



EXPERT OPINION

## Sleep impairment: an obstacle to achieve optimal quality of life in rheumatoid arthritis

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### Abstract

Sleep impairment is a common clinical condition in patients with rheumatoid arthritis. There are several confounding factors for poor sleep quality including inflammation, pain, comorbidities, and medications. Consequences of impaired sleep vary within a wide spectrum, as well. These include exacerbated inflammation and inflammation-related symptoms, mental and physical fatigue, mood disorders, daytime sleepiness, and poor quality of life. Sleep impairment in rheumatoid arthritis and its association with disease-related variables including health-related quality of life have been studied several times in the literature. Therefore, it would be of value to review the existing data on the crosstalk between sleep and rheumatoid arthritis. In the present article, the mechanism, confounders, and consequences of this association will be reviewed in detail. The evaluation of sleep impairment in rheumatoid arthritis along with the potential management strategies will be discussed.

**Keywords** Quality of life · Rheumatoid arthritis · Sleep · Sleep disorder · Sleep impairment

### Introduction

“Both sleep and wakefulness, when immoderate, detrimental” remarked Hippocrates (460–377 B.C.). The legendary physician highlighted the importance of sleep balance and quality nearly 25 centuries ago. Getting the right amount of sleep with good quality is essential for an individual’s psychological, physical, and social wellness, thus for quality of life [1].

Sleep disorders are classified in seven major categories including insomnia disorders, parasomnias, central disorders of hypersomnolence, sleep-related breathing disorders, circadian rhythm sleep-wake disorders, sleep-related movement disorders, and other sleep disorders [2]. There are several determinants of sleep such as gender, income, marital status, and concomitant diseases [3, 4]. A recent paper by Dong et al. reported that concomitant chronic diseases such as diabetes, hypertension, and cancer were significantly associated with poor sleep quality [3]. Sleep impairment has been an issue of concern in chronic rheumatic diseases including rheumatoid arthritis [5–8]. Common sleep disorders in

rheumatic diseases include non-restorative sleep, repeated nightly awakenings, and/or insomnia, hypersomnia, which, in turn, lead to fatigue and daytime sleepiness [6].

The relationship between rheumatoid arthritis and sleep quality has been studied several times in the literature [9–18]. A study by Goes et al. revealed that only 18.5% of rheumatoid arthritis patients had good sleep quality [13]. There are several contributors of impaired sleep in rheumatoid arthritis including pain and depressive mood [9]. Disease activity and associated inflammation are also responsible for poor sleep quality in patients with rheumatoid arthritis [18]. There are various consequences of sleep impairment, as well. These are mental and/or physical fatigue, reduced daily activity [19], mood disorders, and increased pain perception [20]. As a final consequence, sleep disturbances inevitably impair patient’s health-related quality of life [21, 22].

In line with the above-mentioned knowledge, the aim of the present article is to review the recent literature on sleep in rheumatoid arthritis. Mechanisms of this interaction, confounders/consequences of poor sleep quality in rheumatoid arthritis, and possible management strategies will be discussed.

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## Search strategy

Search strategy of the current review was based upon the recommendations published in *Rheumatology International* [23]. The following MeSH terms in combination with appropriate logical connectors were searched through PubMed/MEDLINE: “rheumatoid arthritis”, “sleep”, “sleep disorder”, “sleep deprivation”, “sleep disorders”, and “quality of life”. Articles (1) written in English, (2) reporting the data of observational/randomized-controlled studies, and (3) published during the past 7 years till August 2018 were included. Case reports/short reports, animal studies, letter to editors, preliminary studies, study protocols, and any unpublished data (i.e. abstract, theses) were excluded (Table 1).

## Relation between rheumatoid arthritis and sleep

Sleep deprivation, as a frequent finding in rheumatoid arthritis, has been a common topic of research for decades [4, 10, 12–18, 24–26]. Majority of the studies on this topic evaluated overall sleep quality and its association with disease-related parameters in rheumatoid arthritis [10, 11]. On the other hand, the consequences of sleep deprivation (fatigue, impaired quality of life, etc.) have also been studied by researchers [21, 22].

The relationship between rheumatoid arthritis and sleep quality stands as a “chicken and egg” dilemma. Rheumatoid arthritis, as an autoimmune disorder and with its

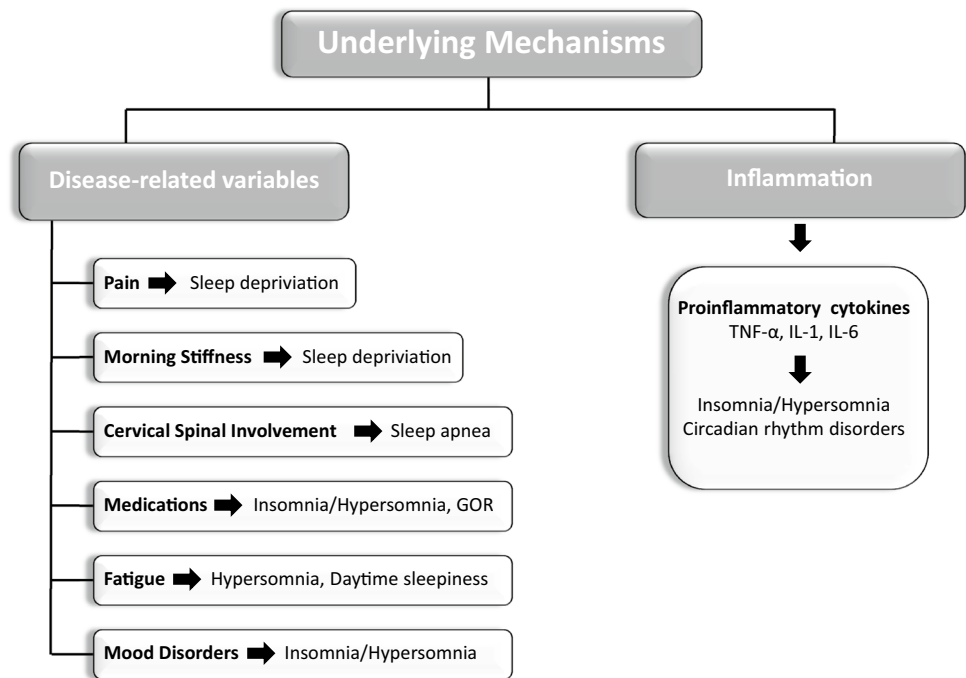
overcomplicated multisystem pathophysiology, may contribute to sleep deprivation either through immunological or hormonal pathways. On the other hand, vice versa might be the case, as well. Sleep disorder itself in long term can serve as a potential trigger of autoimmunity [27–29]. Accordingly, a large cohort study showed an increased risk of autoimmune diseases including rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and Sjögren’s syndrome among patients with non-apnea sleep disorders [30]. Another retrospective cohort study confirmed that overall risk for incident rheumatoid arthritis, Behcet’s disease, and Sjögren’s syndrome was higher in patients with obstructive sleep apnea than that in controls [31]. Furthermore, management of obstructive sleep apnea was shown to be associated with overall reduced risk of rheumatoid arthritis [31]. A nationwide cohort study in Taiwan revealed a 1.49-fold greater risk for the development of rheumatoid arthritis in patients with sleep disorders when compared to controls [28]. Not only the sleep apnea group, but also the non-apnea sleep disorder cohort showed increased risk of rheumatoid arthritis. The adjusted hazard ratio of rheumatoid arthritis was 2.56 and 1.47 times higher in the sleep apnea and non-apnea sleep disorder cohorts, respectively [28]. The potential underlying mechanism of increased autoimmunity and breakdown of self-tolerance is the impaired T regulatory cell function due to poor sleep quality, since sleep is required for proper suppressive activity of T regulatory cells on CD4<sup>+</sup>CD25<sup>-</sup> reporter T cells. Suppressive activity follows a circadian rhythm, being maximum at night, whilst minimum in the morning [32]. Impaired T regulatory cell function, in turn, leads to the upregulation of certain proinflammatory cytokines (tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ] and interleukin-6 [IL-6]), which take place in the pathogenesis of rheumatoid arthritis [28]. Sleep impairment might also contribute to the elevated expression of TNF- $\alpha$  and IL-6 from monocytes through lipopolysaccharide-stimulated activation of Toll-like receptor-4 [33]. Besides, partial night deprivation of sleep leads to the activation of beta adrenergic signaling and thus nuclear factor (NF)- $\kappa$ B, which is a key transcription control pathway in inflammation cascade. This activation contributes to the upregulation of several inflammatory response genes [34].

The mechanism of rheumatoid arthritis-related sleep deprivation is complicated, as well (Fig. 1). Not only the inflammation itself but also disease-related variables contribute to sleep disturbances [35]. Cytokines play the major role in inflammation-associated sleep impairment. Highly known cytokines in rheumatoid arthritis [TNF- $\alpha$ , IL-1, and IL-6] bear the potential of both somnogenic and inhibitory effects on sleep. This dual effect depends upon the circadian phase and the levels of certain cytokines [33]. Proinflammatory cytokines lead to the alteration of clock gene function, and, thus, interfere with the homeostatic regulation of sleep [35]. For cytokine level,

**Table 1** Search strategy

SEARCH FILTERS	
<i>Database</i>	Pubmed/MEDLINE
<i>Time interval</i>	6 August 2011-6 August 2018
MeSH TERMS	
Rheumatoid arthritis	} In combination with logical connectors (AND/OR)
Sleep	
Sleep disorder	
Sleep deprivation	
Sleep disorders	
Quality of life	
Inclusion Criteria	Exclusion Criteria
Written in English	Case reports
Observational studies	Short reports
Randomized-controlled trials	Animal studies
	Letter to editors
	Preliminary/pilot studies
	Study protocols
	Unpublished data

**Fig. 1** Underlying mechanisms of sleep disorders in rheumatoid arthritis (*GOR* gastroesophageal reflux, *TNF* tumor necrosis factor, *IL* interleukin)



a U-shaped interaction exists with sleep. Administration of TNF and IL-1 at somnogenic doses increases the intensity and duration of non-rapid eye movement (NREM) sleep. However, they show inhibitory effects on sleep, at increased doses [36]. Cytokines might interfere with the sleep quality, as well. Exogenous administration of certain cytokines such as IL-6 may lead to a transient non-physiological hypercortisolemia during the early sleep period through the activation of hypothalamic–pituitary–adrenal axis. Therefore, increased IL-6 level in rheumatoid arthritis might also be associated with reduced sleep quality during the first hours of sleep [37].

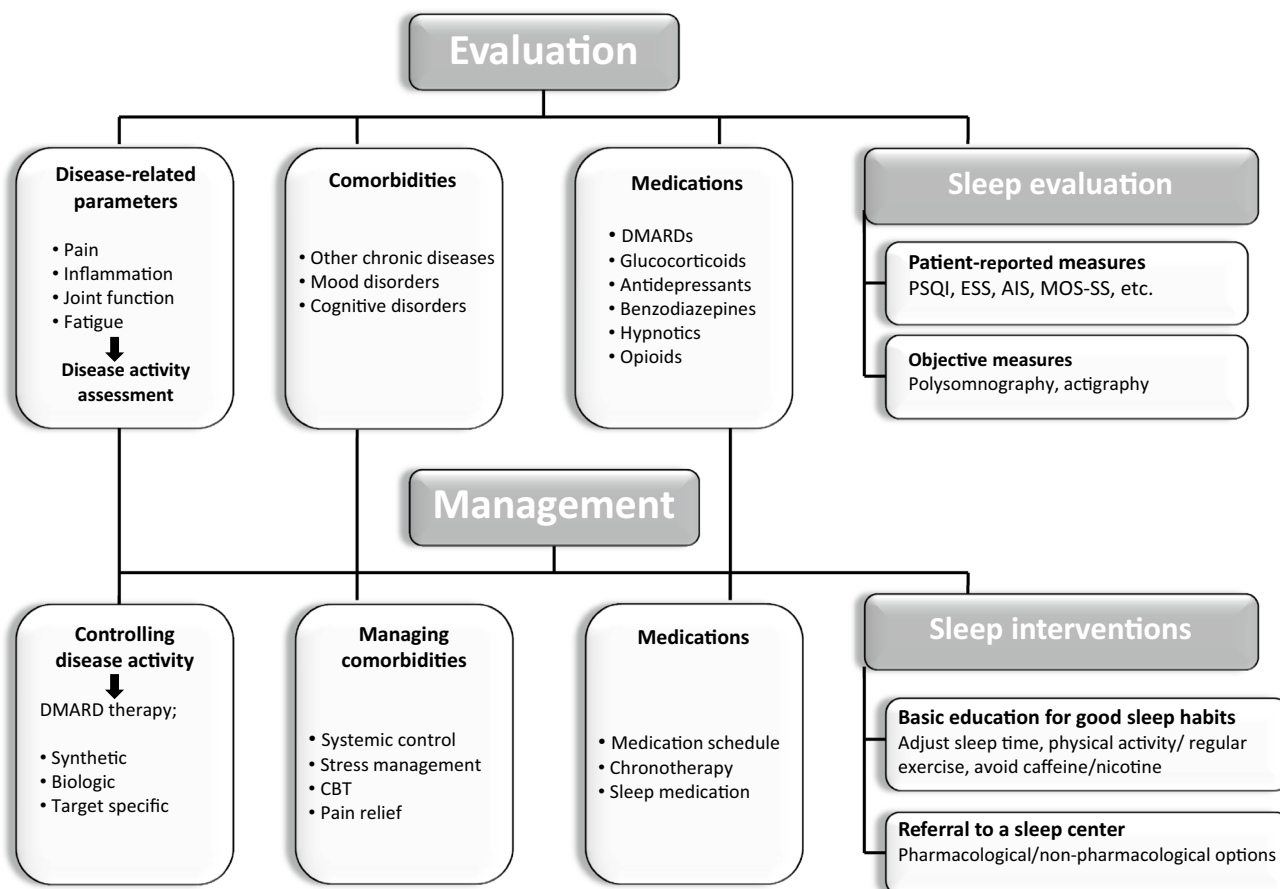
Disease-related variables such as pain, stiffness, secondary fibromyalgia, as well as the medications taken interfere with sleep in rheumatoid arthritis (Fig. 1). Pain itself may disrupt sleep. The early morning stiffness might interfere with the second half of the sleep. Another important factor to consider is secondary fibromyalgia that is known to be associated with various sleep disorders. On the other hand, medications may lead to gastroesophageal reflux and manifestations like nocturnal cough. Advanced joint disease, particularly the cervical spinal involvement, contributes to sleep disorders in rheumatoid arthritis. Vertical translocation might lead to the collapse of upper airway and cause obstructive sleep apnea [38].

## Evaluation of sleep in rheumatoid arthritis

The evaluation of sleep in rheumatoid arthritis requires a full assessment of the patient in daily clinical practice (Fig. 2). Not only the disease-related variables such as systemic

inflammation, synovitis, joint function, but also the concomitant problems including restless leg syndrome and mood disorders might contribute to sleep deprivation [4, 33]. Therefore, multi-dimensional clinical evaluation of the patient should be the first step to identify the potential cofactors for sleep impairment. Patient history should include the symptoms related to the disease, as well as those related to sleep disturbance. A detailed history of comorbidities and current medications should be taken. The presence/suspicion of a sleep disorder requires further assessment of sleep quality.

Evaluation of sleep quality in rheumatoid arthritis is based upon patient-reported measures and objective measures such as actigraphy and polysomnography. The studies on this topic, in general, used patient-reported measures including Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, Athens Insomnia Scale, the Medical Outcomes Study Sleep Scale, and the sleep components of the Rheumatoid Arthritis Impact of Disease [4, 11, 15, 16, 19, 21, 26]. Among these, Pittsburgh Sleep Quality Index is the most commonly used scale, with a score  $\geq 5$  is recommended as the cutoff for detecting sleep impairment [19, 39]. A study by Austad et al. evaluated sleep disorders using four different patient-reported measures: Medical Outcomes Study sleep disturbance scale and the sleep components of the Rheumatoid Arthritis Impact of Disease, the 15-dimensional quality of life questionnaire, and the Multi-Dimensional Health Assessment Questionnaire. The results revealed a high correlation among four measures [11]. A systematic review of sleep instruments in rheumatoid arthritis identified 45 sleep instruments and 14 domains for sleep.



**Fig. 2** Evaluation and management of sleep impairment in rheumatoid arthritis (DMARD disease modifying anti-rheumatic drug, PSQI Pittsburgh sleep quality index, ESS Epworth sleepiness scale, AIS

Athens insomnia scale, MOS-SS medical outcomes study sleep scale, CBT cognitive behavioral therapy)

Daytime functioning, maintenance, adequacy, and initiation of sleep were appeared as top ranked domains [40]. Medical Outcome Study Sleep, Women's Health Insomnia Rating Scale, Insomnia Severity Index, and Insomnia Rating Scale were the top ranked instruments on feasibility [40].

On the other hand, a number of studies used polysomnography to assess sleep in rheumatoid arthritis [12, 20, 33]. Overnight polysomnography, as an objective measure, enables the assessment of sleep continuity and its architecture. Sleep continuity refers to the latency, efficiency, and total time of sleep, as well as waking after sleep onset. Sleep architecture comprises the basic structural components of sleep including NREM and REM sleep [33].

## Correlates of sleep impairment in rheumatoid arthritis

There are many correlates and/or contributors of sleep impairment in rheumatoid arthritis. Both demographic and the disease-related variables might be associated with sleep deprivation. These include age, gender, pain, mood disorders/mental health, fatigue, medications, inflammatory markers, and overall disease activity [4, 8–11, 15–18, 21, 22, 24, 26, 41]. There is limited evidence confirming the hypothesis that sleep in rheumatoid arthritis impairs by aging [10, 16].

Several disease-related parameters including pain, fatigue, number of tender/swollen joints, inflammatory markers, and overall disease activity contribute to sleep impairment. The relation of sleep with these variables is rather bidirectional. Pain stands as an independent contributor of sleep impairment [9, 16]. In other words, pain can directly interfere with sleep either affecting its quality or quantity, which may include nightly awakenings, sleep fragmentation, and reduced sleep efficiency [9]. On the other hand, pain can contribute to sleep impairment indirectly by triggering depressive mood. With regard to fatigue, a study on 384 patients revealed that 4 of the 5 domains of Multi-dimensional Fatigue Inventory (mental, physical and general fatigue, and reduced motivation) were associated with poor sleep in rheumatoid arthritis. General fatigue and mental fatigue were further identified as independent correlates for poor sleep. This finding was attributed to the overlapping symptoms of depression and fatigue [19].

Disease activity is an important determinant of sleep in rheumatoid arthritis [11, 13, 15, 16, 21]. Accordingly, Goes et al. found that Disease Activity Score-28 was associated with sleep disturbance in patients with rheumatoid arthritis. Furthermore, among the elements of Disease Activity Score-28, the number of tender joints was determined as being responsible for this association [13]. Sariyildiz et al. also confirmed that higher disease activity is a predictor of poor sleep quality [15]. A study comparing poor and good sleepers reported that poor sleepers had higher erythrocyte sedimentation rate and higher disease activity score [21]. Austad et al. found that disease activity assessed by Rapid Disease Activity Index was one of the contributors of sleep disturbance [11]. Conversely, Løppenthin et al. did not find similar association [19].

Mental health in rheumatoid arthritis has also a bidirectional relation with sleep. Depressive mood is highly and independently associated with sleep deprivation in rheumatoid arthritis. In a study by Nicassio et al., multiple regression models eventually revealed that depressive symptoms over the past month and pain assessed by Short Form-36 were the most important predictors of sleep quality [9]. The study further determined that the interaction between pain and sleep is partially mediated by depression [9]. As a different point of view, Yoon et al. studied cognitive functions in rheumatoid arthritis. Researchers determined that sleep quality and depressive mood were significantly associated with perceived cognitive function, even after controlling for functional limitations and disease severity [42].

Current medications might be related to sleep quality, as well. For instance, Goes et al. confirmed that poor sleep was associated with daily dose of prednisone [13]. This is partly due to the direct effects of exogenous glucocorticoids on sleep. On the other hand, this relation may also be attributed indirectly to the disease activity, since higher doses

of glucocorticoids are used in patients with higher disease activity [13]. On a different point of view, concomitant use of non-benzodiazepine hypnotic drugs with benzodiazepines was emerged as a significant contributor of sleep impairment in patients with rheumatoid arthritis [11]. The impact of disease modifying anti-rheumatic drugs (DMARD) (synthetic/biologic/target specific) on sleep quality was also evaluated in studies [15, 43, 44]. Most of them supported the favorable effect of biologics on sleep parameters [43–48]. Karatas et al. showed the beneficial effect of anti-TNF therapy on sleep parameters of Pittsburgh Sleep Quality Index, but not on polysomnographic sleep parameters [49]. On the other hand, Sariyildiz et al. found that Pittsburgh Sleep Quality Index score did not differ by medications used for rheumatoid arthritis [15].

### Sleep impairment and quality of life in rheumatoid arthritis

Sleep impairment has a number of consequences such as fatigue, pain exacerbation, mood disorders, daytime sleepiness/dysfunction, decreased social participation, reduced work productivity, and eventually poor quality of life [18, 20, 50]. Irwin et al. studied the impact of experimental partial night sleep deprivation on fatigue, mood, and pain in patients with rheumatoid arthritis [20]. Partial night deprivation is related to increases in number of painful joints, self-reported fatigue, and mood symptoms. Furthermore, the effect of sleep fragmentation on pain was found to be regardless of mood symptoms [20]. Patients with rheumatoid arthritis have diminished central modulation of pain. Sleep impairment was also suggested as a mediator that plays role on the attenuated central modulation and, thus, centralization of pain in rheumatoid arthritis [50]. With regards to fatigue, Katz et al. confirmed that poor sleep was an independent confounder of fatigue in patients with rheumatoid arthritis [51]. Sleep fragmentation was suggested as being responsible for this association [51].

With these above-mentioned consequences, poor sleep eventually leads to overall poor health and poor health-related quality of life of [4, 12, 20–22, 52]. Studies so far used several measures to assess the impact of impaired sleep on health and health-related quality of life [12, 15, 21, 22]. Most widely used measures were the Health Assessment Questionnaire and the Short Form-36 health survey [12, 21]. Gjevre et al. assessed daytime somnolence by Epworth Sleepiness Scale in a sample of rheumatoid arthritis patients. Individuals with hypersomnolence revealed significantly higher scores in the modified Health Assessment Questionnaire [12]. Guo et al. found that poor sleepers had significantly more impaired health-related quality of life in all the dimensions of Short Form-36 [21]. A study on 210 patients



also confirmed the negative association between quality of life and sleep disorders [22]. Recently, Druce et al. reported the protocol for a prospective cohort study, which would evaluate the association between quality of life and sleep in patients with rheumatoid arthritis [53]. Patients will report the data via a smart phone/tablet application and a triaxial accelerometer will be used to collect data on sleep parameters and daytime activity [53].

## Management strategies for sleep impairment in rheumatoid arthritis

Management plan for sleep impairment in rheumatoid arthritis might be based upon three basic principles: to control rheumatoid arthritis disease activity, to manage the co-factors for poor sleep quality, and to tailor treatment/to consult a sleep specialist (Fig. 2).

### Controlling rheumatoid arthritis disease activity

Poor disease activity in rheumatoid arthritis is associated with poor sleep quality [18]. Inflammation is the major determinant of disease activity in rheumatoid arthritis. Therefore, it is of great importance to control inflammation to obtain good sleep quality. Treatment strategy should be reviewed in patients with signs of persistent inflammation. Considering biologic DMARD therapy would be of value in patients non-responsive to synthetic DMARD therapy. In a study using polysomnography and patient-reported sleep measures, initiation of anti-TNF treatment was shown to improve sleep efficiency [48]. A randomized, double-blind, controlled trial confirmed the efficacy of adalimumab in combination with methotrexate on patient-reported outcomes including sleep quality [43]. Etanercept was found superior to methotrexate with regard to the effect on sleep parameters [54]. Certolizumab pegol, which is another biologic DMARD, also provided a significant improvement in sleep compared to placebo [46]. The Janus kinase inhibitor, tofacitinib (either 5 or 10 mg daily), combined with background conventional DMARD therapy improved sleep in a phase III trial [55]. However, another phase III trial with tofacitinib in combination with methotrexate failed to show this effect [56]. When the efficacy of tofacitinib or adalimumab evaluated versus placebo, both drugs were shown to improve sleep [57]. Inhibition of IL-6 was suggested to improve sleep quality either in a direct or an indirect manner. Tocilizumab 8 mg/kg improved sleep quality in moderately or severely active rheumatoid arthritis [45]. Gossec et al. reported that response to rituximab was more prominent in physical aspects of rheumatoid arthritis than that in other patient-reported outcomes including sleep quality [47].

As a different point of view, chronobiologic intervention might also be taken into consideration when managing high disease activity in rheumatoid arthritis. Chronobiologic intervention addresses scheduling the medical interventions according to the circadian rhythm determinants to improve the drug efficacy and benefit–risk ratio [58, 59]. This strategy should be integrated into routine medical practice, particularly for patients with symptoms following circadian rhythm and with signs of sleep disorders [60]. Inflammatory cells including macrophages, mast cells, and T cells are tightly mediated by circadian clock, which is responsible for the circadian pattern in certain proinflammatory cytokines (TNF and IL-6) and for the increased inflammatory response in mornings. Chronotherapy targeting nocturnal rise in inflammatory cytokines might improve the benefit-to-risk balance [58]. In CAPRA-1 trial, the efficacy and safety of bedtime taken modified-release prednisone tablet was compared to the morning administration of immediate-release prednisone. Although the safety profile was similar between groups, the mean relative change in duration of morning stiffness was significantly higher with the modified-release prednisone [59]. It also reduced IL-6 serum concentrations after 3 months [59]. In CAPRA-2 trial, modified-release prednisone in addition to the existing DMARD therapy was compared to placebo plus DMARD therapy. Low-dose prednisone chronotherapy revealed higher response rates, greater reduction in morning stiffness, disease activity, and fatigue, with a similar safety profile compared to placebo [60]. Therefore, chronobiology should be kept in mind when tailoring treatment regimens in rheumatoid arthritis. However, chronotherapy should not only target cytokines, but also take the other determinants of inflammation (humoral, endocrine, and oxidative stress) into consideration [58].

### Managing the co-factors for poor sleep quality

Co-factors for poor sleep quality include disease-related variables, concomitant diseases, and medications/diet. Disease-related variables such as fatigue, pain, and joint dysfunction should be evaluated and managed properly. On the other hand, concomitant disorders such as mental health problems (depression, anxiety, etc.), craniofacial pathologies, and systemic diseases might also interfere with sleep quality [4, 8–11, 15–18, 21, 22, 24, 26]. Assessment of the concomitant conditions and consulting the patient accordingly would be of benefit. As a common accompanying condition, attention should be paid to rule out fibromyalgia, which may also interfere with sleep quality. Medications and diet-related factors should be reviewed. Excessive alcohol and/or caffeine intake and smoking should be avoided. Anti-depressants, benzodiazepines, non-benzodiazepine hypnotics, and opioids might impair sleep quality and should be scheduled properly. Using a daily medication schedule, in

which the times of administration and the drug dosages are noted, can avoid drug side effects, which will interfere with sleep quality.

### Tailoring treatment/consulting a sleep specialist

As an important comorbidity in rheumatoid arthritis, sleep impairment should be treated properly when necessary. European League Against Rheumatism recommended taking sleep quality into consideration in osteoarthritis and inflammatory arthritis. Offering basic education regarding good sleep hygiene habits such as stress management, regular exercising, sleep timing, avoidance of caffeine, and nicotine is of importance. Referring the patient to the specialists or specialized sleep clinics for pharmacological and non-pharmacological interventions would be of value [61].

Physical activity/exercise as a potential non-pharmacological management strategy for sleep disorders has been studied several times in rheumatoid arthritis (Table 2). Exercise might improve anxiety, depressive mood, circadian rhythm, and thermoregulation. It can also interfere with cytokine levels in rheumatoid arthritis [62]. Durcan et al. evaluated the effect of 12-week exercise program on self-reported sleep quality and pain [62]. The program included home-based strengthening (three times per week), range of motion/stretching (daily), and light–moderate-intensity aerobic (walking) exercises. After 12 weeks, sleep quality improved significantly in the exercise group [62]. A recent study by McKenna confirmed that total sleep time had a

positive relationship with physical activity in patients with rheumatoid arthritis [63]. On the other hand, as a contradicting finding, Løppenthin et al. failed to detect this relation [64]. Authors attributed the lack of association to measuring physical activity behavior rather than focusing specifically on physical exercise [64]. Evans et al. evaluated the impact of 6-week Iyengar yoga program on quality of life in patients with rheumatoid arthritis. Although the program led to some benefits regarding quality of life, it showed no effect on weekly reported sleep difficulties [65]. On the other hand, weekly progressive resistance training for 6 weeks was shown to improve sleep scale significantly [66]. Bakir et al. presented the results of reflexology on pain and sleep in rheumatoid arthritis. Reflexology, once a week for 6 weeks, provided a significant improvement in sleep quality [67]. A systematic review presented the current evidence regarding the impact of exercise on sleep in rheumatoid arthritis. Partly because the included studies had high risk of bias and in part due to the heterogeneity of study designs, the authors could not present a firm conclusion on this issue [68]. These results, overall, confirm the need for further research on this particular area.

Anti-depressants, analgesics, non-benzodiazepines, benzodiazepines, and other muscle relaxants are among the various pharmacological treatment options in sleep impairment. The nature of the sleep disorder is of importance when selecting the right medication. Since hypersomnia and insomnia would definitely require different sleep interventions/medications. It would be of great value to consult

**Table 2** Studies evaluating the effect of exercise on sleep in rheumatoid arthritis

Study	Exercise type	Exercise intensity	Exercise frequency/time	Intervention duration	Results
Durcan et al. [62]	Home-based Strengthening	40–50% 1 RM	Two-to-three times/week (15–20 reps/set) <sup>a</sup>	12 weeks	Sleep quality improved in the exercise group
	ROM/stretching	Point of tightness	Daily (30 s for static stretch)		
	Aerobic (walking)	Light-moderate	Five times/week (150 min/w)		
Evans et al. [65]	Iyengar yoga program	–	Twice per week (1.5 h/class)	6 weeks	Pain disability, two subscales of HRQOL (general health and vitality) and many of the psychological outcomes improved No significant effect on weekly reported sleep difficulties
Morsley et al. [66]	Supervised PRT	Not defined	Weekly (30–60 min) <sup>b</sup>	6 weeks	Sleep scale improved significantly

ROM range of motion, HRQOL health-related quality of life, RM repetitive maximum, PRT progressive resistance training

<sup>a</sup>When specific strength deficits were identified, 8–12 reps of 60–70% 1 RM were prescribed

<sup>b</sup>Patients were also encouraged to exercise twice weekly according to an illustrated exercise sheet

a sleep physician when sleep remains disturbed despite the first-line interventions [61].

### Implications in clinical practice and future recommendations

Sleep in rheumatoid arthritis is a complex issue. With its multi-system nature, rheumatoid arthritis requires a multi-dimensional clinical assessment. At routine follow-ups of a patient with rheumatoid arthritis, rheumatologist's awareness regarding a potential accompanying sleep disorder is of great importance. In case of any concomitant sleep disturbance, proper management strategies should be tailored, since the sleep pathology would inevitably interfere with patient's health-related quality of life.

Several determinants of poor sleep quality have already been defined in patients with rheumatoid arthritis. Nevertheless, further research focusing on the neurobiology of this association would be of benefit. The existing data regarding the management of sleep impairment in rheumatoid arthritis are still limited. Prospective controlled studies would better identify the potential effectiveness of pharmacological and non-pharmacological treatment options proposed for sleep disorders in rheumatoid arthritis.

**Author contributions** ICB: contributed to the conception and design of the study; collection and interpretation of data; drafting and revising the article; approval of the final version.

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### Compliance with ethical standards

**Conflict of interest** The author declares no conflicts of interest.

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