Appendix 1

SEARCH STRATEGY

PubMed (MEDLINE) 2022-01-19

#1

"Polysomnography"[MeSH Terms] OR "Polysomnography"[Title/Abstract] OR "Sleep Wake Disorders"[MeSH Terms] OR "Sleep Disorders"[Title/Abstract] OR "sleep disturbance"[Title/Abstract] OR "Actigraphy"[MeSH Terms] OR "Actigraphy"[Title/Abstract] OR "Sleep Initiation and Maintenance Disorders"[MeSH Terms] OR "insomnia"[Title/Abstract] OR "Sleep"[MeSH Terms]

182,061

#2

"Zolpidem"[Mesh] OR zolpidem[Title/Abstract] OR zaleplon[Title/Abstract] OR "Melatonin"[Mesh] OR melatonin[Title/Abstract] OR zopiclone[Title/Abstract] OR "Eszopiclone"[Mesh] OR Eszopiclone[Title/Abstract] OR suvorexant[Title/Abstract] OR triazolam[Title/Abstract]

33,807

#3

"Pain"[Mesh] OR "Rheumatic Diseases"[Mesh] OR "Fatigue Syndrome, Chronic"[Mesh] OR "chronic pain"[Title/Abstract] OR "Autoimmune Diseases"[Mesh]

1,050,180

#4

#1 AND #2 AND #3

136

Embase 2022-01-19

#1

'polysomnography'/exp OR 'actimetry'/exp OR 'sleep disorder'/exp OR 'sleep disorder':ti,ab

307,816

#2

'zolpidem'/exp OR 'zolpidem' OR 'melatonin'/exp OR 'melatonin' OR 'zaleplon' OR 'zaleplon'/exp OR 'zopiclone' 'zopiclone'/exp OR 'eszopiclone' OR 'eszopiclone'/exp OR 'suvorexant' OR 'suvorexant'/exp OR 'ramelteon':ab,ti OR 'ramelteon' OR 'ramelteon'/exp OR 'triazolam' OR 'triazolam'/exp

12,372

#3

'pain'/exp OR 'autoimmune disease'/exp OR 'rheumatic disease'/exp OR 'chronic fatigue syndrome'/exp OR 'chronic pain'/exp

2,121,303

#4

#1 AND #2 AND #3

1,223

#5

“article”/it AND [english]/lim

#6

#4 AND #5

495

Cochrane 2022-01-19

#1

MeSH descriptor: [Sleep] explode all trees OR MeSH descriptor: [Actigraphy] explode all trees OR MeSH descriptor: [Polysomnography] explode all trees OR MeSH descriptor: [Sleep Wake Disorders] explode all trees OR (insomnia):ti,ab,kw

22,172

#2

("melatonin"):ti,ab,kw OR ("zolpidem"):ti,ab,kw OR ("zaleplon"):ti,ab,kw OR ("zopiclone"):ti,ab,kw OR ("eszopiclone"):ti,ab,kw OR (suvorexant):ti,ab,kw OR ("triazolam"):ti,ab,kw

5297

#3

[Pain] explode all trees

53449

#4

#1 AND #2 AND #3

36 (35 trials + 1 Cochrane Review)

Summary

Total: 667

Sum after duplicates removed: 622

Supplementary Table 2. Outcome measures and sleep/pain-related inclusion/exclusion criteria.

First author, year [ref#]	Primary outcome	Sleep outcome measures	Pain outcome measures	Other relevant outcome measures	Exclusion medications	Sleep-/pain-related inclusion/exclusion criteria
Altiparmak 2018 [5]	ESS	PSQI	Pain NRS (scale 0-10)	List of 8 specific AEs (e.g., headache, nausea, fatigue)	Ongoing gabapentinoid or insomnia treatment prior to randomization	NeuP as defined by: LANSS score >12 and DN4 score >4; non-malignant etiology of NeuP. No OSAS.
Drewes 1991 [26]	Not specified	PSG (pre-, postintervention incl. analysis of sleep microstructure; 20 participants), sleep diary incl. sleep quality, LSEQ	Pain VRS (scale 1-5), pressure algometry (tenderpoints), analgesic consumption	VRS fatigue, stiffness	Sleep-interfering and psychotropic drugs	Not specified
Drewes 1998 [27]	Not specified	PSG (pre-, postintervention incl. analysis of sleep microstructure), sleep quality, LSEQ, sleepiness VAS	MPQ (incl. present pain intensity scale 0-5)	Clinical joint evaluation, VRS fatigue	Psychotropic drugs discontinued 14 days before study; no changes in medications during study	No medical disease thought to influence sleep structure, no FM diagnosis
Goforth 2014 [34]	TST (sleep diary)	Sleep diary (TST, SOL, WASO, SE, sleep quality), ISI	Pain VAS (0-100), global impression of pain rating	HAM-D (depression), RMLBPDQ (disability)	Meds w sig renal effects, anticoagulants, corticosteroids (<1 mo prior to screening); sleep-influencing meds	Comorbid (CLBP) insomnia; TST < 6.5h and/or SOL > 30 min; ISI > 14 / pain duration > 3 mo; pain VAS > 4; back pain > leg pain; no spinal nerve root compression
Gronblad 1993 [35]	Not specified	Multicomponent sleep NRS (e.g., sleep quality, sleep duration, #awakenings)	Multicomponent pain NRS, pain drawings Pressure algometry	NRS fatigue, stiffness	No analgesic, psychiatric or other sleep-influencing medications during study	Not specified

First author, year [ref#]	Primary outcome	Sleep outcome measures	Pain outcome measures	Other relevant outcome measures	Exclusion medications	Sleep-/pain-related inclusion/exclusion criteria
Roth 2009 [54]	Self-reported WASO during week 1	Self-reported SOL, WASO, TST, sleep quality/sleep depth (scale 0-10), ISI	subjective pain severity assessment scale (scale 0-10), pain severity score (scale 0-5), analgesic consumption	Self-reported daytime function (scale 0-10), ASES, ACR response criteria, SF-36 (health-related quality of life), spontaneously reported adverse events	No change in RA medications ≥90 days prior to enrollment; >10 mg prednisone, monoamine oxidase inhibitors, TCAs, SNRIs, bupropion, mirtazapine, tramadol, gabapentinoids, bensodiazepines, narcotic pain medications	DSM-IV criteria for insomnia, WASO ≥45 min and TST <6.5 h at least 3x/week previous month; no FM diagnosis, no primary sleep disorder (e.g., OSAS)
Schwertner 2013 [59]	Pain intensity	Sleep diary: sleep quality (scale 0-10)	Pain diary: pain VAS (multicomponent, scale 0-10) Analgesic consumption	Serum BDNF Adverse events (structured assessment)	Antidepressants, anticonvulsants	Pain NRS ≥4/10, regular analgesic use; no non-gynecologic causes of pelvic pain
Song 2005 [68]	Not specified	PSQI, ESS PSG (pre-, postintervention)	Abdominal pain NRS (included in IBSSESQ, scale 0-10), rectal distension pain threshold	IBSSESQ HADS	No sleep-influencing medications within a month prior to study	Sleep problems as defined by: PSQI-score >5, insomnia symptoms ≥2 nights/week for ≥12 weeks
Vidor 2013 [74]	Maximum pain intensity	Sleep quality (multicomponent, VAS 0-10)	Pain intensity (pain diary, VAS 0-10), analgesic consumption, PPDT	Adverse events (structured assessment)	Steroids, anticonvulsants	No FM, RA, OA (temporomandibular joint)
de Zanette 2014 [24]	Pain intensity	PSQI	Pain VAS (pain diary, average pain last 24h scale 0-10), analgesic consumption, PPDT, CPM	FIQ Hamilton depression scale PCS Serum BDNF	None specified	Average pain intensity ≥5/10 No other painful disorders

Supplementary Table 3. Additional demographic, clinical information and results.

First author, year [ref#]	Mean age (y)	Pain duration	Relationship sleep – pain	Other relevant results incl. adverse events
Altiparmak 2018 [5]	48.2	NR	Not analyzed	Fatigue↓ No serious AEs
Drewes 1991 [26]	50.0 (median)	NR	No correlations pain variables – PSG data$^{\Phi}$	Fatigue↓ Six AEs (4 ZOP, 2 placebo), no serious AEs
Drewes 1998 [27]	50.9	NR (mean duration RA 13.7 y)	Not analyzed	Number tender/swollen joints n.s. Fatigue n.s. Minor AEs only in ZOP-group (8 pts, bitter taste, sleepiness, dizziness)
Goforth 2014 [34]	43.5	>3 months (NR)	Improvement of sleep variables associated with reduced pain scores	HAM-D↓, RMLBPDQ n.s. No serious AEs. Three AEs (2 ESZ, 1 placebo).
Gronblad 1993 [35]	45.0 (median)	4.5 y (median)	Not analyzed	Minor AEs more common in ZOP-group (e.g., bitter taste), no serious AEs

First author, year [ref#]	Mean age (y)	Pain duration	Relationship sleep - pain	Other relevant results incl. adverse events
Roth 2009 [54]	52.1	NR	Not analyzed	SF-36 role physical↑, ACR RA joint assessment tender joint count↓; unpleasant taste more common in ESZ group, no diff regarding overall AEs
Schwertner 2013 [59]	37.2	>6 months	Not analyzed	Serum BDNF↓ No serious AEs
Song 2005 [68]	27.4	NR	Not analyzed	HADS n.s. No AEs reported
Vidor 2013 [74]	30.9	NR	Improvement of sleep variables not associated w decreased pain intensity	No serious AEs
de Zanette 2014 [24]	49.0	NR	Not analyzed	FIQ↓ (same group-differences as for pain intensity results) Melatonin group: 5/21 minor AEs, 5/21 major AEs (n.s. between groups)

Appendix 3

SUMMARY OF RISK OF BIAS ASSESSMENTS

Selection bias

All 10 trials were randomized according to titles and/or text. Procedures for random sequence generation (randomization) were sufficiently described in 4/10 trials [5, 34, 58, 72]. In all these instances, randomization was performed through dedicated computer software. Methods for allocation concealment were outlined in 6/10 trials [5, 24, 34, 58, 67, 72].

Performance bias

All 10 trials were described as double-blind. However, description of blinding procedures (participants, personnel) was only provided in 6/10 trials [5, 24, 34, 58, 67, 72].

Detection bias

Description of measures for blinding of outcome assessors was provided in 5/10 trials [5, 24, 34, 58, 72].

Attrition bias

There was no apparent incomplete outcome data reporting in 7/10 trials [5, 24, 26, 27, 58, 67, 72]. The study by Roth et al. [53] was originally planned to include 440 subjects; due to slow enrolment the study was converted to a pilot study with a new target sample size of 150, and significance tests were changed to 1-sided. It is stated that the analytic plan was amended prior to patient unblinding. We identified two cases of high attrition bias [34, 35]. In the study by Goforth et al. [34], 58 patients were randomized (33 eszopiclone, 25 placebo). Four participants in the eszopiclone group and 8 in the placebo group discontinued intervention, i.e., only 76% completed treatment. In the study by Grönblad et al. [35], 49 patients were randomized (24 zopiclone, 25 placebo). Due to a high drop-out ratio (different reasons, including side effects) only 33/49 patients (67%) completed all procedures.

Reporting bias

Most study protocols were not preregistered prior to start of study activities. Preregistration of study protocols was only found for 3/10 trials [5, 34, 53]. It should however be noted that for studies conducted in the 1990s, preregistration was not to be expected [26, 27, 35].

Other bias

Two trials were sponsored by the pharmaceutical industry [34, 53].

In 4/10 trials there was no power calculation or motivation of sample size [26, 27, 35, 67]. In the remaining 6 trials, power calculations were based on Epworth sleepiness scale [5], total sleep time [34], wakefulness after sleep onset [53], and pain intensity [24, 58, 72].

Appendix 4

GRADE ASSESSMENT OF QUALITY OF EVIDENCE FOR EACH OUTCOME

Sleep-promoting medication in combination with analgesic vs analgesic alone or sleep-promoting medication vs placebo

Risk of bias: <25% (13.1%) of participants from studies with a high risk of bias

Inconsistency: Chi^2 p-value =.003; I^2 = 72% → downgrade 1 point

Indirectness: No major issue

Imprecision: Relatively few participants (n=397), total number <400 → downgrade 1 point

Sleep-promoting medication vs placebo

Risk of bias: No study with high risk of bias

Inconsistency: Chi^2 p-value =.005; I^2 = 77% → downgrade 1 point

Indirectness: No major issue

Imprecision: Relatively few participants (n=265), total number <400 → downgrade 1 point

Sleep-promoting medication in combination with analgesic vs analgesic alone

Risk of bias: 1 out of 2 studies high risk of bias → downgrade 1 point

Inconsistency: Chi^2 p-value =.76; I^2 = 0%

Indirectness: No major issue

Imprecision: Few participants (n=132), total number <400 → downgrade 1 point

Melatonin vs placebo

Risk of bias: No study high risk of bias

Inconsistency: Chi^2 p-value =.42; I^2 = 0%

Indirectness: No major issue

Imprecision: Very few participants (n=72) → downgrade 2 points

Eszopiclone with or without analgesic vs placebo or analgesic alone

Risk of bias: 1 out of 2 studies high risk of bias → downgrade 1 point

Inconsistency: Chi^2 p-value =.02; I^2 = 82% → downgrade 1 point

Indirectness: No major issue

Imprecision: Relatively few participants (n=205), total number <400 → downgrade 1 point

Rheumatoid arthritis: zopiclone, eszopiclone

Risk of bias: Unclear in >50% of domains for both studies → downgrade 1 point

Inconsistency: Chi^2 p-value =.26; I^2 = 22%

Indirectness: No major issue

Imprecision: Few participants (n=193), total number <400 → downgrade 1 point

Only studies at low risk of bias

Risk of bias: No issue

Inconsistency: Chi^2 p-value =.68; I^2 = 0%

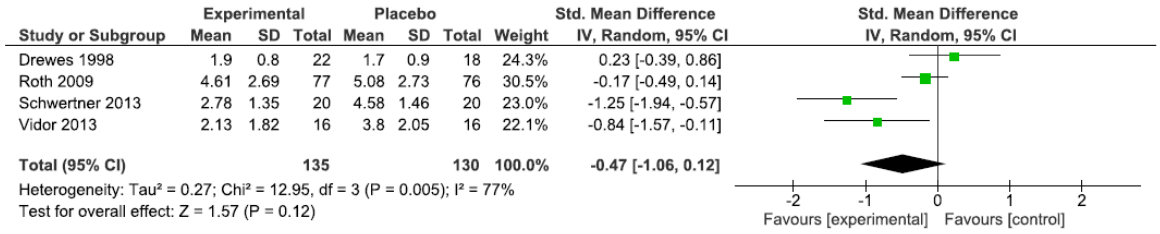
Indirectness: No major issue

Imprecision: Few participants (n=112), total number <400 → downgrade 1 point

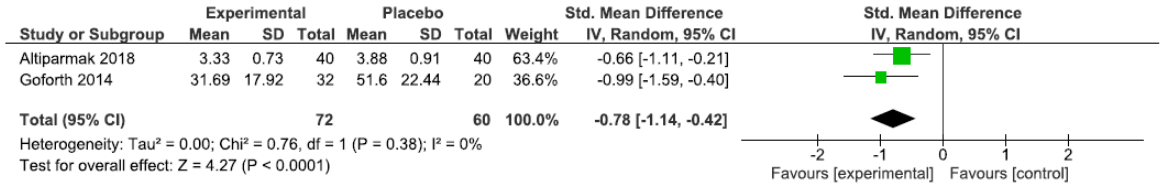
Appendix 5

Additional Forest plots

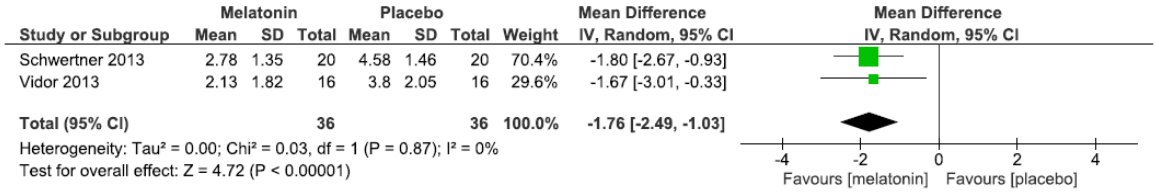
Sleep-promoting medication vs placebo



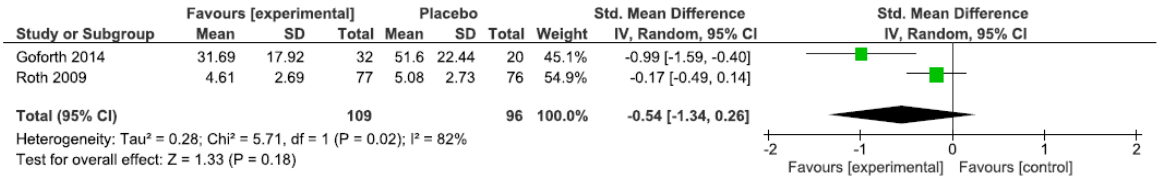
Sleep-promoting medication in combination with analgesic vs analgesic alone



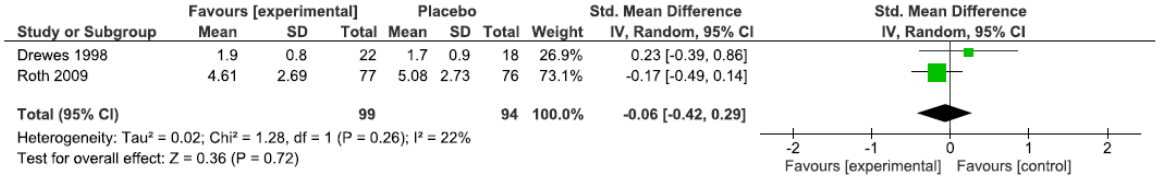
Melatonin vs placebo



Eszopiclone with or without analgesic vs placebo or analgesic alone



Rheumatoid arthritis: zopiclone, eszopiclone



Only studies at low risk of bias