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The interplay between symptoms of insomnia and pain in people with osteoarthritis: A narrative review of the current evidence

Liesbet De Baets [a, *], Nils Runge [a, b], Céline Labie [a, b, c], Olivier Mairesse [d, e], Anneleen Malfliet [a, f], Sabine Verschueren [b], Dieter Van Assche [b, c], Kurt de Vlam [c, g], Frank P. Luyten [g], Iris Coppieters [a, h], Alberto Herrero Babiloni [i, j, k], Marc O. Martel [i, l], Gilles J. Lavigne [i, j, k], Jo Nijs [a, m, n, o]

[a] Pain in Motion Research Group (PAIN), Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium
[b] Musculoskeletal Rehabilitation Research Group, Department of Rehabilitation Sciences, Faculty of Movement and Rehabilitation Sciences, KU Leuven, Belgium
[c] Division of Rheumatology, University Hospitals Leuven, Belgium
[d] Department of Brain Body and Cognition (BBCO), Vrije Universiteit Brussel (VUB), Brussels, Belgium
[e] Sleep Laboratory and Unit for Chronobiology U78, Department of Psychiatry, Brugmann University Hospital, Université Libre de Bruxelles (ULB) and Vrije Universiteit Brussel (VUB), Brussels, Belgium
[f] Research Foundation Flanders (FWO), Brussels, Belgium
[g] Skeletal Biology & Engineering Research Center, Dept. of Development & Regeneration, KU Leuven, Belgium
[h] The Laboratory for Brain-Gut Axis Studies (LaBGAS), Translational Research Center for Gastrointestinal Disorders (TARGID), KU Leuven, Leuven, Belgium
[i] Division of Experimental Medicine, McGill University, Montreal, Québec, Canada
[j] Center for Advanced Research in Sleep Medicine, Research Centre, Hôpital du Sacré-Coeur de Montréal (CIUSSS du Nord de-l'Île-de-Montréal) and University of Québec, Canada
[k] Faculty of Dental Medicine, Université de Montréal, Québec, Canada
[l] Faculty of Dentistry & Department of Anesthesia, McGill University, Canada
[m] Department of Health and Rehabilitation, Unit of Physiotherapy, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden
[n] University of Gothenburg Center for Person-Centred Care (GPCC), Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[o] Chronic Pain Rehabilitation, Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Belgium

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ABSTRACT

Osteoarthritis (OA) is a leading cause of disability worldwide and clinical pain is the major symptom of OA. This clinical OA-related pain is firmly associated with symptoms of insomnia, which are reported in up to 81% of people with OA. Since understanding the association between both symptoms is critical for their appropriate management, this narrative review synthesizes the existing evidence in people with OA on i) the mechanisms underlying the association between insomnia symptoms and clinical OA-related pain, and ii) the effectiveness of conservative non-pharmacological treatments on insomnia symptoms and clinical OA-related pain. The evidence available identifies depressive symptoms, pain catastrophizing and pain self-efficacy as mechanisms partially explaining the cross-sectional association between insomnia symptoms and pain in people with OA. Furthermore, in comparison to treatments without a specific insomnia intervention, the ones including an insomnia intervention appear more effective for improving insomnia symptoms, but not for reducing clinical OA-related pain. However, at a within-person level, treatment-related positive effects on insomnia symptoms are associated with a long-term pain reduction. Future longitudinal prospective studies offering fundamental insights into

Abbreviations: CBT-I, Cognitive behavioural therapy for insomnia; CBT-PI, Cognitive behavioural therapy for pain and insomnia; CRP, C-reactive protein; EMA, Early morning awakenings; HPA, Hypothalamic–pituitary–adrenal; IL, Interleukin; ISI, Insomnia Severity Index; NMDA, N-methyl-D-aspartate; OA, Osteoarthritis; PSQI, Pittsburgh Sleep Quality Index; RCT, Randomized controlled trial; SE, Sleep efficiency; SOL, Sleep onset latency; WASO, Wake after sleep onset.

* Corresponding author. Vrije Universiteit Brussel - Pain in Motion Research Group (PAIN), Faculty of Physical Education and Physiotherapy, Dept. KIMA, Building F Laarbeeklaan 103, 1090, Brussels, Belgium.
E-mail address: Liesbet.de.baets@vub.be (L. De Baets).

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neurobiological and psychosocial mechanisms explaining the association between insomnia symptoms and clinical OA-related pain will enable the development of effective treatments targeting both symptoms.

1. Introduction

Osteoarthritis (OA) is the most common type of chronic arthritis [1]. The knee and hip joint are the most commonly affected joints, and are therefore responsible for the greatest OA burden [2]. While pain is the key clinical symptom in people with OA [3], OA is also a leading cause of disability and decreased life functioning in older adults [2]. Given that people with OA commonly live with symptoms for three decades or more, the personal and societal burden, as well as the healthcare utilization and related costs, are enormous [4]. Furthermore, the prevalence of OA is expected to increase in the upcoming decades, concurrent with the aging of world population and increasing obesity [2].

OA is characterized as a whole joint disease [5,6], with multiple mechanisms driving the disease processes and contributing to clinical OA-related pain. These mechanisms are dependent on the disease stage and disease phenotype, and include, but are not limited to, matrix degradation, cell apoptosis/senescence, activation of the innate immune system, metabolic reprogramming and inflammation [7,8].

The current first-line guideline for OA management is non-pharmacological and nonsurgical, with disease-based education, physical activity promotion and exercise therapy as core elements, and weight management if appropriate [9]. However, treatment effects of behavioural pain management and exercise therapy on improvements in clinical OA-related pain, physical function and quality of life are moderate at best [10,11]. A potential reason for these suboptimal effects is that pertinent coexisting conditions or symptoms in people with OA are nowadays largely neglected in OA management, due to its main focus on joint pain and pain-related disability [9].

This is especially true for symptoms of insomnia (referred to as '*insomnia symptoms*' in this narrative review) such as prolonged sleep onset latency (SOL), increased wake after sleep onset (WASO), early morning awakenings (EMA) or decreased sleep quality, amongst others. Indeed, insomnia symptoms are highly prevalent in people with OA [12–22], and have been clearly shown to be related to various OA-related clinical features, like pain and disrupted physical functioning [23–36]. Among the various insomnia symptoms, WASO appears to be most prevalent in people with OA (i.e., 71–83%) [22,37], and has been shown to be strongly associated with a higher clinical OA-related pain intensity and with worse physical functioning and performance [38]. Hence the presence of insomnia symptoms is not only an acknowledged factor associated with clinical OA-related pain, it is also considered a major barrier for effective OA management, which consists of physical activity promotion and exercise therapy as key elements [9]. In this context, it has already been shown that treatment-related improvements in insomnia symptoms often precede reductions in clinical OA-related pain, which makes insomnia symptoms a putative treatment target in people with OA [39–43].

How insomnia symptoms might be associated to clinical pain intensity is described in a number of reviews for people with chronic pain (e.g., Refs. [33,44,45]). One systematic review of studies of mediation found that negative affect/mood, depressive and/or anxiety symptoms, pain-related emotions and cognitions (i.e., attention to pain, pain helplessness), fatigue, and cortisol reactivity (i.e., activation of hypothalamic–pituitary–adrenal (HPA) axis)) could be linking mechanisms between insomnia symptoms and clinical pain [45]. Specifically for people with OA, Smith and colleagues (2009) describe in their conceptual model that dysregulated central nociceptive inhibitory and facilitatory mechanisms, altered inflammatory processes at serum level (at rest and in response to pain), negative mood and decreased physical functioning are possible neurobiological and psychological mechanisms linking insomnia symptoms to clinical OA-related pain [46]. Given their suggestion for these shared neurobiological and psychological pathways, and their proposition that both symptoms are promoting and exacerbating each other, an up-to-date understanding of the association between insomnia symptoms and clinical OA-related pain in people with OA is vital. This is not only essential for the development of effective treatment programs targeting both symptoms to reduce the patient burden, but also for reducing health care utilization and related costs in people with OA [15,47,48].

This aim of the narrative review is to synthesize the current evidence-based knowledge on the interplay between insomnia symptoms and clinical OA-related pain in people with OA. It focuses on two specific goals, namely to provide a description and synthesis of the evidence of i) the mechanisms underlying the association between insomnia symptoms and clinical OA-related pain in people with OA, and ii) the effectiveness of conservative non-pharmacological treatments on insomnia symptoms and clinical OA-related pain in people with OA (as it is currently considered the first line treatment). Furthermore, we critically appraise the current state of knowledge regarding these two points and provide a series of recommendations for further research to increase our understanding in this topic.

2. Review methodology

To ensure the quality of this review, it was prepared with the aid of the SANRA scale, which is developed for assessing the quality of narrative review articles [49]. Relevant scientific studies were identified using broad search terms for insomnia symptoms and OA in Medline (Pubmed), Web of Science, ProQuest PsycInfo and the Cochrane Library. The database search was done in March 2023 by two authors (LDB and NR). The search details and results are provided in Supplementary Material 1. Based on the eligibility criteria, which are described in detail in Table 1, studies were selected for this narrative review by LDB and NR.

In the Results section, we synthesize the evidence and provide the study details of the selected papers with regard to the goals of this narrative review. First, the mechanisms underlying the association between insomnia symptoms and clinical OA-related pain are outlined and summarized. This is followed by the description and synthesis of the evidence on the effectiveness of non-pharmacological conservative interventions on insomnia symptoms and clinical OA-related pain in people with OA.

Table 1
Eligibility criteria.

	Inclusion criteria	Exclusion criteria
Regarding the narrative review of the mechanisms underlying the association between insomnia symptoms and clinical OA-related pain in people with OA (Goal 1)	Regarding the study sample: (a) The study sample consists of people with OA and insomnia symptoms. This latter implies that the participants are included in the original study because they complain or suffer from (an) insomnia symptom(s), but do not adhere to the formal definition of insomnia disorder (according to the Research Diagnostic criteria defined by the American Academy of Sleep Medicine [94] or according to the Diagnostic or Statistical Manual of Mental Disorders (DSM) criteria [95]); OR (b) the study sample consists of people with OA and insomnia disorder. This latter implies that the participants are included in the original study because they adhered to the definition of insomnia disorder [94,95]; OR (c) The study sample consists of people with OA in whom (an) insomnia symptom(s) is/are assessed and reported as a study outcome. This latter implies that there is no inclusion criteria in the original study on the presence of (an) insomnia symptom(s) or insomnia disorder, but that (an) insomnia symptom(s) is assessed as a study outcome, and that the study explicitly reports the values of the assessed insomnia symptom.	Studies in which participants with chronic pain in general are included or studies in people after joint arthroplasty, are excluded.
	AND A variable in relation to clinical OA-related pain intensity/severity and (an) insomnia symptom(s) is assessed.	Studies that solely describe day-time insomnia-related consequences (e.g. fatigue, poor concentration, sleepiness, tiredness, memory problems, day-time napping) as part of the inclusion criteria or as study outcome
	AND Full text, peer-reviewed journal paper	
Regarding the narrative review of the effectiveness of conservative non-pharmacological treatments on insomnia symptoms and clinical OA-related pain in people with OA (Goal 2)	The study sample consists of people with OA with insomnia symptoms OR people with OA and insomnia disorder OR people with OA who are not specifically recruited in the original study based on the presence of (an) insomnia symptom(s) or insomnia disorder.	Studies in which participants with chronic pain in general are included or studies in people after joint arthroplasty
	The experimental therapy is a non-pharmacological conservative intervention that targets (an) insomnia symptom(s) or clinical OA-related pain. The control therapy is a comparator of standard care, an active placebo, no treatment, attentional, or wait list control.	Studies in which the experimental therapy consists of pharmacological treatment, including nutritional supplements. Studies that solely describe day-time insomnia-related consequences (e.g. fatigue, poor concentration, sleepiness, tiredness, memory problems, day-time napping) as part of the inclusion criteria or as study outcome
	AND The effectiveness of a non-pharmacological conservative interventions on (an) insomnia symptom(s) and clinical OA-related pain is assessed.	
	AND An in full-text described, peer-reviewed, adequately powered randomized controlled trial.	Feasibility studies with treatment efficacy reporting and pilot studies

3. Results

3.1. Mechanisms underlying the association between insomnia symptoms and clinical OA-related pain

The studied mechanisms linking insomnia symptoms to clinical OA-related pain in people with OA are alterations in nociceptive modulatory processes, inflammation, depressive symptoms, pain-related and sleep-related cognitions, and fatigue. In the paragraphs below, we first describe the evidence per mechanism. Subsequently, we summarize the evidence across all identified mechanisms. For details on the study sample characteristics and the study outcomes, we refer to Supplementary Material 2.

3.1.1. Alterations in nociceptive modulatory processes, insomnia symptoms and clinical OA-related pain

In people with hip OA [21] and in people with knee OA and insomnia disorder [32], cross-sectional analyses indicate that sleep quality (defined with the PSQI) [21] and sleep efficiency (SE - assessed by diary) [32] are associated with enhanced nociceptive sensitivity. Indeed, people with knee OA and insomnia disorder report more signs of central sensitization (assessed via quantitative sensory testing) than people with knee OA without insomnia disorder, and increases in temporal summation of pain are observed in association with lower SE in people with knee OA [32]. Furthermore, these signs of enhanced central sensitization are linked to the intensity of clinical OA-related pain [32].

In a randomized controlled trial (RCT) that investigated whether improvements in insomnia symptoms were linked with alterations in nociceptive modulatory processes and reductions in clinical pain in people with knee OA and insomnia disorder [43], polysomnography and sleep-diary reported reductions in WASO are predictive for subsequent reductions in clinical OA-related pain. However, no parallel changes in laboratory measures of nociceptive modulation (i.e., conditioned pain modulation and temporal summation) are found [43].

Although the available evidence indicates that more signs of central sensitization are associated with decreased sleep quality, decreased SE and increased clinical OA-related pain, the role of nociceptive modulatory processes as a mechanism linking improvements in insomnia symptoms to reductions in clinical OA-related pain is currently mainly unknown in people with OA.

3.1.2. Inflammation, insomnia symptoms and clinical OA-related pain

One prospective pilot study in people with knee OA and insomnia disorder provides an indication that improvements in insomnia severity (assessed with ISI) lead to reductions in clinical OA-related pain and alterations in inflammatory responses across a pain testing session (cold pressure test) [41]. More specifically, a decline in clinical OA-related knee pain during transfer activities, improved physical function, and a reduced increase in IL-6 and reduced decrease in tumour necrosis factor-α across the pain testing session are seen in people with knee OA with improved insomnia severity, as compared to people with knee OA without improved insomnia severity [41]. No parallel improvements in acute experimental pain ratings during the pain testing session in the people with knee OA with improved insomnia severity are reported. In the same study, further exploratory correlation analyses in context of IL-6, clinical OA-related knee pain and insomnia severity changes indicate that insomnia severity change scores are significantly correlated with clinical OA-related knee pain change scores during transfer activities, but not with mean IL-6 level change [41]. Mean IL-6 levels change is also not significantly correlated with clinical OA-related knee pain change scores during transfer activities [41].

Therefore, although the current findings suggest that improving insomnia severity among people with knee OA and insomnia disorder can alter acute inflammatory responses to experimental pain and reduce clinical OA-related pain during transfers, the clinical evidence regarding insomnia symptoms governing clinical OA-related pain and nociceptive sensitivity via inflammatory dysregulations in people with OA remains largely to be investigated.

3.1.3. Depressive symptoms, insomnia symptoms and clinical OA-related pain

One prospective study was found in people with knee OA who were not specifically recruited based on the presence of symptoms of insomnia. However, of the 367 study participants, 31%, 50.0% and 40% reported problems with SOL, WASO, and EMA, respectively. In this study, depressive symptomatology partially explains the association between these insomnia symptoms (i.e., interview-derived problems with SOL, WASO, and EMA) and clinical OA-related knee pain at baseline [50]. Furthermore, the baseline level of insomnia symptoms is predictive of the level of depressive symptoms, but not intensity of clinical OA-related knee pain at one-year follow-up [50].

Based on two secondary analyses of RCTs in people with OA and insomnia disorder [40] or insomnia symptoms (defined as an ISI $\geq$11) [42], inconsistent results are reported on depression in relation to insomnia symptoms and clinical OA-related pain. While both studies found that short-term improvements in insomnia severity (defined as $\geq$30% baseline to 2-month reduction on the ISI) preceded long-term benefits in clinical OA-related pain [40,42], a long-term improvement in depression was only found in one of both studies [42]. Hence the role of depression as a putative mechanism on the path between insomnia symptoms and clinical OA-related pain in people with OA over time is currently mainly unknown.

3.1.4. Pain-related and sleep-related cognitions, insomnia symptoms and clinical OA-related pain

In people with knee OA and insomnia disorder, pain catastrophizing moderates the cross-sectional relationship between SE and central nervous system sensitization (assessed via quantitative sensory testing) [32]. Very specifically, SE is associated with central nervous system sensitization when pain catastrophizing is above 7,4 points on the Pain Catastrophizing Scale. In this study sample of people with knee OA and insomnia disorder, 77% had a score of 7,4 or higher on the Pain Catastrophizing Scale [32]. Another cross-sectional analysis indicates that pain catastrophizing and pain self-efficacy partially mediate the association between insomnia symptoms (assessed via a single item "how often in the preceding two weeks they were bothered by trouble falling or staying asleep, or sleeping too much") and clinical OA-related pain intensity in people with knee OA [51]. In this study, participants were not recruited based on the presence of insomnia symptoms. However, 26%, 17% and 27% of the 517 included participants reported trouble falling or staying asleep, or sleeping too much on several days, more than half the days, or nearly every day of the week, respectively.

A secondary analysis of an RCT in people with OA and insomnia disorder reports that people with OA with improved insomnia severity in the short-term following treatment (defined as $\geq$30% baseline to 2-month reduction on the ISI) have related long-term improvements in intensity of clinical OA-related pain, fear-avoidance beliefs and dysfunctional beliefs about sleep, but not in the level of pain catastrophizing [40]. Considering the conflicting results on pain catastrophizing, the role of pain catastrophizing on the path between insomnia symptoms and clinical OA-related pain is currently unclear. Furthermore, based on the current evidence, the role of pain-related and sleep-related cognitions and behaviour as putative mechanisms on the path between insomnia symptoms and clinical OA-related pain in people with OA remains largely to be investigated.

3.1.5. Fatigue, insomnia symptoms and clinical OA-related pain

In people with hip OA who were not specifically recruited based on the presence of insomnia symptoms, but whose mean PSQI score was 8 points (which is above the cut-off of 5 points and indicates relevant decreased sleep quality [52]), poor sleep quality (assessed with PSQI) and greater fatigue are associated with increased odds of exacerbations in clinical OA-related hip pain, as based on a multivariate regression analysis on cross-sectional data [53]. However, sleep quality and fatigue do not significantly interact with each other in this regression model, indicating their independent relationship to clinical-OA related pain intensity [53].

Based on two secondary analyses of RCTs in people with OA and insomnia disorder [40] or insomnia symptoms (defined as an ISI $\geq$11) [42], consistent results are reported on fatigue in relation to insomnia symptoms and clinical OA-related pain. Both studies found that short-term improvements in insomnia severity (defined as $\geq$30% baseline to 2-month reduction on the ISI) preceded long-term benefits in clinical OA-related pain and fatigue [40,42].

Based on the current findings, the role of fatigue as a putative mechanism on the path between insomnia symptoms and clinical OA-related pain in people with OA remains largely unexplored.

3.1.6. Narrative synthesis on the mechanisms underlying the association between insomnia symptoms and clinical OA-related pain

Although several mechanisms are described in relation to insomnia symptoms and clinical OA-related pain in people with OA, only three papers included an analysis that specifically assessed the mechanism's mediating role in the association between the assessed insomnia symptom(s) and clinical OA-related pain

[50,51,53]. This research indicates that depressive symptoms, pain catastrophizing and pain self-efficacy partially mediate the association between self-reported problems with SOL, WASO, and/or EMA and intensity of clinical OA-related pain in people with knee OA [50,51]. Regarding fatigue, it is indicated that the level of fatigue does not interact with sleep quality in its association with clinical OA-related hip pain [53]. Important to mention is that all these analyses are performed on data collected in cross-sectional studies and from people with OA who were not specifically included based on the diagnosis of insomnia disorder, thereby decreasing their generalizability towards people with OA with insomnia disorder.

3.2. The effectiveness of non-pharmacological conservative interventions on insomnia symptoms and clinical OA-related pain in people with OA

Our literature search identified six RCTs (described in 7 papers) assessing the effectiveness of psychological interventions (n = 3), physical therapy/exercise programs (n = 2) or physical therapy and rehabilitation modalities (n = 1) on insomnia symptoms and clinical OA-related pain in people with OA. Below, we first describe between-group treatment effects per treatment approach for insomnia symptoms and clinical OA-related pain, and subsequently, we synthesize the results across all treatment approaches. In Supplementary Material 3, an overview of these studies' sample and outcome characteristics, together with their main between-group treatment effects on all assessed treatment outcomes is provided.

3.2.1. Targeting insomnia symptoms and clinical OA-related pain via psychological interventions

Three studies assessed the effectiveness of psychological interventions versus other psychological interventions and/or a control treatment in people with OA and insomnia disorder [43,54,55] or insomnia symptoms (i.e., ISI $\geq$11) [56]. These studies controlled for the use of sleep-related or pain-related medication in their eligibility criteria [43] and/or statistical analysis [54–56].

Two studies (outlined in three papers) compared cognitive behavioural therapies (CBT) which specifically included behavioural sleep management (i.e., CBT for insomnia (CBT-I) or combined CBT for pain and insomnia (CBT-PI)) to a non-behavioural intervention [54–56]. In the first study, the effectiveness of six 20- to 30-min sessions of telephone CBT-I spread over eight weeks was compared to the effectiveness of six 20- to 30-min of educational control sessions (i.e., educational sessions conducted in an informative, supportive, nondirective format, with education relevant to living with chronic OA), also spread over eight weeks [56]. In the second study, the effectiveness of six weekly 90-min group sessions of CBT-P (i.e., pain education, physical activation, goal setting, relaxation, activity pacing, guided imagery, and cognitive restructuring) was compared to the effectiveness of the same amount/duration of sessions of CBT-PI (i.e., CBT-P plus standard components of CBT-I) and the same amount/duration of educational content (i.e., material related to pain and sleep management, in a nondirective, self-help format without homework assignments or guided practice or instruction in CBT principles, and without daily behavioural self-monitoring) [54,55]. It is found that CBT-I/CBT-PI resulted in greater improvements in insomnia severity (assessed with ISI) and actigraphy-recorded SE up to 1 year post-intervention when compared to the control educational treatment [55,56]. These positive results however were not long-term and did not last when followed up 18 months post-intervention [54]. Only one study compared CBT-I to a behavioural intervention without a sleep component (i.e., a behavioural desensitization program designed an active behavioural placebo, presented as a means of eliminating the "conditioned arousal" which prolongs nocturnal awakenings) [43]. Both the CBT-I and behavioural desensitization program consisted of eight 45-min sessions, spread over 8 weeks. It was found that CBT-I did not result in significantly greater improvements in ISI-score or sleep-diary, polysomnography- or actigraphy-recorded SE at the short and medium-term (6 months) follow-up in comparison to behavioural desensitization [43]. Only for diary-reported and actigraphy-recorded WASO, CBT-I resulted in greater improvements than behavioural desensitization [43].

In the abovementioned studies, no significant differences between the interventions groups are found for clinical OA-related pain intensity or pain interference at short-, mid- or long-term follow-up [43,54–56], with the exception of McCurry et al. (2021) who reported a significant but not clinically relevant improvement in OA-related pain at 2 months follow-up [56]. However, post-hoc analyses on one RCT's data indicate that people with OA with greater insomnia severity and clinical OA-related pain intensity at baseline show significant 18-months reductions in pain when CBT-PI is compared to CBT-P [54,55]. This suggests that people with OA with higher levels of clinical OA-related pain and insomnia severity may be most likely to experience sustained benefits from specific sleep management over time [54,55].

3.2.2. Targeting insomnia symptoms and clinical OA-related pain via physical activity/exercise interventions

Two studies assessed the effectiveness of a physical activity/exercise intervention versus an educational control treatment in people with OA [57,58]. No specific inclusion criteria regarding the presence of insomnia symptoms were applied in both studies. Furthermore, these studies did not control for the use of sleep or pain medication in their eligibility criteria or in their statistical analyses.

A 24-week Tai Ji Quan intervention (i.e., traditional Chinese exercise characterized by range of motion and low-impact physical activity) that consisted of three 60-min sessions per week resulted in significant greater improvements in clinical OA-related pain, in global PSQI score, and in PSQI-subscales sleep latency, sleep duration, daytime dysfunction, and total sleep time at the post-intervention time point, when compared to an education control treatment (consisting of 60-min bi-weekly wellness education classes regarding health promotion) [57]. A significant but weak association is reported between the change in sleep quality and the change in clinical OA-related pain [57]. A 12-weeks Tai Chi group exercise program (3 sessions of 60 min per week) resulted in improved clinical OA-related pain and sleep quality (assessed with PSQI) at post-intervention and at the 3-month follow-up, when compared to a 12-weeks wellness educational program (1 session of 60 min per week) [58]. However, at the 6-month follow-up, no significant differences in sleep quality or clinical OA-related pain between the two groups are seen [58]. In this trial, the association between improvements in sleep quality and clinical OA-related pain is not specifically assessed. One needs to consider that the unbalanced treatment arms with regard to number of treatment sessions provided is a major weakness in the quality of both trials on the effectiveness of physical activity/exercise interventions.

3.2.3. Targeting insomnia symptoms and clinical OA-related pain via physical therapy and rehabilitation modalities

One study in people with OA (who were not specifically included based on the presence of insomnia symptoms) was identified assessing the effectiveness of 15 sessions of exercise therapy plus 10 sessions of physical therapy modalities (i.e., hot pack, therapeutic ultrasound, and transcutaneous electrical nerve stimulation) in comparison to 15 sessions of exercise therapy alone. In both groups, there was a significant improvement in sleep

quality assessed with the PSQI) and clinical OA-related pain after the treatment [59]. This improvement was significantly greater in the intervention group for both sleep quality and clinical OA-related pain. However, when assessing the relationship between improvements in sleep and clinical OA-related pain, this relationship was not significant. The fact that the treatment arms with regard to number of provided treatment sessions are not balanced in this trial, is a major weakness in study quality.

3.2.4. Narrative synthesis on the effectiveness of non-pharmacological conservative interventions on insomnia symptoms and clinical OA-related pain in people with OA

Cognitive behavioural interventions including a sleep component (CBT-I and CBT-PI) are nowadays the only interventions studied in high qualitative RCTs (i.e., controlling for pharmacological sleep and pain treatment and with balanced treatment arms), that result in more favourable outcomes on insomnia severity and SE when compared to an education control [54–56], or WASO when compared to a behavioural desensitization program [43]. This is not unexpected since CBT-I is the recommended and effective primary intervention to treat insomnia symptoms in people with primary insomnia disorder [56]. Despite the existing evidence for a bi-directional relationship between insomnia symptoms and clinical OA-related pain in people with OA, CBT-(P)I appears to be no more effective than other treatments on short-, mid- and long-term clinical OA-related pain [43,54–56].

4. Discussion including research agenda

Multiple aspects need to be investigated in people with OA and symptoms of insomnia. First, specific sleep-related treatment targets with the largest potential to influence clinical OA-related pain, should be identified. This requires a further understanding of the mechanisms linking insomnia symptoms to clinical OA-related pain in people with OA. Second, appropriate interventions should be designed specifically for these goals.

4.1. Expanding knowledge on mechanisms linking insomnia symptoms to clinical OA-related pain

The available evidence on the mechanisms influencing the association between insomnia symptoms and clinical OA-related pain indicates that depressive symptoms, pain catastrophizing and pain self-efficacy mediate the cross-sectional association between self-reported insomnia symptoms and intensity of clinical OA-related pain in people with knee OA [50,51]. Hence the sleep-pain association in people with OA and its underlying mechanisms remain an important knowledge gap. Studies with healthy people receiving experimental pain and people with chronic pain indicate that several phenotypic factors (i.e., observable characteristics, traits, or clinical presentations without mechanism implication [60]), require further investigation in people with OA. These factors include sociodemographic characteristics (like race, ethnicity, sex [61–64] and social participation [65]) and psychological variables (like trait-anxiety and depression [29,66–68], positive and negative affect [69–73], and pain- and sleep-related cognitions and behaviour [63,64,74]). The same applies to several endotypes (i.e., a subtype of a disease condition, implying a distinct pathophysiological mechanism [60]). Here, the dysregulation of the wake and sleep circadian rhythm [75], the disturbance of sleep architecture [76], HPA axis dysregulation [77], and a disturbed inflammatory activity require further investigation in people with clinical OA-related pain and comorbid insomnia symptoms. The latter is especially interesting for OA, since inflammation is considered a driving mechanism of the disease progress in a subset of the OA population [7,8]. Therefore, local cellular inflammatory markers like elevated levels of pro-inflammatory cytokines in the synovium [78,79], altered levels of systemic inflammatory markers [80–83], and inflammatory markers in the brain (i.e., increased glial activation which is indicative of neuro-inflammation [84,85]) can act as mechanisms underlying the sleep-pain association in people with OA and comorbid insomnia symptoms. Increases in pain-evoked cytokine levels are described in people with OA, with serum C-reactive protein (CRP) levels being associated with pain pressure thresholds and Interleukin (IL)-6 levels with cold pain tolerance [86]. This suggests that inflammatory mediators can influence clinical OA-related pain by influencing nociceptive modulatory processes. Mechanisms involved in this interaction might be the pain-evoked cytokine responses, which implicate the sensitizing effects of inflammatory markers on the afferent nociceptive pathways in the spinal dorsal horn and dorsal root ganglia [87], the mediating effects of these inflammatory markers on increased synaptic N-methyl-D-aspartate (NMDA) receptor functioning [88], and potentially even the brain's microglia [85]. When taking the anti-inflammatory effect of sleep into account [89], insomnia symptoms might thus be related to clinical OA-related pain by further modulating inflammatory processes [81]. In experimental studies in healthy participants, elevated levels of circulating inflammatory markers are observed after sleep restriction, and their upregulation is strongly associated with increased pain ratings and spontaneous pain [90,91]. The suggested mechanism underlying these increases in pain intensity and spontaneous pain following sleep restriction are the increased glutamate release in the dorsal horn and dorsal ganglia which is stimulated by the inflammatory mediator prostaglandin [90,91]. Thereby, prostaglandin facilitates nociceptive neurotransmission, and increased nociceptive sensitivity by acting on NMDA receptors [92,93]. One should however be careful with applying knowledge from experimental models of sleep restriction to clinical insomnia populations, since insomnia disorder is mainly characterized by disturbed rather than restricted sleep [37,38,94,95]. Recently Haack and colleagues (2023) employed in their mechanistic study in healthy participants an experimental sleep disturbance model which appropriately mimics the sleep patterns observed in people with chronic pain [96]. It was demonstrated that experimental sleep disturbances compromised central pain-inhibitory pathway predominantly in females, and activated the inflammatory cyclooxygenase pathway (by producing inflammatory prostaglandins), predominantly in males [97]. This study provides proof-of-concept that alterations in pain pathways by sleep disturbance might be sex-specific, implying different pain therapeutic targets in females and males.

Several lifestyle factors (like obesity, substance intake, smoking, physical inactivity and psychological distress) are known contributors to abovementioned phenotypic factors and endotypes in the context of insomnia symptoms and clinical OA-related pain [98–103]. Therefore, conceptualizing OA-related pain and insomnia disorder in people with OA as a system of dynamically interacting phenomena, which mutually influence each other via shared underlying factors and mechanisms is pertinent (Fig. 1).

Suitable designs to explain such mechanisms' interacting effect on the sleep-pain relationship are RCTs (in which insomnia symptoms are addressed in the experimental therapy) or high-intensive longitudinal designs (to take the highly dynamic nature of all factors involved into account) [45]. These designs can provide fundamental insights on how specific insomnia symptoms, clinical OA-related pain, and underlying driving mechanisms of both insomnia symptoms and clinical OA-related pain co-develop, co-occur and interact with each other within one day, from day to day, and over a longer period of time. This has strong clinical implications as this knowledge could unravel the specific targets of

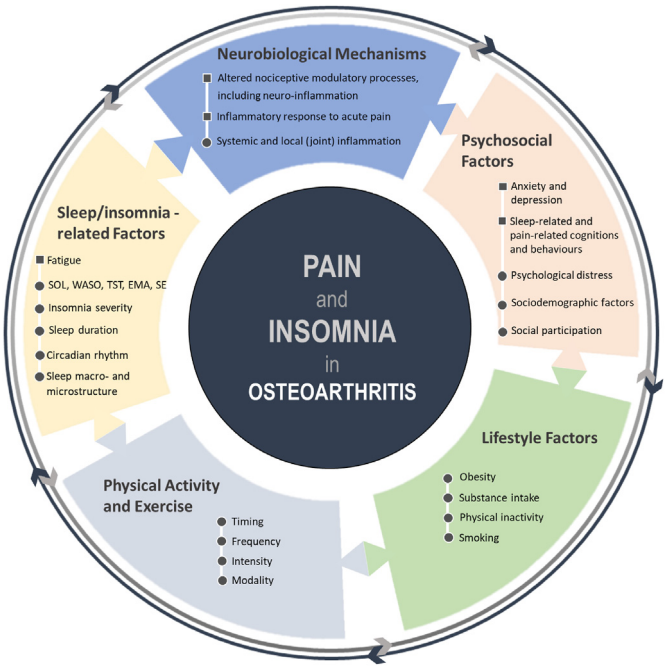

Fig. 1. OA-related pain and insomnia symptoms in people with OA as a system of dynamically interacting phenomena, mutually influencing each other.
Legend: Evidenced mechanisms on the path between clinical OA-related pain and insomnia symptoms in people with osteoarthritis are marked with a box, while hypothesized pathways are marked with a circle.

treatment which have the greatest effect on clinical OA-related pain. High-intensive longitudinal data sampling might thus be an assessment tool in clinical practice, enabling the identification of person-specific treatment targets.

4.2. Sleep management integrated in guideline-based conservative OA care

Based on gained insights in the specific factors and mechanisms underlying the sleep-pain interaction that are associated with improved clinical OA-related pain, specific (phenotype- and endotype-driven) sleep management can be developed for people with clinical OA-related pain and comorbid insomnia symptoms. Recent studies showed that cognitive and behavioural aspects of CBT-I differ in their specific effects in people with insomnia [104,105], i.e., cognitive components, such as education, acted most on interference and difficulty initiating sleep, worry, impaired quality of life, and dysfunctional beliefs, while behavioural components, such as bed-time restriction, mainly affected SE, WASO, EMA, time in bed, sleep incompatible behaviours and bed- and rise time variability [104,105]. While such evidence gives important insights into the possible path(s) of how CBT-I components work for people with insomnia only, it is unclear if these results are transferrable to the more complex clinical populations such as people with OA and comorbid insomnia symptoms. In people with OA and insomnia disorder, there are indications that improvements in clinical OA-related pain could be more linked with changes in total sleep time than in other sleep parameters (i.e., SE, SOL, WASO) [39]. Since both the studies of Blanken et al. (2021) in people with insomnia and the study of Smith et al. (2015) in people with OA and insomnia disorder did not find cognitive and behavioural CBT-I components to affect total sleep time [43,104], the value of these CBT-I components in people with OA and comorbid insomnia symptoms might thus be debatable. However, these are preliminary results that need to be considered with caution. Firm research is warranted on the effectiveness of components of CBT-I on short- and long-term pain responses in people with OA.

Apart from CBT-I, it seems appropriate to further explore the role of other potential sleep-improving interventions for people with OA, such as physical activity/exercise therapy which were already demonstrated to have favourable effects on sleep parameters in older adults [106], and are the key element in the management of people with OA to improve clinical OA-related pain [9]. High-quality evidence on the value of physical activity programs or exercise therapy on improvements in insomnia symptoms is essentially lacking today in people with OA and comorbid insomnia, as the only studies available include an intervention in people with OA without specifically including people with insomnia disorder or insomnia symptoms [57,58]. The assessment of efficacy and effectiveness of exercise versus mind-body interventions should investigate, together with the effect of the frequency, duration, and timing of these approaches on insomnia symptoms and potential underlying mechanisms of the sleep-pain interaction (e.g., systemic inflammation, activation of the stress system). In this context, it may be of interest to study the added value of a combined intervention of guideline-based insomnia treatment (i.e., CBT-I) and guideline-based OA management (education/advice, physical activity promotion, exercise therapy) [107] on both insomnia symptoms and clinical OA-related pain in comparison to standard guideline in use.

Research agenda

- Longitudinal prospective studies are needed, in which neurobiological and psychological mechanisms, and lifestyle factors are assessed as potential mediating mechanisms of the bi-directional sleep-pain association in people with OA and comorbid insomnia disorder.
- Future research should identify the specific aspects of sleep management which are most linked with clinical improvement in OA-related pain according to phenotype of a given individual.
- Randomized controlled trials or pragmatic trials are needed that examine the effectiveness of a combined insomnia and OA management on insomnia symptoms and clinical OA-related pain.

Practice points

In the screening of people with osteoarthritis, attention should be paid towards.

- the presence of insomnia symptoms by integrating a sleep-anamnesis in the patient interview, given its high prevalence in people with osteoarthritis. More specifically, information regarding sleep quality and quantity, onset and triggers of sleeping problems, sleeping habits, thoughts and cognitions about sleep, coping behaviours and treatment history can be gathered.
- the presence of depressive symptoms, the level of pain catastrophizing and pain self-efficacy given their influence on the interaction between insomnia symptoms and clinical osteoarthritis-related pain.

In the management of people with osteoarthritis and comorbid insomnia symptoms, non-pharmacological sleep management should be added to usual care, e.g. by integrating CBT-I components. This way insomnia symptoms might be improved, thereby eliminating a major barrier for effective guideline-based osteoarthritis care and for general physical and mental health. Improvement in clinical OA-related pain might be expected as well.

Declaration of competing interest

None to declare in relation to this review.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2023.101793.

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