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Title: An investigation into the prevalence of sleep disturbances in primary Sjögren's syndrome: a systematic review of the literature

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Abstract

Objectives

To identify whether sleep disturbances are more prevalent in primary Sjögren's syndrome (PSS) patients compared with the general population and to recognise which specific sleep symptoms are particularly problematic in this population.

Methods

Electronic searches of the literature were conducted in PubMed; Medline (OVID); Embase (OVID); PsychINFO (OVID) and Web of Science and the search strategy registered a priori. Titles and abstracts were reviewed by two authors independently against a set of pre-specified inclusion/exclusion criteria, reference lists examined and a narrative synthesis of the included articles was conducted.

Results

Eight whole text papers containing nine separate studies met the inclusion criteria and were included in the narrative analysis. Few of these studies met all of the quality assessment criteria. The studies used a range of self-reported measures and objective measures including polysomnography. Mixed evidence was obtained for some of the individual sleep outcomes, but overall compared to controls PSS patients reported greater subjective sleep disturbances and daytime somnolence and demonstrated more night awakenings and pre-existing obstructive sleep apnea.

Conclusions

A range of sleep disturbances are commonly reported in PSS patients. Further polysomnography studies are recommended to confirm the increased prevalence of night awakenings and obstructive sleep apnea in this patient group. PSS patients with excessive

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daytime somnolence should be screened for comorbid sleep disorders and treated appropriately. Interventions targeted at sleep difficulties in PSS such as cognitive behavioural therapy for insomnia and nocturnal humidification devices have potential to improve quality of life this patient group and warrant further investigation.

Key words

Sjögren's syndrome, systematic review, sleep, quality of life, disability evaluation.

Introduction

Primary Sjögren's syndrome (PSS) is a systemic autoimmune disease characterised by sicca symptoms[1]. Extraglandular features are commonly seen in PSS patients including fatigue[2], orthostatic intolerance[3], pain[4], and depression[5]. These patients commonly experience impaired function[6] and poor health related quality of life[8]. Fatigue is seen in 75% of patients with PSS[7], is strongly correlated with poor quality of life [8-10] and is associated with functional impairment[6]. Due to the prevalence and impact of fatigue, there has been much research into factors associated with this symptom including potential genetic associations[11], and anti-inflammatory mechanisms[12]. Sleep disturbances have also been reported in the PSS literature[13] and are associated with fatigue [2]. In the general population, impaired sleep is associated with adverse health outcomes including weight gain, depression, pain, impaired immune function, impaired functional performance, increased risk of early mortality and cognitive symptoms including increased errors and increased risk of accidents[14]. Current recommendations are that adults should regularly have between seven and nine hours sleep, consistently per night[14].

Many sleep disturbances are potentially modifiable[15-18]. Therefore the successful identification and treatment of sleep problems may have a positive effect on symptoms such as pain, mood and fatigue, resulting in improvements in physical and cognitive functioning and quality of life.

A previous review of sleep disturbances in rheumatological diseases included PSS[19], but was published some time ago and the PSS section was predominantly based on one comparative study which used RA patients as controls. Therefore an up-to-date systematic

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review of the PSS sleep literature, which includes normative data on healthy controls, is required.

The aim of this review was to identify all the published literature on sleep difficulties in PSS in order to answer the following questions:

- Are sleep difficulties more prevalent in PSS patients than in the general population?
- Which sleep difficulties are more prevalent in PSS patients than in the general population?

Methods

A systematic review of the published literature on sleep and PSS was conducted. The protocol was published prospectively with PROSPERO (CRD42015024977)[20]. The methodological framework used was the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[21].

Eligibility criteria

Eligible studies were English language, primary research papers published in full. These included intervention, diagnostic, prognostic and aetiological studies with adult participants (>18 years) with a diagnosis of PSS. Case studies and review papers were excluded. Where papers report mixed populations, only studies which analysed the PSS population separately were included. Outcomes had to include sleep outcomes and other outcomes which have a relationship with sleep. In mixed population studies PSS data had to be reported separately for PSS patients. Data for PSS data had to be compared with a control population, which could be healthy controls or controls with other diseases. Therefore studies which did not

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compare data from a PSS group with a non-PSS control group were excluded from this review.

Search strategy

Databases (PubMed; Medline (OVID); Embase (OVID); PsychINFO (OVID) and Web of Science) were searched from inception to September 2015 using a pre-specified search string (Supplementary Table 1). The references of all included studies were also searched. Two reviewers (KH, ZG) independently examined the titles and abstracts of all records identified and full papers were retrieved for all papers which met inclusion criteria. All full text articles were screened by two review authors independently (KH, KD) for inclusion.

Data extraction and quality assessment

Data were extracted by one author (KH) onto a piloted form. These were checked by a second author (KD). Risk of bias was assessed at study level separately by two authors (KH and KD) using the Joanna Briggs Institute Prevalence Critical Appraisal Tool[22] and specific notes for questions within to tool were agreed between the authors (KH, KD) to reduce ambiguity prior to making a decision for each criteria (Supplementary Table 2).

Disagreements between reviewers were resolved through discussion.

Summary measures

Any sleep summary measure which compared a PSS cohort with a comparative group was extracted. These include difference in means and medians and odds ratios. Data were combined in a narrative synthesis due to the expected heterogeneity of the included studies.

Results

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Nine studies from eight publications were identified for inclusion in this narrative review[13, 23-29] (Figure 1). A summary of the included studies are in Table 1. Sixteen studies did not meet the inclusion criteria. Excluded studies with reasons for exclusion can be seen in Supplementary Table 3. One excluded study was a small uncontrolled study (n=9) of a nocturnal humidification device, which reduced nocturnal sicca symptoms in the participants[30]. Another excluded study included the use of an artificial saliva water spray, compared to placebo, to improve nocturnal oral dryness symptoms and improvements were demonstrated in both placebo and intervention groups[31]. This review did not set out to investigate interventions for PSS sleep disturbances, but these findings are considered in the context of potential future interventions in the discussion.

Ninety-three records were screened. Most studies were excluded at the title stage as they were not relevant to the review or did not fit the inclusion criteria (Figure 1). 14 publications were examined in more detail before exclusion (Supplementary Table 1) and nine studies from eight publications were included in this narrative review[13, 23-29] (Table 1).

Gudbjörnsson et al[23] included two studies in their paper and these are referred to as Gudbjörnsson et al Study 1 (a comparative study of sleep symptoms in three populations) and Study 2 (a polysomnography study) in this review for clarity.

----- Insert Figure 1 around here -----

----- Insert Table 1 around here -----

Assessment of bias

----- Insert Figure 2 around here -----

The risk of bias quality assessment findings of the included studies can be viewed in Figure 2. Three studies included only female PSS participants[13, 24, 29] and were consequently deemed as not being representative of the target population. Two studies (Gudbjörnsson et al Study 1 and Study 2)[23] used the Copenhagen Classification Criteria[32] to identify their subjects. These criteria were not validated or accepted universally[33], therefore these studies were also scored as not being representative of the target population. The remaining studies[13, 24-29] used either the European Community criteria[34] or the American European Consensus Group criteria[33].

Several studies did not fully specify how their participants were recruited (including Gudbjörnsson et al Study 1 and Study 2)[13, 23, 24, 28] and uncertainty remained for this item for these studies. The sample size was small (<40) for a number of studies (including

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Gudbjörnsson et al Study 2)[13, 23, 24, 27, 28] and these studies were scored as being at high risk of bias for this question.

Overall, three studies were deemed to be of high risk of bias (including Gudbjörnsson et al Study 2)[13, 23, 24], four at medium risk of bias (including Gudbjörnsson et al Study 1)[23, 27-29] and two at low risk of bias[25, 26].

Prevalence of specific sleep difficulties in PSS

The main sleep outcomes can be viewed in Table 2.

----- Insert Table 2 around here -----

Perceived sleep disturbance, (measured by sleep diary or patient reported sleep questionnaires) was reported in four studies (including Gudbjörnsson Study 1)[13, 23, 26, 28]. Odds ratios were calculated from the data provided by one study[26]. PSS patients scored significantly worse than healthy controls for this outcome. It was unclear whether overall there is a higher prevalence of sleep disturbance in PSS patients compared with other disease groups (osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)) as there were inconsistent findings between the studies.

Time spent in bed was assessed in two studies with conflicting findings. One study objectively assessed this outcome with polysomnography (Gudbjörnsson Study 2,[23]), and the other measured time in bed subjectively with a patient reported sleep questionnaire[25]. However the study which reported no difference for this outcome between PSS patients and healthy controls (Gudbjörnsson Study 2)[23] had very small numbers and took the measurements in a laboratory. The polysomnography study protocol and environment may

have influenced how long a participant remained in bed. Therefore it is not clear whether PSS patients do spend longer in bed compared with other populations.

We identified five separate studies that examined total sleep duration including Gudbjörnsson Studies 1 and 2[13, 23, 24, 27]. Three small studies[13, 24, 27] compared a total of 53 PSS patients with RA patients (n=25)[13] or healthy controls (total n=26)[24, 27]. They found no significant differences between the groups in terms of total sleep time. However Gudbjörnsson et al (Study 1)[23] compared 40 people with PSS with 42 people with RA and 60 healthy controls. They identified that people with PSS reported significantly less sleep than the comparators as measured by sleep diaries (between 40 min to 1hour 45 min less) and in their smaller polysomnography study (Study 2) they identified that PSS patients experienced between 1 hour 18 min to 2 hours less sleep than healthy controls.

Three studies examined the proportions of time spent in each of the stages of sleep between PSS patients and controls (including Gudbjörnsson et al Study 2[23, 24, 27]. Two found that PSS patients spent more time in Stage 1 sleep than controls (Gudbjörnsson et al Study 2)[23, 24]. However Usmani et al[27] found no such difference. None of the studies found between group differences for other stages of sleep.

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Sleep onset latency (time taken to fall asleep) was not significantly different between PSS patients, RA patients and healthy controls using self-reported methods in one study (Gudbjörnsson Study 1)[23], although the authors had not made a direct comparison between the PSS and control groups. However two studies (including Gudbjörnsson Study 2)[23, 27] involving objective testing of this outcome (polysomnography) studies did find sleep onset latency to be greater in PSS patients (mean of 20 to 22 minutes) compared with controls (mean of 13.8[27], range 1.5 to 13.6 minutes[23]).

Sleep efficiency (percentage of time spent in bed asleep) was identified as reduced in people with PSS in two studies (including Gudbjörnsson Study 2)[13, 23] both of which used objective measures. In a third study[24] with very low numbers, the sleep efficiency was very poor for both groups. However this could be due to the nasal mask that participants wore and the regular negative pressure pulses used to measure airway collapsibility, which may have interfered with their sleep. Therefore the environment was not ideal to examine sleep efficiency in this study.

All studies which examined the number of night awakenings found that these were increased in PSS patients (Gudbjörnsson Study 2 and Theander et al)[23, 25] (see Table 2). That said, the polysomnography studies that report an arousal index (number of times sleep is interrupted) found no difference between PSS patients and comparison groups[24, 27].

Factors associated with disturbed sleep

A number of studies examined specific reasons for waking in the night.

Theander et al[25] noted that 13% of their PSS group reported sicca symptoms which disturbed their sleep, compared with none of their controls.

Hilditch et al[24] found that nocturnal oral dryness did not differ significantly between PSS patients and controls which is surprising, but due to their very low numbers, could be a type II error. The same authors found that saliva surface tension showed no difference between the groups in the early morning, but was significantly higher in the PSS group in the late evening.

Nocturnal pain and disturbed sleep was more common in PSS compared with controls and RA patients (Gudbjörnsson Study 1 and Theander et al)[23, 25]. Gudbjörnsson and colleagues (Study 1)[23] reported that 54% of their PSS group experienced nocturnal pain compared with 37% of their RA group ($p < 0.01$) and 0% of their healthy control group ($p < 0.0001$). Theander et al[25] found that nocturnal pain which disturbed sleep was present in 19% of their PSS group, which was greater than the 9% of those in the control group - although this difference was not significant ($p = 0.07$).

There was conflicting evidence from two studies for nocturia disturbing sleep in PSS patients. Walker et al[29] investigated in nocturia and found no difference between PSS patients and an OA population for the occurrence of this symptom (OR 0.93, $p = 0.85$).

Conversely, Theander et al[25] found that 53% of their PSS participants experienced nocturia which disturbed sleep was present in 53% of their PSS participants, in comparison to 26% of their healthy controls ($p = 0.001$).

Autonomic Symptoms

Nocturnal autonomic symptoms were only investigated by Gudbjörnsson et al (Study 1)[23], which found 20% of the PSS participants in this study reported experiencing nocturnal sweating, which was greater than their RA comparison group (12%, NS) and their healthy

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controls (2%, $p < 0.01$). Palpitations at night were reported in 5% of their PSS group and these were not present in either their RA or healthy control groups.

Presence of co-morbid sleep disorders

In Theander et al's study[25], 2 of their 72 PSS cohort self-reported a diagnosis of narcolepsy compared with none of their controls, but this was not reported as an outcome in any of the other included studies.

Using polysomnography, one study noted the occurrence of obstructive apneas and hypopneas were double in their PSS group compared with healthy controls[27]. In this study, continuous positive airway pressure (CPAP) treatment was offered to eight out of twenty eight PSS study participants who were identified as having severe sleep apnea (with an apnea-hypnea index score ≥ 40). Five participants accepted the treatment and significant improvements were demonstrated both in their Epworth Sleepiness Scale (ESS) scores and fatigue scores at 2-6 months after commencing CPAP treatment.

However another study[24] investigated the upper airway collapsibility and found no difference in both the upper airway collapsibility index and a range of respiratory variables between their PSS and control groups but this could be due to the study being underpowered.

Daytime somnolence

Four studies identified increased daytime sleepiness in patients with PSS compared to healthy controls. Gudbjörnson et al (Study 1)[23] found their PSS patients were sleepy in the daytime five-times more frequently than RA controls and almost three-times more frequently than healthy controls. Theander et al (2010), Usmani et al (2012) and Walker et

al (2003) reported that Epworth Sleepiness Scale scores were significantly higher in PSS patients than in controls[25, 27, 29].

Discussion

Findings of the review

We have found that subjective and objective sleep disturbances are more common in PSS patients. Further research is needed to examine the differences between PSS patients and other disease groups.

There were inconclusive findings regarding whether PSS patients spend more time in bed than comparative groups, however, if they do spend longer in bed it is likely that this is due to the sleep disturbances and night awakenings they experience. Further studies are needed to confirm whether PSS patients have a short sleep duration compared with other groups, due to the conflicting findings in this review. However PSS patients do seem to experience more frequent nocturnal awakenings than other groups. Despite this finding, the arousal index scores were not found to be greater for PSS patients in the studies that examined this outcome. One reason could be due to low numbers of participants in these studies.

However an alternative suggestion is that the PSS patients awaken more frequently during these arousals, due to their symptoms such as dryness, pain and autonomic symptoms. A further possibility is that PSS patients may demonstrate high frequency EEG throughout the night which may influence their perception of sleep and wakefulness. Further investigations would be required to test this.

Sicca symptoms did disturb sleep in one study[25] and potential interventions to reduce these symptoms, and thus improve sleep will be discussed shortly. Pain is another symptom which is more common in PSS patients during the night. Segal and colleagues have observed

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that sleep quality reduced as pain increases[4]. If pain is reduced, sleep quality might therefore improve.

There were conflicting findings regarding the symptom of nocturia in PSS patients. However, PSS patients regularly drink to ease the symptoms of their dryness. Needing the toilet during the night could be a natural consequence of this.

Although autonomic symptoms were only reported in one included study, there is a greater prevalence of these symptoms in PSS patients[3] and it is logical that these symptoms, which can include palpitations, dizziness and sweats, may interfere with sleep.

There does seem to be an increased prevalence of obstructive sleep apnea in PSS patients, although further studies are needed to reproduce this finding. The Epworth Sleepiness Scale can be used as a screening to identify patients who are at risk of obstructive sleep apnea[35] and these patients should be referred for further investigations.

This review has demonstrated that daytime sleepiness is a problem in PSS patients. Daytime sleepiness correlates with reduced quality of life[10], fatigue[25, 29], autonomic dysfunction[3] and functional impairment[6]. Furthermore, patients with who are functionally impaired have significantly greater Epworth Sleepiness Scale scores than those who experience no functional disability[6].

Potential interventions for sleep disturbances in PSS

Interventions which address the perception of poor sleep without the necessity for objective verification, include addressing unhelpful beliefs surrounding sleep, addressing sleep efficiency and prescribing time in bed. These are all components of a Cognitive Behavioural Therapy for Insomnia (CBT-I) intervention[36]. CBT-I is considered as a first line

treatment for insomnia associated with a medical condition[37] and is an effective intervention in other long term conditions[38], therefore could be beneficial in PSS. Time in bed and sleep efficiency are both addressed in the sleep restriction component of a CBT-I intervention and this may be a useful way of addressing longer spells spent in bed awake in this patient group, and lead to improved sleep. Further studies of CBT-I and various modes of delivering this intervention are therefore warranted in this patient group.

Nocturnal humidification and artificial saliva sprays may ease nocturnal sicca symptoms and decrease sleep disturbances in PSS patients and are unlikely to contribute towards bladder disturbances during the night. Although a humidification device did seem to be a promising intervention in an excluded study[30], further appropriately powered studies comparing nocturnal humidification devices in PSS with controls are required to demonstrate efficacy.

For autonomic symptoms which interfere with sleep, appropriate interventions addressing these symptoms, such as water bolus treatment during the day[39] may also help to improve sleep, particularly if these symptoms are regularly experienced during the night.

Further research is required to demonstrate the efficacy of interventions for dysautonomia such as blood pressure dysregulation in PSS on sleep outcomes.

Further considerations

A more detailed sleep assessment, including polysomnography, may be beneficial for this group when considering the level of sleep apnea reported in this population. Moreover, polysomnography will afford a closer examination of other objectively verifiable sleep disorders which may influence sleep (e.g. narcolepsy, periodic limb movement disorder,

restless legs syndrome and hypersomnolence disorders). If severe sleep apnea is identified in PSS patients, CPAP treatment should be offered[40].

Pain is another symptom which can interrupt sleep. PSS patients who experience pain which is interfering with their sleep should be offered appropriate pain management interventions[4]. CBT-I is efficacious at improving sleep duration, continuity and perceived quality in chronic pain patients with co-morbid insomnia and CBT-I with an additional pain component is feasible[38]. A pain adjunct to a CBT-I intervention may therefore improve sleep in PSS patients with chronic pain. Interventions targeting sleep disturbances in PSS may improve daytime sleepiness and fatigue which could result with increased functional capacity and quality of life.

There are some limitations to this review. Firstly, although we did not specifically investigate potential causes of sleep disturbances, we have uncovered several potential contributing factors from within the included studies. However there may be further potential complications in PSS which might play a role in sleep disturbance, such as gastroesophageal reflux[41]. Further work needs to be done to determine the causes of sleep disturbances in this patient group. Secondly, although we did not set out to investigate specific interventions for sleep disturbances, we have identified some uncontrolled studies of interventions for sleep in PSS. There may therefore be further studies of interventions for sleep disturbances in PSS uncovered by our search. However a recent systematic review of all non-pharmacological interventions for PSS did not identify any randomized controlled trials for sleep difficulties in this patient group[42]. Furthermore recent meta-analysis of twenty three studies determined that CBT-I was efficacious at

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reducing sleep disturbances and improving sleep quality in patients with insomnia secondary to a comorbid condition[43].

This review included a total of 350 PSS patients in nine separate studies. Only two studies (with 142 PSS patients) were deemed to be at low risk of bias. This highlights the paucity of high quality existing research into sleep disturbances in PSS patients.

Conclusion

From the included studies in this review, we found an increased prevalence of sleep disturbances in PSS patients compared with controls, including; daytime somnolence; subjective sleep disturbances including disturbance due to dryness symptoms, and increased occurrence of night awakenings. Sleep apnea may be more common, but further polysomnography studies are required to confirm this.

Although we did not set out to investigate interventions, logic dictates that CBT-I for sleep disturbances and night awakenings and nocturnal humidifiers for nocturnal sicca symptoms would be beneficial in this patient group. However further studies are required to confirm their effectiveness in PSS. Due to the variable quality of the included studies, the mix of outcomes assessed within these studies and the overall low numbers of patients included within them, we recommend further studies to add to the body of PSS sleep prevalence literature. Finally, in the presence of sleep difficulties in PSS patients, primary sleep disorders should be screened for and treated appropriately.

Key Messages

- This is the first published review of sleep disturbances of primary SS.
- Sleep disturbances are common in primary SS patients and should be identified and treated appropriately.
- Future investigations of sleep interventions for primary SS are warranted.

Conflict of interest

The authors declare no conflict of interest.

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References

- 1 Fox RI. Sjogren's syndrome. *Lancet* (London, England) 2005;366(9482):321-31.
- 2 Karageorgas T, Fragioudaki S, Nezos A, Karaiskos D, Moutsopoulos HM, Mavragani CP. Fatigue in primary Sjogren's syndrome: Clinical, laboratory, psychometric and biological associations. *Arthritis Care Res* (Hoboken) 2015.
- 3 Newton JL, Frith J, Powell D, et al. Autonomic symptoms are common and are associated with overall symptom burden and disease activity in primary Sjogren's syndrome. *Ann Rheum Dis* 2012;71(12):1973-9.
- 4 Segal BM, Pogatchnik B, Henn L, Rudser K, Sivils KM. Pain Severity and Neuropathic Pain Symptoms in Primary Sjogren's Syndrome: A Comparison Study of Seropositive and Seronegative Sjogren's Syndrome Patients. *Arthritis Care & Research* 2013;65(8):1291-8.
- 5 Westhoff G, Dorner T, Zink A. Fatigue and depression predict physician visits and work disability in women with primary Sjogren's syndrome: results from a cohort study. *Rheumatology* (Oxford) 2012;51(2):262-9.
- 6 Hackett KL, Newton JL, Frith J, et al. Impaired functional status in primary Sjogren's syndrome. *Arthritis Care and Research* 2012;64(11):1760-4.
- 7 Hartkamp A, Geenen R, Bijl M, Kruize AA, Godaert GL, Derksen RH. Serum cytokine levels related to multiple dimensions of fatigue in patients with primary Sjogren's syndrome. *Ann Rheum Dis* 2004;63(10):1335-7.
- 8 Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjogren's syndrome. *Rheumatology* (Oxford) 2009;48(9):1077-82.
- 9 Cornec D, Devauchelle-Pensec V, Mariette X, et al. Severe Health-Related Quality-of-life Impairment in Active Primary Sjogren's Syndrome Is Driven by Patient-Reported Outcomes: Data from a Large Therapeutic Trial. *Arthritis Care Res* (Hoboken) 2016.

Systematic review of sleep disturbances in primary Sjögren's syndrome

- 10 Lendrem D, Mitchell S, McMeekin P, et al. Health-related utility values of patients with primary Sjogren's syndrome and its predictors. *Ann Rheum Dis* 2014;73(7):1362-8.
- 11 Norheim KB, Le Hellard S, Nordmark G, et al. A possible genetic association with chronic fatigue in primary Sjogren's syndrome: a candidate gene study. *Rheumatol Int* 2014;34(2):191-7.
- 12 Howard Tripp N, Tarn J, Natasari A, et al. Fatigue in primary Sjogren's syndrome is associated with lower levels of proinflammatory cytokines. *RMD open* 2016;2(2):e000282.
- 13 Goodchild CE, Treharne GJ, Booth DA, Bowman SJ. Daytime patterning of fatigue and its associations with the previous night's discomfort and poor sleep among women with primary Sjogren's syndrome or rheumatoid arthritis. *Musculoskelet* 2010;8(2):107-17.
- 14 Watson NF, Badr MS, Belenky G, et al. Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 2015;38(6):843-4.
- 15 Anderson K, Jones DE, Wilton K, Newton JL. Restless leg syndrome is a treatable cause of sleep disturbance and fatigue in primary biliary cirrhosis. *Liver international : official journal of the International Association for the Study of the Liver* 2013;33(2):239-43.
- 16 Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *The Cochrane database of systematic reviews* 2006(3):CD001106.
- 17 Montgomery P, Dennis J. Physical exercise for sleep problems in adults aged 60+. *The Cochrane database of systematic reviews* 2002(4):CD003404.
- 18 Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. *The Cochrane database of systematic reviews* 2003(1):CD003161.
- 19 Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. *Sleep Med Rev* 2008;12(3):211-28.

Systematic review of sleep disturbances in primary Sjögren's syndrome

- 20 Hackett K, Deane K, Gotts Z, et al. The incidence of sleep impairments in primary Sjogren's syndrome: a systematic review of the literature. In. *PROSPERO: International prospective register of systematic reviews*; 2015.
- 21 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine* 2009;151(4):264-9, W64.
- 22 Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *International journal of health policy and management* 2014;3(3):123-8.
- 23 Gudbjornsson B, Broman JE, Hetta J, Hallgren R. Sleep disturbances in patients with primary Sjogren's syndrome. *Br J Rheumatol* 1993;32(12):1072-6.
- 24 Hilditch CJ, McEvoy RD, George KE, et al. Upper airway surface tension but not upper airway collapsibility is elevated in primary Sjogren's syndrome. *Sleep* 2008;31(3):367-74.
- 25 Theander L, Strombeck B, Mandl T, Theander E. Sleepiness or fatigue? Can we detect treatable causes of tiredness in primary Sjogren's syndrome? *Rheumatology* 2010;49(6):1177-83.
- 26 Tishler M, Barak Y, Paran D, Yaron M. Sleep disturbances, fibromyalgia and primary Sjogren's syndrome. *Clinical and Experimental Rheumatology* 1997;15(1):71-4.
- 27 Usmani ZA, Hlavac M, Rischmueller M, et al. Sleep disordered breathing in patients with primary Sjogren's syndrome: a group controlled study. *Sleep Medicine* 2012;13(8):1066-70.
- 28 van Oers ML, Bossema ER, Thoolen BJ, et al. Variability of fatigue during the day in patients with primary Sjogren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis. *Clinical and Experimental Rheumatology* 2010;28(5):715-21.
- 29 Walker J, Gordon T, Lester S, et al. Increased severity of lower urinary tract symptoms and daytime somnolence in primary Sjogren's syndrome. *Journal of Rheumatology* 2003;30(11):2406-12.
- 30 Hay KD, Morton RP. Optimal nocturnal humidification for xerostomia. *Head and Neck- Journal for the Sciences and Specialties of the Head and Neck* 2006;28(9):792-6.

Systematic review of sleep disturbances in primary Sjögren's syndrome

- 31 Kaarela K, Mutru O. Xerostomia in Sjogren's syndrome treated with Sali-Synt. A double-blind cross-over trial. *Scandinavian journal of rheumatology* 1982;11(1):39-40.
- 32 Manthorpe R, Oxholm P, Prause JU, Schiødt M. The Copenhagen criteria for Sjogren's syndrome. *Scand J Rheumatol Suppl* 1986;61:19-21.
- 33 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61(6):554-8.
- 34 Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjogren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993;36(3):340-7.
- 35 Rosenthal LD, Dolan DC. The Epworth sleepiness scale in the identification of obstructive sleep apnea. *The Journal of nervous and mental disease* 2008;196(5):429-31.
- 36 Arnedt JT, Cuddihy L, Swanson LM, Pickett S, Aikens J, Chervin RD. Randomized controlled trial of telephone-delivered cognitive behavioral therapy for chronic insomnia. *Sleep* 2013;36(3):353-62.
- 37 Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clinical psychology review* 2005;25(5):559-92.
- 38 Finan PH, Buenaver LF, Coryell VT, Smith MT. Cognitive-Behavioral Therapy for Comorbid Insomnia and Chronic Pain. *Sleep medicine clinics* 2014;9(2):261-74.
- 39 Low PA, Tomalia VA. Orthostatic Hypotension: Mechanisms, Causes, Management. *Journal of clinical neurology* 2015;11(3):220-6.
- 40 NICE. *Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome*: National Institute for Health and Care Excellence; 2008.
- 41 Tufik SB, Bennedsen L, Andersen ML, Tufik S. The interaction of Sjogren's syndrome, gastroesophageal reflux and sleep. *Sleep Medicine* 2013;14(2):222.

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- 42 Hackett KL, Deane KH, Strassheim V, et al. A systematic review of non-pharmacological interventions for primary Sjogren's syndrome. *Rheumatology (Oxford)* 2015;54(11):2025-32.
- 43 Geiger-Brown JM, Rogers VE, Liu W, Ludeman EM, Downton KD, Diaz-Abad M. Cognitive behavioral therapy in persons with comorbid insomnia: A meta-analysis. *Sleep medicine reviews* 2015;23:54-67.
- 44 Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31(3):315-24.
- 45 Hetta J, Almqvist M, ÅĒgren H, Hambert G, Liljenberg GB, Roos BE. Prevalence of sleep disturbances and related symptoms in a middle-aged Swedish population. In: Koella W, Ruther E, Schultz H, eds. *Sleep '84*; 1985:373-6.
- 46 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14(6):540-5.
- 47 Ekbohm K, Leissner L, Olsson JE, Widner H. [Restless legs--common but often missed disease. Successful treatment possibilities are now available]. *Lakartidningen* 2006;103(4):207-11.
- 48 Meijman TF, Thunnissen MJ, Devriesgriever AGH. The after-Effects of a Prolonged Period of Day-Sleep on Subjective Sleep Quality. *Work Stress* 1990;4(1):65-70.
- 49 Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Seminars in hematology* 1997;34(3 Suppl 2):13-9.
- 50 Barry MJ, Fowler FJ, Jr., O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *The Journal of urology* 1992;148(5):1549-57; discussion 64.

Tables

Table 1. Summary of included studies

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Author, year and country	Study design	Participants	Sleep Outcomes
Goodchild 2010 UK [13]	Observational prospective study	PSS: n=14, AECG diagnostic criteria for PSS[29], 100% female, mean age=58, mean disease duration (MDD)=13 RA: n=25, 100% female, mean age=62, MDD=9 years	Sleep diary Actigraphy
Gudbjörnsson 1993 Sweden [23]	Study 1 Cross sectional sleep questionnaire Study 2 Observational study. Polysomnography for 2 consecutive nights.	Study 1: PSS: n=40, Copenhagen diagnostic criteria for PSS [32], 95% female, mean age-53. 10 PSS patients also had PSG RA: n=42, ARA criteria for classical RA [44], 100% female, 10 had symptoms of secondary Sjögren's syndrome HC: n=60, 100% female, Age matched with the PSS participants Study 2: PSS: n=10, no demographic information provided. HC: n=30, Middle aged	Study 1: Uppsala Sleep Inventory [45] Study 2: Polysomnography

Author, year and country	Study design	Participants	Sleep Outcomes
Hilditch 2008 Australia [24]	Observational study over a nights sleep	PSS: n=11, AECG diagnostic criteria for PSS, 100% female, mean age=61, MDD not reported HC: n=8, All female, mean age=55.9, Age matched with patient group	Electroencephalogram, electrooculogram, submental electromyogram. Respiratory (inspiratory flow, end-tidal CO ₂ and mask leak). Breathing effort. Upper airway collapsibility. Oral wetness and saliva surface tension
Theander 2010 Sweden [25]	Cross sectional survey	PSS: n=77, AECG criteria for PSS, 90% female, median age=61, MDD=12 HC: n=59, 90% female, Median age=55	Epworth Sleepiness Scale [46], Restless Legs Syndrome questionnaire [47], Lund University Sleep Questionnaire [25], Profile of Fatigue, fatigue VAS
Tishler 1997 Israel [26]	Cross sectional survey.	PSS: n=65, AECG classification criteria for PSS, 92% female, Mean age =57.3, MDD=8.3	Mini Sleep Questionnaire [26]

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Author, year and country	Study design	Participants	Sleep Outcomes
		<p>RA (Group A): n=67, 83% female, MDD=12.6 years</p> <p>RA with sicca symptoms (Group B): n=63, 70% female, MDD=15.1 years</p> <p>OA: n=31, 94% female, MDD=10.3 years</p>	
<p>Usmani 2012 Australia [27]</p>	<p>Observational study</p>	<p>PSS: n=28, 100% female, AECG classification criteria for PSS, mean age=58.7, MDD not stated</p> <p>HC: n=18, 100% female, mean age=55.8</p>	<p>Epworth Sleepiness Scale</p> <p>Polysomnography</p> <p>Apnea-Hypopnea Index [27]</p>
<p>van Oers 2010 Netherlands [28]</p>	<p>Repeated measures study to compare variability of fatigue during the day</p>	<p>PSS: n=29, 100% Female, AECG criteria for PSS, mean age 53.3, MDD not stated</p> <p>SLE: n=23, 100% Female</p> <p>RA: n=19, 100% Female</p> <p>HC: N=52, 100% Female, Mean age 51</p>	<p>15 Item Dutch questionnaire on sleep quality [48]</p>

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Author, year and country	Study design	Participants	Sleep Outcomes
Walker 2003 Australia [29]	A study comparing differences in urinary symptoms and daytime sleepiness	PSS: n=76, European Community criteria for PSS, 100% female, median age=58, MDD not stated OA: n=43, 100% female, median age=64	Epworth Sleepiness Scale, FACIT-F [49], American Urological Symptom Index [50]

Notes: AECG, American-European Consensus Group Criteria; ARA, American Rheumatism Association; HC, healthy controls; MDD, mean disease duration; OSA, Obstructive sleep apnea; RA, Rheumatoid arthritis; SLE, systemic lupus erythematosus; OA, Osteoarthritis; PSS, primary Sjögren’s syndrome; VAS, Visual analogue scale,

Table 2. Differences in specific sleep outcomes between PSS patients and controls

	Study	Results	PSS
Perceived sleep disturbance	Goodchild 2010 [13]	PSS vs RA not significantly different for quality of sleep or feeling of refreshment	ND
	Gudbjörnsson 1993 Study 1 [23]	44% PSS not feeling rested after sleep vs 9.8% RA (p<0.001) and 15.3% HC (p<0.01)	+
	Tishler 1997 [26]	Moderate/severe sleep disturbance 75% PSS. Significantly greater than OA and RA (p<0.01)	+
	van Oers 2010 [28]	Significant differences sleep disturbance (p<0.001) between all groups (SLE, RA, HC, PSS). PSS highest median (6/15), HC lowest (2.3/15).	+
	Gudbjörnsson 1993 Study 2 [23]	PSS mean time in bed (500 min, range 444-532) similar to HC, range 419-514	ND
Time spent in bed	Theander 2010 [25]	PSS 45 min more in bed vs HC (8.24 vs. 7.72 hours; p=0.048)	+
	Goodchild 2010 [13]	PSS mean 7h asleep, similar to RA	ND

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	Gudbjörnsson 1993	PSS mean of 5.2h asleep (SD=1.90), significantly less than RA (6.8h SD=1.30) P<0.05) & HC	+
	Study 1 [23]	(7.2h SD=0.77, P<0.0001)	
	Gudbjörnsson 1993	PSS mean 358 min asleep (range 183-473) less than HC range (396-466 min)	+
	Study 2 [23]		
	Hilditch 2008 [24]	No difference total sleep time PSS vs HC	ND
	Usmani 2012 [27]	No difference total sleep time PSS vs HC	ND
Sleep onset	Gudbjörnsson 1993	Mean time to fall asleep greatest in PSS (30 min SD=52.49) vs RA (21 min SD=19.44) and HC	ND
latency	Study 1 [23]	(19 min SD=6.97) difference not significant.	
	Gudbjörnsson 1993	PSS mean 20 min to fall asleep (range 3-65), greater than HC range (1.5 to 13.6 min)	+
	Study 2 [23]		
	Usmani 2012 [27]	PSS mean 22.8 min to fall asleep (range 14-40) vs 13.8 for HC (range 6-22) (p=0.035)	+
Sleep efficiency	Goodchild 2010	PSS 84% sleep efficiency significantly less than RA 89.4% (p<0.05)	+
	[13]		
	Gudbjörnsson 1993	PSS 70% mean sleep efficiency, well below control range (94%-100%)	+
	Study 2 [23]		

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	Hilditch 2008 [24]	No difference PSS group vs HC (combined mean 44% sleep efficiency)	ND
Number of night awakenings	Gudbjörnsson 1993 Study 1 [23]	PSS woke mean 2.6 times, significantly more than RA (1.5) ($p < 0.0001$) and HC(1.0) ($p < 0.05$)	+
	Gudbjörnsson 1993 Study 2 [23]	PSS woke mean 19 times (polysomnography) vs HC (range 1-7)	+
	Theander 2010 [25]	PSS awakenings (mean 2.7 SD=0.17) higher than HC(mean 1.7 SD=0.18, $p = 0.001$)	+
Arousal index	Hilditch 2008 [24]	Trend of higher mean nocturnal arousals in PSS vs HC ($p < 0.06$)	ND
	Usmani 2012 [27]	No difference PSS vs HC ($p = 0.18$)	ND
Ventilatory measurements & sleep apnea	Hilditch 2008 [24]	No difference PSS vs HC for upper airway collapsibility index and respiratory variables	ND
	Usmani 2012 [27]	Twice frequency of apneas and hypoapneas in PSS vs HC ($p = 0.032$) Sleep apnea 64% PSS vs 28% controls ($p = 0.03$)	+
Daytime somnolence	Gudbjörnsson 1993 Study 1 [23]	PSS significantly more daytime sleepiness vs HC ($p < 0.001$) or RA ($p < 0.0001$). PSS significantly more daytime naps PSS 15.2% vs HC 0% ($p < 0.01$) but not RA 21.4%	+

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Theander 2010 [25]	PSS significantly worse daytime sleepiness (ESS; mean 9.5, SD=5.2) vs HC (mean 7, SD=4.0) (p=0.003) and significantly more excessive sleepiness (15.3%) vs HC (11.9%) (p=0.016)	+
Usmani 2012 [27]	PSS significantly worse for daytime sleepiness (ESS; mean 10.1, SD=5.82) vs HC (mean 6.5, SD=3.39) p=0.014	+
Walker 2003 [29]	PSS daytime sleepiness significantly worse vs OA (OR 2.50, p=0.01)	+

Notes: + Favours controls; ESS Epworth Sleepiness Scale; h hours; HC healthy controls; min minutes; ND No difference; OA osteoarthritis; PSS primary Sjogren's syndrome; RA rheumatoid arthritis, SLE systemic lupus erythematosus. P values are reported when provided in the published studies.