

Fatigue Countermeasures in support of CF CC130 Air Transport Operations

From the operation to the laboratory and back to the operation

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Abstract

Deployment of troops in foreign theatres requires a massive airlift capability. The fatigue encountered in such operations can be severe enough to pose a flight safety hazard. The work reported here was done in support of CF air transport aircrews conducting re-supply missions to Bosnia. This work was carried out in 3 Phases. In Phase 1 aircrew sleep hygiene was assessed immediately prior to and throughout 10 missions to Bosnia. Aircrew psychomotor performance was also assessed during flight. The aircrews started the missions with an acute sleep debt because of having to report for duty at 0600 hrs. A fatigued-induced impact on psychomotor performance was found towards the end of the out-bound transatlantic leg. The aircrew experienced difficulty sleeping at an early circadian time (approximately 1700 hrs body clock) in the U.K. prior to flying into Bosnia. In Phase 2, we conducted a laboratory-based fatigue countermeasure study in which we determined that melatonin and zopiclone are effective facilitators of early circadian sleep, and caused no residual effects on aircrew performance after sleep on these medications. Based on the results of Phases 1 and 2, we were given permission to conduct Phase 3, an operational evaluation of the lab-proven countermeasures that involved 70 missions to Bosnia. The actigraphic data of Phase 3 indicated that relative to placebo, when aircrew were on melatonin they got to sleep quicker ($p < .01$), slept more ($p < .02$), had fewer awakenings after sleep onset ($p < .004$), and spent less time awake after sleep onset ($p < .01$). Again relative to placebo, when they were on zopiclone they got to sleep quicker ($p < .003$), slept more ($p < .005$), had fewer awakenings ($p < .01$) and less time awake after sleep onset ($p < .05$). The aircrew subjective ratings indicated relative to placebo, while on melatonin, they experienced less difficulty getting to sleep ($p < .0001$), fewer awakenings ($p < .005$), less difficulty returning to sleep after awakening ($p < .0001$) and a better sleep quality ($p < .0003$). Also relative to placebo, while on zopiclone, aircrew experienced less difficulty getting to sleep ($p < .001$), fewer awakenings ($p < .001$), less difficulty returning to sleep after awakening ($p < .0001$), and a better sleep quality ($p < .0004$). There were no statistically significant differences between melatonin and zopiclone in any of the actigraphic or subjective sleep parameters. As phase 3 was drawing to a close, we also carried out a laboratory study to compare a new short-acting sleeping medication (zaleplon) against two other sleeping medications (zopiclone and temazepam) and melatonin, not for their ability to induce sleep, but to quantify the depth of their respective impacts on psychomotor performance and to quantify the post-ingestion time required for return to normal performance. Melatonin produced a significant increase in sleepiness for 4¼ h post ingestion but did not cause an impact on psychomotor performance. The post ingestion time to recovery of normal performance for zaleplon, zopiclone and temazepam were 2¼ h, 6¼ h, and 5¼ h respectively. In spite of a prolonged period of perceived sleepiness, melatonin was superior to zaleplon in causing no impact on performance. The remaining drugs listed in increasing order of performance impact duration are zaleplon, temazepam and zopiclone. It was recommended that Central Medical Board (CMB) draft policy guidelines for aircrew use of sleeping medications during operations that can limit or restrict aircrew sleep.

Résumé

Le déploiement des troupes dans des théâtres étrangers nécessite une capacité d'emport instantané massive. La fatigue associée à ce type d'opérations peut être suffisamment importante pour présenter un danger menaçant la sécurité des vols. Les travaux dont nous faisons ici état ont été effectués afin d'appuyer les équipages de transport aérien des CF menant des missions de réapprovisionnement en Bosnie. Ces travaux comportaient trois phases. Au cours de la phase 1, nous avons évalué l'hygiène du sommeil des membres d'équipage immédiatement avant et pendant 10 missions à destination de la Bosnie. Nous avons également évalué la performance psychomotrice des équipages en vol. L'étude a révélé que les membres d'équipage avaient déjà, au début de leur mission, un important déficit de sommeil puisqu'ils avaient dû se présenter au travail à 6 h. Nous avons observé une altération induite par la fatigue de la performance psychomotrice vers la fin du parcours d'éloignement transatlantique. Au Royaume-Uni, avant le vol vers la Bosnie, les membres d'équipage ont de plus éprouvé de la difficulté à s'endormir plus tôt par rapport à leur horloge biologique (c.-à-d. vers 17 heures selon l'horloge biologique). Pendant la phase 2, nous avons effectué une étude en laboratoire de contre-mesures à la fatigue. Cette étude a révélé que la mélatonine et le zopiclone facilitaient le sommeil à une heure avancée par rapport à l'horloge biologique et n'avaient pas d'effets résiduels, après le sommeil, sur la performance de l'équipage qui avait pris ces médicaments. À la lumière des résultats des phases 1 et 2, on nous a autorisés à procéder à la phase 3, qui consistait en une évaluation opérationnelle, pendant 70 missions vers la Bosnie, des contre-mesures qui avaient fait leur preuve en laboratoire. Selon les données actigraphiques recueillies au cours de la phase 3, les sujets qui avaient pris de la mélatonine s'endormaient plus rapidement ($p < 0,01$), dormaient davantage ($p < 0,02$), se réveillaient moins souvent après s'être endormis ($p < 0,004$) et passaient aussi moins de temps réveillés après l'endormissement initial ($p < 0,01$) que s'ils avaient pris le placebo. De même les sujets qui avaient reçu du zopiclone plutôt qu'un placebo s'endormaient plus rapidement ($p < 0,003$), dormaient davantage ($p < 0,005$), se réveillaient moins souvent ($p < 0,01$) et passaient moins de temps réveillés après l'endormissement initial ($p < 0,05$). Les évaluations subjectives des équipages indiquaient que les sujets ayant pris de la mélatonine plutôt qu'un placebo estimaient avoir eu moins de difficulté à s'endormir ($p < 0,0001$), s'être réveillés moins souvent ($p < 0,005$), avoir eu moins de difficulté à se rendormir après un réveil ($p < 0,0001$) et avoir eu un sommeil de meilleure qualité ($p < 0,0003$). Toujours comparativement au placebo, les sujets ayant pris du zopiclone avaient eu moins de difficulté à s'endormir ($p < 0,001$), s'étaient réveillés moins souvent ($p < 0,001$), avaient eu moins de difficulté à se rendormir après un réveil ($p < 0,0001$) et avaient eu un sommeil de meilleure qualité ($p < 0,0004$). Nous n'avons pas relevé de différences significatives entre la mélatonine et le zopiclone dans les données actigraphiques ou les paramètres subjectifs du sommeil. Comme la phase 3 tirait à sa fin, nous avons également effectué une étude en laboratoire afin de comparer un nouveau somnifère d'action brève (le zaleplon) à deux autres somnifères (le zopiclone et le témazépam) et à la mélatonine, non dans le but de déterminer leur aptitude à provoquer le sommeil, mais plutôt pour quantifier l'ampleur de leurs répercussions respectives sur la performance psychomotrice et pour déterminer le temps écoulé entre l'ingestion et le retour à un niveau de performance normal. La mélatonine a provoqué une augmentation significative de la somnolence pendant une période de 4 ¼ heures après l'ingestion, mais n'a pas eu de répercussions sur la performance psychomotrice. Dans le cas du zaleplon, du zopiclone et du témazépam, le retour au niveau normal de performance s'est

effectué, respectivement, 2¼ h, 6¼ h et 5¼ h après l'ingestion. Malgré une période prolongée de somnolence perçue, la mélatonine a eu moins de répercussions sur la performance que le zaleplon. Les autres médicaments se sont classés de la façon suivante, par ordre croissant de durée des répercussions sur la performance : zaleplon, témazépam et zopiclone. On a recommandé que la Commission centrale médicale (CCM) rédige une ébauche de directives concernant l'utilisation de somnifères par les membres d'équipage, pendant les opérations qui peuvent limiter ou restreindre le sommeil de ces derniers.

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Executive summary

Deployment of troops in foreign theatres requires a massive airlift capability. The fatigue encountered in such operations can be severe enough to pose a flight safety hazard. The work reported here was done in support of CF air transport aircrews conducting re-supply missions to Bosnia. This work was carried out in 3 phases. Phase 1 was a study in which aircrew sleep hygiene was monitored immediately before and during 10 missions to Bosnia, and where aircrew psychomotor performance was assessed in-flight. This study found that the aircrew started the mission with an acute sleep debt and developed a corresponding fatigued-induced impact on psychomotor performance during the out-bound transatlantic leg. Further, the aircrew experienced difficulty sleeping at an early circadian time (approximately 1700 hrs body clock) in the U.K. prior to flying into Bosnia. Phase 2 was a laboratory-based fatigue countermeasure study in which we determined that melatonin and zopiclone are effective facilitators of early circadian sleep, and caused no residual effects on aircrew performance after sleep on these medications. Phase 3 was an operational evaluation of the lab-proven countermeasures and was conducted over 27 months during 70 missions to Bosnia and involved 219 aircrew. The actigraphic data from Phase 3 indicated that relative to placebo, when subjects were on melatonin or zopiclone they got to sleep quicker, slept more, had fewer awakenings after sleep onset, and spent less time awake after sleep onset. The aircrew subjective ratings indicated that relative to placebo, while on melatonin or zopiclone, they experienced less difficulty getting to sleep, fewer awakenings, less difficulty returning to sleep after awakening and a better sleep quality. There was no difference between melatonin and zopiclone in either objective actigraphic data or aircrew subjective ratings of sleep parameters. As Phase 3 was drawing to a close, we also carried out a laboratory study to compare a new short-acting sleeping medication (zaleplon) against two other sleeping medications (zopiclone and temazepam) and melatonin, not for their ability to induce sleep, but to quantify the depth of their respective impacts on psychomotor performance and to quantify the post-ingestion time required for return to normal performance. This placebo-controlled double blind repeated measures protocol involved a morning baseline psychomotor test session followed by ingestion of a single dose of their scheduled medication at 0945 hrs. Thereafter psychomotor performance was assessed every hour, at the top of the hour throughout the rest of the experimental day with the subjects being released at 1700 hrs. Melatonin produced a significant increase in sleepiness for 4¼ h post ingestion but did not cause an impact on psychomotor performance. The post ingestion times to recovery of normal performance for zaleplon, zopiclone and temazepam were 2¼ h, 6¼ h, and 5¼ h respectively. In spite of a prolonged period of perceived sleepiness, melatonin was superior to zaleplon in causing no impact on performance. The remaining drugs listed in increasing order of performance impact duration are zaleplon, temazepam and zopiclone. It was recommended that Central Medical Board (CMB) draft policy guidelines for aircrew use of sleeping medications during operations that can limit or restrict aircrew sleep.

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Sommaire

Le déploiement des troupes dans des théâtres étrangers nécessite une capacité d'emport instantané massive. La fatigue associée à ce type d'opérations peut être suffisamment importante pour présenter un danger menaçant la sécurité des vols. Les travaux dont nous faisons ici état ont été effectués afin d'appuyer les équipages de transport aérien des CF menant des missions de réapprovisionnement en Bosnie. Ces travaux comportaient trois phases. La phase 1 était une étude dans le cadre de laquelle nous avons évalué l'hygiène du sommeil des équipages immédiatement avant et pendant 10 missions à destination de la Bosnie. Nous avons également évalué la performance psychomotrice de l'équipage en vol. L'étude a révélé que les membres d'équipage avaient déjà, au début de la mission, un important déficit de sommeil et qu'ils avaient souffert d'une altération correspondante, induite par la fatigue, de la performance psychomotrice pendant le parcours d'éloignement transatlantique. Au Royaume-Uni, avant le vol vers la Bosnie, les membres d'équipage ont de plus éprouvé de la difficulté à s'endormir plus tôt par rapport à leur horloge biologique (c.-à-d. vers 17 heures selon l'horloge biologique). La phase 2 consistait en une étude en laboratoire de contre-mesures à la fatigue. Elle a révélé que la mélatonine et le zopiclone facilitaient le sommeil à une heure avancée par rapport à l'horloge biologique et n'avaient pas d'effets résiduels, après le sommeil, sur la performance de l'équipage qui avait pris ces médicaments. Au cours de la phase 3, nous avons procédé à une évaluation opérationnelle des contre-mesures qui avaient fait leur preuve en laboratoire. Cette phase s'est déroulée sur 27 mois pendant 70 missions vers la Bosnie et a mis à contribution 219 équipages. Selon les données actigraphiques recueillies au cours de la phase 3, les sujets qui avaient pris de la mélatonine ou du zopiclone s'endormaient plus rapidement, dormaient davantage, se réveillaient moins souvent après s'être endormis et passaient aussi moins de temps réveillés après l'endormissement initial que s'ils avaient pris le placebo. Les évaluations subjectives des équipages indiquaient que les sujets ayant pris de la mélatonine ou du zopiclone plutôt qu'un placebo estimaient avoir eu moins de difficulté à s'endormir, s'être réveillés moins souvent, avoir eu moins de difficulté à se rendormir après un réveil et avoir eu un sommeil de meilleure qualité. Nous n'avons relevé aucune différence entre la mélatonine et le zopiclone, ni dans les données actigraphiques objectives, ni dans les évaluations subjectives, par les équipages, des paramètres du sommeil. Comme la phase 3 tirait à sa fin, nous avons également effectué une étude en laboratoire afin de comparer un nouveau somnifère d'action brève (le zaleplon) à deux autres somnifères (le zopiclone et le témazépam) et à la mélatonine, non dans le but de déterminer leur aptitude à provoquer le sommeil, mais plutôt pour quantifier l'ampleur de leurs répercussions respectives sur la performance psychomotrice et pour déterminer le temps écoulé entre l'ingestion et le retour à un niveau de performance normal. Ce protocole à double insu, contrôlé contre placebo et faisant appel à des mesures répétées, comprenait une séance d'évaluation psychomotrice matinale de référence, suivie de l'ingestion, à 9 h 45, d'une seule dose du médicament attribué au sujet. Par la suite, la performance psychomotrice était évaluée toutes les heures, à l'heure juste, pendant le reste de la journée d'étude; les sujets étaient libérés à 17 heures. La mélatonine a provoqué une augmentation significative de la somnolence pendant une période de 4 ¼ heures après l'ingestion, mais n'a pas eu de répercussions sur la performance psychomotrice. Dans le cas du zaleplon, du zopiclone et du témazépam, le retour au niveau normal de performance s'est effectué, respectivement, 2¼ h, 6¼ h et 5¼ h après l'ingestion. Malgré une période prolongée

de somnolence perçue, la mélatonine a eu moins de répercussions sur la performance que le zaleplon. Les autres médicaments se sont classés de la façon suivante, par ordre croissant de durée des répercussions sur la performance : zaleplon, témazépam et zopiclone. On a recommandé que la Commission centrale médicale (CCM) rédige une ébauche de directives concernant l'utilisation de somnifères par les équipages, pendant les opérations qui peuvent limiter ou restreindre le sommeil de ces derniers.

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Phase 1. Impact of fatigue on aircrew performance

Introduction

While pilots must undertake their flying tasks with a high degree of psychomotor performance, stressors such as noise and vibration, long crew days, irregular work schedules, circadian disruptions, and inadequate sleep can interact to produce dangerous levels of fatigue (13). The correlation between increased fatigue and decreased performance has been reported by Barth et al (6), French et al (25, 26), Mortimer (42), Perelli (48), and Shingledecker and Holding (57). Although the initial effects of fatigue can go unnoticed, eventually, vigilance, judgement, situational awareness, and crew co-ordination may all be compromised (13). Belenky et al (7) found that for an artillery firing task, during continuous combat operations, when sleep is limited to less than six hours per day, performance deteriorates. Ritter (52) reviewed incident reports from the Aviation Safety Reporting System and concluded that sleep loss, circadian disruption and improper nutrition contributed to fatigue-related cognitive errors made by aircrews. In fact some of these incident reports demonstrated that aircrews routinely obtained less than six hours of sleep per night. McCauley (40) found that several aircraft mishaps have been attributed to pilot fatigue because of disrupted and inadequate sleep. Billings (9) states that more than half of all aviation accidents are probably the direct result of fatigue-related pilot inattentiveness.

Deployment of troops in foreign theatres requires a massive airlift capability. Transport squadrons are called upon to deliver personnel and material, day and/or night, around the clock, usually during long transmeridian flight. The relentless fatigue encountered in such operations can be severe enough to pose a flight safety hazard (64). Crew days are often pushing the upper limits of the maximum allowable 16-hour crew day. At the end of the crew day, crews get a minimum of about 14 hours rest (during which they are often unable to sleep soundly because of circadian rhythm disruption) and then are required to start all over again.

The key to minimizing the impact of such demanding missions is appropriate scheduling concessions to afford aircrews the opportunity to obtain adequate rest, both during and between missions. During the early to mid 1970s, several publications provided scheduling guidelines to limit the impact of long transmeridian flights on aircrews in an effort to avoid compromising flight safety (12, 28, 41). One of these systems (12) was under consideration by what was then the Air Transport Command of the Canadian Forces. While routine transport missions can normally be scheduled with a view to providing ample opportunity for crew rest, the same cannot be said for contingency operations. The imperatives of contingency operations do not easily lend themselves to the notion of scheduling concessions, especially when crews are required to fly tactical transports designed for three to four hour long missions in a strategic role with crew days approaching the maximum allowable crew day, and sometimes, of necessity, exceeding it.

In Operation Alliance, a month long airlift that took place during January 1996 in support of Canadian troops in Bosnia, 18 Air Transport Group (ATG) CC-130 Hercules carried out 86 missions from Trenton to Split with aircraft landing in theatre every four hours. During

operation Alliance, most crews attained the 120 hour maximum allowable flying time per 30 day period, in as little as two weeks. There were several reports of aircrew falling asleep at the controls during these types of missions. Despite this anecdotal information, to date little research has provided a detailed scientific documentation of the impact of fatigue upon aircrew performance.

After the main airlift was completed, only three of these missions were flown each week. This frequency of re-supply flights was adequate to sustain Canadian troops in former Yugoslavia. Because these sustainment flights were flown in a more relaxed manner, aircrew were given 32 hours on the ground in the United Kingdom on arrival from Trenton, Canada (five time zones), before proceeding to Zagreb, Croatia (one time zone). This is contrasted with the 14 hours they were given at this stage of the mission, during the original airlift.

The current study is an attempt to document to what extent fatigue (and time zone changes of five and six hours) can impact on aircrew performance during routine re-supply missions to former Yugoslavia. If we can document significant fatigue-related lapses in performance in this study, we can assume that the fatigue problem will only worsen when crews are asked to fly repeated missions back-to-back with minimum crew rest as was done during Operation Alliance.

Methods

Subjects

The MOC (military occupation code) demographics for the 53 subjects (10 crews) who participated in the study are illustrated in Table 1.

TABLE 1. Demographics of participating subjects

	<i>Aircraft Commanders</i>	<i>Co-Pilots</i>	<i>Navigators</i>	<i>Flight Engineers</i>	<i>Loadmasters</i>
#/gender	9 males	9 males/1female	8 males/2 females	10 males	15 males
mean age (yr)	35.5	29.6	32.5	40.4	34.5
age range	29 to 42	24 to 32	23 to 49	36 to 49	31 to 44
rank range	Capt to LCol	Lt to Capt	Lt to Maj	Sgt to MWO	M/Cpl to MWO

One limitation of this study was the difficulty of gaining access to the CC-130 aircrews for several days prior to the missions. Such access would have allowed for time to train them to a level of stable performance on the psychomotor tasks.

Therefore the results will have to be interpreted carefully to factor out learning effects.

Equipment and Data Collection Strategy

In order to establish the number of hours of sleep each aircrew member obtained during these missions, as well as in the period immediately prior to the commencement of the missions, all aircrew were asked to wear wrist actigraphs from approximately 5 days prior to the mission until the mission was completed. Further, all aircrew were asked to complete sleep/activity/mood questionnaires in a paper log prior to the missions (pre-mission questionnaire), during the missions (mission questionnaire), and on a laptop computer, also during the mission. The questions relating to the amount and quality of sleep obtained each night were to be answered each morning, for five days prior to the mission, and just prior to the commencement of daily flying operations during a mission. The computer-based questions relating to their fatigue states were answered each time the aircrew performed a psychomotor test battery during the mission.

While it was anticipated that the crews on these missions would experience fatigue due to the length of the mission, they also likely experienced some fatigue due to the circadian stresses inherent in such long transmeridian flights. Thankfully, all of these missions departed from Trenton at approximately 0800 hrs local time. Therefore, we should not have any confounding of results due to different circadian rhythm stresses across crews.

Existing psychomotor test batteries, such as the DRDC-Toronto sustained operations (SUSOPS) test battery, have a long history of well-documented laboratory-based findings concerning the effects of fatigue on performance (2, 50). Thus, it was essential to include these tasks to tie any obtained findings to the existing literature. As valuable as these cognitive tasks are, one possible concern is the degree of applicability that lower level cognitive tasks have to a flying task. Therefore we also included a multi-tasking test (32, 65) thought to possess greater context validity to flying, as well as requiring higher levels of cognitive activity to complete. Beyond providing a link to the existing fatigue literature, the present study represents one of the first attempts to fully validate this multitasking task. As a result, two different psychomotor performance batteries were run from a single lap-top computer;

- a subset of 3 tests (SRT (serial choice reaction time), LRT (logical reasoning task), and SST (serial subtraction task)) from the DCIEM SUSOPS battery which were performed, one at a time, over 10 minutes and
- a multi-tasking battery developed by Dr Hal Weinberg which took 15 minutes per data collection iteration (32, 65).

The crews were only tested on the psychomotor performance batteries during actual flight in the following manner;

- three times on the outbound leg from Trenton (Canada) to Lyneham (U.K.)
- once during the leg from Lyneham to Zagreb (Croatia) and return, and
- three times on the inbound leg from Lyneham to Trenton.

All crew positions (pilots, navigator, flight engineer, and loadmasters) performed the serial iterations of the SUSOPS test battery, while only the pilots performed the multi-tasking battery (because it is essentially a flying task and the other crew positions would not have the pre-requisite training to give us meaningful data on this task). However, all crew positions were asked to take part in the wrist actigraphy/sleep logs and to complete the questionnaires relating to sleep quality/mood/alertness/fatigue ratings.

Task Descriptions

SUSOPS tasks.

All of the SUSOPS tasks were performed on lap-top computers (Pentium 133 Mhz chips with 16 Mb RAM and 1 Mb of video memory) using an external 'bus' mouse as the input device. All subjects performed the tasks in the rear of the fuselage, in order to avoid distractions by cockpit instrumentation or interfering with the aircraft controls, and to perform the task in relative privacy. The subjects were seated in the standard collapsible web-seats used for troops and had a custom-contoured board (with an anti-skid surface) on their laps. The computers were placed on this 'lapboard' that was large enough to accommodate the computer and a mouse pad (approximately 59 cm x 42 cm). Subjects responded to the computer questionnaire and all three SUSOPS tasks by moving the mouse until the cursor was super-imposed over their chosen response, and then by clicking the mouse. Subjects were instructed to work as quickly as possible without sacrificing accuracy. The subjects wore headsets to defend against the high ambient noise but in order to avoid distractions by routine communications between crew-members, the headsets were not plugged into the aircraft intercom while they were performing the psychomotor tests.

Computer Questionnaire.

The first item of any SUSOPS test battery iteration was the computer questionnaire that involved a brief response to the following four questions;

- the subject's assessment of his/her own state of alertness by selecting the most appropriate response from the 7 point Stanford Sleepiness Scale (34),

- the subject's assessment of his/her own mental fatigue state by selecting any number on a continuous scale from 1 (very mentally fresh) to 7 (very mentally fatigued),
- the subject's assessment of his/her own physical fatigue state on a continuous scale from 1 (very physically fresh) to 7 (very physically fatigued), and
- current aircraft position (latitude and longitude) in order to track where each testing session took place.

The aircraft position was obtained from the cockpit crew by the experimenter, via the intercom system.

Serial Reaction Time (SRT).

This task required the subjects to select which of four letters (A, B, C, or D, which were presented on the computer screen in a rectangular response grid) corresponded to the single stimulus letter (again A, B, C, or D) which was briefly presented on the computer screen (immediately above the response letter grid) and was subsequently replaced by single serial random presentations of any of the four stimulus letters immediately after each response.

Logical Reasoning Task (LRT).

This task was developed by Baddeley (4) and described by him as involving higher mental processes, based on grammatical transformation: the task involves understanding of sentences of varying syntactic complexity. It consists of presentations (on the computer screen) of one of 16 sentences (such as 'A is not preceded by B') followed by a pair of letters (either 'AB' or 'BA'). The subjects were required to indicate whether the sentence was a true or false description of the associated letter pair by selecting either the 'True' or 'False' response box on the computer screen. There were 32 possible combinations of sentence and letter pairs.

Serial Subtraction Task (SST)

This task is similar to a task described by Cook, Cohen, and Orne (18). Here the subjects were presented with a randomly chosen three-digit number between 500 and 999 (on the computer screen) (e.g., 763) and were also presented with a randomly chosen subtrahend between 5 and 9 (e.g., 9). The subjects were required to perform serial subtractions (e.g., $763-9=754$, $754-9=745$, $745-9=736$, etc). The task also involved a short-term memory component in that after the first subtraction was performed, all numbers disappeared from the computer screen, forcing the subjects to remember the last solution as well as the subtrahend.

Multitask (MT).

The other test battery was a recently developed multitask designed to simulate the information processing characteristics of flight performance (66). The task simulated flying an aircraft to specific targets or 'waypoints', and was developed during approximately 8 months of study and observation of flight simulators, including the Airbus A-310, the Boeing 747, and the Cessna Citation. The computer screen showed four separate displays representing four sub-tasks to be performed simultaneously (figure 1.1). Three of these four tasks interacted. There were vigilance sub-tasks with altitude assignment changes visible for only 5 seconds and the subjects also had to be vigilant in order to determine when the two "attitude indicators" disagreed with each other and then determine which of the attitude indicators accurately reflected the "aircraft attitude". A bar task (analogous to managing the power quadrant of a large multi-engine transport) did not interact with the other three sub-tasks. The measures of performance include scores related to error detection and selective attention, visuo-motor tracking and coordination, short-term memory, mental arithmetic, and scanning strategies. The raw output data file was merged with a computer reduction algorithm to yield a single final weighted composite score that reconciles correct responses and errors. This task is explained in more detail elsewhere (47).

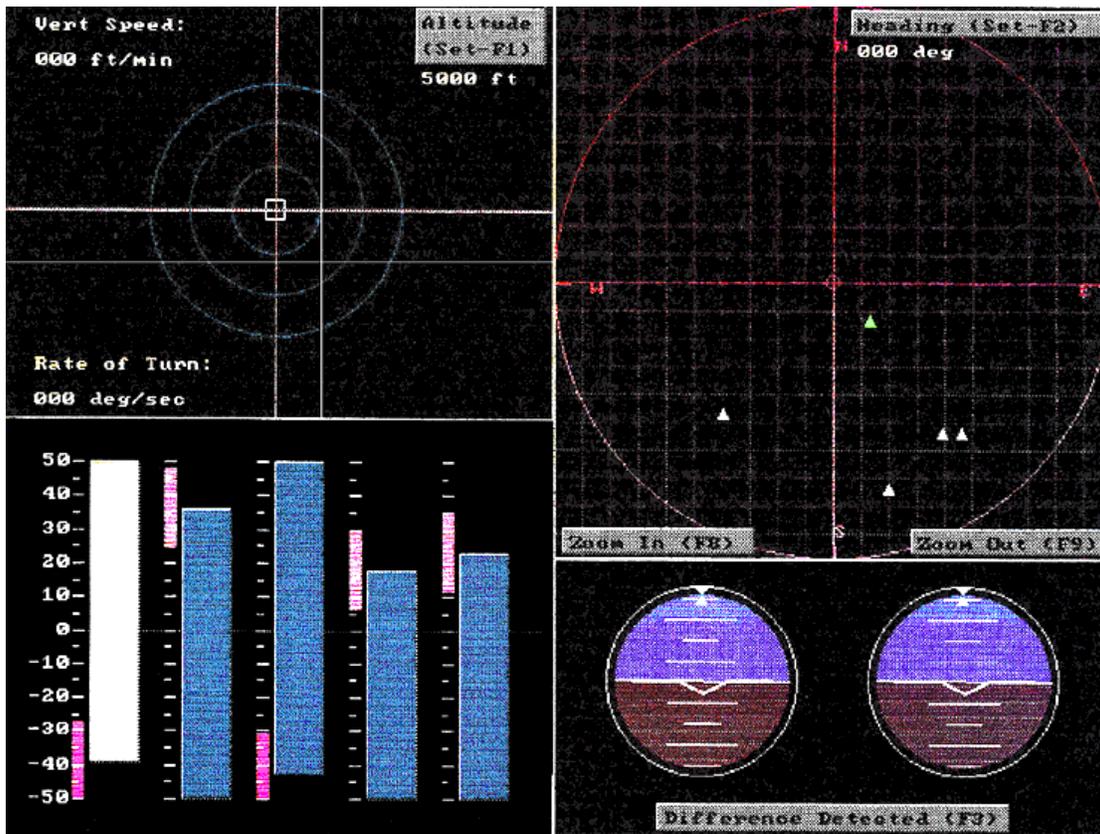


Figure 1.1 Computer screen 'capture' of multi-task display in grey scale instead of the colors that are present on the computer.

Experimental Design Considerations

Because of the requirement to collect aircrew performance data without interfering with their flying duties, we did not use rigorously defined time intervals over which we collected data. However, pilots and navigators from ATG HQ identified the following possible data collection opportunities.

1) Trenton (Canada) to Lyneham, (United Kingdom) leg

Upon reaching top of climb (TOC) after departure from Trenton, the first testing cycle was commenced with the concurrence of the aircraft commander (AC) and, one at a time, each crew member rotated through the test site, located in the after end of the fuselage. For all such testing, the aircrew wore their head-sets to defend against the high ambient noise level but they were not plugged into the intercom system, so as to avoid the possibility of distractions from normal crew communications. Approximately half way across the Atlantic (about 6 hours elapsed time after take-off), all crew

positions were again asked to perform the second iteration of the test batteries. Approximately 2.5 hours out from Lyneham, all crew members were asked to perform a third iteration, such that all data collection for this leg was completed by the time the aircraft was about one hour out from Lyneham, in order not to interfere with the relatively busy approach to landing in Lyneham through congested European airspace.

2) Lyneham to Zagreb (Croatia) & return

Given that this entire leg was flown in very congested airspace, each crew member was tested only once on this part of the mission, either in-bound to Zagreb, or during the return leg to Lyneham. Often, it was most convenient to test one or both of the pilots on the ground in Zagreb.

3) Lyneham to Trenton leg

The data collection protocol on this final leg was similar to the first leg of the mission (i.e. from Trenton to Lyneham) except that there were fewer constraints toward the end of this leg, given that Canadian airspace was not as congested as the airspace over Europe. Further, the average flying time on this return leg was two hours longer than for the outbound leg, because of the normal westerly headwinds. The approximate psychomotor testing locations for all mission legs are illustrated in figure 1.2.

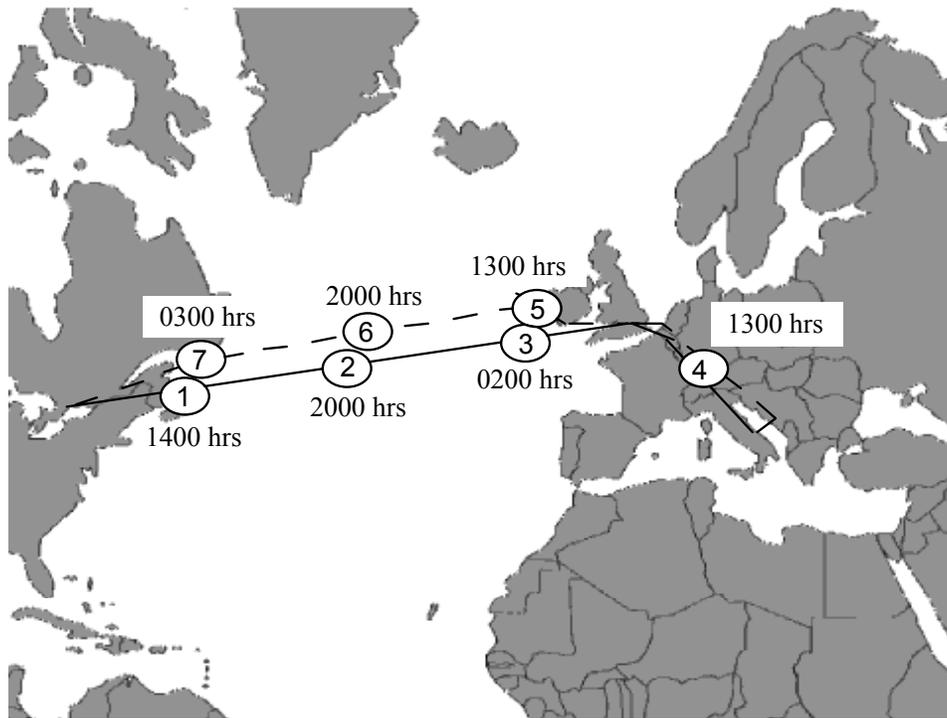


Figure 1.2. Map illustrating approximate outbound (solid lines) and return (dashed lines) tracks including approximate psychomotor performance testing locations. Locations 1, 2, and 3 correspond to testing locations for the outbound transatlantic leg, while location 4 averaged about 3 degrees East Longitude on either the outbound leg from Lyneham to Zagreb or several hours later on the return leg from Zagreb to Lyneham. Locations 5, 6, and 7 represent the test locations during the return transatlantic leg from Lyneham to Trenton.

Statistical Analysis

The tests results from the SUSOPS battery, the multi-tasking battery, and the wrist actigraphs were submitted to one way analysis of variance with "MOC" (military occupation code) as the between factor and days or trials as the within factor. We used the Duncan Multiple Range Test to analyse any simple main effects or interactions. Because of low compliance with the request to maintain the paper logs, the pre-mission and mission sleep/activity/mood questionnaire data was not analysed.

Results

For the sake of brevity, only the most relevant results will be presented here.

Wrist Actigraphy

Wrist actigraphs measure every tenth of a second, whether a movement was detected from the wearer. Software (a program called Win ACT, version 1.2, developed by Tim Elsmore from Activity Research Services of San Diego, California) looks at the frequency of such movements over time in order to quantify the number and duration of sleep episodes. The number of minutes spent asleep in a 24 hour period demonstrated a highly significant main effect of days ($p < .0001$) as illustrated in figure 1.3 where “daily sleep in minutes” are plotted over pre-mission and mission ‘days’. The results of post hoc analyses are shown as ‘p’ values between adjacent cells in figures 3 and 5. The amount of sleep the subjects experienced during the days leading up to a mission steadily decreased from 475 minutes per day to 380 per day (figure 3). Given that the planned take-off time was 0800 hrs local time and that the crews reported to operations two hours before take-off, having arisen at their respective homes anywhere from one to two hours prior to reporting at operations, this result is not surprising. This is only 20 minutes more sleep than Belenky (4) found as the threshold minimal sleep that produced performance impairment in continuous combat operations. The 380 minutes (6 hrs and 20 minutes) of sleep during the last night in Trenton before the start of the mission is an average value across all aircrew. In fact, 23% of the aircrew received less than 6 hours of sleep with one individual receiving only 248 minutes (4 hours and 8 minutes) for that last pre-mission night.

Total sleep time tended to recover somewhat during the first day in Lyneham, then drop significantly again during the second night in Lyneham, before recovering over the last night in Lyneham. This can be explained by the fact that on arrival in England after a long crew day and carrying a sleep deficit from their last night at home, the crews were so tired that they were able to sleep relatively easily. However, after obtaining some restorative sleep upon arrival, by the second night in Lyneham, circadian rhythm disruption tended to make sleep more difficult. Here, 15% of the aircrew received less than 6 hours of sleep with one individual receiving only 259 minutes (4 hours and 19 minutes). By the time the crews returned from Zagreb for their last night in Lyneham their total sleep time was significantly increased and back to the levels evident two or three nights before the mission.

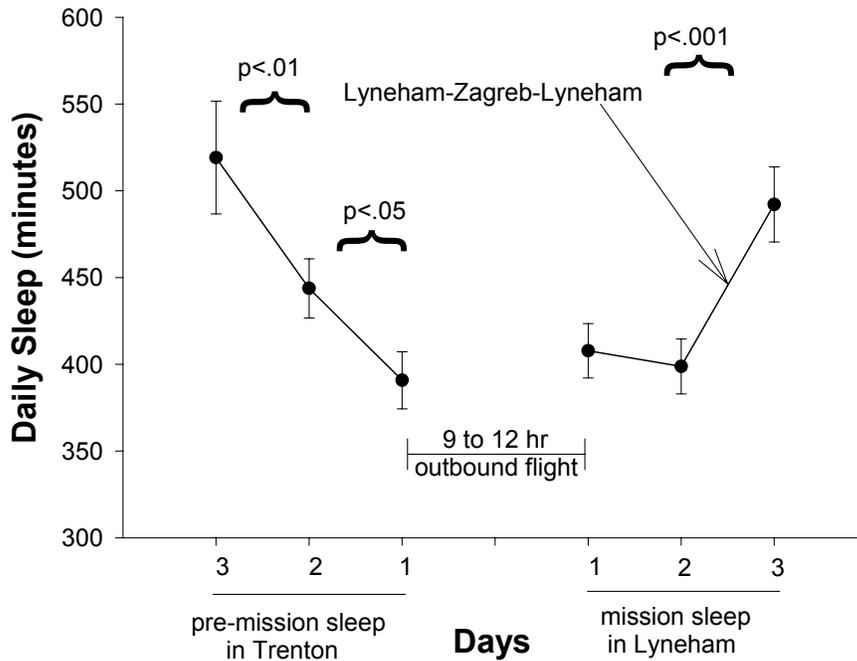


Figure 1.3. Plot of Daily Sleep Minutes over pre-mission and mission days, collapsed over MOCs

Subjective Fatigue

For the Stanford Sleepiness Scale, the main effect of trials was significant $F(2,34) = 37.34, p < .001$ and is illustrated in figure 1.4a. This indicates that with respect to the pilots' self-rating (Stanford Sleepiness Scale), sleepiness increases progressively during both transatlantic legs.

For both "mental fatigue rating" $F(2,34) = 12.99, p < .001$ and "physical fatigue rating" $F(2, 34) = 10.33, p < .001$, the main effects of trials were also significant and are plotted in figures 1.4b and 1.4c.

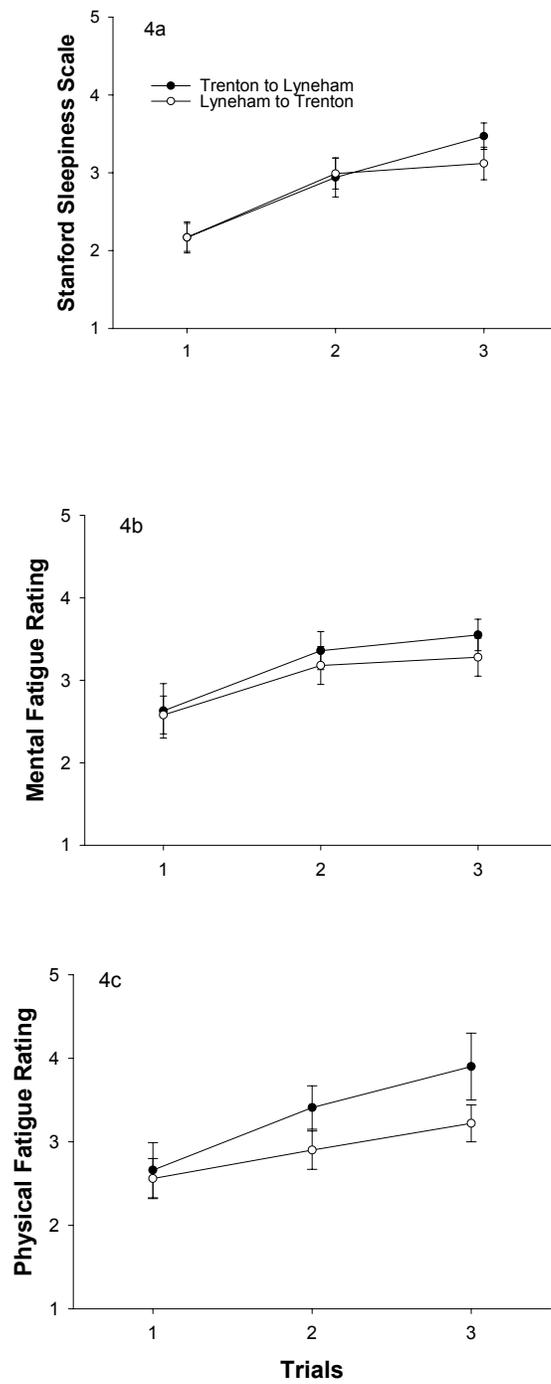


Figure 1.4. Subjective assessments of sleepiness and fatigue (mean values \pm s.e.m.) plotted over trials for departure (Trenton to Lyneham) and return (Lyneham to Trenton) legs.

Multitask

A combined subjective fatigue index was generated by averaging subjective fatigue data (from the Stanford Sleepiness Scale, as well as the mental and physical fatigue scales) which is shown in figure 1.4. By superimposing an estimate of subjective fatigue onto the plots for cognitive tasks, it is possible to judge the relative effect on performance (figure 1.5). The 3 psychomotor trials of the outbound leg (from Trenton to Lyneham) as well as those of the return leg (from Lyneham to Trenton) were performed serially approximately every 3 hours. The interval between the trial 3 of the outbound leg and trial 4 (the in-theatre trial) was approximately 36 hours while the interval between trials 4 and 5 (the first transatlantic trial of the return leg) was approximately 24 hours. The orthogonal polynomial contrasts in the combined subjective fatigue index data indicate significant linear functions for the three trials of the outbound transatlantic leg $F(1,17) = 21.75, p < .0002$) and the return transatlantic leg $F(1,17) = 18.62, p < .0005$). These orthogonal polynomial contrasts indicate no significant quadratic component to these functions for either transatlantic leg thus confirming a linear increase in subjective fatigue over both transatlantic legs. The performance curve for the multitask indicates that learning appears to be disrupted during the last trial of the transatlantic departure leg when the subjects were experiencing significant subjective fatigue (significant quadratic trend $F(1,17) = 7.64, p < .019$). On the return transatlantic leg, performance appears to have reached a learning asymptote.

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When data were looked at individually, thirteen of the eighteen pilots and co-pilots demonstrated a drop in multitask performance during the transatlantic legs of these missions, apparently due to fatigue. Of these “fatigue sensitive” individuals, twelve showed a performance decrement in the outbound transatlantic leg, while nine showed a performance decrement during the return transatlantic leg, and eight showed a fatigue-induced performance decrement on both transatlantic legs.

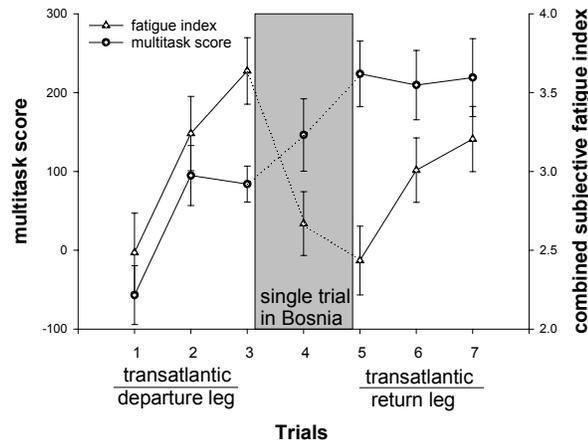


Figure 1.5. Multitask score plotted over trials for departure (Trenton to Lyneham), in-theatre (Lyneham-Zagreb-Lyneham), and return (Lyneham to Trenton) legs, and superimposed over combined subjective fatigue index (all values are mean \pm s.e.m.).

Discussion

The psychomotor performance results can be interpreted from the perspective of an interruption of a ‘learning’ paradigm where the significant quadratic trend for the 3 trials of the outbound leg (for the multitask) suggests a probable impact of fatigue on learning. This conclusion is supported by the linear rise in subjective levels of fatigue during the long transatlantic legs (figures 1.4), especially during the outbound leg, which began with a relative sleep deficit (figure 1.3). The impact of fatigue on the multitask occurs during trial 3 of the outbound transatlantic leg in that learning of this task is interrupted in response to the highest levels of subjective fatigue of the entire mission (figure 1.5). However, after the pilots have rested, performance on these tasks continues to improve.

Prior to the mission there is a progressive deterioration in sleep time during the last 3 nights of home-based sleep with the least amount of sleep (6 hours and 30 minutes) occurring during the last night before commencement of the mission (figure 1.3). This is in sharp contrast to the 8 hours and 12 minutes of sleep these pilots received during their last sleep in Lyneham before returning to Canada (figure 3). This return leg was flown over a similar route as the outbound leg, but due to the restorative sleep obtained during the last night in Lyneham, fatigue is lower during the return leg than during the outbound leg. Consequently psychomotor performance appears to be free of any impact from fatigue during that leg.

One of the most compelling series of statistics in the fatigue literature is provided by Coren (19) who examined Canadian Ministry of Transportation data on motor vehicle accidents. He compared the number of accidents immediately before and after shifts to and from daylight savings time for 1991 and 1992. He found that for every province except Saskatchewan (which does not shift to and from daylight savings time), on the Monday after the spring time change, traffic accidents increased by seven percent, and this effect disappeared within a week. Conversely, in the fall, when we gain an extra hour of sleep, Coren found that this pattern is reversed resulting in a decrease of seven percent in the number of reported

accidents. However a week later, the accident rate increases again, to “normal”. This data is compelling because it represents over 1.5 million accidents from all over Canada. If a one hour change in sleep time affects the motor vehicle accident rate by seven percent in a two-dimensional task like driving, then there is every reason to expect that when crews take-off with a more significant sleep deficit than one hour, fly long transatlantic missions in slow aircraft (a more demanding 3-dimensional task), encounter jet lag for several days in Europe, and then return home via another long transatlantic flight, deleterious effects of fatigue on crew performance would be expected, along with an attendant potential to compromise flight safety.

With respect to the limitations of sleep hygiene for the pilots and crews flying the missions monitored in this study, for the last night at home before the mission, departure should be delayed by 2 hours. During the second night in the England, the mission schedule dictates sleep at an inappropriately early circadian body clock time and the crews have difficulty sleeping. In an effort to facilitate such mission-driven early circadian sleep, we will undertake a study to determine whether or not melatonin or zopiclone can facilitate early circadian sleep, and if so, whether or not there is an attendant psychomotor performance liability. A psychomotor performance liability would preclude the use of either of these medications in aircrew.

The purpose of this study was to document the impact of fatigue on psychomotor performance and to assess the corresponding implications for flight safety. The scheduling demands on the aircrew undertaking these re-supply missions in support of our troops in Bosnia were minimal in comparison with the huge effort of Operation Alliance (the initial airlift to deliver heavy vehicles and equipment to the theatre of operations). Therefore the results of this study can be considered a baseline with respect to the genesis of fatigue on routine transatlantic air transport operations. Should transport crews be called upon to perform another airlift similar to Operation Alliance, with minimum opportunity for crew rest both during and between missions, aircrew fatigue would be expected to be much more severe than the fatigue we were able to measure on these routine re-supply missions.

Conclusions

1. Overall, our transport aircrews showed a linear pattern of decreasing sleep over the last three days before embarking on these re-supply missions, with the last night at home in Trenton providing the least sleep of the entire mission period.
2. The self-rated scores for sleepiness, mental, and physical fatigue, indicate increases in sleepiness and fatigue throughout the long transatlantic flights.
3. Multitask performance indicates a probable impact of fatigue toward the end of the outbound transatlantic leg.

Phase 2. Laboratory development of pharmaceutical fatigue countermeasures

Introduction

In a recent study, we monitored 10 CC130 re-supply missions to the former Yugoslavia (47). During that study we measured aircrew performance in the air (using computer-based psychomotor test batteries) and sleep hygiene throughout the mission (using wrist actigraphs). Analyses of those data confirmed a significant impact of fatigue on psychomotor performance during the long transatlantic flights. Further, during their second night in the United Kingdom, due to the operational schedule, the crews had to sleep at inappropriately early circadian times, relative to their home base, and therefore had difficulty getting sufficient sleep.

The provision of ample opportunity for crew rest between successive legs of long transmeridian missions is the first line of defence against the development of fatigue and the accrual of sleep debt. However, the operational imperatives that drive military taskings often preclude such scheduling concessions. In such situations, appropriate pharmacologic intervention has the potential to improve crew rest and therefore, sustain crew performance.

Literature Review

Melatonin

Melatonin is a naturally occurring hormone synthesized by the pineal gland from the precursor amino acid tryptophan (11). In pharmacologic doses, melatonin has a large margin of safety (11), producing a mild soporific effect with minimal side-effects. This along with melatonin's ability to advance or retard circadian rhythms depending on the dosage and the timing of ingestion (3, 11) has resulted in increased research interest. Several studies suggest that melatonin is able to adjust circadian rhythms and reduce the effects of jet lag on cabin crew (49) or passengers (3, 24). Dawson and Armstrong (21) refer to melatonin as a chronobiotic because of its ability to advance or retard circadian rhythms. Other studies have demonstrated the hypnotic effect of melatonin (24, 37) in a laboratory environment. The effects of melatonin on human performance are controversial. One recent study showed that aircrew who were administered melatonin on a long transmeridian mission had improved sleep patterns and fewer errors on a choice reaction task after arrival (16). Several studies have concluded that melatonin does not act as a hypnotic in the classic sense, but rather as a sleep-promoting agent (21, 35, 54). In a recent review paper Caldwell (14)(page 243) stated that "Performance in a laboratory shows that reaction time is slowed and sleepiness is increased when tests are given 30 minutes to 2 hours after melatonin administration. However, if taken before a night's sleep, then melatonin does not seem to adversely affect next-morning performance". Caldwell (14) also states that "Melatonin appears to open the 'sleep gate' when circumstances are right for sleep, but does not induce sleep."

Some studies have documented small decrements in simple auditory reaction time and visual serial choice reaction time (24, 69) whereas another study (3) found no difference in a logical reasoning task or in a letter cancellation task. A study by Lieberman (37) reported a slowing of reaction time but a decrease in errors of commission on this task. This study also found that sustained fine motor performance, memory and sensitivity were not impaired by melatonin. One hour after ingestion of a 5 mg dose of melatonin, Suhner et al. (60) assessed twenty healthy subjects in a standardized computer test battery to assess driving skills such as attention, reaction time, power of concentration and sensorimotor coordination. They found that just one of the 16 variables, selective attention, was significantly affected by melatonin, and even those values were within the normal range. Slotten and Krekling (58) used logical reasoning, serial addition/subtraction, visual-spatial and four-choice reaction time tasks to assess performance after ingestion of a 1.6 mg dose of melatonin. They found no effect on performance speed and accuracy during the post ingestion melatonin peak (about 35 to 95 minutes after ingestion), but found that during the temperature trough (240 to 300 minutes after ingestion), reaction times to the serial addition/subtraction task increased by about 45 milliseconds. They postulate that this was due to melatonin's hypothermic properties that caused a slowing of cerebral processing speed. While this is interesting work, the major limitation of the study is the single subject, double-blind, alternating treatments design. The study should be repeated with multiple subjects, using a repeated-measures, double-blind crossover protocol in order to confirm these interesting results. Lieberman et al. (37) gave 14 subjects three 80 mg doses of melatonin, one hour apart, and found a slowing of reaction time (about 23 milliseconds) but a concurrent decrease in errors of commission. This apparent sacrifice of speed for accuracy suggests that the subjects simply shifted their performance on the speed/accuracy curve. Zhdanova et al. (70) used evening doses of 0.3 or 1.0 mg of melatonin to significantly reduce sleep latency and there was no impact of melatonin on either simple or 4-choice reaction time on the morning after treatment. Dollins et al (24) used 20 male subjects on 5 separate occasions with melatonin doses of 10, 20, 40, 80 mg or placebo, administered at 11:45 h. They observed significant decreases in the number of correct responses to an auditory vigilance task within 15 minutes of ingestion for all melatonin doses as well as 2 hours and 15 minutes post ingestion. Four-choice reaction time latencies also increased significantly during the melatonin treatments.

Comperatore et al. (17) performed two studies using 20 female subjects in each between-groups study. In their first study, the subjects were administered a 10 mg dose of melatonin or placebo at 23:00 h for 7 days. The subjects were awakened at 06:30 h for psychomotor testing that continued until 18:30 h. The melatonin subjects appear to have made more errors on the 4-choice reaction time task than the placebo subjects from 6 to 12 hours after ingestion, but because their figures of performance results do not show standard error bars, it is difficult to appreciate the difference in performance between these 2 groups of subjects. In view of the Slotten and Krekling results (58) it would have been interesting to determine the location of the core body temperature trough for these data. In the second Comperatore study (17) the subjects were given a 10 mg dose of melatonin or placebo at 13:00 h for 5 days. The subjects slept 8 hours from 16:30 h to 00:30 h and were tested after awakening at 01:30 h, 03:30 h, and 06:10 h. The melatonin subjects made significantly more errors than the

placebo subjects when tested at 01:30 h (one hour after awakening), but not in the 2 subsequent test sessions. Again, because the graphed performance results do not show standard error bars, it is difficult to appreciate the extent of any melatonin-induced increase in errors on this task.

Zopiclone

Zopiclone (Imovane®) is a cyclopyrrolone derivative with a half-life of approximately 5 hours (27, 36) that produces a short-acting sedative/hypnotic effect. Daurat et al (20) used a 7.5 mg dose of zopiclone to accelerate readjustment of the rest/activity cycle and to normalize the phase relationship between sleep and temperature rhythm after a westward flight across five time zones. They concluded that zopiclone exerted its “resetting” effects on jet lag desynchronization by facilitating sleep induction rather than via a chronobiotic action. Griffiths et al. (29) used the Stroop task, serial reaction time, and logical reasoning tasks as well as saccadic eye movement in response to a 7.5 mg dose of zopiclone and found impaired saccadic eye movement up to 3 hours after ingestion. Memory was not affected, and 6 hours after ingestion, there was no evidence of any other effect. In contrast, Nicholson and Stone (45) conducted a dose-response study of zopiclone (2.5, 5.0, 7.5 and 10 mg) using a digit-symbol substitution and symbol copying tasks to measure performance 9 hours after ingestion. They found an 8 percent decrease in substitutions at the 7.5 and 10 mg doses but not at the 2 lower doses. They also found less than a 7 percent decrease in symbol copying at the 10 mg dose, but not for the 3 lesser doses.

Virtually all studies assessing zopiclone report an effective hypnotic response. Using a 7.5 mg dose (the standard clinical dose), various studies (8, 10, 31, 36, 56, 59, 61) have been unable to demonstrate residual effects of zopiclone on various aspects of psychomotor performance. O’Hanlon et al (46) used a car driving task to evaluate a 7.5 mg dose of zopiclone for two consecutive nights and found slightly impaired performance among 16 female subjects during the morning, 10 hours after drug ingestion. Several studies investigated the residual effects of zopiclone beginning almost immediately after ingestion (1, 29, 39, 53, 59, 62). Subjan and Hindmarch (59) found increased reaction times for a memory scan task, one hour after drug ingestion, but no impact on performance 10 hours after ingestion. Warot et al. (62) used flicker fusion, choice reaction time, digit symbol substitution, and memory tests to find no impairment beyond 6 hours after ingestion. Mattila et al. (39) assessed simulated driving, divided attention, digit-symbol substitution, symbol copying, flicker fusion and body sway in response to 7.5 mg zopiclone. They found increased tracking error and prolonged reaction times at 1.5 hours, reduced substitutions at 1.5 and 3.5 hours, with lowered threshold flicker fusion and increased body sway. There was impaired memory after 3.5 hrs but no effects were present at 6 hours.

The objective of the present study was to induce sleep and monitor sleep quality during an inappropriately early circadian time (similar to the sleep imperatives encountered by aircrew during overseas air transport operations). Our specific interests were to evaluate the efficacy of melatonin and zopiclone in improving early circadian sleep, and to determine whether or not there would be a performance liability associated with either drug immediately upon awakening as well as

throughout a 7-hour post-sleep psychomotor test period. Further, we wanted to determine whether or not there would be any potentiation of the normal sleep inertia effect (transient impaired performance occurring immediately after awakening) with either melatonin or zopiclone.

Methods

Subjects

The study protocol was approved by the DRDC Toronto Human Ethics Committee. Fourteen volunteer male subjects between 22 and 50 years of age passed a screening medical, provided written informed consent, and were studied in a double-blind repeated-measures design in which subjects received all three drug treatment conditions in a counterbalanced order. One subject did not complete the study.

Experimental Design

The three drug conditions were placebo (lactose monohydrate powder), zopiclone 7.5 mg, and melatonin 10 mg. The 10 mg dose of melatonin consisted of 5 mg pure melatonin (from Biosynth International Inc, Naperville, Illinois) to facilitate initial sleep, together with 5 mg of controlled-released melatonin (Circadin®, Neurim Pharmaceuticals, Tel Aviv, Israel), to sustain sleep. Melatonin is classified as an Investigative New Drug in Canada, and regulatory approval was granted for its use in this investigation. All study medications were made up in identical gelatin capsules by the Chief Pharmacist at the Clarke Institute of Psychiatry (Toronto, ON), who also generated the medication blinding code. The medication code was revealed only at the end of the study, after all the data were collected.

To avoid any confounding due to circadian influences, all subjects were asked to avoid long transmeridian flights in the 2 weeks prior to the study and to maintain regular sleep/waking schedules during the week prior to the study. Therefore all subjects were asked to wear wrist actigraphs (Precision Control Design Inc., Fort Walton Beach, Florida) which contain a small accelerometer to detect body movement such that a waking state can be differentiated from a sleeping state (51).

The subjects were asked to avoid taking medications, alcohol and sleeping pills for 36 hrs prior to the study. Subjects were also instructed to avoid using caffeine (coffee, tea, soft drinks, and chocolate) for 6 hours prior to each experimental session.

Four subjects were run concurrently in a 4-week protocol, resulting in three syndicates of 4 subjects and one syndicate with 2 subjects. The repeated-measures protocol was identical for all subjects. The first week was a baseline session designed to familiarize the subjects with the requirement to sleep in the laboratory and to collect baseline data. During this session, subjects slept in the laboratory, at normal circadian time (23:00 h to 06:45 h), for 2 consecutive familiarization nights and

underwent one psychomotor testing iteration before sleep and again within 15 minutes of awakening.

During each of the next three weeks, one experimental session (placebo, zopiclone, or melatonin in counterbalanced order) per week was conducted for each group of 4 subjects. These sessions involved 2 consecutive nights; a normal circadian drug-free control sleep night, (23:00 h to 06:45 h), followed the next day by an early circadian drug sleep, (17:00 h to 23:45 h). One week between sessions was allowed for drug “wash-out”. The events and timings for the experimental sessions are illustrated in figure 2.1.

As illustrated in Figure 1, the subjects began an extended period of psychomotor testing upon awakening from their early circadian sleep period. Each performance session lasted about 30 minutes providing the subjects with 30 minutes rest each hour. However, they were not allowed to sleep during this interval. After the 2nd post-sleep performance assessment, subjects were provided a standardized snack.

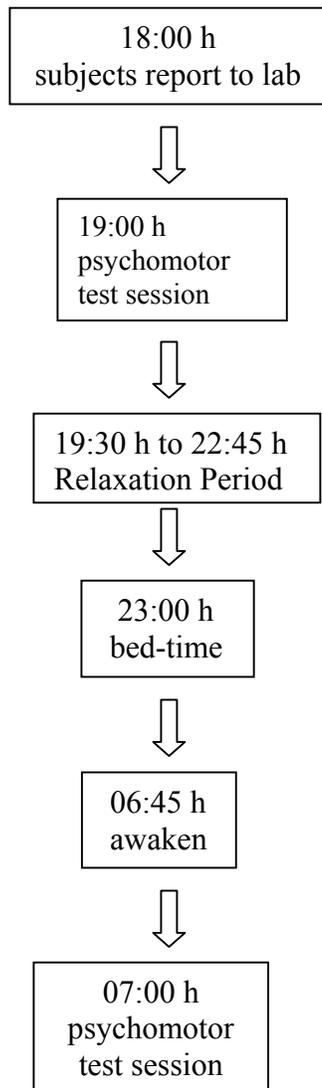
Immediately before commencing each psychomotor test session, a one-minute computer questionnaire presented on the same lap-top computers asked for the following subjective assessments.

- a) assessment of alertness by selecting the most appropriate response from the 7 point Stanford Sleepiness Scale (34),
- b) assessment of mental fatigue state by selecting any number on a continuous scale from 1 (very mentally fresh) to 7 (very mentally fatigued) (30),
- c) assessment of physical fatigue state on a continuous scale from 1 (very physically fresh) to 7 (very physically fatigued) (30).

During the psychomotor performance sessions, the following tasks were presented: three psychomotor tests from the DRDC Toronto SUSOPS (sustained operations) test battery (2, 4) were performed in the following order; SRT (serial reaction time) (67) for three minutes, LRT (logical reasoning task) (4) for three minutes, and SST (serial subtraction task) (33) for three minutes followed by, a multitask (MT) designed to simulate the information processing characteristics of flight performance (66) and taking 15 minutes per data collection iteration. The task simulated flying an aircraft to specific targets or ‘waypoints’. The computer screen showed four separate displays representing four sub-tasks to be performed simultaneously. Three of these four tasks interacted. There were vigilance sub-tasks with altitude assignment changes visible for only 5 seconds and the pilots also had to be vigilant in order to determine when the two “attitude indicators” disagreed with each other and then determine which of the attitude indicators accurately reflected the “aircraft attitude”. A bar task (analogous to managing the power quadrant of a large multi-engine transport) did not interact with the other three sub-tasks. The measures of performance include scores related to error detection and selective attention, visuo-motor tracking and co-ordination, short-term memory, mental arithmetic, and scanning strategies. The raw output data file was merged with a computer reduction algorithm to yield a single

final weighted composite score that reconciles correct responses and errors. This task is explained in more detail elsewhere (66).

Normal Circadian Control Sleep



Early Circadian Drug Sleep

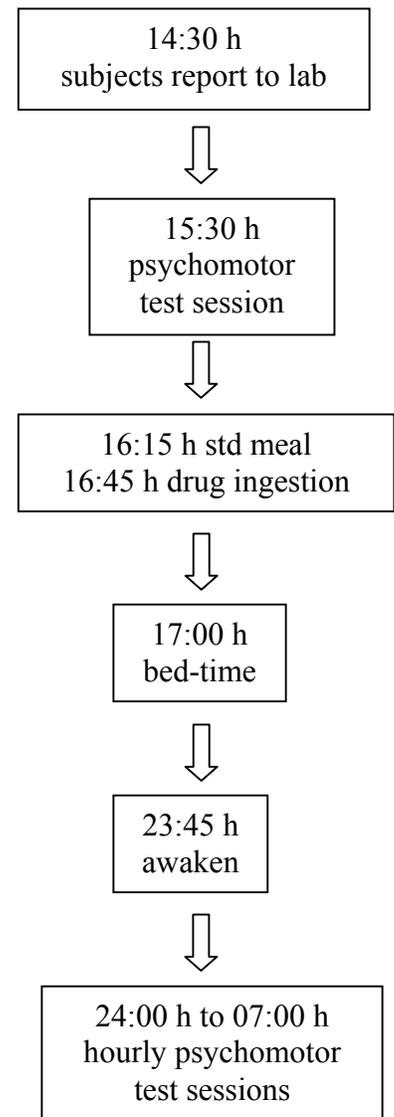


Figure 2.1. Schematic of events/times for experimental sessions

The SUSOPS tests have a history of well-documented laboratory-based validations concerning the effects of fatigue on performance (2, 4). Thus it was considered important to include these tasks to compare data obtained in this study to the existing literature. To assess higher order cognitive function and use a test with greater face validity to flying, the multitask was also used.

Lighting conditions in the psychomotor testing suite were kept constant (blackout curtains were used with fixed florescent lighting similar to the illumination found in a well-lit reading room) during psychomotor testing to preclude any effect of variation in lighting conditions on endogenous melatonin levels.

All subjects were trained to asymptote levels of performance by performing 12 iterations of the psychomotor tasks within the week prior to the study. The subjects slept in separate bedrooms in which the windows were covered with blackout curtains, creating a consistently dark sleep environment.

Although other measurements were taken, these data will be reported in separate publications. These measures include 40 Hz EEG recordings taken during psychomotor test sessions, continuous core temperature via radio pills, sleep recordings via actigraphic mattresses during bed-rest, and neuro-endocrine samples (melatonin from saliva as well as 6-sulphatoxymelatonin and cortisol from pooled urine).

Statistical Analysis

All data were submitted to standard parametric analyses of variance with repeated-measures. The actigraph data were analyzed using a 2-factor (3 levels of drugs x 2 levels of circadian sleep period) repeated-measures analysis of variance. The subjective and psychomotor data were analyzed in the following 3 groups of trials; a) in order to quantify sleep-inertia, pre- and post-sleep data are compared for the normal circadian control sleep (19:00 h and 06:45 h) and the early circadian drug sleep (17:00 h and 23:45 h), using a 3-factor (3 levels of drugs x 2 levels of circadian period x 2 levels of trials (pre- and post-sleep)) completely within-subjects repeated measures analysis of variance b) to assess recovery from sleep-inertia, the 15:00 h, 24:00 h, and 01:00 h trials for the early circadian drug sleep are compared using a 2-factor (3 levels of drugs x 3 levels of trials) completely within-subjects repeated measures analyses of variance and c) the post-sleep trials of the early circadian drug night from 01:00 h to 07:00 h are compared in order to determine to what extent subjects' psychomotor performance changed over the course of their all-night vigil. This 'c' comparison was accomplished with a 2-factor (3 levels of drug x 7 levels of trials) completely within-subjects repeated measures analysis of variance. Further, for the 'c' comparisons we also performed orthogonal polynomial analyses in order to look for linear, quadratic, and cubic trends in the data over time.

The Least Significant Difference Test was used to assess planned comparisons. The acceptable level of significance for all main effects or interactions was 0.05.

Results

Sleep duration and quality

The normal circadian control sleep period (23:00 h to 06:45 h) was 465 minutes long while the early circadian drug sleep period was (17:00 h to 22:45 h) 405 minutes. To standardize the comparison, the last 60 minutes of the normal circadian control sleep period were not included in the analysis.

The software to analyze the wrist actigraph recordings was a program called 'Action W' (Ambulatory Monitoring Inc., Ardsley, New York). In order to score sleep this program used an algorithm to compute a weighted sum of the activity in the current minute, the preceding 4 minutes, and the following 2 minutes as follows.

$$S = 0.0033 * (1.06 * a_n4 + .54 * a_n3 + .38 * a_n2 + .76 * a_n1 + 2.3 * a_0 + .74 * a_1 + .67 * a_2)$$

Where $a_n4 - a_n1$ are activity counts from the prior 4 minutes, a_0 is the current minute and a_1 and a_2 are the following 2 minutes (15, 55). The current minute is scored as sleep if $S > 1$.

The number of minutes spent asleep during each of the normal circadian control and early circadian drug nights is plotted in figure 2.2a. Of the 405 minutes available for sleep, subjects slept an average of 378 minutes (pooled data) during the control sleep. Total sleep time data were submitted to a 2-factor (3 levels of drugs x 2 levels of circadian sleep period) repeated measures analysis of variance. This analysis yielded a significant drugs x circadian sleep period interaction $F(2,26)=3.62$, $p<.04$. Post hoc analysis revealed that during early circadian sleep subjects slept more on melatonin (31 minutes) and zopiclone (34 minutes) than on placebo ($p<.01$). With both melatonin and zopiclone, subjects lost no sleep during the early circadian compared with the normal circadian condition.

The number of sleep-episodes (periods of sleep uninterrupted by wake) during each of the normal circadian and early drug nights are plotted in figure 2.2b. These data were submitted to the same 2-factor analysis of variance as the total sleep time data. There was a significant interaction drugs x circadian sleep period interaction $F(2,26)=3.24$, $p<.05$. Post hoc analysis revealed that during early circadian sleep, subjects on placebo had significantly more sleep episodes (awakenings) than when they were on melatonin or zopiclone ($p<.01$). While on melatonin or zopiclone, subjects had no more awakenings during early circadian sleep than during normal circadian sleep.

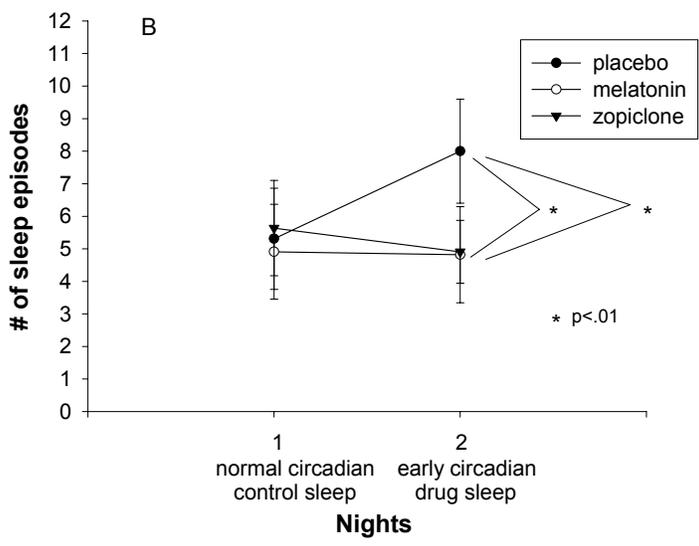
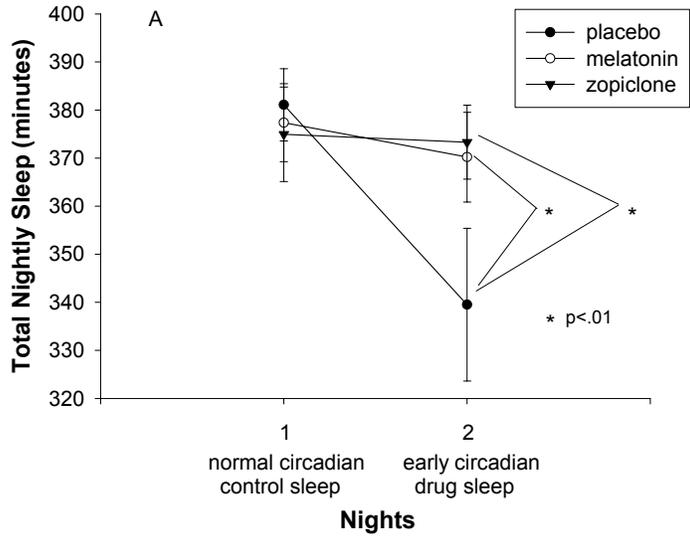


Figure 2.2. Total nightly sleep and number of sleep episodes (mean ± S.E.M.) across drugs for normal circadian control night and early circadian drug night.

Psychological Data

Data from the questionnaire and psychomotor performance are presented in the following 3 groups of analyses; a) in order to quantify sleep-inertia, pre- and post-sleep data are compared for the normal circadian control sleep (19:00 h and 06:45 h) and the early circadian drug sleep (17:00 h and 23:45 h), b) to assess recovery from sleep-inertia, the 15:00 h, 24:00 h, and 01:00 h trials for the early circadian drug sleep night are compared, and c) the post-sleep trials of the early circadian drug night from 01:00 h to 07:00 h are compared in order to determine to what extent subjects' psychomotor performance changed over the course of their all-night vigil.

Subjective Data

Subjective assessments of sleepiness (Stanford Sleepiness Scale) are plotted in figure 2.3. The pre- and post-sleep differences in sleepiness (comparison a) were submitted to a 3-way (3 levels of drugs x 2 levels of circadian period, x 2 levels of trials (pre- and immediate post-sleep) repeated measures analysis of variance. The pre- to post-sleep increases in Stanford Sleepiness Scale were significant $F(1,12)=44.86$, $p<.0001$. These results indicate a significant subjective degree of sleep-inertia upon arising for each of the normal control and early circadian drug sleeps. There were no differential drug effects on the sleep-inertia.

The trials from 15:00 h, 24:00 h and 01:00 h of the early circadian drug night (comparison b) were submitted to a 2-way (3 levels of drug x 3 levels of trials (pre-sleep, immediate post-sleep, and one hour post awakening) repeated measures analysis of variance. The results indicate a significant main effect of trials for the Stanford Sleepiness Scale $F(2,24)=25.38$, $p<.00001$. Post hoc analyses revealed that the increased subjective assessments of sleepiness evident at 24:00 h improved by 01:00 h, and approached the pre-sleep levels taken at 15:00

Trials from 01:00 h to 07:00 h (comparison c) were submitted to a 2-way (3 levels of drug x 7 levels of post-sleep trials) repeated measures analysis of variance. The results indicate a significant main effect of trials for the Stanford Sleepiness Scale

$F(6,72)=5.68$, $p<.0001$. Polynomial analysis on the trials from 01:00 h to 07:00 h reveals a significant cubic effect for Stanford Sleepiness Scale $F(1,38)=7.11$, $p<.01$. This cubic function indicates that subjective levels of sleepiness, were similar between 01:00 h and 03:00 h, after which they slowly increased until 06:00 h. The sleepiness and fatigue levels improved from 06:00 h to 07:00 h. This improvement in subjective sleepiness levels is probably due to the energizing effects the subjects experienced by knowing that their all-night vigil was almost completed and they were about to be released upon completion of this last psychomotor test session. There were no main effects or interactions involving either zopiclone or melatonin on any of these subjective variables.

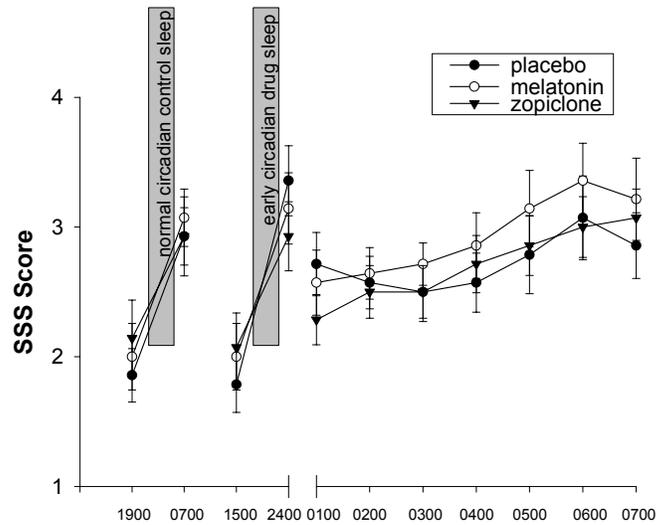


Figure 2.3. Subjective assessments of sleepiness and fatigue (mean ± S.E.M.) across drugs and trials for normal circadian control night and early circadian drug night.

Psychomotor Data

Serial Reaction Time (SRT)

The serial reaction time results are illustrated in figure 2.4. The pre- and post-sleep differences in serial reaction time were submitted to the 3-way repeated measures analysis of variance (comparison a) using the number of correct responses as the independent variable. A completely repeated-measures analysis of variance reduces overall variability by removing between-subject differences from the error term. Note that figures 2.4, 2.5, 2.6, 2.7, and 2.8 are graphed with z-scores in order to better demonstrate the within subjects treatment effects. The analyses of variance were equivalent whether done with z-scores or with original units. Neither melatonin nor zopiclone had any effect on serial reaction time. There was a significant difference in pre- and post-sleep performance $F(1,12)=10.57$, $p<.007$ a main effect of circadian period $F(1,12)=22.46$, $p<.0005$, and a significant interaction between circadian period and pre- and post-sleep $F(1,12)=10.43$, $p<.007$. These results indicate that serial reaction time performance immediately upon awakening is worse than pre-sleep performance for both the normal circadian control night and the early circadian drug night, but that this “sleep inertia” (30) is worse for the early circadian sleep than for the normal circadian sleep.

The serial reaction time trials from 15:00 h, 24:00 h, and 01:00 h of the early circadian drug night were submitted to the 2-way analysis of variance (comparison b) which revealed a significant main effect of trials ($p<.0001$).

Post hoc analysis reveals that SRT performance at 15.00 h is better than at 24:00 h ($p < .0001$), SRT performance at 01:00 h is better than at 24:00 h ($p < .0001$), and there is no difference in performance between the SRT trials at 15:00 h and 01:00 h. This indicates that for the early circadian drug sleep, the impact of sleep inertia has totally dissipated by 01:00 h at which time performance returned to pre-sleep levels.

The serial reaction time trials from 01:00 h to 07:00 h were submitted to final 2-way analysis of variance (comparison c). The results indicated no significant main effects or interactions. Essentially, serial reaction time performance between 01:00 h and 07:00 h is sustained at pre-sleep performance levels, again with no drug effect.

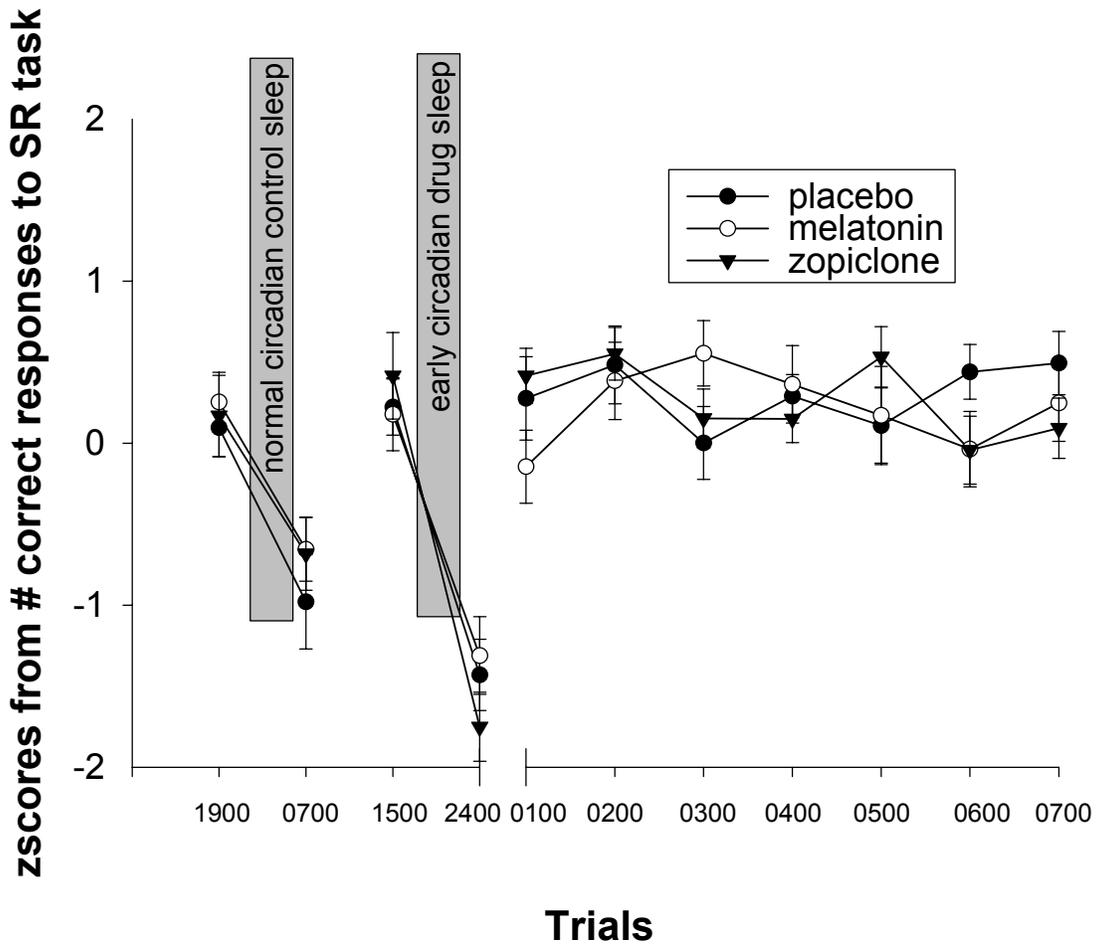


Figure 2.4. z-scores for number of correct responses to Serial Reaction Time (SRT) task (mean \pm S.E.M.) plotted over drugs and trials for normal and circadian control and early circadian drug night.

Logical Reasoning Task (LRT)

The logical reasoning task results are illustrated in figure 2.5. The pre-and post-sleep differences in logical reasoning were submitted to a 3-way repeated measures analysis of variance. There was no drug effect on logical reasoning performance. There was however, a significant effect of circadian period $F(1,12)=10.64$, $p<.007$, and significant difference in pre- and post-sleep performance $F(1,12)=28.73$, $p<.0002$. These results (figure 2.5) demonstrate a sleep-inertia effect on logical reasoning performance upon awakening relative to pre-sleep performance for both the normal circadian control night and the early circadian drug night.

The logical reasoning trials from 15:00 h, 24:00 h and 01:00 h of the early circadian drug night were submitted to the 2-way 'comparison b' analysis of variance which revealed a significant main effect of trials $F(2,24)=5.55$, $p<.004$. Post hoc analysis reveals that LRT performance at 15:00 h is better than at 24:00 h ($p<.004$), LRT performance at 01:00 h is better than at 24:00 h ($p<.02$), and there is no difference in performance between the LRT trials at 15:00 h and 01:00 h. These results indicate that for the early circadian drug sleep, the impact of sleep inertia on logical reasoning has totally dissipated by the 01:00 h.

The logical reasoning trials from 01:00 h to 07:00 h were submitted to the 'comparison c' 2-way analysis of variance. The main effect of trials was significant $F(6,72)=2.49$, $p<.03$. The main effect of drugs was not significant, nor was the drug x trials interaction. This indicates that logical reasoning task performance changed over time between 01:00 h and 07:00 h but there were no differential effects on performance due to drugs. Polynomial analysis reveals that this trials curve was a significant quadratic function $F(1,38)=16.29$, $p<.0003$ with the point of inflection at 04:00 h. This indicates that LRT performance began to fall after 04:00 h, arguably due to fatigue but there was no differential fatigue effect across drugs. In order to illustrate this impact of fatigue, the logical reasoning performance between 01:00 h and 07:00 h is collapsed over drugs (because there were no drug effects) and plotted in figure 2.6, and a combined subjective fatigue index is superimposed on these data. This combined subjective fatigue index was generated by averaging subjective fatigue data (from the Stanford Sleepiness Scale (SSS) shown in figure 2.3, as well as the mental and physical fatigue scales which are similar to the SSS but are not shown in this report). By superimposing this estimate of subjective fatigue onto the logical reasoning performance it is possible to judge the relative effect of fatigue on performance. Like the three separate indices of subjective fatigue (Stanford Sleepiness Scale, mental and physical fatigue), the combined fatigue index for the trials between 01:00 h and 07:00 h also produces a significant cubic function $F(1,116)=22.77$, $p<.0001$. This cubic function reflects that the fatigue level is stable between 01:00 h and 03:00 h, after which it increases until 06:00 h, and then improves somewhat by the last trial at 07:00 h. In

response to increasing fatigue levels, logical reasoning performance falls off after 04:00 h.

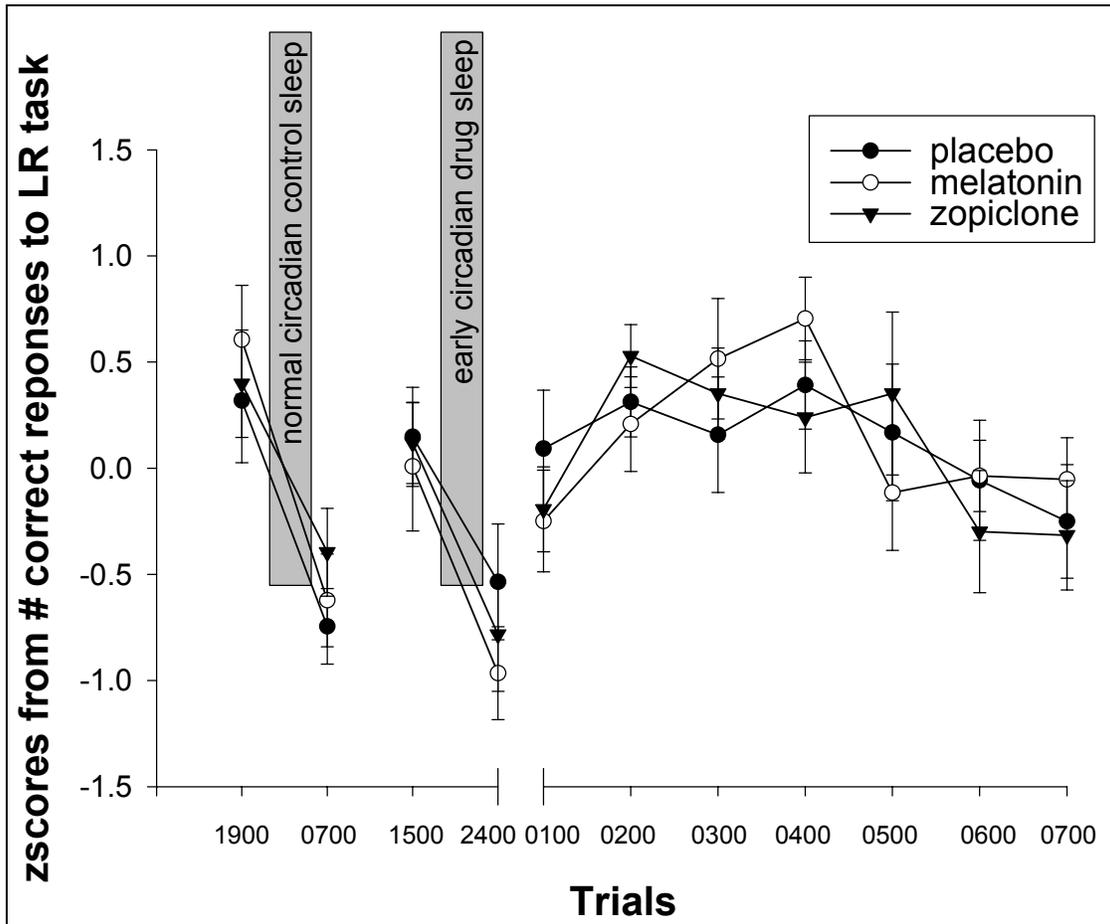


Figure 2.5. z-scores for number of correct responses to Logical Reasoning task (LRT) (mean \pm S.E.M.) plotted over drugs and trials for normal circadian control night and early circadian drug night.

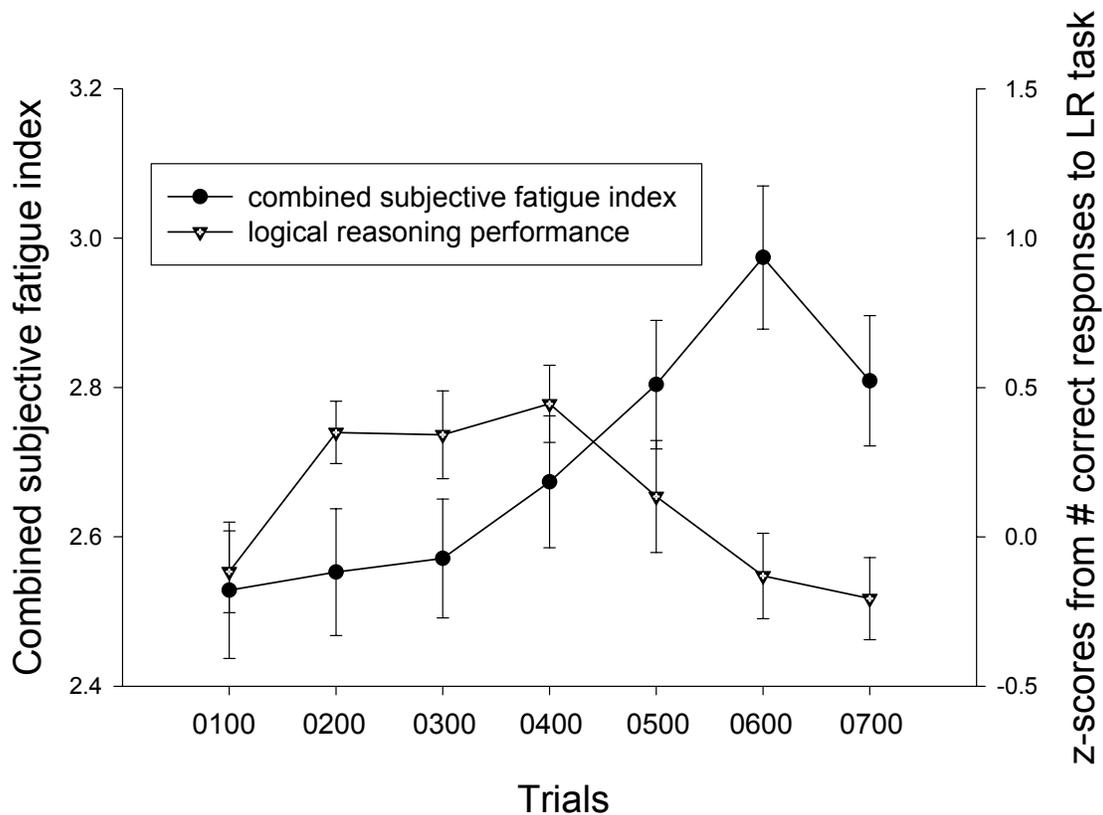


Figure 2.6. Combined Subjective Fatigue Index super-imposed onto LRT performance during overnight psychomotor testing. All values are mean \pm S.E.M.

Serial Subtraction Task (SST)

The serial subtraction task results are illustrated in figure 2.7. The pre- and post-sleep differences in serial subtraction were submitted to the ‘comparison a’ 3-way repeated measures analysis of variance. There was no drug effect on SST performance for either medication. There was a significant effect in pre- and post-sleep performance $F(1,12)=7.73, p<.017$. These results demonstrate a sleep inertia effect on serial subtraction performance upon awakening relative to pre-sleep performance.

The serial subtraction task trials from 15:00 h, 24:00 h and 01:00 h of the early circadian drug night were submitted to the 2-way ‘comparison b’ analysis of variance which revealed a significant main effect of trials $F(2,24)=4.30, p<.025$. Post hoc analysis reveals that SST performance at 15.00 h is better than at 24:00 h ($p<.05$), SST performance at 01:00 h is better than at 24:00 h ($p<.009$), and there is no difference in performance between the SST trials at 15:00 h and 01:00 h. These results indicate that for the early circadian drug sleep, the impact of sleep inertia on serial subtraction performance has totally dissipated by the 01:00 h.

The SST trials from 01:00 h to 07:00 h were submitted to the ‘comparison c’ 2-way analysis of variance. There were no significant main effects or interactions. Performance on the serial subtraction task between 01:00 h and 07:00 h remained unchanged throughout the period.

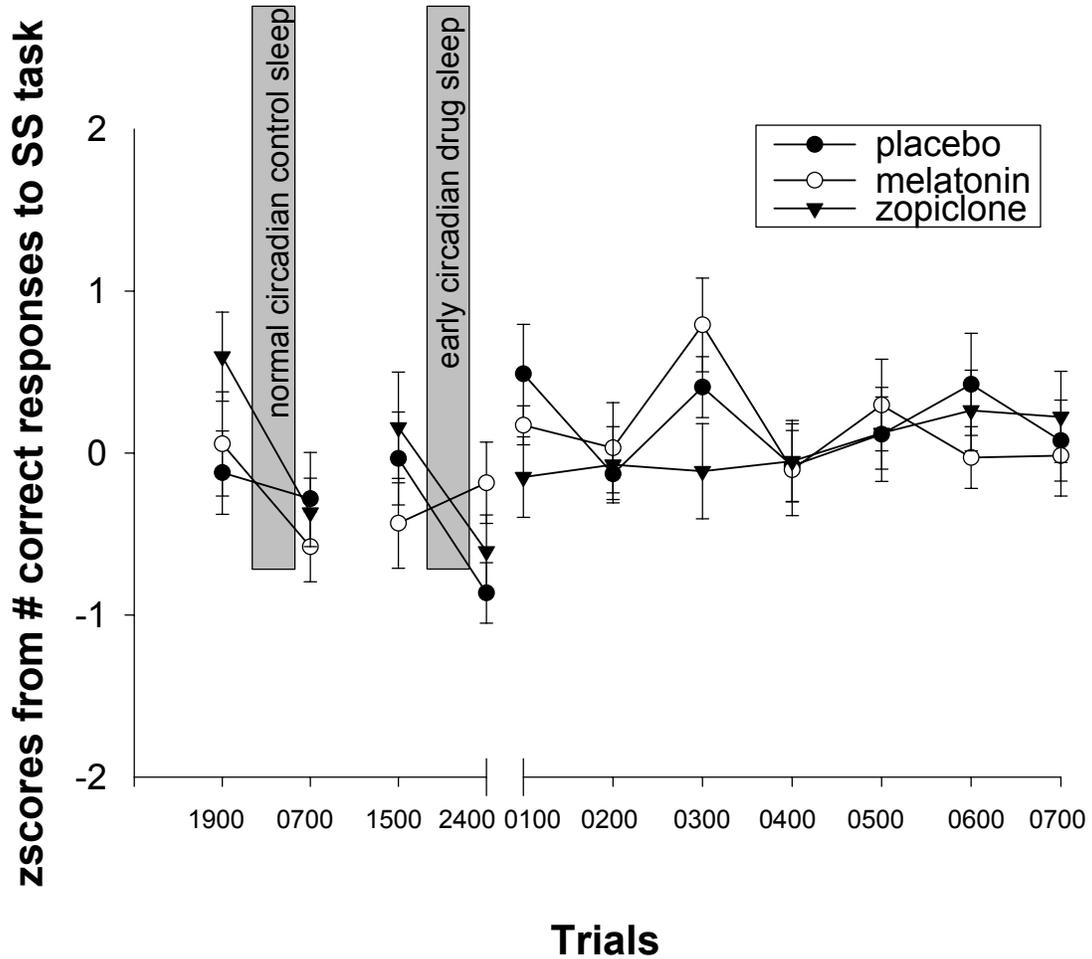


Figure 2.7. z-scores for number of correct responses to Serial Subtraction task (SST) (mean \pm S.E.M.) plotted over drugs and trials for normal circadian control night and early circadian drug night.

Multitask (MT)

The multitask results are illustrated in figure 2.8. The pre- and post-sleep differences in multitask score were submitted to the ‘comparison a’ 3-way repeated measures analysis of variance. There was no drug effect on multitask performance for either medication. There was a significant drugs x circadian period x pre- and post-sleep interaction $F(2,24)=4.95$, $p<.016$. This interaction indicates that upon awakening from the normal circadian control night, multitask performance was not impacted by sleep inertia for the

subjects who were going to receive melatonin and zopiclone the following night. However, during the first psychomotor trial after awakening from the early circadian medicated sleep, there was a mild sleep inertia effect.

The multitask scores from the 15:00 h, 24:00 h and 01:00 h trials were submitted to the 'comparison b' 2-way analysis of variance which revealed a significant main effect of trials $F(2,24)=3.46$, $p<.048$). Post hoc analysis indicates that the multitask performance at 24:00 h is worse than at 15:00 h ($p<.02$), and by 01:00 h multitask performance is still worse than at 15:00 h ($p<.05$). Therefore the comparison b anova was repeated using the three original trials plus (15:00 h, 24:00 h, and 01:00 h) plus the 02:00 h trial. This iteration of the comparison b anova also indicated a significant main effect of trials $F(3,36)=3.38$, $p<.029$. In this instance, post hoc analysis indicates no difference in multitask performance between the 15:00 h and the 02:00 h trials. This result indicates that while the sleep inertia during the multitask was less than during the previous tasks (SRT, LRT, and SST) it did persist longer (until the 02:00 h trial).

The multitask trials from 01:00 h to 07:00 h were submitted to 'comparison c' 2-way analysis of variance. There were no significant main effects or interactions. Performance on the multitask task between 01:00 h and 07:00 h remained unchanged throughout that period.

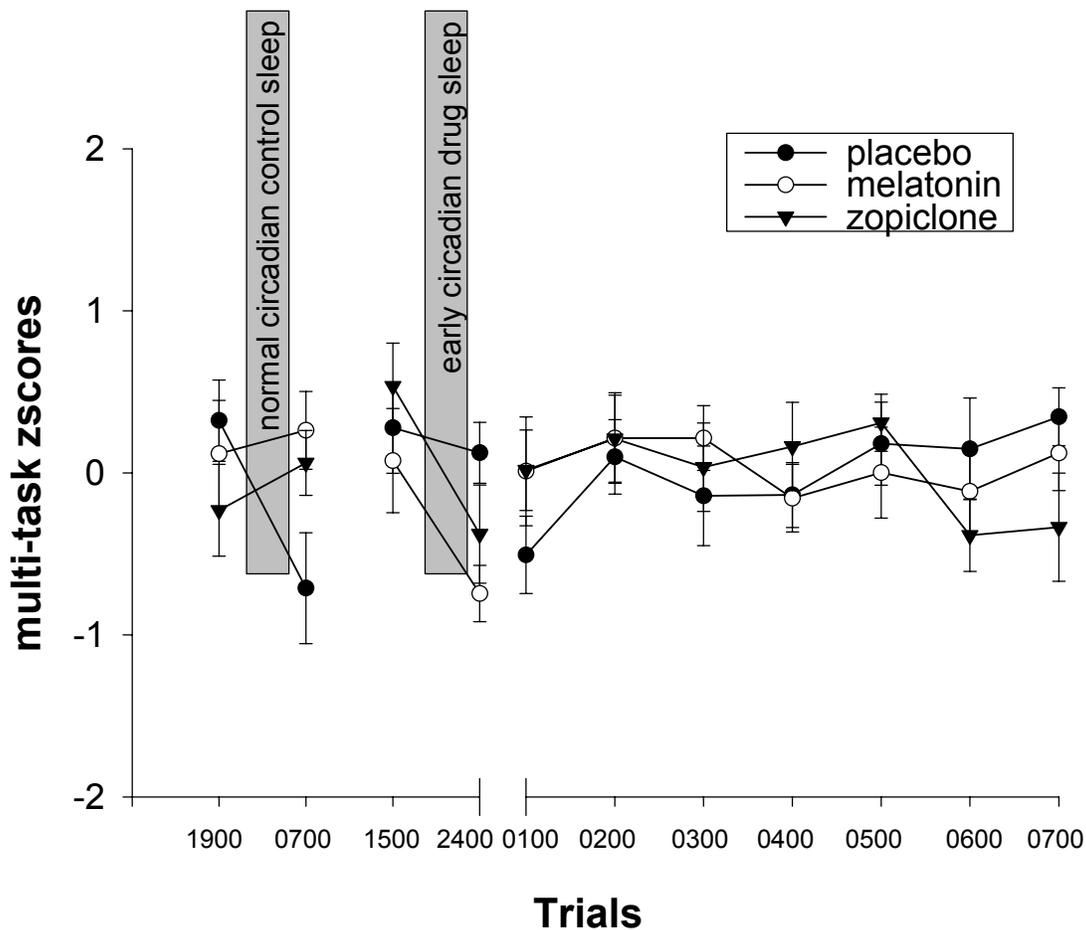


Figure 2.8. Multitask z-scores (mean \pm S.E.M.) plotted over drugs and trials for normal circadian control night and early circadian drug night.

Discussion

Sleep-induced decrements in performance immediately upon awakening have been termed ‘sleep-inertia’ by Lubin et al. (38) who described sleep-inertia as ‘reduced vigilance and impaired performance during the period that follows awakening. Sleep-inertia has been referred to as a phenomenon of impaired task performance and/or disorientation occurring immediately after awakening (43). Sleep-inertia effects have been observed on a range of psychomotor tasks (22): simple reaction time, complex reaction time, steadiness and coordination, visual perception tasks, memory tasks, time estimates, mental arithmetic, cancellation and clock reversal. The severity of sleep-inertia can vary as a function of sleep stage upon awakening (22) and the amount of prior sleep deprivation (5). Estimates on the duration of sleep-inertia vary from one minute (63) to more than 3 hours (22). With no prior sleep deprivation, Wilkinson showed that sleep-inertia lasted a few minutes (68). However, Dinges et al. (23) showed that even after 56 hours of sleep deprivation, sleep-inertia never exceeded 30 minutes.

In our study, the subjective manifestations of sleep-inertia are evident for all three parameters (Stanford Sleepiness Scale, as well as mental and physical fatigue ratings (figure 2.3)). The psychomotor manifestation of sleep-inertia was evident in all four tasks, but was most pronounced during the serial reaction time task, perhaps because this was the first task performed by the subjects during each psychomotor test session. After the normal circadian sleep the subjects were awakened at 0645hrs and began the post-sleep psychomotor test session 15 minutes later at 07:00 h. After the early medicated sleep, the subjects were awakened at 23:45 h and began the post-sleep psychomotor test session 15 minutes later at 24:00 h. Subjective assessments of sleepiness and fatigue occupied the first minute of each psychomotor test session, after which the serial reaction task was presented to the subjects. The subjects, therefore, started the serial reaction time task 16 minutes after awakening and finished it 19 minutes after awakening. Sleep-inertia effects on the logical reasoning task (which was presented to the subjects over the subsequent 3 minutes, that is, between 20 and 22 minutes after awakening) were not as strong as the effects on the serial reaction time task. The sleep-inertia effects on the serial subtraction task (which occurred between 23 and 25 minutes after awakening) were even milder. Overall, the sleep-inertia effects on the three SUSOPS tasks were dissipated by the second test session after awakening (01:00 h). Sleep-inertia effects on the multitask (a higher order cognitive task) appear to be equivocal upon awakening from the normal circadian sleep, quite possibly because it was performed last in the test-battery sequence. After awakening from the early circadian medicated sleep, sleep inertia was evident during the multitask, however it was milder than that seen during the preceding SUSOPS tasks. This lower level of sleep inertia during the multitask persisted an extra hour relative to the duration of the sleep inertia during the SUSOPS tasks. We did not measure sleep stages, however it is possible that the subjects were waking from a deeper sleep stage at the end of the early circadian sleep period. Such a shift in sleep architecture could explain the potentiation of the sleep-inertia effect during the first post-sleep trial of serial reaction time task after the early circadian sleep period. The duration of the sleep inertia effects in this study, appears to be consistent with the findings of other sleep-inertia researchers.

Comperatore et al. performed an influential study (16) on the effects of melatonin on aircrew. They demonstrated that 10 mg of melatonin improved sleep patterns and resulted in fewer errors on a choice reaction time task immediately after long range transmeridian flight. In subsequent work Comperatore and Kirby (17) performed 2 between group studies in an effort to determine Aviator's grounding time after melatonin administration. In their second study, the subjects were given a 10 mg dose of melatonin or placebo for 5 days, awakened daily at 00:30 h after 8 hours of sleep and were tested at 01:30 h, 03:30 h, and 06:10 h. The melatonin subjects made significantly more errors than the placebo subjects when tested at 01:30 h (one hour after awakening), but not in the 2 subsequent test sessions. In view of our own results, it is possible that the Comperatore and Kirby subjects were suffering from sleep inertia during the first post sleep test session at 01:30 h.

With respect to the effects of zopiclone on performance, after a sleep period of six hours and 45 minutes (seven hours and 15 minutes after ingestion) we found the normal sleep-inertia effects but no differential effects across drugs. Our work thus supports the Griffiths et al (29) work and various other studies (8, 10, 31, 36, 56, 59, 61) which were unable to demonstrate residual effects of zopiclone on various aspects of psychomotor performance.

Other than sleep-inertia, the only other impact on psychomotor performance in our study occurred during the logical reasoning task. While our protocol was not designed to cause significant fatigue, the increased levels of subjective fatigue (figure 5) reported by our subjects coincided with an attenuation of logical reasoning performance after 04:00 h. However there was no difference in performance across the drug treatments. In an earlier study (47), we found that the logical reasoning task was quite sensitive to fatigue.

Our work indicates that both melatonin and zopiclone were similarly effective facilitators of early circadian sleep, and neither of these medications had any effect on psychomotor performance upon awakening than placebo. Given that melatonin and Zopiclone provide more sleep than placebo during an early circadian sleep period, the expectation would be that psychomotor performance would be better after early circadian sleep on either melatonin or zopiclone than on placebo. In contrast with this expectation, we found performance after early circadian sleep on placebo was as good as that on either either melatonin or zopiclone. This would suggest that there is no performance benefit associated with getting more sleep by using melatonin or zopiclone. However, our protocol was designed to test for residual effects of either melatonin or zopiclone, but not to demonstrate an improved performance after sleep on either or these two medications. Certainly, if we had found residual performance effects associated with either melatonin or zopiclone, we would not be able to consider their operational use for aircrew. If our goal had been to show a psychomotor performance advantage with either melatonin or zopiclone, we would have stressed the subjects more by either running a longer post-sleep experimental period or by running multiple nights of early circadian sleep in order to develop a chronic fatigue state.

The melatonin dose we used (10 mg in a single capsule containing 5 mg of regular-release melatonin and 5 mg of sustained availability or time-released melatonin) is probably much higher than necessary to facilitate early circadian sleep. However, given that we have demonstrated no impact on psychomotor performance with this relatively high dose of melatonin, a lower dose should provide an extra margin of safety when used to facilitate aircrew sleep.

Based on their dose-response study Nicholson and Stone stated that the optimal clinical dose range of zopiclone is likely up to 7.5 mg. The 7.5 mg dose of zopiclone provides a useful hypnotic effect with minimal residual effects the next day, while "5.0 mg is the appropriate dose for those involved in skilled tasks where even the most minor changes in performance during the early part of the day must be avoided" (44, 45). While the 7.5 mg zopiclone dose we used in this study indicates no residual effects on performance, in the interests of flight safety, we will heed the advice of Nicholson and Stone by using a smaller dose in a follow-on operational evaluation. In such an operational evaluation we will use 5.0 mg of zopiclone and 2 mg of time-released melatonin in order to determine their relative efficiency at facilitation of early circadian sleep during long-range transmeridian air transport operations.

Conclusions

The melatonin and zopiclone doses used in this study have been shown to facilitate early circadian sleep relative to placebo. While we have documented normal, transient, sleep-inertia effects upon arising from sleep, there is no indication of any impact of either melatonin or zopiclone on psychomotor performance after sleep in the dosages we used.

Phase 3. Operational Evaluation of pharmaceutical fatigue countermeasures

Introduction

The results of phase 2 (6) showed that the melatonin and zopiclone doses we used (10 mg and 7.5 mg respectively) were effective in facilitating early circadian sleep relative to placebo. Further, although we documented normal sleep inertia affects on psychomotor performance upon awakening, we found no impact of either of these medications on psychomotor performance.

The Wing Commander of 8 Wing was briefed about the phase 2 results in April of 2000. Based on the phase 2 results, the Wing Commander endorsed an operational evaluation of these laboratory-proven pharmaceutical fatigue countermeasures.

The purpose of this operational evaluation was to determine whether reduced doses of the countermeasures would facilitate early circadian sleep during missions that were similar to those flown in phase 1.

Methods

Subsequent to squadron-level briefings, CC130 Aircrew from 8 Wing (Trenton) were asked to participate as subjects in this study during air transport operations to Bosnia.

The data collection period for this work was run during 27 months of study, over 70 missions to Bosnia and involved 219 aircrew. Some aircrew participated in only a single mission. Others participated in two missions, and 30 aircrew participated in three missions, and therefore trialed each of the 3 drug conditions (placebo, melatonin, and zopiclone). This report is based on repeated measures data from the 30 aircrew who participated in 3 missions (one for each drug condition). The three drug conditions are placebo, zopiclone 5.0 mg (we used 7.5 mg in our phase 2 study), and melatonin 2 mg (we used 10 mg in phase 2). In the case of melatonin, during the laboratory-based study (phase 2) we used the very high dose of 10 mg which we would never use operationally. This high dose was used in order to avoid a Type II error where we would conclude that melatonin was safe when in fact it was not. Given that in phase 2 we have found even the high dose of 10 mg did not impact on psychomotor performance after a nominal 7-hr post ingestion sleep, we felt much safer using only 20% of this dose (2 mg) for an operational study. In the case of zopiclone, most studies using the standard 7.5 mg dose have found no deleterious effects on performance. However, one study has documented a small psychomotor performance decrement in response to 7.5 mg (45). In order to improve the margin of safety we used the smallest available dose of zopiclone; i.e. 5 mg. Further, all participating aircrew were given a single dose of their scheduled medication immediately prior to sleep at home, about a week prior to departure for the mission. Subsequent to that dose, before departure on the mission, all participating aircrew were seen

by a flight surgeon at CFB Trenton, in order to screen out anyone who might have had an idiosyncratic reaction to the medication.

Because melatonin and zopiclone could be potentially harmful to a fetus, any female aircrew who wished to participate was first required to undergo a pregnancy test (from a serum sample) prior to participation on any study mission.

The melatonin was a sustained availability (time released) formulation (Circadin®) made by Neurim Pharmaceuticals in Tel Aviv, Israel and previously approved by the Health Protection Branch (HPB) of Health Canada in our phase 2 study. Prior to commencement of the current study, regulatory approval was again obtained for the use of Circadin®. In order to maintain the double-blind nature of this work, all medications (placebo, melatonin and zopiclone) were packaged in identical capsule format by our contract pharmacy. Subjects were not using any medications during these missions other than those prescribed by their flight surgeon. Subjects were asked to abstain from, or at least minimize alcohol consumption within the current Air Transport regulations (i.e. 12 hours from bottle to throttle).

The following assessments/measurements were performed:

- a) wrist actigraphy
- b) questionnaire data measuring aircrew self-reports of fatigue, sleep quality, and mood, and to quantify any alcohol consumed
- c) questionnaire data soliciting aircrew self-reports of drug effects/side-effects

The crews were issued wrist actigraphs and questionnaires by the study coordinator in Trenton, 4 days prior to departure. The Wing Surgeon, a co-investigator for this study, supervised and co-ordinated the provision of the mission medications to the aircraft commander on the day of departure. These single doses of medications (2 mg melatonin or 5 mg zopiclone, or placebo) were given to the crew-members, 30 minutes before retiring to bed for their second sleep overseas. Upon awakening, the crews completed the questionnaires soliciting their subjective levels of sleepiness and fatigue, sleep quality and any drug side-effects. In order to monitor sleep hygiene before and during the missions, the crews were asked to wear their wrist actigraphs from three days prior to the mission until they returned from the mission. The only extra time commitment for the participating aircrew was the extra few minutes required to complete the questionnaire upon awakening from the medicated sleep.

Statistical Analysis

The sleep data gathered from the wrist actigraphs (total sleep time, number of sleep episodes, sleep latency etc) were plotted for each of the three drug conditions, in order to establish the

manner in which sleep quantity changes across drug conditions. The sleep data and questionnaire were submitted to a repeated-measures analysis of variance. The acceptable level of statistical significance for all main effects or post hoc testing was 0.05.

Results

Actigraphic assessments of Sleep duration and quality

The number of hours spent asleep during the medicated sleep in the U.K. is illustrated in figure 3.1. Both melatonin and zopiclone provided significantly more sleep than the placebo. There was no significant difference between melatonin and zopiclone in terms of total sleep time benefit.

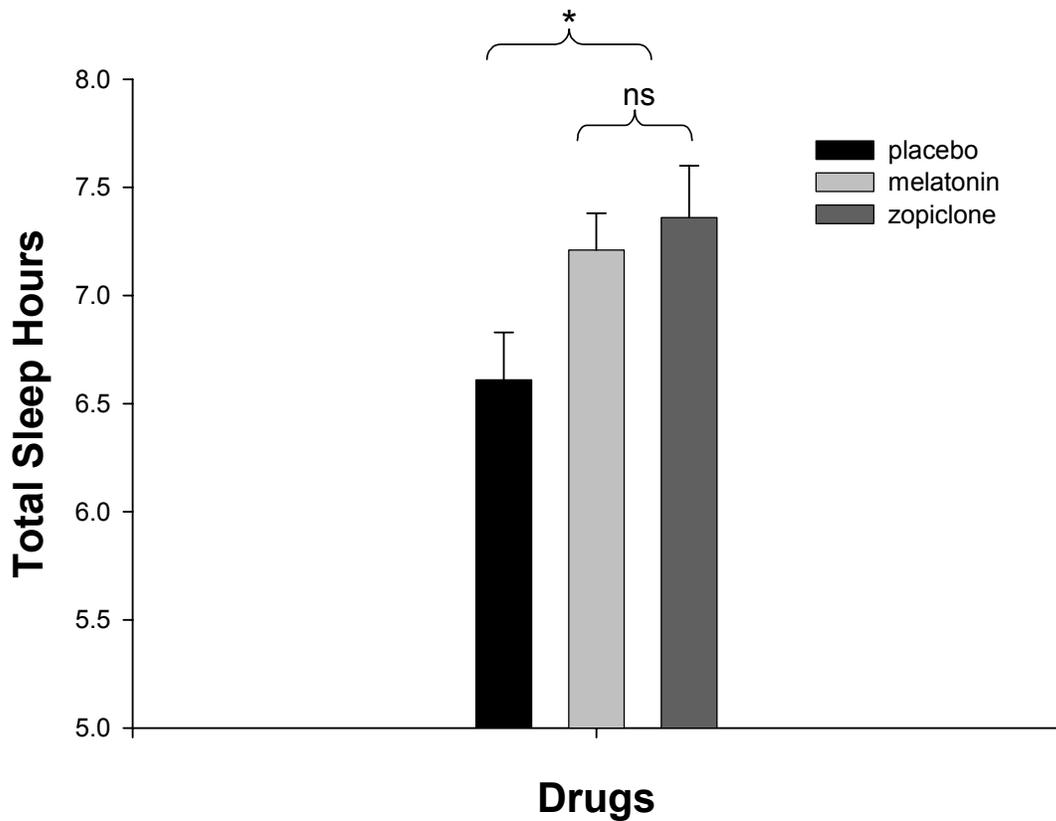


Figure 3.1 Total sleep hours (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

Sleep latency (time required to fall asleep) is shown in figure 3.2. Sleep latency was significantly longer for placebo than for melatonin or zopiclone. There was no significant difference in sleep latency between melatonin or zopiclone.

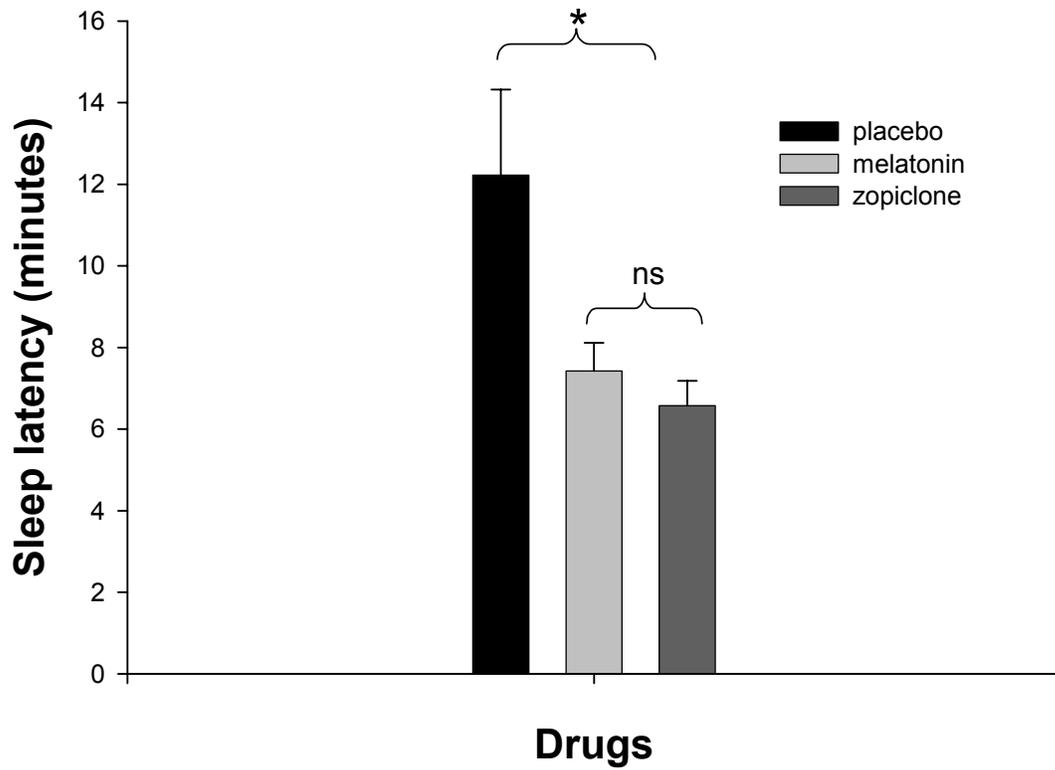


Figure 3.2 Sleep Latency (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

Number of sleep episodes (effectively the number of awakenings) is shown in figure 3.3. There were significantly more sleep episodes for placebo than for melatonin or zopiclone. There was no significant difference in the number of sleep episodes between melatonin or zopiclone.

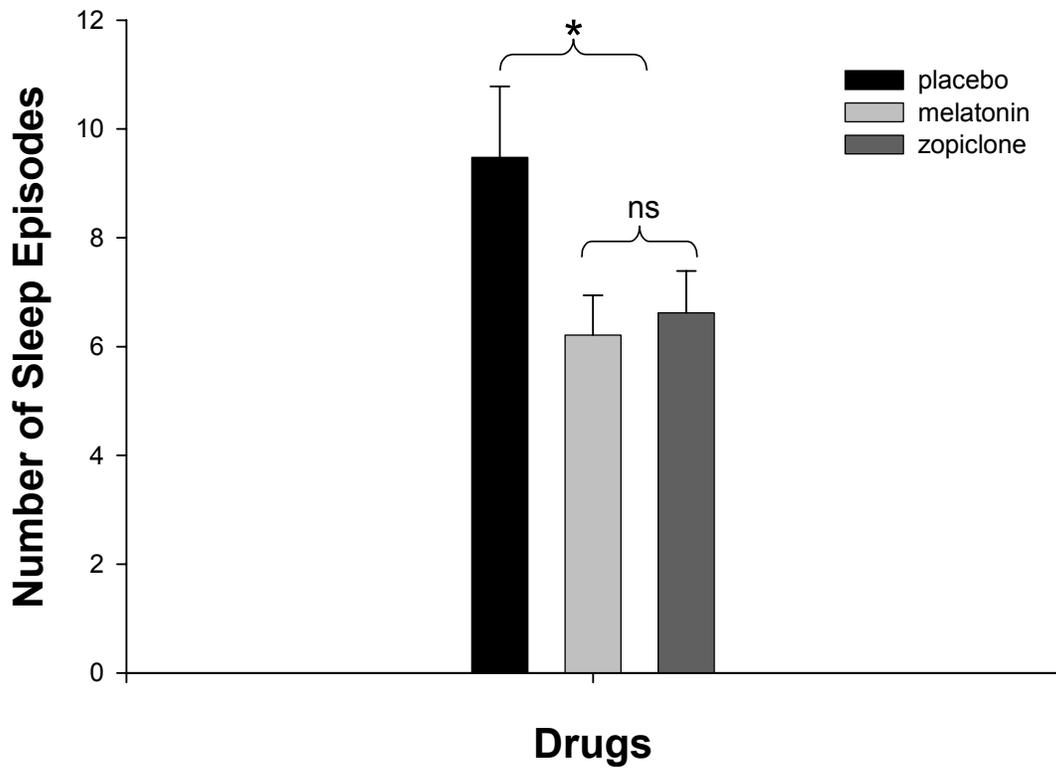


Figure 3.3 Number of sleep episodes (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

The time spent awake after sleep onset is shown in figure 3.4. There was significantly more time spent awake after sleep onset for placebo than for placebo, melatonin or zopiclone. However, there was no significant difference between melatonin or zopiclone in the amount of time spent awake after sleep onset.

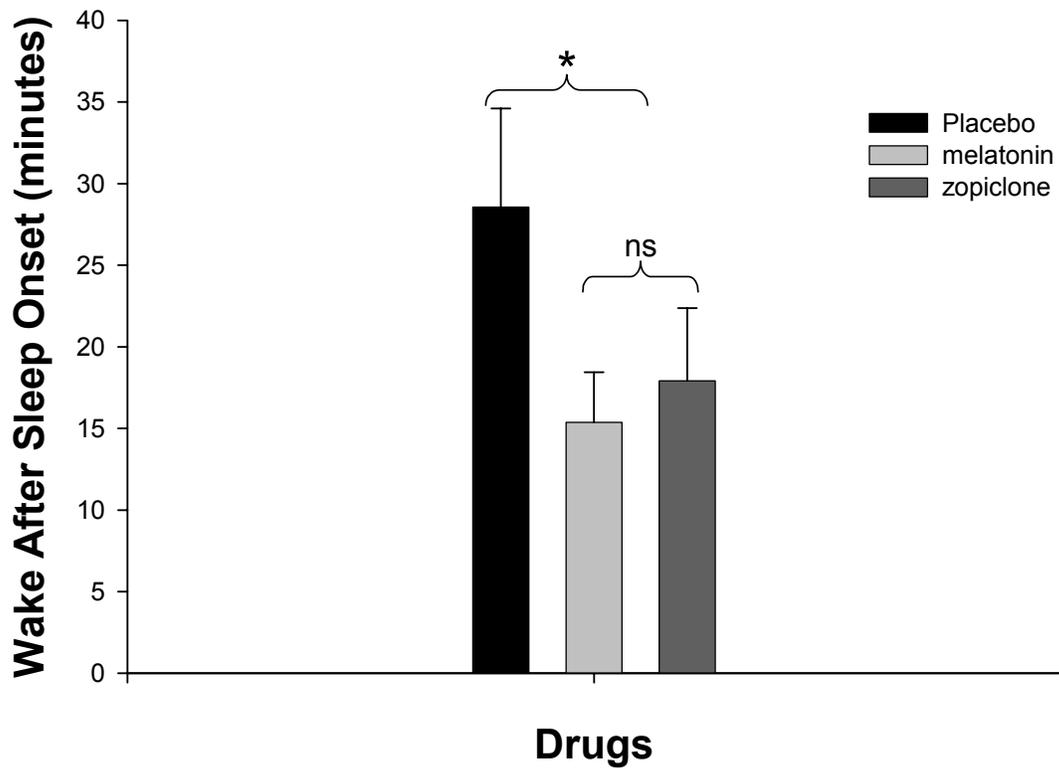


Figure 3.4. Time spent awake after sleep onset (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

Questionnaire-based subjective assessments of sleep quality and side effects

Reported difficulty in getting to sleep is illustrated in figure 3.5. The subjects reported significantly more difficulty getting to sleep when they were on placebo relative to when they were on either melatonin or zopiclone. There was no difference between melatonin or zopiclone in terms of difficulty in getting to sleep.

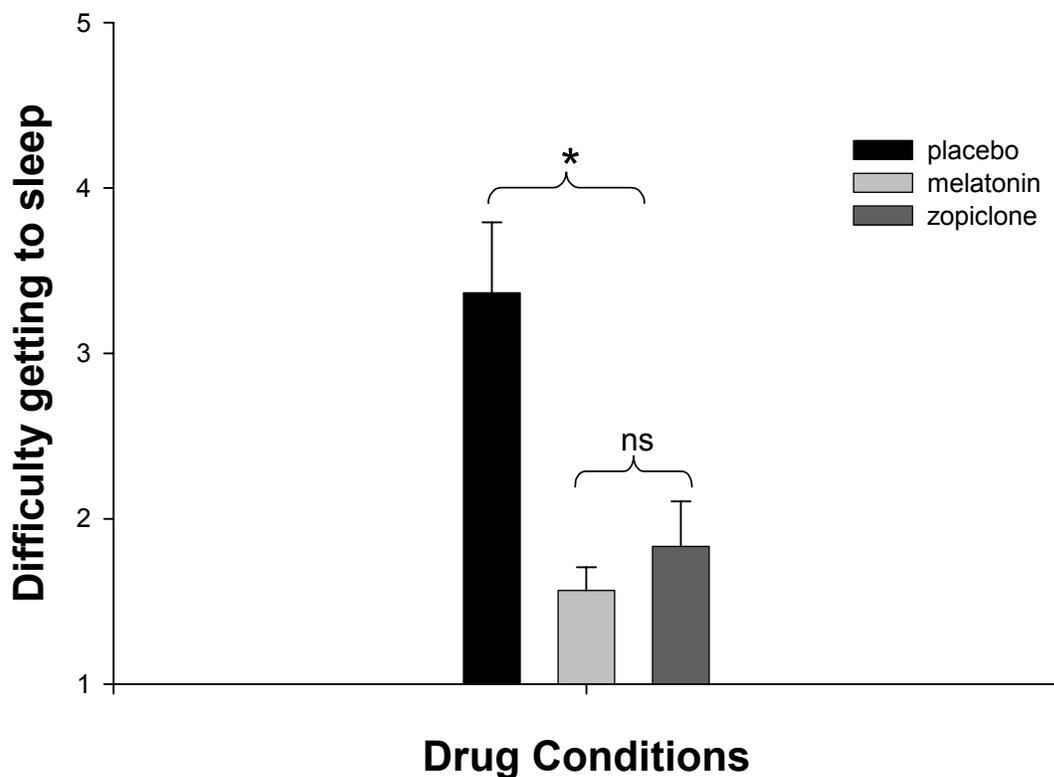


Figure 3.5. Subjective difficulty getting to sleep (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

The subjective number of awakenings is illustrated in figure 3.6. The subjects had more awakenings when they were on placebo relative to when they were on melatonin or zopiclone. There was no significant difference in the number of awakenings between melatonin and zopiclone.

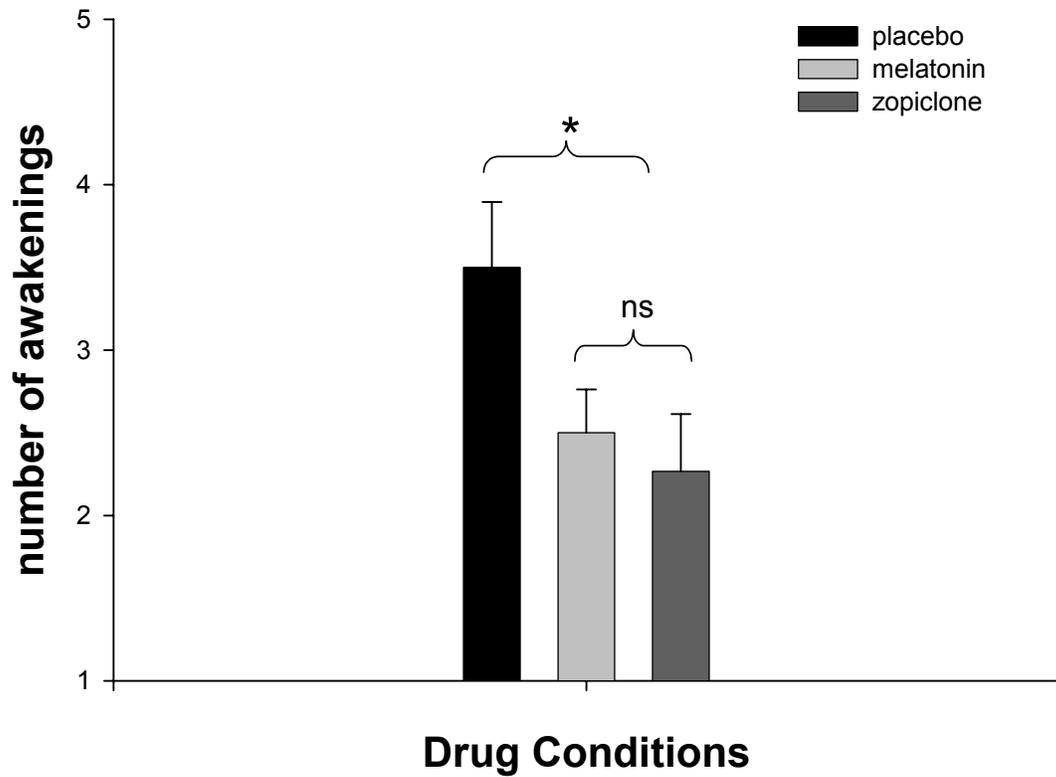


Figure 3.6. Subjective number of awakenings (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

The difficulty returning to sleep after awakening is illustrated in figure 3.7. The subjects had significantly more difficulty returning to sleep after awakening when they were on placebo, relative to when they were on either melatonin or zopiclone. There was no difference in the reported difficulty returning to sleep between melatonin and zopiclone.

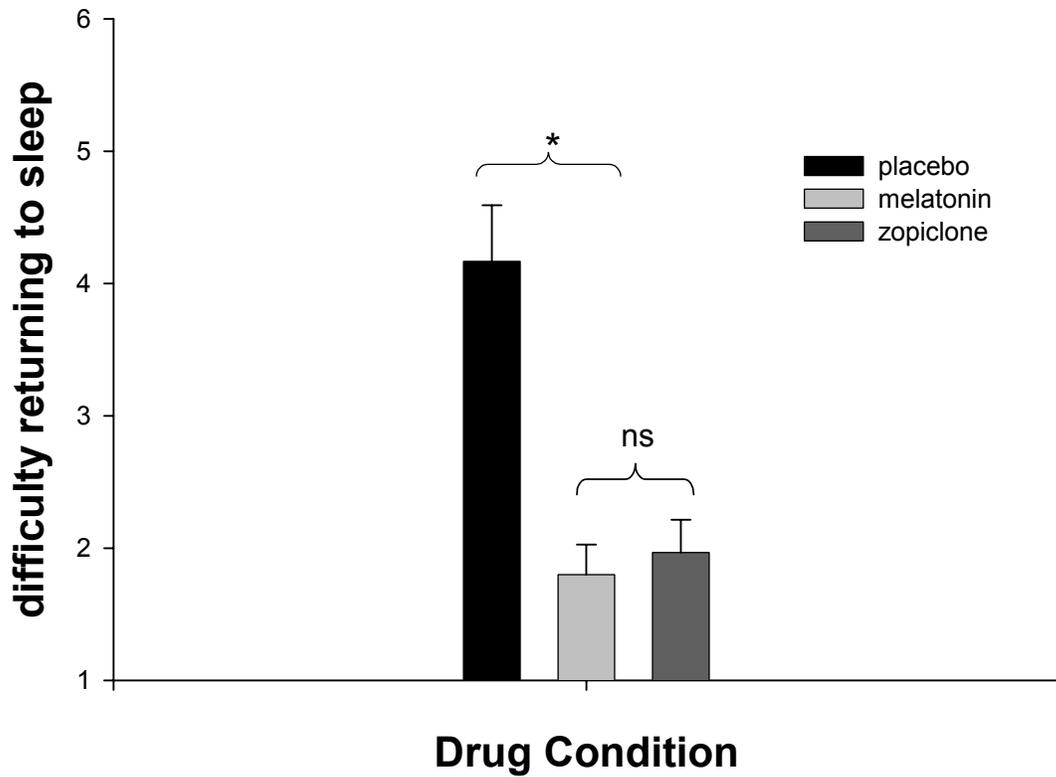


Figure 3.7 Subjective difficulty returning to sleep after awakening (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

The subjective levels of post sleep grogginess are illustrated in figure 3.8. There are no significant differences in post sleep grogginess across drugs.

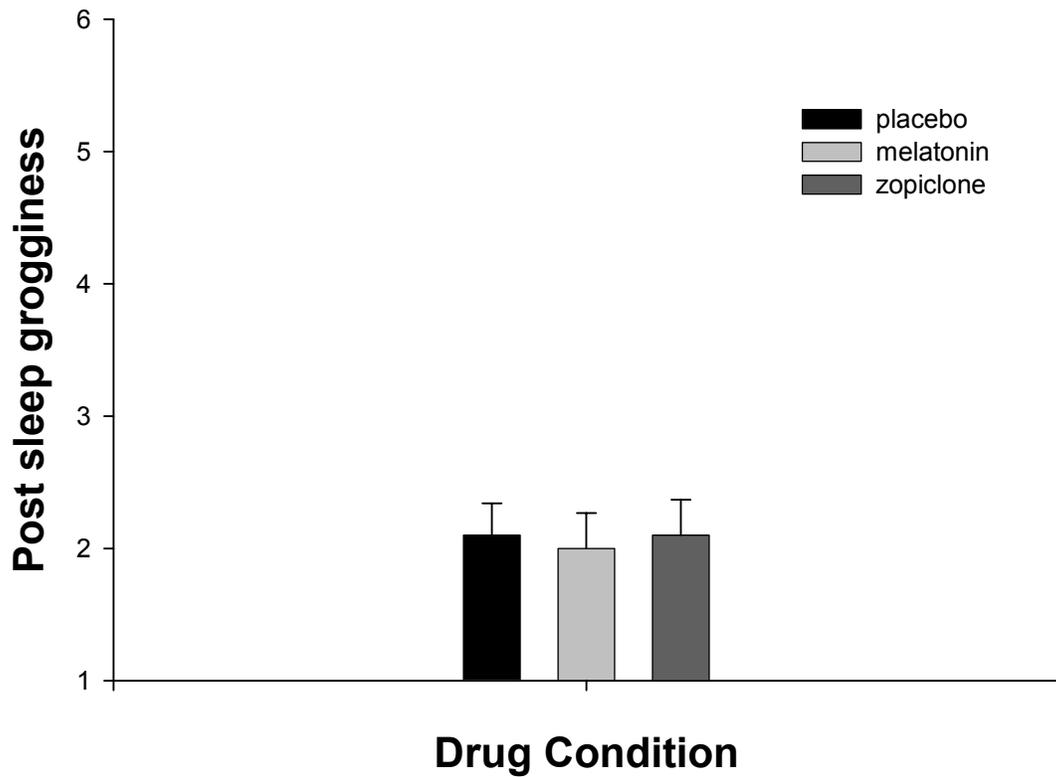


Figure 3.8. Subjective post sleep grogginess (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

Subjective sleep quality is illustrated in figure 3.9. Quality of sleep was rated significantly higher when the subjects were on melatonin and zopiclone than when they were on placebo. There was no difference between melatonin and zopiclone relative to quality of sleep.

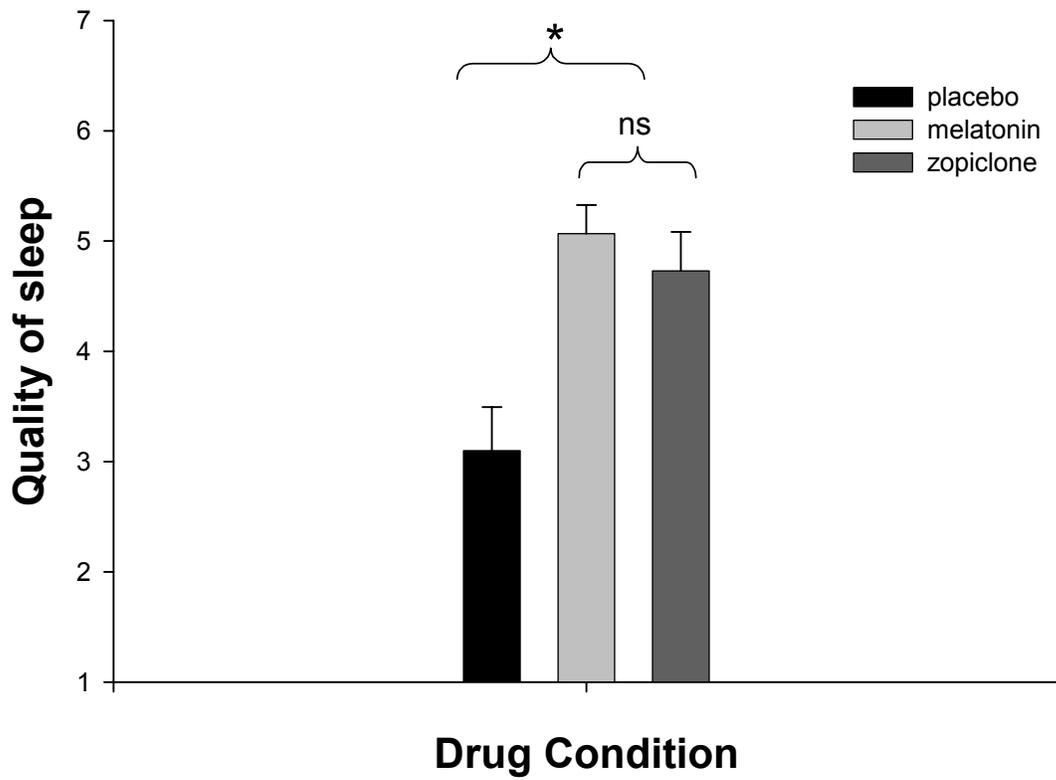


Figure 3.9. Subjective quality of sleep (mean ± S.E.M.) plotted across drugs during medicated sleep in the U.K.

The subjective levels of post sleep dizziness are plotted in figure 3.10. There were no differences in post sleep dizziness across drugs.

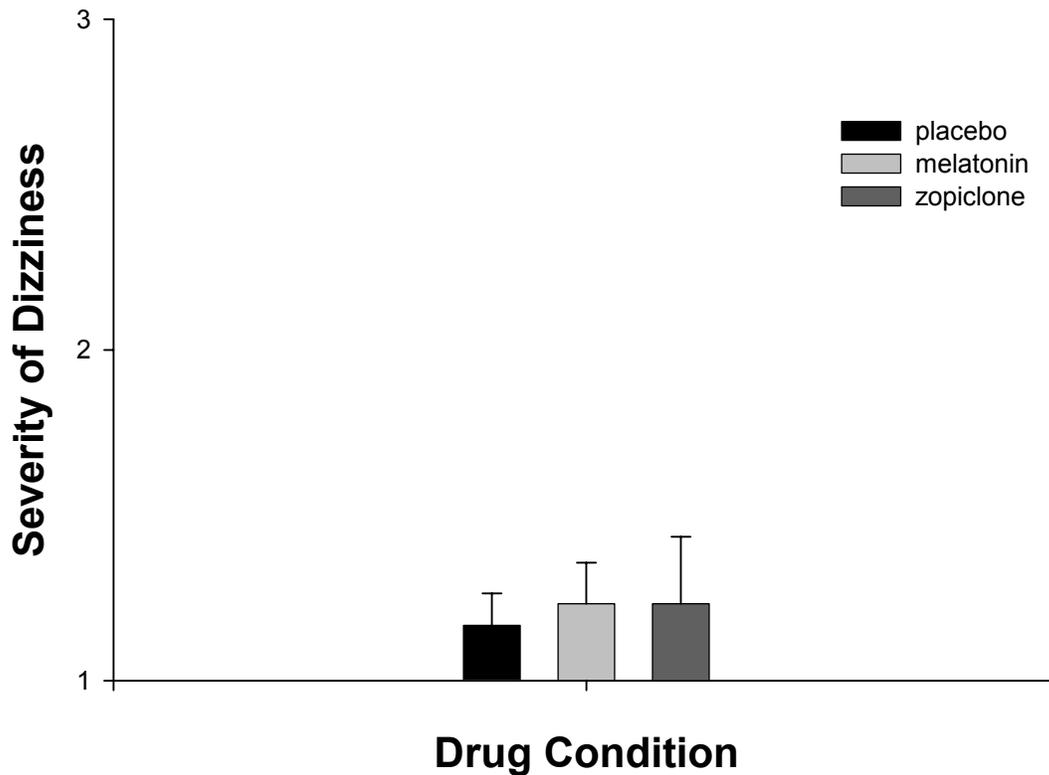


Figure 3.10. Subjective dizziness (mean \pm S.E.M.) plotted across drugs during medicated sleep in the U.K.

Discussion

Our work in Phase 1 demonstrated that during routine Air Transport Operations to Bosnia, our Air Transport aircrews began their missions with an acute sleep deficit, resulting in a fatigue-induced impact on psychomotor performance during the outbound transatlantic leg. They also had limited sleep in the subsequent 2 sleep periods during the mission, with the 2nd sleep period resulting in the least amount of sleep during the entire mission. While there was ample opportunity for the crews to sleep during the 2nd mission sleep period, the approximate 2200

hr bedtime in the UK amounted to an inappropriately early circadian sleep (about 1700 hrs circadian body clock time).

In response to the operational difficulties with early circadian sleep we carried out work in the Phase 2 laboratory study to determine whether or not melatonin or zopiclone would be effective and safe facilitators of early circadian sleep. Our findings indicated that melatonin and zopiclone, in the doses we used, are effective facilitators of early circadian sleep, and after sleep on those medications, there are no negative residual effects on psychomotor performance. The 10 mg total melatonin dose used in Phase 2 was quite high, however, we chose such a high dose in order to avoid a Type II error where we would conclude that melatonin was safe when in fact it was not. The 7.5 mg Phase 2 dose of zopiclone was a standard clinical dose.

In Phase 3 we conducted an operational evaluation of the laboratory-proven medications that facilitate early circadian sleep. However, the 2 mg melatonin dose was only 20% of the dose used in the Phase 2, whereas the 5 mg zopiclone dose was the smallest clinical dose available.

Our Phase 3 wrist actigraph data indicates that relative to placebo, even these low doses of melatonin and zopiclone are equipotent facilitators of early circadian sleep. Further relative to placebo, melatonin and zopiclone are equipotent in their ability to reduce sleep latency, to reduce the number of awakenings after sleep onset, and to reduce the time spent awake after sleep onset.

Our Phase 3, questionnaire data indicates that aircrew who slept using melatonin or zopiclone, reported less difficulty getting to sleep, fewer awakenings, less difficulty returning to sleep, and rated their quality of sleep significantly higher than when they slept on placebo.

Conclusion

Melatonin and zopiclone, in the Phase 3 doses, are effective and safe facilitators of early circadian sleep.

Recommendation

The CF Central Medical Board (CMB) should draft a policy statement to guide CF flight surgeons with respect to the possibility of employing these medications for short-term support of our air transport crews.

Annex A. A very recent laboratory comparison of sleeping medications

Just before completing Phase 3 of this work (July-August 2002), we undertook a study to investigate another recently developed sleeping medication, zaleplon. This study was a placebo-controlled comparison of zaleplon 10 mg against 3 other sleeping medications (Circadin® 6 mg a regulatory grade time-released formulation of melatonin, zopiclone 7.5 mg, and temazepam 15 mg). The purpose of the study was to compare the depth of impact on psychomotor performance across drugs, as well as the post-ingestion recovery time required for return to normal performance. On each experimental day, the subjects performed a baseline psychomotor test session at 0900 hrs, ingested their scheduled medication at 0945 hrs, and were tested for psychomotor testing at the ‘top of the hour’ for every hour thereafter until 1600 hrs. In order to compare the soporific (sleep-inducing) power of the medications, the subjects completed the Stanford Sleepiness Scale each time they undertook a psychomotor assessment.

The relative depths and duration of impact on psychomotor performance across drugs are illustrated in figure A.1.

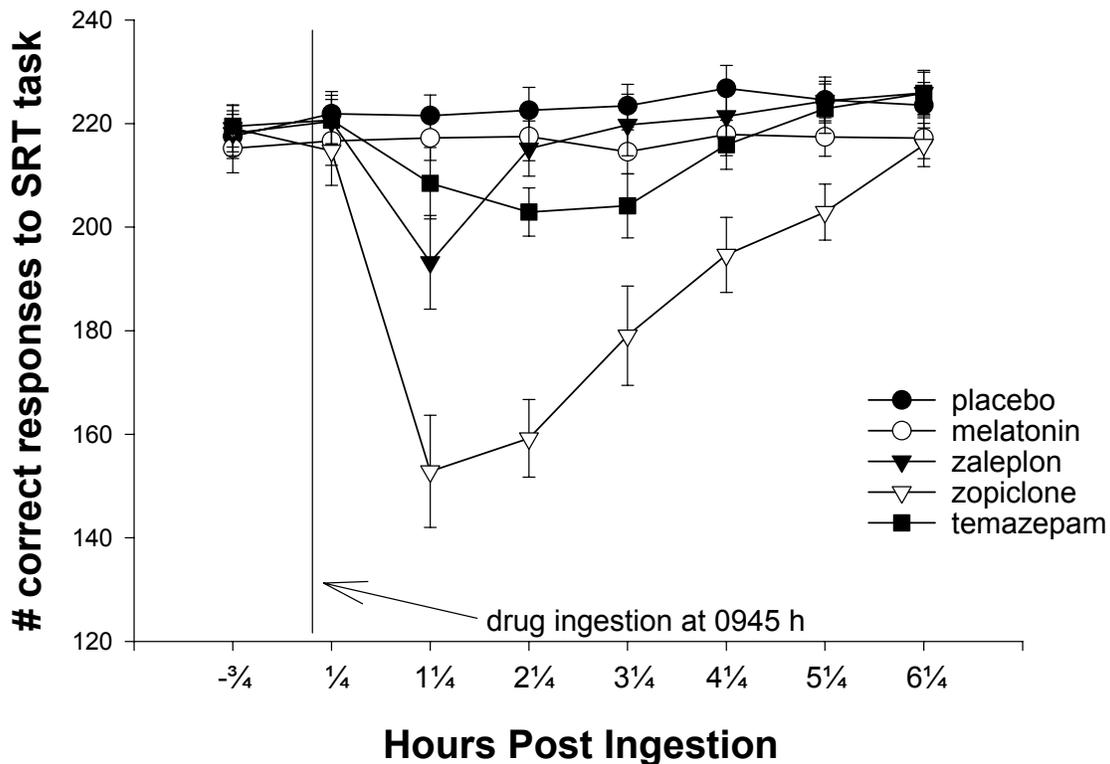


Figure A.1. Number of correct response to Serial Reaction time (SRT) task. All values are (mean \pm S.E.M.) and are plotted over drugs and 'hours post ingestion'.

The ANOVA (5 drugs x 8 trials) assessing impact on SRT performance (figure A.1) indicates a significant main effect of drugs $F(4,88) = 33.45$ $p < .00001$, and significant main effect of trials $F(7, 154) = 28.27$ $p < .00001$, and a significant drugs x trials interaction $F(28, 616) = 10.58$ $p < .00001$.

Post hoc testing of the drugs x trials interaction reveals that relative to placebo, there was no impact of melatonin on SRT performance. Zaleplon produced a transient but relatively large drop in performance 1 1/4 h after ingestion ($p < .00001$), which was gone by 2 1/4 h after dosing. Zopiclone resulted in a large drop in performance ($p < .00001$) evident 1 1/4 h after ingestion and which slowly attenuated over time not reaching equivalence to placebo until 6 1/4 h after ingestion. The impact of temazepam on SRT was first evident ($p < .009$) 1 1/4 h after ingestion with the maximum impact not occurring until 2 1/4 h after ingestion ($p < .0001$). This temazepam-induced impact on SRT performance then slowly attenuated over time reaching placebo equivalence at 4 1/4 h after ingestion.

The relative impact on subjective sleepiness (Stanford Sleepiness Scale) across drugs is illustrated in figure A.2.

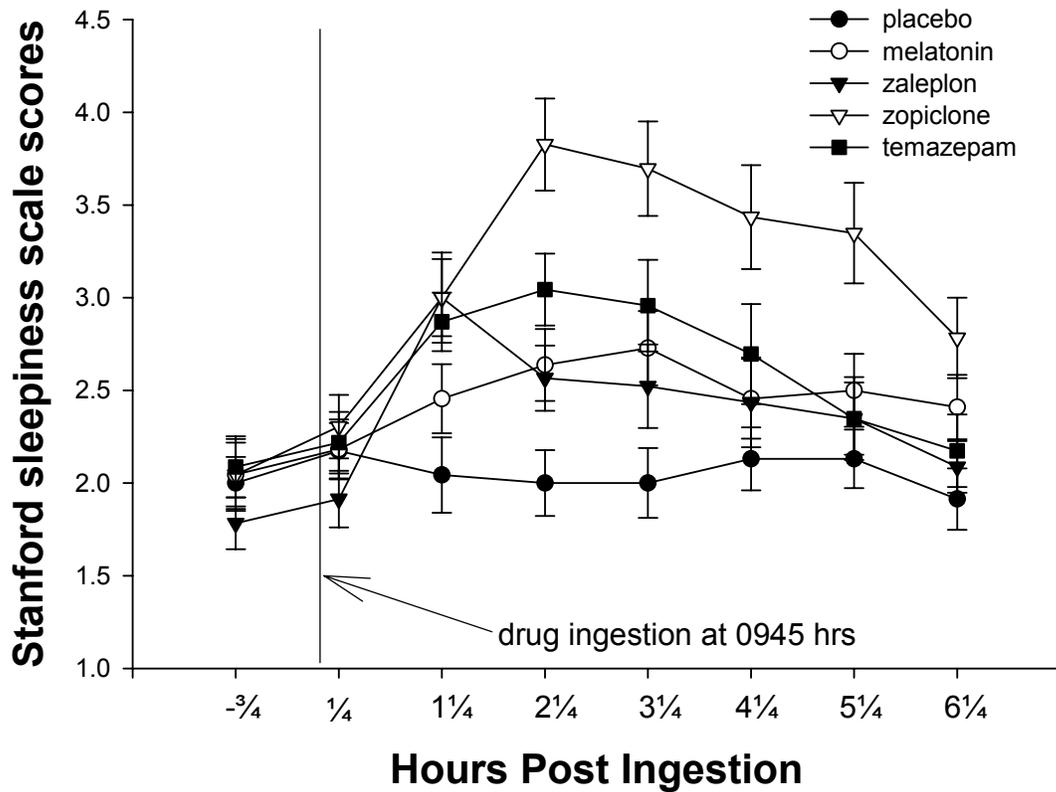


Figure A.2. Subjective sleepiness scores (Stanford Sleepiness Scale). All values are (mean ± S.E.M.) and are plotted over drugs and 'hours post ingestion'.

The ANOVA assessing the impact of drugs on subjective sleepiness (Figure 2) yields a main effect of drugs $F(4,88) = 11.74$ $p < .00001$, a significant main effect of trials $F(7, 154) = 15.99$ $p < .00001$, and a significant drugs x trials interaction $F(28, 616) = 4.44$ $p < .00001$.

Post Hoc testing of the drugs x trials interaction indicates that relative to placebo, melatonin first increased subjective sleepiness 1 1/4 hours after ingestion ($p < .028$). Melatonin-induced sleepiness was briefly not significant 4 1/4 h after dosing but reappeared at 5 1/4 and 6 1/4 h after ingestion. Zaleplon increased sleepiness scores within 15 minutes of ingestion ($p < .004$), peaking at 3 1/4 h post ingestion ($p < .0001$). On zaleplon, peak sleepiness occurred 1 1/4 h after

ingestion ($p < .00001$), and remained significant until $3\frac{1}{4}$ h after dosing. Peak sleepiness on zopiclone occurred $1\frac{1}{4}$ h after ingestion ($p < .00001$) and remained significantly elevated beyond the monitored period. While temazepam caused a significant increase in sleepiness at $1\frac{1}{4}$ h ($p < .0001$), peak sleepiness did not occur until $2\frac{1}{4}$ h after ingestion. Temazepam-induced sleepiness was still evident $4\frac{1}{4}$ h after dosing but not thereafter.

Conclusions

This study compared the effects of melatonin, zaleplon, zopiclone and temazepam on psychomotor performance, and subjective sleepiness for a $6\frac{1}{4}$ h period after acute ingestion. Melatonin (as the 6 mg time release formulation Circadin®) produced no impact on psychomotor performance in spite of having produced a prolonged period of subjective sleepiness. Zaleplon (Starnoc®) produced a short-acting effect on sleepiness and performance. The 7.5 mg dose of zopiclone (Imovane®) produced a sustained effect on sleepiness and impacted performance beyond the $6\frac{1}{4}$ h period of observation in this study. Temazepam (Restoril®), in the 15 mg hard-gelatin formulation used in this study, while resulting in sustained elevated drug levels beyond $6\frac{3}{4}$ h produced less sustained subjective sleepiness with less effect on performance than the 7.5mg dose of zopiclone.

Annex B. Central Medical Board Recommendations for the Use of Medications to Facilitate Sleep in Aircrew

These recommendations are based on the laboratory and operational field trials reported in this Technical Document, and are for short-term support (5 days consecutive maximum) of aircrew during Operations that can impact on aircrew sleep hygiene. Such pharmaceutical support must be directly under the supervision of a flight surgeon. Prior to any operational use, all aircrew are required to have home trials of any medication listed below in order to preclude any idiosyncratic reactions.

1. To facilitate sleep when there is a minimum of eight (8) hours before the next duty period, the use of zopiclone (Imovane) 5 or 7.5 mg is recommended.
2. If the recall to duty may occur in less than eight hours, but is greater than three hours, zaleplon (Starnoc) 10 mg may be used to facilitate sleep. Starnoc may also be used for longer sleep opportunity windows if preferred by individual aircrew, but because of its shorter action, it is less likely to produce sustained sleep.
3. Although melatonin shows promise as a sleep aid, it is not yet approved for use in Canada without special approval from Health Canada. CMB recommends that DPharmS seek approval from the Health Protection Branch for limited use of melatonin (Circadin 2mg) for use by aircrew during layovers to facilitate sleep.

References

1. Allain H, Patat A, Lieury A, Le Coz F, Janus C, Menard G, Gandon JM. Comparative study on the effects of zopiclone (7.5 mg), zolpidem, flunitrazepam, and a placebo on nocturnal cognitive performance in healthy subjects in relation to pharmacokinetics. *Eur. Psychiatry* 1995; 10 (Suppl 3): 129-35.
2. Angus RG, Pigeau RA, Heslegrave R. Why we Nap: Evolution, Chronobiology, and Functions of Polyphasic and Ultrashort Sleep, in *Sustained Operations Studies: From the field to the laboratory*, Stampi C, Editor. 1992, Birkhauser: Boston 217-41.
3. Arendt J, Aldhous M, English J, Marks V, Arendt JH. Some effects of jet-lag and their alleviation by melatonin. *Ergonomics* 1987; 30 (No. 9): 1379-93.
4. Baddeley AD. A 3 min reasoning test based on grammatical transformation. *Psychonomic Science* 1968; 10: 341-2.
5. Balkin TJ, Badia P. Relationship between sleep inertia and sleepiness: cumulative effects of four nights of sleep disruption/restriction on performance following abrupt nocturnal awakenings. *Biological Psychology* 1988; 27 (245-258).
6. Barth JL, Holding JH, Stamford BA. Risk versus effort in the assessment of motor fatigue. *Journal of Motor Behaviour* 1976; 8 (3): 189-94.
7. Belenky G, Penetar DM, Thorne D, et al. The effects of sleep deprivation on performance during continuous combat operations, in *Food Components to enhance performance*, Marriott BM, Editor. 1994, National Academy Press: Washington, DC.
8. Billiard M, Besset A, de Lustrac C, Brissaud L, Cadilhac J. Effets de la zopiclone sur le sommeil, la somnolence diurne et les performances nocturnes et diurnes chez le volontaire sain. *Neurophysiol. Clin.* 1989; 19: 131-43.
9. Billings CE, Reynard WD. Human factors in aircraft incidents: results of a 7-year study. *Aviat Space Environ Med* 1984; 55: 960-65.
10. Broadhurst A, Cushnagan RC. Residual effects of zopiclone (Imovane). *Sleep* 1987; 10 (Suppl 1): 48-53.

11. Brown GM. Melatonin in Pyschiatric and Sleep Disorders; Therapeutic Implications. *Pharmacology and Pathophysiology* 1995; 3: 209-26.
12. Buley LE. Experience with a Physiologically-based Formula for Determining Rest Periods on Long-Distance Air Travel. *Aerospace Medicine* 1970; 41: 680-3.
13. Caldwell JA. Fatigue in the Aviation Environment: An Overview of the Causes and Effects As Well As Recommended Countermeasures. *Aviat Space Environ Med* 1997; 68: 932-8.
14. Caldwell JL. The use of melatonin: am information paper. *Aviat Space Environ Med* 2000; 71: 238-44.
15. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic Sleep/Wake Identification From Wrist Activity – Technical Note. *Sleep* 1992; 15 (5): 461-9.
16. Comperatore CA, Lieberman HR, Kirby AW, Adams B, Crowley JS. Melatonin efficacy in aviation missions requiring rapid deployment and night operations. *Aviat Space Environ Med* 1996; 67: 520-4.
17. Comperatore CA, Wright D, Day-Clayton M, Riuvera P, Bey-Wright R, Kirby AW. Aviator's grounding time after melatonin administration during rapid deployment missions. in *Aeromedical Support Issues in Contingency Operations*. 1998. Rotterdam, The Netherlands: NATO, Advisory Group for Aerospace Research and Development.
18. Cook MR, Cohen H, Orne MT. Recovery from Fatigue. 1972, Army Research and Development Command: Fort Detrick, MD.
19. Coren S. *Sleep Thieves: An Eye-Opening Exploration Into the Science and Mysteries of Sleep*. 1996, New York, NY: The Free Press. 304.
20. Daurat A, Benoit O, Buguet A. Effects of zopiclone onthe rest-activity rhythm after a westward flight across five time zones. *Psychopharmacology* 2000; 149: 241-5.
21. Dawson D, Armstrong SM. Chronobiotics - drugs that shift rhythms. *Pharmacol. Ther.* 1996; 69: 15-36.

22. Dinges DF, Orne MT, Orne ET. Performance after naps in sleep-conducive and alerting environments, in *Biological Rhythms, Sleep and Shiftwork*, Johnson LC, *et al.*, Editors. 1981, Spectrum: New York 539-52.
23. Dinges DF, Orne MT, Whitehouse WT, Orne ET. Temporal placement of a nap for alertness: contributions of circadian phase and prior wakefulness. *Sleep*. 1987; 10: 313-29.
24. Dollins AB, Lynch HJ, Wurtman RJ, Deng MH, Kischka KU, Gleason RE, Lieberman HR. Effect of pharmacological daytime doses of melatonin on human mood and performance. *Psychopharmacology* 1993; 112 (4): 490-6.
25. French J, Bisson RU, Storm WF, Boll PA, Martinez J, Mitchida J, Neville KJ, Vogel E, Whitmore J. Crew Performance and Fatigue during Sustained B1-B Sorties. 1993, Armstrong Laboratory, Crew Systems Division: Brooks Air Force Base, TX.
26. French J, Hannon P, Brainard GC. Effects of Bright Illuminance on Body Temperature and Human Performance. *Annual Review of Chronopharmacology* 1990; 7: 45-9.
27. Gaillot J, Heusse D, Houghton GW, Marc-Aurele J, Dreyfus JF. Pharmacokinetics and metabolism of zopiclone. *Pharmacology*. 1983; 27 (Suppl 2): 76-91.
28. Gerathewohl SJ. Simple Calculator for Determining the Physiological Rest Period after Jet Flights Involving Time Zone Shifts. *Aerospace Medicine* 1974; 45: 449-50.
29. Griffiths AN, Jones DM, Richens A. Zopiclone produces effects on human performance similar to flurazepam, lormetazepam and triazolam. *Br J Clin Pharmacol* 1986; 21 (6): 647-53.
30. Harris DA, Pegram FV, Hartman BO. Performance and fatigue in experimental double-crew transport missions. *Aviat. Space Environ. Med.* 1971; 24: 980-6.
31. Harrison C, Subhan Z, Hindmarch I. Residual effects of zopiclone and benzodiazepine hypnotics on psychomotor performance related to car driving. *Drugs Exp Clin Res* 1985; 11 (12): 823-9.

32. Heron RM, Weinberg H, Robertson A, Jantzen KJ. Development of a Multitasking Device for the Measurement of Air Traffic Controller Skills. in In: Proceedings of Eighth International Symposium on Aviation Psychology. 1995. Columbus, OH: Ohio State Press.
33. Heslegrave RJ, Angus RG. The effects of task duration and work-session location on performance degradation induced by sleep loss and sustained cognitive work. *Behav. Res. Meth. Inst. Comp.* 1985; 17: 592-603.
34. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of Sleepiness: A new approach. *Psychophysiology* 1973; 10: 431-36.
35. Hughes RJ, Badia P. Sleep-promoting and hypothermic effects of daytime melatonin administration in humans. *Sleep* 1997; 20: 124-31.
36. Ladner M, Denny SC. A double-blind study to establish the residual effects of zopiclone on performance in healthy man, in *Zopiclone: A Third Generation of Hypnotics*, Nicholson AN, Scholsberg A, and Dreyfus JF, Editors. 1983, Karger: Basel 98-108.
37. Lieberman HR, Waldhauser F, Garfield G, Lynch HJ, Wurtman RJ. Effects of Melatonin on Human Mood and Performance. *Brain Research* 1984; (323): 201-7.
38. Lubin A, Hord D, Tracy M, Johnson LC. Effects of exercise, bedrest, and napping on performance during 40 hours. *Psychophysiology* 1976; 13: 334-9.
39. Mattila MJ, Vanakoski J, Mattila-Evenden ME, Karonen SL. Suriclone enhances the actions of chlorpromazine on human psychomotor performance but not on memory or plasma prolactin in healthy subjects. *Eur J Clin Pharmacol.* 1994; 46 (3): 215-20.
40. McCauley SF. Aircrew fatigue countermeasures. in *AGARD Conference Proceedings*, 495. Symposium on Progress in Military Airlift. 1990, May 23-31. Lisbon, Portugal: Advisory Group for Aerospace Research and Development: Neuilly sur Seine, France; 1991.
41. Mohler SR. Physiological Index as an Aid in Developing Airline Pilot Scheduling Patterns. *Aviat Space Environ Med* 1976; 47: 238-47.

42. Mortimer RG. Illness, Drugs, Fatigue, and Stress in the Cockpit Reported by Pilots. in Proceedings of the Seventh International Symposium on Aviation Psychology. 1993. Columbus: Ohio State University, Dept. of Aviation.
43. Naitoh P. Circadian cycles and restorative power of naps., in Biological Rhythms, Sleep and Shift Work, Johnson LC, *et al.*, Editors. 1981, SPP Medical and Scientific Books: New York 553-80.
44. Nicholson AN. Residual Sequelae of Zopiclone. Rev. Contemp. Pharmacother. 1998; 9: 123-9.
45. Nicholson AN, Stone BM. Zopiclone: Sleep and Performance Studies in Healthy Man. Pharmacology 1983; 27: 92-7.
46. O'Hanlon JF, Volkerts ER, Louwerens JW, Gloerich ABM, Brookhuis KA. Zopiclone's residual effect upon actual driving performance versus those of nitrazepam and flunitrazepam. Clin Neuropharmacol. 1984; 7 (Suppl 1): 337-8.
47. Paul MA, Pigeau RA, Weinberg H. Human Factors of CC-130 Operations. Volume 6: Fatigue in Long-haul re-supply missions. 1998, DCIEM.
48. Perelli LP. Fatigue Stressors in Simulated Long-Duration Flight: Effects on Performance, Information Processing, Subjective Fatigue, and Physiological Cost. 1980, School of Aerospace Medicine: Brooks Air Force Base, TX.
49. Petrie K, Dawson AG, Thompson L, Brook R. A Double-Blind Trial of Melatonin as a treatment for Jet Lag in International Cabin Crew. Biol Psychiatry. 1993; 22: 526-30.
50. Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, Thompson M, Mack I. Modafinil, d-amphetamine, and placebo during 64 hours of sustained mental work: Effects on mood, fatigue, cognitive performance, and body temperature. Journal of Sleep Research 1995; 4 (4): 212-28.
51. Pigeau RA. A Comparison of Actigraph Data with EEG Defined Movement During Sleep. 1991, DCIEM.

52. Ritter RD. "And we were tired" fatigue and aircrew errors. in IEEE AES Systems Magazine. 1993.
53. Saano V, Hansen PP, Paronen P. Interactions and comparative effects of zopiclone, diazepam, and lorazepam on psychomotor performance and on elimination pharmacokinetics in healthy volunteers. *Pharmacol Toxicol.* 1992; 70: 135-9.
54. Sack RL, Lewy AJ, Hughes RJ. Use of melatonin for sleep and circadian rhythm disorders. *Ann Med.* 1998; 30: 115-21.
55. Sadeh A, Alster J, Urbach D, Lavie P. Actigraphically based automatic bedtime sleep-wake scoring: Validity and clinical applications. *J. Ambulatory Monitoring* 1989; 2: 209-16.
56. Seppala T, Nuotto E, Dreyfus JF. Drug-alcohol interactions on psychomotor skills: Zopiclone and flunitrazepam. *Pharmacology.* 1983; 27 (Suppl 2): 127-35.
57. Shingledecker CA, Holding DH. Risk and Effort Measures of Fatigue. *Journal of Motor Behaviour* 1974; 6: 17-25.
58. Slotten HA, Krekling S. Does melatonin have an effect on cognitive performance? *Psychoneuroendocrinology* 1996; 21 (8): 673-80.
59. Subhan Z, Hindmarch I. Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory. *Neuropsychobiology* 1984; 12: 244-8.
60. Suhner A, Schlagenhaut P, Tschopp A, Hauri-Bionda R, Friedrich-Koch A, Steffen R. Impact of melatonin on driving performance. *J. Travel Med.* 1998; 5 (1): 7-13.
61. Tafti M, Besset A, Billiard M. Effects of zopiclone on subjective evaluation of sleep and daytime alertness and on psychomotor and physical performance tests in athletes. *Prog Neuropsychopharmacol Biol Psychiatry.* 1992; 16: 55-63.
62. Warot D, Bensimon G, Danjou P, Puech AJ. Comparative effects of zopiclone, triazolam and placebo on memory and psychomotor performance in healthy volunteers. *Fundam Clin Pharmacol* 1987; 1 (2): 145-52.

63. Webb WB, Agnew H, Jr. Reaction time and serial response efficiency on arousal from sleep. *Perceptual and Motor Skills* 1964; 18: 783-4.
64. Wegman HM, Klein KE. Jet-lag and aircrew scheduling, in *Hours of work*, Folkard S and Monk TH, Editors. 1985, Wiley: New York.
65. Weinberg H, Heron R, Svoboda J, Jantzen KJ, Robertson A, Gaetz W, Gordon R. The assessment and classification of complex information-processing in multitasking environments. in *12th Triennial Congress of the International Ergonomics Association*. 1994. Toronto: Human Factors Association of Canada: Mississauga, Ontario.
66. Weinberg H, Jantzen KJ, Cheyne D, Carson P, Joly R. Jetlag, Gamma Activity and Managing Pilot Fatigue. in *Transport Canada Conference Proceedings TP 13375. Fatigue in Transportation Workshop: Multimodal Issues and Solutions*. 1998. Ottawa: Transport Canada.
67. Wilkinson RT, Houghton D. Portable four-choice reaction time test with magnetic tape memory. *Behav. Res. Meth. Inst. Comp.* 1975; 7: 441-6.
68. Wilkinson RT, Stretton M. Performance after awakening at different times of night. *Psychonomic Science*. 1971; 23: 283-5.
69. Wynn VT, Arendt J. Effect of Melatonin on the Human Electrocardiogram and Simple Reaction Time Responses. *Journal of Pineal Research*. 1988; 5: 427-35.
70. Zhdanova IV, Wurtman RJ, Lynch HJ, Ives JR, Dollins AB, Morabito C, Matheson JK, Schomer DL. Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther.* 1995; 57 (5): 552-8.

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(U) Deployment of troops in foreign theatres requires a massive airlift capability. The fatigue encountered in such operations can be severe enough to pose a flight safety hazard. The work reported here was done in support of CF air transport aircrews conducting re-supply missions to Bosnia. This work was carried out in 3 Phases. In Phase 1 aircrew sleep hygiene was assessed immediately prior to and throughout 10 missions to Bosnia. Aircrew psychomotor performance was also assessed during flight. The aircrews started the missions with an acute sleep debt because of having to report for duty at 0600 hrs. A fatigued-induced impact on psychomotor performance was found towards the end of the out-bound transatlantic leg. The aircrew experienced difficulty sleeping at an early circadian time (approximately 1700 hrs body clock) in the U.K. prior to flying into Bosnia. In Phase 2, we conducted a laboratory-based fatigue countermeasure study in which we determined that melatonin and zopiclone are effective facilitators of early circadian sleep, and caused no residual effects on aircrew performance after sleep on these medications. Based on the results of Phases 1 and 2, we were given permission to conduct Phase 3, an operational evaluation of the lab-proven countermeasures that involved 70 missions to Bosnia. The actigraphic data of Phase 3 indicated that relative to placebo, when aircrew were on melatonin they got to sleep quicker ($p < .01$), slept more ($p < .02$), had fewer awakenings after sleep onset ($p < .004$), and spent less time awake after sleep onset ($p < .01$). Again relative to placebo, when they were on zopiclone they got to sleep quicker ($p < .003$), slept more ($p < .005$), had fewer awakenings ($p < .01$) and less time awake after sleep onset ($p < .05$). The aircrew subjective ratings indicated relative to placebo, while on melatonin, they experienced less difficulty getting to sleep ($p < .0001$), fewer awakenings ($p < .005$), less difficulty returning to sleep after awakening ($p < .0001$) and a better sleep quality ($p < .0003$). Also relative to placebo, while on zopiclone, aircrew experienced less difficulty getting to sleep ($p < .001$), fewer awakenings ($p < .001$), less difficulty returning to sleep after awakening ($p < .0001$), and a better sleep quality ($p < .0004$). There were no statistically significant differences between melatonin and zopiclone in any of the actigraphic or subjective sleep parameters. As phase 3 was drawing to a close, we also carried out a laboratory study to compare a new short-acting sleeping medication (zaleplon) against two other sleeping medications (zopiclone and temazepam) and melatonin, not for their ability to induce sleep, but to quantify the depth of their respective impacts on psychomotor performance and to quantify the post-ingestion time required for return to normal performance. Melatonin produced a significant increase in sleepiness for 4¼ h post ingestion but did not cause an impact on psychomotor performance. The post ingestion time to recovery of normal performance for zaleplon, zopiclone and temazepam were 2¼ h, 6¼ h, and 5¼ h respectively. In spite of a prolonged period of perceived sleepiness, melatonin was superior to zaleplon in causing no impact on performance. The remaining drugs listed in increasing order of performance impact duration are zaleplon, temazepam and zopiclone. It was recommended that Central Medical Board (CMB) draft policy guidelines for aircrew use of sleeping medications during operations that can limit or restrict aircrew sleep.

(U) Le déploiement des troupes dans des théâtres étrangers nécessite une capacité d'emport instantané massive. La fatigue associée à ce type d'opérations peut être suffisamment importante pour présenter un danger menaçant la sécurité des vols. Les travaux dont nous faisons ici état ont été effectués afin d'appuyer les équipages de transport aérien des CF menant des missions de réapprovisionnement en Bosnie. Ces travaux comportaient trois phases. Au cours de la phase 1, nous avons évalué l'hygiène du sommeil des membres d'équipage immédiatement avant et pendant 10 missions à destination de la Bosnie. Nous avons également évalué la performance psychomotrice des équipages en vol. L'étude a révélé que les membres d'équipage avaient déjà, au début de leur mission, un important déficit de sommeil puisqu'ils avaient dû se présenter au travail à 6 h. Nous avons observé une altération induite par la fatigue de la performance psychomotrice vers la fin du parcours d'éloignement transatlantique. Au Royaume-Uni, avant le vol vers la Bosnie, les membres d'équipage ont de plus éprouvé de la difficulté à s'endormir plus tôt par rapport à leur horloge biologique (c.à.d. vers 17 heures selon l'horloge biologique). Pendant la phase 2, nous avons effectué une étude en laboratoire de contre-mesures à la fatigue. Cette étude a révélé que la mélatonine et le zopiclone facilitaient le sommeil à une heure avancée par rapport à l'horloge biologique et n'avaient pas d'effets résiduels, après le sommeil, sur la performance de l'équipage qui avait pris ces médicaments. À la lumière des résultats des phases 1 et 2, on nous a autorisés à procéder à la phase 3, qui consistait en une évaluation opérationnelle, pendant 70 missions vers la Bosnie, des contre-mesures qui avaient fait leur preuve en laboratoire. Selon les données actigraphiques recueillies au cours de la phase 3. les sujets qui avaient pris de la mélatonine

s'endormaient plus rapidement ($p < 0,01$), dormaient davantage ($p < 0,02$), se réveillaient moins souvent après s'être endormis ($p < 0,004$) et passaient aussi moins de temps réveillés après l'endormissement initial ($p < 0,01$) que s'ils avaient pris le placebo. De même les sujets qui avaient reçu du zopiclone plutôt qu'un placebo s'endormaient plus rapidement ($p < 0,003$), dormaient davantage ($p < 0,005$), se réveillaient moins souvent ($p < 0,01$) et passaient moins de temps réveillés après l'endormissement initial ($p < 0,05$). Les évaluations subjectives des équipages indiquaient que les sujets ayant pris de la mélatonine plutôt qu'un placebo estimaient avoir eu moins de difficulté à s'endormir ($p < 0,0001$), s'être réveillés moins souvent ($p < 0,005$), avoir eu moins de difficulté à se rendormir après un réveil ($p < 0,0001$) et avoir eu un sommeil de meilleure qualité ($p < 0,0003$). Toujours comparativement au placebo, les sujets ayant pris du zopiclone avaient eu moins de difficulté à s'endormir ($p < 0,001$), s'étaient réveillés moins souvent ($p < 0,001$), avaient eu moins de difficulté à se rendormir après un réveil ($p < 0,0001$) et avaient eu un sommeil de meilleure qualité ($p < 0,0004$). Nous n'avons pas relevé de différences significatives entre la mélatonine et le zopiclone dans les données actigraphiques ou les paramètres subjectifs du sommeil. Comme la phase 3 tirait à sa fin, nous avons également effectué une étude en laboratoire afin de comparer un nouveau somnifère d'action brève (le zaleplon) à deux autres somnifères (le zopiclone et le témazépam) et à la mélatonine, non dans le but de déterminer leur aptitude à provoquer le sommeil, mais plutôt pour quantifier l'ampleur de leurs répercussions respectives sur la performance psychomotrice et pour déterminer le temps écoulé entre l'ingestion et le retour à un niveau de performance normal. La mélatonine a provoqué une augmentation significative de la somnolence pendant une période de 4 ¼ heures après l'ingestion, mais n'a pas eu de répercussions sur la performance psychomotrice. Dans le cas du zaleplon, du zopiclone et du témazépam, le retour au niveau normal de performance s'est effectué, respectivement, 2¼ h, 6¼ h et 5¼ h après l'ingestion. Malgré une période prolongée de somnolence perçue, la mélatonine a eu moins de répercussions sur la performance que le zaleplon. Les autres médicaments se sont classés de la façon suivante, par ordre croissant de durée des répercussions sur la performance : zaleplon, témazépam et zopiclone. On a recommandé que la Commission centrale médicale (CCM) rédige une ébauche de directives concernant l'utilisation de somnifères par les membres d'équipage, pendant les opérations qui peuvent limiter ou restreindre le sommeil de ces derniers.

15. KEYWORDS, DESCRIPTORS or IDENTIFIERS

(U) Air Transport Operations; Aircrew Fatigue; psychomotor performance; fatigue countermeasures