Prevalence and factors associated with disturbed sleep in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review

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Abstract

This review explores the prevalence and factors associated with disturbed sleep for patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis in order to clarify consistent findings in this otherwise disparate research field. The association of physical, demographic and psychological factors correlating with poor sleep was explored, and the effectiveness of interventions assessed. Ten electronic databases were searched: AMED, CINAHL, Embase, Medline, PsycINFO, PubMed, Scopus, Web of Science, OpenGrey and BASE. Following application of inclusion and exclusion criteria, 29 articles were critically assessed on the basis of methodology, experimental design, ethics and quality of sleep data, leading to the selection of 15 studies for final review. Poor sleep was reported in 35–90% of patients with axial spondyloarthritis and is more prevalent within this clinical population compared to healthy control subjects. Disturbed sleep is an important aspect of disease for patients and reflects the severity of disease activity, pain, fatigue and functional disability. However, the direction of this relationship is undetermined. Associations with age, gender, years spent in education, quality of life and depression have also been demonstrated. Anti-TNF medication is effective in reducing poor sleep, and exercise has also produced beneficial results. Future research into poor sleep should take account of its multifactorial nature. There is also a current lack of research investigating nonpharmacological interventions or combination therapies. A standardised, validated measurement of poor sleep, appropriate for regular patient screening, would be a useful first step for future research.

Keywords

Spondyloarthritis, Insomnia, BASDAI, ASQoL, Anti-TNF, Inflammation

Introduction

Patients with ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nraxSpA) share similar burdens of illness in terms of pain, functional impairment, quality of life (QoL) and the need for effective treatment [1, 2]. Pain and stiffness in the axial spine impact functional ability and QoL [3, 4] and patients have associated these symptoms with poor sleep [5, 6]. In an early reference to the problems of sleep in AS, the secretary for the National Ankylosing Spondylitis Society wrote, 'it is at night that the spondylitic feels his condition most and is most conscious of the skeletal prison within him' [7].

For patients with early AS, pain and stiffness are thought to be caused by inflammation and associated with active disease [8]. Awakening in the early morning hours may help distinguish inflammatory back pain from mechanical low back pain [5]. Prevalence of disturbed sleep is evident in other chronic inflammatory conditions such as psoriatic arthritis [9, 10], rheumatoid arthritis [11] and inflammatory bowel disease [12], and research suggests that disturbed sleep is associated with active disease, pain, reduced physical functioning, demographics and mood within these wider populations [13, 14, 15].

Patients with AS prioritise improvement in sleep [16] and have rated poor sleep as one of the most prevalent quality of life concerns [17]. The impact of poor sleep reaches beyond the individual due to associations with fatigue and daytime functioning [18], and sleep disruption resulting from pain, may disrupt full time employment [19].

To date, there has been no systematic review investigating the prevalence and modifying factors of sleep in AS and nraxSpA patients. The objective of this systematic literature review is to make an assessment of our current knowledge in this area, in order to provide a focus for future research to improve physical, psychological and social outcomes for patients with axial spondyloarthritis (AxSpA).

Methods

Search strategy

The following subject-relevant, electronic databases were searched for peer-reviewed, primary research articles concerning sleep disturbance within the AxSpA population in

September 2015: AMED, CINAHL, Embase, Medline, PsycINFO, PubMed, Scopus and Web of Science.

The search strategy was a textword search using Boolean logic and did not utilise methodologies such as Medical Subject Headings (MeSH) terms. Dates were unrestricted, and the following search terms were used: 'Ankylosing spondylitis', 'spondyloarthr*', 'spondylitis', 'Strumpell', 'Bechterew' AND 'sleep'. OpenGrey and BASE were also searched for the unpublished, relevant literature in order to limit publication bias.

This review of the current literature adhered to the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) [20] and a PRISMA checklist submitted as supplementary material.

Study selection

As the literature is limited within this field, a total of 101 full text, relevant articles were obtained from following this search protocol. Titles, abstracts and, where required, full text of all articles were explored and selected according to the criteria stated below:

Inclusion Criteria:

1. Published literature is peer reviewed.
2. Grey literature details a process of ethical review.
3. The article is a primary research study.
4. Studies which explore sleep disturbance or insomnia as a main area of interest, explored using a discrete measure, through qualitative or quantitative analysis and referenced within the method or results section of the research paper.
5. Sleep disruption data specific to patients with a diagnosis of AS or nraxSpA.
6. The methodology provides clear description of the way in which sleep data are collected.

Exclusion Criteria:

1. The article is an essay, letter, conference presentation or abstract, review or meta-analysis.
2. The article includes secondary analysis of data previously included for review.

3. There is no clear distinction between sleep and fatigue data.
4. The article has no published, full text, English translation.

Any relevant conference reports, posters or abstracts were followed up with an extensive online search and direct contact with key authors where possible. This was in order to access any unpublished, full text material for inclusion. Although it was beyond the scope of this review to obtain unpublished data from the authors of all relevant conference abstracts and posters, to our knowledge all existing full text versions of relevant, published papers were obtained. Additional snowball search strategies included reference searching for relevant published or unpublished literature, but these strategies yielded no further studies for inclusion. In total, 29 papers adhered to the inclusion and exclusion criteria (Fig. 1). All screening against inclusion/exclusion criteria and critical appraisal for included studies were independently performed by two authors (SL, ED) with strong inter-rater agreement (κ = 0.9). Any disagreement in evaluation was resolved through discussion and consensus.

Main outcome variables

Data collection for each included study followed a template form, in order to extract important information such as population characteristics, experimental design and methodology, details of intervention, outcome measures, descriptive statistics, analysis and findings. In order to examine their validity, reliability, quality and relevance of these articles, critical appraisal was based on the CASP checklist tools for RCTs, case control studies, cohort and qualitative studies [36].

Through the process of applying inclusion and exclusion criteria, which included elements of quality assessment, each remaining study was then evaluated on 14 yes/no questions, available as supplementary material.

Data extraction and quality assessment was formed independently by 2 authors (SL, ED). Studies were first rated on recognised diagnosis of AS and nraxSpA (1 question) and quantity and quality of sleep data (2 questions). At this stage, studies were excluded if both reviewers independently considered there was a lack of sufficient, focussed and relevant

sleep data for inclusion, for example, if data were limited to a single item yes/no outcome measure for sleep.

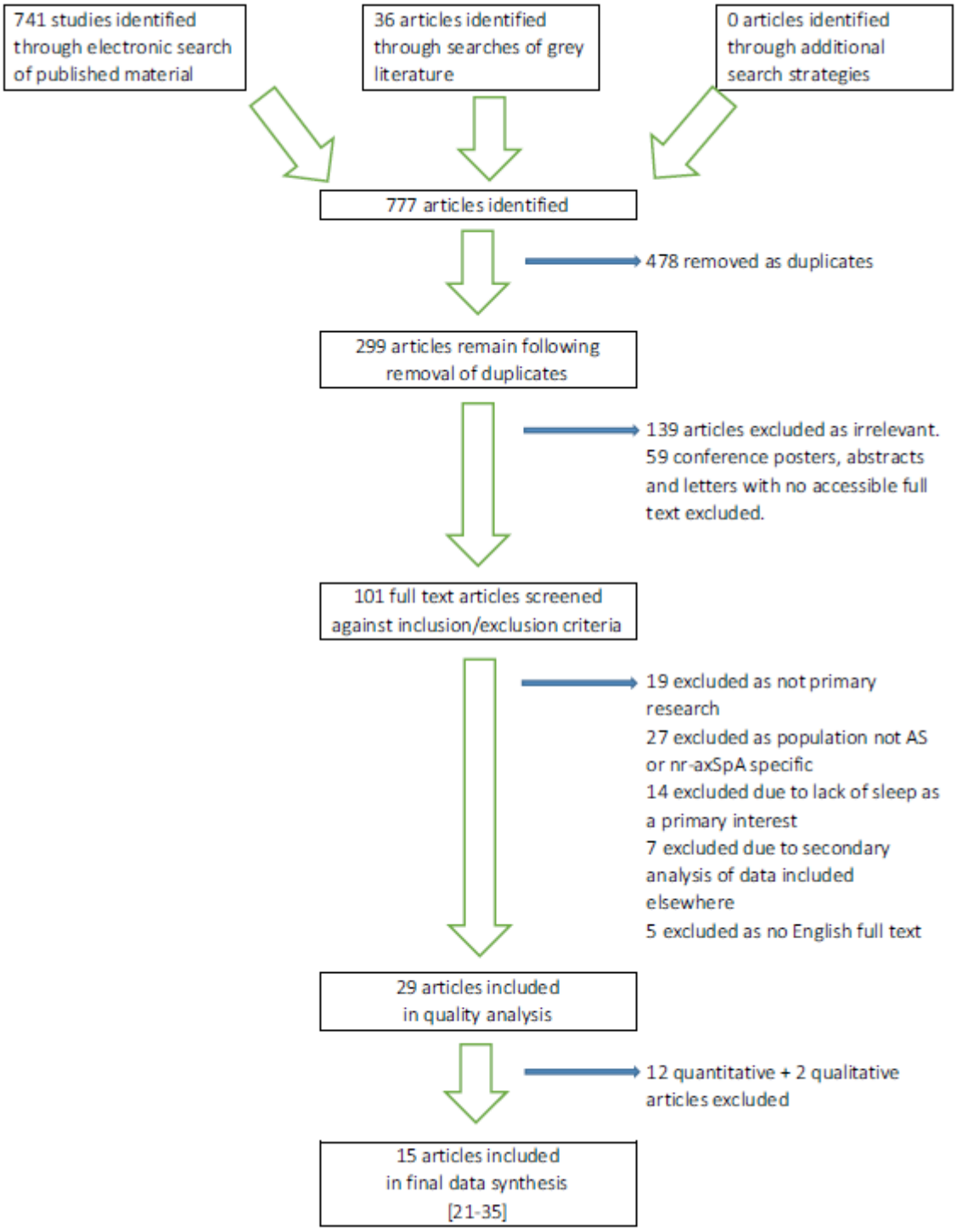

Fig. 1 Search results detailing number of studies identified, screened, assessed and included in final review.

Additional questions included: reliability and validation of the instrument used to measure sleep disturbance (1 question), experimental study design (4 questions), reported variables and independent differences (2 questions), reporting of clinically important outcomes and assessment of harmful outcomes (2 questions) and assessment of the reliability and validity of conclusions (2 questions). Statements of ethical approval and informed consent were also checked. Those studies with the strongest design and greatest relevance to the research questions were selected for inclusion. Full details of the checklists utilised for data extraction and critical appraisal are available as supplementary material.

Due to these strict selection criteria, it is possible that some trends were lost during critical appraisal, for example, the exclusion of papers with minimal, presence/absence data. The measures of disturbed sleep utilised within included studies of this review are summarised in Table 1 . Data synthesis within this descriptive review is achieved through tabulation and narrative structure to draw conclusions and recommendations.

Results

Demographic data were presented in all 15 studies, and an early age for disease onset for AS is evident. Across AS studies (excluding 2 studies incorporating nraxSpA populations [27, 34] and 1 study reporting median (IQR) data [26]) the mean population age in years M (SD) = 36.7 (9.7). The mean disease duration (where reported from age from symptom onset) in years M (SD) = 12.3 (7.5). The method of collection of sleep data varied within the 15 studies as shown in Table 2 . Two studies included objective measurements of sleep: polysomnography (PSG), [21, 35] and measurement of Apnoea–Hypopnoea Index (AHI) [35]. Both studies supplemented objective data with subjective data. Therefore, all 15 studies included analysis of sleep data collected from subjective questionnaires and reported prevalence of sleep disturbance for AS or nraxSpA patients. However, it should be noted that the 5 studies that utilised the PSQI sleep scale used a variety of thresholds to determine ‘poor sleep’, from a PSQI global score ≥5 [21] to PSQI > 7 [29, 32]. This is reflected in the % of poor sleep reported, with lower PSQI thresholds resulting in a higher % of AS patient sample reporting poor sleep quality (Table 2). However, healthy control comparisons within 4 of the 5 PSQI studies support statements that the prevalence of sleep disturbance is significantly higher within this clinical group.

Table 1 Overview of measures utilised for the collection of sleep data within this review

Objective measures	
Name	Apnoea–Hypopnoea Index (AHI)
Description	A measure of the number of apnoea (complete cessation of airflow for at least 10 s) and hypopnoea (abnormally low respiratory rate or shallow breathing) per hour
Name	Polysomnography (PSG)
Description	Sleep laboratory recording which monitors physical and psychological processes such as electroencephalographic, electrooculographic, electromyographic, respiratory events, oxygen saturation and leg movements
Subjective measures	
Name	Ankylosing Spondylitis Quality of Life Index (ASQoL)
Description	18-item measurement of quality of life for AS patients [37]. 1 question directly relates to sleep Q5 = 'It's impossible to sleep'
Name	Epworth Sleepiness Scale (ESS)
Description	8-item subjective questionnaire measuring daytime sleepiness, assessing the likelihood of falling asleep in everyday situations (for example, sitting reading or stopped at a traffic light) [38]
Name	Jenkins Sleep Evaluation Questionnaire (JSEQ)
Description	4-item subjective questionnaire measuring frequency and severity of sleep disturbance experienced over the past 30 days [39]. Assesses problems falling asleep, night waking, problems staying asleep and feeling tired upon waking after usual amount of sleep. The questionnaire relates to the number of nights experiencing problems
Name	Medical Outcomes Study Sleep questionnaire (MOS)
Description	12-item subjective questionnaire measuring the experience of sleep quality and quantity over the past 4 weeks [40]. 12 items cover 6 domains: 'Sleep disturbance' (4 items—length of time to fall asleep, sleep is restless/tense, trouble falling asleep, trouble getting back to sleep), 'Daytime somnolence' (3 items—drowsy/sleepy during the day, trouble staying awake, napping during the day), 'Sleep adequacy' (2 items—enough sleep to feel rested, get amount of sleep needed), 'Snoring' (1 item), 'Awakening short of breath or with headache' (1 item) and 'Quantity of sleep' (1 item). Each item is rated on a 6-point scale from 'none of the time' to 'all of the time', except for sleep quantity which is measured in hours *2 MOS Sleep Problem Indexes SPII and SPI-II can be derived from the MOS scale* SPII is a measure of 6 of the 12 items, and SPI-II is a measure of 9 of the 12 items
Name	The Nottingham Health Profile (NHP)
Description	2-Part questionnaire to measure the patient's subjective view of health [41] 5 questions in Part I relate to sleep
Name	Pittsburgh Sleep Quality Index (PSQI)
Description	19 questions measuring sleep disturbance over the past month [42]. The 7 areas covered are: 'Subjective sleep quality', 'Sleep latency', 'Seep duration', 'Habitual sleep efficiency', 'Sleep disturbances', 'Use of sleep medication' and 'Daytime dysfunction'
Name	Uppsala Sleep Inventory (USI)
Description	89- item questionnaire measuring sleep and sleep related problems [43]. Majority of questions are on a 5-point scale (range from 1 = 'no problems' to 5 = 'severe problems' or from 'never occurring' to 'very often'). Some questions are yes/no, and 1 question utilises qualitative data description

Table 2 Summary of study design and sleep data within 15 included studies

References	Country	Study design	Sample size (AS/nraxSpA)	Intervention	Comments/ findings	Sleep measure	Prevalence of sleep disturbance at baseline for AS/ nr-axSpA	Prevalence of sleep disturbance in reference group (significance)
Abdulaziez and Asaad [21]	Egypt	Case control, Cross-sectional	20	n/a	Sleep laboratory study Objective and subjective data collected	PSG + PSQI	Mean total PSQI = 8.2 ± 1.5 PSQI ≥ 5 = poor sleep 90% of AS sample reported as poor sleep quality	Mean total PSQI = 2.4 ± 0.95 (p < 0.001)
Altan et al. [22]	Turkey	RCT	54	Balneotherapy + exercise	Mixed findings for sleep improvement at 3 and 24 weeks	NHP (part 1)	Mean total NHP sleep score = 26.0	No healthy control
Aydin et al. [23]	Turkey	Case control, Cross-sectional	55	n/a		PSQI	Median total PSQI = 7 PSQI > 5 = poor sleep 58.1% reported as poor sleep quality	Median total PSQI = 5 (med) (p < 0.001)
Bao et al. [24]	China	RCT	203	Golimumab	Significant sleep improvement found from baseline to week 14 (p = 0.013) and to week 24 (p < 0.001) Ongoing improvement for those participating to 52 weeks	JSEQ	Mean JSEQ score (0–20) at baseline = 9.5	No healthy control
Batmaz et al. [25]	Turkey	Case control, Cross-sectional	80	n/a		PSQI	Mean total PSQI = 6.4 ± 3.7 PSQI > 5 = poor sleep 50% reported as poor sleep quality	Mean total PSQI = 4.6 ± 3 (p = 0.004)
Deodhar et al. [26]	Multi-national	RCT	356	Golimumab	Significant sleep improvement with treatment at week 14 (p < 0.001). Improvement sustained at week 24	JSEQ	Mean JSEQ score (0–20) at baseline = 10.6	No healthy control
Dougados et al. [27]	Multi-national	RCT	215	Etanercept	nr-axSpA No statistically significant sleep improvement found for MOS SPI sleep scores.	MOS	Mean SPI-II = 46.8	No healthy control Population norm cited as =25.8

					Singular difference at week 12 for 'sleep quantity' ($p < 0.05$)			
Hultgren et al. [28]	Sweden	Cohort study, Cross-sectional	70	n/a	7 participants classified as 'probable AS' Analysed gender differences in detail	USI	62% reporting too little sleep	No control but utilised community based reference group report 25%
Jiang et al. [29]	China	Cohort study, Cross-sectional	683	n/a	9.1% aged 12–17	PSQI	Mean total PSQI = 7 ± 4.14 PSQI > 7 = poor sleep 37.3% reported as poor sleep quality	No control group
Karadağ et al. [30]	Turkey	Case control, Cross-sectional	171	n/a	Unusual gender ratio (% male = 47.4) Individuals on anti-TNF medication had no significant difference in sleep parameters compared with healthy control subjects	MOS	Mean SPI-II = 39.7 ± 197	Mean SPI-II = 34 ± 20.2 ($p = 0.034$)
Karapolat et al. [31]	Turkey	Case control, Longitudinal	38	Group (I)-/homebased Exercise (II)	Significant sleep improvements found at 6 weeks ($p < 0.05$)	NHP (part 1)	Mean total NHP sleep score = 27.4	No healthy control
Li et al. [32]	China	Case control, Cross-sectional	314	n/a		PSQI	Mean total PSQI = 6.6 ± 3.6 PSQI > 7 = poor sleep 35.4% reported as poor sleep quality	Mean total PSQI = 5.5 ± 2.51 ($p = 0.02$)
Rudwaleit et al. [33]	Multi-national (Europe)	Cohort, Longitudinal	1135	Adalimumab	Significant sleep improvements found at 6, 12, 20 weeks ($p < 0.001$)	MOS + 'optimal sleep'	Mean SPI-II = 48.1 ± 19.0	No control group
Sieper et al. [34]	Multi-national	RCT	325	Certolizumab pegol	55% AS: 45% nraxSpA Significant sleep improvement found at week 4 ($p < 0.001$) and week 24 ($p < 0.001$)	MOS SPI-II	Mean SPI-II = 49.0	No healthy control
Solak et al. [35]	Turkey	Cohort, Cross-sectional	31	n/a	Sleep laboratory study Objective and subjective data collected	PSG, AHI, ESS	22.6% prevalence of OSAS reported	No control but reported 2–7% prevalence of OSAS in normal population

Within the 8 descriptive studies that explored associations between total sleep scores and patient data, 2 studies lacked data suitable for comparison [28, 35]. The remaining 6 studies reported correlating outcomes of the MOS Sleep Problem Index II (SPI-II) and total PSQI scales. Correlations reported within these studies as large (≥0.5), medium (≥0.3) and small (≥0.1) effect sizes, as rounded to 1 decimal place, are summarised as an illustration in Fig. 2 .

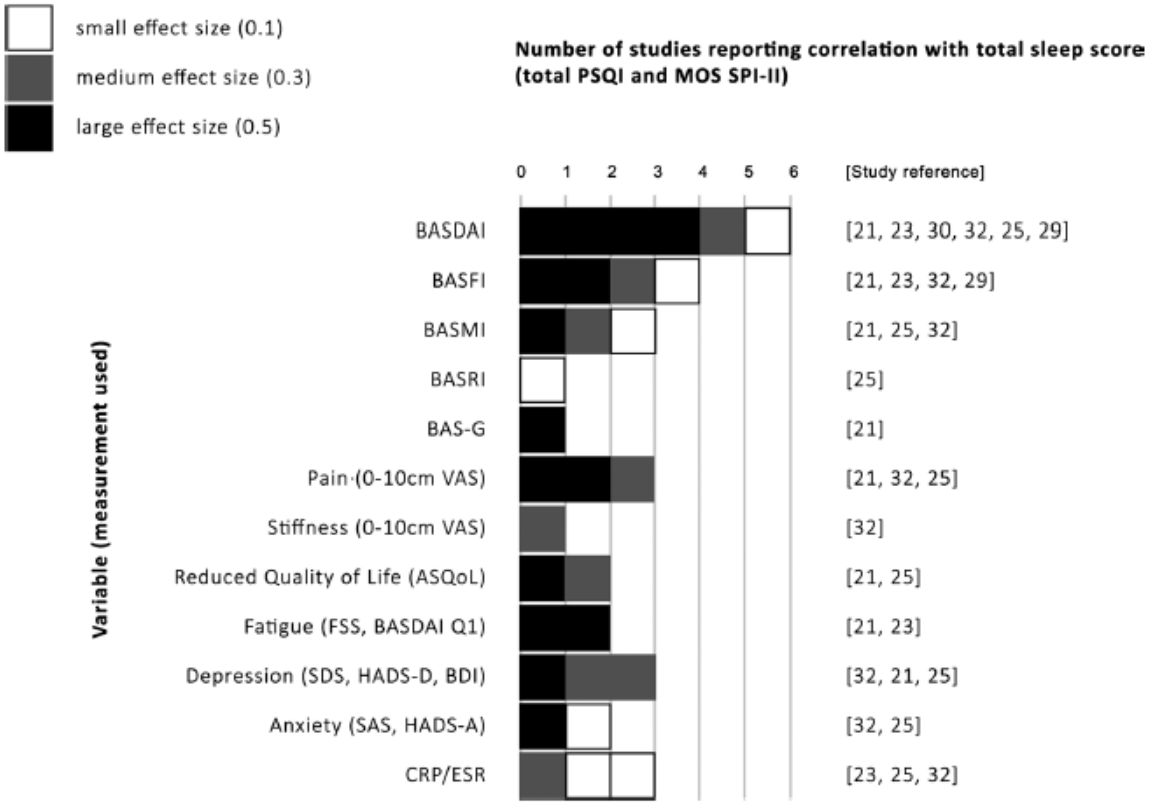

Fig. 2 An illustration describing the disease-specific, psychological and QoL correlates of sleep quality.

Sleep quality was reported in 6 descriptive studies, described by total sleep scores from the MOS SPI-II [30] and total PSQI [21, 23, 25, 29, 32]. Outcome measures include: BASDAI Bath Ankylosing Spondylitis Disease Activity Index, Q1 Question 1, BASFI Bath Ankylosing Spondylitis Functional Index, BASMI Bath Ankylosing Spondylitis Metrology Index, BASRI Bath Ankylosing Spondylitis Radiology Index, BASG Bath Ankylosing Spondylitis Patient Global Score, VAS Visual Analogue Scale, ASQoL The Ankylosing Spondylitis Quality of Life Scale, FSS Fatigue Severity Scale, BDI Beck's Depression Inventory, HADSD Hospital Anxiety

and Depression Scale for Depression, HADSA Hospital Anxiety and Depression Scale for Anxiety, SDS Zung Self-Rating Depression Scale, SAS Zung Self-Rating Anxiety Scale. CRP CReactive Protein, ESR Erythrocyte Sedimentation Rate.

Subset questions of the PSQI, MOS and the USI (for example, sleep latency, night awakenings, daytime dysfunction) were analysed in greater depth in 5 studies {23, 25, 28, 30, 32]. Inconsistency between the results, alongside variation in questions that define aspects of disturbed sleep, precludes reliable comparisons and conclusions. However, consistent trends may emerge with more comparable measurement. Suggested areas for exploration include a significantly greater amount of night awakening and disturbance during the night for patients with AS compared to control and reference groups in 4 of 5 studies [23, 28, 30, 32]. Poorer sleep efficiency, measured by the hours slept/hours spent in bed, or the number of hours slept/subjective estimate of need for sleep, was reported by AS groups in 4 of 5 studies [23, 25, 28, 32]. In addition, those studies reporting the use of sleep medication found that patients with AS do not appear to use sleep medications significantly more than healthy control subjects, despite prevalence of poor sleep [23, 25, 32]. Reasons for this are unclear.

Discussion

Prevalence of sleep disturbance

On the basis of 15 studies that describe total sleep scores utilising the PSQI, MOS SPI-II, JSEQ, USI and NHP (part 1), poor sleep is more prevalent for patients with AxSpA than within cited normal populations (Table 2). Five studies directly compared overall sleep scores in a healthy control group with those in an AS group [21, 23, 25, 30, 32]. All of these studies found significant differences between AS patients and the control subjects. It is likely that poor sleep is also more prevalent in patients with nraxSpA that for control subjects, however, only 2 studies focussed on this research group [27, 34]. In comparison between nraxSpA and AS patients, patients with nraxSpA reported greater sleep disturbance at baseline with greater improvement during treatment with certolizumab pegol [34].

Objective data and primary sleep disorders

Two laboratory-based studies utilised objective sleep measures (PSG) and support the existence of sleep disturbance within the AS population [21, 35]. Abdulaziez and Asaad [21] report that patients with AS have a higher % of light sleep (Stage I and II), a lower % of deep, slow wave sleep (SWS), and decreased sleep efficiency (total sleep time/time in bed) compared with healthy control subjects. The second PSG (cohort) study [35] reported similar mean values for % Stage II sleep (55.4 ± 11.7 compared with 55.1 ± 1.6) and % sleep efficiency (75.3 ± 16 compared with 75.1 ± 4.3) [35].

Abdulaziez and Asaad [21] also report that, compared to healthy control subjects, AS patients suffer from increased periodic leg movements (PLM). This was reflected by Hultgren et al. [28] who describe high reports of 'creeping sensation in legs' ($p = 0.0004$ for female AS patients) and 'muscular tension' ($p = 0.001$). A high incidence of restless leg syndrome (RLS) has previously been found in patients with AS [44] and associated with inflammatory and immune changes [45]. Therefore, reports of PLM and uncomfortable leg sensations may be an important aspect of poor sleep within AS.

The presence of obstructive sleep apnoea syndrome (OSAS) for patients was emphasised by Solak et al. [35] with 7 of 31 patients in their cohort meeting their required criteria for OSAS and a 40% prevalence of OSAS for patients over 35, compared with 6.3% prevalence for patients under 35. Despite a lack of significant findings for increased abnormal apnoea and hypopnoea by Abdulaziez and Asaad [21], the high prevalence of OSAS in patients over 35 may have important clinical implications. Considering the various possible causative associations between AS and OSAS such as impaired mobility, restricted thoracic capacity, physiological changes or underlying aetiology [46], more research is required to replicate these findings.

Factors associated with sleep disturbance—demographic variables: age, education and gender

AGE

Increasing age is correlated with a significant increase in subjective experience of disturbed sleep as measured by total PSQI [21, 32]. Age is also associated with poorer improvement on MOS SPI-II during intervention assessment [33]. However, this does not necessarily

relate to disease duration, which was only found to have a significant relationship with overall sleep scores in one of these studies [21]. In addition, it is important to consider that sleep naturally changes through life, for example, SWS decreases in older age [47].

EDUCATION

Poor sleep quality had an inverse relationship with the number of years in education [33], with years of education emerging as a significant contributor to sleep disturbance during hierarchical multiple regression ($p = 0.011$) [32]. A reflection of this may carry through to working life, with correlations of poor sleep with increased work time missed and work impairment [33].

GENDER

Relationships between total sleep scores and age, disease duration, education and gender were not explored in the majority of studies. However, Hultgren et al. [28] focussed on gender differences in explanation of disturbed sleep. In their study of 70 AS patients, 81% of female patients reported they were not getting enough sleep, compared to 50% of male patients. Female patients also suffered more with night time insomnia and were twice as likely to experience pain at bedtime, pain at night and fatigue.

Gender differences were either not found [23] or not reported [21, 25, 30, 32] in other descriptive studies within this review. In addition, some larger sample studies not included in this review do not support a marked gender difference in sleep disruption for AS populations [16, 17]. However, sleep disturbance has been reported as greater for females in a large study of 8676 patients with rheumatoid arthritis [13]. In a study of 47,700 households, prevalence for insomnia was higher in women and also linked with increased age, less education, chronic pain and various comorbidities, many of which are associated with inflammation such as osteoporosis, rheumatoid arthritis, depression, ankylosing spondylitis and stroke [48, 49].

A recent study of fatigue in SpA patients found marked associations with gender [50], and there is mounting evidence to suggest that the experience of rheumatologic disease varies between women and men [51], so it will be of great interest for future research to explore

whether demographic trends hinted at within this review can be replicated. They may not only point towards variation in subjective experience, but towards differences in underlying mechanical manifestation of the disease.

Medical variables: disease activity, function, pain, stiffness and fatigue

DISEASE ACTIVITY

When investigating trends in subjective measures, few conclusions can be drawn from single reported measures. Figure 2 describes the strong relationships found between increased BASDAI and poor sleep scores across 6 comparable studies. All 6 studies report this relationship as statistically significant at $p < 0.01$. PSG data support subjective correlations between BASDAI and disturbed sleep [21]. This mirrors findings for patients with rheumatoid arthritis, where prevalent sleep disturbance was significantly associated with disease activity [11].

Despite this striking association, only 2 of 4 papers that investigating correlations between total sleep scores and (CRP/ESR) inflammatory blood markers [23, 25, 30, 32] reported significant correlations [23, 32] and in only one study was the effect size classified as medium strength. This may be due to the questionable validity of ESR/CRP to accurately reflect disease activity within this population [52].

FATIGUE

Abdulaziez and Asaad [21] report highly significant correlations between fatigue and all PSG measures. This finding is reflected in a strong correlation ($p < 0.001$) between total sleep scores and fatigue (as measured with the first question of the BASDAI) in two further selected studies [23, 33]. Fatigue has been highlighted in external studies as a major symptom associated with AS, with high disease activity predicting high levels of fatigue [53]. Further studies also support the hypothesis that fatigue is negatively influenced by sleep disorders, associated with poor sleep quality and interrupted sleep for patients with spondyloarthritis (SpA) [54, 55]. It has also been proposed that sleep deprivation or chronic insomnia may cause shifts in cytokine secretion which then mediate inflammation and play a role in the experience of daytime fatigue [56, 57].

FUNCTIONAL ABILITY

This review shows a likely, important interrelationship between increased disturbed sleep and lower functional ability [21, 23, 29, 32]. All these studies utilised the PSQI scale which showed significant correlations at $p < 0.01$. Batmaz et al. [25] found no significant relationships between total sleep scores and BASFI but, alongside Abdulaziez and Asaad [21], they did discover a relationship between poor sleep and decreased mobility as measured by the BASMI [21, 25].

PAIN

Pain was measured by a separate VAS in three descriptive studies [21, 25, 32] and positively correlated with higher total PSQI in all 3. In two of these studies, pain also remained an important independent factor that significantly contributes to total sleep scores during multiple regression analysis [25, 32]. Pain also correlated with increased % Stage I sleep, increased movement at night and decreased % SWS [21]. It also has strong association with increased use of sleep medication [25, 32].

Patients' report shows pain as an important factor in disturbed sleep. In a sample of 43 AS patients who reported sleep disturbance, 36% stated that pain was the most important factor [28]. Pain at bedtime, during the pre-sleep period and during the night, was a major problem both for men and women in this study, associated with night awakenings and increased movement at night ($p < 0.0001$). Decreased night pain was also the most significant predictor of improvement in observed JSEQ scores in an intervention study by Deodhar et al. [26]. However, this relationship is not clear, for example, a highly significant improvement in night pain with balneotherapy and exercise was not always accompanied by significant improvement in sleep [22].

Wider research suggests a reciprocal relationship between the subjective experience of chronic pain and disturbed sleep [58] with some evidence suggesting that sleep deprivation can even reduce the analgesic effects of pharmacological treatment [59]. As pain is known to affect fatigue, psychological distress, QOL and ability to work [60], AxSpA patients would benefit from a greater understanding of the role that refreshing sleep may play in the management of pain [61].

Psychological variables: quality of life, depression and anxiety

Psychological factors such as mood have been shown to contribute to sleep disturbance in rheumatoid arthritis [13] and in a mixed SpA population [15]. This review also showed that psychological factors such as depression, anxiety and overall QoL are associated with poor sleep quality for patients with AxSpA [21, 25, 32]. QoL as measured by the ASQoL was utilised in two studies [21, 25], both of which found a significant relationship between disturbed sleep and reduced ASQoL score. However, it should be noted that the ASQoL contains a measure of sleep within it.

17% of 43 AS patients reported sociopsychological factors as the most important factor affecting disturbed sleep [28]. Physical and mental components were both significant predictors of improvement in JSEQ scores in a drug study investigating golimumab [26]. Depression was investigated in four separate studies [21, 25, 28, 32] using four different measures (including a single question 'do you have problems with feeling depressed?' [28]). Depression had a positive correlation with poor sleep quality in two of these studies ($p < 0.01$) [25, 32], and despite a nonsignificant result reported by Abdulaziez and Asaad [21] ($p = 0.173$) the effect size is still classified as medium (Fig. 2). A recent Korean study of 40 patients with AS supports a positive association between depression and poor sleep, finding that depression as assessed by the BDI, alongside duration of morning stiffness, remained as independent risk factors that affected poor sleep (total PSQI) [62]. Li et al. [32] also report a large and statistically significant association between anxiety and total PSQI sleep score. They suggest that psychological variables play an important role and may contribute as much as medical variables when assessing disturbed sleep.

Effectiveness of interventions

MEDICATION

Seven studies included in this review looked at effectiveness of interventions with sleep disturbance as an outcome measure. Five of them investigated anti-TNF therapy, specifically golimumab [24, 26], etanercept [27], adalimumab [33] and certolizumab pegol [34].

Four of the five studies found that anti-TNF medication was effective in reducing overall sleep scores, with improvement maintained throughout the trial period [24, 26, 33, 34]. In one study, the median JSEQ further improved to week 52 for those receiving treatment for the full year, indicating that individuals may see continued improvement into the long term [24]. Improvements in sleep score from baseline were associated with improved back pain, fatigue, QoL, disease activity and functional ability [26, 34]. One of the descriptive studies grouped individuals depending on current use of anti-TNF medication. They found that sleep scores for AS patients (MOS scores for sleep disturbance, somnolence, waking with a headache or shortness of breath and the Sleep Problem Index II) were significantly worse the group taking NSAID and/or DMARDs compared to control subjects. The patients taking anti-TNF medication did not differ from control subjects. In this study, the BASDAI and BASFI scores were also significantly worse for the NSAID/DMARD group. Therefore, the poor sleep scores may be a reflection of the poorer control of disease activity in this group.

In contradiction to this trend, one intervention study reports no statistically significant improvement in overall MOS Sleep scores with etanercept intervention [27]. Two descriptive studies [23, 25] also found no significant correlation between the type of medication used to control disease activity (NSAIDS, DMARDS and anti-TNF) and total PSQI, despite a large proportion of the patients (20.4% [23] and 53.8% [25]) of the patients taking anti-TNF medication. However, this review concludes that there is a likely association between use of anti-TNF medication and a reduction in disturbed sleep for patients. This is supported by growing research into the complex interplay of cytokines, sleep and immunity [63].

Few studies controlled for other medications which may impact sleep. Amitriptyline, a tricyclic antidepressant often used for pain relief, may result in improved sleep and a reduction in BASDAI [64]. Therefore, future studies investigating sleep in AxSpA must control medication use, particularly for current and recent use of anti-TNF medication [33], in order to strengthen the validity and reliability of findings.

EXERCISE

Few studies have looked at naturalistic or psychological interventions. The two included in this review investigate the effects of exercise and used Part 1 of the NHP to assess disturbed sleep in AS [22, 31].

Altan et al. [22] found mixed improvement in sleep scores between Group I (balneotherapy + exercise) and Group II (exercise only). For Group I, a significant improvement in sleep found at 3 weeks was not maintained at 24 weeks, with NHP sleep scores recorded at 18.30 ± 28.26 at week 0 and 18.60 ± 29.98 at week 24. Conversely with Group II, the improvement was not significant at 3 weeks, but highly significant 24 weeks ($p < 0.001$). Outcome measures such as night pain and disease activity had a more significant and more sustained improvement over 24 weeks with the intervention than improved sleep [22]. The second study [31] investigated homebased and group-based exercise and found significant improvement in sleep scores of the NHP in both groups with a statistically significant greater, between-group improvement for sleep scores in favour of group-based exercise.

Regular exercise is already emphasised as an important aspect of the long-term management of AS [1] and has been shown to have an analgesic effect [65] which may help AS patients cope with pain. Masiero et al. [66] found that exercise, in combination with an educational–behavioural program and anti-TNF therapy, had a greater effect on symptoms of disease activity in AS patients than either intervention used alone. Within the 2 studies of this review, regular exercise also saw benefits in BASDAI, BASFI, BASMI, morning stiffness, pain, energy and emotional reaction [22, 31]. Further research is required to clarify the possible mediating effects of exercise on improving poor sleep.

Increased recognition and a validated measure for poor sleep

Many studies call for raised awareness of disturbed sleep by clinicians [21, 23, 25, 29]. Screening for sleep problems during patient assessment will benefit those who consider sleep disturbance as a primary concern that impacts QoL [17, 28, 67] as well as identifying primary sleep disorders that may require treatment.

However, there is currently no validated sleep measure for this clinical population. A variety of sleep-relevant scales are used within papers investigating sleep (Table 1), but

inconsistencies in the choice of sleep scales and methods for determining 'poor sleep' across studies obscured conclusions that could have be drawn. A standard, efficient, easily administered questionnaire that clearly distinguishes fatigue and disturbed sleep would be a useful first step for future research. Incorporation of a question that utilises qualitative data may provide important insights. For example, a qualitative question on the USI used by Hultgren et al. [28] enabled the researchers to discover that 9% of the 43 patients who reported sleep disturbance were waking in the night for reasons unrelated to disease, such as being woken by children or snoring. In addition, a new questionnaire should report on normal sleeping habits. Many individuals have a natural sleep pattern, free from disease, that involves night time awakenings or initial insomnia. Finally, the option of the inclusion of objectively observed data from a bed partner or from wearable sleep-monitoring devices could provide valuable supplementary data which may be particularly useful when assessing the presence of apnoea and hypopnoea.

Limitations

The majority of studies investigating sleep disturbance as the primary focus are a cross-sectional design utilising questionnaires which reveal close correlations in subjective scoring for symptoms such as disease activity, pain, fatigue and sleep. Greater consideration of longitudinal design would provide some control for individual differences which may contribute to these strong correlations.

It is also noted that, during longitudinal intervention studies, improvement was greatest for individuals with more severe AS symptoms at baseline, for example, BASDAI [33] or sleep scores [34]. This is an important consideration for highly significant improvements in studies where participants are specifically recruited with a high BASDAI at baseline.

It also should be noted that a lack of significant findings in sleep disturbance between control subjects and AS subjects may not reflect an absence of that sleep disorder. Studies within this review found a measure of sleep disturbance within the general population [23, 28]. For example, 1 in 10 individuals from a large population reference group had consulted a doctor for sleep disturbance [28]. This may call into question whether the insignificant

finding of use of sleep medication is more reflective of a prevalence within the general population.

Conclusions

This review highlights disturbed sleep as a significant problem within this population that requires more extensive evaluation. Disturbed sleep is a multifactorial, prevalent and important aspect of disease that concerns patients with AxSpA. There are associations between poor sleep quality and disease activity, function, fatigue, pain and QoL. It is probable that demographic aspects (including gender, age and education) alongside psychological factors, such as depression, play a role in disturbed sleep. The direction of these relationships, or whether disturbed sleep is driven by common, underlying processes, is unclear. Research has shown both that activation of the immune system disturbs sleep [56, 68] and that abnormal sleep can disrupt immune system function [69, 70]. Future research may shed light on these complex relationships. There is some evidence from patients to suggest that sleep provides relief from disease flares [71]. Whether treatments that target sleep disturbance can affect disease activity, pain, function or severity of fatigue remains to be seen.

Interventions such as anti-TNF medication and regular exercise are associated with a reduction in sleep problems. However, there are very few studies investigating nonpharmacological interventions. Recognition of the physical, psychological and sociological influences associated with sleep can lead to the development of more holistic interventions that target the many facets of disturbed sleep through a combination of therapies. Full consideration of the use of current medication and exercise habits is important in order to allow more rigorous and practical conclusions to be drawn in future research.

Abnormal sleep may exacerbate chronic inflammatory conditions [72]. It has also been proposed that management of poor sleep could be a non-invasive method to evaluate subclinical inflammation and may even play a role in keeping disease in remission [13]. Whether sleep disruption could act as an early warning flag, due to association of underlying

inflammation, is a further interesting step for investigation. The presence of abnormal sleep for patients with Crohn's disease in remission at baseline has been linked with 2× increased risk of disease flare within the subsequent 6 months [14]. Two separate longitudinal studies found that individuals with sleep disorder [73] and patients with obstructive sleep apnoea [74] were at a higher risk for developing autoimmune diseases (including ankylosing spondylitis). It is therefore possible that regular screening for disturbed sleep could be useful in assessing disease activity and predicting future flares. Considering the close correlations between poor sleep and the signs and symptoms of active disease, a combination of pharmacological, psychological and naturalistic interventions targeted at disturbed sleep may break a cycle that aggravates inflammation, thus reducing disease impact and improving quality of life for those who suffer with AxSpA.

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Compliance with ethical standards

Conflict of interest Shaaron Leverment declares that she has no conflict of interest. Alison Wadeley declares that she has no conflict of interest. Emily Clarke declares that she has no conflict of interest. Dr. Raj Sengupta has received research grants from Abbvie and Pfizer, speaker honoraria from Abbvie, Pfizer, UCB, Novartis, Roche, MSD and is a member of BSR Biologics guideline group, Advisor to NICE Guideline TA383.

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

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