Accepted for publication in the *British Journal of Sports Medicine* on the 15th August 2023

Editorial:

Reversing the state of arousal and accelerating sleep onset: pharmacological and non-pharmacological manipulation of sleep in athletes

Charles R Pedlar[1,2,3] Orcid: 0000-0002-3075-9101

Neil Stanley[4]

Shona Halson[5] Orcid: 0000-0002-1047-3878

Luke Edinborough[1,6] Orcid: 0000-0002-2806-9478

Phoebe Law[2]

Mike Harrison[7]

Paul Catterson[8]

[1]Faculty of Sport, Allied Health and Performance Sciences, St Mary's University, Twickenham, UK

[2]Orreco Ltd. Business Innovation Unit, University of Galway, Ireland.

[3]Institute of Sport, Exercise and Health, Division of Surgery and Interventional Science, UCL, London, UK

[4]Independent Sleep Expert, UK

[5]Australian Catholic University, Banyo, Queensland, Australia

[6]Southampton Football Club, Southampton, UK,

[7]Chelsea Women Football Club, London, UK

[8]Newcastle United Football Club, Newcastle, UK

Word count: 826 (excluding table)

Competing interests: None

Contributorship: CRP instigated the editorial, all authors contributed to writing and editing the article.

Acknowledgements: None

Funding, grant/award info, name and numbers: None

Ethical approval information, institution and number(s): Not applicable

Introduction

The necessity of sufficient sleep for health and sustained high performance in athletes is increasingly recognised. There are frequently scenarios where an athlete's *opportunity* for sleep (e.g. travelling East across several time zones, sports fixture congestion) and *propensity* for sleep (e.g. over-arousal, anxiety, insomnia, circadian rhythm shifts) may compromise sleep quality and/or quantity(1). For example, transitioning from a highly stimulating night game (often purposefully accentuated with caffeine) to entering a full night of good quality sleep can be highly problematic for athletes, resulting in insomnia. The demand for quick, effective recovery including restful sleep prior to the next training session or game, is top-of-mind for athletes and leads their desire to optimise the time available for recovery. At these times, using a pharmacological intervention can provide a potential solution, however, the risks should also be considered against the benefits. For example, the potential impact on performance, and the risk of an athlete forming a habit.

Guidance on sleep medications in sports medicine is limited (2), and the use of sleep agents was not covered by a recent sleep consensus paper (1). The purpose of this commentary is to highlight key considerations in the use of pharmacological and non-pharmacological strategies to optimize sleep in athletes.

Categories of sleeping medications and mechanism of action

Table 1 provides an overview of the categories of sleeping pills and their mechanism of action (see Supplementary **Table S1** for fully referenced table). Melatonin can be considered the safest option, followed by Z-drugs and then Benzodiazepines (BNZs). Anti-depressants and anti-histamines can also have a sedative effect, albeit secondary to the primary aim of their therapy, and these are included for completeness.

Risks

Dependency may develop if the athlete feels that taking a pill is the only way to guarantee sleep. This can become a self-fulfilling prophecy: if they don't take a pill, then they will worry about their ability to sleep and this worry results in poor sleep confirming their belief in the power of the 'pill'(3). It should be noted that no long-term studies of sleeping pill use and mental or physical health in athletes have been conducted. Achieving better sleep via non-pharmacological strategies can remove or reduce these risks while also providing

athletes with an important life-skill, and it could be argued that only when these methods have been attempted, should pharmacological approaches be considered.

The impact of sleep medications on laboratory measured sleep architecture has been described mainly in insomnia patients. Here, melatonin generally increases total sleep and slow wave sleep (stage 3) duration, whereas BNZs generally increase non-slow wave sleep (stages 1 and 2) and decrease slow wave sleep (4, 5). Whether sleep is more restorative overall with any intevention is not easy to quantify objectively and is dependant largely on daytime performance and perception of efficacy.

Performance impact

Studies are sparce examining the impact of sleeping pills on sports performance in athletes, however, performance effects of melatonin have been reported. For example, in male international soccer players, morning melatonin ingestion caused some short term negative performance effects (medicine ball throw and hand-grip strength) but other variables were not impacted and all tests were normalised by the evening (6). In male healthy adolescents, sleep was improved following strenuous evening exercise followed by melatonin ingestion and morning performance was unaffected or improved (7). No performance studies have been conducted in athletes with Z-drugs or BNZs and apparently no data at all have been published in female athletes. Research in non-athletes generally reports inconsistent or negative effects on both BNZs and Z-drugs on physical and cognitive performance.

Non-pharmacological sleep-enhancing strategies

The National Institute of Health and Care Excellence (NICE) guidelines state that for adults of all ages, the first line of treatment for insomnia is Cognitive Behavioural Therapy for Insomnia (CBTi), delivered either face-to-face or virtually (8). The American Academy of Sleep Medicine and the European Sleep Research Society also make the same recommendation and indeed extensive literature demonstrates that CBTi is as effective as hypnotics in treating insomnia. Moreover, its effects can persist for at least one year after completing therapy (9). However, while CBTi would likely be effective for improving sleep overall, it is not an effective short-term treatment and is not a practical solution in high pressure situations that occur in sport. Specific treatments may also be applicable for sleep problems such as continuous positive airway pressure devices for the treatment of obstructive sleep apnoea, which may be particularly prevalent in contact sports (10). Other non-pharmacological strategies for enhancing sleep including nutritional, psychological and

behavioural approaches are described in **Figure 1** (see Supplementary **Figure S1** for an expanded and referenced table).

Conclusions and future directions

Although there are many unknowns, the risk of habit forming appears to be the most prominent concern with pharmacological intervention. Greater emphasis on non-pharmacological strategies and sleep education should be a priority, particularly for younger athletes where learning to manage sleep is an important life-skill. Given the unknowns, judicious use of sleeping pills appears to be sensible and a 'Keeping Score' approach as recently advocated for non-steroidal anti-inflammatory drug use in football may also be applicable (11). Further research is needed to understand the patterns of use, the efficacy, and long term impact of pharmacological and non-pharmacological sleep interventions in male and female athletes.

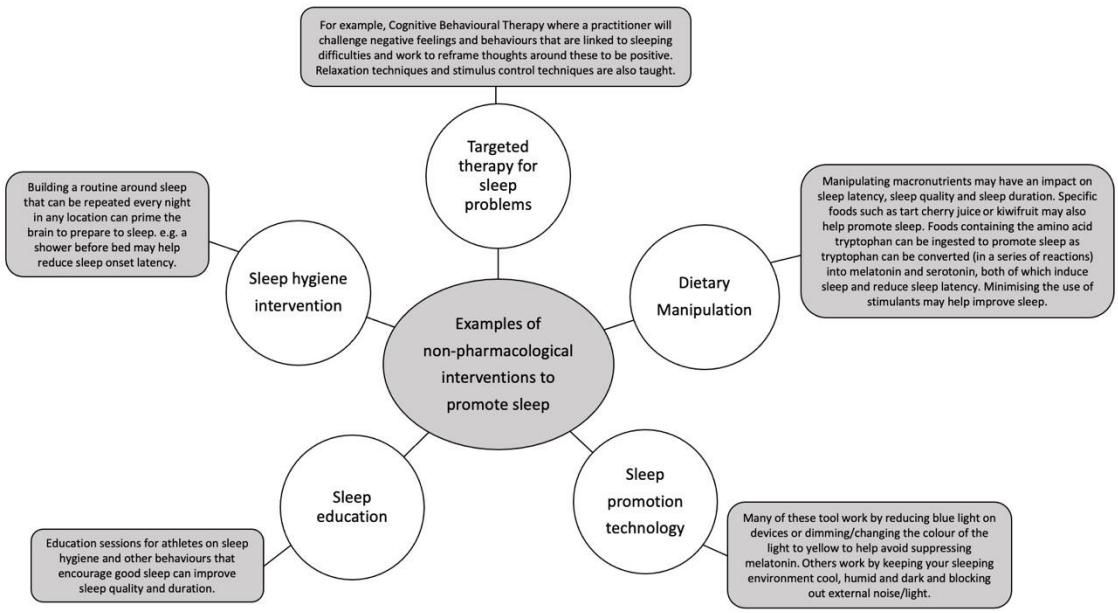

Figure captions:

Figure 1: Examples of non-pharmacological interventions to promote sleep

Accepted for publication in the *British Journal of Sports Medicine* on the 15th August 2023

Table 1: Pharmacological interventions to promote sleep. GABA = gamma-aminobutyric acid; BNZ = benzodiazepines; Cl^- = chloride ion; TCAs = Tricyclic antidepressants

	Description and mechanism of action	Performance effects and side effects	Other considerations?
Melatonin	Melatonin boosts the action of endogenous melatonin by lowering core temperature through vasodilation and by acting at the suprachiasmatic nucleus of the hypothalamus to signal the brain to sleep. Considered natural, and in many countries, is freely available over the counter; however, elsewhere it is only available on prescription. There is little evidence that melatonin improves objective sleep in otherwise healthy adults.	Strength, balance, and proprioception are likely impaired shortly after ingestion, however, performances the morning after taking an evening dose of melatonin are unlikely to be compromised. Side effects include headaches, increased risk of infection; pain; however, some data suggests that melatonin may have largely *beneficial* effects against viral infections.	When bought over the counter (and not prescribed) there is an increased risk of contamination and accidental doping violations. Considerable variation may exist in the amount of melatonin present in these products.
Z-drugs	These are non-benzodiazepine sedative-hypnotic drugs e.g. zopiclone and zolpidem, also referred to as 'Z-drugs'. They act in a similar way to benzodiazepines by targeting GABA receptors in the brain to reduce excitability and have an anxiolytic effect. They are considered safer than BNZs due to their short duration of action (varies by drug from 1 – 6 hours), meaning there is less chance of hangover upon waking. However, this also means that while they can put you to sleep faster than a placebo, their effects can wear off after 4-5 hours, meaning they cannot guarantee a whole night's sleep.	Immediate effects can include impaired attention, memory, decision making and coordination. However, minimal performance affects are reported after a full night of sleep (8 hours plus). Side effects: Use can exacerbate/ cause symptoms of gastroesophageal reflux disease. Hallucinations and amnesia are also commonly reported side-effects. Z-drugs also leave a metallic distaste in the mouth. Dependency is also a significant risk.	Often have a short half-life so cannot guarantee a whole night of uninterrupted sleep.
Benzodiazepines	BNZs are a class of drugs, some of which are used in treating anxiety; others are more suited to treating sleep problems. Here we refer to hypnotic BNZs as opposed to anxiolytic BNZs. Some authors caution against the use of BNZs in athletes and cite the risks of addiction and negative performance and safety outcomes. BNZs act on GABA receptors to activate Cl^- channels to open and an influx of Cl^- into neurons. This inhibits action potential firing in the neurons as they become more negatively charged, leading to a sedative effect.	Conflicting studies, some suggest use is likely to cause subsequent lethargy and drowziness, they may also reduce motor coordination, peak power and negatively affect decision-making. However, other studies have found no negative impact of an acute benzodiazepine dose on performance. Side effects: The duration of action of BNZs can often exceed the time in bed of the patient leading to cognitive and psychomotor impairment in the morning.	High risk of dependency and substance abuse. Chronic use can cause tolerance and so require increased dosages to give a sedative effect. Different benzodiazepines have varying half-lives and this will impact the duration and severity of side effects.
Anti-depressants	Trazadone: Multifunctional drug that can serve as both an antidepressant or hypnotic. Lower doses have a hypnotic effect by blocking histamine receptors (which reduces the firing of histaminergic neurons to promote sleep) and α1adrenergic receptors. Higher doses increase the availability of serotonin by inhibiting its uptake in the brain.	Likely to cause sleepiness the day after ingestion.	Anti-depressants may impact upon physical performance although findings are inconsistent between studies. No studies have been conducted in athletes.
	TCAs: Older type of antidepressant. Acts on several receptors and this action varies depending on the drug used. Most TCAs will prevent the uptake of serotonin and noradrenaline and block muscarinic and histaminergic receptors to cause a sedative effect and help the onset of sleep.	Can increase heart rate and increase the risk of cardiovascular events in those with a pre-existing condition (known or unknown). Some TCAs are also associated with weight gain.	
Sedating anti-histamines	Histamine is considered an 'alert' signal in the brain and histamine receptor antagonists can promote sleep although there are few studies in humans.	First generation antihistamines cross the blood-brain barrier and cause considerable sedation, impacting on cognitive tasks, and persisting for more than 1 day. The second generation antihistamines cause little or no sedation. There is a negative effect of blocking histamine on endurance cycling performance.	There are marked individual differences in sensitivity to the sedating effects of antihistamines.

References

1. **Walsh NP, Halson SL, Sargent C, Roach GD, Nédélec M, Gupta L, Leeder J, Fullagar HH, Coutts AJ, Edwards BJ, Pullinger SA, Robertson CM, Burniston JG, Lastella M, Le Meur Y, Hausswirth C, Bender AM, Grandner MA, and Samuels CH**. Sleep and the athlete: narrative review and 2021 expert consensus recommendations. *British Journal of Sports Medicine* 55: 356-368, 2021.
2. **Baird MB, and Asif IM**. Medications for Sleep Schedule Adjustments in Athletes. *Sports Health* 10: 35-39, 2018.
3. **Lennane KJ**. Treatment of benzodiazepine dependence. *Medical Journal of Australia* 144: 594-597, 1986.
4. **Zisapel N**. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *Br J Pharmacol* 175: 3190-3199, 2018.
5. **de Mendonça FMR, de Mendonça G, Souza LC, Galvão LP, Paiva HS, de Azevedo Marques Périco C, Torales J, Ventriglio A, Castaldelli-Maia JM, and Sousa Martins Silva A**. Benzodiazepines and Sleep Architecture: A Systematic Review. *CNS Neurol Disord Drug Targets* 22: 172-179, 2023.
6. **Ghattassi K, Hammouda O, Graja A, Boudhina N, Chtourou H, Hadhri S, Driss T, and Souissi N**. Morning melatonin ingestion and diurnal variation of short-term maximal performances in soccer players. *Physiol Int* 103: 94-104, 2016.
7. **Cheikh M, Hammouda O, Gaamouri N, Driss T, Chamari K, Cheikh RB, Dogui M, and Souissi N**. Melatonin ingestion after exhaustive late-evening exercise improves sleep quality and quantity, and short-term performances in teenage athletes. *Chronobiol Int* 35: 1281-1293, 2018.
8. **NICE**. Insomnia: Management. National Institute for Health and Care Excellence. https://cks.nice.org.uk/topics/insomnia/management/. [5 December, 2022].
9. **Jacobs GD, Pace-Schott EF, Stickgold R, and Otto MW**. Cognitive behavior therapy and pharmacotherapy for insomnia: a randomized controlled trial and direct comparison. *Arch Intern Med* 164: 1888-1896, 2004.
10. **Howarth NE, White AJ, Pearce AJ, Nowinski C, Cantu R, Ji C, and Miller MA**. Obstructive Sport Apnea (OSA) and contact sports: A systematic review and meta-analysis. *Sleep Epidemiology* 2: 100036, 2022.
11. **Rosenbloom C, Okholm Kryger K, Carmody S, and Broman D**. Non-steroidal anti-inflammatory drugs in football - a "Keeping SCORE" approach to judicious use. *Sci Med Footb* 1-5, 2022.