Systematic Review

Effects of pharmacological therapy on sleep quality in a postoperative setting: A systematic review of randomized controlled trials

Jinny Tsang[1,2], Jasmine Kang[3], Nina Butris[2,4], Ellene Yan[2,4], Tina Shahrokhi[5], Jennita Ariaratnam[5], Aparna Saripella[2], Marina Englesakis[6], Dong-Xin Wang[7], David He[8], Frances Chung[2,4]

[1]Department of Immunology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [2]Department of Anesthesia and Pain Management, Toronto Western Hospital, University Health, [3]Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada, Network, University of Toronto, Toronto, ON, Canada, [4]Institute of Medical Science, University of Toronto, Toronto, ON, Canada, [5]School of Medicine, Royal College of Surgeons in Ireland, Dublin, Ireland, [6]Library and Information Services, University Health Network, Toronto, ON, Canada, [7]Department of Anesthesiology, Peking University First Hospital, Beijing, China, [8]Department of Anesthesiology and Pain Medicine, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada

David He and Frances Chung shared senior authorship

Abstract

Background and Aims: Postoperative sleep disturbances are associated with delayed recovery and increased incidences of complications. This systematic review aims to determine the impact of perioperative pharmacological therapies on postoperative sleep quality in the hospital.

Material and Methods: We searched MEDLINE, MEDLINE ePubs and In-Process Citations (Daily), Embase Classic + Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and PubMed for randomized controlled trials (RCTs) from inception to May 2022, with continued literature surveillance until August 2023. Studies included consisted of noncardiac surgical patients aged ≥18 years with postoperative sleep in the hospital. The primary outcome was improvement in postoperative sleep outcomes such as sleep quality, duration, efficiency, architecture, and insomnia ratings after pharmacological treatment. Additional outcomes included postoperative pain scores and opioid consumption.

Results: The search strategy yielded 21 studies (n = 3276), and 18 reported improved sleep outcomes using eight validated sleep measurement tools. Eight of 10 studies using dexmedetomidine via patient-controlled analgesia or intravenous infusion reported better sleep quality versus controls. Opioids (nalbuphine, tramadol plus sufentanil), nonopioids (zolpidem, midazolam, pregabalin), propofol total intravenous anesthesia (TIVA), *S*-ketamine, and ropivacaine nerve blocks were superior to controls in enhancing postoperative sleep quality. Eleven studies (52%) which included the combination of dexmedetomidine with opioids reported concurrent improvements in postoperative pain and sleep. Dexmedetomidine also decreased postoperative opioid analgesia consumption.

Conclusions: Evidence for the effects of perioperative pharmacological approaches on postoperative sleep are limited. High-quality RCTs of adequate power and methodology on the effects of pharmacology interventions on postoperative sleep are warranted.

Keywords: Dexmedetomidine, pain, perioperative medicine, pharmacological therapy, sleep disturbances, surgery

Address for correspondence: Dr. Frances Chung, Department of Anesthesia and Pain Management, Toronto Western Hospital, University Health Network MCL 2-405, 399 Bathurst St Toronto, ON, M5T 2S8, Canada.
E-mail: frances.chung@uhn.ca

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Introduction

Sleep is essential for memory, cardiovascular health, and metabolism.[1] Poor sleep, characterized by decreased sleep efficiency, increased sleep disturbances, longer time to fall asleep, wake after sleep onset, and decreased sleep duration,[2] is prevalent among hospitalized patients due to noise, light levels, and nurse interventions.[3] Many continue to experience sleep disturbances 6 months after hospitalization.[4]

Understanding the perioperative factors affecting sleep is important, as poor postoperative sleep can prolong hospitalizations, delay recovery, increase pain, and elevate the risk of delirium and cardiac complications.[5] Sleep quality is often worse in hospitals than at home,[6] and medications like dexmedetomidine and zolpidem have been used to address perioperative sleep disturbances.[5,7–9] Opioid overuse after low-risk surgeries is concerning due to its negative impact on sleep, increasing postoperative nausea and vomiting (PONV) and adverse reactions.[8,10,11] In addition, the choice of anesthesia and method of administration impacts postoperative sleep quality.[12]

Addressing sleep disturbances in surgical settings can help optimize perioperative outcomes.[12] While pharmacological anesthesia and analgesia are widely used, their impact on postoperative sleep quality using validated sleep measurement tools is not well characterized. This systematic review aims to summarize the impact of different pharmacological interventions on sleep quality and examines differences in other outcomes such as pain and opioid consumption compared to controls.

Material and Methods

Study design and registration

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (Prospero #CRD42022354073) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=354073). Preferred reporting items for systematic reviews and meta-analyses (PRISMA) was used as a reporting guide.[13]

Study selection criteria

The inclusion criteria were studies which 1) investigated patients 18 years or older undergoing noncardiac surgery and staying in the hospital for at least one night, 2) had patients that received pharmacological interventions, 3) provided either a standard pharmacological intervention as a control or placebo, 4) were randomized controlled trials (RCTs), and 5) evaluated outcomes of postoperative sleep disturbance using a validated subjective or objective sleep assessment tool. The exclusion criteria were 1) studies which were case studies, retrospective or prospective cohorts, 2) studies which had patients in the intensive care unit (ICU), and 3) non-English articles.[14,15]

Search strategy

An information specialist conducted the literature search. The following databases were searched from inception to May 19, 2022 via the Ovid platform: MEDLINE, MEDLINE ePubs and In-Process Citations (daily), Embase Classic + Embase, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Continued literature surveillance was done via PubMed till August 2023.

We followed the Cochrane Handbook[16] and the Cochrane Methodological Expectations of Cochrane Intervention Reviews (MECIR)[17] for conducting the search, PRISMA 2020[18] for reporting, and the Peer Review of Press Strategies (PRESS) guideline for peer-reviewing the search strategies[19] while drawing upon the PRESS 2015 Guideline Evidence-Based Checklist to avoid potential search errors. Preliminary searches were conducted, and full-text literature was mined for potential keywords and appropriately controlled vocabulary terms (such as Medical Subject Headings for MEDLINE and Emtree descriptors for Embase). The Yale MeSH Analyzer[20] facilitated the medical subject headings (MeSH) and text word analysis. The search strategy concept blocks were built on the topics of (Sleep Disturbance) AND (Postoperative OR Surgery) AND (Pharmacological Therapy) using both controlled vocabularies and text word searching for each component. Searches were limited to the English language, humans, and adults.

Study selection and data extraction

Duplicates were removed, and screening was completed using Rayyan systematic review application.[21] Using the inclusion criteria, two reviewers screened for titles and abstracts. Full-text studies were assessed for inclusion by two reviewers. Disagreements on the inclusion of studies were resolved by the senior author. Three reviewers independently extracted data from the included studies. The extracted data included demographics, study design and setting, surgery type, sleep measurement(s), intervention(s), mean preoperative and postoperative sleep scores, and prevalence of preoperative and postoperative sleep disturbances.

Quality assessment of studies

Two reviewers assessed each study's quality. For RCTs, the Cochrane Collaboration tool was used to assess

study quality based on six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[22]

Measures of sleep disturbances – subjective and objective sleep assessment tools

The standard subjective sleep assessment tools include the Pittsburgh Sleep Quality Index (PSQI) and the Richards–Campbell Sleep Questionnaire (RCSQ). PSQI is a 19-item, self-rated questionnaire that assesses sleep in the past month.[23] RCSQ is a self-rated questionnaire to assess sleep quality in the past night.[24] Other subjective assessment tools include Consensus Sleep Diary, Athens Insomnia Scale, St. Mary Hospital Sleep Questionnaire, and Insomnia Severity Index.[25–28] Objective sleep assessment tools such as polysomnography and bispectral index-Vista (BIS-Vista) provided quantitative sleep parameters.[29,30]

Results

Search strategy, study characteristics, and quality assessment

The literature search resulted in 15,076 articles [Figure 1]. After removing 975 duplicates and screening titles and abstracts, 183 articles were eligible for full-text review. Additional literature search yielded three RCTs. Altogether, 21 articles[31–51] met the inclusion criteria.

The characteristics of the included articles are listed in Tables 1 and 2. They were from five different countries: China (17),[32–39,43–46,48–51] USA (2),[41,47] Australia (1),[42] Egypt (1),[31] and South Korea (1).[40] There were 3276 patients (dexmedetomidine: 1885; opioids: 486; nonopioids and hypnotic: 230; general anesthetics [GA]: 517; regional anesthetics [RA]: 158). Eight (36%) studies consisted of orthopedic surgeries[31,35,40,41,44,45,50] and three had noncardiac mixed surgeries.[38,42,49] Fourteen (67%) studies had mainly male participants,[31–34,36,38,39,42–44,46–49] four studies with all females,[33,34,47,48] and one study not reporting gender.[35] Ten (48%) studies comprised participants with a mean age over 60.[32,36,38–40,44–46,49,50] Four (19%) studies excluded participants with a history of sleep disorders or disturbances,[37,39,43,47] one (5%) excluded participants with sleep apnea,[42] and six (29%) excluded both.[32,35,41,45,48,49] Six (29%) studies that did not have these exclusions reported nonsignificant differences in baseline sleep quality between the control and intervention groups[33,34,36,46,50,51] and four (18%) did not.[31,38,40,44]

Ten RCTs used dexmedetomidine infusion,[32,34–39,48–50] three used opioids,[33,42,44] and three used nonopioids and hypnotics.[31,41,45] Two trials used GA[46,51] and three used RA[40,43,47] [Tables 1 and 2].

Fourteen studies used subjective sleep measurements: PSQI ($n = 5$),[41,43,44,46,50] RCSQ ($n = 3$),[33,38,51] St. Mary Hospital Sleep Questionnaire ($n = 2$),[36,42] Consensus Sleep Diary ($n = 2$),[31,40] Athens Insomnia Scale ($n = 1$),[35] and Insomnia Severity Index ($n = 1$)[34] [Table 3 and Supplementary Table 1]. Seven studies used objective sleep measurement tools like BIS or BIS-Vista ($n = 2$)[37,39] and polysomnography ($n = 5$).[32,45,47–49]

Quality assessments are presented in Supplementary Figure 1a and b. Four studies had an unclear risk of bias

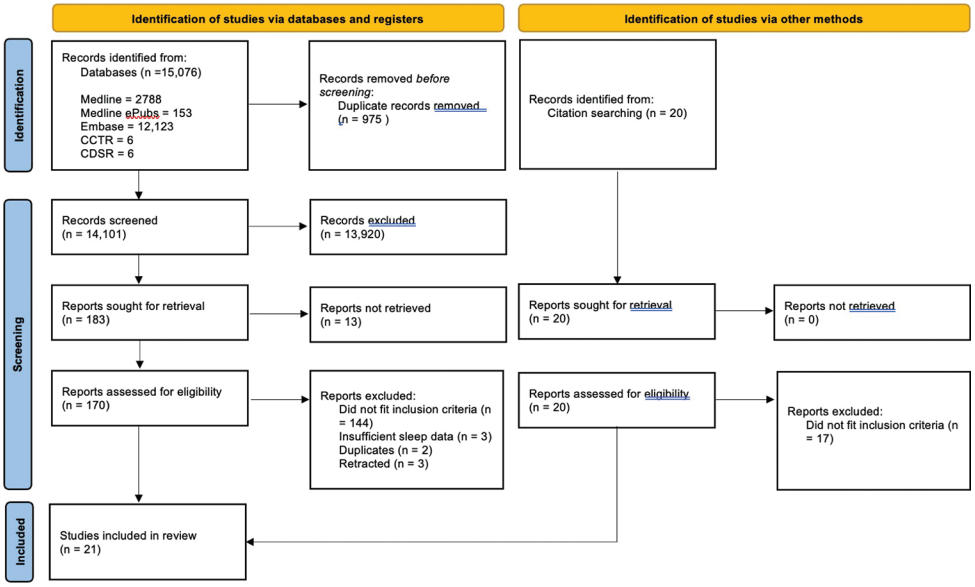

Figure 1: PRISMA flow diagram

Table 1: Demographic data and study characteristics for dexmedetomidine approaches

Author, year country	Patients (*n*)	Surgery	Preop/intraop/ postop	Intervention	Male %	Age (mean±SD)
Dexmedetomidine						
Niu, 2023[China]	49	Orthopedic	Preop	DEX IV preop + ropivacaine intraop	45	71±7
	50		Preop	DEX intranasal preop + ropivacaine intraop	50	70±6
	49		Intraop	DEX intratracheal + ropivacaine	47	71±7
Zhang, 2022[China]	44	Noncardiac mix	Postop	DEX + morphine PCA ×24–72 h	50	69±5*
	41			Placebo (saline) + morphine PCA ×24–72 h	68	69±4*
Wang, 2021[China]	23	Orthopedic	Postop	DEX + Sufentanil IV PCA	NR	50±6
	25			DEX + Sufentanil SC PCA		48±8
	25			Sufentanil IV PCA		49±7
	24			Sufentanil SC PCA		50±6
Mao, 2020[China]	29	Lateral thoracotomy	Preop, intraop, postop	DEX IV infusion preop, intraop, postop ×5 d	79	65±7
	29			Placebo (saline)	83	63±8
Sun, 2019[China]	276	Noncardiac mix	Postop	DEX + sufentanil PCA ×48 h	57	69±5*
	281			Sufentanil PCA ×48 h	56	69±7*
Yu, 2019[China]	281	Cesarean section	Postop	DEX + sufentanil PCIA	0	32±4
	276			Sufentanil PCIA	0	31±5
Jiang, 2018[China]	32	Laparoscopic abdominal	Postop	DEX^{low} (2.4 μg/kg, low-dose DEX) + oxycodone PCA	63	64±7
	33			DEX^{high} (4.8 μg/kg, high-dose DEX) + oxycodone PCA	61	64±5
	32			Oxycodone PCA	53	65±6
Chen, 2017[China]	30	Abdominal (hysterectomy)	Postop	DEX + sufentanil PCA	0	43±7
	29			Sufentanil PCA	0	45±8
Tan, 2016a[China]	22	TURP	Intraop	DEX IV infusion	100	71±7
	22			Midazolam IV infusion	100	73±9
	22			Placebo (saline)	100	71±7
Tan, 2016b[China]	53	Thoracic	Preop + postop	DEX IV infusion, GA, sufentanil PCA	31	56±7
	55			Ropivacaine TEA, GA, ropivacaine + fentanyl PCEA	24	53±7
	53			GA, sufentanil PCA	27	56±8

*DEX=Dexmedetomidine, GA=General anesthesia, intraop=Intraoperative, IQR=Interquartile range, IV=Intravenous, NR=Not reported, PCA=Patient-controlled analgesia, PCIA=Patient-controlled intravenous analgesia, PCEA=Patient-controlled epidural analgesia, preop=Preoperative, postop=Postoperative, SC=Subcutaneous, SD=Standard deviation, TEA=Thoracic epidural anesthesia, TURP=Transurethral resection of the prostate. Noncardiac mix: Gastrointestinal, pulmonary, hepatobiliary, renal, prostatic, vesical, cancer, spinal, orthopedic, urologic, thoracic, general, abdominal, superficial, plastic, neurosurgical, ear, nose, and throat, vascular, and others. *Estimated from mean (IQR)*

for random sequence generation (n = 193),[41,43,44,47] five had unclear allocation concealment (n = 353),[43,44,46–48] two had unclear blinding of participants and personnel and blinding of outcome assessment (n = 210),[44,46] and one had unclear risk for incomplete outcome data (n = 80),[44] with a total of three studies having an overall unclear risk of bias (n = 285)[43,44,46] and two having an overall low risk of bias (n = 88).[41,48] One study also had high risk of bias in blinding of participants and personnel, other bias, and overall bias (n = 9).[47] Fifteen studies had low risk of bias across all components (n = 2894),[31–40,42,45,49–51] and none had bias for selective reporting.

Changes in sleep quality after pharmacological intervention in postoperative patients

Eighteen of 21 studies reported favorable sleep outcomes when comparing pharmacological intervention to controls or placebos [Tables 3 and 4].[31–40,43–46,48–51] The timing of study interventions varied among perioperative,[33,36,37,47,50] preoperative,[31,40,43,51] intraoperative,[39,46] and postoperative.[32,34,35,38,41,42,44,45,48,49] Most studies performed sleep assessments on postoperative nights one to three,[31–35,37–40,43,44,47–51] with some assessing up to postoperative night seven.[36,46]

Dexmedetomidine

Postoperative patient controlled analgesia (PCA) with dexmedetomidine as an adjuvant to sufentanil,[34,35,38,48] oxycodone,[32] or morphine[49] resulted in better sleep outcomes in orthopedic,[35] mixed,[38,49] cesarean section,[34] or abdominal[32,48] surgical patients compared to controls [Table 3]. Dexmedetomidine combined with opioids decreased the insomnia scores,[34,35] increased the percentage of nonrapid eye movement (NREM) stage II (N2) sleep but caused no differences in N3 sleep,[32,48,49] and improved subjective sleep quality.[38]

Table 2: Demographic data and study characteristics for opioid/opiate, nonopioids/hypnotic, anesthetic approaches

Author, yearcountry	Patients (*n*)	Surgery	Preop/intraop/postop	Intervention	Male %	Age (mean±SD)
Opioid/opiates						
Fu, 2022 China	100	Abdominal	Intraop + postop	Tramadol + sufentanil IV bolus and PCA	0	42±10
	100			Sufentanil IV bolus and PCA	0	43±11
Gong, 2017 China	40	Orthopedic	Postop	Nalbuphine PCA ×48 h	63	80±2
	40			Sufentanil PCA ×48 h	53	76±3
Lee, 2012 Australia	102	Noncardiac mix	Postop	Alfentanil + morphine PCA ×48 h	59	57±13*
	104			Fentanyl PCA ×48 h	51	60±13*
Nonopioid/opiates and hypnotics						
Omara, 2019 Egypt	30	Orthopedic	Preop	Pregabalin PO	83	38±5
	30			Placebo	77	40±6
Eloy, 2017 USA	17	Orthopedic	Postop	Gabapentin PO ×2 N	41	55 (SD NR)
	12			Placebo	50	53 (SD NR)
Gong, 2015 China	70	Orthopedic	Postop	Zolpidem PO ×14 d	13	65±5
	71			Placebo	17	66±6
General anesthetics						
Zhou, 2023China	195	Thoracic	Preop	*S*-ketamine bolus before induction	37	52±9
	192			Placebo (saline)	43	51±9
Ding, 2021China	65	Abdominal	Intraop	Propofol TIVA	54	75±6
	65			Sevoflurane inhalation	52	75±6
Regional anesthetics						
Lee, 2021 South Korea	37	Orthopedic	Preop	Naloxone + ropivacaine femoral nerve block	38	63±6
	37			Ropivacaine femoral nerve block	35	65±10
Kang, 2020 China	34	Thoracoscopic lobectomy	Preop	Ropivacaine TPVB bolus, GA	62	52±11
	41			GA	39	56±10
Cronin, 2001 USA	4	Gynecologic	Intraop + postop	Bupivacaine epidural infusions ×24 h	0	41 (range 29–42)
	5			Fentanyl epidural infusions ×24 h	0	36 (range 32–49)

*GA=general anesthesia, intraop=intraoperative, IQR=interquartile range, IV=intravenous, N=night(s), NR=not reported, PCA=patient-controlled analgesia, PO=per oral, preop=preoperative, postop=postoperative, SD=standard deviation, TIVA=total intravenous anesthesia, TPVB=thoracic paravertebral nerve block. Noncardiac mix: gastrointestinal, pulmonary, hepatobiliary, renal, prostatic, vesical, cancer, spinal, orthopedic, urologic, thoracic, general, abdominal, superficial, plastic, neurosurgical, ear, nose, and throat, vascular, and others. *Estimated from mean (IQR)*

Four small-scale studies found mixed results on postoperative sleep quality after dexmedetomidine intravenous (IV) infusion.[36,37,39,50] Perioperative IV infusion of dexmedetomidine in lateral thoracotomy patients improved subjective sleep quality and increased clear-headedness versus placebo.[36] However, intraoperative dexmedetomidine infusion in patients undergoing transurethral resection of the prostate resulted in lower objective sleep quality, efficiency, and duration versus midazolam or placebo.[39] Preoperative and postoperative dexmedetomidine infusion with sufentanil PCA in thoracic surgical patients did not yield differences in objective sleep outcomes compared to GA plus sufentanil PCA.[37]

Two trials investigated different methods of dexmedetomidine administration. Subjective sleep quality after orthopedic surgery was better using IV infusion compared to intranasal and intratracheal administration,[50] but insomnia ratings remained similar versus subcutaneous administration.[35] No differences were found in subjective sleep quality, efficiency, or time spent in sleep stages on using a higher (4.8 μg/kg) or lower dose (2.4 μg/kg) of dexmedetomidine with oxycodone in PCA.[32]

Opioids, nonopioids, and hypnotics

Three articles used opioids, but results are difficult to compare because of heterogeneity in drug types [Table 4]. PCA nalbuphine significantly improved subjective sleep quality in orthopedic patients than PCA sufentanil.[44] Similarly, combining tramadol and sufentanil for intraoperative infusion and PCA in abdominal surgical patients improved subjective sleep quality than sufentanil alone.[33] In contrast, alfentanil plus morphine PCA after noncardiac surgery did not enhance subjective sleep quality versus fentanyl PCA.[42]

Results on nonopioids and hypnotics are less robust due to small cohorts restricted to orthopedic patients. While patients receiving preoperative oral pregabalin had better subjective sleep quality versus placebo,[31] patients given oral gabapentin postoperatively rated no differences.[41] However,

Table 3: Objective and subjective sleep quality assessments of surgical patients after dexmedetomidine approaches

Author, year	Assessment tool	Preop/intraop/postop	Treatment versus control	Major findings
Dexmedetomidine				
Niu, 2023	PSQI	Preop + intraop	DEX IV versus intranasal and intratracheal	↑ sleep quality N2
			DEX intranasal versus intratracheal or IV	n.s. sleep quality
Zhang, 2022	PSG	Postop	DEX + morphine versus placebo + morphine	↑ sleep quality, %NREM stage 2, sleep efficiency and duration, ↓ sleep fragmentation, %NREM stage 1, n.s. %NREM stage 3, %REM N1
Wang, 2021	AIS	Postop	DEX + sufentanil versus sufentanil	↑ sleep quality (↓ insomnia score) on N1–2
			IV versus SC	n.s. sleep quality
Mao, 2020	SMH	Preop + intraop + postop	DEX versus placebo	↑ sleep quality N2, 5, ↑ clear-headedness N5, n.s. sleep satisfaction
Sun, 2019	RCSQ	Postop	DEX + sufentanil versus sufentanil	↑ sleep quality N1–3
Yu, 2019	ISI	Postop	DEX + sufentanil versus sufentanil	↑ sleep quality (↓ insomnia score) N2
Jiang, 2018	PSG	Postop	DEX^{low} + oxycodone and DEX^{high} + oxycodone versus oxycodone	↑ sleep quality, sleep efficiency, %NREM stage 1, 2, ↓ arousal N1-2, n.s. %REM, %NREM stage 3
			DEX^{low} + oxycodone versus DEX^{high} + oxycodone	n.s. sleep outcomes
Chen, 2017	PSG	Postop	DEX + sufentanil versus sufentanil	↑ sleep efficiency, %NREM stage 2 N1–2, ↓ arousal, %NREM stage 1 N1–2, n.s. %REM, %NREM stage 3 N1–2
Tan, 2016a	BIS-Vista	Intraop	DEX versus placebo	↓ sleep efficiency, sleep duration N1
			DEX versus midazolam	↓ sleep efficiency, sleep quality, sleep duration N1
			Midazolam versus placebo	↑ sleep efficiency, sleep duration N1
Tan, 2016b	BIS-Vista	Preop + postop	Ropivacaine TEA versus DEX + GA and GA only	↑ sleep quality, sleep efficiency N1
			DEX + GA versus GA only	n.s. sleep quality

ASI=Athens Insomnia Scale, BIS-Vista=bispectral index-Vista, DEX=dexmedetomidine, GA=general anesthesia, intraop=intraoperative, ISI=insomnia severity index, IV=intravenous, N1=night 1, NREM=non-rapid eye movement, n.s. = not significant, PCA=patient-controlled analgesia, postop=postoperative, preop=preoperative, PSG=polysomnography, PSQI=Pittsburgh Sleep Quality Index, RCSQ=Richards–Campbell Sleep Questionnaire, REM=rapid eye movement, SC=subcutaneous, SEI=sleep efficiency index, SMH=St. Mary's Hospital Sleep Questionnaire, SWS=slow wave sleep, TEA=thoracic epidural anesthesia

postoperative oral zolpidem resulted in better sleep quality and efficacy than placebo.[45]

Anesthetic techniques

Participants given propofol total IV anesthesia (TIVA) for abdominal surgery experienced better objective sleep quality than those given inhalational anesthesia [Table 4].[46] A S-ketamine bolus before GA induction for thoracoscopic lobectomy surgery resulted in better sleep quality versus placebo.[51]

Studies on postoperative sleep quality after RA were limited by small samples. Using ropivacaine thoracic paravertebral nerve block (TPVB) with GA for thoracoscopic lobectomy resulted in better objective sleep quality than GA alone.[43] Naloxone as an adjuvant to ropivacaine in femoral nerve block for total knee arthroplasty also improved subjective sleep quality versus ropivacaine alone.[40] In contrast, intraoperative and postoperative epidural bupivacaine infusions for gynecologic patients were largely inferior in enhancing postoperative sleep architecture, such as the proportion of rapid eye movement (REM), NREM sleep, and sleep duration, versus fentanyl alone.[47]

Other outcomes

In 17 (81%) RCTs evaluating postoperative pain [Table 5],[31,32,34–38,40–45,47–49,51] 12 demonstrated reduced pain ratings with experimental treatment. Five studies using dexmedetomidine reported lower postoperative pain,[32,34,35,38,48] while three found no differences.[36,37,49] Studies using pregabalin,[31] nalbuphine,[44] alfentanil plus morphine,[42] zolpidem,[45] and ropivacaine with naloxone or alone also showed improved pain outcomes.[40,43] However, patients receiving bupivacaine experienced more pain than those receiving fentanyl.[47] Eleven studies that had reported improved pain outcomes had enhanced sleep: five using dexmedetomidine[32,34,35,38,48] and the remaining studies using nalbuphine, pregabalin, zolpidem, ropivacaine, or naloxone adjuvant.[31,37,40,43–45]

Four studies reported the rates of postoperative complications.[32,40,43,44] A higher dose of dexmedetomidine caused more severe hypotension.[32] Fewer adverse reactions were reported when comparing nalbuphine to sufentanil.[44] Seven studies assessed PONV after surgery,[35,36,40,42,45,50,51] with one showing reduced

Table 4: Objective and subjective sleep quality assessments of surgical patients after opioid/opiate, nonopioid/hypnotic, and anesthetic approaches

Author, year	Assessment tool	Preop/intraop/postop	Treatment versus control	Major findings
Opioid/opiates				
Fu, 2022	RCSQ	Intraop + postop	Tramadol + sufentanil versus sufentanil	↑ sleep quality N1, 2, 3
Gong, 2017	PSQI	Postop	Nalbuphine versus sufentanil	↑ sleep quality N1–2
Lee, 2012	SMH	Postop	Alfentanil + morphine versus fentanyl	n.s. sleep quality, pain-related awakenings
Nonopioid/opiates and hypnotics				
Omara, 2019	CSD	Preop	Pregabalin versus placebo	↑ sleep quality N1
Eloy, 2017	PSQI	Postop	Gabapentin versus placebo	n.s. sleep quality
Gong, 2015	PSG	Postop	Zolpidem versus placebo	↑ sleep quality, efficacy
General anesthetics				
Zhou, 2023	RCSQ	Preop	*S*-ketamine versus placebo	↑ sleep quality N1, n.s. N3
Ding, 2021	PSQI	Intraop	Propofol TIVA versus sevoflurane	↑ sleep quality N1, 3, 7
Regional anesthetics				
Lee, 2021	CSD	Preop	Naloxone + ropivacaine versus ropivacaine	↑ sleep quality N1
Kang, 2020	PSQI	Preop	Ropivacaine TPVB + GA versus GA	↑ sleep quality N1, 2, 3
Cronin, 2001	PSG	Intraop + postop	Bupivacaine epidural versus fentanyl	↑ %SWS N1–2, ↓ %SWS N3, n.s. %REM, %NREM, sleep duration, subjective sleep quality N1–3

CSD=Consensus Sleep Diary, GA=general anesthesia, intraop=intraoperative, IV=intravenous, N1=night 1, NREM=non-rapid eye movement, n.s. = not significant, postop=postoperative, preop=preoperative, PSG=polysomnography, PSQI=Pittsburgh Sleep Quality Index, RCSQ=Richards–Campbell Sleep Questionnaire, REM=rapid eye movement, SMH=St. Mary's Hospital Sleep Questionnaire, SWS=slow wave sleep, TIVA=total intravenous anesthesia, TPVB=thoracic paravertebral nerve block

incidences using a combination of dexmedetomidine and sufentanil versus sufentanil alone, one using IV dexmedetomidine versus intranasal and intratracheal administration, one using a combination of alfentanil and morphine versus fentanyl, and one using zolpidem versus placebo.[35,42,45,50]

Postoperative opioid and nonopioid analgesia consumption was reported in seven studies.[32,35,38,43,45,48,49] Combining dexmedetomidine and sufentanil in PCA decreased overall sufentanil consumption.[35,48] In contrast, opioid consumption did not differ between patients receiving PCA dexmedetomidine and those receiving placebo with morphine.[49] Dexmedetomidine infusion combined with sufentanil[38] or oxycodone[32] decreased the requirement for nonopioid analgesia. Opioid consumption also decreased when postoperative oral zolpidem or ropivacaine thoracic paravertebral block was provided.[43,45]

Two studies investigated postoperative serum inflammatory biomarkers. Ropivacaine thoracic epidural anesthesia (TEA) resulted in lower postoperative interleukin-6 (IL-6) plasma levels but no changes in tumor necrosis factor-alpha (TNF-α) levels versus dexmedetomidine plus GA and GA alone.[37] Likewise, propofol TIVA not only decreased cortisol, IL-6, and S-100β levels, but also lowered melatonin levels.[46]

Discussion

In our systematic review of 21 RCTs on pharmacological therapies, 18 reported enhanced postoperative sleep outcomes, particularly with dexmedetomidine. These outcomes included objective measurements of sleep efficiency, duration, architecture, subjective sleep quality, and insomnia ratings. However, the diverse sleep assessment tools made study comparisons challenging. Polysomnography, PSQI, and RCSQ are widely used and reliable for measuring sleep quality,[23,24,30] but BIS index is predominantly used for monitoring sedation during surgery and less frequently for sleep assessment,[52] given its lower reliability to identify REM sleep.[29,53] Nevertheless, its simplicity and accessibility have made it ideal for measuring sleep in ICU compared to polysomnography and is gaining popularity in other settings.[53]

Due to additional heterogeneity in intervention types, surgeries, and outcomes, we were unable to synthesize consistent metrics to perform a meta-analysis. Heterogeneity arose from limiting our inclusion only for studies using a validated sleep measurement tool. Most excluded RCTs used nonvalidated tools such as a 0–100 scale for subjective sleep rating, with little standardization on the outcomes measured within this subjective rating. Our focus on in-hospital sleep

Table 5: Other outcomes

Author, year	Treatment versus control	Secondary outcomes
Dexmedetomidine		
Niu, 2023	DEX IV versus intranasal	↓ delirium POD1–3
	DEX IV versus intratracheal	n.s. delirium
	DEX IV versus intranasal and intratracheal	↓ PONV, ↑ bradycardia
Zhang, 2022	DEX + morphine versus placebo + morphine	n.s. pain, morphine consumption, opioid and sedative use, delirium, LOS, adverse events
Wang, 2021	DEX + sufentanil versus sufentanil	↓ pain, sufentanil consumption 24 and 48 h postop, PONV, n.s. pruritus
	DEX + sufentanil IV versus SC	n.s. pain, sufentanil consumption 24 and 48 h postop, PONV
Mao, 2020	DEX versus placebo	n.s. pain, PONV, recovery rate
Sun, 2019	DEX + sufentanil versus sufentanil	↓ pain at rest and movement, ↓ nonopioid pain rescue requirement, n.s. delirium
Yu, 2019	DEX + sufentanil versus sufentanil	↓ pain at 24, 48 h postpartum, n.s. antenatal depressive symptoms, sedation score, adverse events
Jiang, 2018	DEX^{high} and DEX^{low} versus oxycodone DEX^{high} versus DEX^{low} and oxycodone	↓ pain at 4, 6, 12 h postop, ↓ rates of nonopioid rescue analgesia ↑ incidence of hypotension, n.s. incidence of bradycardia, respiratory depression
Chen, 2017	DEX + sufentanil versus sufentanil	↓ pain, sufentanil consumption 6, 24, 48 h postop; ↑ sedation levels
Tan, 2016a	DEX and midazolam versus placebo	↑ intraop sedation
Tan, 2016b	Ropivacaine TEA versus DEX + GA and GA	↓ pain D1, intraop blood pressure, plasma IL-6 conc., n.s. plasma TNFα conc.
	DEX + GA versus GA	n.s. pain, plasma IL-6 and TNF-α conc.
Opioid/opiates		
Fu, 2022	Tramadol + sufentanil versus sufentanil	↓ depression scores on D1–3, n.s. anxiety symptoms
Gong, 2017	Nalbuphine versus sufentanil	↓ pain, PCIA use, adverse reactions, and sedation scores
Lee, 2012	Alfentanil + morphine versus fentanyl	↓ pain and PONV, ↑ pruritis D1, n.s. sedation levels
Nonopioid/opiates and hypnotics		
Omara, 2019	Pregabalin versus placebo	↓ pain at 4, 6, 12 h postop, n.s. postop Cx
Eloy, 2017	Gabapentin versus placebo	n.s. pain
Gong, 2015	Zolpidem versus placebo	↓ pain N3 and 5, opioid analgesic consumption, and PONV, sleep efficacy associated with ROM D5 and 7
General anesthetics		
Zhou, 2023	*S*-ketamine versus placebo	n.s. pain at rest and coughing, postop analgesic use, anxiety and depression scores, PONV, delirium, dizziness POD1–3
Ding, 2021	Propofol TIVA versus sevoflurane	↑ cognitive function, ↓ plasma melatonin, cortisol, IL-6, S-100β conc. on D1, 3, 7
Regional anesthetics		
Lee, 2021	Naloxone + ropivacaine versus ropivacaine	↓ pain at rest, 12 h, 18 h postop and during activity 12 h postop, n.s. PONV, ROM, Cx
Kang, 2020	Ropivacaine TPVB + GA versus GA	↓ pain and oxycodone consumption on D1, n.s. analgesia deficiency, pulmonary Cx, LOS
Cronin, 2001	Bupivacaine epidural versus fentanyl	↑ pain on D2

conc. = Concentration (pg/ml), Cx=complications, D1=day 1, DEX=dexmedetomidine, GA=general anesthesia, IL-6=interleukin-6, intraop=intraoperative, IV=intravenous, LOS=length of hospital stay, N3=night 3, n.s. = not significant, PCA=patient-controlled analgesia, PCEA=patient-controlled epidural analgesia, POD=postoperative day, PONV=postoperative nausea and vomiting, postop=postoperative, ROM=range of motion, SC=subcutaneous, TEA=thoracic epidural anesthesia, TNF-α=tumor necrosis factor-alpha, TPVB=thoracic paravertebral nerve block

measurements further restricted the inclusion of studies using PSQI and RCSQ, which are commonly used to perform meta-analyses.

Postoperative sleep disturbances are influenced by factors such as pain, anxiety, excessive light, noise, and nursing activities during nighttime,[4,5,54,55] leading to disruptions in sleep architecture, increased sleep latency, and shifts from REM and N3 "deep" sleep to N1 and N2 "light" sleep, negatively impacting illness severity.[4,54] Dexmedetomidine, a central α-2 adrenergic receptor agonist, promotes sleep by inhibiting noradrenaline release in the locus coeruleus.[5,9,56] While it can promote biomimetic sleep by increasing the proportion of N3 sleep to better approximate natural sleep,[57] our findings instead reported increases in N1 and N2 sleep but not REM or N3 sleep proportion.[32,48,49]

Low-dose dexmedetomidine infusion in two large retrospective surgical studies (n = 11,797) decreased the incidences of postoperative sleep disturbances compared to placebo,[58,59] confirming that low-dose dexmedetomidine can improve sleep without risking hypotension.[32,49,60] Findings are consistent with debates surrounding the optimal dosage of dexmedetomidine and its potential to cause adverse sympatholytic effects at higher doses.[61]

Hypnotics and benzodiazepines are commonly used for postoperative sleep improvement,[55] but we found limited studies using our inclusion criteria. Zolpidem acts on gamma-aminobutyric acid type A ($GABA_A$) receptors in the cerebellum to induce sedative effects to enhance sleep,[45,62] but incorrect dosage can cause complex sleep behaviors and delirium.[55,63] Midazolam infusion has shown mixed results, with a Cochrane review reporting outcomes of drowsiness, pain, and anxiety after midazolam use during medical procedures.[39,64]

Propofol GA increases sleep duration, but disrupts circadian rhythms and melatonin production by interacting with hypothalamic GABAergic neurons to produce a state of unconsciousness.[55,65,66] While propofol TIVA improved sleep and cognitive outcomes versus sevoflurane, it also decreased postoperative plasma melatonin levels,[46] which may contribute to sleep disruption.[67,68] Comparisons between propofol TIVA and volatile anesthesia on postoperative sleep are limited, with no differences found in incidences of postoperative cognitive dysfunction.[69]

Combining RA with GA offers benefits for postoperative pain, recovery, and delirium.[70] Ropivacaine may improve sleep through better pain control,[37,43] but further research is needed to understand the underlying mechanisms.[8,71] Bupivacaine is less preferred than ropivacaine due to toxicity concerns[72] and lacks evidence in promoting postoperative sleep and pain control due to a small sample size.[47] Further RCTs are needed to better understand the impact of RA on postoperative sleep quality and recovery.

High doses of short-acting opioids disrupt sleep by binding to μ-opioid receptors involved in sleep regulation,[8,71] resulting in postoperative ileus, urinary retention, PONV, longer hospital stays, and increased pain, which may exacerbate sleep disruptions.[8,73] However, tramadol with sufentanil improved sleep quality,[33] possibly due to its opioid-sparing effects and inhibition of serotonin and norepinephrine reuptake.[74] Nonopioid analgesics with opioid-sparing effects, such as dexmedetomidine-opioid combinations,[35,48] are more desirable for postoperative sleep,[35,48,73,75] likely due to a dditive and synergistic analgesic effects.[76] In particular, IV dexmedetomidine allows for direct action on α-2 receptors to prolong analgesia, compared to other routes of administration.[50,76]

While zolpidem reduced the need for opioid rescue analgesia,[45] hypnotics are not considered opioid-sparing medications.[77] Instead, local anesthetics like ropivacaine provide pain relief by inhibiting sodium influx and blocking impulse conduction in nerve fibers, potentially reducing opioid consumption.[78] While ropivacaine TPVB combined with GA decreased postoperative oxycodone consumption,[43] more studies with larger sample size are required to confirm this finding.

Multimodal approaches that combine different analgesics can optimize pain management by targeting nociceptive, neuropathic, psychogenic, and idiopathic surgical pain simultaneously.[79] This minimizes adverse effects, promotes opioid sparing, and accommodates personal tolerance to medications,[12,79] which was consistent with the combination of dexmedetomidine with sufentanil, oxycodone, and morphine.[34,35,38,48,49,61] Combining naloxone with ropivacaine enhanced sleep and pain outcomes,[40] possibly by acting in the nucleus accumbens and amygdala to decrease spontaneous pain behavior, but supporting evidence is limited.[80] Although combining RA and GA showed improvements in sleep and pain, more studies and larger samples are required to validate these findings.[37,43]

The pain–sleep relationship is bidirectional, with pain disrupting sleep architecture and poor sleep altering pain perception.[8] Dexmedetomidine use improved both pain and sleep,[32,34,35,38,48] likely through the suppression of substance P and glutamate, neurotransmitters that mediate pain perception.[5,81] Although pregabalin improved sleep and pain after orthopedic surgery,[31] anticonvulsants primarily relieve neuropathic pain,[82] and nerve injuries are rare after total knee or hip arthroplasty.[83–85]

REM disruption is usually more pronounced after major surgeries.[5] Tissue trauma from invasive surgeries and sympathetic activation from sleep deprivation can lead to the release of proinflammatory cytokines and reduce melatonin secretion, which are associated with major cardiac events.[5,55] We found ropivacaine TEA and propofol TIVA helped to lower IL-6 while improving postoperative sleep,[37,46] but research is needed to characterize the relationship between surgical trauma and postoperative sleep.

There are several limitations to this systematic review. First, studies varied in sample size, patient characteristics, interventions, surgeries, timing of intervention, and sleep assessment tools, which hindered direct comparisons of sleep outcomes. This heterogeneity was unavoidable even

with the strict selection criteria. Trends in sleep outcomes were also difficult to compare, given that sleep is a highly subjective experience, and most studies used a subjective method to measure sleep quality. Second, studies measuring objective sleep may have intentionally limited overnight interventions to decrease sleep disturbance and artifacts in sleep architecture, leading to inaccurate assessment of hospital sleep quality. Third, many of the studies we have included measured sleep as a secondary outcome and may not be powered to accurately measure sleep quality. Nevertheless, this systematic review gave a summary of the best evidence that we have on the pharmacological therapy on postoperative sleep quality.

A recent systematic review and meta-analysis found that the pooled prevalence of sleep disturbances at preoperative assessment was 60% and the risk factors for postoperative sleep disturbances were pre-existing disturbed sleep and anxiety.[86] Also, patients with postoperative delirium had a higher prevalence of sleep disturbances, and sleep disturbances in surgical patients negatively impacts postoperative outcomes and well-being. This emphasizes the need for future studies that investigate the effects of pharmacological therapies on sleep as a primary outcome.

In conclusion, pharmacological treatments found in our systematic review were favorable for enhancing postoperative sleep. Improved postoperative sleep was associated with better pain scores and decreased opioid consumption. However, evidence for the effects of perioperative pharmacological approaches on postoperative sleep quality are limited, especially those using validated sleep measurement tools. High-quality RCTs of adequate power and methodology are warranted.

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Conflicts of interest

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References

1. Mukherjee S, Patel SR, Kales SN, Ayas NT, Strohl KP, Gozal D, *et al*. An Official American Thoracic Society Statement: The Importance of Healthy Sleep. Recommendations and Future Priorities. Am J Respir Crit Care Med 2015;191(12):1450–8.
2. Nelson KL, Davis JE, Corbett CF. Sleep quality: An evolutionary concept analysis. Nurs Forum (Auckl) 2022;57(1):144–51.
3. Elliott R, Rai T, McKinley S. Factors affecting sleep in the critically ill: An observational study. J Crit Care 2014;29(5):859–63.
4. Altman MT, Knauert MP, Pisani MA. Sleep Disturbance after Hospitalization and Critical Illness: A Systematic Review. Ann Am Thorac Soc 2017;14(9):1457–68.
5. Rampes S, Ma K, Divecha YA, Alam A, Ma D. Postoperative sleep disorders and their potential impacts on surgical outcomes. The Journal of Biomedical Research 2020;34(4):271.
6. Wesselius HM, van den Ende ES, Alsma J, ter Maaten JC, Schuit SCE, Stassen PM, *et al*. Quality and Quantity of Sleep and Factors Associated With Sleep Disturbance in Hospitalized Patients. JAMA Intern Med 2018;178(9):1201.
7. Wright CE, Bovbjerg DH, Montgomery GH, Weltz C, Goldfarb A, Pace B, *et al*. Disrupted Sleep the Night Before Breast Surgery Is Associated with Increased Postoperative Pain. J Pain Symptom Manage 2009;37(3):352–62.
8. Chouchou F, Khoury S, Chauny JM, Denis R, Lavigne GJ. Postoperative sleep disruptions: A potential catalyst of acute pain? Sleep Med Rev 2014;18(3):273–82.
9. Huang X, Lin D, Sun Y, Wu A, Wei C. Effect of Dexmedetomidine on Postoperative Sleep Quality: A Systematic Review. Drug Des Devel Ther 2021;Volume 15:2161–70.
10. Ladha KS, Neuman MD, Broms G, Bethell J, Bateman BT, Wijeysundera DN, *et al*. Opioid Prescribing After Surgery in the United States, Canada, and Sweden. JAMA Netw Open 2019;2(9):e1910734.
11. Fiore JF, El-Kefraoui C, Chay MA, Nguyen-Powanda P, Do U, Olleik G, *et al*. Opioid versus opioid-free analgesia after surgical discharge: A systematic review and meta-analysis of randomised trials. The Lancet [Internet] 2022;399(10343):2280–93. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673622005827.
12. Su X, Wang DX. Improve postoperative sleep. Curr Opin Anaesthesiol 2018;31(1):83–8.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6(7):e1000097.
14. McKenzie J, Brennan S, Ryan R, Thomson H, Johnston R, Thomas J. Defining the criteria for including studies and how they will be grouped for the synthesis [Internet]. In: Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, *et al*., editors. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane; 2023 [cited 2023 Nov 14]. Available from: www.training.cochrane.org/handbook.
15. Cumpston MS, McKenzie JE, Thomas J, Brennan SE. Current practice in systematic reviews including the 'PICO for each synthesis' and methods other than meta-analysis: Protocol for a cross-sectional study [version 1; peer review: Awaiting peer review]. F1000Res 2021;9:1–9.
16. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, *et al*., editors. Cochrane Handbook for Systematic Reviews of Interventions [Internet]. 6.4. Cochrane; 2023 [cited 2023 Apr 23]. Available from: www.training.cochrane.org/handbook.
17. Higgins J, Lasserson T, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews: London [Internet]. 2016 [cited 2023 Apr 23];Available from: https://community.cochrane.org/mecir-manual.

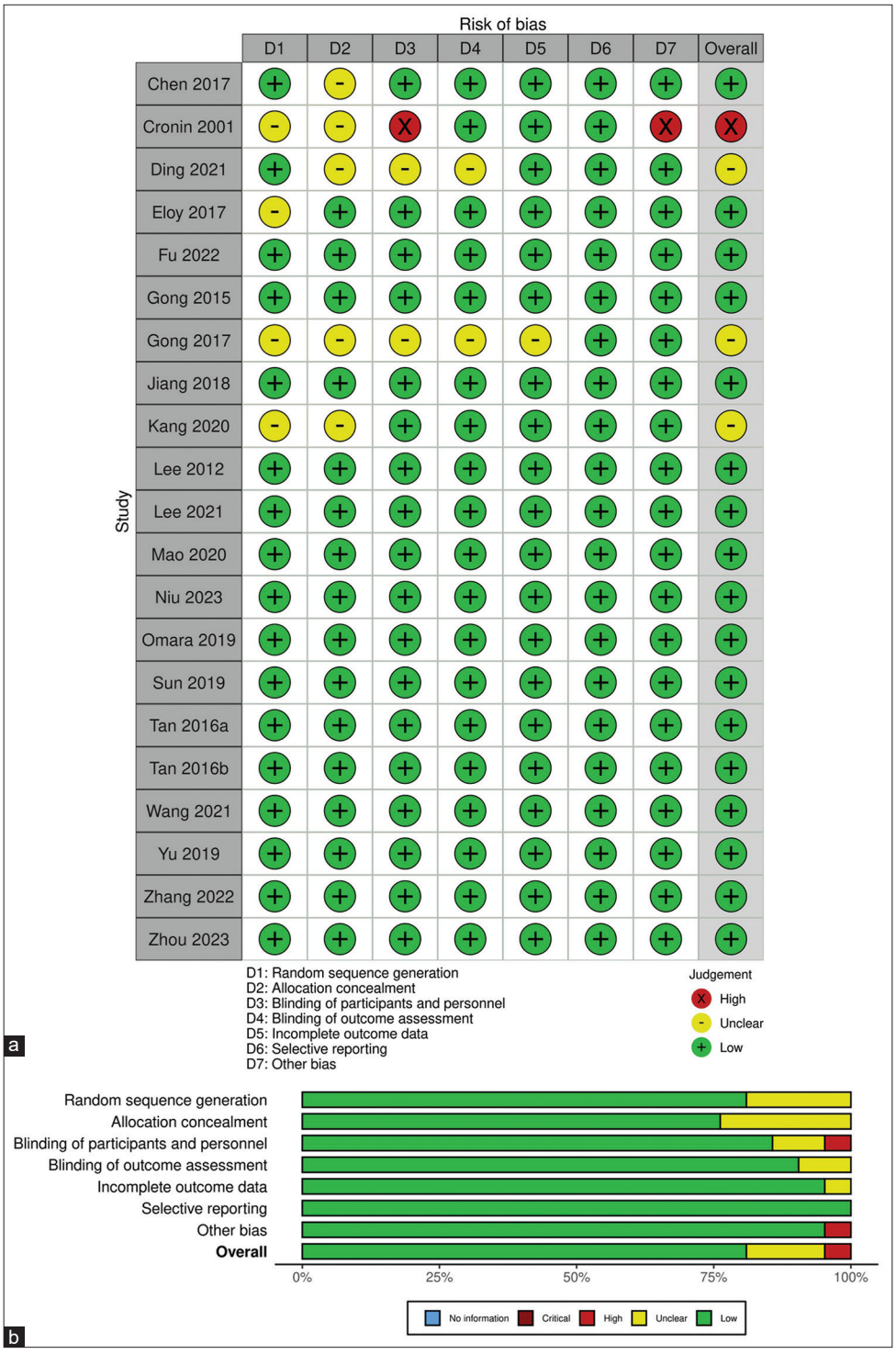
18. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.
19. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40–6.
20. Grossetta Nardini H, Wang L. The Yale MeSH Analyzer [Internet]. New Haven, CT: Cushing/Whitney Medical Library2021 [cited 2023 Apr 23];Available from: https://mesh.med.yale.edu.
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016;5(1):210.
22. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343(oct18 2):d5928–d5928.
23. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res 1989;28(2):193–213.
24. Elliott R, Axelin A, Richards KC, Vahlberg T, Ritmala-Castren M. Sensitivity and specificity of proposed Richards-Campbell Sleep Questionnaire cut-off scores for good quality sleep during an ICU stay. J Clin Nurs 2023;32(11–12):2700–8.
25. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. The diagnostic validity of the Athens Insomnia Scale. J Psychosom Res 2003;55(3):263–7.
26. Carney CE, Buysse DJ, Ancoli-Israel S, Edinger JD, Krystal AD, Lichstein KL, *et al*. The Consensus Sleep Diary: Standardizing Prospective Sleep Self-Monitoring. Sleep 2012;35(2):287–302.
27. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. Sleep 2011;34(5):601–8.
28. Ellis BW, Johns MW, Lancaster R, Raptopoulos P, Angelopoulos N, Priest RG. The St. Mary's Hospital Sleep Questionnaire: A Study of Reliability. Sleep 1981;4(1):93–7.
29. Giménez S, Romero S, Alonso JF, Mañanas MÁ, Pujol A, Baxarias P, *et al*. Monitoring sleep depth: Analysis of bispectral index (BIS) based on polysomnographic recordings and sleep deprivation. J Clin Monit Comput 2017;31(1):103–10.
30. Rundo JV, Downey R. Polysomnography. In: Handbook of Clinical Neurology. Elsevier B.V.; 2019. page 381–92.
31. Omara AF, Ahmed SA, Abusabaa MMA. The Effect Of The Use Of Pre-Emptive Oral Pregabalin On The Postoperative Spinal Analgesia In Patients Presented For Orthopedic Surgeries: Randomized Controlled Trial . J Pain Res 2019;Volume 12:2807–14.
32. Jiang Z, Zhou G, Song Q, Bao C, Wang H, Chen Z. Effect of Intravenous Oxycodone in Combination With Different Doses of Dexmedetomdine on Sleep Quality and Visceral Pain in Patients After Abdominal Surgery. Clin J Pain 2018;34(12):1126–32.
33. Fu M, Chen S, Xu R, Chen J, Chen X, Gan W, *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;Volume 16:1289–300.
34. Yu H, Wang S, Quan C, Fang C, Luo S, Li D, *et al*. Dexmedetomidine Alleviates Postpartum Depressive Symptoms following Cesarean Section in Chinese Women: A Randomized Placebo-Controlled Study. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 2019;39(10):994–1004.
35. Wang J, Cui L, Fan L, Wang J. Clinical Effect of Different Drugs and Infusion Techniques for Patient-controlled Analgesia After Spinal Tumor Surgery: A Prospective, Randomized, Controlled Clinical Trial. Clin Ther 2021;43(6):1020–8.
36. Mao Y, Sun X, Si L, Chen L, Liu X, Zhang Z, *et al*. Perioperative Dexmedetomidine Fails to Improve Postoperative Analgesic Consumption and Postoperative Recovery in Patients Undergoing Lateral Thoracotomy for Thoracic Esophageal Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial. Pain Res Manag 2020;2020:1–12.
37. Tan W, Guo B, Ma H, Li X, Fang B, Lv H. Changes in postoperative night bispectral index of patients undergoing thoracic surgery with different types of anaesthesia management: A randomized controlled trial. Clin Exp Pharmacol Physiol 2016;43(3):304–11.
38. Sun Y, Jiang M, Ji Y, Sun Y, Liu Y, Shen W. Impact of postoperative dexmedetomidine infusion on incidence of delirium in elderly patients undergoing major elective noncardiac surgery: A randomized clinical trial . Drug Des Devel Ther 2019;Volume 13:2911–22.
39. Tan W fei, Miao E ya, Jin F, Ma H, Lu H wei. Changes in First Postoperative Night Bispectral Index After Daytime Sedation Induced by Dexmedetomidine or Midazolam Under Regional Anesthesia. Reg Anesth Pain Med 2016;41(3):380–6.
40. Lee SC, Kim JH, Choi SR, Park SY. A Low Dose of Naloxone Added to Ropivacaine Prolongs Femoral Nerve Blockade: A Randomized Clinical Trial. Pain Res Manag 2021;2021:1–8.
41. Eloy JD, Anthony C, Amin S, Caparó M, Reilly MC, Shulman S. Gabapentin Does Not Appear to Improve Postoperative Pain and Sleep Patterns in Patients Who Concomitantly Receive Regional Anesthesia for Lower Extremity Orthopedic Surgery: A Randomized Control Trial. Pain Res Manag 2017;2017:1–5.
42. Lee A, O'Loughlin E, Roberts LJ. A double-blinded randomized evaluation of alfentanil and morphine vs fentanyl: Analgesia and sleep trial (DREAMFAST). Br J Anaesth 2013;110(2):293–8.
43. Kang K, Meng X, Li B, Yuan J, Tian E, Zhang J, *et al*. Effect of thoracic paravertebral nerve block on the early postoperative rehabilitation in patients undergoing thoracoscopic radical lung cancer surgery. World J Surg Oncol 2020;18(1):298.
44. Gong Y, Zhang Y, Tao S. Nalbuphine for analgesia after fracture surgery and its effect on circulating inflammatory factors. Exp Ther Med 2017;15(1):859–63.
45. 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(11):1897–901.
46. Ding F, Wang X, Zhang L, Li J, Liu F, Wang L. Effect of propofol-based total intravenous anaesthesia on postoperative cognitive function and sleep quality in elderly patients. Int J Clin Pract 2021;75(7).
47. Cronin AJ, Keifer JC, Davies MF, King TS, Bixler EO. Postoperative Sleep Disturbance: Influences of Opioids and Pain in Humans. Sleep 2001;24(1):39–44.
48. Chen Z, Tang R, Zhang R, Jiang Y, Liu Y. Effects of dexmedetomidine administered for postoperative analgesia on sleep quality in patients undergoing abdominal hysterectomy. J Clin Anesth 2017;36:118–22.
49. Zhang ZF, Su X, Zhao Y, Zhong CL, Mo XQ, Zhang R, *et al*. Effect of mini-dose dexmedetomidine supplemented intravenous analgesia on sleep structure in older patients after major noncardiac surgery: A randomized trial. Sleep Med 2023;102:9–18.
50. Niu JY, Yang N, Tao QY, He Y, Hou YB, Ning RD, *et al*. Effect of Different Administration Routes of Dexmedetomidine on Postoperative Delirium in Elderly Patients Undergoing Elective Spinal Surgery: A Prospective Randomized Double-Blinded Controlled Trial. Anesth Analg 2023;136(6):1075–83.
51. Zhou R, Zhang Y, Tang S, Zhang X, Wang Y, Liu Y, *et al*. A Single Preoperative Dose of S-Ketamine Has No Beneficial Effect on Chronic Postsurgical Pain in Patients Undergoing Video-Assisted Thoracoscopic Surgical Lung Lesion Resection: A Prospective

Randomized Controlled Study. J Cardiothorac Vasc Anesth 2023;37(8):1433–41.
52. Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, *et al*. Anesthesia Awareness and the Bispectral Index. New England Journal of Medicine 2008;358(11):1097–108.
53. Pedrão RAA, Riella RJ, Richards K, Valderramas SR. Viability and validity of the bispectral index to measure sleep in patients in the intensive care unit. Rev Bras Ter Intensiva 2020;32(4):535–41.
54. Pisani MA, Friese RS, Gehlbach BK, Schwab RJ, Weinhouse GL, Jones SF. Sleep in the Intensive Care Unit. Am J Respir Crit Care Med 2015;191(7):731–8.
55. Luo M, Song B, Zhu J. Sleep Disturbances After General Anesthesia: Current Perspectives. Front Neurol 2020;11.
56. Yu SB. Dexmedetomidine sedation in ICU. Korean J Anesthesiol 2012;62(5):405.
57. Akeju O, Hobbs LE, Gao L, Burns SM, Pavone KJ, Plummer GS, *et al*. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: A pilot study. Clinical Neurophysiology 2018;129(1):69–78.
58. Cai J, Chen Y, Hao X, Zhu X, Tang Y, Wang S, *et al*. Effect of Intraoperative Dexmedetomidine Dose on Postoperative First Night Sleep Quality in Elderly Surgery Patients: A Retrospective Study With Propensity Score-Matched Analysis. Front Med (Lausanne) 2020;7.
59. Duan G, Wang K, Peng T, Wu Z, Li H. The Effects of Intraoperative Dexmedetomidine Use and Its Different Dose on Postoperative Sleep Disturbance in Patients Who Have Undergone Non-Cardiac Major Surgery: A Real-World Cohort Study . Nat Sci Sleep 2020;Volume 12:209–19.
60. Wu XH, Cui F, Zhang C, Meng ZT, Wang DX, Ma J, *et al*. Low-dose Dexmedetomidine Improves Sleep Quality Pattern in Elderly Patients after Noncardiac Surgery in the Intensive Care Unit. Anesthesiology 2016;125(5):979–91.
61. Imani F, Zaman B, De Negri P. Postoperative Pain Management: Role of Dexmedetomidine as an Adjuvant. Anesth Pain Med 2021;10(6):1–2.
62. Edinoff AN, Wu N, Ghaffar YT, Prejean R, Gremillion R, Cogburn M, *et al*. Zolpidem: Efficacy and Side Effects for Insomnia. Health Psychol Res 2021;9(1).
63. Mittal N, Mittal R, Gupta MC. Zolpidem for Insomnia: A Double-Edged Sword. A Systematic Literature Review on Zolpidem-Induced Complex Sleep Behaviors. Indian J Psychol Med 2021;43(5):373–81.
64. Conway A, Rolley J, Sutherland JR. Midazolam for sedation before procedures. Cochrane Database of Systematic Reviews 2016;2018(12).
65. Shen J hua, Ye M, Chen Q, Chen Y, Zhao H lin, Khan A, *et al*. Effects of circadian rhythm on Narcotrend index and target-controlled infusion concentration of propofol anesthesia. BMC Anesthesiol 2021;21(1):215.
66. Poulsen RC, Warman GR, Sleigh J, Ludin NM, Cheeseman JF. How does general anaesthesia affect the circadian clock? Sleep Med Rev 2018;37:35–44.
67. Lewis SR, Schofield-Robinson OJ, Alderson P, Smith AF. Propofol for the promotion of sleep in adults in the intensive care unit. Cochrane Database of Systematic Reviews 2018;2019(1).
68. Kondili E, Alexopoulou C, Xirouchaki N, Georgopoulos D. Effects of propofol on sleep quality in mechanically ventilated critically ill patients: A physiological study. Intensive Care Med 2012;38(10):1640–6.
69. Ștefan M, Predoi C, Goicea R, Filipescu D. Volatile Anaesthesia versus Total Intravenous Anaesthesia for Cardiac Surgery—A Narrative Review. J Clin Med 2022;11(20):6031.
70. Pöpping DM, Elia N, Van Aken HK, Marret E, Schug SA, Kranke P, *et al*. Impact of Epidural Analgesia on Mortality and Morbidity After Surgery. Ann Surg 2014;259(6):1056–67.
71. Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev 2007;11(1):35–46.
72. Jakobsson JG, Johnson MZ. Perioperative regional anaesthesia and postoperative longer-term outcomes. F1000Res 2016;5:2501.
73. de Boer HD, Detriche O, Forget P. Opioid-related side effects: Postoperative ileus, urinary retention, nausea and vomiting, and shivering. A review of the literature. Best Pract Res Clin Anaesthesiol 2017;31(4):499–504.
74. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in Tramadol: Pharmacology, Metabolism, and Misuse. Anesth Analg 2017;124(1):44–51.
75. Ghai B, Jafra A, Bhatia N, Chanana N, Bansal D, Mehta V. Opioid sparing strategies for perioperative pain management other than regional anaesthesia: A narrative review. J Anaesthesiol Clin Pharmacol 2022;38(1):3.
76. Donatiello V, Alfieri A, Napolitano A, Maffei V, Coppolino F, Pota V, *et al*. Opioid sparing effect of intravenous dexmedetomidine in orthopaedic surgery: A retrospective analysis. Journal of Anesthesia, Analgesia and Critical Care 2022;2(1):49.
77. O'Hagan ET, Hübscher M, Miller CB, Gordon CJ, Gustin S, Briggs N, *et al*. Zolpidem reduces pain intensity postoperatively: A systematic review and meta-analysis of the effect of hypnotic medicines on post-operative pain intensity. Syst Rev 2020;9(1):206.
78. Kuthiala G, Chaudhary G. Ropivacaine: A review of its pharmacology and clinical use. Indian J Anaesth 2011;55(2):104.
79. Schwenk ES, Mariano ER. Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean J Anesthesiol 2018;71(5):345–52.
80. Lee GJ, Kim SA, Kim YJ, Oh SB. Naloxone-induced analgesia mediated by central kappa opioid system in chronic inflammatory pain. Brain Res 2021;1762:147445.
81. Kaye AD, Chernobylsky DJ, Thakur P, Siddaiah H, Kaye RJ, Eng LK, *et al*. Dexmedetomidine in Enhanced Recovery After Surgery (ERAS) Protocols for Postoperative Pain. Curr Pain Headache Rep 2020;24(5):21.
82. Tomić M, Pecikoza U, Micov A, Vučković S, Stepanović-Petrović R. Antiepileptic drugs as analgesics/adjuvants in inflammatory pain: Current preclinical evidence. Pharmacol Ther 2018;192:42–64.
83. Vergne-Salle P. Management of neuropathic pain after knee surgery. Joint Bone Spine 2016;83(6):657–63.
84. Speelziek SJA, Staff NP, Johnson RL, Sierra RJ, Laughlin RS. Clinical spectrum of neuropathy after primary total knee arthroplasty: A series of 54 cases. Muscle Nerve 2019;59(6):679–82.
85. Hasija R, Kelly JJ, Shah N V., Newman JM, Chan JJ, Robinson J, *et al*. Nerve injuries associated with total hip arthroplasty. J Clin Orthop Trauma 2018;9(1):81–6.
86. Butris N, Tang E, Pivetta B, He D, Saripella A, Yan E, *et al*. The prevalence and risk factors of sleep disturbances in surgical patients: A systematic review and meta-analysis. Sleep Med Rev 2023;69:101786.

Supplementary Table 1: Sleep assessment tools

Author, year	Assessment tool	Evaluation criteria
Dexmedetomidine		
Niu, 2023	PSQI	Sleep quality (0–21 score)
Zhang, 2022	PSG	Sleep architecture, duration, efficiency, sleep fragmentation index
Wang, 2021	AIS	NR
Mao, 2020	SMH	Subjective sleep quality, being clear-headed after waking, sleep satisfaction
Sun, 2019	RCSQ	VAS
Yu, 2019	ISI	Insomnia score
Jiang, 2018	PSG	Sleep efficiency index, arousal index, REM, sleep stages 1–3 (N1–3)
Chen, 2017	PSG	Sleep efficiency index, arousal index, % REM, stage 1, 2, and 3 sleep
Tan, 2016a	BIS-Vista monitor	Sleep duration, sleep efficiency index, objective sleep quality (BIS-AUC)
Tan, 2016b	BIS-Vista monitor	Sleep efficiency index, objective sleep quality (BIS-AUC)
Opioid/opiates		
Fu, 2022	RCSQ	Six measures of sleep quality
Gong, 2017	PSQI	NR
Lee, 2012	SMH	Overall sleep quality, frequency of awakenings, satisfaction. reason for awakening, awakening due to pain, ability to sleep subsequently
Nonopioid/opiates and hypnotics		
Omara, 2019	CSD	Sleep quality (scale 0–4)
Eloy, 2017	PSQI	Sleep quality
Gong, 2015	PSG	Sleep efficacy
General anesthetics		
Zhou, 2023	RCSQ	Sleep quality
Ding, 2021	PSQI	Sleep quality: sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, and use of sleep medication
Regional anesthetics		
Lee, 2021	CSD	Sleep quality (scale 0–4)
Kang, 2020	PSQI	NR
Cronin, 2001	PSG	% wakefulness, NREM, SWS, REM sleep, subjective sleep quality, sleep duration

AIS=Athens Insomnia Scale, AUC=area under the curve, BIS=bispectral index, CSD=Consensus Sleep Diary, ESS=Epworth Sleepiness Scale, ISI=Insomnia Severity Index, NR=not reported, NREM=non-REM, PSD=Pittsburgh Sleep Diary, PSG=polysomnography, PSQI=Pittsburgh Sleep Quality Index, RCSQ=Richard–Campbell Sleep Questionnaire, REM=rapid eye movement, SEI=sleep efficiency index, SMH=St. Mary Hospital Sleep Questionnaire, SWS=slow wave sleep, VAS=visual analog scale



Supplementary Figure 1: Risk of bias traffic light plot (a) and risk of bias summary plot (b)