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(REVIEW ARTICLE)

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A review of treatment plans for the biological clock of astronauts: A systematic review

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Abstract

Since the start of civilization and even further back, humankind has been dreaming of flying. Recently, this dream has come true and reached beyond that and sends astronauts to outer space. However, by achieving this milestone, we encountered new problems that were new to humanity. One of the biggest problems is having a sleeping disorder and disruption of the biological clock. It is essential because having a sleep disorder makes astronauts unable to function at 100% capacity, and in outer space, it is dangerous. Some treatments for sleep disorders include drug therapy, such as Dexedrine, temazepam, modafinil, bupropion, melatonin, zolpidem, dextroamphetamine, light treatment, or a trickling sleep/wake schedule, according to NASA's guidelines. This study aimed to review the treatments for sleep disorders and disruption of the biological clock aimed at astronauts during space flights. We presented the different treatments and discussed and oriented the next prospect of research on sleep in space. Therefore, there will be guidelines for astronauts during their flights. Since the beginning of space travel, there have been many papers regarding space and weightlessness on the adverse effects on health.

Studies have described the effect of space travel and the environment of microgravity on health. A few studies include both the short- and long-term effects of microgravity on the biological clock. With this new dawn and sending new astronauts to International Space Station (ISS) with NASA and SpaceX commercial Falcon 9 rocket, which opened a new horizon for spaceflights, it is even more important to consider the adverse effects microgravity on health.

Purpose: This review aims to specifically analyze the biological clock, sleep deficiency, and circadian disorders. As we acknowledge, there is a sleep deficiency associated with complex microgravity environs and space missions before and after launch.

Material and methods: Two researchers searched a thorough and detailed search of the PubMed database with the keywords mentioned below. The search was performed in November 2020 without any time limitations. We only included human studies and articles in the English language.

Results: A total of 148 articles were found, and after going through titles, 77 articles were chosen for checking abstracts. Finally, only 12 manuscripts were accepted for data extraction.

Conclusion: It is essential for health care involved in space travel providers to help pre-emptively identify problems that may prevent severe consequences during a microgravity environment.

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Sleep and circadian factors are the fundamental issues of human fatigue, and aviation schedules significantly impact both. We should admire a computerized fatigue model for having a better approach to studying the impact of scheduling.

Keywords: Sleep disorder; Spaceflight; Biological clock; Medication; Astronaut

1. Discussion

The hazards of lost sleep can range from on-the-job errors to chronic disease. People worldwide with disruptions in quotidian rhythm, or the body's natural regulator for sleep and wake cycles based on a 24-hour schedule, every day. This instinctual process can be disrupted by unwonted work schedules, wide-stretching traveling between time zones, and daily life for International Space Station hairdo members, who could stand 16 sunrises a day.

Unfortunately, there have been few changes to aircrew scheduling provisions and flight time limitations since they were first introduced, despite evidence that updates are needed. Although the scientific understanding of fatigue, sleep, shift work, and circadian physiology has advanced significantly over the past several decades, current regulations and industry practices have, in large part, failed to incorporate the new knowledge adequately (2-3).

Sleep is triggered by a cocktail of hormones, proteins, and neurons by our circadian rhythm, the trundling that helps us maintain an approximately 24-hour trundling of bodily functions. Toward evening, melatonin, perhaps the most well-known hormone, is zingy in the pineal gland in the smart ass and released to help us get to sleep.

Much of the time, long-haul pilots ascribe their weariness to lack of sleep and circadian aggravations related to time zone advances. Short-pull (residential) pilots most regularly accuse their weakness of rest deprivation and high remaining burden. Both prolonged- and short-pull pilots regularly partner their weakness with night flights, fly slack, early wakeups, time pressure, various flight legs, and successive obligation periods without sufficient recuperation breaks. Corporate/official pilots experience weariness-related issues such as those revealed by their business partners. In any case, once more, they most often refer to planning issues (multi-portion flights, night flights, late appearances, and early arousals) as the most imperative benefactor (4).

The USA air force admits the demand for crewmembers to unexpectedly alter between daylight hours and midnight responsibility and continue to be effective. Under ordinary operations, crewmembers are anticipated to use nonpharmacologic skills to modify their sleep and obligation schedules. These measures include making sure the possibility for eight of continuous, uninterrupted sleep time; the use of 30-min naps in the course of durations of intense fatigue; get right of entry to surroundings that promotes sleep and expansion (darkened, quiet room with temperature control); avoidance of caffeine and alcohol earlier than sleep periods; balanced whole meals, and great exercising earlier than beginning responsibility shifts (5-9).

The essential complications at the commonly deployed fight base are austere locations, vulnerability to enemy attack, and proximity to the flight line. The USA air force has generally been in a position to grant excellent local weather-managed snoozing areas, healthful meals consisting of sparkling fruits and vegetables, and amenities to promote crew members' fitness at most airbases. There are commonly no extra necessities positioned on the crew members' backyard of their fundamental crewmember duties, and the fight obligation tour is frequently confined. Flight line noise at these bases is regularly demanding and cannot be controlled (10).

1.1. Zolpidem in Fatigue management

Zolpidem (AMBIEN) is a sedative-hypnotic medication that had FDA approval in 1993 to treat short insomnia. It influences the GABA-A receptor. The adverse effect is based on walking during sleep, sleep-driving, eating spontaneous food, no memory, or loss of memory, and on the other hand, it will cause drowsiness and dizziness in the morning (11).

Based on many investigations, melatonin is much more effective than melatonin in the jetlag period. Zolpidem collapse in the cognitive performance 1.5 hours after the optimal result in inducing sleep, and on the other hand, there will be cognitive complications 2 hours after sleep induction. However, compared to the other benzodiazepines, there will be a daily improvement after 8 hours of zolpidem administration. During the observation of management of sleep disorder by using zolpidem. (7-11).

Caldwell wrote a brief outline of medication used to prevent fatigue in the U.S. Armed Forces. Jaeger and Russo inspected the ethics of consumption of medication as a fatigue measurement. As we acknowledge, the USA Air Force permits zolpidem to control fatigue during the operation.

The utilization of zolpidem requires endorsement from the central command, past testing of the individual crewmember in a non-flying obligation status, individual recommendation of the medicine for a specific activity by a flight specialist as per the significant command crucial, and a base 6-h period from taking the prescription to the beginning of the "obligation daytime frame. "All remotely piloted aircraft (RPA) crewmembers were required to take zolpidem in a non-flying obligation status to distinguish medicine reactions and rest adequacy in every person (8).

Due to the article derived from Roscoe Van Camp, Zolpidem advanced the safe enlistment of sleep and was utilized achievement by a majority of the RPA crewmembers. Reactions occurred in some crewmembers, although they had recently tried the medication without symptoms. A small subset of the experimental group intensely depended on taking drugs to deal with their rest cycle effectively (8,9).

1.2. Bupropion and the performance

Achievement in neuroscience probes has yielded new treatment alternatives for depression, including selective serotonin reuptake inhibitors (SSRIs) and related compounds such as noradrenaline and dopamine retake-up inhibitors (NDRIs). These medications are comparable to the more acclimatized tricyclic antidepressants, yet their various active components bring about unique reaction profiles. Bupropion is an NDRI that has both noradrenergic and dopaminergic activity.

Bupropion sustained-release (S.R.) is bolded as Wellbutrin S.R. for depression management and nicotine management. It was no brilliant outcome of Bupropion S.R. on reaction time, logical reasoning, multitasking performance, task persistence, mental status, or evaluation of dementia (12).

1.3. Temazepam and induction of sleep

Working in the reverse cycle demonstrates difficulties in maintaining alertness during the night shift. When the night shift is prolonged, a lack of cumulative sleep is made. An accurate elixir is necessary to assist better achievement for having better and effective duty performance.

Astronauts who took temazepam slept longer and had fewer breakups than the study without the medication; temazepam has less fatigue and more subjective alertness. Temazepam performed better on psychomotor surveillance tasks (13).

1.4. Modafinil and reduction of fatigue and enhancement of mood

Modafinil is a new achievement compound in military aviation. It is well documented in clinical trials, but more investigation is needed to establish safety guidelines in space flight and aviation armies.

Even though modafinil did not continue execution at pre-deprivation levels, the current examination proposes that modafinil should be considered for the military's combat hardware of transient exhaustion countermeasures. Future research will assess whether 200-mg portions are more valuable than the 100-mg dosages utilized here.

Benefits were more tangible after 24 to 32 hours of continuous wakefulness.

Modafinil did not execute at pre-deprivation levels; the current examination recommends that modafinil be considered for the military's combat hardware of momentary exhaustion countermeasures. Future research will assess whether 200-mg dosages are more valuable than the 100-mg portions utilized here, and still, the dosage is on a bias (14).

1.5. Dextroamphetamine and impact on sleep deprivation

Dextroamphetamine (Dexedrine) is a viable exhaustion measurement for use in military subject pilots who are denied rest. Episodic reports have demonstrated that Dexedrine (Dex) is viable in the world's ongoing activities, and controlled research center tests have yielded positive outcomes. The point of this examination was to validate the viability of Dex for continuing the sharpness and execution of pilots during times of lack of sleep by indicating the substantial impacts of the medicine and its predictable impacts over a few research endeavors (15).

The advantages of the Dex were not balanced by stamped interruptions in recuperation rest, albeit some negative impacts were studied, and rest was lighter for a few hours following Food and Drug Administration (FDA) guidelines. Dex is a remedy for fatigue in aviation, but there is still no replacement for proper crew-test timing.

1.6. Sleeping better with melatonin

Many investigations and clinical trials of melatonin have established that sleep quality during space flight will be improved. It is currently unoccupied in health stores as a supplement; these medications may have bothersome symptoms on execution and mental sharpness. In the quest for a superior tranquilizer, specialists have focused on melatonin, an ordinarily active hormone created in the cerebrum's pineal organ (11). Ground-based research shows that melatonin may encourage rest, a characteristic that is especially significant if space explorers are planned to rest during the day when their bodies are not delivering the hormone (16).

1.7. LED and assistance in insomnia

There is a working achievement that encourages the health of astronauts during space flight, and propositions include special blue LED lights to assist insomnia during spacecraft missions. As we know that the space station moves around the earth every 92 minutes, an astronaut on the board can see the sunrise and sunset 16 times every day (17).

NASA's new approach is based on a better human response to light cycles. Since 2016, the science cast of NASA has been trying to determine the solution to have a special LED that can alter into low-high-or normal-intensity modes to these meds, be that as it may, it may have irritating symptoms on execution and mental sharpness. To combat this, lightening on the space-based solid-state-light assemblies (SLAs). Promotes crew members to adopt alertness and circadian resetting with light.

1.8. Sleep Cognitive Behavioral Therapy

These negative thoughts involve worries and stress that keep you awake. A therapist helps you process your thoughts and feelings about sleep.

Crew members learn ways to conquer negative thoughts and promote positive attitudes and beliefs. This might involve setting a "worry time" in the afternoon or early evening. It will help to focus on getting all of the worries out of your system. This helps the mind to be at rest. Behavioral therapy for insomnia (CBTI) is often structured as a 6-week treatment program to help patients who have difficulty falling asleep, staying asleep, or finding that sleep is unrefreshing. CBTI is scientifically proven, highly effective, and does not rely on medications. CBTI has life-long benefits, and most participants report improved sleep satisfaction (18).

With sleep, cognitive-behavioral intervention measures, astronauts' direct or oblique psychological guide had tremendous impacts, which began from the USA and Russia's station missions. It has been impacted directly or indirectly by psychological support, relieving stress, and increasing rest and sleep.

The countermeasures towards sleep troubles in spaceflight include enhancing the sleep environment, designing a sensible on-orbit work-rest schedule, pharmacologic interventions, mild treatment, psychological support, crew decisions, and training. These measures are frequently rationally built-in under mission traits and natural aid allocation ability. Among them, drug screening and the improvement of new preparations must be connected with exclusive importance (19). As a new technology, mild therapy is being used and examined on ISS, which must additionally be viewed in the plan and building of the Chinese area station. Specific determination and crew education, especially gene selection, as a viable method, need to be similarly tested and verified. More ground-based studies and preparations must be carried out, and on-orbit checks should be carried out as quickly as possible.

Author	Year	Number of Participants	Methodology	Treatment of use	Outcome
Boulos, Z., et al.	2002	20	Twenty subjects were exposed to bright white light (3000 lux) or dim red light (10 lux) for three hours on the first two evenings after a flight from Zurich to New York. Salivary dim light melatonin onset (DLMO), assessed two days before and two days after the flight, provided a measure of the circadian phase. Sleep was recorded by actigraphy, while post-flight performance testing and subjective scales provided additional indices of jet lag severity.	Light treatment	bright light treatment can accelerate circadian entrainment following trans meridian travel. However, the effect on the entrainment rate was modest and was not accompanied by any improvement in sleep, performance, or subjective assessments of jet lag symptoms.
Caldwell, J. A. and J. L. Caldwell	1997	10 UH-60 pilots	flight performance, mood, and alertness were during sleep deprivation periods under Dexedrine or placebo	Dexedrine	Relative to placebo, Dexedrine improved flight performance during straight-and-levels, climbs, descents, right turns, and a left-descending turn, with tendencies toward better performance during the left turns and the instrument landing system approach. Dexedrine markedly reduced subjective feelings of fatigue, confusion, and depression while increasing feelings of vigor. Central nervous system arousal was enhanced by Dexedrine relative to placebo.
Caldwell, J. A., et al.	1995	6 U.S. Army helicopter pilots	A placebo-controlled, double-blind study was conducted. Six U.S. Army helicopter pilots completed five flights in a UH-60 simulator while their performance was evaluated. Immediately following each flight, data were collected on electroencephalographic (EEG) activity and subjective mood ratings. Testing sessions occurred at 0100, 0500, 0900, 1300, and 1700. One hour before each of the first three flights on drug-administration days, the aviators were given 10 mg of Dexedrine or a placebo	Dexedrine	Dexedrine appears to effectively sustain helicopter pilot performance during short periods of sleep loss without producing adverse side effects.
Caldwell, J. A., et al.	2003	Review of articles		dextroamphetamine	Dex is a viable remedy for fatigue in aviation sustained operations. However, Dex is not a substitute for proper crew-rest scheduling because there is no replacement for adequate restful sleep.

Caldwell, J. A., et al.	2004	10 Air Force F-117 pilots	A quasi-experimental, single-blind, counter-balanced design tested the effects of modafinil (100 mg after 17, 22, and 27 h without sleep) in 10 Air Force F-117 pilots.	Modafinil	Although modafinil did not sustain performance at pre-deprivation levels, the present study suggests that modafinil should be considered for the military's armament of short-term fatigue countermeasures.
Caldwell, J. A., et al.	2000		Dexedrine (10 mg) or placebo was given at midnight, 0400, and 0800 hours on two deprivation days in each of two 64-h cycles of continuous wakefulness. Test sessions consisting of simulator flights, electroencephalographic evaluations, mood questionnaires, and cognitive tasks were conducted at 0100, 0500, 0900, 1300, and 1700 hours on both deprivation days. Two nights of recovery sleep separated the first and second 64-h sleep-deprivation cycles.	Dexedrine	Dexedrine sustained aviator performance and alertness during periods of extended wakefulness, but its use should be well controlled. Although effective, Dexedrine is no replacement for adequate crew rest management or restful sleep.
Caldwell, J. L., et al.	2003	Sixteen UH-60 Army aviators	Sixteen UH-60 Army aviators were randomly assigned to either temazepam or a placebo group. Test sessions, consisting of vigilance assessments, flight simulation, and mood state questionnaires, were administered during baseline, three nights of reverse cycle, and three days following a return to day shift. Temazepam (30 mg) was administered before daytime sleep to one group, while another group received a lactose-filled capsule.	temazepam	Temazepam helps prolong daytime sleep, with some attenuation of performance decrements during the night shift. However, physicians should be careful when administering this substance to ensure the aviator has a minimum of 8 h in which to sleep.
Monk, T. H., et al.	2006	Ten subjects	a 16-d (384 h) simulated mission was conducted for each of 10 subjects. Temporal cues and light levels approximated those experienced in space. All sleep periods were precisely eight hours. Before the study, for 14 d, subjects were required to live on a schedule with a 23:00 bedtime and 07:00 wake time. Laboratory sessions then started with a 4-d baseline segment on that schedule. The fourth night and the day following it were then taken as baseline. Repeated 30-min phase advances in bedtime were then required on each of the next 12 successive nights, resulting in an eventual movement of bedtimes to a 6-h phase-advanced position (bedtime: 17:00, wake time: 01:00).	trickling in" a 6-h phase advance in sleep/wake schedule by 12 consecutive 30-min phase advances as per NASA's Appendix K guidelines	Though statistically significant, the disruption was less than we observed from repeated 2-h phase delays reported in a 2004 ASEM paper. Evidence would thus seem to favor repeated 30-min phase advances over repeated 2-h phase delays.

Monk, T. H., et al.	2004	Ten subjects (5 men, five women, mean age: 41.2 yr.),	A 16-d (384-h) mission was simulated in 10 subjects (5 men, five women, mean age: 41.2 yr.), studied singly or in pairs. After 14 d on a 23:00-07:00 sleep/wake cycle, the subject entered the laboratory. After a 4-d baseline segment, repeated 2-h phase delays were then required on each of the next nine successive nights of the study (i.e., bedtimes at 01:00, 03:00, 05:00, etc.), resulting in an eventual movement of bedtimes to an 18-h phase delayed (equivalent to a 6-h phase advanced) position with bedtime at 17:00.	trickling in" a 6-h phase advance in sleep/wake schedule by nine consecutive 2-h phase delays, as would be recommended by NASA's Appendix K guidelines	Doubt must be cast on the assertion that circadian dysfunction and sleep loss can be avoided by limiting repeated phase delays in routine to 2 h.
Paul, M. A., et al.	2002	24 subjects (18 men and six women)	subjects were assessed for psychomotor performance during placebo and bupropion S.R. treatment in a double-blind cross-over in counter-balanced order. Each treatment arm lasted 5 wk. The daily bupropion S.R. dose was 150 mg during week 1 and 300 mg during weeks 2 to 5. Subjects completed a drug side-effect questionnaire and were tested on two psychomotor test batteries once per week during each placebo and drug arm.	bupropion	There was no significant Impact of bupropion S.R. on serial reaction time, logical reasoning, serial subtraction, or multitask performance. With respect to drug side effects there was a main effect of drug on "number of awakenings" ($p < 0.048$), "difficulty returning to sleep" ($p < 0.004$), and "dry mouth" ($p < 0.049$). There was no impact of bupropion S.R. on dizziness.
Suhner, A., et al.	2001	137 Human	a double-blind, randomized, placebo-controlled study is based on 137 volunteers flying from Switzerland to the American continent and back (6-9 time zones). The participants either received melatonin 5 mg (n = 35), zolpidem 10 mg (n = 34), a combination thereof (n = 29) or placebo (n = 39) on the eastbound flight back to Switzerland and once daily at bedtime on 4 consecutive days after the flight	melatonin and zolpidem	All active treatments led to a decrease in jet lag severity, with zolpidem being the most effective treatment, particularly in facilitating sleep on night flights. Potential individual adverse reactions to this hypnotic have to be considered.
Van Camp, R. O.	2009	43 Human	They evaluated zolpidem in managing sleep-work cycles for remotely piloted aircraft (RPA) crew during surge combat operations. Three 10-mg tablets of zolpidem were dispensed to each of 43 crew members tasked to support RPA surge combat operations requiring rapid unscheduled shift changes. All personnel was required to take the drug on a non-flying day to evaluate its effect.	Zolpidem	Zolpidem promoted the safe induction of sleep and was used successfully by a majority of the RPA crewmembers. Side effects occurred in some crewmembers even though they had previously tested the drug without side effects. A small subset of the test group heavily relied on medication to successfully manage their sleep-rest cycle.

2. Conclusion

Since the beginning of the space program, astronauts have dealt with the facts of spaceflight, from microgravity in muscle atrophy and space radiation to sleep deprivation and disorientation. Human sleep is sensitive to the individual's environment. Research and investigation on sleep disorders among astronauts are new aspects of astronomical medicine. The concept of sleep disturbances in astronauts occurs more during space flight than on the ground. Sleep insufficiency will promote worse sleep quality, and it will cause the decline of cognition and operation performance, but it is still complicated. As we acknowledge, it will affect mood state and secretion of hormones such as cortisol, depression, and other stress-related disturbance, elevated the cortisol, altered the norepinephrine levels.

Several mechanisms may be responsible for these alterations in sleep regulation and the circadian phase. A negative impact on sleep leads to sleep fragmentation, decreased deep slow-wave sleep, and shortened sleep time and contributes to increased use of sleep-promoting medications. NASA and space stations are working to improve astronaut crew health during space flight by using medication, LED lights, CBTI, etc., but more demands should be understood about the human body's limitations in space.

Compliance with ethical standards

Disclosure of conflict of interest

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Statement of ethical approval

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