BMJ Open

Pharmacotherapy for improving postoperative sleep quality: a protocol for a systematic review and network meta-analysis

Di Yang,[1,2] Lei Yang,[1] Qian Li,[1] Yunxia Zuo [1]

To cite: Yang D, Yang L, Li Q, *et al*. Pharmacotherapy for improving postoperative sleep quality: a protocol for a systematic review and network meta-analysis. *BMJ Open* 2023;**13**:e069724. doi:10.1136/bmjopen-2022-069724

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069724).

Received 31 October 2022
Accepted 09 February 2023

[1]Department of Anaesthesiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[2]Department of Anaesthesiology, Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan, China

Correspondence to
Dr Yunxia Zuo; zuoyunxia@scu.edu.cn and Dr Lei Yang; yanglei.wcha@scu.edu.cn

ABSTRACT

Introduction Improving the quality of sleep may promote enhanced recovery in surgical patients. In addition to controversial or conflicting study conclusions, the current clinical studies on pharmacotherapy for improving postoperative sleep quality are mostly limited to evaluating the effect of a specific drug or supplement compared with placebo, and they lack comparisons between drugs or supplements. Therefore, we plan to conduct a systematic review and network meta-analysis to compare the efficacy of different drugs or supplements for improving postoperative sleep quality.

Methods and analysis We will search the MEDLINE, Embase, Cochrane Central Register of Controlled Trials, CNKI and Wanfang databases from the dates of their inception to December 2022. We will only include randomised controlled trials, irrespective of language and publication status. The primary outcome is postoperative sleep quality assessed by any validated tools or polysomnography. We will assess the quality of all included trials according to version 2 of the Cochrane risk-of-bias tool for randomised trials. We will use the GeMTC package of R software to perform direct and indirect comparisons via a Bayesian framework using a random-effects model. We will use the Confidence in Network Meta-Analysis approach to evaluate the quality of evidence.

Ethics and dissemination Ethical approval is not required for this protocol because we will only be pooling published data. We plan to submit our review to academic conferences and peer-reviewed academic journals.

PROSPERO registration number CRD42022356508.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our study will comprehensively evaluate the effect of pharmacotherapy on improvement of postoperative sleep quality.
⇒ Three major databases (MEDLINE, Embase and Cochrane Central Register of Controlled Trials) and Chinese literature databases will be comprehensively searched, with no language restrictions.
⇒ We will assess the quality of included trials on the basis of version 2.0 of the risk-of-bias tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions.
⇒ We will use the Confidence in Network Meta-Analysis approach to evaluate the quality of evidence.
⇒ Despite planning a subgroup analysis, the potential heterogeneity between studies, such as the effect of different types of surgery on the results, cannot be completely eliminated.

INTRODUCTION

Sleep disturbance refers to the abnormal time, rhythm, cycle or pattern of sleep, which affects the quality of sleep during the night. The incidence of perioperative sleep disturbance varies from 37.9% to 88.1%, and symptoms may even last up to 1 year after surgery in some patients.[1–5] Sleep disturbance, which is one of the most common aspects of severe postoperative discomfort,[6] is associated with delayed recovery,[7] postoperative pain,[8] postoperative cognitive dysfunction,[9] inflammatory response[10] and cardiac complications.[11] Therefore, improving the quality of sleep may promote the enhanced recovery of surgical patients.[12]

Postoperative pain is believed to be one of the main causes of sleep disturbance.[12] However, why sleep disturbance still occurs in patients with adequate analgesia is difficult to explain.[13] This finding suggests that postoperative sleep disturbance may not only be associated with pain, but also with other factors (eg, sex, anxiety, comorbidity, anaesthesia techniques, anaesthesia drugs and postoperative complications),[14–17] and the underlying mechanisms of postoperative sleep disturbance are complex. In addition to non-pharmacological therapy, such as relaxation therapy and improving the sleep environment,[18] pharmacotherapy is also an important aspect of improving postoperative sleep quality.[12] Some clinical studies have found that drugs or supplements with different mechanisms can improve postoperative sleep quality. These drugs or supplements include the following: melatonin, which is a

pineal hormone agent[19]; zolpidem, which is a short-acting non-benzodiazepine compound of the imidazopyridine class[20]; midazolam, which is a benzodiazepine[21]; dexmedetomidine, which is a selective alpha-2 adrenoceptor agonist[22]; tramadol, which is an opioid agonist[23]; lidocaine, which is a local anaesthetic[24]; and magnesium, which is a mineral and electrolyte.[25] However, there are divergent conclusions regarding zolpidem, melatonin and lidocaine regarding the improvement of sleep.[25–27] In addition to these controversial study conclusions, the current clinical studies on pharmacotherapy for improving postoperative sleep quality have mostly been limited to evaluations of the effects of a specific drug or supplement compared with placebo, and they are lacking in comparisons between them.[28 29] Consequently, clinicians have difficulty in choosing the most suitable and effective drug or supplement to improve postoperative sleep quality.

Therefore, we plan to conduct a systematic review and network meta-analysis to compare the efficacy of different drugs or supplements for improving postoperative sleep quality.

METHODS AND ANALYSIS

This protocol (CRD42022356508) was registered in the International Prospective Register of Systematic Reviews.[30] We reported this protocol in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.[31]

Patient and public involvement

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

Data sources and searches

We will search the following databases via OVID: MEDLINE, Embase and the Cochrane Central Register of Controlled Trials. We will also search the Chinese databases CNKI and Wanfang. All databases will be searched from their dates of inception to December 2022. No language restrictions will be applied to the search strategy. The original keywords used for this search will include the postoperative period, perioperative period, sleep, sleep disturbance, sleep disorders and sleep quality. Full details of the original search strategy are shown in online supplemental table 1. We will search for conference papers by SCOPUS, limiting 'source type' to 'conference proceeding'. We will also search for ongoing trials by ClinicalTrials.gov and the Chinese Clinical Trial Registry. In the available studies, we will reassess any subject terms or free-text terms for postoperative sleep quality that have not been used. We will add newly identified terms to the final modified search strategy. The final search strategy will be reported in our review.

Eligibility criteria

Types of study

We will only include randomised controlled trials, irrespective of the language or publication status. Conference abstracts will also be included if sufficient data are available.

Types of participants

We will include studies of adult patients who underwent any surgical procedures and were administered any drugs or supplements aiming to improve postoperative sleep quality.

Types of interventions

We will include studies using any of the following interventions:

- Melatonin
- Dexmedetomidine
- Zolpidem
- Tramadol
- Lidocaine
- Midazolam
- Any other drugs or supplements to improve postoperative sleep quality

Types of comparisons

We will compare different interventions with each other and with placebo.

Types of outcomes

The primary outcome is postoperative sleep quality assessed by any validated tools, such as the Pittsburgh Sleep Quality Index,[32] Richards-Campbell Sleep Questionnaire,[33] General Sleep Disturbance Scale[34] and Epworth Sleepiness Scale,[35] or polysomnography.

The secondary outcomes are as follows: treatment-related adverse effects; quality of life assessed by the Quality of Recovery 15-item Questionnaire,[36] the Medical Outcomes Study 36-Item Short Form,[37] the Health-Related Quality of Life Scale[38] or any other validated tools; postoperative pain intensity assessed by the Visual Analogue Scale or analgesics consumption; risk of mental disturbance, such as anxiety, depression and stress; and the length of hospital stay.

Study selection

Two investigators (DY and LY) will independently review and screen all of the titles and abstracts for eligibility and complete the study selection form (online supplemental table 2). If the information for eligibility is insufficient, we will retrieve the full text. Any disagreements will be resolved by consulting with a third author (QL). Finally, we will list all of the eligible trials in the eligible trials form (online supplemental table 3).

Data extraction and quality assessment

We will obtain the full-text versions of all eligible trials for data extraction. Two investigators (DY and LY) will independently extract the data from studies into an electronic data extraction form (online supplemental table 4). A third investigator will verify the data and integrate them into the final version of the data extraction form.

Two investigators (DY and LY) will independently assess the quality of all included trials on the basis of version 2.0 of the Cochrane risk-of-bias tool for randomised trials (RoB 2), as described in the Cochrane Handbook for Systematic Reviews of Interventions.[39] The assessment of the RoB 2 will include the following five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome and bias in selection of the reported result. One of the three risk-of-bias judgements (low risk of bias, some concerns or high risk of bias) will be assigned to each domain. Any disagreements will be resolved by discussion. We will report a risk-of-bias table and a risk-of-bias summary figure in the review process.

Statistical analysis

We will calculate the risk ratios with 95% CIs for dichotomous data, and mean differences with 95% CIs for continuous data. We will calculate the standardised mean difference with the 95% CI in the case of outcomes with continuous data in different scales.

We will use the GeMTC package of R software to perform direct and indirect comparisons via a Bayesian framework using a random-effects model. Network graphs and ranking probabilities will be generated and presented. We will perform a sensitivity analysis by using different imputation methods (low risk of bias studies and large sample size studies) and different statistical methods (including a fixed-effects model). We will generate a funnel plot to assess the publication bias if more than nine studies are included in the meta-analysis.[40]

We will use the X^2 test and I^2 statistic to describe heterogeneity. We will consider significant statistical heterogeneity when the p value is <0.05, and substantial heterogeneity will be considered when the I^2 statistic is >50%. We will investigate the clinical heterogeneity by a subgroup analysis when there is significant statistical heterogeneity. Subgroup analyses will be performed on the basis of age, disease, surgical type and anaesthesia techniques. Transitivity will be considered between study results when there are similar patients' characteristics, interventions, outcomes and study design. We will use the node-splitting method to evaluate the inconsistency if there are three or more nodes in the loop. A p value of >0.05 will indicate that the difference between direct and indirect comparisons was not statistically significant. We will use directly compared results as the estimated effect size when there are inconsistencies in the study results.

Assessing the quality of evidence

We will use the Confidence in Network Meta-Analysis approach to evaluate the quality of evidence. This approach covers the following six domains: (1) within-study bias, (2) reporting bias, (3) indirectness, (4) imprecision, (5) heterogeneity and (6) incoherence.[41]

Ethics and dissemination

Ethics approval is not required for this protocol because we will only pool published data. We plan to submit our review to academic conferences and peer-reviewed academic journals.

Acknowledgements We thank John Daniel from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Contributors DY, LY, QL and YZ conceived and designed the study. LY developed the search strategy. DY, QL and YZ drafted the manuscript. All authors approved on submitting the article for publication.

Funding This study was supported by a research grant from the 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD20005) and Key Research and Development Program of Science and Technology Department of Sichuan Province (no. 2023YFS0139)

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 required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Yunxia Zuo http://orcid.org/0000-0002-3539-5706

REFERENCES

1 Ida M, Onodera H, Yamauchi M, *et al*. Preoperative sleep disruption and postoperative functional disability in lung surgery patients: a prospective observational study. *J Anesth* 2019;33:501–8.
2 Halle IH, Westgaard TK, Wahba A, *et al*. Trajectory of sleep disturbances in patients undergoing lung cancer surgery: a prospective study. *Interact Cardiovasc Thorac Surg* 2017;25:285–91.
3 Wang J-P, Lu S-F, Guo L-N, *et al*. Poor preoperative sleep quality is a risk factor for severe postoperative pain after breast cancer surgery: a prospective cohort study. *Medicine (Baltimore)* 2019;98:e17708.
4 Hou H, Wu S, Qiu Y, *et al*. The effects of morning/afternoon surgeries on the early postoperative sleep quality of patients undergoing general anesthesia. *BMC Anesthesiol* 2022;22:286.
5 Allen RW, Burney CP, Davis A, *et al*. Deep sleep and beeps: sleep quality improvement project in general surgery patients. *J Am Coll Surg* 2021;232:882–8.
6 Fan YL, Qian JL, Ma EL, *et al*. Incidence and risk factors of postoperative severe discomfort after elective surgery under general anesthesia: a prospective observational study. *J Perianesth Nurs* 2021;36:253–61.
7 Gong L, Wang Z, Fan D. Sleep quality effects recovery after total knee arthroplasty (TKA) -- a randomized, double-blind, controlled study. *J Arthroplasty* 2015;30:1897–901.
8 Bjurström MF, Irwin MR, Bodelsson M, *et al*. Preoperative sleep quality and adverse pain outcomes after total hip arthroplasty. *Eur J Pain* 2021;25:1482–92.
9 Wang X, Hua D, Tang X, *et al*. The role of perioperative sleep disturbance in postoperative neurocognitive disorders. *Nat Sci Sleep* 2021;13:1395–410.

10 Hu X-M, Wei W-T, Huang D-Y, *et al*. The assessment of sleep quality in patients following valve repair and valve replacement for infective endocarditis: a retrospective study at a single center. *Med Sci Monit* 2021;27:e930596.
11 Choudhury M, Gupta A, Hote MP, *et al*. Does sleep quality affects the immediate clinical outcome in patients undergoing coronary artery bypass grafting: a clinico-biochemical correlation. *Ann Card Anaesth* 2017;20:193–9.
12 Su X, Wang DX. Improve postoperative sleep: what can we do? *Curr Opin Anaesthesiol* 2018;31:83–8.
13 Cronin AJ, Keifer JC, Davies MF, *et al*. Postoperative sleep disturbance: influences of opioids and pain in humans. *Sleep* 2001;24:39–44.
14 Wang SJ, Shen SY, Lin B, *et al*. Factors affecting postoperative sleep quality of patients undergoing flap transfer for head and neck reconstruction. *Oral Oncol* 2022;127:105804.
15 Wang Y, Liu Y, Li X, *et al*. Prospective assessment and risk factors of sleep disturbances in total hip and knee arthroplasty based on an enhanced recovery after surgery concept. *Sleep Breath* 2021;25:1231–7.
16 Yang S, Zhang Q, Xu Y, *et al*. Development and validation of nomogram prediction model for postoperative sleep disturbance in patients undergoing non-cardiac surgery: A prospective cohort study. *Nat Sci Sleep* 2021;13:1473–83.
17 Yilmaz S, Aksoy E, Doğan T, *et al*. Angina severity predicts worse sleep quality after coronary artery bypass grafting. *Perfusion* 2016;31:471–6.
18 Machado F de S, Souza RC da S, Poveda VB, *et al*. Non-pharmacological interventions to promote the sleep of patients after cardiac surgery: a systematic review. *Rev Lat Am Enfermagem* 2017;25:e2926.
19 Ivry M, Goitein D, Welly W, *et al*. Melatonin premedication improves quality of recovery following bariatric surgery - a double blind placebo controlled prospective study. *Surg Obes Relat Dis* 2017;13:502–6.
20 Shakya H, Wang D, Zhou K, *et al*. Prospective randomized controlled study on improving sleep quality and impact of zolpidem after total hip arthroplasty. *J Orthop Surg Res* 2019;14:289.
21 Tan W, Miao E, Jin F, *et al*. Changes in first postoperative night bispectral index after daytime sedation induced by dexmedetomidine or midazolam under regional anesthesia: a randomized controlled trial. *Reg Anesth Pain Med* 2016;41:380–6.
22 Wu X-H, Cui F, Zhang C, *et al*. Low-Dose dexmedetomidine improves sleep quality pattern in elderly patients after noncardiac surgery in the intensive care unit: a pilot randomized controlled trial. *Anesthesiology* 2016;125:979–91.
23 Fu M, Chen S, Xu R, *et al*. Effects of intravenous analgesia using tramadol on postoperative depression state and sleep quality in women undergoing abdominal endoscopic surgery: a randomized controlled trial. *Drug Des Devel Ther* 2022;16:1289–300.
24 Xu S, Liu N, Yu X, *et al*. Effect of co-administration of intravenous lidocaine and dexmedetomidine on the recovery from laparoscopic hysterectomy: a randomized controlled trial. *Minerva Anestesiol* 2023;89:10–21.
25 Saadawy IM, Kaki AM, Abd El Latif AA, *et al*. Lidocaine vs. magnesium: effect on analgesia after a laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2010;54:549–56.
26 Krenk L, Jennum P, Kehlet H. Postoperative sleep disturbances after zolpidem treatment in fast-track hip and knee replacement. *J Clin Sleep Med* 2014;10:321–6.
27 Clarkson SJ, Yayac MF, Rondon AJ, *et al*. Melatonin does not improve sleep quality in a randomized placebo-controlled trial after primary total joint arthroplasty. *J Am Acad Orthop Surg* 2022;30:e287–94.
28 Zhang J, Wang Y, Xu H, *et al*. The influence of melatonin on sleep quality after laparoscopic cholecystectomy: a meta-analysis of randomized controlled trials. *Surg Laparosc Endosc Percutan Tech* 2019;29:1–6.
29 Bjurström MF, Irwin MR. Perioperative pharmacological sleep-promotion and pain control: a systematic review. *Pain Pract* 2019;19:552–69.
30 Schiavo JH. Prospero: an international register of systematic review protocols. *Med Ref Serv Q* 2019;38:171–80.
31 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
32 Buysse DJ, Reynolds CF 3rd, Monk TH, *et al*. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
33 Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. *J Nurs Meas* 2000;8:131–44.
34 Lee KA. Self-Reported sleep disturbances in employed women. *Sleep* 1992;15:493–8.
35 Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness scale. *Sleep* 1991;14:540–5.
36 Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the qor-15. *Anesthesiology* 2013;118:1332–40.
37 Stewart M. The medical outcomes study 36-item short-form health survey (SF-36). *Aust J Physiother* 2007;53:208.
38 Centers for Disease Control and Prevention. Health-related quality of life HRQOL. 2016. Available: https://www.cdc.gov/hrqol/methods.htm
39 Higgins JPT, Thomas J, Chandler J, *et al*. *Cochrane handbook for systematic reviews of interventions version*. Cochrane, 2022: 3. Available: Wwwtrainingcochraneorghandbook
40 Egger M, Smith GD, Phillips AN. Meta-Analysis: principles and procedures. *BMJ* 1997;315:1533–7.
41 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al*. Cinema: an approach for assessing confidence in the results of a network meta-analysis. *PLOS Med* 2020;17:e1003082.

Search strategy via OVID

1.postoperative period.mp.
2.Postoperative Period/
3.Perioperative Period/
4.perioperative period.mp.
5.Sleep/
6.sleep disturbance.mp.
7.sleep disorder.mp.
8.sleep quality.mp.
9. 1or2or3or4
10.5or6or7or8
11.9and10
12.((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
13.11 and 12

Search strategy via CNKI database： TKA='术后睡眠障碍'

Search strategy via Wangfang database：题名或关键词:(术后睡眠障碍)

Search strategy via SCOPUS：“postoperative AND sleep” *limited to* “Conference paper”

Search strategy via ClinicalTrials.gov：“sleep disturbance” and “postoperative” limited *study type* to “Interventional studies（Clinical trials）” or “sleep disorder” and “postoperative” limited *study type* to “Interventional studies（Clinical trials）” or “sleep quality” and “postoperative” limited *study type* to “Interventional studies（Clinical trials）”

Search strategy via Chinese Clinical Trial Registry: “术后睡眠障碍” *limited to* 注册题目

Study selection form

first author	Journal/Conference Proceedings etc	Year	Study eligibility				NOTE(IN OR EX)	Freehand space for comments on study design and treatment
			RCT	Relevant participants	Relevant interventions	Relevant outcomes		

Eligible trials form

Code each paper	Author(s)	Journal/Conference Proceedings etc	Year

Data Extraction Form

Code of paper:

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Disease	
Surgery	
Anesthesia technique	
Other	

Trial characteristics	
	Further details
Single centre / Multicentre	
Country / Countries	
How many people were randomized?	
Number of participants in intervention group/control group	/
Number of participants who received intended treatment	
Number of participants who were analysed	
Intervention (name/dose/route)	
Comparison (name/dose/route)	
Trial design (e.g. parallel / cross-over)	
Other	

Data extraction

Outcomes	**Reported in paper (circle)**
Primary outcome	
Outcome 1 - postoperative sleep quality assessed by the Pittsburgh Sleep Quality Index (PSQI) or any other tools.	Yes / No
Secondary outcomes	
Outcome 1 - Treatment-related adverse effects.	Yes / No
Outcome 2 - Quality of life.	Yes / No
Outcome 3 - Postoperative pain intensity	Yes / No
Outcome 4 - Risk of mental disturbance: anxiety, depression, stress et al.	Yes / No

Outcome 5 - Length of hospital stay.	Yes / No
Subgroups	**Reported in paper**
age	
disease	
surgical type	
anesthesia techniques	

For Continuous data							
Code of paper	Outcomes	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (SD)	n	Mean (SD)	
	Sleep quality						
	Quality of life						
	Postoperative pain intensity						
	Length of hospital stay.						

For Dichotomous data			
Code of paper	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
	Treatment-related adverse effects.		
	Risk of mental disturbance		

Other information which you feel is relevant to the results

Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports **of potentially eligible trials not already identified for this review?**		
First author	**Journal / Conference**	**Year of publication**
Did this report include any references to unpublished data **from potentially eligible trials not already identified for this review? If yes, give list contact name and details**		