



SYSTEMATIC REVIEW

REVISED **A scoping review of the evidence for the impact of pharmacological and non-pharmacological interventions on shift work related sleep disturbance in an occupational setting [version 2; peer review: 2 approved, 1 approved with reservations]**

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Abstract




Background: Shift work is essential in society but can be detrimental to health and quality of life and is associated with decreased productivity and increased risk of accidents. Interventions to reduce these consequences are needed, but the extent and range of trial evidence for interventions for those most affected by their shift-work schedules is unclear. We therefore carried out a scoping review to assess the availability of evidence to inform the development and evaluation of future interventions.



Methods: We aimed to identify clinical trials of any intervention for shift work-related sleep disturbance that included a comparator group, where the intervention was delivered in an occupational setting. We searched Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, EMBASE, Medline and Science Citation Index from inception to 30th March 2020 for relevant citations. Citations were screened by two independent reviewers, a third reviewer resolved disagreements. Data were extracted by two independent reviewers.

Results: From 1250 unique citations, 14 studies met inclusion criteria for comparative trials of treatment in an occupational setting. There were five trials of hypnotics, five trials of stimulants, and four trials of non-pharmacological therapies (cognitive behavioural therapy, light

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therapy, aromatherapy and herbal medicine). Outcomes included sleep parameters, day-time sleepiness, and quality of life. There were no consistently reported outcomes across trials.

Conclusions: Interventions fell into three distinct groups investigated in distinct time periods without progression from efficacy trials to wider-scale interventions. The lack of consistent patient-reported outcome measures limits synthesising findings. Some trials focussed on optimising sleep, others on reducing wake-time sleepiness. Adequately powered trials of existing interventions are needed, with the development and testing of novel combination treatments in patients with well-defined shift work sleep disorder. A core set of clinically relevant outcomes will develop and standardise the evidence-base for shift work sleep disorder.

Keywords

Shift work disorder, shift work related sleep disturbance, occupational health, shift work, armodafinil, modafinil, hypnotics

Mexico

Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

The most significant change in the new version of this article is the inclusion of a further paper in the review. This was a clustered randomised controlled trial of a combination intervention targeting shift-workers identified as high risk for shift work disorder. The intervention comprised coaching sessions, caffeine/melatonin and workplace lighting. Adding this paper did not change our overall conclusions that there is a general paucity of evidence for any intervention/s for shift work disorder.

Other changes include highlighting that one of the studied interventions (Brotizolam) is not actually licensed for use in the UK, US or Canada and another studied intervention (Shimian granules) are not mentioned in PubMed other than in the article we make reference to. If anything, this furthers our conclusions that studies of pragmatic interventions in this area are broadly lacking.

Any further responses from the reviewers can be found at the end of the article

Introduction

Shift work is often unavoidable in modern society. In 2015, 21% of the European Union working population carried out shift work¹. Simplistically, shift work is a work schedule organised such that teams cover more than the usual 8 hour working day. More specifically it has previously been defined as “a work schedule in which at least 25% of work days involve the majority of working hours outside the time period between 08:00 and 17:00”². For individuals, shift work has been linked to reduced quality of life, increased risk of workplace accidents^{3,4}, sleep loss, obesity, type 2 diabetes, coronary heart disease, some cancers⁵ and depression⁶. In an occupational setting this has been associated with lost productivity and increased errors⁴. This is of particular concern where work performance is related to health and safety, for example in healthcare, emergency response and mining industries.

Shift work sleep disorder (SWD) refers to the sleep disturbance experienced by a subset of shift workers who respond particularly poorly to their shift work schedule⁷. SWD is chiefly defined as having insomnia and/or excessive sleepiness temporally associated with shift work lasting ≥ 3 months, and where the sleep disturbance is not better explained by another diagnosis⁸. A diagnosis of SWD is associated with a greater risk of poor quality sleep, subjective health complaints and poor coping⁹, peptic ulcers, sleepiness-related accidents, absenteeism and depression when compared to shift workers without SWD³. SWD represents an area of therapeutic interest for individuals and institutions alike. However, the range of and evidence for interventions in mitigating associated impairments is unclear.

Existing reviews of interventions to improve sleep, sleepiness and related outcomes for shift workers found low quality evidence for some interventions^{2,10}. Melatonin, armodafinil, modafinil, caffeine and naps were all found to have low-quality evidence for their efficacy in improving one or more outcome domains².

Another review found studies of bright light, napping, physical exercise and sleep education as interventions for shift-workers, but concluded there was too much uncertainty to determine their impact¹⁰. To our knowledge, there has been no systematic review of clinical trials encompassing the full range of interventions focusing on shift-work related sleep disruption.

Here we present a scoping review of the available evidence from comparative studies examining the impact of interventions for SWD. We set out to identify all trials of shift workers with SWD, or sleep disturbance likely to be SWD that had a comparator group. We sought to establish the types and extent of available outcome data on this topic; how this has been reported and whether an informative quantitative data synthesis would be possible.

Methods**Study design**

We carried out a scoping review to identify the main sources and extent of evidence available in the published literature¹¹.

Eligibility criteria

Type of trials. We included randomised controlled trials (RCTs), randomised crossover trials and parallel group trials.

Population. We included trials carried out with workers who were undertaking shift work and who had SWD as defined by the International Classification of Sleep Disorders (ICSD) criteria at the time when the trial in question was carried out. We also included studies where shift-workers were selected for having some level of sleep disturbance, that was not better explained by a known, non-SWD diagnosis, such as obstructive sleep apnoea (OSA) or narcolepsy. We excluded trials conducted on shift-workers unselected for having sleep problems, or conducted solely on shift-workers selected for having OSA or narcolepsy. We excluded studies in which airline cabin-crew or military personnel were the primary population group, as we considered the aetiology of SWD alongside frequent crossing of time zones likely to be different to that of SWD in the general population².

We included only trials where shift workers received a study treatment in an occupational setting. We included trials where final outcomes were measured in a simulated shift work environment, if participants had been undergoing the treatment in a real shift-work environment previously. For example, where participants had taken modafinil or armodafinil before shifts for a number of months, and then completed a study night in a laboratory setting¹².

Interventions. We included trials with any intervention, or combination of interventions, aimed at preventing or reducing the effects of SWD on sleepiness when awake, sleep disturbance, and associated functional impairment (e.g. reduction in wellbeing, depressive symptoms). We categorised interventions into pharmacological hypnotics, pharmacological stimulants, and non-pharmacological therapies. We included trials where

interventions were compared to placebo, ‘usual care’, no intervention or to each other. Example interventions for pharmacological stimulants might include modafinil or armodafinil. Example interventions for pharmacological hypnotics might include melatonin or zopiclone.

Outcomes

We set out to identify and record when studies had used the following types of outcome measures.

1. Sleep-wake outcomes:
 - a. Sleep outcomes: Measures of sleep parameters, such as total sleep time (TST), sleep efficiency (SE), sleep onset latency (SOL) or wake after sleep onset (WASO), or other measures of sleep quality such as number of awakenings.
 - b. Wake-time outcomes: Measures of alertness or sleepiness during waking hours, including Karolinska, Epworth or Stanford sleepiness scales (KSS, ESS, SSS); multiple sleep latency tests (MSLT).
 - c. Combined sleep-wake outcomes: Comprising both wake-time and sleep-time components, for example the Insomnia Severity Index (ISI) or Pittsburgh Sleep Quality Index (PSQI)
2. Measures of impairment, including global measures of health-related quality of life, daytime functioning, and depressive symptoms.

We did not define the instrument of measurement to be used for any given parameter.

We also planned to record when studies reported outcomes of:

- Adverse events
- Injuries or accidents whilst at work or commuting.

Search method

Electronic searches were conducted for [Cochrane Central Register of Controlled Trials](#), [Cochrane Database of Systematic Reviews](#), [CINAHL](#), [EMBASE](#), [Medline](#) and [Science Citation Index](#) from inception to 30th March 2020. An example search strategy is shown in [Table 1](#). The same search terms were used for all databases. We did not restrict by language. Title and abstract of all citations identified using this search strategy were screened for exclusion by two independent reviewers (R.C-J., E.D.) using [Rayyan](#) software¹³. Conflicts were resolved with a third reviewer (A.F.). The full text of the remaining citations was then reviewed. Citations were only included in the study where they referred to a published journal article. Therefore, drug-company listed trials without an associated journal publication were not included¹⁴.

Data extraction, analysis and synthesis

Data were extracted manually by two independent reviewers using a custom spreadsheet [Microsoft Excel, Version 16.37, Copyright 2020]. We extracted study characteristics. We aimed

to extract data about all outcomes relevant to this review to establish the extent of available data. Where studies reported multiple measures in the same domain (for example, multiple measures of quality of life), we selected externally validated measures.

Results

Search results and study characteristics

From 1250 unique citations, 14 trials met inclusion criteria for data extraction and analysis. Two included citations reported different outcomes from the same trial^{15,16}. As each citation reported different outcome data the trial is referenced to both citations^{15,16}. [Figure 1](#) presents a Preferred Reporting Items for

Table 1. Search Strategy Used for Medline.

1	shift work schedule/ or work schedule tolerance/
2	((shift* or night*) adj3 work*).ti,ab,kw.
3	((night* or rotat* or late) adj3 shift*).ti,ab,kw.
4	1 or 2 or 3
5	exp Sleep Wake Disorders/
6	(sleep* adj3 (disorder? or disturb* or problem?)).ti,ab,kw.
7	sleeplessness.ti,ab,kw.
8	(insomnia? or dysomnia? or parasomnia?).ti,ab,kw.
9	5 or 6 or 7 or 8
10	4 and 9
11	limit 10 to (“systematic review” or systematic reviews as topic or “reviews (maximizes specificity)”)
12	randomized controlled trial.pt.
13	controlled clinical trial.pt.
14	randomized.ab.
15	placebo.ab.
16	drug therapy.fs.
17	randomly.ab.
18	trial.ab.
19	groups.ab.
20	(crossover or cross over).ti,ab.
21	(quasi* adj2 random*).ti,ab.
22	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	exp animals/ not humans.sh.
24	22 not 23
25	10 and 24
26	11 or 25

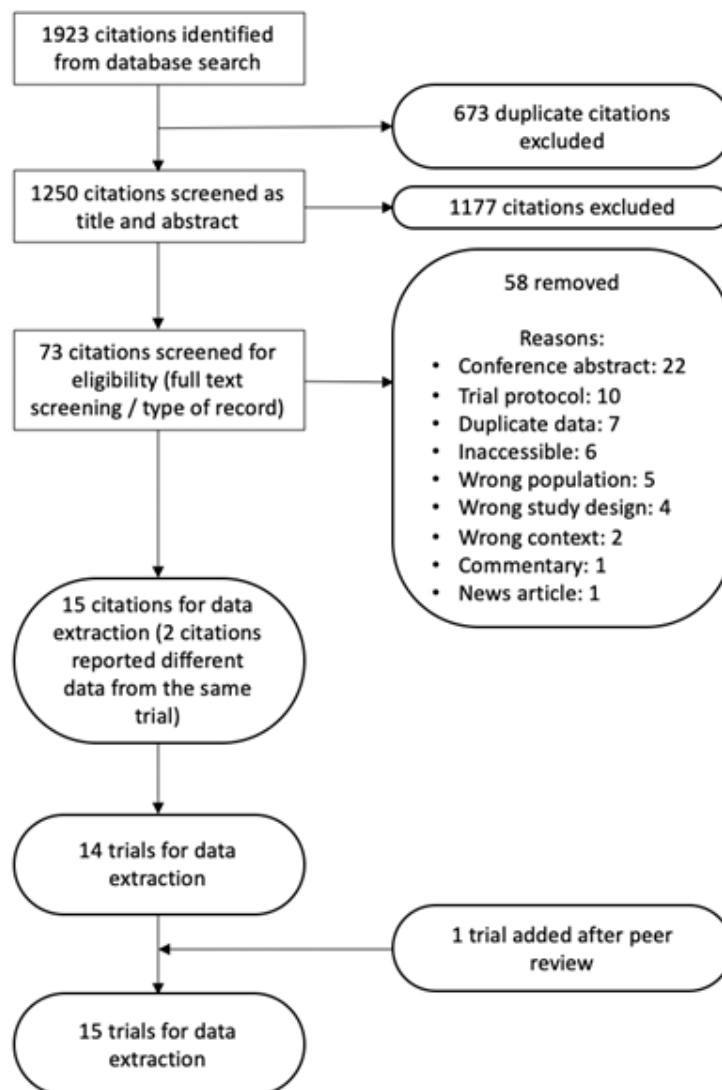


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing reasons for study exclusions. In total, eight of the original included trials were randomised controlled trials^{12,15–22}. The remainder were cross-over^{23–25} and a parallel group design^{26–28}. On peer review of this paper a further clustered randomised controlled trial was highlighted by a reviewer²⁹. It was published after our pre-defined search period. However, it otherwise met inclusion criteria and so has been included to add to the data covered by this review²⁹.

The studies were carried out over a wide geographical area, including Europe, Asia, and North America (Table 2). There were a wide range of occupations evaluated including jobs in health care, industry, security services and broadcasting. Studies included those with rotating and fixed shifts. Five trials applied ICSD criteria for SWD in use at the time of the study; these were

all studies of stimulants^{12,15,16,21,27,28}. Interventions evaluated were hypnotic^{22–26} and stimulant drugs^{12,15,16,21,27,28}, cognitive behaviour therapy¹⁸, aromatherapy¹⁹, light therapy²⁰ and Shimian granules (a form of a Chinese herbal medicine)¹⁷ and a mixed regimen comprising pharmacological and non-pharmacological interventions²⁹. Shimian granules is a form of Chinese herbal medicine which is not described in any other PubMed listed articles at time of writing. With one exception, the studies of hypnotics were carried out between 1989 and 2008, stimulants between 2005 and 2012 and the non-pharmacological interventions since 2013. The mixed intervention trial was published in 2022²⁹. Funding came from a variety of sources, although those studies evaluating stimulants were funded by pharmaceutical companies. All studies whose authors declared a potential conflict of interest with a relevant pharmaceutical company were studies of stimulants^{12,15,16,21,27,28}.

Table 2. Characteristics of included studies.

Author	Date	Country	Industry & Role	Type of shift work	Hours worked if reported	Population		Intervention, Control was placebo unless otherwise stated	Design	Outcome focus	Timing		Funding Source	Conflict of interest relevant pharmaceutical company declared?
						Criteria used for SWD or sleep disorder*	Sample size. Total completed (recruited and eligible)				Duration of intervention	Duration of study		
Hypnotics	Sadeghnia-Haghighi, K	2016	Iran	Oil refinery	Rotating, 1 week day shift, 1 week night shift.	N/A	Sleep disturbance assessed with ISI, item 1a, PSQI item 2.	Melatonin 3mg OD	Randomised, double-blind, placebo-controlled crossover study	Sleep outcomes and other	3 nights, 2 week wash out	3 weeks	Tehran University of Medical Sciences, Health Sciences Research Pharmaceutical Co	No
	Sadeghnia-Haghighi, K	2008	Iran	Nursing	Unspecified.	N/A	Sleep problems reported in a baseline questionnaire	Melatonin 5mg OD	Randomised, double-blind, placebo-controlled crossover study	Sleep outcomes	1 night, 4 days wash out	<2 weeks	Tehran University of Medical Sciences	No
	Bozin-Juricic, J	1996	Croatia	Security firm	Rotating, 7 night shifts, week rest, week 5 days and week of afternoons.	Night shifts with 5:00-06:00	Self-reported night-related insomnia.	Zopiclone 7.5mg OD Nitrazepam 5mg OD	Parallel group	Sleep outcomes	1 week for each treatment, 3 week wash outs	12 weeks	May and Becker and Phone-Pulenc Santé	No
	Gigli	1993	Italy	Nursing	5 day rotation	Shifts: 7:00-14:00; 14:00-22:00; 22:00-7:00	Symptoms of insomnia considered by subjects or physicians to be clinically relevant.	Brotizolam 0.25mg OD	Double-blind crossover study	Other	15 days with 15 day wash out	45 days	Boehringer Ingelheim Italia	No
Stimulants	Monchesky	1989	Canada	Automobile plant	Rotating, two weeks alternating	Shifts: 07:00-15:30; 18:00-02:30 Monday to Friday.	Insomnia for 3 or more consecutive night shifts via sleep awakenings, ISI and poor sleep quality.	Zopiclone 7.5mg OD	RCT	Sleep outcomes	2 weeks	2 weeks	None declared	No
	Erman, M K** &	2011 & 2012	USA	Varied	Mixture, 93% permanent	Excessive sleepiness associated with ICD2 SWD. Functionally impaired (GAF<70)	Armodafinil 150mg OD	RCT	Wake outcomes and AE	6 weeks	6 weeks	Cephalon Inc	Yes	
	Terabe, D V	2011	India	Unspecified	Unspecified.	ICD criteria for SWSD	Armodafinil 150mg OD (Control: Modafinil 200mg OD)	RCT	Wake outcomes and AE	12 weeks	12 weeks	Emcure Pharmaceuticals Ltd.	Yes	
	Czeisler, C A	2009	USA & Canada	Varied	Mixture, 86.5% permanent.	ICD2 criteria: <6 hr of sleep during a night shift; SE of <67.5% or less on daytime polysomnography	Armodafinil 150mg OD	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study	Sleep outcomes, wake outcomes, other & AE	12 weeks	12 weeks	Cephalon Inc	Yes	
Erman, M K	2007	USA	Varied	Unspecified.	ICD criteria: <6 hr of sleep during a night shift; SE of <67.5% or less on daytime polysomnography	Modafinil 200mg or Modafinil 300mg OD	Randomised double blind placebo controlled parallel group trial	Other	12 weeks	12 weeks	Cephalon Inc	Yes		
Czeisler, C	2005	USA	Varied	Mixture, 90% permanent.	ICD criteria: <6 hr of sleep during a night shift; SE of <67.5% or less on daytime polysomnography	Modafinil 200mg OD	RCT	Sleep outcomes, wake outcomes, other & AE	12 weeks	12 weeks	Cephalon Inc	Yes		

	Study		Population					Sample size: Total completed and eligible		Intervention. Control was placebo unless otherwise stated	Design	Outcome focus	Timing		Funding Source	Conflict of interests with relevant pharmaceutical company declared?		
	Author	Date	Country	Industry & Role	Type of shift work	Hours worked if reported	Criteria used for SMD or sleep disorder	Intervention					Control				Duration of intervention	Duration of study
								Intervention	Control				Intervention	Control				
Non-pharmacological	Zhang, L.	2020	China	Nursing	Forward rotating shift nurses	Shifts: 07:30-17:30; 17:30-22:30; 22:30-06:00; 06:00-17:30; 5/7 days a week	Score of ≥8 on the PSQI	15 (19)	23 (25)	Shimian granules and sleep hygiene education (Control: sleep hygiene education only)	RCT	Other	1 month	1 month	Youth Science and Technology Innovation Personnel Training Project of Shaanxi Province, Special Support Program for Shaanxi Province	No		
	Järnfeldt, H.	2019	Finland	Variety: health and social care, education, aviation	Varied	≥10% shifts beginning 07:00 or earlier, or ending 22:00 or later or at least 3 hours of a shift starting between 23:00-06:00.	Non-organic insomnia, difficulty maintaining sleep for >30 min and use of sleep promoting medication at least 3 nights a week for at least 1 month, full time shift work	18 (30)	15 (24)	Group CBT-I (Control: Sleep hygiene education)	RCT	Sleep outcomes, other	Up to 10 weeks	6 months	Finnish Work Environment Fund; Nordström, the Nordic Programme for Health and Welfare	No		
Combination	Chang, Y. Y.	2017	Taiwan	Nursing	Monthly rotating shifts.	N/A	A total PSQI ≥5	27 (27)	23 (23)	Aromatherapy massage	RCT	Other	4 weeks. 1 hour long treatment weekly.	5 weeks	Taichung Veterans General Hospital	No		
	Huang, L. B.	2013	Taiwan	Nursing	Rotating shifts	16:00-00:00; 00:00-08:00	ISI=14.	(46)	(46)	Bright light during night shift + avoid daytime sun	RCT	Other	At least 10 days during 2 weeks.	At least 10 days during 2 weeks.	Chang Gung Memorial Hospital	No		
Combination	Booker, L. A.	2022	Australia	Healthcare	Regular rotating or permanent night shifts.	N/A	High risk of SMD or Australian Sleep Trials Network Questionnaire	19***	15****	Evening 1-to-1 coaching sessions + caffeine/melatonin; sleep/work/driving diaries + high intensity lighting in workplace; education on benefits of low glycaemic diet.	A clustered randomised controlled trial.	Other, Sleep Outcomes	10 weeks	6 months	Cooperative Research Centre for Alertness, Safety and Productivity (Melbourne), Victorian Health and the Institute for Breathing and Sleep (Melbourne and Sleep (Melbourne and Australia).	No		

Legend: Shift work disorder (SMD); insomnia severity index (ISI); Pittsburgh Sleep Quality Index (PSQI); circadian rhythm (CR); total sleep time (TST); multiple sleep latency test (MSLT); International Classification of Disease (ICD); sleep efficiency (SE).

* All patients being involved in shiftwork as defined by the study, and having no other conditions which better explain their sleep disturbance was an inclusion criterion so is not repeated here.

** Different outcomes or timepoints from the same treatment population published separately.

*** 19 participants identified as high risk of SMD. Whole study population: 79 participants completing protocol of 101 recruited.

**** 15 participants identified as high risk of SMD. Whole study population: 70 completing protocol of 101 recruited.

The most commonly studied intervention was armodafinil (three trial populations)^{15,16,21,27}. The other studies of stimulants used modafinil^{12,28}. For hypnotics, there was variation in class, including studies of non-benzodiazepines (zopiclone^{22,26} and melatonin^{23,25,29}), one study of a benzodiazepine (nitrazepam²⁶) and one study of a benzodiazepine analogue which is no longer licensed for use in the UK, US or Canada (brotizolam²⁴). No identical non-pharmacological intervention was studied by more than one study.

Four of the hypnotic intervention trials were conducted with rotating shift-workers^{22–24,26}. Studies of stimulants were on mixed populations of rotating and permanent shift-workers or did not specify their population characteristics in this way^{12,15,16,21,27,28}. All included studies with an SWD population sample size >50 participants were studies of stimulants^{12,15,16,21,27,28}. Non-pharmacological studies were on mixed populations of rotating and permanent shift-workers¹⁸, or rotating shift workers^{17,19,20}.

Reported outcomes

Table 3 shows the outcomes reported by the studies included in this review; the most commonly reported outcomes were TST and SOL, though they were measured by a variety of tools (polysomnography, actigraphy and sleep diaries).

Sleep-wake outcomes. The most commonly used wake-time outcome was KSS. Studies of pharmacological interventions predominantly used MSLT and sleepiness scales^{12,15,21,27}. No study used the ESS. Three studies of non-pharmacological interventions used the ISI^{17,18,20}, as did the study of a combination intervention²⁹. No non-pharmacological study used a sleepiness scale.

Outcomes focused on other aspects of impairment. Clinical Global Impression of Change (CGI-C) score was used by three studies. Regarding depressive symptoms the Hospital Anxiety and Depression Scale (HADS) was used by two studies^{17,20}. Two studies reported the 36-item Short Form Survey (SF-36)^{18,28}, and two reported reaction time^{24,27}.

Adverse events and drop-outs. Adverse events were only reported by pharmacological studies. All studies of stimulants described monitoring for adverse events throughout the study periods. The protocols described varied but included combinations of subjective symptom reporting, physical examination and bedside and laboratory investigations. One study of zopiclone relied on study participants spontaneously reporting symptoms that they felt might be related to the study intervention²². Few studies reported total counts of participants affected by any adverse events. Some, but not all, studies reported where drop-outs were due to adverse events. Only one study explicitly defined how adverse event severity was categorised¹² and one other stated only that event severity was determined by a site investigator²⁷.

Discussion

Our scoping review provides evidence that a review to assess the effectiveness of interventions to treat SWD would not provide sufficient data for a comprehensive meta-analysis. There

are too few studies amongst shift workers with SWD for any particular intervention or category of intervention. Even where there is more than one study, there are often methodological limitations preventing pooling of data using meta-analysis, such as different measurement tools for one outcome. At least one of the hypnotic medications studied is no longer licensed in the UK, US or Canada²⁴ and one non-pharmacological supplement¹⁷ is not described elsewhere in published literature. This limits the practical usage of these studies. Whilst we considered that a narrative review might be possible, the represented methodologies, interventions and data were so heterogeneous it was not deemed appropriate at this point.

We did not critically appraise the included sources of evidence as this scoping review was conducted to provide an overview of the existing evidence regardless of methodological quality or risk of bias. However, we note that there were high rates of participant attrition in experimental and control arms in both pharmacological and non-pharmacological studies. Many drop-outs were unexplained.

Previous systematic reviews looking at a wider population of all shift-workers have similarly found a paucity of evidence regarding impact of interventions^{2,10}. There are many interventions that have been considered in the literature for sleep disturbance^{30,31} that do not appear to have been evaluated in clinical trials with populations that meet the criteria for SWD, for example individual level interventions such as napping³² and institutional level interventions such as optimising shift schedules³³. These interventions could be considered in future work looking at the SWD population specifically.

In this scoping review, we have grouped the short-term trial outcomes into sleep outcomes (ease of falling asleep, the continuity, duration and quality of obtained sleep), wake-time outcomes (sleepiness during waking hours), combined sleep-wake outcomes and other aspects of impairment. Sleep outcomes are the primary target of hypnotic pharmacological interventions whilst wake-time outcomes are that of wakefulness-promoting (stimulant) pharmacological agents. Non-pharmacological interventions vary in their putative mode of action.

The lack of consistent measurement of sleep outcomes was perhaps unsurprising then. Studies of the efficacy of stimulant pharmacological agents were aiming to promote wakefulness whilst at work and so often used real time state-based assessments like KSS and SSS. These were not used by any study of hypnotics or non-pharmacological interventions. Multiple studies reported a range of sleep outcomes (TST, SOL) but instrument of measurement was variable. Further work in this area could establish useful and replicable outcome measures for SWD.

The MSLT is described as the gold standard measure of sleepiness and is objective but many of the studies included in this review only used subjective measures of sleepiness^{15,16,21}. Whilst subjective measures of sleepiness are clinically relevant and sensitive to insufficient sleep acutely³⁴, they have a non-linear relationship to sleep debt and correlate poorly with sleep debt in the context of chronic sleep deprivation³⁵.

Further, occupational impairment in SWD has been shown to be more strongly correlated to insomnia than to sleepiness so focusing on sleepiness may be unhelpful for work related outcomes³⁶. As such, it is likely a useful set of outcome measures for SWD will cover multiple domains of the disorder: insomnia symptoms, excessive waketime sleepiness and impact on functioning. These need to be consistent and standardised to prevent research waste where data from one study cannot be used to inform subsequent work or contribute to systematic reviews of the problem. We envisage shift-worker participation in future outcome measure development will be beneficial.

Advice for shift workers using available evidence has been described pragmatically elsewhere³⁷. There are also multiple

guidelines available for clinicians treating patients with sleep disturbance due to shift work^{38,39}. The evidence for the effectiveness of interventions currently available is unclear and the lack of follow-on evaluations from those identified in this review confirms the continuing uncertainty and gap in the evidence. Novel treatments and combinations of current treatment, targeting individuals where the type of shift work and the combination of symptoms experienced by an individual are needed.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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Open Peer Review

Current Peer Review Status: ? ✓ ✓

Version 2

Reviewer Report 15 June 2023

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Ulises Jiménez Correa 

Universidad Nacional Autonoma de Mexico, Mexico City, Mexico City, Mexico

It is a very interesting scoping review with the aim to describe the evidence for the impact of pharmacological and non-pharmacological interventions on shift work disorder. Beyond interesting, I consider that it review is necessary.

I believe that the strength of this review consists in highlighting the little research that aims to determine the evidence of pharmacological/psychological treatment for sleep disorder due to work hours. The issue is very important because we live in a 24-hour society (i.e. factories, public security, mobility, hospital services), that require of workers for night shift and shift rotation; those who are at high risk of suffering symptoms of insomnia and daytime sleepiness; as well as metabolic alterations related to circadian rhythm disorders and accidents.

Methods are according to introduction; results with the aim; and discussion with the results. However, with the aim of complementing the results section with the necessary information, I think that it is necessary to include an extra column in table 3 with the main findings of the included studies.

I do not have any more comments.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Sleep disorders

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 05 August 2022

<https://doi.org/10.21956/wellcomeopenres.18774.r51643>

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Bobby Joseph 

Department of Community Health, St. John's Medical College, Bangalore, India

This being a scoping review, the authors have achieved their stated objectives of wanting to establish the types and extent of available outcome data on the impact of pharmacological and non-pharmacological interventions on shift work related sleep disturbance in the occupational setting.

Having identified 1250 unique studies and whittling this down to just 14 trials that met the inclusion criteria, it was obviously a lengthy process. The findings of these 14 studies have been presented concisely both in the text as well as in the table. The paper has been well written and presents easy avenues for researchers who want to carry out their own research on the topic. If scoping reviews such as these fall within the purview of the journal, this article must surely be approved.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public health, primary health care, occupational health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 16 May 2022

<https://doi.org/10.21956/wellcomeopenres.18774.r50051>

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Kirstie N. Anderson

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The paper is clear, well written and comes from expert colleagues. However, this is essentially stating that there is insufficient evidence to carry out meta-analysis - I agree with this and that there is very limited data. In fact there are no two trials using the same methodology or intervention. A minor point but I disagree with the opening sentence, there isn't really any evidence for shift work increasing, most work fewer hours with more protection of sleep periods in legislation compared to any period from the industrial revolution onwards. About 20% of people work some form of shift but this figure has been consistent over some time. Therefore many people work shifts, but always have. There isn't a clear definition of what a shift is or what makes a shift worker to help the non-expert.

I had some questions about the interventions that were included and discussed. Brotizolam is a potent, old hypnotic no longer licensed for use in the UK, US or Canada which I think either needs to be clearly stated in the text or this study not used for those reasons. Likewise - there is a single PubMed reference only to shimian granules - a product that is not licensed and there is simply no information at all on what they are - a chinese complimentary medicine not in any way standard for sleep clinics. Again, there is a single RCT but nothing else at all in PubMed relevant for shimian granules.

I appreciate the authors decided against critical review or narrative review but a small amount of extra information still seems necessary here.

Accepting the timelines of any systematic review and inevitably - more studies will follow. However given such limited data - there is a very recent RCT using CBTi strategies just published¹. I think the paper ideally should be revised and this paper should be included, there is so little data that this would be a valuable addition, no stats were possible and all information presented is simply descriptive so I do not see this taking the authors significant time.

There is also another drug company-listed trial with all results in clinicaltrials.gov I think it may

have been reasonable to discuss this - [Study of the Efficacy and Multiple-Dose Plasma Concentration-Time Profiles of Armodafinil and PROVIGIL - Study Results - ClinicalTrials.gov](#).

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Sleep medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 29 Nov 2022

Rebecca Conway-Jones

Dear Dr Anderson,

Firstly, thank you for your considered and clear review. We appreciate the time and care which you took in reading this paper and making your comments. Our responses to the points raised are below. I have endeavoured to give line numbers for each change to make reviewing the changes easier but am aware formatting carried out by the editorial team might alter these:

Revision 1

- "A minor point but I disagree with the opening sentence, there isn't really any evidence for shift work increasing, most work fewer hours with more protection of sleep periods in legislation compared to any period from the industrial revolution onwards. About 20% of people work some form of shift but this figure has been consistent over some time. Therefore many people work shifts, but always have."
- *Thank you for clarifying this – we have edited the first part of the introduction to reflect*

this.

Revision 2

- "There isn't a clear definition of what a shift is or what makes a shift worker to help the non-expert."
- *Apologies for this oversight. We have added in a definition of shift-work to the first paragraph of the introduction.*

Revision 3

- "I had some questions about the interventions that were included and discussed. Brotizolam is a potent, old hypnotic no longer licensed for use in the UK, US or Canada which I think either needs to be clearly stated in the text or this study not used for those reasons."
- *This is a very useful point. We have chosen to keep the study included as it does otherwise fit the inclusion criteria we have previously stated. However, we have made it clear in the third paragraph of the Results section that it is not licensed in the UK, US or Canada. For both this and the point about Shimian Granules we have then highlighted this again in the first paragraph of Discussion.*

Revision 4

- "Likewise - there is a single PubMed reference only to shimian granules - a product that is not licensed and there is simply no information at all on what they are - a chinese complimentary medicine not in any way standard for sleep clinics. Again, there is a single RCT but nothing else at all in PubMed relevant for shimian granules. I appreciate the authors decided against critical review or narrative review but a small amount of extra information still seems necessary here."
- *Yes, similarly we agree this is important and are grateful for your highlighting this. We have added a sentence to this effect in Results (second paragraph). For both this and the point about Brotizolam we have then highlighted this again in the first paragraph of the Discussion.*

Revision 5

- "Accepting the timelines of any systematic review and inevitably - more studies will follow. However given such limited data - there is a very recent RCT using CBTi strategies just published¹. I think the paper ideally should be revised and this paper should be included, there is so little data that this would be a valuable addition, no stats were possible and all information presented is simply descriptive so I do not see this taking the authors significant time."
- *Yes thank you so much for raising this. We agree this is a useful trial to highlight given the paucity of trials otherwise. We have simply included it and explained in the Results section how it has been added after peer review (first paragraph of Results). Whilst this isn't perfect we agree that including it, even post-hoc, is in keeping with the goals of a scoping review. It is a valuable addition for completeness of this paper though it has not changed our conclusions*
- *The main edits pertaining to this are found in Figure 1, Tables 2 and 3 and within the Results section.*

Revision 6

- "There is also another drug company-listed trial with all results in clinicaltrials.gov I think it may have been reasonable to discuss this - [Study of the Efficacy and Multiple-Dose Plasma Concentration-Time Profiles of Armodafinil and PROVIGIL](#) - Study

[Results - ClinicalTrials.gov."](#)

- *Thank you for highlighting this. To acknowledge this study we have added a line in the Methods under 'Search Method' in order to make reference to it. In contrast to the above (Booker et al 2022), we couldn't fully include this study as our Methods included only trials published in journal articles. Therefore, we cannot exclude the possibility we excluded other drug company-listed trials with a similar profile to this one on the basis they had not been published. However, we hope that by making reference to it our review will still serve to make readers aware of this available data.*

Competing Interests: No competing interests were disclosed.
