How to manage travel fatigue and jet lag in athletes? A systematic review of interventions

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Word count (excluding title page, abstract, references, figures and tables)**: 5233**

What is already known
► Misalignment of the circadian system with the new local time may impair cognitive and physical performance ► Light and melatonin can induce a phase-shift in the circadian system if appropriately timed ► Measuring the phase of the circadian system and proper timing of interventions are challenging in real life such as for sportspeople ► Interventions seem to be successful in laboratory settings, but limited data are available in actual travel conditions

What are the new findings
► Few studies investigated interventions to advance or delay circadian phase-shifts in athletes who experience jet-lag ► There is no research-based evidence to manage *travel fatigue* in athletes! ► Low quality evidence exists for effective interventions to recover from jet-lag in athlete populations ► Comparing studies is complicated by large intra-study variation in determining circadian phase, along with a wide variety of outcome measures

ABSTRACT:

Objectives We investigated the management of travel fatigue and jet-lag in athlete populations by evaluating studies that have applied non-pharmacological- (exercise, sleep, light, and nutrition), and pharmacological interventions (melatonin, sedatives, stimulants, melatonin analogues, glucocorticoids, and antihistamines) following long-haul transmeridian travel, and/or laboratory-based circadian system phase-shifts.

Design Systematic review.

Eligibility criteria Randomised controlled trials (RCTs), and non-RCTs including experimental- and observational studies, exploring interventions to manage travel fatigue and jet-lag involving actual travel or laboratory-based phase-shifts. Studies included participants who were athletes, except for interventions rendering no athlete studies, then the search was expanded to include studies on healthy populations.

Data sources Electronic searches in PubMed, MEDLINE, CINAHL, Google Scholar, and SPORTDiscus from inception to March 2019. We assessed included articles for risk of bias, methodological quality, level of evidence and quality of evidence.

Results Twenty-two articles were included: 8 non-RCTs and 14 RCTs. No relevant travel fatigue papers were found. For jet-lag, only 12 athlete specific studies were available (6 non-RCTs, 6 RCTs). In total (athletes and healthy populations), 11 non-pharmacological (participants 600; intervention group 290; 4 non-RCTs, 7 RCTs) and 11 pharmacological studies (participants 1202; intervention group 870; 4 non-RCTs, 7 RCTs) were included. For non-pharmacologic interventions, 7 studies across interventions related to actual travel and 4 to simulated travel. For pharmacologic interventions, 8 studies were based on actual travel and 3 on simulated travel.

Conclusions We found no literature pertaining to the management of travel fatigue. Evidence for the successful management of jet-lag in athletes was of low-quality. More field studies specifically on athlete populations are required with a multifaceted approach, better design and implementation to draw valid conclusions.

Keywords: non-pharmacological interventions [exercise, sleep, light, nutrition]; pharmacological interventions [melatonin, sedatives, stimulants, melatonin analogues, glucocorticoids, antihistamines]; circadian rhythm; phase-shift

INTRODUCTION

Globally, athletes are frequently required to embark on long-haul transmeridian travel for competition purposes e.g. Olympic Games, IAAF Diamond League Series and the Super Rugby Tournament, exposing them to travel fatigue and jet-lag.[1-6] Travel fatigue follows any long journey irrespective of the mode of travel and can accumulate over time.[2-5] Jet-lag follows travel across multiple time-zones (>3) with subsequent desynchronisation of the circadian system to the new external environment at the destination.[2,4-6] The human circadian system requires time to adjust, leading to persistence of jet-lag symptoms including sleep disruption, daytime fatigue, gastrointestinal disturbances and reduced performance.[2,5,7] Literature on jetlag focuses mostly on interventions with a determined phase response curve, able to induce a circadian phase-shift.[3,8-13] Few studies describe effective interventions to recover (i.e. reverse a phase-shift) from jet-lag.

Current clinical applications rely heavily on opinions, collective experience and findings from simulated travel (laboratory-based) studies due to a lack of well-designed actual travel (field-based) studies.[1] The most promising interventions have been tested in a simulated travel environment in the laboratory, but not necessarily in an actual travel scenario.[3,14] Even though simulated- and actual travel are not directly comparable, laboratory-based studies provide valuable information that can be used to design field-based studies.[15] The latter is expensive, difficult to control and population recruitment challenging especially in the athlete context. Due to these constraints, most of the literature comes from non-athlete studies.[1,14,16-17]

For this paper we systematically reviewed non-pharmacological- [exercise, sleep, light (exposure/avoidance), nutrition (mealtime/-composition)], and pharmacological interventions [melatonin, sedatives, stimulants, melatonin analogues, glucocorticoids, and antihistamines], that can be applied in managing travel fatigue and jet-lag in athlete populations following transmeridian travel.

METHODOLOGY

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement.[18] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019126852).

Data sources and search strategy

We conducted a comprehensive literature search from inception to March 2019 to obtain relevant peer-reviewed publications. Initially, we studied all relevant literature in relation to the management of travel fatigue and/or jet-lag. We included all populations (animal and human) to identify any intervention used. We then selected only those interventions that were research-based and relevant to our review question regarding athlete populations. We excluded interventions based on opinions and collective experience. Relevance was determined based on the collective expertise and experience of the authors, all of which are active in this specific area of research. Electronic databases searched included PubMed, MEDLINE, CINAHL, Google Scholar, and SPORTDiscus. Authors were assigned to project groups covering a specific non-pharmacological intervention [i.e. exercise, sleep, light (exposure/avoidance), nutrition (mealtime/-composition)], and pharmacological intervention [i.e. melatonin, sedatives, stimulants, melatonin analogues, glucocorticoids and antihistamines]. To exclude the risk of inter-individual variability in screening and identification of studies, project groups consisted of different authors (overlapping group membership), and two authors (CJvR, AJvR) independently performed literature searches on all interventions. A search strategy was developed using relevant Medical Subject Heading search terms, adding identified subject keywords in different combinations. Boolean operators 'OR' and 'AND' were used to combine or exclude keywords in the search, resulting in more focused and refined results (provided in online Supplement A). We manually searched the reference list of included studies to identify other relevant studies. Some of the interventions did not yield any athlete-specific studies, but showed promise in healthy population studies. After intense discussions and careful consideration, the author group decided to, where available, include only athlete-specific studies for interventions (i.e. exercise, sleep, light, melatonin and sedatives) but to infer from healthy population studies for those interventions (i.e. nutrition, stimulants and melatonin analogues) where no athlete-specific studies were found. No year limits were applied. We conducted a search in July 2019 and before submission to identify any new eligible studies.

Eligibility criteria

Inclusion criteria for selected studies:

1. Randomised control trials (RCTs) and non-randomised control trials (non-RCTs) including experimental- and observational studies (cross-sectional, case-control and cohort studies) exploring an intervention to manage travel fatigue or jet-lag
2. Involve long-haul transmeridian travel, or laboratory-based circadian system phase-shifts (i.e. studies that observed usefulness of interventions following a phase-shift of the circadian system)
3. Published as original research in a peer-reviewed journal

4. Published as full-text
5. Athlete specific (healthy individual studies were included only for those interventions where no athlete specific studies were available)
6. Participants ≥ 18 years of age
7. No restrictions towards gender, ethnicity, and follow-up duration (in case of longitudinal studies)
8. Only human participants
9. Only English language

Exclusion criteria for selected studies:

1. If light-dark or sleep-wake cycle was shifted without a period of travel or simulated travel (i.e. studies that observed efficacy of interventions to induce a phase-shift in the circadian system)
2. Investigating shift work disorder and social jet-lag
3. Participants with mobility impairment (e.g. Paralympians), diseased populations (e.g. cancer) or animals
4. Reviews, case series, case reports, editorials and abstracts

Study selection

We identified relevant studies on each intervention combining findings from each project group and the independent searches performed (CJvR, AJvR). From the compiled list, the titles and abstracts for each article was screened to identify relevant studies. Full texts of potentially relevant articles were reviewed to determine eligibility for the systematic review. All authors agreed on inclusion of studies. In the event of any disagreement, accord of decision was made by three authors (CJvR, AJvR, TC), when at least two reviewers independently agreed on the eligibility of the studies, and achieved consensus on which studies to include and which data to extract.

Data extraction

For each specific intervention, data were extracted from eligible studies. Data included level of evidence, publication details (first author, study title, year of publication), study design (type of study), study duration, participants (sex, sample size, age), control group or not, induced phase-shift, aim of the study, intervention used, measurements used and main outcomes.

Risk of Bias, Methodological Quality, Level of Evidence and Quality of Evidence

We evaluated RCT studies using the Cochrane Risk of Bias Tool.[19] The domains of risk of bias assessment included: selection-, reporting-, performance-, detection- and attrition bias. For non-RCTs, we used the Downs and Black Tool to assess each study in its entirety, not simply a specific outcome or result.[20-21]

Additionally, the level of evidence of each eligible study was critically appraised using the Oxford Centre for Evidence-based Medicine (OCEBM) levels of evidence.[22] The OCEBM ranking levels evaluate studies according to best evidence for clinical focus (diagnosis, prognosis, harm, treatment and prevention) based on the relative strengths and weaknesses of each study design. We used the clinical focus for "treatment and prevention".

The quality of the evidence of each intervention was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[23] Criteria included risk of bias, directness, consistency, precision, and publication bias. Each outcome is graded as either high, moderate, low or very low, and reflects the degree of confidence in the effect estimate. Three authors (CJvR, AJvR, TC) assessed all studies independently for bias, methodological quality, level of evidence and quality of evidence, with any disagreements resolved by consensus from other authors.

RESULTS

Study identification

A PRISMA flow chart documents the search and selection process for non-pharmacological- (Figure 1a) and pharmacological interventions (Figure 1b). The initial electronic database search returned 1366 non-pharmacological- and 5622 pharmacological articles. Additional articles were sourced from the reference lists of the reviewed articles. Duplicate records were removed. After reviewing titles and abstracts, and reviewing the full text of potential articles, 11 articles remained for each intervention category. Two reviewers (CJvR and AJvR) re-evaluated all relevant articles for each intervention.

Data synthesis and analysis

We grouped and summarised studies as non-pharmacological- [exercise, sleep, light (exposure/avoidance),nutrition (mealtime/-composition)] and pharmacological interventions [melatonin, sedatives, stimulants, melatonin analogues, glucocorticoids and antihistamines]; as depicted in online Supplement B. After broad consultation with statisticians and investigating the literature regarding the guidelines on conducting a meta-analysis, a collective decision was made that a

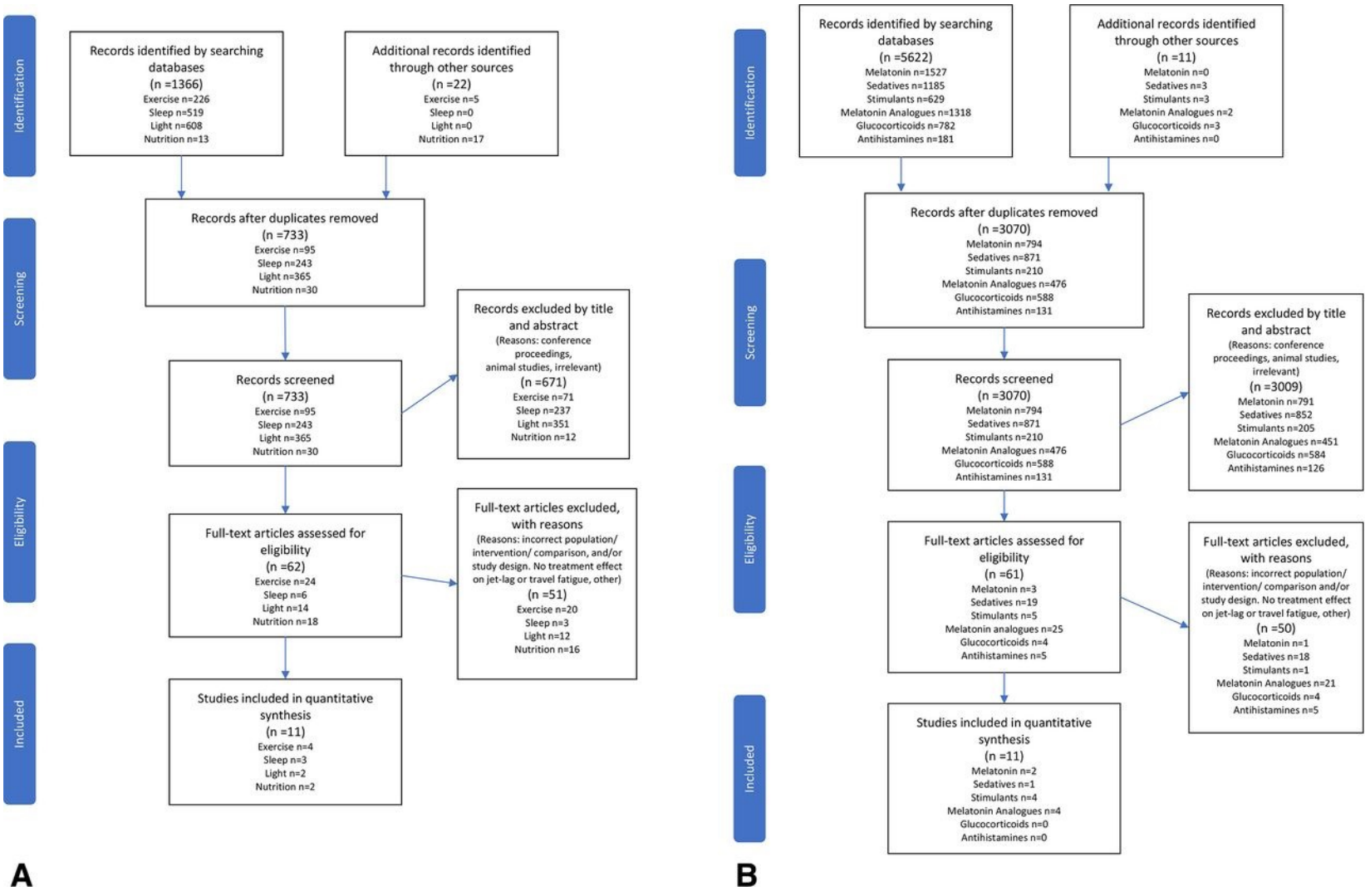

Figure 1.

A: PRISMA flow diagram of the systematic review on non-pharmacological interventions for the management of travel fatigue and jet-lag in athletes;

B: PRISMA flow diagram of the systematic review on pharmacological interventions for the management of travel fatigue and jet-lag in athletes.

meta-analysis was not feasible. This was due to the diverse nature and lack of consistency of the studies regarding population, flight direction, study design (implementation of the intervention protocol differed), outcomes measured, and statistical parameters. A sensible combination of such diversity was not possible and could produce misleading results.[24-28]

NON-PHARMACOLOGICAL INTERVENTIONS: No relevant travel fatigue papers were found. For jet-lag, three interventions (exercise: 4[29-32], sleep: 3[33-35], light: 2[30,36]) yielded athlete specific studies. There were no athlete specific studies for the category on nutrition (mealtime/-composition) and we subsequently inferred from 2 healthy population studies.[37-38] Seven studies across interventions related to actual travel (exercise: 2[29-30], sleep: 1[35], light: 2[30,36], nutrition: 2[37-38]) and 4 to simulated travel (exercise: 2[31-32], sleep: 2[33-34]). In total 11 non-pharmacological intervention studies (participants 600; intervention group 290) were included, of which 4 were non-RCTs[29-30,37] and 7 were RCTs[31-36,38] (Table 1a and 1b).

Table 1a: Grading of evidence for non-pharmacological (RCTs) interventions to manage jet-lag in athletes

Category	Number of studies	Total Participants (intervention group)	Actual (A) or Simulated (S) travel	Athlete specific	Risk of bias	Consistency	Directness	Precision	Publication bias	Total GRADE rating
Exercise Barger, et al.[31] Yamanaka, et al.[32]	2	35 (18) 18 (9) 17 (9)	 S S	 Yes Yes	High	¥ clinical homogeneity, methodological heterogeneity	‡ (the evidence answers the review question)	§ (small sample sizes, no effect sizes reported, randomisation process unclear)	¥ #	Very low + Serious RoB downgraded 1 level from low
Sleep Petit, et al.[33] (2014) Petit, et al.[34] (2018) Straub, et al.[35]	3	48 (40) 16 (16) 16 (16) 16 (8)	 S S A	 Yes Yes Yes	High	§ / ¥ only 2 of 3 studies used same methodology and intervention	‡ (the evidence answers the review question)	§ (small sample sizes, no effect sizes reported)	¥ #	Low ++ Serious RoB downgraded 1 level from moderate
Light Thompson, et al.[36]	1	22 (11) 22 (11)	 A	 Yes	Moderate	§ participants females only	‡ (the evidence answers the review question)	¥ / § (effect size reported, small sample size)	¥ #	Low ++
Nutrition (meal timing/ composition) Ruscitto & Ogden[38]	1	61 (31) 61 (31)	 A	 No	High	§ many confounders, many limitations	‡ (the evidence answers the review question)	§ (low response rate, self-reported)	§	Very low +
TOTAL	7	166 (100)								

All athlete specific studies have small sample sizes that may lead to publication bias
‡ No serious problems
§ Major problems
¥ Some problems

Table 1b: Grading of evidence non-pharmacological (non-RCTs) interventions to manage jet-lag in athletes

Category	Number of studies	Total Participants (intervention group)	Actual (A) or Simulated (S) travel	**Athlete specific**	**Methodological quality**	**Consistency**	**Directness**	**Precision**	**Publication bias**	**Total GRADE rating**
Exercise Montaruli, et al.[29] Cardinali, et al.[30]	2	40 (34) 18 (12) 22 (22)	 A A	 Yes Yes	Poor 10/28 10/28	§ / ¥ 1 study no control group, clinical heterogeneity, methodological heterogeneity	‡ (the evidence answers the review question)	§ (small sample sizes, no effect sizes reported)	¥ #	Very low +
Sleep	0									
Light Cardinali, et al.[30]	1	22 (22) 22 (22)	 A	 Yes	Poor 10/28	§ participants males only, multi factorial interventions	‡ (the evidence answers the review question)	¥ / § (small sample sizes, no effect sizes reported)	¥ #	Very low +
Nutrition (meal timing/ composition) Reynolds & Montgomery[37]	1	372 (134) 186x2 (95+39)	 A	 No	Poor 10/28	§ Participants could choose	‡ (the evidence answers the review question)	§ (no effect sizes, changing sample size)	§	Very low +
TOTAL	4	434 (190)								

All athlete specific studies have small sample sizes that may lead to publication bias
‡ No serious problems
§ Major problems
¥ Some problems

PHARMACOLOGICAL INTERVENTIONS: We did not find any relevant papers on travel fatigue. For jet-lag, limited athlete specific studies were available (melatonin: 2[30,39], sedatives: 1[40]). For the remainder of the interventions the search was expanded to include studies on healthy populations (stimulants: 4[41-44], melatonin analogues: 4[45-48]). In total 8 studies were based on actual travel (melatonin: 2[30,39], sedatives: 1[40], stimulants: 4[41-44], melatonin analogues: 1[48]) and 3 on simulated travel (melatonin analogues: 3[45-47]). We found no eligible studies for the categories on glucocorticoids and antihistamines. Overall, 11 pharmacological intervention studies (participants 1202; intervention group 870) were included, of which 4 were non-RCTs[30,39-40,45] and 7 were RCTs[41-44,46-48] (Table 2a and 2b).

Table 2a: Grading of evidence pharmacological (RCTs) interventions to manage jet-lag in athletes

Category	Number of studies	Total Participants (intervention group)	Actual (A) or Simulated (S) travel	Athlete specific	Risk of bias	Consistency	Directness	Precision	Publication bias	Total GRADE rating
Melatonin	0									
Sedatives	0									
Stimulants Rosenberg, et al.[41] Lagarde, et al.[42] Piérard, et al.[43] Beaumont, et al.[44]	4	508 (339) 427 (285) 27 (18) 27 (18) 27 (18)	 A A A A	 No No No No	Low to moderate	¥ / ‡ 1 study explored Armodafinil, the other 3 studies had clinical and methodological homogeneity	‡ (the evidence answers the review question)	¥ / § Effect size and Confidence intervals not reported	‡ / ¥ Pharma industry driven (Armodafinil)	Moderate to High +++
Melatonin Analogues Rajaratnam, et al.[46] Richardson, et al.[47] Zee, et al.[48]	3	635 (480) 39+411 (31+308) 75 (60) 110 (81)	 S S A	 No No No	Low to moderate	‡ Well designed and executed studies	‡ (the evidence answers the review question)	¥	¥ Pharma industry driven	Moderate +++
Glucocorticoids	0									
Antihistamines	0									
TOTAL	7	1143 (819)								

‡ No serious problems
§ Major problems
¥ Some problems

Table 2b: Grading of evidence pharmacological (non RCTs) interventions to manage jet-lag in athletes

Category	Number of studies	Total Participants (intervention group)	Actual (A) or Simulated (S) travel	Athlete specific	Methodological quality	Consistency	Directness	Precision	Publication bias	Total GRADE rating
Melatonin Cardinali, et al.[30] Manfredini, et al.[39]	2	34 (34) 22 (22) 12 (12)	 A A	 Yes Yes	Poor 10/28 9/28	§ Both studies no control group, clinical heterogeneity, methodological heterogeneity	‡ (the evidence answers the review question)	§ Effect size and Confidence intervals not reported, No control group	¥ #	Very low +
Sedatives Reilly, et al.[40]	1	17 (9) 17 (9)	A	Mixed (Gymnasts & support staff in 1 group)	Poor 9/28	§ Mixed Gymnasts & Support staff into 1 group	‡ (the evidence answers the review question)	§ Mixed athletes & non-athletes.	¥ #	Very low +
Stimulants	0									
Melatonin Analogues Nickelsen, et al.[45]	1	8 (8) 8 (8)	S	No	Moderate 19/28	¥ / ‡ Although small sample size, well described methodology & reported results	‡ (the evidence answers the review question)	§ Effect size and Confidence intervals not reported	¥	Low ++
Glucocorticoids	0									
Antihistamines	0									
TOTAL	4	59 (51)								

All athlete specific studies have small sample sizes that may lead to publication bias
‡ No serious problems
§ Major problems
¥ Some problems

Risk of bias, Methodological Quality and Quality of Evidence

Details of the risk of bias and methodological quality assessment are provided in online Supplement C.

NON-PHARMACOLOGICAL INTERVENTIONS: The degree to which RCT studies met the risk of bias criteria varied from moderate to high (Table 1a). The methodological quality of the non-RCTs were poor (Table 1b). The quality of evidence of studies demonstrated no serious problems with directness, but some to major problems with consistency, precision, and publication bias (Table 1a and 1b).

PHARMACOLOGICAL INTERVENTIONS: The degree to which RCTs met the risk of bias criteria varied from low to moderate (Table 2a). The methodological quality of the non-RCTs varied from poor to moderate (Table 2b). The quality of evidence of studies demonstrated no serious problems with directness, a variety of problems with consistency, some to major problems with precision and some problems with publication bias (Table 2a and 2b).

Outcomes of interventions:

NON-PHARMACOLOGICAL INTERVENTIONS:

- *Exercise:* 4 athlete specific studies (2 non-RCT[29-30] and 2 RCT[31-32]) recognised exercise as an intervention. All studies (2 laboratory-based[31-32] and 2 field-based[29-30]), suggested that exercise may help with resynchronisation of the circadian system following long-haul travel, but that timing of the exercise session was important. Conclusion: Judiciously timed exercise may help to recover from jet-lag. (Non-RCT: GRADE⊕OOO; RCT: GRADE⊕OOO)
- *Sleep:* Napping (2 laboratory-based studies[33-34]) and diaphragmatic breathing combined with listening to a sleep training CD (1 field-based study[35]) were explored in 3 athlete specific RCTs. Napping had some positive influence on reducing jet-lag, but different nap durations or schedules were not tested. The combined intervention[35] of breathing and sleep training had no positive outcome. Conclusion: Current evidence from athlete specific laboratory- and field-based studies does not support the use of sleep interventions for reducing jet-lag symptoms, but more specific research is required. (RCT: GRADE⊕⊕OO)
- *Light:* 2 field-based athlete specific studies (1 non-RCT[30] and 1 RCT[36]) investigated the effect of light on recovery from jet-lag. The non-RCT[30] reported faster resynchronisation after light treatment, but was part of a multifactorial intervention also including judiciously timed exercise and melatonin administration , making inferences for a specific intervention difficult. The RCT[36] specifically observed the effect of a light intervention for a small group of female athletes and they reported no benefit of light treatment. Conclusion: Athlete specific studies with light as intervention to reduce jet-lag shows contrasting results. (Non-RCT: GRADE⊕OOO; RCT: GRADE⊕⊕OO)

- *Nutrition:* (mealtime/-composition): No athlete specific studies were identified. The search was then expanded to include healthy populations. A non-RCT[37] and a RCT[38] reported that mealtime may alleviate jet-lag following actual travel. The non-RCT[37] further implied that the meal composition can have an effect. However, both studies had many confounders. Conclusion: Appropriate timing and composition of meals may be a valuable treatment strategy to reduce jet-lag, but athlete specific research is required. (Non-RCT: GRADE⊕OOO; RCT: GRADE⊕OOO)

PHARMACOLOGICAL INTERVENTIONS:

- *Melatonin*: 2 field-based non-RCTs[30,39] explored exogenous melatonin administration as an intervention in athletes. One study[30] claimed that melatonin administration reduced time for resynchronisation of the circadian system following long-haul travel, the other study[39] had mixed results. Neither study had a control group and sample sizes were small. One study had multiple interventions[30] (melatonin, exercise and light exposure). Conclusion: Exogenous melatonin may be important to recover from jet-lag, but larger studies with control groups are required. (Non-RCT: GRADE⊕OOO)
- *Sedatives*: Only 1 non-RCT[40] involved an athlete population and investigated benzodiazepines (temazepam) as a possible intervention following actual travel. In addition, the intervention group was not homogenous and included both athletes and support staff. No athlete specific studies on short-acting hypnotics (e.g. zolpidem, zopiclone) are available. Conclusion: Current evidence on the use of sedatives in the athlete population is limited. (Non-RCT: GRADE⊕OOO)
- *Stimulants:* No athlete specific studies are available. Healthy population studies yielded 4 well designed field-based RCTs.[41-44] One large study[41] specifically examined armodafinil and reported promising results as treatment strategy for alleviation of jet-lag. Three smaller studies[42-44], each using the same methodology and participants reported improved physical performance, resynchronisation of hormonal rhythms and better sleep after timely ingestion of caffeine. Conclusion: Although athlete specific literature is not available, studies in healthy populations show encouraging results to reduce jet-lag symptoms and improve resynchronisation of the circadian system following long-haul travel. (RCT: GRADE⊕⊕⊕O)
- *Melatonin analogues*: We found no athlete specific studies. The search was then expanded to include studies on healthy populations. Three well designed RCTs (2 laboratory-based[46-47] and 1 field-based[48]) were identified investigating tasimelteon (a phase II and phase III study reported in 1 publication[46]) and ramelteon[47-48]. One laboratory-based non-RCT[45] investigated LY15673. Improvement of jet-lag symptoms was reported for all analogues,

but was dose and time dependent. Conclusion: Correct administration of a melatonin analogue may be a valuable treatment strategy to reduce jet-lag, but athlete specific and field-based research is required. (Non-RCT: GRADE⊕⊕OO; RCT: GRADE⊕⊕⊕O)

DISCUSSION

Our systematic review of all available literature found no evidence for non-pharmacological or pharmacological interventions to manage travel fatigue in athletes. When present, the evidence for interventions to manage jet-lag in athletes was of poor quality.

Exercise

Some evidence from laboratory-based studies suggests that exercise may induce phase-shifts comparable in size to bright light[49] and the timing of exercise appears to be critical. A phase response curve (PRCs) to a 1h bout of moderate-intensity exercise was recently established.[50] We identified four studies reporting the positive effect of judiciously timed exercise on adaptation of the circadian system to a new time-zone following a transmeridian flight.[29-32] Only two studies were field-based, involving actual air travel and athletes or trained participants.[29-30] Montaruli et al.[29] reported that the timing of moderate-intensity exercise prior to a 9h flight west, across 6 time-zones from Milan to compete in the New York Marathon, had a significant impact on sleep and adaptation of the circadian system post travel.[29] Specifically, evening training (19:00-21:00) 5 days prior to the flight resulted in improved sleep quality on night 1 and 2 post-flight, compared to morning training (07:00-09:00) and no training. Evening training also resulted in a greater phase-delay (4h) in the circadian system compared to morning training (1h) and control (1h). No significant differences in subjective jet-lag symptoms existed between the groups. Unexplored differences between the groups, particularly light exposure could confound results. The inclusion of a longer post-flight monitoring period and a more reliable marker of circadian phase such as core body temperature or melatonin as opposed to actigraphy would have been more insightful. Cardinali et al.[30] exposed a group of professional male soccer players travelling 12h west from Buenos Aires to Tokyo to a combined intervention of 3mg melatonin, sunlight exposure/avoidance and physical exercise exposure/avoidance to facilitate circadian adaptation.[30] These soccer players had a significantly shorter resynchronisation period (2.13±0.88 days) rather than the expected 6 days after a 12h time-zone change. This study was limited by being observational and was poorly controlled with exercise intensity appearing to be self-selected by participants. Additionally, being a combined intervention, it is difficult to ascertain the contribution of exercise to the circadian adaptation.

Whilst there is no evidence that the effects of light and exercise are additive, appropriate times to conduct exercise for its phase-shifting properties appear to coincide with that of light exposure.[51] Judiciously timed outdoor training sessions could be used by coaches and athletes as a strategy to reduce severity and duration of jet-lag symptoms. Our review returned studies that used vastly different exercise protocols and doses. The effects of physical activity on circadian phase and on jet-lag symptoms require further exploration.

Sleep

Literature supports sleep preservation as an important strategy of jet-lag management.[8] In an athlete specific study, Petit et al.[34] showed that a strategic 20min nap between 08:00-09:00 following a simulated 5h phase-shift, may alleviate jet-lag and result in increased cognitive performance. Petit et al.[33] further conducted a randomised crossover counterbalanced design investigating a simulated 5h phase-advance, and found no changes in physical performance or facilitation of resynchronisation after a 20min post-lunch nap. Athletes, however, did experience an increase in the time to fall asleep on the night after the nap.[33] Novel strategies are often employed to support sleep during travel or to manage jet-lag. One study investigated the effect of a combined intervention (diaphragmatic breathing and listening to a sleep training CD) to improve sleep, mood, and performance, and to reduce jet-lag after a rapid time-zone shift of 10h east (Sweden to Australia). This resulted in no significant findings for any measure of sleep, mood or performance.[35]

No studies have evaluated the impact of sleep timing during travel on the succeeding sleep-wake cycle at the destination[52] and there are no athlete specific studies on sleep hygiene. Sleep hygiene has been shown to help healthy participants recover from travel fatigue following 24h of simulated international travel and although good sleep hygiene may not force a phase-shift of the circadian system, bad sleep habits including incidental exposure to electronic equipment may induce phase-shifts, even in the wrong direction.[53] Research on the sleep patterns of athletes during and following transmeridian travel is limited and needs further investigation. [54-56]

Light

Appropriately timed light exposure/avoidance to facilitate re-entrainment of the circadian system is widely recommended.[7,57-59] To facilitate maximum circadian phase-shift, the duration, intensity and wavelength applied are most critical.[12,60-61] Observing the effect of light treatment in athletes, a RCT of 22 elite female soccer players assessed the efficacy of light intervention to facilitate recovery after a 5h and 8h phase-advance following air travel.[36] Results indicated

insignificant and variable effects of light on physical functioning, diet, gastrointestinal and sleep symptoms. As discussed in the exercise intervention section Cardinali et al.[30] reported that a multifactorial intervention (exercise, light and melatonin) significantly reduced the period (2.13±0.88 days) to resynchronise as opposed to the expected 6 days after a 12h time-zone change. Due to the multifactorial nature of the interventions, the direct impact of light exposure is difficult to elucidate. The lack of evidence for the effective use of light may also be attributed to small sample sizes and inter-individual variability in circadian phase. Although appropriate light exposure/avoidance proved effective in laboratory-based studies, field-based studies are difficult to implement due to the level of control required e.g. avoiding incidental light exposure and practicalities such as sharing of light boxes and timing of exercise sessions.[36] Future research should focus on a multifaceted approach.

Nutrition

When manipulating jet-lag, the master clock (the conductor situated in the suprachiasmatic nucleus) rather than the peripheral clocks (situated in most cells of all tissues) are targeted. Peripheral clocks may not respond to the same interventions that influence the master clock, such as light application, and resynchronisation may be different to that of the master clock.[8] Presumably food will affect peripheral clocks, and nutrition may be a promising intervention to enhance circadian system adjustment.[62-63] Human studies are limited, and we could only find two, non-athlete studies in healthy individuals, that studied the effect of nutrition on circadian phase-shifts.[37-38] In a case control study soldiers were given the option of using the Argonne Diet 4 days before deployment and on returning home (USA to South-Korea). Those using the Argonne Diet reported fewer symptoms of jet-lag.[37] The Argonne Diet consists of 4 days of alternating between feasting (no calorie limit: a protein-rich breakfast and lunch, with a carbohydrate-rich supper) and fasting (<800 kcal/day: fruit for breakfast and lunch, and vegetable soup for supper). The soldiers' interpretation of and adherence to the diet was not supervised and jet-lag symptoms were based on self-report. Restricted feeding or fasting to adjust the body clock may not be appropriate for athletes. The value of fasting remains to be tested and weighed against the potential disadvantage of compromising current, proven sports nutrition recommendations for optimising training, competition performance and recovery.[64] In a RCT, long-haul cabin crew implemented a self-selected meal plan, primarily focused on eating 3 regular meals, synchronised with the light dark cycle, upon arrival. These cabin crew reported fewer symptoms of jet-lag.[38] This dietary strategy aligns well with current, proven sports nutrition recommendations and could be a worthwhile consideration for athletes.

We could not find any human or athlete-specific studies evaluating the effects of hydration during transmeridian travel. Although research on dietary interventions is in its infancy, such interventions are usually easy to implement, have fewer potential side effects, are relatively cheap and more acceptable to athletes.[14]

Melatonin

A previous Cochrane Review reported melatonin to be effective and safe in adult travellers.[16] Currently, there is little or no evidence supporting the ingestion of exogenous melatonin to accelerate resynchronisation in athletes. We found two single-group field-based studies, both with small sample sizes and no control groups.[30,39] Cardinali et al.[30] reported a significantly shorter period (2.13±0.88 days) of resynchronisation in contrast to the expected 6 days after a 12h time-zone change using combined interventions (3mg melatonin, sunlight exposure/avoidance and physical exercise exposure/avoidance). Manfredini et al.[39] reported widely differing effects of melatonin ingestion on the circadian system. Although laboratory studies have showed that melatonin can induce a phase-shift,[65-66] a study in a healthy population that travelled east across 10 time-zones indicated that 5mg of melatonin ingested at local bedtime had neither a chronobiotic nor a hypnotic effect.[67]

Phase-shifting effects of light can be partially counteracted by appropriately timed exogenous melatonin,[68] and an additive effect on phase-shift can occur when correctly timed.[69] There is however limited evidence that exogenous melatonin can enhance resynchronisation of the circadian system in athletes following travel.[8,15,67] Purity and dose accuracy are often not regulated and several countries have usage restrictions.[70]

Sedatives

We could only find one athlete specific case control study, including gymnasts and support staff who ingested benzodiazepines.[40] Participants in the intervention group reported fewer jet-lag symptoms and improved mean sleep quality from day 1 to day 5. Most studies investigating the use of sedatives to mitigate jet-lag and travel fatigue in healthy populations only managed to present low quality evidence.[40] Limited research shows that benzodiazepines can accelerate re-entrainment of the circadian system (chronobiotic effect) and normalise markers of sleep-wake homeostasis (hypnotic effect).[71] Midazolam has been shown to significantly lengthen sleep after eastward travel.[72] Zopiclone has been shown to accelerate readjustment of the rest/activity rhythm and normalise the phase relationship between sleep and the temperature rhythm after westward travel,[73] as well as increase sleep duration and quality.[74] Sedatives may offer an

alternative solution to alleviating jet-lag symptoms by inducing sleep upon arrival to normalise circadian rhythms to the arrival time-zone. Strictly speaking, sedatives reduce jet-lag symptoms by inducing sleep rather than via a chronobiotic effect.[40,75-77] Sedatives may have side effects including amnesia, confusion,[78] and immobility which, in restricted spaces such as aircraft, increase the risk of deep vein thrombosis.[79] Given the conflicting evidence for the efficacy of sedatives, coupled with the risk of abuse and long-term harm, we are hesitant to recommend sedatives for regular jet-lag management.

Stimulants

In this review, we could only find studies investigating the effects of the stimulants, armodafinil and caffeine to manage jet-lag, in healthy non-athletes. For armodafinil, a double-blind RCT revealed increased alertness after 150mg/day following 6h of eastbound travel in travellers with a history of jet-lag.[41] In a between-subject study, caffeine, depressed cortisol release, increased alertness, and enhanced physical performance. Lagarde et al.[42] found that participants who ingested 300mg slow release caffeine in the local morning for 5 days, after 7h of eastward travel, had stronger static grip-strength performance but no improvement in dynamic jumping tasks when compared to a control group. In two other RCTs, U.S. military Air Force reservists who ingested 300mg of slow release caffeine had lower cortisol concentrations[43] and improved alertness, but poorer sleep quality.[44] These results suggest that caffeine may have undesirable effects on athletes. Although caffeine is generally not seen as a chronobiotic and is used mainly to improve alertness at the destination time-zone, a recent study demonstrated a phase-delay in the circadian system following caffeine consumption.[80] The topic of stimulants is contentious due to most being performance enhancing.[81] Further research is required to determine appropriate timing and dose and implication of usage in athlete populations.

Melatonin analogues

Melatonin analogues were initially developed to treat sleep disorders not related to jet-lag. We could not find any studies specifically on athletes, and included studies on healthy populations. In a large phase II and III double-blind RCT,[46] where 450 healthy volunteers were subjected to a 5h phase advance, results showed that Tasimelteon initiated a phase-shift as measured by melatonin onset, as well as improved subjective and objective sleep variables. Tasimelteon also seems to have the ability to treat transient insomnia associated with jet-lag.[46] Another double-blind RCT[48] (110 heathy volunteers) investigated the effects of different dosages of Ramelteon on improving sleep onset problems associated with jet-lag, after crossing 5 time-zones east. Only the 1mg dose, not the 4mg and 8mg, reduced the time to sleep onset. The 4mg dose

improved daytime alertness, concentration, quality of sleep and ease of awakening. All dosages however, caused a significant reduction in the immediate memory recall test, and no significant phase-shift.[48] Conflicting results were reported in a double-blind RCT[47] (75 heathy volunteers) on Ramelteon where the 1, 2 and 4mg dosages significantly advanced the phase of circadian rhythm following a 5h simulated phase-advance with no improvement in sleep.[47] In a small (8 healthy volunteers) double-blind non-RCT[45] 5mg of LY156735 significantly shifted the circadian system and also enhanced daytime performance after a 9h simulated phase-advance. It seems as if melatonin analogues have chronobiotic effects in a healthy population when tested in a simulated environment, however more research is needed to clarify the efficacy in actual jet-lag in athlete populations.

Glucocorticoids and Antihistamines

No relevant studies on either glucocorticoids or antihistamines were found. Given the fact that athletes may consume these products to overcome jet-lag, available information on the topic is discussed. Endogenous glucocorticoids (produced by the hypothalamus-pituitary-adrenal axis), are tightly linked with circadian rhythms,[82] and are believed to prepare the body for physical activity. Exogenous glucocorticoids are used to treat a range of conditions, especially those causing systemic inflammatory responses.[83] Although not investigating phase shifts, one study in humans[84] found that glucocorticoids effectively realigned circadian rhythms after 40 hours of sleep deprivation. Given the potential side effects and being listed as a banned substance,[81] we do not recommend the use of glucocorticoids for overcoming jet-lag in travelling athletes until more large-scale RTCs have been conducted.

Antihistamines counter the action of histamine, a compound in the body that causes itching and flushing of the skin such as in allergic and inflammatory reactions. First generation antihistamines are able to cross the blood-brain barrier (BBB) causing sedation, with drowsiness listed as a potential side effect.[85] Second and third generation antihistamines are not effective for sleep as they are unable to pass through the BBB. Whilst effective at inducing sleep, no study has examined the efficacy or effectiveness of using antihistamines for overcoming jet-lag, making recommendations difficult. Most people quickly develop a tolerance to the sedative/sleep inducing effects of antihistamines.[86-87] Therefore we do not recommend the use of first-generation antihistamines for overcoming jet-lag or travel fatigue.

Tolerability and side effect profile of interventions

As part of management, users should know about the tolerability and possible adverse events of any intervention. Athletes in particular need to adhere to the most recent World Anti-Doping Agency (WADA)[81] regulations for all pharmacological interventions. The efficacy and side-effects of interventions may vary for different users, who may also experience jet-lag differently. Most of the articles that we reviewed did not mention possible side effects except in clinical trial studies[45-48] and few studies eluded to acceptability of the intervention to the participants. To complicate matters, athletes are usually reticent to change or add to their routines for research purposes.

Strengths and limitations of this review

This is the first systematic review on the management strategies for travel fatigue and jet-lag in athletes. Athletes may differ from the average healthy population due to higher fitness and motivation levels, potentially safeguarding them from travel demands. All athlete specific studies had small sample sizes and represented different sporting codes (e.g. marathon runners, soccer players, swimmers), complicating the interpretation of results. Vast differences in methodological design, subject demographics (age and sex), and outcome measures existed within and between laboratory- and field-based studies, complicating comparison. Most studies included a varied range of subjective (e.g. sleep diaries, subjective questionnaires, visual analogue scale) and objective (e.g. actigraphy, polysomnograms, grip-strength) outcome measures further complicating comparison. Studies also used different methods to determine the circadian phase, and subsequent timing of interventions. Some studies used dim light melatonin onset, others used habitual sleep time, core body temperature minimum, plasma melatonin or urinary melatonin metabolite 6-sulphatoxymelatonin as demonstrated in online Supplement B. Future studies should aim to standardise outcome measures and circadian phase determination for meaningful comparisons between studies and to enable conduction of a meta-analysis. A strength of our study is that we followed a systematic approach and although we could not perform a meta-analysis we made use of the well validated GRADE system.

CONCLUSION

Well-designed studies assessing interventions for managing travel fatigue and jet-lag in athletes in actual travel scenarios are limited. We systematically reviewed the literature and found no evidence related to travel fatigue. We could only find low-quality evidence of successful interventions for managing jet-lag in athletes. Some interventions only included healthy participants (nutrition, stimulants and melatonin analogues) and require testing in athlete populations. Current

recommendations for managing jet-lag appear to be based on opinions, collective experience and results from laboratory-based studies on non-athletes. Comparison of laboratory- and field-based studies remains questionable with difficulties in controlling incidental light exposure and determining circadian phase in the field. We included two non-pharmacological interventions (exercise and sleep) where both laboratory- and field-based interventions were reported. For both interventions the laboratory- and field-based studies showed similar outcomes, but the laboratory-based studies were limited in their design and these findings should be interpreted with caution. Symptoms of travel fatigue and jet-lag are entwined and focussing only on circadian re-alignment following transmeridian travel may not be sufficient to safeguard well-being. Future studies should focus on multifaceted strategies to overcome these challenges and aim to find a balance between the efficacy and practicality of interventions in well-designed field-based studies using athlete populations.

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Acknowledgements The authors would like to express their gratitude to Mrs Brenda Weder for editing, Mrs Madeleen Scheepers for upload of publications to Endnote library and to Dr Cheryl Tosh for grammar and language editing.

Contributors CJvR: responsible for the overall idea for this review article, content concept, manuscript planning, search strategy, search and manuscript (first draft), manuscript editing. AJvR: manuscript (first draft), content contribution, manuscript planning, search strategy, manuscript editing. All authors and co-authors searched library bases, identified relevant studies, reviewed studies, selected eligible studies, wrote the article with contributing input, manuscript editing. All authors revised and approved the final draft.

Funding The authors did not receive any grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

did not receive any grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

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