Sleep and alertness management during military operations: review and plan of action

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Achtergrond

De ervaringen met de South Atlantic Campaign en Operation 'Desert Storm' hebben geleerd dat de nadelige effecten van slaaptekort een zeer belangrijke rol speelden bij de uitvoering van de missies. Slaaptekort wordt veroorzaakt door de eisen en effecten van operaties, verstoring van het biologische ritme en matige slaapfaciliteiten. Slaaptekort leidt tot ernstige vermoeidheid en heeft als zodanig nadelige effecten op de prestatie en alertheid. Bovendien moeten missies worden uitgevoerd op tijdstippen waarop de biologische klok slaap dicteert. Het is gebleken dat ernstig vermoeide manschappen vooral tijdens de nachtdienst onvrijwillig in slaap kunnen vallen en dat er tijdens de nachtdienst significant meer fouten worden gemaakt dan overdag.
In deze context is de preventie van slaapgebrek en vermoeidheid een zeer belangrijk aandachtspunt voor zowel leidinggevenden als de medische begeleiding van intensieve en langdurige operaties. Er dienen voor dit doel praktische richtlijnen ontwikkeld te worden die een onderdeel moeten vormen van missie-specifieke managementplannen.

Operationele problemen

Bij de ontwikkeling van praktische richtlijnen en protocollen zal de aandacht gericht moeten zijn op de volgende gebieden.

Korte slaapperioden en missie-effectiviteit
Bij late avondmissies en nachtelijke missies, wordt vóór de missie vaak slecht geslapen door een onaangepast circadiaan ritme en bedrijvigheid en lawaai in de directe omgeving. Het tekort aan slaap verergert het gebrek aan alertheid, dat tijdens een nachtelijke missie toch al optreedt omdat dan de biologische klok slaap dicteert. Ook vroege ochtendmissies die plaatsvinden wanneer het circadiane prestatieritme zich in een dal bevindt kunnen tot problemen leiden. De slaap voorafgaand aan starts tussen 3 en 6 uur 's ochtends kenmerkt zich door een korte duur en een verminderde kwaliteit. Preventief eerder gaan slapen biedt

meestal geen uitkomst, omdat men vroeg in de avond de slaap niet kan vatten. In beide scenario's is het belangrijk te kunnen beschikken over een adequaat hypnoticum en stimulantia om de prestaties en alertheid zo optimaal mogelijk te houden.

Langdurige intensieve operaties
Tijdens langdurige intensieve operaties moet men optimaal blijven functioneren. Dergelijke operaties worden gekenmerkt door continu-diensten. Bij het omschakelen van dag- naar nachtshifts duurt het een aantal dagen voordat het slaap/waakritme zich aanpast. De ervaring leert dat tijdens langdurige operaties cumulatief slaapgebrek en vermoeidheid de missie-effectiviteit nadelig beïnvloeden. Daarom vereisen deze operaties een structureel slaap-waakmanagement.

Nachtdiensten
Gedurende de eerste dagen van de nachtdienst gaat het slapen overdag meestal slecht. Prestatie- en alertheidsniveau worden tijdens nachtdiensten verminderd door de gecombineerde effecten van slaapgebrek en het circadiane ritme, dat 's nachts slaap dicteert. Om prestaties zo optimaal mogelijk te houden, kunnen circadiane fase-verschuiving, strategisch gedoseerde slaapperioden en hypnotica van nut zijn. Stimulantia kunnen nuttig zijn om 's nachts zo optimaal mogelijk te functioneren.

Jet Lag
De missie-effectiviteit heeft in de eerste dagen na verplaatsing over meerdere tijdzones te lijden onder de gevolgen van jet lag, zoals verstoorde slaap, verminderde prestaties en slaperigheid overdag. Het is daarom van belang dat de biologische klok zich zo snel mogelijk aanpast aan het lokale dag-nachtritme. Naast het gehoorzamen aan de lokale fysische en sociale "tijdcues", kunnen melatonine en/of "bright light" hierbij nuttige hulpmiddelen zijn.

Slaap- en alertheidsmanagement

In de bovenstaande situaties speelt slaap- en alertheidsmanagement een belangrijke rol. Om een optimale inzetbaarheid van manschappen te bewerkstelligen is een aantal algemene en specifieke maatregelen noodzakelijk. Algemene maatregelen bestaan uit het opstellen van een missie-specifiek begeleidingsplan, het optimaliseren van de rust- en slaapfaciliteiten en een adequate begeleiding met betrekking tot missie-stress en individuele problemen. Dergelijke maatregelen zullen geïmplementeerd en uitgevoerd moeten worden onder verantwoordelijkheid van de leidinggevenden (command level) in nauwe samenwerking met de medische staf. Als belangrijk onderdeel van een missie-specifiek begeleidingsplan zullen artsen vervolgens specifieke maatregelen kunnen inzetten om ernstige vermoeidheid te voorkomen en de prestaties te optimaliseren. Deze specifieke maatregelen betreffen de

planning van slaapperioden, inductie van voldoende slaap tijdens de waakfase van het circadiane ritme, het antagoneren van slaap inertia en/of residuele effecten van hypnotica en verbetering van de prestaties en alertheid op tijdstippen waarop het circadiane ritme zich in de slaapfase bevindt.
De onderhavige literatuurstudie geeft een overzicht van de beschikbare kennis op het gebied van de specifieke maatregelen, tevens worden voor de Krijgsmacht relevante gebieden, waarop nog onvoldoende kennis bestaat, geïdentificeerd. In dat kader wordt achtereenvolgens aandacht besteed aan strategische korte slaapperioden ("power naps"), hypnotica, chronobiotica en stimulantia. Bovendien wordt aandacht besteed aan de inter-individuele verschillen in de effecten van slaapgebrek, nachtdienst, jet lag en in het effect van preventieve maatregelen. Op grond van literatuurgegevens wordt vastgesteld welke middelen in aanmerking kunnen komen voor gebruik door de Krijgsmacht en welke (militair) relevante vragen ten aanzien van deze middelen nog beantwoord moeten worden. Het gaat hierbij om de volgende geselecteerde methoden en middelen:

- power naps met een duur van 30 minuten tot 2 uur
- hypnotica: temazepam, zolpidem en zaleplon
- chronobiotica: melatonine en bright light
- stimulantia: (slow release) cafeïne en modafinil

Op grond van de resultaten van deze literatuurstudie wordt een werkprogramma voorgesteld met als doel het bepalen van de bruikbaarheid en effectiviteit van bovenstaande middelen en methoden om slaap en alertheid te bevorderen, teneinde de prestaties en inzetbaarheid van manschappen tijdens intensieve operaties en "out of area"operaties te optimaliseren.

Summary

Sleep and alertness management is a major point of attention for commanders and the medical support of military round the clock operations. Awareness on the effects of fatigue and sleepiness should be enhanced both on command level and crew level. Flight surgeons and safety officers should be trained to develop and implement mission specific crew endurance plans. Practical guidelines on methods to prevent serious fatigue and to enhance performance and alertness of the crew play a key role in these crew endurance plans. Useful methods include the use of strategic naps, hypnotics, stimulants, and chronobiotic treatment. In the context of the development of guidelines to optimize performance and alertness during sustained and stressful missions, this literature review describes the available knowledge and identifies areas where knowledge is lacking. In this context military relevant research issues related to the use of strategic naps, hypnotics, stimulants, and chronobiotic treatment are put forward. Based on the results of this study, a work program is drawn up, aimed at developing guidelines to optimize performance and alertness during sustained intensive operations.

Contents

1 Background

1.1 Introduction

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 (French, Neville, Storm, Bisson & Boll, 1993), which is known to be an important cause of impaired performance of aircrew (e.g. Perelli, 1980; Penetar, Belenky, Garrigan & Redmond, 1989; Caldwell, 1997; Simons & Valk, 1998). Moreover, experiences from the Gulf War have learned that aircrew was confronted with much longer continuous duty hours, than they were accustomed to. Fighter aircraft that ordinarily flew 3-4 hour sorties were flying 8-10 hours with multiple aerial refuelings during night time missions and transport aircraft were flying 10-18 hour sorties 2-3 times per week (French & Storm, 1999).

In this context, prevention of sleep loss and fatigue is a major point of attention in the support of a mission. Although several strategies for sleep-wakefulness management are available, many commanders and 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 minimize serious fatigue and sleep deprivation in their crews. In order to develop useful guidelines, it will be necessary to evaluate established strategies, such as used during the South Atlantic Campaign (Nicholson, 1984) and Operations Desert Shield and Storm (Emonson & Vanderbeek, 1995) and to assess the usefulness of recently developed preventive strategies and countermeasures.

General and specific measures are necessary to prevent serious fatigue and sleep loss in crews and to optimize mission performance. In most cases general measures will include proper preparation of the mission, optimization of sleep facilities (e.g. light control, sound masking), and adequate support of the 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, inducing sleep at times when the body clock dictates wakefulness, stimulating performance and alertness at times when the body clock dictates sleep, antagonizing sleep inertia and/or residual effects of hypnotics, and accelerating adaptation to phase shift after transmeridian deployment. General and specific measures should be integral parts of mission specific crew endurance plans, a responsibility of the commanding level.

Mission specific crew endurance plans

Mission specific endurance plans should be designed to maximize alertness during a mission by prescribing countermeasures to protect the quality and duration of sleep and to optimize sleep efficiency during rest periods. In the design of crew endurance plans, a model can be used to coordinate rest periods (naps and daily sleep) with unit activities necessary to accomplish each mission (e.g. flight schedules, briefings and planning sessions, maintenance schedules, meal schedules, etc.). Comperatore (1997) describes a model which includes four levels of organization: mission requirements (level 1), personal endurance plans (level 2), the unit level (3), and materiel level (4). Because mission requirements (during training or actual combat) cannot change, they are in the centre of the model in the first level of organization. The centre of the model is the most rigid location where activities cannot be modified. Thus mission requirements, such as flight schedules, are the reference for all other coordination. All other levels of organization and activities must be coordinated to meet the requirements of the first level of organization. At the second level, the personal endurance plan (PEP) can be developed. This plan consists of elements to be implemented by the individual crewmember such as: a sleep management schedule (best circadian times for sleep and naps, use of sleeping aids), recommendations to optimize sleep environment (control of light and noise intrusions), daylight exposure schedules, meal schedules and measures to enhance alertness. The maintenance of crew rest throughout the mission depends on the successful coordination of PEP elements in the unit (third) and materiel (fourth) level of the model. These levels consist of scheduled activities that must be carried out to accomplish the mission. Examples of these activities are briefings, planning sessions, mission rehearsals, training, design of rotation schedules, aircraft maintenance, aircraft refuelling, aircraft scheduling, etc. If left without coordination, these activities may potentially conflict with PEP level schedules. For instance, a battalion level briefing may be inadvertently scheduled during the sleep period of pilots conducting night operations. Pilots may disrupt their sleep to attend the briefing, while commanders may not consider this light-duty activity a disruption of crew rest. The effectiveness of this form of management of crew endurance relies on its emphasis on preventing conflict between PEP level and unit level elements (schedules, activities) while still meeting mission objectives.

1.2 Operational issues

In order to develop practical guidelines to be used when designing endurance plans for military missions, the following issues should be addressed.

Short sleep periods and mission effectiveness

Operations during late evening or night require an adequate amount of sleep prior to the mission. Crew has to sleep during the day, while their body clock dictates wakefulness. In many cases this daytime sleep will be short and disrupted (Nicholson & Stone, 1998).

Moreover, sleep during the day will further be hindered by inadequate sleep facilities (e.g. light and noise intrusions, and activities at the site).
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 performance rhythm is in its trough and their body clock still dictates sleep. Sleep preceding such missions is characterized by short total sleep times and impaired quality (Gander & Graeber, 1987; Simons & Valk, 1998). Crew often tries 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 (Simons & Valk, 1998).

As deficient sleep is significantly correlated with impaired performance and alertness (Carskadon & Dement, 1981; Carskadon & Dement, 1982; Dinges & Kribbs, 1991; Simons & Valk, 1997b), both above-mentioned scenarios may require pharmacological induction of sleep, "assisted awakening", and alertness enhancers to preserve performance and alertness during the mission. To further optimize performance and alertness, the use of short naps should be considered.

Sustained operations
During sustained operations, performance and alertness have to be preserved for a long time period. In most cases, sustained operations are characterized by shift work. It takes some days before the sleep-wakefulness rhythm has adapted to changes from day to night shifts (Nicholson & Stone, 1998). During sustained operations cumulative fatigue is caused by cumulative sleep deprivation and mission stresses (Carskadon & Dement, 1981; Dinges et al. 1997 ; Belenky, 1997). Sleep deprivation is known to impair performance and alertness and to reduce mental and physical fitness (Dinges et al. 1997). Therefore, structural sleep-wakefulness management should be aimed at keeping the crew as fit as possible during extended time periods.

Shifted work
Efficiency of sleep prior to the first night shifts will often be reduced and performance and alertness during the night will be impaired due to the combined effects of sleep deprivation and the body clock dictating sleep, while one has to work. Between 03:00 and 06:00 am., significantly more accidents and errors occur than in a day shift (Åkerstedt, Czeisler, Dinges & Horne, 1994). Acceleration of adaptation to phase shift may be beneficial when crews change from day to night shift. In addition to potential phase shifting strategies (melatonin, light, meals), strategic naps and hypnotics may be useful aids to preserve sleep and alertness in these situations.

Shifted time: Jet lag
Following transmeridian deployment, mission effectiveness may suffer from jet lag symptoms, such as impaired performance and increased daytime sleepiness, in the first days

after arrival in the new time zone (Ferrer, Bisson & French, 1995). 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 time cues ("Zeitgebers" such as meal-times and bed-times) adaptation might be accelerated by the use of melatonin and bright light (alone or in combination). Moreover, performance and alertness can be enhanced by pharmacological means.

1.3 Aim of the study

Extensive research on the topic has already been performed both in civil aviation and in the military. In civil aviation, research has been focussed mainly on non-pharmacological strategies, while in the military environment, research on the pharmacological approach has predominated. However, study results have not been translated into practical guidelines for the flight surgeon and commanders. The aeromedical research community should be able to draw guidelines from what is already known and identify areas where knowledge is lacking. Therefore, the aim of this study is to make an inventory of available knowledge and to identify military relevant issues that need further study in order to develop practical guidelines on sleep and alertness management.
In this context, available knowledge on the following major tools for sleep and alertness management will be discussed:

- strategic naps
- hypnotics
- chronobiotic treatment
- performance and alertness stimulants

Furthermore, the problem of inter-individual variability will be addressed. A recommended plan of action, based on the results and conclusions of the literature study, will be presented.

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 (Dinges, 1992; Rosekind, Graeber, Dinges, Connell, Rountree & Gillen, 1992; Gillberg, Kecklund, Axelsson & Åkerstedt, 1996; Valk & Simons, 1998). 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 (Bonnet, 1991; Lumley, Roehrs, Zorick, Lamphere & Roth, 1986). There is discussion on the minimum time required for a nap to be recuperative. Although Naitoh (1992) reported a nap of 5-10 minutes to be beneficial, most authors consider a nap of less than 30 minutes as not very effective. In general, long naps (>3 hrs) 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 (Simons & Valk, 1997b) or remain drowsy for long time periods after the nap. When naps are planned at times when the body clock dictates wakefulness, use of hypnotics to induce sleep has to be considered. In that case, residual effects of these hypnotics should be absent or should be antagonized after awakening. However, knowledge on which hypnotic is most useful to induce a short daytime sleep is insufficient as yet.

An important issue is the duration of sleep inertia after a nap. For practical purposes, sleep inertia can best be defined as the performance impairment that occurs immediately after awakening. However, the definition varies among different authors, mainly depending on their background; i.e. definitions are related to behavior, performance, and sleepiness parameters. As the definition is unclear, it is difficult to assess the duration of sleep inertia. This duration is generally assumed to be related to the sleep stage at awakening (e.g. in stage 1 inertia may be shorter than in Slow Wave Sleep), time of awakening (e.g. in the middle of the night or in the morning), duration of the preceding sleep, and the character of the activities that have to be performed after awakening (e.g. arousing or sedating). 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, Khalsa, Dijk and Czeisler (1999), who found no effects of going out of bed, breakfast, or showering on the duration of sleep inertia after a full 8-hour sleep period. Furthermore, they found no effects of the sleep stage at awakening on severity or duration of sleep inertia. Bruck and Pisani (1999), using a fire alarm to awake subjects once during Slow Wave Sleep and once during REM sleep, found a reduction of decision-making performance of at least 30 minutes after awakening with the greatest impairments being found within 3 minutes after abrupt nocturnal awakening. Initial effects of inertia were significantly greater after arousal during Slow Wave Sleep than during REM sleep.

After a 40-min controlled nap in the cockpit seat, sleep inertia was estimated to last less than

15 minutes on average (Rosekind et al., 1992; Valk & Simons, 1998). However, duration of sleep inertia was not explicitly assessed in these studies. In contrast, Caldwell & Caldwell (1998) found that post-nap 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 circadian phase in which the nap was taken, this finding might have important consequences for the planning of naps. It can be concluded that results of the few studies on sleep inertia depend strongly on the design and the endpoints of the study.

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

- necessity and feasibility of pharmacological induction of sleep for daytime naps
- duration of impairment of performance (sleep inertia) after short naps at various times of day
- duration of impairment of performance (residual effects) after hypnotic induced short naps
- effectiveness of stimulants and/or bright light in enhancing performance and alertness after awakening (reducing sleep inertia) and/or reducing residual effects of hypnotics after a nap
- usefulness of a combination of short naps and stimulants and/or bright light to enhance performance and alertness
- effectiveness of strategic napping when used for a prolonged time span; e.g. during sustained operations

3 Hypnotics

Whether hypnotics just induce and sustain sleep or at the same time shift the phase of circadian rhythmicity, remains a matter of study. There is evidence that benzodiazepines are capable of shifting the circadian phase, thus reinforcing the rest-activity cycle (Turek & Losee-Olsen, 1986). In any event, a hypnotic will assist sleep at an unusual time of day, and it will reduce nocturnal wakefulness during the adaptation phase in a new time zone. In this way, even if it did not have powerful entraining effects, it might improve daytime functioning by avoiding undue sleep loss (Lancet, 1986).

In this chapter the benzodiazepines midazolam, triazolam, temazepam, and brotizolam will be discussed, as well as the non-benzodiazepines zopiclone, zolpidem, and zaleplon. Furthermore, considerations on l-tryptophan, a potential alternative for sleep induction, and the hypnotic properties of melatonin will be given.

3.1 Midazolam

Midazolam has the shortest elimination half-life of the 'ultra-short benzodiazepine' group: 1.77 ± 0.83 hrs. The maximum plasma concentration is reached within 30 minutes after ingestion, due to the very rapid absorption. In doses up to 30 mg there is no evidence for impairment of performance the next day (Borbely, Loepfe, Mattmann & Tobler, 1983; Nicholson & Stone, 1983; Wehli, Knüsel, Schelldorfer & Christeller, 1985). However, tests used in these studies did not include tasks relevant for flying ability. Although its profile indicates that midazolam would be useful to induce short periods of sleep, prescription of midazolam as hypnotic is currently discouraged due to the relatively high frequency of adverse reactions such as rebound insomnia, anterograde amnesia and hazardous behaviour shortly after ingestion, and other benzodiazepine withdrawal symptoms (Ashton, 1984; Schneider-Helmert, 1985; Häcki, 1986). Currently, midazolam is mainly used for pre-medication in anaesthesia.

3.2 Triazolam

Triazolam is a triazolodiazepine with an elimination half-life of ±3 hours. In 1979 it was withdrawn from the Dutch market after 1000 reports of benzodiazepine withdrawal symptoms, such as anxiety, agitation, abnormal perception, depression, delusions, paranoia, depersonalization, derealization, and amnesia (Meyboom, 1989). Most reports concerned doses of 0.5-1.0 mg, and the manufacturer has now regained marketing rights with an advocated dose of 0.125 mg. In the past, the higher dose was most probably recommended because of the difficulty of sustaining sleep with this drug. The presently recommended dose therefore might not be efficaceous to preserve sleep. A dose of 0.50 mg leads to residual

effects the next day (Greenblatt, Scader, Divoll & Harmatz, 1984; Nicholson, 1986). Based on the above-mentioned observations, triazolam should not be considered for use in military settings.

3.3 Temazepam

Extensive research has been carried out on the hydroxylated metabolites of diazepam, viz. temazepam, lormetazepam, and oxazepam. These compounds are free of long-acting metabolites. Oxazepam is slowly absorbed and therefore not useful in the treatment of transient insomnia. This compound is used as an anxiolytic drug. In rapidly absorbed formulations, temazepam and lormetazepam have well-defined distribution phases. Their elimination phases have a half-life of ±10 hours. Lormetazepam is not further considered for use in military crew, due to its association with residual sedative effects after awakening (Subhan & Hindmarch, 1983). Nicholson (1984) 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. Due to critical operational requirements, crew often flew missions as soon as six hours after ingestion of the drug with no untoward effects on actual flying performance. Performance was subjectively measured in missions up to 28 hours duration. Workload during these missions was high and some new tasks had to be performed, such as air-to-air refuelling procedures. In previous studies it was found that with 20 mg temazepam the duration of impaired performance was limited to a few hours after ingestion and so likely to be contained by the sleep period (Nicholson & Stone, 1983). The limited duration of action of a single dose is related to its sustained distribution phase. Temazepam has no active metabolites. Valk and Simons (1994) recommended use of temazepam 10 or 20 mg for aircrew, in those cases where preservation of sleep (circa 7 hours) is crucial. This recommendation was based on the results of a randomised, double-blind, placebo controlled study in 15 healthy volunteers using vigilance, monitoring and complex tasks, and psycho-physiological tests, as well as a sleep quality questionnaire. As compared to placebo, temazepam in doses up to 20 mg (and also brotizolam 0.25 mg) showed no significant performance decrement in a period of 8 to 15 hours after drug ingestion.

3.4 Brotizolam

The triazolo-thienodiazepine brotizolam has an elimination half-life of ±5 hours. In the recommended dose range of 0.125-0.25 mg this drug seems free of residual effects the next day, while the duration of activity is long enough to sustain sleep (Nicholson, Pascoe, Roehrs, Roth, Spencer, Stone & Zorick, 1985; Itil, Michael, Seaman, Kunitz, Bowers & Itil, 1983; Laurell & Törnros, 1986). Although this was confirmed by Valk and Simons (1994), brotizolam has not been an option for the RNLAF because this drug is not marketed in The Netherlands.

3.5 Zopiclone

The cyclopyrrolone zopiclone also has an elimination half-life of 5 hours and seems to be useful in sustaining sleep. Zopiclone differs essentially from the diazepines and it is claimed that this drug is devoid of side-effects on voluntary muscles (e.g. relaxation). Nicholson (1986) described residual effects of zopiclone on performance 8 hours after ingestion. These effects are likely to be of little significance in day-to-day use by non-working subjects, however they should be taken into consideration in critical situations such as flight operations. Therefore zopiclone should not be selected for use by aircrew (Nicholson, 1986).

3.6 Zolpidem

While the benzodiazepine temazepam is 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 is 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. There is evidence that 10 mg zolpidem is free of residual effects from 6 hours after ingestion (Sicard, Trocherie, Moreau, Vieillefond & Court, 1993; Wesensten, Balkin & Belenky, 1996). It was found that 10 mg zolpidem increased sleep efficiency in a 2 hour nap, whereas performance and alertness measured 4½ hours post-administration showed no differences between zolpidem and placebo (Caldwell & Caldwell, 1998).
However, recently Nicholson and Stone (1999, personal communication) found that zolpidem caused significant residual sedative effects in women, while men were unaffected. This effect is still unexplained and needs further investigation. The consequence might be that a lower dose should be prescribed to women. Another point of consideration with respect to zolpidem might be hepatotoxicity. Another imidazopyridine, alpidem, has been withdrawn from the market because of its hepatotoxicity. In the past, hepatotoxicity has been suspected in association with zolpidem, but was not clearly established because of concomitant drug treatment (Garnier, 1994). Recently Karsenti, Blanc, Bacq & Metman (1999) reported a case of acute hepatitis after treatment with zolpidem alone at a therapeutic dose, with reappearance of the hepatotoxicity after the drug was reintroduced.
It is concluded that the pharmacokinetic profile of zolpidem justifies further studies on the usefulness of this hypnotic in military settings.

3.7 Zaleplon

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 (Gebu,

1999). Dietrich, Emilien and Salinas (1998) 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. O'Hanlon, Vermeeren, Fournie & Danjou (1998), found no evidence for residual effects 5 to 6 hours after the last dose of 10 or 20 mg zaleplon. These results may justify further consideration of zaleplon in the context of induction of sleep in military crew. Although zaleplon is not a benzodiazepine, it binds to the $GABA_A$-benzodiazepine-receptor complex. 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. For zaleplon, the frequency of these reactions is not known, because it has only recently appeared on the market. Based on its pharmacokinetic profile, zaleplon may be considered for induction of sleep in case short naps are pursued.

3.8 Tryptophan

Almost each commercially available hypnotic is a sedating sleeping aid. They produce an impairment window, which is a period of time after ingestion when performance and responsiveness are impaired. In military operations adequate responsiveness (e.g. to alarms) during sleep, followed by an adequate performance, can be important. Therefore, the Naval Health Research Center (San Diego, USA) investigated the non-sedating sleeping aid l-tryptophan, which is the sole non-sedating compound that has shown some efficacy in promoting and sustaining sleep. It was demonstrated that l-tryptophan increased total sleep time in US Marines who were air-lifted from California to Okinawa (Spinweber, 1987). L-tryptophan seemed a promising sleeping aid, although no consensus exists on efficacy and useful dose. In 1990 l-tryptophan was withdrawn from the market because cases of eosinophilia-myalgia syndrome were attributed to the use of this compound (Gilliland, 1994). Based on the above-mentioned observations, tryptophan should not be considered for use in military settings.

3.9 Melatonin: hypnotic properties

In humans, as in many other mammals, the pineal gland acts as a photoneuroendocrine transducer by transmitting information about day length via the secretion of the 5-methoxyindole melatonin.
In normal entrained conditions pineal melatonin synthesis shows marked rhythmicity, most synthesis occurring at night (blood concentrations of melatonin are 10-times higher at night). Light, of suitable intensity, serves both to entrain and suppress melatonin secretion (Lincoln, Ebling & Almeida, 1985). Melatonin secretion is also suppressed by beta-blockers, such as atenolol (Deacon, English, Tate & Arendt, 1998). Melatonin has hypnotic and circadian phase shifting properties in humans (Arendt, Skene, Middleton, Lockley & Deacon, 1997).

In the context of induction of daytime sleep during intensive military operations, the usefulness of exogenous physiological or supra-physiological doses of melatonin is 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. Doses of 10 mg or more are reported to have residual effects the next day (Wurtman, Dollins, Lieberman & Lynch, 1993).
It was observed that melatonin administration during the day produces more consistent reductions in sleep latency than does nocturnal administration (Lavie, 1997). Hughes and Badia (1997) reported 1mg, 10 mg , and 40 mg of melatonin to be equally effective in promoting sleep for non-sleep deprived individuals attempting to sleep during their subjective day. However, results from studies on the efficacy of melatonin after night-shift work were disappointing (Wright, Lawrence, Wrenn, Haynes, Welch & Schlack, 1998; James, Tramea, Jones & Krohmer, 1998; Jorgensen & Witting, 1998). It appears that in laboratory studies with non-sleep deprived volunteers melatonin is more effective in inducing daytime sleep, than in real life situations, such as after a busy night shift. Moreover, the sleep promoting action in insomniacs with *non-circadian* sleep disturbance has not been convincingly evidenced (Mendelson, 1997). Melatonin might be considered as a gentle promoter of general relaxation and sedation, which -in favourable conditions- might facilitate sleep onset (Zhdanova, Lynch & Wurtman, 1997). However, when efficient (daytime) sleep induction in military crew is pursued, hypnotics such as temazepam or zolpidem appear to be more efficacious than melatonin.

3.10 Conclusion

Although the ideal hypnotic for aircrew engaged in military missions does not exist, hypnotics are probably essential to preserve sleep under difficult conditions. It can be concluded that the "ultra-short" benzodiazepines midazolam and triazolam, as well as the cyclopyrrolone zopiclone are not to be considered for use in military crew, because of afore-mentioned side effects. The efficacy of melatonin to induce sleep remains questionable. Application of l-tryptophan remained in an experimental stage, due to the occurrence of unacceptable adverse effects.

The recently marketed non-benzodiazepine zaleplon needs further study to assess its risk for "ultra-short benzodiazepine" adverse reactions and its usefulness in military settings.
The usefulness of temazepam during sustained operations has been well established. Although experiences from the South Atlantic Campaign with temazepam for sleep periods shorter than 7 hours are promising, further study is needed to determine whether temazepam is free of residual effects 5-6 hours after administration. For shorter sleep periods (naps)

zolpidem seems useful, although further research is needed on residual effects in females and on the risk of hepatotoxicity. For practical use, the question remains whether zolpidem has advantages over temazepam, especially when taking into account that residual effects, if any, might be sufficiently counteracted by a stimulant drug to be administered to crew members after the wake up call. Studies at the Defence Research Agency/Centre for Human Sciences (DERA/CHS, UK) showed favourable results with a combination of temazepam, to induce daytime sleep, and 300 mg caffeine, to enhance alertness during the night (Nicholson, personal communication, 1999).

In summary, in the context of hypnotics the following issues 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
- hepatotoxicity risk of zolpidem
- usefulness of zolpidem for induction of sleep periods of approx. 8 hrs, compared with temazepam
- usefulness of zaleplon for induction of sleep during 2 hour naps
- effectiveness of stimulants and/or bright light in counter-acting residual effects of hypnotics

4 Chronobiotic treatment

4.1 Melatonin

It appears that in military settings melatonin's chronobiotic effects are more important than its hypnotic properties. Exogenous melatonin is able to shift the endogenous circadian system according to a phase-response curve: in diurnally active persons, melatonin given in the afternoon advances the body clock, while melatonin taken in the early morning delays the circadian system (Lewy, Ahmed, Jackson & Sack, 1992). There is sufficient evidence that melatonin, when suitably timed, is able to accelerate adaptation to phase shift and decrease jet lag symptoms in both field and simulation studies of jet lag (Arendt, Skene, Middleton, Lockley & Deacon, 1997; fig. 1; table 1). Arendt et al. (1997) found that the effect of exogenous melatonin is most pronounced when >8 time zones were crossed (fig 1). However, most studies employed volunteer travellers who, unlike military crew, were free of duties at their destination. Moreover, in some studies, such as the study by Arendt et al (1997; fig 1) there were far more subjects receiving active treatment than subjects receiving placebo.

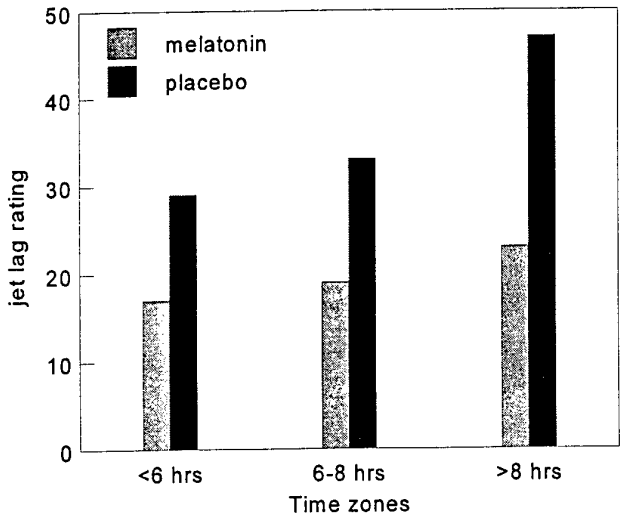

Figure 1. Jet lag ratings (visual analogue scale: 0=negligible, 100=very bad) for combined eastward and westward flights over different time zones. (according to Arendt et al. 1997)

Studies in aircrew on duty showed less favourable results (Table 1: Petrie, Dawson, Thompson & Brook, 1993). 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. Most studies used subjective assessment methods and/or objective sleep-wakefulness monitoring (acti-graphy). However, studies which have used objective performance measurements are very scarce, so there is still no convincing evidence that melatonin treatment improves performance after transmeridian travel. Larger studies will have to be conducted in which objective performance and alertness measures should be used in a military setting.

It is generally acknowledged that adaptation should not be pursued during very short missions and/or rapid shift rotations. For a one-day mission in a new time zone, it is recommended to stick as much as possible to the home-base clock; e.g. try to sleep at times one is used to at home, irrespective of the local time in the new time zone ("anchor sleep"). In most cases, this anchoring method becomes impractical when a stay is longer than 2 days. For an isolated single night shift, it is recommended to induce daytime sleep and administer stimulants to enhance performance and alertness at night. However, when missions involve prolonged transmeridian deployment or prolonged shift rotations acceleration of adaptation by melatonin treatment may be useful.

There is discussion about the usefulness of pre-travel melatonin treatment. Some authors suggest that pre-travel treatment is beneficial in that it specifies the direction of entrainment (Samel, Wegmann, Vejvoda, Maass, Gundel & Schütz, 1991). Others claim that pre-travel melatonin is unnecessary (Lino, Silvy, Condorelli & Rusconi, 1993), or that it adversely affects the resynchronization (Petrie et al., 1993). Pre-travel phase shifting by melatonin also leads to practical problems, because daytime administration of melatonin may induce sleepiness (Dollins et al., 1993; Zhdanova et al.,1995) and impair driving safety (Suhner, Schlagenhauf, Tschopp, Hauri-Bionda, Friedrich-Koch & Steffen, 1998a).

Post-travel treatment with melatonin is generally considered as beneficial. However, most research has used leisure travellers who did not have to perform professional tasks after arrival in the new time zone. Only a few studies assessed the effects of melatonin treatment on post-travel professional performance. The study with the smallest sample size showed a beneficial effect of melatonin, using only subjective assessment methods (table 1: Petrie et al. 1989). A larger study, using objective methods, showed no significant beneficial effects (Petrie et al. 1993). Comperatore et al. (1996) found significant improvement of performance on a vigilance task, however this study used a relatively high dosis of melatonin. Most studies used treatments of 3 to 5 days (table 1). Although no investigator assessed the subjects for a longer time period, 5 days appear to be a reasonable period for treatment.

Table 1.Melatonin and jet lag: controlled field studies with healthy volunteers. All reported studies used a double-blind, placebo-controlled between-groups design. (pax=passengers).

study	*#subjects, conditions*	*melatonin dosage*	*findings*
Arendt et al. 1986	17 pax across 8 time zones eastwards	5 mg 3 days pre-travel + 4 days post-travel	melatonin decreased subjective jet lag complaints
Arendt & Aldhous 1988	52 pax across 9 time zones west- and eastwards	5 mg 2 days pre-travel + 4 days post-travel	melatonin decreased subjective jet lag complaints
Petrie et al. 1989	20 aircrew across 11 time zones west- and eastwards	5 mg 3 days pre-travel + once during flight + 3 days post-travel	melatonin: less tired + better sleep (subjective)
Claustrat et al. 1992	30 pax across 6 time zones eastwards	8 mg day of departure + 3 days post-travel	melatonin: less fatigue
Petrie et al. 1993	52 aircrew across 11 time zones west- and eastwards	5 mg or placebo 3 days pre-travel + 5 days post-travel / placebo 3 days pre-travel + 5 mg melatonin 5 days post-travel	no significant differences between melatonin and placebo
Comperatore et al. 1996	29 Army personnel across 7-9 time zones eastwards	10 mg 3 days pre-travel + once during flight + 5 days post-travel	melatonin improved sleep duration and vigilance
Suhner et al. 1998b	234 pax across 6-8 time zones eastwards	0.5 mg / 5 mg at bedtime for 4 days post-travel	0.5 mg and 5 mg effective in reducing fatigue and daytime sleepiness; 5 mg for best sleep

Exogenously administered doses of 0.1-0.5 mg produce physiological peak blood levels of melatonin (i.e. mimicking the nightly endogenous melatonin production), while doses of 5-10 mg clearly lead to supra-physiological blood levels.

Whether physiological (0.1-0.5 mg) or supra-physiological (5-10 mg) doses should be recommended is still a matter of discussion. Arendt and coworkers successfully used 5 mg in their studies (Arendt et al., 1997), while others advocate use of physiological doses of 0.1-0.3 mg (Zhdanova, Lynch & Wurtman, 1997). In their large trial (n=234), Suhner, Schlagenhauf, Johnson, Tschopp and Steffen (1998b) found 0.5 mg and 5 mg melatonin equally effective in reducing subjective fatigue and daytime sleepiness in travellers crossing 6-8 time zones in eastward direction (table 1). Only the hypnotic properties of 5.0 mg were slightly, but significantly, better (improved sleep quality and reduced sleep latency) than those of the 0.5 mg dose. Arendt found no clinically relevant differences in effects between 0.5 and 5.0 mg. She also found no differences between both doses of melatonin in the effect on the body temperature curve (Arendt, personal communication, 1999).

Melatonin formulation

All successful studies on the phase shifting properties of melatonin used fast release formulations. For study purposes, synthetic melatonin, formulated as fast-release gelatin capsules with lactose filler should be used. Caution should be exercised with melatonin preparations of obscure origin, as the active dose and purity are often not guaranteed.

Side-effects

Arendt and co-workers (Arendt et al., 1997) analyzed the occurrence of side effects in 474 subjects, taking 5 mg melatonin for 4 days on average, and found drowsiness as the only significant side effect of melatonin, compared to placebo (112 subjects). They noted that in a considerable number of cases drowsiness could be attributed to taking melatonin on the wrong time in the circadian phase. With regards to the effects on secretion of other hormones, it is evidenced that exogenous melatonin increases prolactin release in healthy men and women, while there is no effect on other hormone levels (Kostoglou-Athanassiou, Treacher, Wheeler & Forsling, 1998; Terzolo et al., 1993). With regards to long-term effects, Terzolo, Piovesan, Puligheddu, Torta, Osella and Pacotti (1990) showed that 2 mg melatonin given daily at 18:00 during 2 months had no effects on hormone levels or cardiovascular variables in men, other than phase advance of the rhythms of cortisol and testosterone. Apart from this study, there is a paucity of data on long-term effects of melatonin administration.

Conclusion

Adaptation should not be pursued during short missions and/or rapid shift rotations. However, in other cases of transmeridian deployment or long shift rotations acceleration of adaptation will be beneficial. When the aim is to accelerate adaptation after transmeridian deployment, melatonin is recommended. Although, the beneficial effects of melatonin on subjective jet lag symptoms in leisure travellers is quite convincing, the effects on objectively assessed performance in professional travellers still awaits confirmation.
With regards to the application of melatonin as chronobiotic in a military setting, the following issues should be addressed in future studies:

- useful dose: physiological or supra-physiological?
- usefulness of pre-travel treatment
- usefulness of post-travel treatment: effects on relevant task performance
- post-travel treatment: which duration is effective?
- long-term effects on hormone secretion, cardiovascular parameters, sleep, mood.

4.2 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 (Campbell, Eastman, Terman, Lewy, Boulos & Dijk, 1995). Scheduled exposure to bright light can alleviate jet lag symptoms by accelerating circadian re-entrainment to new time zones (Boulos, Campbell, Lewy, Terman, Dijk & Eastman 1995). 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 (Table 2). Although the authors describe their studies as jet lag simulations, in neither case subjects were exposed to the full complement of time cues normally encountered in transmeridian travel. In this respect, field studies will be indispensable.

Table 2. Bright light and jet lag: Laboratory simulation studies with normal volunteers.

study	*design, conditions*	*bright light conditions*	*result*
Wever (1985)	phase delay light-dark cycle	<1500 vs. 2000-5000 lux	slower reentrainment with bright light
Honma et al. (1991)	8h phase advance sleep-wake cycle	dim light vs. 5000 lux 3hrs during 3 days	faster reentrainment with bright light
Moline et al. (1989)	6h phase advance light-dark cycle	300-500 vs. 2500 lux 4hrs during 3 days	no differences between dim and bright light
Samel et al. (1992)	6h phase advance light-dark cycle	2 days bright light at 04:00 vs. 13:00 hr	no differences in reentrainment rate

Thus far, case-studies on reduction of jet lag symptoms with bright light had encouraging results, but their applicability to military operations remains uncertain due to limited sample sizes (e.g. Daan & Lewy, 1984: 2 subjects; Czeisler & Allan, 1987: 1 subject; Sasaki et al., 1989: 4 subjects). One field study with a somewhat larger number of subjects (n=19), found that exposure to bright light in the morning appeared to facilitate the consolidation of sleep into a single nighttime episode (Cole & Kripke, 1989). Regarding the usefulness of bright light to accelerate adaptation to phase shift, knowledge is still deficient on optimal times for light exposure (on the first as well as on subsequent treatment days), inter-individual differences in the effects of bright light, and optimal intensity and duration of exposure.

Martin and Eastman (1998) found no difference in phase shifting efficacy between exposures with 5700 lux 3 hrs/day or 1230 lux 3 hrs/day. Even low intensities and dim light may phase shift the rhythm (Boivin, Duffy, Kronauer & Czeisler, 1996; Jelinkova-Vondrasova, Hajek & Illnerova, 1999).

Exposures of short duration may be important for the implementation of bright light application in military settings. Few studies have examined the effects of short duration bright light exposure in real life settings. In this context, all studies concerned adaptation to shift work. NASA has implemented bright light for phase shifting the sleep-wake rhythm, and found better sleep, performance and physical and emotional well-being following bright light treatment (Czeisler, Chiasera & Duffy, 1991; Stewart, Hayes & Eastman, 1995). Bjorvatn, Kecklund and Åkerstedt (1999) used bright light (10.000 lux 30 min/day during 4 nights or days) to facilitate adaptation to night shift at an oil platform in the North Sea and adaptation after return home (return to "day shift"). They found a modest effect of bright light on the adaptation to night shift -possibly related to the finding that the workers adapt to night work within a few days, even without bright light- but found a significant beneficial effect of bright light on the re-adaptation to day life at home.

Theoretically, acceleration of adaptation to phase shift could best be achieved by administration of melatonin at desired bedtime and exposure to bright light after desired awakening time. This promising combination of exogenous melatonin and bright light at antiphase has not been studied in field studies as yet.

Alertness promoting properties

In the above-mentioned context, bright light is used to shift the phase of the circadian rhythm. Besides this application, bright light may be used to enhance alertness in situations where one is prone to sleepiness, such as during night duty or directly after waking up. Alertness promoting properties of bright light exposure have been described by many authors (Campbell & Dawson, 1990; Czeisler, Johnson, Duffy, Brown, Ronda & Kronauer, 1990; French, Hannon, Brainard, 1990).

However, a study on the effect of bright light exposure on vigilance showed disappointing results (Lafrance, Dumont, Lesperance & Lambert, 1998). Thus far, the efficacy of bright light to reduce sleep inertia and to enhance alertness during night shifts has not been assessed in a military environment. When considering such studies, the feasibility of bright light exposure in a military setting should be determined. In most bright light/night shift studies, subjects were exposed to bright light during an entire night. This will often be impossible in military scenarios, where it appears that there will be only limited time periods (e.g. 30 min) in which bright light may be used.

To preserve alertness during military round the clock operations, the usefulness of combinations of bright light and a stimulant should also be assessed. In this context, Wright, Badia, Myers and Plenzler, (1997) found evidence for the usefulness of a combination of bright light and caffeine.

Apparatus

The method of administration of bright light at the deployment site should also be a matter of concern. Illumination of an entire crew 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 pilots complain about irritating effects. In current light therapy, a large variety of fixtures is used but the spectral emission of lamps is mostly unknown to the user and clinician leading to the potential hazard of ocular lesions. Therefore, standardized therapy fixtures and lamps devoid of damaging spectral emissions should be used (Reme, Rol, Grothmann Kaase & Terman, 1996).

Conclusion

Although laboratory studies produced conflicting results and sample sizes of field studies have been too small, it can be concluded that bright light has some potential with regards to accelerating adaptation to phase shift and to promote alertness after sleep and during night shifts. Much research is still needed with regards to the usefulness of bright light for military purposes. The following issues should be addressed:

in general

- adverse effects: which wavelength is safe?
- what is the most acceptable method to expose a crew
- field studies with adequate sample size should be conducted in realistic military scenarios

phase shifting properties

- optimal times for light exposure on the first as well as on subsequent treatment days
- optimal intensity and duration of exposure
- effects of bright light and melatonin at antiphase

alertness promoting properties

- efficacy of short duration exposure (minimal exposure time)
- optimal intensity
- usefulness of combination bright light and stimulant

5 Stimulants

Although every action should be taken to prevent (cumulative) sleep deprivation, severe fatigue and sleepiness on the job will inevitably occur during military round the clock operations (e.g. Nicholson & Stone, 1998). Therefore, use of pharmacological stimulants will be necessary to optimize performance and alertness during nightly and/or sustained missions. Moreover, stimulants might be needed to minimize sleep inertia and the residual sedative effects of hypnotics. In this context the role of amphetamine, pemoline, modafinil, and caffeine will be discussed, while the alertness promoting properties of bright light have been discussed in section 6.2. Moreover, the effects of the amino acid tyrosine will be discussed.

5.1 Dextroamphetamine

During World War II, amphetamines were distributed to German soldiers to induce aggressiveness and belligerence. In wartime Japan, amphetamine was used to reduce fatigue and increase productivity in soldiers and civilians, which has led to post-war abuse problems (Janowski & Hauger, 1995). The use of amphetamine as readily available "escape and evade" pills in survival kits during the Vietnam War also led to an abuse problem (Holloway, 1974).

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. Senechal, 1988; Emonson & Vanderbeek, 1995; Caldwell & Caldwell, 1997). However, future field studies should assess the usefulness and side-effects of longer-term use of d-amphetamine. Because of potential adverse effects, such as subjective euphoria, sympathomimetic effects, anorexia, 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 used under strict supervision of a flight surgeon, appears to be low (Emonson & Vanderbeek, 1995; Caldwell & Caldwell, 1997), use of amphetamine is not approved in the RNLAF. Main arguments for this policy are the risks that subjective euphoria caused by amphetamine may lead to operational errors and that longer-term use might increase the risk for drug dependence.

5.2 Pemoline

Pemoline has a unique chemical structure that includes a heterocyclic ring system incorporating a substituted side-chain of amphetamine (Janowski & Hauger, 1995). Pemoline has been successfully used for treatment of narcolepsy and attention-deficit hyperactivity disorder (ADHD).

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 a single dose of 20 mg pemoline was able to maintain nocturnal performance without having adverse effects on recovery sleep (Nicholson & Turner, 1998). 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 hepatotoxicity in children (Marotta & Roberts, 1998).

5.3 Modafinil

Recently the eugregoric synthetic stimulant modafinil has been promoted as an alternative for amphetamine (Lyons & French, 1991; Lagarde & Batejat, 1995; Pigeau et al., 1995). It was found that it is as effective as amphetamine with far fewer side effects, such as sympathomimetic activity and dependence. Modafinil is marketed in USA and Europe for treatment of narcolepsy. Lubin & Weil (1995) analyzed data of 300 patients treated with modafinil for narcolepsy or hypersomnia. They found 75% efficiency, 12% side effects, and absence of dependence. Brun et al. (1998) showed that modafinil significantly improved performance during 36 hour sleep deprivation and that it had no effect on melatonin, cortisol or growth hormone secretion. However, Baranski & Pigeau (1997) found an "overconfidence" effect of modafinil, measured with self ratings of performance, when compared to d-amphetamine and placebo. As impairments in self-criticism and self-control have always been considered as potentially dangerous side effects of amphetamines, this finding is reason for concern. Therefore the relation between the subjective and performance enhancing effects of modafinil should be clarified.
Issues to be addressed 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
- combination of modafinil and strategic naps

5.4 Caffeine

In the RNLAF, the only approved stimulant is caffeine. Caffeine has been widely used as a psychostimulant. Several authors have evidenced that caffeine improves the ability to remain awake after sleep deprivation (e.g. Kelly, Mitler, Bonnet, 1997). It is easily accepted and safe, when properly used. Bonnet and Arand (1994) showed the usefulness of 200 mg caffeine administered after a 4 hour nap followed by 24 h sleep deprivation. Reyner and Horne (1997) found that a combination of 200 mg caffeine with a 15 min nap significantly reduced sleepiness in car simulator drivers.

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.

For use in military settings, caffeine has the disadvantage that on average its effects are transient. To overcome this disadvantage, recently a slow release caffeine (SR Caffeine) has been developed. SR Caffeine has shown to be effective in enhancing alertness and performance in sleep deprived subjects (Sicard, Lagarde, Batejat, Chauffard, Enslen & Tachon, 1998). Because the use of caffeine is widely accepted, it seems useful to conduct further research on SR Caffeine, with special reference to:

- combination of (SR)caffeine and naps
- combination of (SR)caffeine and bright light
- establishing the advantages of SR Caffeine over normal caffeine
- side-effects of SR Caffeine
- development of tolerance with prolonged administration.

5.5 Tyrosine

In the past, it has been suggested that the neurotransmitter precursor tyrosine was able to enhance cognitive performance under stressful conditions (Wurtman, 1987). As such tyrosine is not a classic psychostimulant, but may probably be classified as "performance enhancer". While theoretically tyrosine would be helpful for crew operating under stressful conditions, this could not be established in human subjects in real life situations (e.g. Lieberman, Corkin, Spring, Wurtman & Growdon, 1985). Banderet et al. (1987), claimed subtle beneficial effects of tyrosine on performance in subjects exposed to altitude and cold. However, this research group used significance levels of 15% ($p<.15$) and therefore their results are not convincing. Due to disappointing results and some cases of toxicity with high doses tyrosine, interest in tyrosine waned, until recently. Paz & Berry (1997) studied effects of meal composition on alertness and performance of hospital night shift workers and found no significant effects of tyrosine-rich meals. Deijen, Wientjes, Vullinghs, Cloin and Langefeld (1999) found that tyrosine improved cognitive performance in cadets after one week of a combat training course. Although for the objective performance tasks, differences between tyrosine and placebo were not too convincing, they suggest that supplementation with tyrosine reduces the effects of stress and fatigue on cognitive task performance. However, Deijen et al. (1999) used an active placebo, which potentially has the opposite action of tyrosine. Due to this serious methodological limitation, results of this study should not be further considered. It appears that, at present, use of tyrosine in military settings is neither justified nor beneficial.

5.6 Conclusion

During sustained intensive military operations, use of stimulants will be indispensable. Modafinil appears to be a useful substitute for amphetamine, which is not accepted in many countries. To establish usefulness and safety in military settings, further larger scale studies with modafinil should be conducted. The advantages of SR Caffeine over normal caffeine as a "moderate" stimulant are still to be established. Combinations of stimulants and bright light appear to be useful, but await further applied research.
In addition to the issues for further study, as already mentioned for modafinil (§ 5.3) and caffeine (§ 5.4), there are important general issues that need to be studied. Although the efficacy of stimulants to improve performance and alertness is evident, the number of days that sleep deprived individuals can function effectively on stimulants is not well established, and the most effective dose regimen over multiple days is unknown. Evidence from laboratory studies suggests a continual, gradual degradation in performance over 60 hours awake, even after repetitive stimulant administration (Newhouse, Belenky, Thomas, Thorne, Sing & Fertig, 1989; Pigeau et al., 1995). Therefore, future research should concern:

- the number of days that individuals can function effectively on stimulants
- the most effective dose regimen over multiple days

Moreover, for the flight surgeon future research should provide clear guidelines on:

- when stimulants should be used
- which stimulant should be used in which situation.

In addition, it is to be anticipated that ethical considerations will emerge as an important issue when longer term daily administration of stimulants would be recommended.

6 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 desynchronizing effects of transmeridian travel and shift work, and the effects of countermeasures such as melatonin, hypnotics, alertness enhancers, and strategic naps. Although knowledge on individual differences is poor, it has been tried to identify individual factors that may explain inter-individual variability. With regards to disturbed sleep after transmeridian travel, Simons & Valk (1987) found that subjective sleep quality was significantly more impaired in cockpit crew older than 45 years, than in crew under 45 years of age. However, this could not be confirmed in a study in which sleep parameters were objectively measured (Valk & Simons, 1998). In studies on factors of importance to night shift sleepiness, some evidence is found that increasing age (Åkerstedt, 1999) and poor physical condition (Härmä, Ilmarinen, Knauth, Rutenfranz & Hänninen, 1986) might be related to greater sleepiness during night shift. Other factors such as gender, experience with phase shift, morningness or eveningness, circadian amplitude of the body temperature rhythm, and sleep patterns had no significant predictive value, while one of the best predictors for problems due to shift work appears to be the "need for sleep" (Åkerstedt, 1999), in that a higher need for sleep is related to intolerance for shift work.

Inter-individual variability may have important consequences for the medical support of military operations. For instance, 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 (Valk & Simons, 1998). Although the overall effect was statistically significant, for some pilots the nap had no effect and a small minority even showed impaired performance and alertness 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 Program" has been developed for that purpose (Simons & Valk, 1999), which is tailored to the needs of airline pilots. To enhance awareness of the negative effects of fatigue on performance and alertness, and to teach crew how to prevent and counteract fatigue, the civil "Fit-to-Fly Program" should be adapted for use by crew engaged in military operations.

Furthermore, tools should be developed to enable flight surgeons and commanders to collect useful information during training missions and (transmeridian) deployments. Useful information, which can easily be collected using sleep logs, includes subjective data on sleep-wakefulness patterns, alertness / sleepiness during duty, and (cumulative) fatigue. 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 (Simons & Valk, 1998; Valk & Simons, 1998) 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. In the same way, commanders could 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 (Belenky, 1997).

Conclusion

For successful sleep and alertness management, it is important to consider and identify inter-individual differences. Important steps to deal with individual differences will be:

- enhancement of awareness of crew and flight surgeons on the role of fatigue and fatigue counter-measures
- education of commanders and personnel on how to maximize the quality of sleep and prevent shift lag and jet lag
- development of a "Fit-for-Duty" Checklist in analogy to the "Fit-to-Fly"Checklist, which was developed for civil pilots
- development of an easy method to measure sleep characteristics (sleep logs, actigraphy) and alertness

7 Conclusion and recommendations

Sleep and alertness management is a major point of attention for the support of military missions. This literature study is aimed at discussing specific strategies to enhance performance and alertness of military crew. These strategies are tools to be used in the management of crew endurance. Crew's awareness on the negative effects of fatigue and sleepiness on performance and alertness should be enhanced and flight surgeons should be trained how to use practical methods to prevent serious fatigue and to enhance performance and alertness of the crew. Recommended methods include use of strategic naps, hypnotics, chronobiotic treatment, and stimulants. This report describes the available knowledge on these methods. Military relevant issues that need further research are presented at the end of each section on methods (viz. sections 4, 5, 6.1, 6.2, 7). In order to make up a research program, which is both feasible and effective, these issues have been weighed and ranked taking into account the following aspects:

- direct usefulness for prescribing military surgeons
- usefulness in the context of crew endurance plans
- ongoing research in other countries: prevention of duplications. It is considered cost-effective to wait for results of studies known to be conducted, at present or in future, by other organizations. Therefore, issues known to be already dealt with by NATO partners or civil aviation institutes, were given low priority.

Taking into account above-mentioned considerations, an applied research program has been designed to provide the necessary cornerstones for guidelines on sleep and alertness management during military operations. The recommended research program includes four work packages, each work package including several studies. The following work packages are recommended:

- Work Package A: rapid change from day to night shift: prevention of fatigue and enhancement of performance and alertness
- Work Package B: sustained operation with night shifts: prevention of fatigue and enhancement of performance and alertness
- Work Package C: rapid transmeridian deployment: prevention of fatigue and enhancement of performance and alertness
- Work Package D: management of crew endurance

In the context of this report the complete research plan is described on the next pages. As it is anticipated that research budgets will be limited, priorities will have to be considered and a selection of the studies-to-conduct should be made. This selection should be based on operational relevance, logistic feasibility, and coherence of studies.

Work Package A

Rapid change from day to night shift: prevention of fatigue and enhancement of performance and alertness

Intended schedule: 4-5 hours sleep in the afternoon-evening
full night duty

This is a difficult, although realistic, schedule for the crew. It is anticipated that it will be difficult to fall asleep in the afternoon and that sleep efficiency and quality of sleep in the afternoon/evening will be low. Waking up in the late evening will be difficult because at that time the circadian rhythm is approaching its sleep phase. Therefore, sleep inertia might be a serious problem. After insufficient and inefficient sleep, the sleepy crew has to perform and be alert all night, while their body clock dictates sleep, with consequent negative effects on alertness and performance.
To cope with these problems, the following issues will be important:

1. in the afternoon: sleep induction using temazepam, zolpidem, or zaleplon (addressed in study A1)
2. in the late evening: awakening assisted by caffeine and/or bright light (addressed in study A2)
3. during night duty: enhancement of alertness and performance using modafinil, or caffeine and/or strategic naps (addressed in studies A 3-a and A 3-b). It is to be anticipated that after using stimulants or naps during the night, subjects may experience difficulty falling asleep the next morning and impaired daytime sleep. Therefore, this issue will also be addressed in A 3-a (for modafinil and caffeine) and in A 3-b (for use of naps).

Referring to above-mentioned points 1-3, this work package includes the following studies in healthy volunteers functioning in a realistic military setting:

A 1 induction of sleep in the afternoon
In a double-blind placebo controlled design the usefulness of temazepam, zolpidem, and zaleplon will be assessed (4 conditions). Outcome variables will be objective and subjective sleep parameters, and parameters of performance and alertness after awakening (residual effects). Performance measures, which are most relevant for military tasks, will be used. This study (A1) will provide the hypnotic, which is most useful to induce a circa 5-hour sleep in the afternoon/evening and has the fewest residual effects. This hypnotic (named A1) can be used in the next step of the work package:

A 2 assisted awakening

In volunteers, in whom sleep is induced using hypnotic A1, the effectiveness will be assessed of caffeine and/or bright light to enhance performance and alertness immediately after awakening. Four conditions will be compared: caffeine + bright light, caffeine + dim light, placebo + bright light, and placebo + dim light. Outcome variables will be objective and subjective measures on relevant performance and alertness over time, subjective ratings on ease of awakening, and adverse effects. This study (A2) will provide the best tool to reduce sleep inertia and to enhance performance and alertness immediately after awakening in the late evening.

A 3 enhancement of alertness and performance during the night

A 3a In a double-blind placebo controlled design the usefulness of recommended doses of SR-Caffeine and modafinil will be assessed. Outcome variables will be objective and subjective measures on relevant performance and alertness during the night, and objective and subjective parameters of sleep the next day. This study will provide the best stimulant to enhance performance and alertness during the night and information on the consequences of stimulant use for sleep the next day. This stimulant (named A 3) can be used in the next step of the work package:

A 3b Assessment of the usefulness of a nightly strategic nap to enhance performance and alertness during the night. In this study 4 conditions will be compared: stimulant A 3 + strategic nap, stimulant A 3 - no nap, placebo + nap, and placebo - no nap. Outcome variables will be measures on relevant performance and alertness during the night, nap sleep parameters, and parameters of sleep the next day. This study will provide information on the usefulness of a strategic nap -alone or in combination with a stimulant- and information on the consequences of a nightly nap for sleep the next day.

This work package will provide

- A 1, the hypnotic, which is most useful to induce a 5-hour sleep in the afternoon
- A 2, the recommended tool to enhance performance and alertness immediately after awakening in the late evening
- A 3, the recommended stimulant to enhance performance and alertness during the night
- a recommendation on the use of strategic naps during night duty

Work package A will also provide useful knowledge for the issue of early starts (sorties at 3-6 a.m.). Because in that context principal problems are difficulty to fall asleep in the early evening and impaired performance and alertness after awakening in the night or early morning, results of study A1 (hypnotic) and A2 (performance/alertness enhancer) can also provide guidelines for the issue of early starts.

Work Package B

Sustained operation with night shifts: prevention of fatigue and enhancement of performance and alertness

The schedule mentioned in work package A will occur when crew has to shift rapidly from day to night shift. If after this first night duty the crew remains in the night shift, they have to sleep during the day, e.g. after "unwinding" from the stresses of the preceding night they can go to bed in the morning and stay in bed till late afternoon or evening. As a consequence of insufficient "unwinding" and residual effects of stimulants taken during night duty, it might be difficult to fall asleep. Moreover, sleep efficiency and quality of sleep during the day might be impaired, due to circadian problems and daytime activities in the camp (light/noise). In this context the following issues have to be considered:

1. is it necessary to use a hypnotic to preserve sleep during the day? If yes, which hypnotic? (addressed in study B1)
2. sleep efficiency of daytime sleep will be low in many cases. Therefore, the usefulness of taking a short nap before starting the night shift should be considered. (addressed in study B2)
3. how many consecutive nights can individuals function effectively on stimulants? (addressed in study B 3)
4. ethical aspects of longer term administration of stimulants (addressed in B 4)

Referring to the above-mentioned points 1-4, this work package includes the following studies in healthy volunteers functioning in a realistic military setting:

B 1 induction of daytime sleep after night duty

Sleep duration of this daytime sleep is considerably longer than in work package A. In this case, preservation of sleep over a longer time is a more important issue than residual effects. Therefore, the usefulness of temazepam and zolpidem (and/or zaleplon) to preserve an 8 hour daytime sleep will be assessed in a double-blind placebo controlled cross-over design. Outcome variables will be objective and subjective sleep parameters, and parameters of performance and alertness after awakening (residual effects). This study (B1) will provide the hypnotic, which is most useful to preserve an 8-hour daytime sleep in a military environment. This hypnotic (B1) can be used in the next step of the work package:

B 2 usefulness of short nap prior to night duty

In volunteers, in whom daytime sleep is induced using hypnotic B1, the effectiveness will be assessed of a 1 hour nap, taken prior to night duty, to enhance performance and alertness during the night. In a cross-over design the nap condition will be compared with a no-nap condition.

Outcome variables will be objective and subjective measures on relevant performance and alertness during the night, and objective and subjective nap sleep parameters. This study (B2) will provide a recommendation whether or not it is useful to take a nap in the evening in order to enhance performance and alertness during the night.

B 3 effectiveness of stimulants during consecutive nights

Experiences during Operations Desert Shield and Storm have learned that it should be considered that many night shift crews will be (partially) sleep deprived, despite daytime use of hypnotics. Often time to sleep is too short, or stresses and environmental disturbances are too intense to allow for sufficient recuperative sleep. In such cases one can try to improve performance and alertness by means of stimulants, but it is anticipated that when sleep deprivation cumulates, stimulants will fail at a certain point in time. Therefore, study B 3 will be conducted to assess how many consecutive nights individuals can function effectively on stimulants. In a double-blind placebo controlled design recommended doses of SR-Caffeine, and modafinil will be assessed during several consecutive nights. Subjects will be sleep-deprived by allowing them only limited time to sleep. Outcome variables will be objective and subjective measures on relevant performance and alertness during the night, objective and subjective parameters of sleep the next day, and subjective and objective adverse effects.
This study will provide guidelines on how many consecutive nights individuals can safely and effectively use stimulants and can be used as background for B 4.

B 4 ethical considerations of longer term daily administration of stimulants

It is anticipated that politicians and unions of military personnel may question the ethical permissibility of structural daily use of stimulants. Therefore, it is useful to use the results of study B 3 as background for the discussion. In this part of the work package, considerations on this matter will be collected amongst various levels of military personnel and ethicists both nationally and internationally.

This work package will provide

- B1, the hypnotic, which is most useful to preserve an 8-hour daytime sleep
- B2, guidelines on the use of short evening naps in order to enhance performance and alertness during the night.
- B3, guidelines on how many consecutive nights individuals can safely and effectively use stimulants
- a report on the ethical considerations of structural use of stimulants

Work Package C

Rapid transmeridian deployment: Prevention of fatigue and enhancement of performance and alertness

Jet lag will be induced by (simulated) flights across 8-10 time zones eastwards and westwards.
Based on literature data, it is anticipated that eastward travel will lead to more adaptational difficulties than westward travel. A maximum of jet lag symptoms has been described after crossing 8 to 10 time zones and with respect to the severity of symptoms no significant differences were found between 8, 9, or 10 hours time lag.

After crossing 8-10 time zones, crew will experience jet lag symptoms in the next days after arrival. Severity of symptoms is often maximal at the second to fourth day after arrival and symptoms may last for a week to ten days, in most cases lasting longer after eastward than after westward travel. Although large inter-individual differences exist, the majority of crew will suffer from insomnia during the local nights, sleepiness during the local days, gastro-intestinal disturbances, fatigue, and mood disturbances. The major consequence of jet lag is impaired performance and alertness while executing operational tasks (Spinweber, 1987). After eastward travel (shortening the day) it will be difficult to fall asleep in the evening, because the body clock will still dictate wakefulness. Under these circumstances, poorest sleep quality and efficiency is often observed during the second and third local night (Simons, Valk, de Ree, Veldhuijzen van Zanten & D'Huyvetter, 1994). After westward travel (lengthening the day) it is often easy to fall asleep at local bedtime, but one will be wide awake during the second part of the night.

Adaptation of the biological body clock to the conditions in the new time zone can be facilitated by instructing crew to obey the local time cues; i.e. go to bed at local bedtime, whether sleepy or not, and have a meal at local mealtimes, whether hungry or not (Simons & Valk, 1997a).
To optimize crew performance in the first days after arrival, adaptation of the circadian rhythm can be accelerated by:

1. melatonin treatment. Issues to be addressed in this context are the effects of pre- and post-travel treatment on task performance, and efficacy of a physiological dose (0.5 mg) compared to a supra-physiological dose (5 mg)
2. bright light treatment. The main issues to be addressed in this context are intensity and duration of exposure
3. melatonin and bright light administered at anti-phase
4. in addition to 1, 2, or 3, supportive treatment with strategic naps and/or hypnotics and/or stimulants can be considered

Referring to above-mentioned points 1-4, this work package includes the following studies in healthy volunteers functioning in a realistic military setting:

C 1 usefulness of melatonin treatment, comparing 0.5 mg and 5 mg melatonin and placebo

Three days before and 5 days after an eastward flight crossing 8-10 time zones, subjects will receive 0.5, or 5 mg melatonin, or placebo. Depending on logistic opportunities, time zone crossing can be simulated or (preferrably) can be realized by making real flights. Outcome variables will be objective and subjective measures on relevant performance and alertness during 5 days after arrival, and objective and subjective sleep parameters. This design enables the assessment of the usefulness of pre- and/or post-travel melatonin treatment and will provide a recommended dose of melatonin ("C1"). The identical design will be followed with respect to the return flight (westward), which will be planned after a layover period that is sufficient to allow the subjects to completely adapt to the time zone of the deployment site.

C 2 usefulness of bright light treatment

Main issues in this context are intensity (lux) and duration of exposure. As it is anticipated that during military operations only short exposures will be feasible, it seems not useful to assess various exposure periods longer than 1 hour. Therefore, after crossing 8-10 time zones (real flight or simulated), subjects will receive daily exposures of 30-60 minutes for 5 days post-travel. Bright light (proposed intensity 10.000 lux) will be compared to exposures using dim light (intensity <300 lux). It should be taken into account that dim light is not to be considered as an indifferent placebo, as there is evidence that dim light also can phase shift the circadian rhythm.

C 3 usefulness of melatonin and bright light at anti-phase

After crossing 8-10 time zones, subjects will receive the recommended dose (C 1) of melatonin or placebo during 5 days at local bedtime and bright or dim light will be administered for 30 min at the start of the local day. Outcome variables will be objective and subjective measures on relevant performance and alertness during 5 days after arrival, and objective and subjective sleep parameters.

C 4 supportive treatment with strategic naps and/or hypnotics and/or stimulants

Using the results of the work packages A and B, recommendations will be made which supportive treatment can be used to optimize performance and alertness in the first days after transmeridian deployment. For this work package no extra experimental work seems necessary.

This work package will provide

- C 1: guidelines on pre- and/or post-travel melatonin treatment and the recommended dose of melatonin
- C 2: guidelines on the use of bright light treatment
- C 3: determination of the usefulness of melatonin and bright light at anti-phase
- C 4: guidelines on supportive treatment with strategic naps, hypnotics, and stimulants

Work Package D

Management of crew endurance

The management of crew endurance also needs further consideration. In that context, the following activities should be executed in future:

- development of mission specific crew endurance plans
- training of safety officers on how to design and implement unit crew endurance plans for specific missions.

The results of work packages A, B, and C provide essential input for the development of mission specific endurance plans. Moreover, the input of commanders and flight surgeons will be indispensable, because only they will be able to formulate the basic needs and limiting conditions. These operational experts, in close collaboration with scientific experts, should develop the training of safety officers on how to design and implement unit crew endurance plans for specific missions.

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15. ABSTRACT (maximum 200 words, 1044 byte)

Sleep and alertness management is a major point of attention for commanders and the medical support of military round the clock operations. Awareness on the effects of fatigue and sleepiness should be enhanced both on command level and crew level. Flight surgeons and safety officers should be trained to develop and implement mission specific crew endurance plans. Practical guidelines on methods to prevent serious fatigue and to enhance performance and alertness of the crew play a key role in these crew endurance plans. Useful methods include the use of strategic naps, hypnotics, stimulants, and chronobiotic treatment. In the context of the development of guidelines to optimize performance and alertness during sustained and stressful missions, this literature review describes the available knowledge and identifies areas where knowledge is lacking. In this context military relevant research issues related to the use of strategic naps, hypnotics, stimulants, and chronobiotic treatment are put forward. Based on the results of this study, a work program is drawn up, aimed at developing guidelines to optimize performance and alertness during sustained intensive operations.

16. DESCRIPTORS	IDENTIFIERS
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