render individuals more susceptible to contracting the virus because of poor concentration.33 Additionally, different people, infected or not, may be affected during the pandemic and experience varying degrees of sleep disturbance.34 In a case series of 10 patients, all patients with COVID-19 sleep disorder were found to improve their symptoms within 4–5 days after starting high-dose melatonin and clinically stabilise.35 Also, different measurement tools may not necessarily evaluate the same thing, in which case the conclusions drawn may be misleading. The results of this meta-analysis will show whether melatonin improves sleep quality problems in COVID-19 patients during the pandemic. Additionally, it may reveal that melatonin is a key factor affecting sleep quality. If the results of this meta-analysis are inconclusive, they may help generate new hypotheses and aid the design of new RCTs.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

ETHICS AND DISSEMINATION

Ethics board approval is not required. Results will be disseminated through publication in a peer-reviewed journal.

Contributors

JJZ will identify eligible studies after reading titles and abstracts. SG will read the full texts to perform further selection. Several studies from different opinions will be determined by the RS. Data will be extracted from the original reports by SG. The assessment of the risk of bias will be carried out by JJZ, RS and HZ. Any discrepancies will be resolved by discussion with a third RS. JJZ will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. JJZ drafted the manuscript, which was reviewed by RS, SG and HZ. All authors have read, reviewed, contributed in revising and approved the final manuscript.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

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