Sleep and Alertness Management During Military Operations: Questions To Be Answered

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Summary
Sleep and alertness management is a major point of attention for the medical support of military round the clock operations. Crew's awareness on the effects of fatigue and sleepiness should be enhanced. Flight surgeons should be trained on the use of practical methods to prevent serious fatigue and to enhance performance and alertness of the crew. Although, in civil and in military aviation a considerable number of studies have been conducted on fatigue countermeasures and preventive strategies, results are not readily available for practical use by flight surgeons. In order to develop useful guidelines for flight surgeons and crew, the international aeromedical research community should be able to produce a database on what is already known and identify areas where knowledge is lacking. In this context research questions related to the use of strategic naps, hypnotics, stimulants, and chronobiotic treatment are put forward.

1 Background

Military round the clock operations are characterized by circadian disruptions, rapid work shift changes, prolonged duty overnight, sleep loss, and high stress levels. These factors may result in high levels of fatigue and sleepiness when on duty, with consequent reduction of operational effectiveness and safety. Inadequate sleep facilities and mission stress further contribute to serious sleep deprivation (1), which is known to be an important cause of impaired performance of aircrew (e.g. 2, 3, 4, 5). Therefore, prevention of sleep loss and fatigue is a major point of attention in the medical support of a mission. Although several strategies for sleep-wakefulness management are available, many flight surgeons are not trained in the management of these problems. Moreover, useful information on the use of medications or other strategies is often not available at the deployment sites. In this context, it is important to provide flight surgeons with practical information and tools to prevent serious fatigue and sleep deprivation in their crews. In order to develop useful guidelines, it will be necessary to evaluate established strategies as used during the South Atlantic Campaign (6) and Operations Desert Shield and Storm (7) and to assess the usefulness and applications of recently developed preventive strategies and countermeasures.

The usefulness of preventive strategies and countermeasures has to be assessed in the light of the military scenarios in which they might be needed. Therefore, information and feed back from the operational commanders is indispensable for medical research teams.

In practice, the Royal Netherlands Air Force (RNLAF) is confronted with the following scenarios, which potentially cause impaired performance and alertness of the crew:

- Missions in the evening and night. Crew has to sleep during the day, when their body clock dictates wakefulness. In many cases this sleep will be short and disrupted (8). Moreover, sleep during the day will further be hindered by inadequate sleep facilities (e.g. noisy activities at the site).

- Very early missions, taking place when the circadian performance rhythm is in its trough (3-6 a.m.). Sleep preceding such missions is characterized by short total sleep times and impaired quality (5, 9). Crew often try to anticipate very early rising by going to bed in the early evening. However, their sleep efficiency is often impaired and sleep latencies are long.

- Critical activities directly following transmeridian deployment, with consequent jet lag symptoms, impaired performance, and increased daytime sleepiness in the first days after arrival in the new time zone (10).

- Sustained missions during which performance and alertness have to be preserved for a long time period. In most cases, sustained missions are characterized by shift work. It takes some days before the sleep-wakefulness rhythm has adapted to changes from day to night shifts (8). During sustained missions cumulative fatigue is caused by cumulative sleep debt and mission stresses (11, 12, 13).

In the above-mentioned scenarios sleep management plays an important role. General and specific measures are necessary to prevent serious fatigue and sleep loss

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in crews. In most cases general measures will include proper preparation of the mission, optimization of sleep facilities, and adequate support of crew with regards to mission stress and individual problems. More specific measures are needed to optimize performance and alertness. These specific measures include planning of sleep periods and strategic naps, induction of sleep at times when the body clock dictates wakefulness, antagonizing sleep inertia and/or residual effects of hypnotics, stimulating performance and alertness at times when the body clock dictates sleep, and accelerating entrainment after transmeridian deployment.

2 Operational issues to be studied

In civil aviation, research has been focused mainly on non-pharmacological strategies, while in the military environment, research on the pharmacological approach has predominated. Extensive research has been already performed as well in civil aviation as in the military. However results are not readily available for practical use by the flight surgeon. The aeromedical research community should be able to draw guidelines from what is already known and identify areas where knowledge is lacking.

In order to develop practical guidelines to be used by flight surgeons during mission preparation and at the deployment site, the Ministry of Defense of The Netherlands commissioned research on the following issues:

Short sleep periods and mission effectiveness

Operations during late evening or night require a minimum of sleep prior to the mission. Because the circadian phase does not allow for sleep, this daytime sleep has to be facilitated pharmacologically in most cases. Furthermore, proper measures should be taken to reduce sleepiness after waking up and stimulate alertness during the night. Sorties at dawn (3-6 a.m.) also have their specific problems, as pre-duty sleep is often too short and crews have to start when their body clock still dictates sleep. Both scenarios require pharmacological induction of sleep, "assisted awakening", and alertness enhancers to preserve performance and alertness during the mission. In addition, the use of short naps has to be considered.

During extended missions, cumulative sleep deprivation will occur when daily sleep times are too short. Critical sleep deprivation is known to impair performance and alertness and to reduce mental and physical fitness.

Mission effectiveness and jet lag / change to night shift

Optimal performance after transmeridian deployment requires rapid adaptation to the new time zone and measures to counteract the effects of jet lag. In addition to using the local Zeitgebers, entrainment might be accelerated by the use of melatonin and bright-light (alone or in combination) and performance and alertness can be enhanced by pharmacological means. This approach, with the addition of strategic naps and hypnotics, might also be used to preserve sleep and alertness when crews change from day to night shift.

3 Questions to be answered

3.1 Inter-individual differences

Studies concerning the effects of shift work and jet lag, and recommendations on fatigue countermeasures seldom take into account inter-individual variability. However, it is common knowledge that people differ considerably in their capacities to sleep at unusual times of day or to sleep in a hostile environment. Inter-individual differences are also found in sensitivity for the effects of transmeridian travel and shift work, and the effects of countermeasures such as melatonin, hypnotics, alertness enhancers, and strategic naps. In a study on the effects of a controlled rest on the flight deck on performance and alertness in 59 airline pilots, it was found that a 40-minute nap in the cockpit seat significantly improved performance and alertness up to top of descent (14). Although this beneficial effect was statistically significant, for some pilots the nap had no effect and a minority even showed impaired performance and alertness for a longer time after the nap. Although this minority has no statistical consequences, these few affected pilots might have detrimental effects on mission effectiveness and safety. Therefore, when recommending the cockpit nap, it was emphasized that those pilots, for whom such a nap will be disadvantageous, should be enabled to identify themselves. For this purpose, military crew should be educated to identify their personal characteristics and to enhance their awareness of causal relationships between sleep, fatigue, performance, and alertness. In civil aviation, a "Fit-to-Fly Checklist" has been developed for that purpose (15), which is tailored to the needs of airline pilots (and as such not applicable to aircrew engaged in military operations).

Furthermore, tools should be developed to enable flight surgeons and commanders to identify individual characteristics of pilots and other professionals with highly critical tasks. Flight surgeons could collect useful information during training missions involving transmeridian deployment and/or shift work. Information should minimally include "baseline" individual characteristics, such as age, morning/evening type, good/poor sleeper, adaptability to shift work, capacity to nap, duration of sleep inertia, and past experience with jet lag, melatonin, hypnotics, and stimulants. In addition, during a deployment, subjective data on sleep-wakefulness patterns, alertness/sleepiness during duty, and (cumulative) fatigue can be collected, using sleep logs. Ideally, objective data on sleep-wakefulness patterns (actigraphy) and a circadian marker should complement subjective data, but this might not be feasible during an intensive deployment. It should be considered to use a pocket-size computer for data-logging. This method has been extensively used in field studies in civil aviation (5, 14) and has proven its practicability. Data from the personal "pocket-computer" can be downloaded into a PC at the deployment site, enabling easy access to data for the flight surgeon or commander. Using above-mentioned information, flight surgeon and crew can determine the best possible strategy to prevent serious fatigue and to preserve performance and alertness during the mission.

Commanders should also be provided with data on the cumulative sleep debt of themselves and their subordinates. Up to now, commanders often lacked this information and therefore could not estimate the impact on individual and unit effectiveness that lack of sleep would have over the next few days (13). Therefore, an easy method to measure (cumulative) sleep duration (sleeplogs, actigraphy) should be developed for use in a military environment.

3.2 Strategic napping

The effectiveness of short naps (0.5-3 hrs) to counteract fatigue and to prevent inadvertent sleeping during duty has been evidenced by many authors (e.g. 14, 16, 17, 18). When circumstances permit, a strategic nap of 1-2 hrs should be considered as a countermeasure to fatigue and sleepiness. It has been found that performance and alertness improve as a function of sleep duration (19, 20). In general, longer naps are not recommended because these might interfere with the normal sleep-wake rhythm. Inter-individual differences have to be taken into account, because some subjects will not be able to sleep at all (21) or remain drowsy for long time periods after the nap. When naps are planned at times when the body clock dictates wakefulness, pharmacological sleep induction has to be considered. An important question to answer is the duration of sleep inertia after a nap. It seems likely that sleep inertia can be shortened by instructing the napper to follow the normal "morning routine" after awakening (e.g. take a shower, brush teeth, have coffee and breakfast). However, this is questioned by Jewett, Wyatt, Ritz-de Cecco et al. (22), who found no effects of going out of bed, breakfast, or showering on the duration of sleep inertia. After a 40-min controlled nap in the cockpit seat, sleep inertia was estimated to last less than 15 minutes on average (14, 17). However, duration of sleep inertia was not explicitly assessed in these studies. In contrast, Caldwell & Caldwell (23) found that postnap grogginess persisted for about 2 hours after a 2 hour nap taken at 21:00 hr. Although this long sleep inertia might be related to the time the nap was taken, this finding might have important consequences for the planning of naps.

In summary, in the context of strategic napping the following questions should be addressed in future studies:

- necessity and feasibility of pharmacological induction of sleep for daytime naps
- duration of sleep inertia after naps of various duration and at various times of day
- effectiveness of stimulants and/or bright light in reducing sleep inertia after a nap
- combination of short naps and stimulants and/or bright light to enhance performance and alertness

3.3 Induction of sleep

Although the ideal hypnotic for aircrew engaged in military missions does not exist, hypnotics are probably essential to preserve sleep under difficult conditions. Nicholson (6) reported that 20 mg temazepam (the rapidly absorbed formulation) was useful in helping aircrew acquire sleep at irregular times of the day during the South Atlantic Campaign. There is sufficient evidence that the rapidly absorbed formulation of temazepam is free of residual effects on performance and alertness as measured 8 hours after ingestion (24, 25). This also applies for the triazolo-thienodiazepine brotizolam (25, 26), which compound is not marketed in The Netherlands. Both hypnotics are aimed at the preservation of a 7-8 hour sleep. During intensive and sustained operations it is often necessary to ensure sleep during shorter time periods, and the question is whether temazepam and/or brotizolam are free of residual effects 5-6 hours after administration. In this context zolpidem, an imidazopyridine with a short elimination half-life (2.4 hrs on average), is to be considered as an alternative. It was found that 10 mg zolpidem increased effectiveness of a 2 hour nap, whereas performance and alertness measured 4½ hours post-administration showed no differences between zolpidem and placebo (23). There is evidence that 10 mg zolpidem is free of residual effects from 6 hours after ingestion (27, 28). However, the issue of sedative residual effects still needs further study with special reference to the occurrence of residual effects in females using zolpidem.

For practical use, the question remains whether zolpidem 10 mg has an advantage over temazepam (10-20 mg), of which the use in aircrew is well established during the past decades. When answering this question, it has to be taken into account that residual effects, if any, might be completely counteracted by a stimulant drug that will be administered to crewmembers after the wake up call.

The very recently developed non-benzodiazepine zaleplon has a half life of approximately 1 hour and is advocated by the manufacturer as a sleep inducer for people with transient insomnia and sleep disturbances associated with time zone shifts or shift work schedules.

It appears to facilitate falling asleep but the effect on total sleep time is unclear (29). Dietrich, Emilien and Salinas (30) showed that 8.5 to 12.5 hours after ingestion of 5 or 10 mg zaleplon residual effects did not significantly differ from placebo, while 7.5 mg zopiclone showed significant sedative effects. This was confirmed by O'Hanlon, Vermeeren, Fournie & Danjou (31), who found no evidence for residual effects 5 to 6 hours after the last dose of 10 or 20 mg zaleplon. These results justify further consideration of zaleplon in the context of transient insomnia of military crew. Although zaleplon is not a benzodiazepine, it binds to the $GABA_A$-benzodiazepinereceptorcomplex. Therefore, it should be taken into account that adverse reactions such as rebound insomnia, anterograde amnesia and hazardous behaviour shortly after ingestion, might occur as frequently as in the 'ultra-short benzodiazepine' group. The frequency of these reactions is not known, because the compound has only recently appeared on the market.

In summary, in the context of hypnotics the following questions should be addressed in future studies:

- residual effects of temazepam 5-6 hrs after administration
- residual effects of zolpidem 5-6 hrs after administration in females
- comparison of zolpidem 10 mg with temazepam (10-20 mg) for induction of sleep of various duration (2 - 4 - 6 hrs)
- usefulness of zaleplon in the military environment
- effectiveness of stimulants and/or bright light in counter-acting residual effects of hypnotics

3.4 Melatonin

Hypnotic properties

In the context of induction of daytime sleep during intensive military operations, the usefulness of exogenous physiological or supra-physiological doses of melatonin is a matter of discussion. Results of various studies on the sleep inducing properties of melatonin are difficult to compare because of large differences in doses (range 0.1-250 mg) and assessment methods. Moreover, it is known that there is considerable inter-individual variability in endogenous melatonin production and in dose-response and distribution rates of exogenously administered melatonin.

Although it was observed that melatonin administration during the day produces more consistent reductions in sleep latency than does nocturnal administration (32), some results from studies on the efficacy of melatonin after night-shift work were disappointing (33, 34). Moreover, the sleep promoting action in insomniacs with *non-circadian* sleep disturbance has not been convincingly evidenced (35). Melatonin might be considered as a gentle promoter of general relaxation and sedation, which -in favorable conditions- might facilitate sleep onset (36). However, when efficient (daytime) sleep induction in military crew is pursued, hypnotics such as temazepam or zolpidem appear to be more efficacious than melatonin.

Phase shifting properties

It appears that in military settings melatonin's chronobiotic effects are more important than its hypnotic properties. There is sufficient evidence that exogenous melatonin, when suitably timed, is able to accelerate adaptation to phase shift in both field and simulation studies of jet lag and shift work (37). However, most studies employed volunteer travellers who, unlike military crew, were free of duties at their destination. Studies in aircrew on duty showed less favorable results (38). Disappointing results might be caused by subjects receiving melatonin treatment at an inappropriate circadian phase, as there is evidence that the timing of melatonin administration is fairly critical. Moreover, it has to be taken into consideration that there is large inter-individual variability in the phase-shifting properties of exogenous melatonin.

Adaptation should not be pursued during short missions and/or rapid shift rotations. However, in other cases of transmeridian deployment acceleration of adaptation will be beneficial. When the aim is to accelerate adaptation after transmeridian deployment, melatonin is recommended as first choice treatment. However, there is discussion about the usefulness (and recommended duration) of pre-travel treatment (38, 39, 40), duration of post-travel treatment, timing of melatonin, and whether physiological (0.3-0.5 mg) or pharmacological (5-10 mg) doses should be recommended (36, 37, 41).

With regards to the application of melatonin as chronobiotic in a military setting, the following questions should be addressed in future studies:

- physiological or pharmacological dose?
- usefulness of pre-travel treatment
- post-travel treatment: timing of melatonin
- post-travel treatment: duration

3.5 Bright light

Phase shifting properties

It is well accepted that bright light exposure can influence both the amplitude and phase of human circadian rhythms, and there is growing evidence that light may affect human physiology and behavior through non-circadian rhythms as well (42). Scheduled exposure to bright light can alleviate jet lag symptoms by accelerating circadian reentrainment to new time zones (43). Laboratory simulations, in which sleep is advanced by 6 to 8 hours and the subjects exposed to bright light for 3 to 4 hours during late subjective night on 2 to 4 successive days, have produced conflicting results. Field studies had encouraging results, but their applicability to military operations remains uncertain due to limited sample sizes (e.g. 44, 45, 46). One field study with a somewhat larger number of subjects, found that exposure to bright light in the morning appeared to facilitate the consolidation of sleep into a single nighttime episode (47). When bright light is used to accelerate adaptation to phase shift, the timing, duration, and intensity of light exposure are critical. In this context it is interesting that Martin & Eastman (48) found no difference in phase shifting efficacy between exposures with 5700 lux 3 hrs/day or 1230 lux 3 hrs/day. To facilitate adaptation after transmeridian deployment, a combination of exogenous melatonin and bright-light at antiphase seems a promising opportunity.

Alertness promoting properties

The alertness promoting properties of bright light exposure have been described by many authors (e.g. 49, 50, 51). Therefore, the efficacy of bright-light to shorten sleep inertia and to promote alertness during night shifts should be assessed in a military environment. To preserve alertness during long nightly duty hours the usefulness of combinations of bright light and a stimulant should also be assessed. A combination of bright light and caffeine appears to be useful (52), although in this study, as in most bright light/night shift studies, subjects were exposed to bright light during the entire night. This will often be impossible in military scenarios, where bright light can only be administered for limited time periods (e.g. 0.5 hr). The method of administration of bright light at the deployment site should also be a matter of concern. Illumination of a group sleep facility with light of sufficient intensity might be impracticable. Experiences of civil aircrew with small individual light sources, such as the Light Visor, are ambiguous as a number of users complain about irritating effects.

With regards to the application of bright light in a military setting, the following questions should be addressed in future studies:

in general:
- adverse effects (safe wavelength(s)?)
- most acceptable method to expose crew

phase shifting properties:
- optimal times for light exposure on the first as well as on subsequent treatment days
- optimal intensity and duration of exposure

alertness promoting properties:
- efficacy of short duration exposure
- optimal intensity
- usefulness of combination bright light and stimulant
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3.6 Stimulants

Although everything possible should be done to prevent (cumulative) sleep deprivation, severe fatigue and sleepiness on the job will inevitably occur during military round the clock operations. Therefore, use of pharmacological stimulants will be necessary to optimize performance and alertness during nightly and/or lengthy missions. Moreover, stimulants might be needed to minimize sleep inertia and the residual sedative effects of hypnotics.

Dextroamphetamine

The efficacy of d-amphetamine 5 mg for the short-term sustainment of alertness and performance of sleep deprived aircrew, has been established (e.g. 7, 53, 54). However, future field studies should assess the usefulness and side-effects of longer-term use of dextroamphetamine. Because of potential adverse effects, such as subjective euphoria, sympathomimetic effects, insomnia, tolerance, and dependence, use of amphetamine by military crew has been a matter of disagreement. Although the frequency of side-effects of d-amphetamine, when properly used, appears to be low (7, 54), use of amphetamine is not allowed in the RNLAF.

Pemoline

Pemoline has a unique chemical structure that includes a heterocyclic ring system incorporating a substituted side-chain of amphetamine. Pemoline has been successfully used for treatment of narcolepsy and attention-deficit hyperactivity disorder (ADDH). It is a dopamimetic agent that is relatively free of sympathomimetic activity and dependence and has the potential to improve alertness and performance in rested and sleep deprived subjects. In healthy volunteers, who were studied under realistic operational circumstances, it was found that 20 mg pemoline was able to maintain nocturnal performance without having adverse effects on recovery sleep (55). The potential of pemoline justifies further study. However, future studies might be hindered by the fact that pemoline has recently been removed from the market, due to cases of serious adverse events in children.

Modafinil

Recently the eugregoric synthetic stimulant modafinil has been promoted as an alternative for amphetamine (56, 57, 58). It was found that it is as effective as amphetamine with far fewer side effects, such as sympathomimetic activity and dependence. However, Baranski & Pigeau (59) found an "overconfidence" effect of modafinil when compared to d-amphetamine and placebo. This finding is reason for concern and therefore the relation between the subjective and performance enhancing effects of modafinil should be clarified.

Modafinil is now marketed in USA and Europe for treatment of narcolepsy. Questions to be answered regarding the usefulness of modafinil to stimulate alertness and performance in military scenarios concern:

- a more comprehensive understanding of the relation between its subjective and performance enhancing effects (overconfidence effect)
- effects of long term administration: side-effects and development of tolerance.
- comparison of modafinil and d-amphetamine: advantages?
- comparison of modafinil and pemoline: advantages?

Caffeine

In the RNLAF, the only approved stimulant is caffeine. Caffeine has been widely used as a psychostimulant. It is easily accepted and safe, when properly used. Bonnet and Arand (60) showed the usefulness of 200 mg caffeine administered after a 4 hour nap followed by 24 h sleep deprivation. In general, the stimulating effects on alertness and performance appear to be transient and drug tolerance develops easily. Effects of caffeine show large inter-individual variability, primarily dependent on the chronicity of its use. Side-effects with higher doses or in caffeine naive subjects are palpitations, tremors, disturbed sleep, and anxiety.

Recently a slow release caffeine (SR Caffeine) has been developed, which has shown to be effective in enhancing alertness and performance in sleep deprived subjects (61). Because the use of caffeine is widely accepted, it seems useful to conduct further research on SR Caffeine, with special reference to:

- establishing the advantage of SR Caffeine over normal caffeine
- long-term side-effects
- development of tolerance with prolonged administration.

4 Conclusion

Sleep and alertness management is a major point of attention for the medical support of military round the clock operations. Crew's awareness on the negative effects of fatigue and sleepiness on performance and alertness should be enhanced and flight surgeons should be trained on the use of practical methods to prevent serious fatigue and to enhance performance and alertness of the crew. Practical methods include use of strategic naps, hypnotics, stimulants, and chronobiotic treatment. Although, both in civil and in military aviation a considerable number of studies have been conducted on these issues, results are not readily available for practical use by the flight surgeon. In order to develop useful guidelines for flight surgeons and crew, the international aeromedical research community should be able to produce a database on what is already known and identify areas where knowledge is lacking. In this context, it is recommended to study the usefulness of recently developed hypnotics and stimulants, and chronobiotic treatment, such as melatonin and bright light in larger field studies in a realistic military setting. Research programs should also take into consideration potentially useful combinations of treatments, such as hypnotics with stimulants and/or bright light and melatonin with bright light at antiphase.

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