



**Melatonin Efficacy in Aviation Missions Requiring  
Rapid Deployment and Night Operations  
(Reprint)**

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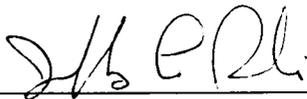
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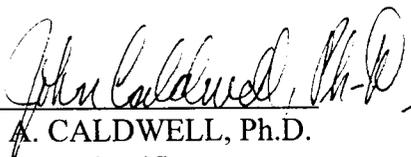


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<b>19. ABSTRACT (Continue on reverse if necessary and identify by block number)</b> The rapid deployment of Army aviation personnel across time zones, combined with missions beginning immediately upon arrival, results in desynchronization of physiological and cognitive performance rhythms. Implementation of effective countermeasures enhances safety, health, well-being, and mission completion. The naturally occurring hormone melatonin has been suggested as an effective countermeasure for jet lag and shift lag because of its influence on the human circadian timing system and its hypnotic properties. This study was conducted to evaluate the efficacy of melatonin (10 mg) in maintaining stable sleep/wake cycles of Army aircrews during a training mission involving rapid deployment to the Middle East and night operations. Melatonin treatment maintained sleep durations between 7-8 hours while placebo treatments resulted in shorter sleep durations. Upon awakening, the melatonin group exhibited significantly fewer errors than the placebo group in a dual-task vigilance test. Therefore, melatonin appears to be a useful treatment for the prevention of sleep disruptions and cognitive degradation, even in the uncontrolled sleeping environments characteristic of military deployments.												
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# Melatonin Efficacy in Aviation Missions Requiring Rapid Deployment and Night Operations

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COMPERATORE CA, LIEBERMAN HR, KIRBY AW, ADAMS B, CROWLEY JS. *Melatonin efficacy in aviation missions requiring rapid deployment and night operations.* *Aviat Space Environ Med* 1996; 67:520-4.

**Background:** The rapid deployment of Army aviation personnel across time zones, combined with missions beginning immediately upon arrival, results in desynchronization of physiological and cognitive performance rhythms. Implementation of effective countermeasures enhances safety, health, well-being, and mission completion. The naturally occurring hormone melatonin has been suggested as an effective countermeasure for jet lag and shift lag because of its influence on the human circadian timing system and its hypnotic properties. **Method:** The efficacy of melatonin (10 mg) in maintaining stable sleep/wake cycles of Army aircrews was tested during a training mission involving rapid deployment to the Middle East and night operations. Cognitive performance was tested before and after travel; activity rhythms were recorded continuously for 13 d. **Results:** Melatonin treatment advanced both bedtimes and rise times (2-3 h) and maintained sleep durations between 7-8 h. Placebo treatment was mostly associated with longer advances in rise times than bedtimes resulting in shorter sleep durations (5-7 h). Upon awakening, the melatonin group exhibited significantly fewer errors (mean: 7.45) than the placebo group (mean: 14.50) in a dual-task vigilance test. **Conclusion:** Melatonin can be a useful treatment for the prevention of sleep disruptions and cognitive degradation, even in uncontrolled sleeping environments characteristic of military deployments.

AMONG MILITARY AVIATION missions, those involving rapid deployment and night operations are the most disruptive to sleep and performance. Mission objectives often require quick response, rapid travel across several time zones, and immediate rotation of work schedules from daytime to either nighttime or early morning duty hours. Missions involving travel across more than four time zones and rotations to early morning or nighttime work schedules result in jet lag and shift lag symptoms. These manifest themselves in varying degrees of sleep loss, fatigue, alertness degradation, digestive disorders, stress, and performance degradation (4,6,12).

Many military tactical situations, such as the case of rapid deployment, are characterized by lack of predictability of travel and work schedules. In many instances, troops are in an alert status and experience a surge in workload and an extension of duty hours for several days prior to deployment. Upon arrival at the destination, work is carried out, following the mission's time line, until mission objectives are accomplished. It is difficult to maintain crew rest using management of sleep, meals, and daylight exposure

schedules under deployment conditions, a situation drastically different from the case of leisure or business travellers and/or shiftworkers. Development of countermeasures that effectively and quickly adapt the sleep/wake cycle to a mission-driven work schedule is necessary to prevent sleep loss and performance degradation.

A candidate countermeasure is the use of the hormone melatonin. Melatonin is a methoxy-indole produced by the pineal gland through the methylation and acetylation of a more commonly known indolamine, serotonin. The pineal gland produces melatonin only during the dark hours of the day. Some of the properties of this hormone resemble those of hypnotic drugs: specifically, the induction of sleep (11,17), increased theta brain wave activity (characteristic of light sleep), and improvement of sleep quality (1-3,7,15). In addition, melatonin prevents jet lag symptoms in studies involving eastward and westward travel across time zones (14).

Melatonin's ultra-short half-life (less than 1 h), its demonstrated safety in humans, and sleep regulating properties make this hormone a potential pharmacological countermeasure for the prevention of sleep loss and performance degradation during extended military missions (16).

In this study we tested the efficacy of melatonin in preventing sleep loss and cognitive degradation in volunteers from a deploying Army aviation unit. Melatonin (10 mg) or placebo was combined with nonpharmacological techniques to prevent the adverse effects of travel across time zones and nightshift on sleep and alertness. The mission required travel to the Middle East across eight time zones (via U.S. Air Force C-5 aircraft) and night operations upon arrival.

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## METHODS

**Subjects:** There were 29 male aircrew members, ranging from 24–41 yr of age, who volunteered for participation. Because of work schedule conflicts, inability to follow instructions, and instrumentation difficulties, analyses were conducted on data from 23 of the 29 participants for activity data and 27 of 29 participants for cognitive data. All participants gave their informed consent and were advised of their right to withdraw at any time. Each subject underwent a medical examination as part of routine preparation for deployment exercises. The study was double-blind and placebo controlled, and volunteers were assigned randomly to either of two groups, melatonin or placebo. A drug sensitivity test, in which placebo or melatonin (depending on group membership) was administered between 0900–1000 CST, was conducted 4 d prior to the beginning of the study. There were no reports of adverse or undesirable side effects.

The entire protocol was reviewed and approved by the USAARL Human Use Committee, the Army Surgeon General's Human Subjects Research Review Board, and the Food and Drug Administration. This study was conducted under melatonin IND 41771.

**Instrumentation:** Activity monitors (AM's) (Computer Science Applications, Inc., Fort Walton Beach, FL) were used to study the rest/activity cycles during shiftwork transitions. Subjects wore AM's continuously on the non-dominant wrist for 13 consecutive days. Changes in counts of movement frequency per minute were used to determine bed times, rise times, and estimated sleep duration (5).

A computerized battery of tests, previously used by Dollins (10), was used to assess the effects of melatonin on alertness, reaction time, mood, and sleepiness. The test battery was selected on the basis of prior demonstrated sensitivity to the effects of melatonin, various hypnotics, other pharmacologic agents, and/or sleep loss. The following tasks were included in each test session: a) dual task vigilance; b) simple reaction time; c) four-choice reaction time; d) profile of mood states; and e) Stanford sleepiness scale. All performance tests and mood inventories were administered on portable computers (GRiD Compass II, Model 1131; GRiD Systems, Fremont, CA) equipped with electroluminescent displays.

Living quarters in the Middle East consisted of a warehouse structure housing approximately 200 Army-style bunk beds and metal wall-lockers. An overhead air duct extended lengthwise through the building providing air cooling and masking noise, measured at approximately 50 dB SPL near the center of the building. Ten portable CD players (Sharp Inc., Mahwah, NJ) were placed around the perimeter of the sleep area and used to play masking sound (ocean waves) continuously. This additional sound masking was provided to attenuate noise produced by daytime personnel also living in the warehouse.

**Procedure:** The deployment training mission required travel to the Middle East aboard a U.S. Air Force C-5 aircraft originating within the central standard time zone in the continental U.S. Air travel began at approximately 1200 in the origination time (OT) zone (2000 in the desti-

nation time [DT] zone) and lasted for approximately 14 h. Participants arrived in the Middle East at 1000 DT (0200 OT). Immediately upon arrival, personnel unloaded equipment, traveled to the site of operations, conducted helicopter maintenance test flights, and began night operations. On the day of arrival, duty hours for most participants ended at 0400 DT (2000 OT). Thereafter, participants usually began their duty day between 2100–2400 DT and retired between 0400–0600 DT.

**Sleep management plan:** Participants maintained their normal sleep/wake cycles throughout study days 1–4. However, pre-adaptation to the destination time zone and mission duty hours was attempted beginning 3 d prior to departure, on day 5 of the study (Table I). This process required participants to advance their bed times from approximately 2200 to 1900 OT, and rise times from 0600 to 0300 OT. During these days, participants were asked to retire as close to 1900–2000 OT as permitted by their work schedules. However, duty hours could not be controlled because of the surge in workload associated with the overseas deployment.

**Daylight exposure management and crew rest plan:** Upon arrival at the destination at 1000 DT, all participants were instructed to avoid exposure to daylight until 1200 DT or later. Daylight avoidance was recommended prior to retiring after the night shift. In cases where unwanted daylight exposure was unavoidable, participants were equipped with UVEX® sunglasses (UVEX Safety Inc., Smithfield, RI). The frames of these sunglasses minimized light leaks by wrapping around the outer canthus of the eye. The lenses attenuated illuminance in bright daylight to the extent that the wearer experienced brightness levels comparable to twilight. For safety reasons volunteers were instructed not to operate vehicles or complicated machinery when wearing the sunglasses. This daylight management schedule was designed to prevent stimulation of the endogenous circadian clock at times of the day which would have delayed rather than advanced the sleep/wake cycle (13).

Upon arrival to the Middle East, a daylight exposure schedule was implemented to advance sleep onset time to approximately 0400 DT (2000 OT). Daylight exposure was scheduled during the Middle Eastern afternoon from approximately 1200 to sunset DT (0400–1000 OT). This daylight exposure schedule stimulated the phase advance of circadian rhythms, and ultimately of the sleep/wake cycle (8,9,13). In addition, participants were asked to adhere to the following crew rest plan: a) rise as close as possible to 1300 DT; b) maintain consistent lunch and dinner schedules; and c) take melatonin (or placebo) 30 min prior to bed time. This strategy promoted an early afternoon exposure to daylight that continued until sunset. This crew rest plan did not interfere with participants' duty hours and completion of mission related tasks.

**Drug regimen:** Melatonin (10 mg) or a placebo (cellulose) was administered prior to travel (study days 5–7), on the day of travel (study day 8), and for 5 d after arrival at the destination (study days 9–13) (Table I). The in-flight dose was administered between 1930–2000 OT. After arrival to the Middle East, melatonin was administered daily at approximately 0400 DT (2000 OT). Since exact control of bed times was not possible during the

TABLE I. SCHEDULE OF DRUG ADMINISTRATION AND DATA COLLECTION.

Study Days	1	2	3	4	5	6	7*	8†	9	10	11	12	13
Preadaptation to DT					P	P	P						
Drug administration					D	D	D	D	D	D	D	D	D
Cognitive testing			T	T	T	T			T	T	T	T	T
Activity data	A	A	A	A	A	A	A	A	A	A	A	A	A

\* Alert; † Travel and arrival day.

P: Preadaptation to destination time zone; D: Melatonin or placebo administered 30 min prior to bed time; T: Cognitive, mood, and sleepiness evaluations; A: Activity data recorded from AM.

mission, administration time varied slightly with individuals' work schedules.

*Cognitive, mood, and sleep evaluations (C-M-S):* Cognitive testing, mood and sleepiness evaluations were conducted prior to travel during study days 3–6, and resumed during days 10–13 at the destination (Table I). During pre-deployment days, tests were conducted in a conference room located in a hanger, where pilots, crew chiefs, and maintenance personnel performed their daily duties. Participants were allowed to take time out from their daily duties to report for testing during the morning hours between 0900 to 1200 OT. In the Middle East, testing took place in a corner of a large warehouse that also served as living quarters for deployed personnel. As was the case for predeployment conditions, participants were tested beginning approximately 3 h after awakening. Since most participants slept until 1000–1200 DT, cognitive testing took place between 1200–1500 DT.

STATISTICS

*Analysis of changes in the sleep/wake cycle:* The magnitude and direction (advance or delay) of the change in post-deployment bed times and rise times, relative to pre-deployment, indicate the effects of travel, work schedules, and drug regimen on the sleep/wake cycle. For both melatonin and placebo groups, changes in bed times (BT) and rise times (RT) were analyzed separately using the STATISTICA® (StatSoft, Inc.; Tulsa, OK) software package. A one-way ANOVA with repeated measures across two levels of deployment (pre- and post-deployment) was applied to bed time and rise time data obtained during days 1–4 (pre) and days 9–12 (post). The overall change in the sleep/wake cycle was determined by subtracting the rise time shift from the bed time shift (calculated in hours), as shown below:

$$(BT_{pre-post}) - (RT_{pre-post}) = \text{Net Advance of Sleep/Wake Cycle}$$

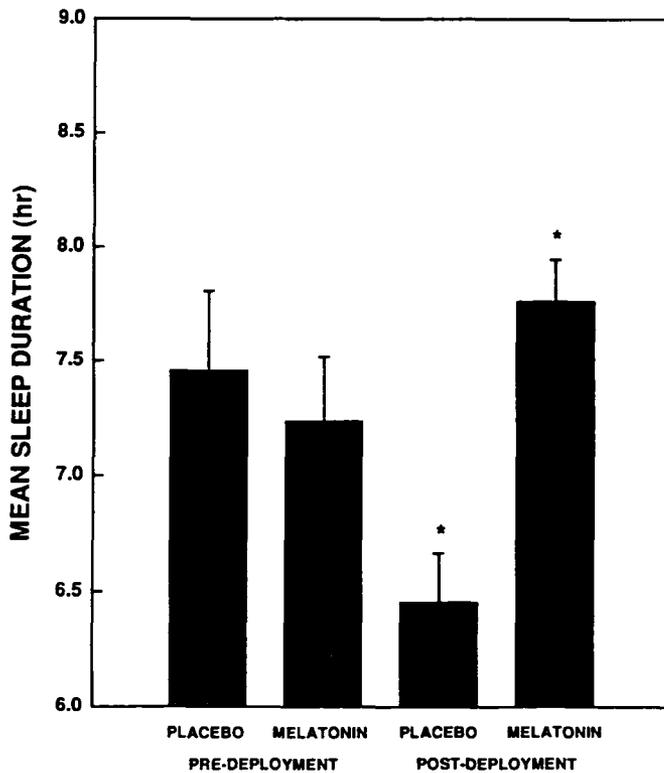


Fig. 1. Mean sleep durations (and standard errors of the mean) calculated from study days 1–4 (pre-deployment) and days 9–12 (post-deployment). Asterisks (\*) indicate significant difference (p = 0.011) between melatonin and placebo groups post-deployment.

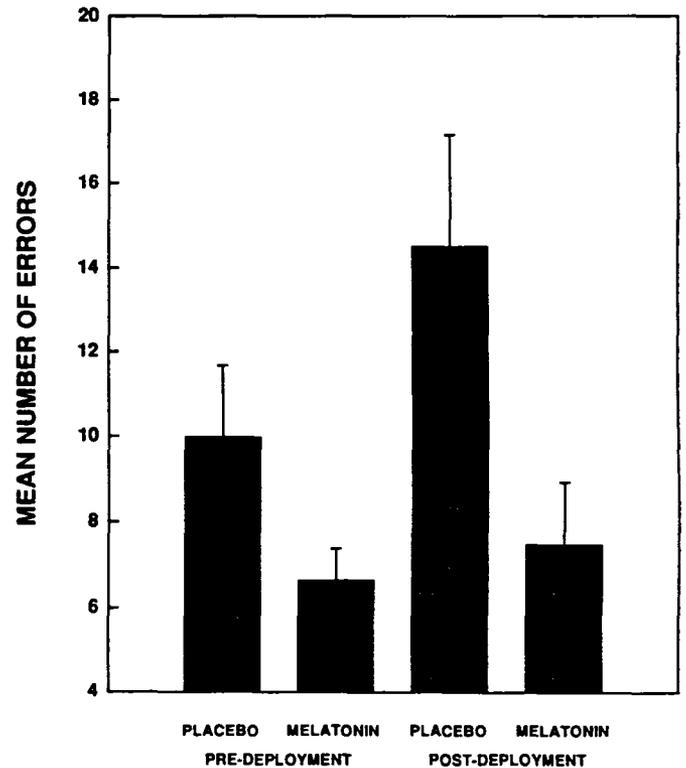


Fig. 2. Mean number of errors during BAKAN sessions plotted across pre-deployment and post-deployment conditions. Each average was calculated from study days 3–5 (pre-deployment) and days 10–13 (post-deployment). Error bars represent the standard error of the mean.

TABLE II. DUAL TASK VIGILANCE MEANS.

	Pre-Deployment		Post-Deployment	
	Placebo	Melatonin	Placebo	Melatonin
Misses*†	9.97 (1.69)	6.63 (0.74)	14.50 (2.66)	7.45 (1.48)
False Rs	12.26 (3.58)	14.69 (5.33)	13.24 (6.71)	12.29 (6.79)

For all p values F(1,25).

\* Significant Drug Main Effect, p = 0.0314.

† Significant Deployment Main Effect, p = 0.0088.

Drug by Deployment Interaction, p = 0.060.

The overall time shift of the sleep/wake cycle is then expressed by a positive or negative number which indicates the direction of the shift. Negative differences between bed time shifts and rise time shifts indicate a larger advance in post-deployment rise times than bed times. Conversely, positive values indicate a larger advance in post-deployment bed times.

**C-M-S data:** The analysis of cognitive performance consisted of a 2 × 2 mixed factorial ANOVA. Deployment status (pre and post) and drug (melatonin and placebo) were used as the within and between subjects factors, respectively. Data collected in the U.S. between days 3–5 were used as pre-deployment baseline data (no melatonin/placebo administered), and data collected in the Middle East between days 10–13 were used as post-deployment data.

**Sleep duration:** Estimated sleep durations were obtained from activity/rest profiles generated from activity monitors (5). Data from days 1–4 were used as baseline. Days 9–12 depicted post-deployment estimated sleep durations. A mixed factorial ANOVA with 2 levels of the between subjects factor drug (melatonin and placebo) and 2 levels of the within subjects factor deployment status (pre- and post-deployment) was used to determine main effects and interactions. The Tukey honest significant difference method for unequal sample sizes was used for post-hoc multiple comparisons.

RESULTS

**Changes in sleep/wake cycle as a function of melatonin therapy:** A significant post-deployment advance of bed times and rise times was found for both melatonin and placebo treated participants. The melatonin group exhibited an average change in bed times from 2246–1942 OT (F [1,43] = 42.53, p < 0.0001), and rise times from 0559–0320 OT (F [1,43] = 60.05, p < 0.0001). The average advance in bed times and rise times (3.07 h and 2.65 h, respectively)

TABLE IV. FOUR CHOICE REACTION TIME MEANS.

	Pre-Deployment		Post-Deployment	
	Placebo	Melatonin	Placebo	Melatonin
# Correct	487.06 (7.71)	450.63 (33.20)	464.87 (23.56)	490.54 (4.36)
RT*	586.41 (20.52)	600.39 (21.09)	563.30 (15.48)	571.30 (18.08)
Errors	0.64 (0.27)	1.25 (0.28)	0.89 (0.22)	0.65 (0.22)
TO Errors	0.17 (0.08)	0.43 (0.17)	0.10 (0.05)	0.09 (0.05)

For all p values F(1,25).

\* Significant Deployment Main Effect, p = 0.0015.

TABLE III. SIMPLE REACTION TIME MEANS.

	Pre-Deployment		Post-Deployment	
	Placebo	Melatonin	Placebo	Melatonin
Simple RT	378.32 (12.95)	370.55 (8.49)	375.48 (7.78)	366.11 (8.40)
RT Errors*	1.20 (0.22)	1.39 (0.22)	1.83 (0.37)	1.12 (0.27)
TO Errors	0.40 (0.19)	0.32 (0.15)	0.29 (0.12)	0.18 (0.10)

For all p values F(1,25).

\* Significant Drug by Deployment Interaction, p = 0.0393.

resulted in a 0.42 h positive net advance of the sleep/wake cycle and an extension of the rest period.

Placebo-treated participants also showed a significant advance in bed times from 2249–2019 OT (F [1,40] = 31.26, p < 0.0001) and rise times from 0546–0247 OT (F [1,40] = 56.91, p < 0.0001). The average advance in bed times and rise times (2.5 h and 2.98 h, respectively) resulted in a 0.48 h negative net advance of the sleep/wake cycle and a reduction of the rest period.

**Estimated sleep duration:** The results of the mixed factorial ANOVA revealed a significant drug main effect (F [1,83] = 5.475, p = 0.022) and a significant interaction of drug by deployment (F [1,83] = 4.791, p = 0.0314). Post-hoc comparisons using Tukey’s honest significant difference for unequal sample sizes showed a significant increase in estimated sleep duration (p = 0.011) for melatonin treated subjects post-deployment (Fig. 1). These results support the analysis of sleep/wake profiles indicating that a significant proportion of placebo-treated participants experienced a reduction in total sleep time and may have had more difficulty staying asleep post-deployment.

**Melatonin effects on vigilance:** In general, there were no significant differences in mood or subjective fatigue scores between melatonin and placebo groups. Mild sleepiness and fatigue were reported occasionally, shortly after melatonin administration, but never upon awakening. The dual vigilance task resulted in the most reliable evidence of the interaction of drug and deployment status. Fig. 2 shows the mean number of errors on the dual vigilance task for both pre- and post-deployment conditions. The placebo group exhibited a clear trend towards greater number of errors post-deployment, while the melatonin group maintained performance almost without change. Upon arrival to destination, melatonin-treated participants exhibited fewer errors in the dual vigilance task compared to their placebo counterparts (Table II and Fig. 2).

TABLE V. PROFILE OF MOOD STATES (POMS) MEANS.

	Pre-Deployment		Post-Deployment	
	Placebo	Melatonin	Placebo	Melatonin
Anger*	5.83 (2.35)	3.47 (1.18)	3.26 (1.11)	1.81 (0.68)
Tension	6.41 (1.84)	5.54 (1.04)	5.51 (1.18)	4.51 (0.91)
Depression	2.71 (1.50)	3.02 (1.04)	2.47 (1.52)	2.11 (0.81)
Vigor	18.53 (0.85)	16.04 (0.97)	16.29 (1.01)	15.83 (0.85)
Fatigue	3.71 (1.23)	5.35 (1.12)	4.14 (1.43)	4.17 (0.91)
Confusion	3.01 (0.81)	4.65 (0.79)	3.22 (1.08)	3.88 (0.66)
SSS	2.22 (0.11)	2.30 (0.24)	2.49 (0.25)	2.19 (0.21)

For all p values F(1,25).

\* Significant Deployment Main Effect, p = 0.0305.

Results of simple reaction time, four choice reaction time, and profile of mood states are presented in Tables III, IV, and V, respectively. Only three statistical outcomes resulted in significant differences. In the simple reaction time task, melatonin-treated participants exhibited fewer errors post-deployment (Table III). In the four choice task, both groups exhibited a significant improvement of reaction times after deployment (Table IV). Lastly, a significant main effect was revealed for the POMS category of Anger (Table V), indicating that both groups scored lower in this factor after arrival to the Middle East. Although statistically significant, these results are probably independent of drug effects.

## DISCUSSION

The post-deployment increase in sleep duration following melatonin administration corroborated previous studies in which exogenous melatonin has been shown to readjust the sleep/wake cycle and reduce jet lag after travel across time zones (6,14). The maintenance of vigilance performance associated with melatonin administration (Fig. 2) may be attributed to average sleep durations of up to 8 h (Fig. 1). Analysis of activity data suggest that melatonin may have stabilized the sleep/wake cycle by facilitating the advance of bed times (3.07 h) and rise times (2.65 h) while preventing sleep loss.

Placebo treatment also resulted in the advance of bed times (2.5 h) and rise times (2.98 h), but was associated with a significant reduction of sleep duration. The greater mean advance of rise times than bed times indicates that participants had difficulty staying asleep. Close examination of deployment bed times and rise times shows that the placebo group awoke earlier (0247 OT or 1047 DT) than the melatonin group (0320 OT or 1120 DT), although they retired about 37 min later (2019 OT or 0419 DT) than the melatonin group (1942 OT or 0342 DT). These differences were not driven by irregular work schedule requirements, as all volunteers did not begin duty hours until after 1200, and usually completed nightly flight missions at the same time.

The extension of the sleep period resulting from this simple melatonin regimen (10 mg, 30 min prior to bed time) supports the already proposed notion that melatonin therapy may be effective in the treatment or prevention of sleep disorders involving premature awakening or insomnia (15). Further, the potential use of melatonin during conditions characteristic of military deployments may significantly facilitate the implementation of sleep management plans in the process of readaptation to new work schedules and time zones. The efficacy of melatonin in the present study suggests that its use in military deployments may not require precise control of environmental conditions. The increase in sleep duration was induced in participants who slept in a noisy, crowded warehouse.

It is difficult to unequivocally ascertain whether the changes reported here are mediated via melatonin's hypnotic or resynchronization (chronobiotic) properties. To test melatonin's chronobiotic efficacy during real-world military missions may require a greater experimental challenge to the biological clock. Further studies involving multiple, successive reversals in the direction of travel, allowing only a few days at each destination, may

be useful in emphasizing the dependence on the resynchronization properties of melatonin rather than its hypnotic properties. Notwithstanding the mechanism of action, the results presented here strongly suggest that exogenous melatonin can be an effective adjunct of maintaining alertness and preventing sleep loss in rapid deployment missions requiring eastward travel and nighttime duty hours.

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