Medications for Sleep Schedule Adjustments in Athletes

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Context: Sleep schedule adjustments are common requirements of modern-day athletes. Many nonpharmacologic and pharmacologic strategies exist to facilitate circadian rhythm shifts to maximize alertness and performance during competition. This review summarizes the evidence for commonly used pharmacologic agents and presents recommendations for the sports medicine provider.

Evidence Acquisition: MEDLINE searches were performed using the following keywords: *sleep aids, circadian rhythm adjustment, athletes and sleep, caffeine and sports, melatonin and athletes*, and *sleep aids and sports*. Pertinent articles were extracted and discussed.

Study Design: Clinical review.

Level of Evidence: Level 2.

Results: There are very few available studies investigating pharmacologic sleep aids in athletes. Data from studies involving shift workers and airline personnel are more abundant and were used to formulate recommendations and conclusions.

Conclusion: Melatonin, caffeine, and nonbenzodiazepine sleep aids have a role in facilitating sleep schedule changes in athletes and maximizing sports performance through sleep enhancement.

Keywords: sleep aids; caffeine; melatonin; circadian rhythm; flight dysrhythmia

Adjusting one's circadian rhythm is a common consideration for many modern athletes. Prior research has demonstrated the importance of time of day and circadian physiology on cognitive and physical performance.[40] For an athlete's given circadian rhythm, peak performance occurs in the late afternoon with a nadir in the early morning, approximately 3 AM.[8] Common requirements for competitive athletes include frequent travel and unpredictable scheduling, which challenge an athlete's ability to maximize alertness and performance potential during competition.

Flight dysrhythmia, or *jet lag*, associated with traveling is the most recognized phenomenon requiring sleep schedule alterations. This condition refers to the desynchrony between the external light-dark cycle and the internal circadian rhythm that occurs with travel over more than 2 time zones. Common symptoms include malaise, diminished mood, sleep disturbance, and gastrointestinal symptoms (nausea, change in bowel habits, appetite changes). Although variable, time to resynchronization is estimated at 1.0 to 1.5 days per time zone traversed, with westward travel being associated with shorter recovery times.[16] Many athletes are unable to take the time to fully acclimatize. For this reason, flight dysrhythmia has been associated with decreased performance levels in elite athletes.[44]

Less dramatic changes in competition times may also adversely affect performance. A 2013 study on the performance of professional American football teams demonstrated that a time change of only 3 hours had significant effects on performance and outcomes.[44] This study investigated 40 years of evening and daytime games between east coast and west coast teams. The investigators demonstrated a consistent advantage for west coast teams over east coast teams for evening games, with no significant advantage found for daytime games. These data, along with preexisting publications, suggest that competition scheduling, often influenced by media and other societal demands, can significantly influence performance.[45]

Multiple strategies have been adopted by athletes and nonathletes to modify circadian rhythms and sleep schedules. Sleep schedule changes in 1-hour increments can effectively adjust circadian rhythms without compromising performance.[10] Short naps of 20 to 30 minutes have also been shown to assist

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in adjustment to a new time zone[11] and improve sprint performance.[49]

Adjusting exercise schedules with the aim to control the time of peak performance has been attempted as well. Investigators have encountered confounding factors, preventing definitive conclusions.[3] Overall, however, studies suggest that adjustment in training schedules plays a role in modifying sleep schedules and maximizing performance.[29,51]

Light exposure, especially bright light exposure, clearly seems to play an important role in circadian rhythm adjustment. Studies in shift workers have also demonstrated improvement in fatigue levels, attention, and overall job performance.[39,43] Paul et al[34] studied the optimum timing for bright light exposure. For individuals with a normal sleep schedule of 23:00 to 07:00 hours, they demonstrated that exposure to bright light initiated between 06:00 and 08:00 hours facilitated the greatest circadian phase advancement (earlier awakening and sleep initiation), with the greatest delays (later sleep initiation and awakening) seen with bright light exposure between 02:00 and 03:00 hours.[34] While there has not been adequate study in athletes, bright light exposure may be used to assist with sleep phase adjustment to help maximize alertness at competition time.

Unfortunately, available publications on modalities for circadian rhythm modification have several limitations with regard to athletes. This is predominantly because of the vast majority of studies involving nonathletic populations. The practical limitations of many nonpharmacologic strategies are significant issues as well. Changes in sleep schedule, exercise schedules, and light exposure are incremental treatments resulting in gradual circadian rhythm modification. Societal demands from the media and other governing bodies often require modern athletes to make rapid adjustments for which these modalities are not intended. Consequently, athletes and their advisors often turn to medications to try to modify sleep schedules or at least minimize negative effects of circadian rhythm disruption. Historically, a large variety of supplements and medications have been used and studied. Over the past 3 decades, however, melatonin, caffeine, and nonbenzodiazepine sedative-hypnotics have come into favor for athletes and investigators due to accessibility, effectiveness, and side effect profiles. The remainder of this review addresses the effectiveness of these common pharmacologic treatments. While other sleep aids are available, such as trazadone, tricyclic antidepressants, and benzodiazepines, they are not discussed in detail due to lack of available evidence and/or side effect profile, including addiction potential.

MELATONIN

Melatonin remains one of the most common sleep aids recommended by physicians because of its favorable safety profile and effectiveness. Stored and secreted by the pineal gland, melatonin is an endogenous hormone that promotes sleep through vasodilation and a decrease in body temperature. It is released approximately 2 hours prior to normal bedtime when light levels are low and usually reaches its nadir 12 hours later during maximum light exposure, maximum body temperature, and peak alertness.[52] The American Academy of Sleep Medicine endorses exogenous melatonin use to combat the effects of time shifts on sleep schedules.[38] For sleep phase delays (eg, westward travel), they recommend use late in the sleep phase or in the early morning. For sleep phase advances (eg, eastward travel), administration is recommended in the evening hours. Side effects include hypotension,[30] gastrointestinal distress, and insulin insensitivity.[27] Doses range from 0.5 to 5 mg, with short- and extended-release formulations available. Immediate-release formulations seem to perform better, with higher doses (5 mg) more effective at inducing sleep.[17]

The effectiveness of melatonin, both immediate- and sustained-release forms, for sleep phase shifts has been demonstrated in numerous studies,[33,37] justifying its acceptance by national and international sleep societies. It has also been shown to have synergistic effects when used in combination with bright light therapy.[32] With regard to athletic performance, there have been some conflicting studies historically. More recent publications recognize that there likely is a negative effect on performance immediately after taking melatonin, but that this effect is very short-lived.[2]

The most recent study by Ghattassi et al[14] in 2016 investigated melatonin's effect on cognitive and physical performance by a group of 12 Tunisian soccer players. In this randomized, placebo-controlled trial, participants took 5 mg of immediate-release melatonin or placebo in the early morning and underwent cognitive and physical testing sessions at 08:00, 12:00, and 16:00 hours. There was a significant decrease in physical performance tests in the melatonin group at 08:00, with no differences identified at 12:00 or 16:00 hours. The authors concluded that morning melatonin ingestion has no unfavorable effects on cognitive and physical performance in well-trained soccer players.

An older study in 2001 by Atkinson et al[1] investigated potential performance effects in morning competitions by athletes ingesting melatonin the night before. Also, in a small, double-blind, placebo-controlled trial, the authors compared 4-km time-trial times on a cycle ergometer, grip strength, and subjective sleep quality in the morning after nocturnal ingestion of 5 mg of immediate-release melatonin. They concluded that any significant effect on morning performance was unlikely.

Although there are few other well-designed studies regarding use of melatonin in athletes, these publications, along with the existing literature, indicate that well-timed use of melatonin is safe and effective in altering sleep schedules in athletes, preventing and treating jet lag without compromising performance. It has been appropriately noted, however, that exogenous melatonin is considered a supplement by the US Food and Drug Administration and thus not subject to the strict quality control standards of prescription medications.[16] Thus, contaminated formulations could risk side effects and violation of antidoping policies. An alternative prescription medication, ramelteon, is an example of a melatonin receptor agonist used predominantly for insomnia that seems to have similar effects on circadian disturbances.[26,36] While ramelteon has not been studied in athletes, it may be a reasonable option for those

weary of the potential contamination of exogenous melatonin. Ramelteon is significantly more expensive, however, costing approximately $12.50 per pill versus $0.10 for melatonin.

CAFFEINE

Caffeine is the only stimulant available to athletes that is not banned or heavily restricted by the World Anti-Doping Agency. Use is allowed at low to moderate doses without a therapeutic use exemption.[46] Multiple investigations have confirmed caffeine's utility as an ergogenic aid for endurance[13] and sprint events[23] as well as resistance training.[6] Thus, it is widely used by athletes at all levels. Recent studies, however, have indicated a deleterious effect of caffeine on sleep-onset latency, sleep efficiency, total sleep time, and duration of rapid eye movement (REM) sleep when taken for late afternoon or evening competitions.[28]

There has not been significant investigation into the ability of caffeine to assist with adjustment of sleep schedules in athletes specifically, but several older studies are applicable and informative. A study in US Air Force reservists by Piérard et al[35] demonstrated improved synchronization of hormonal rhythms (melatonin and cortisol levels) with caffeine use in conjunction with melatonin use after a 7-hour eastbound flight from the United States to France. Clinical parameters (alertness, performance levels, adverse effects) were not included in this study, however. Another study in 2004 demonstrated improvement of daytime sleepiness after transmeridian travel with the initiation of low-dose caffeine treatment beginning the day after arrival.[4] In 2006, Schweitzer et al[42] also demonstrated improved performance and alertness of night shift workers with caffeine use. It is currently unknown whether these benefits vary depending on caffeine tolerance, as this was not adjusted for in any of the available studies. These data, along with previously cited studies, suggest that early daytime caffeine use likely facilitates hormonal re-entrainment while improving alertness and performance. These are certainly promising qualities for athletes who lack adequate time to fully resynchronize after travel or significant schedule adjustments. Further study involving athletes is needed.

It should be noted that caffeine, like melatonin, comes in many forms. Over-the-counter supplements and commercial energy beverages are not fully regulated and may contain restricted supplements, which may result in disqualification from participation or adverse reactions. Such unregulated formulations may contain high levels of caffeine, resulting in urine and blood levels that exceed permitted levels, unbeknownst to the athlete. Several studies have associated commercial energy drinks with adverse cardiovascular changes, including increased blood pressure, prolonged QT intervals, arrhythmias, and cardiac arrest.[18] Caution should be used regarding these products.

SEDATIVE-HYPNOTICS

In addition to melatonin, several sleep aids are available to facilitate sleep phase advancement. Nonbenzodiazepine sedative-hypnotics are the most commonly used medications and are often categorized by half-life. Long-acting zopiclone (brand names Zimovane and Imovane [unavailable in the United States]) and eszopiclone (Lunesta [half-life, 6 hours]), short-acting zolpidem (Ambien [half-life, 2.5 hours]), and ultra-short-acting zaleplon (Sonata [half-life, 1 hour]) are commonly used formulations. True benzodiazepines are typically discouraged in athletes because of high abuse potential and subsequent dependence. Moreover, available studies indicate that the effectiveness and side effect profiles seem comparable between benzodiazepines and nonbenzodiazepine sleep aids, as discussed in a 2004 meta-analysis by Dündar et al.[9] Given risk of abuse and the fact that effective alternatives are readily available, nonbenzodiazepines are preferred.

Unfortunately, there are no well-designed studies on the effect of sedative-hypnotics on circadian rhythm adjustment in athletes; however, several studies involving travel in nonathletes are worth discussion. In 2004, Paul et al[31] demonstrated that treatment with zopiclone and melatonin equally improved overall sleep quality, lengthened sleep duration, and reduced sleep latency and awakenings in aircrews on transatlantic flights. Jamieson et al,[21] in 2001, found that a single dose of 10-mg zolpidem facilitated sleep parameters in seasoned travelers on transmeridian flights covering 5 to 9 time zones without significant adverse events. Their data support prior studies demonstrating overall improvement in sleep parameters for nonbenzodiazepine and benzodiazepine sleep aids alike. While the effect of overall sleep improvement during travel on athletic performance is unknown, poor sleep does negatively affect attention, emotional state, learning, and memory,[50] all of which are vital to athletic performance.

A small study in 2000 on the benzodiazepine temazepam by Buxton et al[5] demonstrated advantageous effects on circadian rhythm markers (melatonin and cortisol) in participants undergoing an 8-hour phase delay. Benefits were seen in normalization of sleep onset and awakening as well as the ratios of REM, non-REM, and slow-wave sleep.[5] These interesting laboratory findings speak to the potential utility of sedative-hypnotics for entrainment in addition to sleep enhancement.

As with all prescribed medications, the potential for adverse effects must be considered. Sleep aids do have immediate effects when taken without sleep, including impairments in attention, psychomotor tasks, and memory.[47] As their pharmacokinetics would suggest, these effects seem to be most pronounced with long-acting formulations (zopiclone), less with zolpidem, and minimally with zaleplon.[7,25,48] After 8 hours of rest, however, no significant adverse effects on the above performance measures have been shown for zolpidem or zaleplon.[19,20] For these reasons, sedative-hypnotic sleep aids are not recommended unless a full 8-hour sleep period is allowed prior to preparation and competition.

Sedative-hypnotic sleep aids have also been linked to increased severity of gastroesophageal reflux disease (GERD). While many athletes, especially elite athletes, suffer from GERD, a cautious approach to the use of sleep aids is recommended in affected athletes.[12,16]

Table 1. Recommendations for medication administration to facilitate sleep schedule changes

	Sleep Phase Delay (Westward Travel, Late Competition)	Sleep Phase Advance (Eastward Travel, Early Competition)
Melatonin	In late sleep phase or early morning at destination until adapted	At destination bedtime nightly until adapted
Caffeine	Prior to competition if needed for ergonomic effects	Morning intake for entrainment. Prior to competition if needed for ergogenic effects
Sedative-hypnotic sleep aids	In early morning if needed for sleep interruptions/ early awakening until adapted. Allow at least 8 hours for sleep to avoid adverse effects	At destination bedtime if needed until adapted

OTHER AGENTS

Alternative pharmacologic agents such as diphenhydramine, amitriptyline, and trazadone are commonly used by nonathletes for insomnia and sleep disturbances. Their pharmacokinetic profiles, however, are relatively unfavorable when compared with the nonbenzodiazepine sleep aids discussed. They have been associated with significant next-day somnolence and are therefore rarely used by athletes and not commonly recommended.[22,41]

Gabapentin is gaining popularity as a sleep aid for nonathletes and was included in a 2016 investigation by Kay et al.[22] After nocturnal administration of gabapentin, there was no significant effect on driving performance or cognitive functioning the next day. Further study on gabapentin as a sleep aid in the general population and athletes is needed before further recommendations can be made.

The importance of nutrition on sleep and athletic performance is an interesting topic of study that is still developing. Research has identified a number of neurotransmitters associated with the sleep-wake cycle, including serotonin, gamma-aminobutyric acid (GABA), histamine, and norepinephrine, that may be affected by nutrition.[15] Research into augmentation of neurotransmitter levels through nutritional supplementation (carbohydrate, tryptophan, valerian, and others) is ongoing and may provide athletes with additional strategies to facilitate sleep schedule adjustments.

Table 1 includes current recommendations for medication use for sleep schedule adjustment based on available evidence. As study in this field advances, other agents, such as gabapentin, are likely to be included.

SUMMARY

Because of travel and scheduling demands, modern athletes are often required to adjust their sleep schedules. Current recommendations favor the use of nonpharmacologic strategies (gradual sleep schedule changes, naps, exercise schedule changes, light exposure) to facilitate circadian rhythm phase changes.[24] However, these modalities are often impractical for busy athletes with time constraints. Thus, the use of select medications can help athletes modify their sleep schedules more quickly without affecting performance. Unfortunately, there is a paucity of data regarding the effects of medications on athletes and athletic performance specifically, requiring inference from comparable nonathlete populations such as shift workers, pilots, and other populations involved in long-haul travel.

Melatonin is the most widely studied agent with benefits in athletes and nonathletes requiring sleep phase advancement, such as in eastward travel and early morning competition times. Decreases in physical performance are seen immediately after ingestion, so allowing for 8 hours of sleep prior to athletic performance is recommended.

Caffeine, although not adequately studied in athletes, does have utility for decreasing sleepiness and improving performance in shift workers and has accepted ergogenic benefits. For these reasons, its use shortly before performance is acceptable. Laboratory data also suggest that caffeine can facilitate re-entrainment (sleep phase delays) when taken early in the day. This characteristic is quite applicable to the athlete involved in a multiday event or with adequate time for entrainment.

Sedative-hypnotic sleep aids do have utility in sleep phase advancement, serving as second-line agents to melatonin. Improvements in sleep quality also make them attractive agents for athletes during travel and the night prior to competition. Short-acting agents (zolpidem, zopeclone) are favored along with an 8-hour period of sleep prior to competition to avoid "hangover" effects and negative effects on performance. Avoidance of benzodiazepines is encouraged due to abuse potential and accessibility of effective alternatives.

Current evidence demonstrates that melatonin, caffeine, and sedative-hypnotic sleep aids can assist with sleep cycle modification (see Table 1). Each athlete's circadian physiology is different, however, so customized care is necessary to avoid adverse effects and abuse while maximizing sleep and athletic preparedness at the time of competition. Clearly, further study is needed on the utility and effects of the above medications on athletes' circadian rhythms and performance parameters.

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