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Sleep disruption, use of sleep-promoting medication and circadian desynchronization in spaceflight crewmembers: Evidence in low-Earth orbit and concerns for future deep-space exploration missions

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ABSTRACT

Introduction: The spaceflight environment presents unique demands on human physiology; among those demands, is sleep. Sleep loss and circadian desynchronization is a major concern for future deep-exploration plans, including long-term crewed missions to the Moon and Mars.
Aims: Analyze evidence of sleep disruption in crewmembers during low-Earth orbit missions, identify the use of sleep-promoting medication among crewmembers and deepen the comprehension of challenges to sleep physiology for future missions to the Moon and Mars.
Results: Evidence consistently indicates a loss of sleep and circadian rhythm disruption during low-Earth orbit missions. Sleep duration is shortened especially the night before a critical operation and during circadian-misaligned sleep episodes. The prevalence of sleep-promoting medication ranges between 71% and 78%; medication is more frequently taken on circadian-misaligned sleep episodes. Regarding the Moon, Apollo astronauts had variable sleep duration. For some, sleep was restful while others had poor-quality sleep. Many reported fatigue and errors due to the lack of rest. A loss of the 24-h light/dark might be expected due to the Moon's complex illumination characteristics. Regarding Mars, one main challenge will consist in synchronizing the circadian clock to a Martian day (24.65 h).

1. Introduction

The spaceflight environment presents unique demands on human physiology. Among those demands, is sleep. Maintaining an adequate total sleep duration, circadian synchronization, and sleep architecture is key for ensuring optimal health of crewmembers, as sleep loss and disruption of circadian rhythm are fatigue-causing factors. Keeping high levels of performance and alertness during space missions is critical to mission success and safety.

In the current low-Earth orbit (LEO) crewed space missions, there's a loss of the 24-h light/dark cycle as the International Space Station (ISS) orbits Earth every 90 min. Furthermore, sleep quality might be impacted by external factors such as confinement, work overload, chronic stress, hypercapnia, light and noise disturbances, temperature, and low back pain [1]. Astronauts have also complained about uncomfortable sleeping bags and the absence of proprioceptive cues [2].

Although space agencies have improved sleeping conditions for astronauts in the last decades, fatigue and lack of sleep continue to be frequent complaints among crewmembers, supporting the hypothesis that microgravity might also interfere with the ability to sleep [3,4].

Sleep loss and circadian desynchronization is also a major concern for future deep-space exploration plans, including long-term missions to the Moon and Mars. The literature on aerospace medicine currently lacks a deep analysis of potential planetary conditions that might disrupt circadian rhythm while exploring those celestial bodies.

The aim of this review is to collect evidence of sleep disruption and fatigue in astronauts in recent years, identify the use of sleep-promoting medication in astronauts, and deepen the comprehension of challenges to sleep physiology for future missions to the Moon and Mars.

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1.1. Methodology

A literature search was conducted between September 2021 and May 2022 using PubMed and Scopus. A broad search was performed using the Mesh string: ((“weightlessness” [tiab] OR “astronauts” [tiab] OR “Space Flight” [tiab]) AND (“sleep” OR “sleep, REM” [tiab] OR “Circadian Rhythm” [tiab] OR “Psychomotor Performance” [tiab])). A total of 182 articles were retrieved. Following a review of the title and abstract, 78 were chosen. After a complete reading of the articles, 22 were selected based on the following eligibility criteria: peer-review journals, study design (observational or experimental), use of quantitative and/or qualitative methodology, reported outcomes (functional status, symptoms, perceived value of treatment), subjects (human participants exclusively), length of follow-up (≥15 days), and setting of the study (real or ground-based space missions). Search for technical information about Mars and Moon was performed by introducing free terms in the following databases: Journal STORage, Astrophysics Data System and Nature Astrophysics.

1.2. Changes in sleep duration and architecture during short and long-duration spaceflight

While in space, spaceflight crewmembers sleep less than they do on Earth. Chen et al. characterized sleep-wake patterns using actigraphy in three crewmembers on a 15-day space mission. The authors found that the mean sleep duration per day was significantly less during spaceflight (6.5 ± 1.3 h) than during the after-landing period (7.2 ± 1.2 h). One crewmember slept for fewer than 6 h (5.6 h) during the spaceflight [5].

Dijk et al. investigated sleep via wrist actigraphy in five astronauts before, during, and after the 16-day Space Transportation System (STS) 90 mission and the 10-day STS 95 mission. During spaceflight, the total sleep time was 6.5 h, and, on some nights, the total sleep time was as short as 3.8 h. Thus, the average daily sleep period time was approximately 30–40 min less than the mean sleep duration prior to and after flight; actigraphy sleep period time in-flight was significantly less than post-flight ($p < 0.05$) [6].

Piltch et al. studied five crewmembers using Nightcap sleep-monitoring system before (pre-flight, $n = 113$ nights), during (in-flight, $n = 68$ nights), and after (post-flight, $n = 61$ nights) missions aboard the Mir space station. The analysis showed that the crew had an hour less sleep in space (5.4 ± 0.66 h) compared to pre-flight (6.6 ± 0.70 h) ($p < 0.0001$). Additionally, percentages of time in bed for REM sleep and NREM sleep in spaceflight decreased by 26.6% and 9.9%, respectively, compared to pre-flight. Also compared to pre-flight, REM latency during spaceflight nearly doubled, to 88 ± 3 min [7].

Stickgold & Hobson conducted a polysomnography study on 5 astronauts. Sleep was recorded during pre-flight ($n = 26$ nights), in-flight ($n = 24$ nights), and post-flight ($n = 14$ nights). Results revealed that the REM sleep time during spaceflight was reduced by 50% compared to pre-flight. Also, in-flight sleep time was reduced by 27% compared to preflight [8].

Barger et al. assessed the sleep-wake cycle of 64 astronauts across multiple Space Shuttle missions (1020 inflight nights recorded) and 21 astronauts on long-duration ISS missions (2951 in-flight nights recorded). Additionally, actigraphy was recorded for the first seven days post-landing. Data showed that Space Shuttle crewmembers obtained significantly less sleep per night during spaceflight (5.96 ± 0.56 h) compared to the first-week post-mission (6.74 ± 0.91 h) ($p < 0.0001$). In 47.1% of the nights (480/1020) astronauts slept less than 6 h, and sleep episodes of 8 h or more were registered in only 3.1% of sleep episodes (32/1020) [3]. On ISS, crewmembers obtained significantly less sleep during spaceflight (6.09 ± 0.67 h) than they did after their return to Earth (6.95 ± 1.04 h) ($p < 0.0001$). Subjects slept less than 6 h on 43.8% of nights (1294/2951). On 51.3% of nights (41/80) before accomplishing Extra-Vehicular Activity (EVA), astronauts slept less than 6 h, and in only one night (1.3%; 1/80) before these critical tasks, a crewmember obtained 8 h of sleep [3].

Flynn-Evans et al. used wrist actigraphy to investigate if circadian misalignment was linked to poor sleep outcomes in 21 astronauts aboard the ISS. Data was collected 11 days before launch ($n = 231$ nights) and for 3248 nights in-flight, across 21 missions. The average sleep duration was 6.4 ± 1.2 h and 5.4 ± 1.4 h during aligned and misaligned sleep episodes, respectively. Thus, the circadian misalignment resulted in losing 1 h of sleep per night; this difference is significant ($p < 0.01$). Circadian misalignment counted for ~20% of days in-flight and tended to occur during critical operations such as the night before an EVA, and when a vehicle was docked with the ISS [9].

Table 1 resumes the perception of sleep quality during spaceflight and changes in alertness in spaceflight crewmembers [3,5,6,9–12].

1.3. Use of sleep-promoting medication during spaceflight

During the Space Shuttle era, the use of sleep-promoting medications was common. Barger et al. found that 78% of Space Shuttle astronauts (61/78 crewmembers) reported taking sleep medication. Medication was taken on 52% of the in-flight nights (500/963) and its use was significantly less prior to flight and after flight, compared to in-flight ($p < 0.0001$). Medicines used during Space Shuttle missions include zolpidem, zaleplon, melatonin, temazepam, quetiapine fumarate and eszopiclone [3].

The crewmembers onboard ISS have a similar prevalence of sleep-promoting medication use. The same study led by Barger L. cited above, showed that 75% (12/16) of astronauts reported using sleep-promoting medications [3]. Wotring V. collected medical data of 24 ISS crewmembers over a 10-year period and analysis showed that 71% of astronauts (17/24) reported using medications to induce or maintain sleep [13]. During ISS missions, sleep medication was taken more frequently on circadian misaligned sleep episodes compared with circadian aligned sleep episodes: 24% v/s 11%, respectively ($P = 0.0002$) [9]. On 19% of days when sleeping drugs were used, two doses were taken [3]. Although sleep-promoting drugs were available during space shuttle and ISS missions, they were not prescribed by doctors as part of supervised treatment, and crewmembers were not restricted in their use on the first or second dose [3,9].

1.4. Sleep in Apollo missions and considerations for future missions to the Moon

Several observations concerning sleep were made by Apollo astronauts. The ability to sleep varied among crewmembers; for some, sleep was very restful while others reported poor-quality sleep. Those who slept poorly, declared sleep being insufficient and frequently interrupted. Sleeping pills were used. Several astronauts slept 2–3 h at most, whereas other crewmembers slept 7–10 h, although it was sometimes described as “light sleep”. Many reported fatigue and committing errors in communication and procedures due to the lack of rest [14].

For future missions to the Moon, such as Artemis Exploration Mission II and III [15] space agencies should consider the environmental factors that hindered the ability to get restful sleep in Apollo missions: ambient noise level, cabin temperature, light penetration into the vehicle, lack of comfortable places to sleep and sleeping bag size [14]. The loss of the 24-h light/dark cycle should also be considered, as a habitable lunar orbital platform is planned to be part

Table 1
Perception of sleep quality among spaceflight crewmembers during low-Earth orbit missions.

Author/s	Participants	Methods	Main findings on sleep quality/alertness
Barger et al. [3]	64 astronauts on 80 Space Shuttle missions.	Via wrist actigraphy and daily logs, sleep-wake timing of 64 astronauts on 80 Space Shuttle missions.	Subjective ratings of sleep quality and alertness were significantly higher post-flight than they were during the Space Shuttle missions ($p < 0,0001$)
Chen et al. [5]	Three astronauts during 15 days in space flight.	Actigraphy and questionnaires. For sleep quality astronauts filled Pittsburgh Sleep Quality Index, preflight, inflight, and postflight.	The average rating of sleep quality from PSQI scale was higher during the spaceflight (6.7 ± 2.6) than that 2 months before spaceflight (5.0 ± 2.2) and that the first 8 days after landing (3.7 ± 2.5), and although there are no significant differences, the results show that astronauts have a lower sleep quality during the flight with PSQI >5.
Dijk et al. [6]	Five astronauts on two Space Shuttle missions	Polysomnography, actigraphy, neurobehavioral assessment, and subjective sleep quality questionnaire after each sleep episode.	Sleep quality decreased from 6.5 ± 0.3 preflight, to 5.4 ± 0.4 inflight and 6.8 ± 0.3 postflight. Subjective estimates of sleep latency, sleep quality, and the feeling of being physically rested on awakening all indicated best sleep after return to Earth, compared to inflight time.
Flynn-Evans et al. [9]	21 astronauts on International Space Station missions	Actigraphy and photometry in 3248 days spaceflight.	The more demanding the scheduled workload was perceived to be, the less easy crewmembers reported being able to fall asleep and stay asleep. Some reported not being ready for sleep at scheduled bedtime due to work scheduling and lack of time to “wind down”.
Stuster J. [10]	10 astronauts on International Space Station missions	Participants were asked to make journal entries at least three times per week while on the ISS and they were encouraged to address whatever topics were most salient to them. The duration covered by the ten journals ranged from 150 to 200 days.	Astronauts reported being tired more often during the first quarter of ISS missions.
Pool-Goudzwaard et al. [11]	20 astronauts on 5 Soyuz missions and 5 Space Shuttle missions	Low back pain questionnaire 10 d (±5) pre-flight, each day during the 12- to 15-d flight, as well as 10 d (±5) post-flight.	Low back pain is present in 70% of the astronauts studied, which is most often provoked during sleep and can be a disrupting factor.
Locke et al. [12]	10 astronauts after two STS missions.	The interview consisted of 44 open-ended items.	54% of shuttle astronauts report difficulty falling asleep during their missions and 43% report that sleep on orbit was interrupted.

of future lunar missions. As an example of this 24-h light/dark cycle disruption, the Apollo 11 command and service module orbited the Moon every 47 min, which included time behind the moon [16].

1.5. *Sleep and fatigue concerns for future Mars missions*

One main challenge for future Mars explorers and mission control personnel on Earth will consist in synchronizing their circadian rhythm to a Martian day, that lasts 24.65 h, 39 min longer than an Earth day [17].

Gemignani et al. studied six healthy male volunteers by collecting urinary cortisol and using high-density EEG (128 channels). Subjects were kept for 105 days (day of 24 h) in an isolation facility, to mock a manned mission to Mars. Crewmembers worked regularly and once every six days they had a longer 24-h shift during which they were required to perform computerized cognitive function tasks. EEG results showed that when high urinary cortisol levels were found, concomitantly there was an increase of arousal, a decrease of sleep duration, and shortening of REM latency. Also, high urinary cortisol levels were associated with a reduction of delta power, enhancement of sigma and beta in NREM N3, right lateralization of beta activity in NREM, and left lateralization of delta activity (NREM and REM) [18]. Barger et al. collected data from this same experience. These authors found that during the extended work shift, subjective sleepiness significantly increased ($p < 0.05$). Additionally, volunteers became less interested ($p < 0.05$), less alert ($p < 0.0001$), energetic ($p < 0.001$), and less well ($p < 0.05$), during the extended duration work shift [19].

Basner et al. obtained objective neurobehavioral data on activity and sleep patterns using a psychomotor vigilance test and wrist actigraphy on six males during a ground simulation of a 520-days mission to Mars. Operations were organized around 24-h clock time, but subjects weren't exposed to Earth's natural light and dark cycles. Data showed interindividual differences among the crewmembers. Four out of six crewmembers experienced one or more of the following problems: frequent reduction in perceived sleep quality ($n = 2$), increased displacement of sleep into the diurnal period ($n = 2$), performance deficits associated with chronic partial sleep deprivation ($n = 1$), and disrupted sleep-wake periodicity ($n = 1$). Analysis by mission quarter showed a 7.0% decrease in active wakefulness (i.e. 1.12 h less of active awake time per crewmember per day) comparing the last with the first mission quarter ($p < 0.0001$). Results also showed that the decrease in active wake and increase in sleep and rest times occurred on both rest and workdays as the mission progressed ($p < 0.0001$), leading the authors to conclude that a 520-days Mars mission simulation led to hypokinesis and behavioral torpor [20].

1.6. *Moon and Mars environment might difficult circadian adaptation*

The current Global Exploration Roadmap outlined by the International Space Exploration Coordination Group reaffirms human lunar exploration as one of the main next goals to expand human presence into the Solar System [21]. Overall, the Moon has several factors that may difficult circadian adaptation:

A lunar day lasts approximately 29.5 Earth days. The equatorial region of the Moon is illuminated for around 15 of those days, followed by a 15 Earth-day long night. Close to the poles, though, the illumination is more complex to simulate for extended periods of time, since the Moon does not have a stable orbit around the Earth-Sun system. Because of the 1.54° rotational obliquity, polar regions are illuminated differently, compared to places in equatorial latitudes. Certain locations get lighting for the majority of the year with only brief periods of darkness due to the combination of diffuse solar reflection and significant local topographic differences. Also, due to the geometry proper of celestial bodies, at the poles of the Moon, the path of the Sun described across the horizon would be nearly invariant in altitude, this results in areas inside craters where there is never direct sunlight exposure [22].

Another factor to take into consideration on the Moon is the atmosphere, which is 10^{13}, times less dense than Earth's atmosphere which produces a permanently black sky [23]. Thus, during waketime, there's no visual clue orienting the time of the day. Additionally, astronauts during daytime missions will never directly perceive the sunlight as we do on Earth, as this could result in serious eye damage. Astronauts will need to use, just like they did for Apollo missions, visors for diminishing sunlight, thus altering the intensity of light received by the retina. In Apollo suits, the transmittance of the total visor assembly was only 10% in the visible range and one percent in the UV range [24].

Furthermore, the Global Exploration Roadmap highlight human exploration of the surface of Mars as a common driving goal. The journey to Mars and the planet itself involves some challenges to circadian adaptation.

When talking about the Earth-to-Mars journey, we can identify that since there are no objects in space to reflect sunlight, the spaceship's face pointing to the Sun will be completely illuminated and the opposite side of the spaceship will be in complete darkness, although periodical rotation of the spaceship might be a countermeasure. Additionally, a future astronaut would not see any color nor illumination through the window of the ship except for the Sun itself. Also, as the spaceship moves away from the Sun toward Mars, the light intensity will be diminishing through the course of the trip.

It is well known that Mars days (also called *Sols)* last 24 h, 39 min. This is 3% more than Earth days [17]. The duration of the day depends on the latitude on which the measurement is made, and complex mathematical models can predict the number of hours of sunlight for every area on the surface of Mars.

Dust storms are one of the defining features of the Martian atmosphere and range from microscale dust devils to global dust events [25]. They are a major characteristic of the atmospheric inter-annual, seasonal, day-to-day, and daily variability and a source of hazards for future human exploration [26]. These clouds of dust can dim the daylight and typically measure up to several hundreds of km in size; most of the time, these clouds form, evolve, and then dissipate over the course of a few days. In some cases, localized dust storms can interact in a way that optically thick suspended dust covers nearly the entire planet remaining aloft for weeks to months (e.g. the last one occurred in summer 2018 and lasted for more than 150 Martian days). These global dust storms can nearly completely obscure the planet [27].

Another common event that frequently occurs is the so-called Marsquake [28], these phenomena unlike Moonquakes (of less intensity) [29] could be a factor that may happen during sleeping time and interrupt it significantly if the integrity of any structure of a future Mars base needs to be checked promptly.

1.7. Discussion

This review synthesizes the available evidence from short and long-duration LEO spaceflights, Apollo missions, and ground-simulated manned missions to Mars related to sleep deprivation, changes in sleep architecture, use of medication and circadian desynchronization. Data collected across decades of spaceflight missions consistently indicates a loss of sleep and circadian rhythm disruption in crewmembers.

The use of sleep-promoting medication is common among astronauts. Moreover, some crewmembers take a second dose, indicating a perception of ineffectiveness, which may underlie a diminished response to the medication. Of concern is the unrestricted use of sleep medication in this population. Although flight surgeons are aware of the administration of these drugs, the number of doses used is at the discretion of each crewmember (e.g., a second dose is auto-medicated), as it is not part of a prescribed daily treatment. This leads to an abuse of this drugs in this population. Available data shows that, the use of sleep medication during space missions is ~6 times higher than that consumed by U.S. general population (~75% vs ~12%) [30].

Another concern is fatigue, which can endanger mission safety and success. Indeed, fatigue has been associated with mistakes in spaceflight history [31,32]. A measure to counteract fatigue is the use of medications that promote wakefulness and alertness, which have been widely taken by crewmembers. For instance, during short-duration spaceflights onboard the Space Shuttle, 75% of the astronauts reported having used modafinil or caffeine pills [33]. On ISS, modafinil is available to the crew to optimize performance while fatigued [34]. Anecdotally, during the Apollo 7 mission, an astronaut had to take 5 mg of amphetamine to keep awake after falling asleep while on duty [2].

There are various aspects that should be considered for future deep-exploration spaceflights. Data from Apollo missions highlight the necessity of controlling and improving environmental factors and considering the disruption of the 24-h light/dark cycle for crew onboard a future lunar orbital platform. As for Mars, a major challenge will be synchronizing the circadian rhythm to a Martian day.

To our knowledge, this is the first review that includes novel associations related to the Moon and Mars environment concerning circadian adaptation. On the Moon, the illumination is complex, there is a permanent black sky, an absence of visual clue orienting the time of the day; the unfeasibility to directly perceive the sunlight as this could result in serous eye damage should also be considered. On Mars, clouds of dust can dim the daylight for days, weeks, and exceptionally, months.

Currently, many backup systems are employed for preventing major failures on the ISS. In addition, mission control personnel on Earth support ISS operations by maintaining constant contact with crewmembers in space. In contrast, because of communication delays, such backup systems won't be reliable in future manned trips to Mars [9]. Thus, crewmembers will rely more on themselves and their neurobehavioral status, increasing the need to develop countermeasures for sleeping problems and fatigue during Mars missions.

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Authors contributions

Manuel Albornoz-Miranda: Conceptualization, Methodology, Writing - Original Draft preparation, Visualization, Supervision, Project administration. Diego Parrao: Conceptualization, Writing - Original Draft preparation, Visualization. Maximiliano Taverne: Conceptualization, Writing - Original Draft preparation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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