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Analgesic efficacy of sleep-promoting pharmacotherapy in patients with chronic pain: a systematic review and meta-analysis

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Abstract

Dysregulation of sleep heightens pain sensitivity and may contribute to pain chronification. Interventions which consolidate and lengthen sleep have the potential to improve pain control. The main objective of this systematic review was to examine the effects of sleep-promoting pharmacotherapy on pain intensity in patients with chronic pain. Multiple electronic databases were searched from inception to January 2022 to identify relevant randomized controlled trials (RCTs). Two independent reviewers screened titles, abstracts, and full-text articles; extracted data; and assessed risk of bias for each included study. The GRADE approach was used to determine the strength of evidence. The search identified 624 articles. After full-text screening, 10 RCTs (n = 574 randomized participants) involving 3 pharmacologic interventions (melatonin, zopiclone, and eszopiclone) and 7 different chronic pain populations were included. Minimum clinically significant pain reduction ≥30% was reported in 4 studies. There is low-quality evidence (downgraded due to inconsistency and imprecision) that 2 to 8 weeks treatment with a sleep-promoting medication alone or in combination with an analgesic (6 trials, n = 397) decreases pain intensity compared with placebo or the same analgesic treatment alone (SMD −0.58 [95% confidence interval −1.00, −0.17], $P = 0.006$). Analyses of associations between changes in sleep and pain outcomes were only provided in 2 articles, with inconsistent findings. Notably, pain-relieving effects were most consistent in melatonin trials. Only 3 studies implemented polysomnography to obtain objective sleep measures. Low-quality evidence indicates that pharmacologic sleep promotion may decrease pain intensity in chronic pain populations. More research is needed to fully understand the influence of sleep-targeting interventions on pain control.

Keywords: Analgesia, Sleep, Insomnia, Chronic pain, Pharmacotherapy, Melatonin, Zopiclone, Eszopiclone

1. Introduction

Experimental studies in animals[4,56,71] and humans,[44,61,66] large-scale longitudinal observational studies,[11,13,55] clinical trials,[50,64] and meta-analytic data[2,21,58,60] show that sleep and pain interact in a bidirectional manner, with a stronger causal influence of sleep on pain, than pain on sleep.[2,30] More than half of patients with chronic pain report insomnia symptoms, such as trouble falling asleep, maintaining sleep, and dissatisfaction with sleep quality.[30,65] Fragmentation and shortening of sleep may heighten pain sensitivity and trigger spontaneous pain through alterations in central nervous system (CNS) pain processes, including proinflammatory mechanisms,[38,42,57] dysregulation of monoaminergic systems,[56] and glutamatergic signaling,[36] which together amplify central sensitization and diminish descending pain inhibitory capacity. Moreover, sleep fragmentation has been shown to decrease the analgesic effects of opioids.[67] The effects

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of sleep disturbance may thus negatively affect pain control and contribute to pain chronicity. Given that treatments of long-term pain are extremely limited, often ineffective and associated with adverse effects,[15,32,73] targeting of sleep may improve both sleep and pain outcomes, in addition to multiple other health benefits.[41,45,63]

We and others have previously found that perioperative pharmacologic sleep-promotion through zolpidem or melatonin may improve postoperative pain control.[10,51] Moreover, eszopiclone has been shown to provide meaningful analgesia during acute pain due to mucositis.[25] In addition, in a pilot study of fibromyalgia patients with comorbid insomnia, use of suvorexant, an orexin receptor antagonist, was recently found to improve sleep continuity and reduce heat pain sensitivity simultaneously.[53] Despite the high frequency of sleep problems in patients with chronic pain, no systematic review has addressed whether pharmacologic treatments that target sleep may have beneficial effects not only on sleep itself but also on pain perception.

Hence, the main objective of the current systematic review was to examine the effects of sleep-promoting pharmacotherapy on pain intensity in patients with chronic pain. Moreover, we wanted to evaluate whether potential improvement of pain control was mediated through improved subjective or objective sleep measures, including sleep continuity and sleep architecture.

2. Methods

This study was conducted as a systematic review and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[49] The protocol for this systematic review was registered with PROSPERO (ID = CRD42022304189) in January 2022.

2.1. Eligibility criteria

Published English language randomized controlled trials (RCTs) with at least 20 participants were considered for inclusion in the systematic review. Inclusion criteria were defined according to the PICO (population, intervention, comparison, and outcomes) framework.

2.2. Population

Patients with nonmalignant or malignant chronic pain (as diagnosed according to the International Association for the Study of Pain [IASP] criteria), ie, "pain that persists or recurs for longer than 3 months."[72] There were no predefined exclusion criteria related to pain intensity or pain interference.

2.3. Intervention

Pharmacologic sleep-promotion included the following medications: zolpidem, zaleplon, zopiclone, eszopiclone, melatonin, ramelteon, suvorexant, and triazolam.

Medications used for off-label treatment of sleep problems were excluded (eg, long-acting benzodiazepines, and tricyclic antidepressants).

2.4. Comparison

Any nonexposed control group included (1) placebo, (2) analgesics, (3) nonpharmacological treatment, and (4) no specific treatment.

2.5. Outcomes

The primary outcome was change in pain intensity from baseline to the end of intervention (ie, change in pain Numeric Rating Scale [NRS] score or Visual Analogue Scale [VAS] score). Studies were considered for inclusion even if the primary outcome of the review (change in pain intensity) was not the primary outcome of the identified trial, ie, irrespective of whether the study was primarily designed to assess pain.

Secondary outcomes included changes in analgesic consumption (eg, morphine equivalents), objective sleep continuity, and sleep architecture variables (actigraphy and polysomnography measures, eg, sleep onset latency [SOL], wakefulness after sleep onset [WASO], total sleep time [TST], and sleep efficiency [SE]); subjective sleep quality; subjective estimates of SOL, WASO, TST, and SE; health-related function; anxiety; depression; quality-of-life; physical activity; cognition; and adverse events, from baseline to the end of intervention.

2.6. Search strategy

A comprehensive, systematic search strategy including citation tracking was planned and conducted with assistance from an information specialist (Appendix 1, available at http://links.lww.com/PR9/A185). Multiple electronic databases (MEDLINE, Embase, and Cochrane Central register of controlled trials [CENTRAL]) were searched from inception to January 2022. In addition, reference lists of eligible studies and review articles were scanned for pertinent articles, and other sources of published and unpublished literature were manually searched (eg, clinical trials registries). Searches were executed in January 2022 and rerun before the final analysis. Only English-language RCTs were considered for inclusion. **Figure 1** shows the PRISMA flow diagram.

2.7. Study selection and data collection

Two reviewers (E.A. and M.F.B.) independently screened titles and abstracts and assessed full-text articles for inclusion. The Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to record decisions during the study selection process. Two review authors (E.A. and M.F.B.) extracted data from the eligible full-text articles using data collection forms. In brief, the following data were extracted from study documents: information about study design, methodology (eg, diagnosis of chronic pain condition, intervention (type, dosage, and duration), sleep assessment, and sleep-related and pain-related inclusion or exclusion criteria), participant demographics (eg, age, sex, and body-mass index [BMI]), baseline characteristics (eg, pain intensity, sleep quality, and health-related function), and measures of effect. Disagreements were resolved by discussion and consensus, including a third reviewer (T.K.). In case of missing data, attempts were made to obtain or clarify data from study authors.

2.8. Risk of bias assessment

Study quality and risk of bias were assessed independently by 2 reviewers (E.A. and M.F.B.) for each of the included studies according to the domain-based Cochrane risk of bias tool. Disagreements were resolved by discussion and consensus, including a third reviewer (T.K.).

2.9. Strategy for data synthesis

Since the primary outcome (pain intensity) is typically reported as a continuous variable (eg, NRS/VAS pain scores), mean

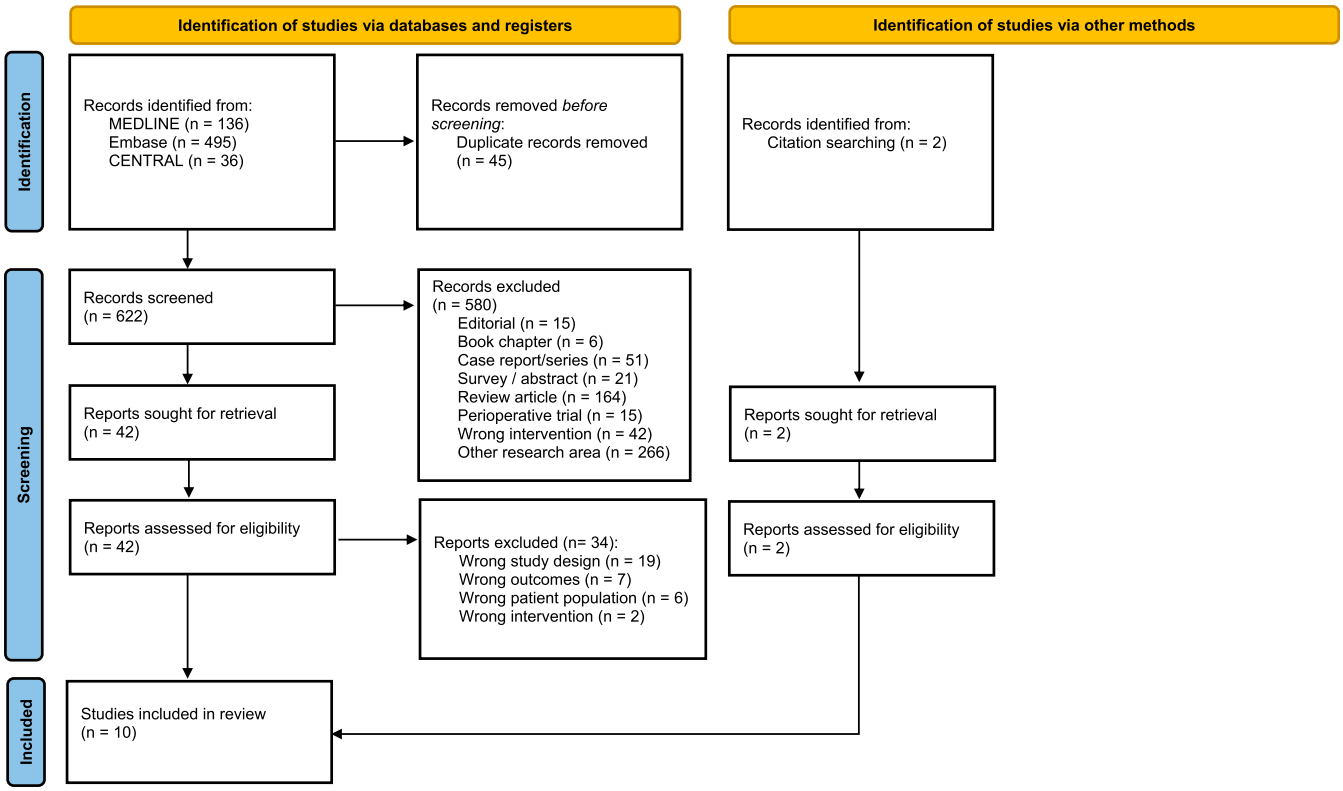

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart depicting study selection.

difference (MD) or standardized mean difference (SMD) (with 95% confidence interval), at end of intervention, was selected as the principal summary measure to determine the effect size. Minimum clinically important difference in pain intensity was defined as a relative reduction of 30% from baseline to end of intervention.

Based on methodology and study design, indicating clinically homogenous studies, meta-analysis of the primary outcome (pain intensity) was planned to synthesize data quantitatively. To assess effect sizes and model parameters, taking into account both within-study and between-study variation in treatment effect, a random-effects model was used. Magnitude of statistical heterogeneity was assessed with the I^2 statistic. Analyses of the following subgroups were preplanned: different pharmacologic interventions, specific chronic pain conditions, and only in studies at low risk of bias. Meta-analysis was performed in RevMan (version 5.4.1, The Cochrane Collaboration). The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to assess the overall quality of evidence for each outcome, taking into account 5 factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias).

3. Results

3.1. Included studies

The search identified 10 studies involving 3 pharmacologic interventions (melatonin, zopiclone, and eszopiclone) and 574 randomized participants (**Fig. 1**, **Table 1**).[5,24,26,27,34,35,54,59,68,74] Attempts were made to contact 4 authors to request additional data not reported in the original article[24,26,35,68]; 2 authors replied but were not able to provide data,[26,68] 2 failed to reply.[24,35]

3.2. Characteristics of included studies

An overview of RCTs examining analgesic effects of sleep-promoting medications in chronic pain populations is provided in **Table 1**. All studies were placebo-controlled. Eight studies were designed as single-site, parallel group RCTs,[5,26,27,34,35,59,68,74] one study was a multicenter, parallel group RCT,[54] and one study was a single-center, 3-group parallel RCT.[24] Sample sizes of the 10 studies ranged from 32 to 153 (**Table 1**). Chronic pain populations included endometriosis-associated chronic pelvic pain,[59] fibromyalgia,[24,26,35] irritable bowel syndrome (IBS),[68] chronic low back pain,[34] mixed neuropathic pain conditions,[5] rheumatoid arthritis,[27,54] and painful temporomandibular disorders.[74]

An overview of outcome measures is provided in Appendix 2 (Supplementary Table 2, available at http://links.lww.com/PR9/A185). Three studies investigated the effects of melatonin vs placebo,[59,68,74] 2 studies investigated the effects of melatonin alone or adjuvant to other analgesic medications vs placebo with or without the same analgesic medications,[5,24] 3 studies evaluated the effects of zopiclone vs placebo,[26,27,35] 1 study investigated the effects of eszopiclone vs placebo,[54] and 1 study examined the effects of eszopiclone adjuvant to analgesic medication vs placebo and the same analgesic medication.[34]

Pain intensity was reported in all 10 studies. Analgesic consumption was assessed in 5 studies. A descriptive and qualitative summary of outcome results are provided in **Table 1**.

3.3. Risk of bias assessment

A summary of risk of bias assessment according to the domain-based Cochrane tool is provided in **Figure 2** and Appendix 3,

Table 1

Overview of randomized controlled studies examining analgesic effects of sleep-promoting medications in chronic pain populations.

First author, y [ref#]	Chronic pain population	N	M:F	Intervention: sleep-promoting medication	Comparison	BL pain intensity*	Sleep outcome results† (intervention vs control)	Pain outcome results† (intervention vs control)	≥30% pain reduction?
Altiparmak 2019[5]	NeuP	80	41:39	Melatonin 3 mg (30 d)	Melatonin + gabapentin 300 mg TID vs placebo + gabapentin 300 mg TID	NRS 0-10: 7.4±1.1 (MEL), 7.5±1.0 (C)	ESS↓ PSQI n.s.	NRS pain↓	Pain NRS: 14.2% reduction
Drewes 1991[26]	FM	41	0:41	Zopiclone 7.5 mg (12 wk)	Zopiclone vs placebo	NR	LSEQ: sleep quality↑, SOL↓ PSG: Sleep architecture n.s.	Pain VRS n.s.‡ pressure algometry n.s.‡ Analgesic consumption n.s.‡	Pain VRS n.s. over time‡
Drewes 1998[27]	RA	40	11:29	Zopiclone 7.5 mg (2 wk)	Zopiclone vs placebo	MPQ PPI (0-5): 1.7 ± 0.9 (ZOP), 2.0 ± 1.1 (C)	LSEQ: sleep quality↑, SOL↓ PSG: N2%↑, power in delta↓, theta↓, alpha↑, sigma↑ bands	MPQ present pain intensity and total pain rating index n.s.	MPQ present pain intensity: +11.8%
Goforth 2014[34]	CLBP	52	19:33	Eszopiclone 3 mg (4 wk)	Eszopiclone + naproxen 500 mg BID vs placebo + Naproxen 500 mg BID	VAS 0-100: 48.5 ± 16.2 (ESZ), 53.8 ± 21.0 (C)	Sleep diary: TST↑, SOL↓, WASO↓, SE↑, sleep quality↑. ISI↓.	Pain VAS↓, patient and clinical global impression of pain ratings n.s.	Pain VAS: 34.6% reduction
Gronblad 1993[35]	FM	33	2:31	Zopiclone 7.5 mg (8 wk)	Zopiclone vs placebo	NR	Global sleep quality score n.s.	Pain NRS scores n.s. pain drawings n.s., pressure algometry n.s.	NR
Roth 2009[54]	RA	153	20:133	Eszopiclone 3 mg (4 wk)	Eszopiclone vs placebo	NRS 0-10: 5.2 ± 2.3 (ESZ), 5.3 ± 1.9 (C)	SOL↓, WASO↓, TST↑, sleep quality↑, sleep depth↑, ISI↓	Subjective pain severity assessment scale↓; pain severity score n.s., SF-36 BP score↑ (i.e., less pain), ASES score pain↓, analgesic consumption n.s.	Subjective pain severity assessment scale score: 9.3% reduction
Schwertner 2013[59]	Endometriosis-associated chronic pelvic pain	40	0:40	Melatonin 10 mg (8 wk)	Melatonin vs placebo	VAS 0-10: 6.5 ± 2.6 (MEL), 6.9 ± 2.1 (C)	Sleep quality↑	Maximum pain last 24 h↓, pain during menstrual period/ intercourse/ evacuation/ urination↓; analgesic consumption↓	Maximum pain last 24 h: 39.3% reduction
Song 2005[68]	IBS	40	16:24	Melatonin 3 mg (2 wk)	Melatonin vs placebo	NRS 0-10: 4.1 ± 0.3 (MEL), 3.9 ± 0.3 (C)	PSQI, ESS n.s. PSG parameters n.s.	Abdominal pain↓ Rectal distension pain threshold↑	Abdominal pain: 42.0% reduction
Vidor 2013[74]	Painful TMD	32	0:32	Melatonin 5 mg (4 wk)	Melatonin vs placebo	VAS 0-10: 4.7 ± 2.3 (MEL), 4.7 ± 2.1 (C)	Sleep quality↑	Maximum pain last 24 h↓, analgesic consumption↓, PPDT↑	Maximum pain last night: 44.0% reduction
de Zanette 2014[24]	FM	63	0:63	Melatonin 10 mg (6 wk)	Melatonin + placebo vs amitriptyline + placebo vs melatonin + amitriptyline	VAS 0-100: 64.9 ± 15.4 (MEL), 62.9 ± 14.3 (C1), 69.6 ± 10.9 (C2)	PSQI n.s.	Pain intensity↓ (melatonin vs amitriptyline; melatonin + amitriptyline vs amitriptyline), analgesic consumption n.s., CPM-effect↑, PPDT↑	Melatonin group pain intensity: 26.8% reduction

* Mean ± SD.

† Change baseline—end of intervention or final follow-up.

‡ No results provided, only comment in text.

ASES, arthritis self-efficacy scale; BL, baseline; BP, bodily pain; C, control; CLBP, chronic low back pain; CPM, conditioned pain modulation; ESS, Epworth Sleepiness Scale; ESZ, eszopiclone; FM, fibromyalgia; IBS, irritable bowel syndrome; ISI, Insomnia Severity Index; LSEQ, Leeds Sleep Evaluation Questionnaire; meds, medications; MEL, melatonin; M:F, male:female; MPQ, McGill Pain Questionnaire; N, number of randomized participants; NeuP, neuropathic pain; NR, not reported; NRS, Numeric Rating Scale; n.s., nonsignificant; PPDT, pressure pain detection threshold; PPI, present pain intensity; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RA, rheumatoid arthritis; SE, sleep efficiency; SOL, sleep onset latency; TMD, temporomandibular disorder; TST, total sleep time; VAS, Visual Analogue Scale; VRS, Visual Rating Scale; WASO, wakefulness after sleep onset; ZOP, zopiclone.

available at http://links.lww.com/PR9/A185. Only 3 of 10 studies were deemed to be at low risk of bias[5,24,74]; 2 studies were labeled high risk of bias (due to attrition bias).[34,35] Given that only 6 studies were included in the meta-analysis, we chose not to assess publication bias with funnel plots.

3.4. Primary outcome: pain intensity

Minimum clinically significant pain reduction ≥30% was reported in 4 studies (**Table 1**).[34,59,68,74] Data from 6 studies were pooled in meta-analyses; results from 4 studies were limited to qualitative synthesis due to inadequate reporting of outcome data (**Table 1**).[24,26,35,68] Detailed information regarding the GRADE assessment of quality of evidence for each outcome is presented in Appendix 4, available at http://links.lww.com/PR9/A185.

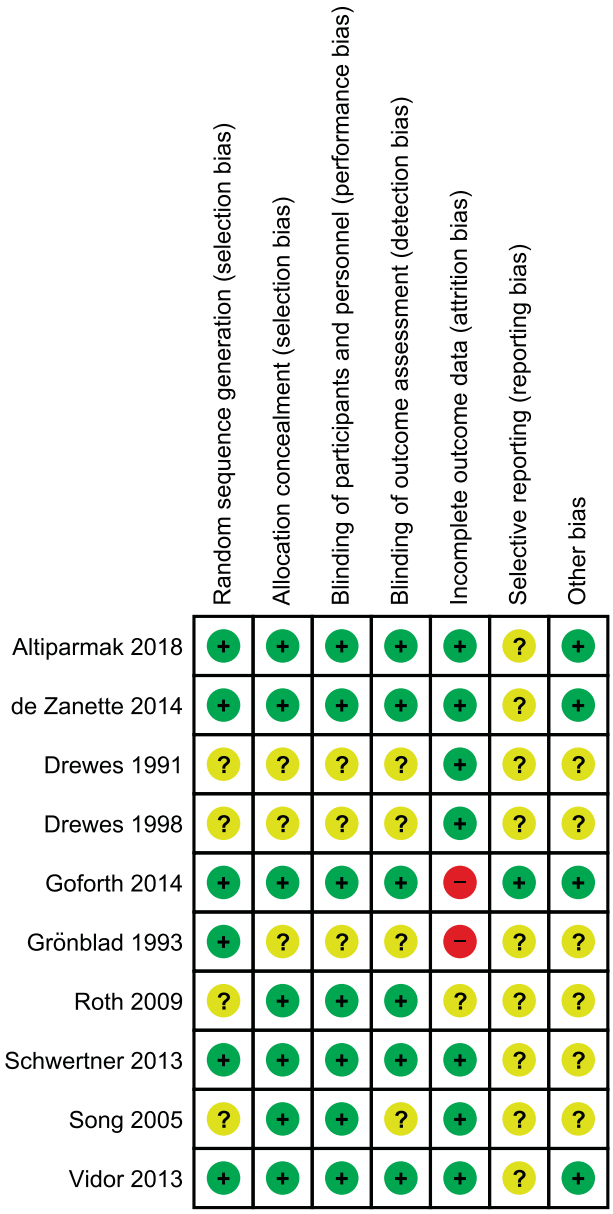

Figure 2. Summary of risk of bias assessment according to the domain-based Cochrane risk of bias tool.

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

There is low-quality evidence (downgraded due to inconsistency and imprecision) that 2 to 8 weeks treatment with a sleep-promoting medication (melatonin, zopiclone, or eszopiclone) alone or in combination with an adjuvant analgesic (gabapentin and naproxen) (6 trials, n = 397)[5,27,34,54,59,74] decreases pain intensity compared with placebo or the same analgesic treatment alone (SMD −0.58 [−1.00, −0.17], $P = 0.006$) (**Fig. 3**).

3.4.2. Sleep-promoting medication vs placebo

There is low-quality evidence (downgraded due to inconsistency and imprecision) that 2 to 8 weeks treatment with a sleep-promoting medication (melatonin, zopiclone, or eszopiclone; 4 trials, n = 265)[27,54,59,74] does not reduce pain intensity compared with placebo (SMD −0.47 [−1.06, 0.12], $P = 0.12$) (Appendix 5, available at http://links.lww.com/PR9/A185).

3.4.3. Sleep-promoting medication in combination with analgesic vs analgesic alone

There is low-quality evidence (downgraded due to risk of bias and imprecision) that a sleep-promoting medication (melatonin or eszopiclone) in combination with an adjuvant analgesic (gabapentin) or an NSAID (naproxen) for 4 weeks (2 trials, n = 132)[5,34] decreases pain intensity compared with the same analgesic treatment alone (SMD −0.78 [−1.14, −0.42], $P < 0.0001$) (Appendix 5, available at http://links.lww.com/PR9/A185).

3.5. Preplanned subgroup analyses related to the primary outcome measure

3.5.1. Pain intensity according to the pharmacologic intervention

Only one zopiclone trial provided sufficient data for meta-analysis.[27] Owing to baseline differences in pain intensity, it was not possible to pool data from one melatonin study to perform meta-analysis of melatonin in combination with an adjuvant analgesic (amitriptyline) vs analgesic alone.[24]

3.5.1.1. Melatonin vs placebo

There is low-quality evidence (downgraded due to imprecision) that 4 to 8 weeks of melatonin treatment (2 trials, n = 72)[59,74] reduces pain intensity compared with placebo (MD −1.76 [−2.49, −1.03], $P <$ 0.0001) (Appendix 5, available at http://links.lww.com/PR9/A185).

3.5.1.2. Eszopiclone with or without analgesic vs placebo or analgesic alone

There is very low-quality evidence (downgraded due to risk of bias, inconsistency, and imprecision) that eszopiclone treatment for 4 weeks, with or without naproxen (2 trials, n = 205),[34,54] does not decrease pain intensity compared with placebo or the same analgesic alone (SMD −0.54 [−1.34, 0.26], $P = 0.18$) (Appendix 5, available at http://links.lww.com/PR9/A185).

3.5.2. Pain intensity according to the chronic pain condition

Seven different chronic pain populations were examined in the 10 trials. Three trials included patients diagnosed with fibromyalgia; it was not possible to conduct meta-analyses of these trials due to

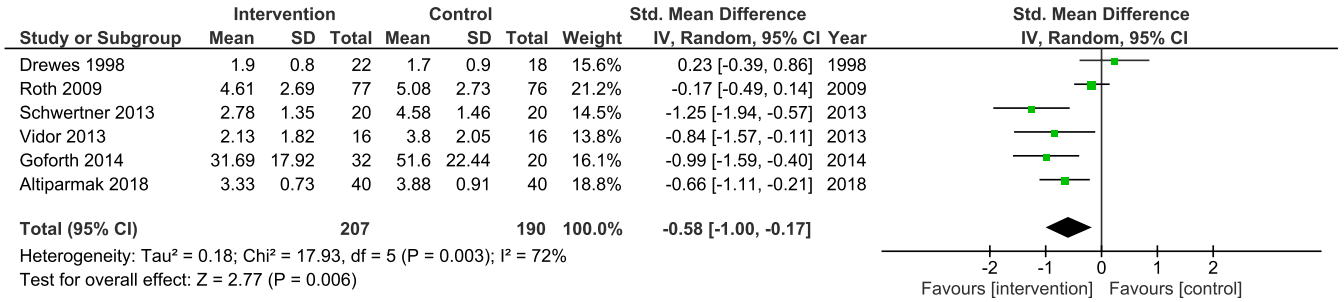

Figure 3. Meta-analysis: Pain intensity after 2 to 8 weeks of treatment with sleep-promoting medication in combination with analgesic vs analgesic alone or sleep-promoting medication vs placebo. 95% CI, 95% confidence interval.

inadequate reporting of outcome data in 2 trials.[26,35] Meta-analyses of zopiclone or eszopiclone treatment for 2 to 4 weeks vs placebo in patients with rheumatoid arthritis (2 trials, n = 193) [27,54] showed no significant effects on pain intensity (SMD −0.06 [−0.42, 0.29], $P = 0.72$; low-quality evidence, downgraded due to risk of bias and imprecision) (Appendix 5, available at http://links.lww.com/PR9/A185).

3.5.3. Pain intensity—only studies at low risk of bias

Three studies (all investigating melatonin) were deemed to be at low risk of bias.[5,24,74] Owing to the reasons stated above, we were only able to pool data from 2 of these trials (n = 112).[5,74] Meta-analysis of these studies (melatonin + gabapentin vs placebo + gabapentin and melatonin vs placebo) showed that melatonin alone or in combination with an analgesic (4–6 weeks treatment) decreases pain intensity compared with placebo or the same analgesic alone (SMD −0.71 [−1.09, −0.33], $P = 0.0003$) (Appendix 5, available at http://links.lww.com/PR9/A185).

3.6. Secondary outcome measures

3.6.1. Effects of sleep-promoting pharmacotherapy on analgesic consumption

Owing to heterogeneous methodologies and reporting of analgesic consumption outcomes, meta-analysis was not possible. Analgesic consumption was assessed in 5 trials. Three trials found no significant group differences regarding analgesic consumption,[24,26,54] whereas 2 trials found significantly lower analgesic consumption in the intervention group compared with placebo.[59,74] In 2 of the trials which found no significant differences in analgesic consumption, brief information was outlined in the text, with no numbers provided.[26,54] Schwertner et al.[59] found that 22.9% of patients in the melatonin group used supplementary analgesics (acetaminophen, ibuprofen, codeine, or tramadol) compared with 42.2% in the placebo group during the 8 week trial; the relative risk for using an analgesic ≥3 times per week was 80% higher for those receiving placebo compared with melatonin. In a similar study design, Vidor et al.[74] found significantly lower adjusted daily mean analgesic consumption (acetaminophen, ibuprofen, codeine, or orphenadrine/dypirone/caffeine) in the melatonin group compared with placebo (0.10 [SD 0.36] vs 0.32 [0.58], $P < 0.01$; medications not specified).[74]

3.6.2. Analysis of association between pharmacologically induced changes in sleep variables and pain control

Analyses of associations between changes in sleep and pain outcomes were only provided in 2 articles.[34,74] Goforth et al.[34] found that improvement of sleep variables (self-reported WASO, SE, TST, and sleep quality) were associated with decreased pain intensity ratings (Spearman correlation analysis). By contrast, Vidor et al.[74] found no significant associations between improvement of sleep quality and pain VAS scores (multivariate linear regression). In addition, Drewes et al.[26] reported that there were no correlations between polysomnography outcomes and pain variables (in text only). Notably, pain intensity decreased in the sleep intervention group despite no clear beneficial effects on sleep measures in 2 melatonin trials,[24,68] whereas 2 trials (melatonin and eszopiclone) showed beneficial effects on pain and sleep measures in parallell.[54,59]

3.6.3. Sleep and sleep-related measures

All 10 trials reported at least one sleep-related outcome measure (Appendix 2, Supplementary Table 2, available at http://links.lww.com/PR9/A185). Objective sleep assessment was only implemented in 3 trials.[26,27,68] Two of the trials using polysomnography found no significant differences between groups,[26,68] whereas 1 trial detected higher relative amounts of N2 sleep and lower delta power in patients receiving zopiclone compared with placebo (**Table 1**).[27] Six trials showed that pharmacologic sleep intervention improved subjective sleep quality according to sleep diary or NRS or Insomnia Severity Index,[26,27,34,54,59,74] whereas 4 trials (3/4 including more comprehensive sleep quality assessment through the Pittsburgh sleep quality index [PSQI]) found no significant differences between groups.[5,24,35,68] Both eszopiclone trials which assessed self-reported sleep continuity parameters found significant decreases in SOL and WASO and increases in TST and SE for the intervention group as compared with the control group.[34,54]

3.6.4. Adverse events

Methods for assessment of adverse events were often poorly described and varied significantly between studies, from no specific details, spontaneous reporting, to structured assessment. Nine of 10 trials reported no serious adverse events (Appendix 2, Supplementary Table 3, available at http://links.lww.com/PR9/A185); only 1 trial reported "major" adverse events, but with no significant between-group differences.[24] Two trials found that minor adverse events were more common in the sleep intervention group compared with the control group.[27,35]

3.6.5. Other relevant reported outcomes

Two trials found beneficial effects related to fatigue,[5,26] whereas 1 trial found no significant effect on fatigue.[27] One trial showed that

eszopiclone in combination with analgesic decreased depression scores compared with analgesic alone,[34] whereas 1 melatonin trial found no significant group differences in anxiety or depression scores.[68] Five trials included QST for the assessment of pain neurophysiology.[24,26,35,68,74] Three of 5 trials indicated salutary changes in pain thresholds related to sleep intervention (decreased rectal pain sensitivity[68] and decreased pressure pain sensitivity[24,74]). One of these trials also evaluated conditioned pain modulation effects and found that melatonin alone or in combination with amitriptyline increased pain inhibitory capacity compared with amitriptyline alone.[24] By contrast, 2 trials evaluating sleep intervention in patients with fibromyalgia found no significant effects on pressure pain thresholds.[26,35]

4. Discussion

4.1. Main findings

In the current systematic review, we found low-quality evidence that sleep-promoting pharmacotherapy may decrease pain intensity in patients with chronic pain. Pain relief exceeded the á priori defined minimum clinically significant level of at least 30% pain reduction in 4 of 10 studies.[34,59,68,74] Overall, effect sizes were medium, except for melatonin vs placebo trials, where subgroup analyses demonstrated large effects (mean difference approximately −1.8 pain VAS units on a scale 0–10).[59,74] Notably, findings from all 5 melatonin trials were positive, whereas all 3 zopiclone trials showed no pain-relieving effects. Conclusions are limited by the low number of included trials, with small sample sizes, and only 3 trials can clearly be labeled low risk of bias.

4.2. Does improvement of sleep mediate decreased pain intensity in chronic pain populations?

Although our results indicate potential benefits associated with short-term to medium-term (2–8 weeks) melatonin and eszopiclone treatment in patients with chronic pain, it is unclear whether analgesic effects are mediated by improved sleep quality, increased sleep quantity, altered sleep architecture, psychological factors, or other mechanisms. Pain-relieving effects were most consistent in melatonin trials, and only 2 of these 5 trials detected improvements in sleep quality. However, characterization of sleep was surprisingly poor in most trials; only 3 trials implemented objective sleep assessment, which severely limits interpretation of associations between changes in sleep measures and pain outcomes. Over the past decades, data from preclinical studies, longitudinal observational studies, clinical trials, and meta-analyses have shown that sleep and pain interrelate closely.[2,4,9,11,30,44,64,66] Nevertheless, further research is needed to fully understand the impact of sleep disturbance on pain perception in various contexts.[47,69] About 50% of people with persistent insomnia disorder suffer from chronic pain, and conversely, about half of patients with chronic pain meet criteria for persistent insomnia disorder.[70] Although the mechanisms whereby dysregulation of sleep may heighten pain sensitivity, trigger spontaneous pain, increase risk for development of chronic pain, and exacerbate existing pain are not fully understood, several possible explanations have been proposed. Sleep disturbance can induce systemic inflammation,[37,42] and systemic inflammation has been linked to elevated pain sensitivity in healthy subjects as well as in patients with chronic pain.[38,57] Furthermore, poor sleep quality and short sleep duration are associated with increased mu opioid receptor (MOR)-binding potential during evoked pain,[19] as well as decreased analgesic effect of morphine in healthy human subjects,[67] indicating reduced analgesic efficacy of the opioid system. In addition, sleep loss can induce increased cortical availability of metabotropic glutamate receptors of subtype 5 (mGluR5), which are involved in both sleep–wake homeostasis and pain regulation, in humans.[22,36] The mGluR5 is widely distributed within the human CNS, in particular in cortical regions and basal ganglia,[52] and is coexpressed and forms heterodimers with MOR.[3,62] In rodents, coadministration of a MOR agonist and an mGluR5 antagonist enhances antinociceptive effects and reduces MOR-induced tolerance and dependence.[3,62] Hence, it could be hypothesized that alterations in the balance between MOR and mGluR5 receptors might account for some of the proalgesic effects induced by sleep loss. Moreover, sleep disturbance leads to detrimental psychological and behavioral effects, such as increased depressive and anxiety symptoms,[39] decreased positive affect,[31] increased attention to pain and pain helplessness,[20] and decreased activity,[43,48] which aggravate pain. Reciprocally, increased pain intensity negatively influences sleep homeostasis through increased sympathetic nervous system outflow, increased inflammation, and adverse effects of analgesics, eg, opioids.[12,40] Hence, multitargeting of the sleep–pain interface, ie, treating sleep disturbance or pain, is likely to impact both sleep and pain beneficially.

4.3. Clinical implications: pharmacologic sleep intervention to target pain

Based on our results, adjuvant treatment with melatonin or eszopiclone may have a role as part of multimodal pain management in patients with chronic pain who suffer from sleep problems. Nevertheless, pharmacologic sleep intervention is considered second-line treatment of persistent insomnia symptoms, to be combined with cognitive behavioral therapy for insomnia (CBT-I).[18] Congruent with our findings, recent meta-analytic data, based on 12 CBT-I trials in patients with chronic pain and comorbid insomnia, showed significant, albeit small, beneficial effects on pain intensity.[60] Pharmacologic treatment is typically recommended for patients with acute insomnia (<3 months), and level of evidence for improvement of sleep in the management of insomnia is overall relatively weak, with small absolute effect sizes.[77] A stepwise, tailored approach to improve sleep, possibly including both behavioral and pharmacologic sleep interventions, may be the most efficient strategy to enhance both sleep and pain outcomes, in addition to other physical and mental health benefits. As for all pharmacologic interventions, it is important to consider potential serious harms, especially during extended treatment periods. Given the small sample sizes, typically limited follow-up periods, and methodology for assessment of adverse events, it is not unlikely that side effects may have been underestimated in these trials. Future large studies are needed to assess the benefit/harm balance. Moreover, optimal dosage and duration of treatment remain to be determined. Previously, results from observational studies and RCTs have raised concerns regarding falls, fractures, impaired driving, cognitive impairment, withdrawal insomnia, and even excess mortality.[33,46] Although there were no group differences regarding adverse events in the 10 included trials, more rigorous monitoring of adverse events should be implemented in future attempts to evaluate sleep-promoting pharmacotherapy in patients with chronic pain.

Interestingly, 3 melatonin trials found significant pain-relieving effects despite no clear evidence of improved sleep.[5,24,68]

However, it is possible that improvements in sleep may not have been detected due to the relatively limited sleep assessment methodologies; numerous existing meta-analyses have demonstrated modest sleep-promoting effects associated with melatonin treatment.[1,14,16,17,28,29,75,76,78,79] Direct antinociceptive effects of melatonin have been documented in a wide range of experimental animal models.[8] Moreover, a recent meta-analysis found that melatonin reduces levels of systemic inflammatory markers (IL-1, IL-6, IL-8, and TNF) in humans.[23] However, conflicting reports regarding the analgesic effects of melatonin in acute pain in humans seem to exist.[6,80] Since most studies have used oral, single-dose administration, it is notable that the bioavailability of oral melatonin in healthy humans may be as low as 3%, albeit with interindividual variability (2%–5%).[7] In an experimental human 3-arm crossover RCT (n = 29) using the contact burn injury model, administration of intravenous melatonin 10 mg and 100 mg, no analgesic, antihyperalgesic, or peripheral anti-inflammatory effects, compared with placebo, could be demonstrated.[8] These findings indicate that in a range from low to very high doses, melatonin does not seem to possess analgesic properties in the context of acute pain, at least after single-dose administration. Obviously, utmost care should be exercised when extrapolating these data to a complex chronic pain scenario including multimodal pain management, but the results could be a putative explanation for an inconsistent relation between pain and sleep outcomes.

4.4. Methodological considerations and future directions

Our findings are limited by a number of factors. We were only able to pool data from 6 of 10 included trials for the quantitative analysis; results might have been different if data from the other 4 trials were also included. Results from 2 of these trials (both zopiclone vs placebo in patients with fibromyalgia) were negative, whereas the 2 other trials (both melatonin) showed benefits associated with sleep intervention. All trials were relatively small and included different, often heterogeneous, chronic pain populations. Dosage and duration of treatment, as well as sleep-related and pain-related exclusion criteria, varied significantly between trials, which limits generalizability. Given that the pain intensity was the primary outcome and the basis for power calculation in only 3 trials, baseline pain intensity varied from relatively mild–moderate to severe levels; these differences and the fact that most trials were not primarily designed to assess pain may have affected results. Indeed, exploratory meta-analysis of the studies which assessed pain as a secondary outcome failed to identify a significant pain-relieving effect of sleep-promoting pharmacotherapy (SMD −0.40 [−0.85, 0.06], $P = 0.09$),[5,27,34,54] whereas those designed to examine pain intensity as primary outcome measure showed meaningful analgesic effects (see subgroup analysis melatonin vs placebo).[59,74] Conclusions are further limited given that the 4 oldest trials (published 1991–2005) provided no specification of primary outcome or motivation of sample size. Moreover, instruments used to assess pain intensity were heterogeneous, whereas 5 of the 6 trials included in the main meta-analysis used different continuous VAS or NRS scores (0–10 or 0–100), 1 study used the McGill pain questionnaire present pain intensity score (0–5), which may not be validated in this setting. Nevertheless, given the relatively low number of identified trials, we chose to include these results to provide a more balanced image of the evidence base. Notably, only 3 trials implemented inclusion criteria related to degree of insomnia symptoms. Analgesic consumption was only assessed in half of trials, and sleep was typically not comprehensively characterized. To fully understand the relationship between sleep and pain, it is essential to include objective measures of sleep, such as actigraphy or polysomnography.

5. Conclusion

In this systematic review, we found low-quality evidence that pharmacologic sleep promotion, in particular through melatonin or eszopiclone, may achieve significant reductions in pain intensity in patients with chronic pain. Given the low number of included trials, with small patient samples, and potential harms associated with pharmacotherapies for insomnia symptoms, the clinical impact of large-scale pharmacologic sleep promotion must be further investigated before wide implementation as part of multimodal pain treatment.

Disclosures

The authors have no conflict of interest to declare.

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Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A185.

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