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Management of Circadian Desynchrony (Jetlag and Shiftlag) in CF Air Operations

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Defence R&D Canada
Technical Report
DRDC Toronto TR 2010-002
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The DRDC study protocols reported here were approved by the DRDC Human Research Ethics Committee and met the ethical standards of the Declaration of Helsinki.

Abstract

Background: In response to operational difficulties resulting from the effects of fatigue (secondary to jetlag and shiftlag) on performance of Air Force personnel, the Air Force funded a 4-year project to optimize Canadian Forces (CF) ability to manipulate circadian rhythms forwards or backwards to counter jetlag and shiftlag. This report presents the highlights of that work and offers recommendation for exploitation of this new capability to sustain operational readiness. **Methods:** The project consisted of 7 studies. Four studies involved light treatment, 2 studies involved efficacy comparisons of 3 melatonin formulations to produce a phase advance and a phase delay, and the final study involved a combination of melatonin and light treatment. **Results:** We identified the best 2 of 4 light treatment devices, confirmed optimal melatonin doses and determined the correct treatment times with light and melatonin for circadian phase advance and phase delay. **Discussion**: We can now develop circadian treatments using light and melatonin along with shifting sleep/wake times and avoidance of light at key times across a broad range of operational scenarios. We are therefore in a position to exploit circadian phase shifting to counter jetlag and shiftlag. **Recommendations:** 1. That this knowledge-base be translated into an operational implementation plan through an interface with Air Force operational personnel. This should include the development of appropriate directives, and training of squadron personnel on the use of scheduling tools such as FAST™ (Fatigue Avoidance Scheduling Tool) for fatigue management. 2. That the Air Force aerospace medical community develop medical doctrine in the utilization of circadian interventions to improve and sustain operational readiness. This should include training Bioscience Officers in circadian physiology and how to generate circadian phase-shift protocols, and Flight Surgeons in the pharmaceutical management of circadian phase shifting with melatonin, light therapy, and sleep medications. 3. That the Surgeon General acquires several different melatonin dose sizes and formulations for the CF formulary, along with light treatment devices for use at squadron/wing level.

Résumé

Contexte : À la suite des difficultés opérationnelles découlant des effets de la fatigue (causée par le décalage horaire et par le décalage lié au travail par roulement) sur le rendement de son personnel, la Force aérienne a financé un projet échelonné sur quatre ans visant à tirer avantage au maximum de la capacité de manipulation du rythme circadien (avance ou retard de phase) en vue de contrer les effets du décalage horaire et du décalage lié au travail par roulement. Le présent rapport expose les faits saillants de ce projet et contient des recommandations relatives à la mise à profit de cette nouvelle façon de maintenir l'état de préparation opérationnelle. **Méthodologie :** Le projet comprenait 7 études. Quatre études portaient sur la luminothérapie, deux comparaient l'efficacité de trois préparations de mélatonine pour l'avance et le retard de phase du rythme circadien et la dernière portait sur l'administration de mélatonine associée à la luminothérapie. **Résultats :** Nous avons déterminé les deux meilleurs des quatre dispositifs de luminothérapie, nous avons confirmé les meilleures doses de mélatonine et nous avons établi le moment opportun des luminothérapies et des administrations de mélatonine pour l'avance et le retard de phase du rythme circadien. **Analyse :** Nous pouvons maintenant élaborer des traitements circadiens qui font appel à la lumière et à la mélatonine en plus de la resynchronisation des heures de sommeil/d'éveil et de l'évitement de la lumière à certaines heures en vue d'un large éventail de contextes opérationnels. Nous sommes donc en mesure d'utiliser la resynchronisation du rythme circadien pour contrer les effets du décalage horaire et du décalage lié au travail par roulement. **Recommandations :** 1. Cette base de connaissances doit être intégrée dans un plan de mise en œuvre opérationnelle par l'intermédiaire d'une interface avec le personnel opérationnel de la Force aérienne. Elle doit être utilisée dans l'élaboration de directives appropriées et dans l'instruction du personnel de l'escadron concernant l'utilisation des outils d'établissement des horaires (tels que FAST^MC) pour la gestion de la fatigue. 2. La collectivité de la médecine aérospatiale de la Force aérienne doit établir une doctrine médicale relative à l'utilisation des interventions circadiennes destinées à améliorer et à maintenir l'état de préparation opérationnelle. L'instruction doit comprendre l'éducation des officiers des sciences biologiques sur la physiologie circadienne et sur la préparation de protocoles de resynchronisation du rythme circadien et l'éducation des médecins de l'air sur la gestion pharmaceutique de la manipulation du rythme circadien par la mélatonine, la luminothérapie et les somnifères. 3. Le médecin-chef doit ajouter plusieurs préparations et doses de mélatonine au formulaire des FC, de même que des dispositifs de luminothérapie qui seront utilisés à l'échelle des escadrons/escadres.

Executive summary

Management of Circadian Desynchrony (Jetlag and Shiftlag) in CF Air Operations

Michel A. Paul; Gary W. Gray; Harris R. Lieberman; Ryan J. Love: James C. Miller; Josephine Arendt; DRDC Toronto TR 2010-002; Defence R&D Canada – Toronto; December 2010.

Background: Due to the problems associated with jetlag and shiftlag such as fatigue-induced impairment of cognitive effectiveness, the Air Force funded a 4-year project to optimize Canadian Forces (CF) ability to manipulate circadian rhythms forwards or backwards to counter jetlag and shiftlag. The project consisted of 7 studies. Four studies involved light treatment, 2 studies involved efficacy comparisons of 3 melatonin formulations for each of phase advance and phase delay, and the final study involved a combination of melatonin and light treatment.

Results: We identified the best 2 of 4 light treatment devices, confirmed optimal melatonin doses and determined the correct treatment times with light and melatonin for achieving optimal circadian phase advance and phase delay. We used phase response curves, which define optimum treatment times for light and melatonin for phase advance and phase delay, to make these determinations.

Significance: We can now develop circadian treatment protocols, using light and melatonin along with shifting sleep/wake times and avoidance of light at key times, across a broad range of operational scenarios. We are in a position to exploit circadian phase shifting to counter jetlag and shiftlag and enhance operational effectiveness, as part of an overall fatigue management plan. Employment of phase shifting to counter jetlag will facilitate rapid deployment across time zones enabling aircrew to be operationally effective upon arrival at their destination. For ground crew and control personnel, phase shifting to counter shiftlag can facilitate the shift from day to night work or the reverse. Phase shift protocols can also improve performance effectiveness at destination for any Canadian Forces members required to travel across multiple time zones, for example senior Department of National Defence (DND) staff attending international meetings.

Future plans: The next step is to translate circadian phase shift science into aeromedical and operational protocols for implementation. Under the guidance of the operational community, the scientific, aeromedical and operational communities need to work together to develop operational implementation plans for fatigue management, including utilization of circadian science. The aeromedical community needs to develop a specific aeromedical doctrine (e.g., a Flight Surgeon Guideline) for the use of pharmaceutical and light treatment modalities for circadian management. A key component of implementation is appropriate training for squadron scheduling personnel on the use of scheduling tools for fatigue management, and Medical/Bioscience personnel on the generation of circadian treatment protocols. We also recommend that the Surgeon General acquires several different melatonin formulations for the CF formulary, along with light treatment devices for use at squadron/wing level.

Sommaire

Resynchronisation du rythme circadien pour contrer les effets du décalage horaire et du décalage lié au travail par roulement

Michel A. Paul; Gary W. Gray; Harris R. Lieberman; Ryan J. Love: James C. Miller; Josephine Arendt; RDDC Toronto TR 2010-002; Recherche et développement pour la défense Canada – Toronto; décembre 2010.

Contexte : À la suite des problèmes associés au décalage horaire et au décalage lié au travail par roulement, la Force aérienne a financé un projet échelonné sur quatre ans visant à tirer avantage au maximum de la capacité de manipulation du rythme circadien (avance ou retard de phase) en vue de contrer les effets du décalage horaire et du décalage lié au travail par roulement. Le projet comprenait sept études. Quatre études portaient sur la luminothérapie, deux comparaient l'efficacité de trois préparations de mélatonine pour l'avance et le retard de phase du rythme circadien, et la dernière portait sur l'administration de mélatonine associée à la luminothérapie.

Résultats : Nous avons déterminé les deux meilleurs des quatre dispositifs de luminothérapie, nous avons confirmé les meilleures doses de mélatonine et nous avons établi le moment opportun des luminothérapies et des administrations de mélatonine pour l'avance et le retard de phase du rythme circadien. Pour ce faire, nous avons utilisé des courbes phase-réponse, qui indiquent quand la luminothérapie et l'ingestion de mélatonine font le plus avancer ou reculer les phases du rythme circadien.

Importance : Nous pouvons maintenant élaborer des protocoles de traitement circadien qui font appel à la lumière et à la mélatonine en plus de la resynchronisation des heures de sommeil/d'éveil et de l'évitement de la lumière à certaines heures en vue d'un large éventail de contextes opérationnels. Nous sommes en mesure d'utiliser la resynchronisation du rythme circadien pour contrer le décalage horaire et le décalage lié au travail par roulement et améliorer l'efficacité opérationnelle dans le cadre d'un plan de gestion de la fatigue. L'utilisation de la resynchronisation du rythme circadien pour contrer le décalage horaire facilitera les déploiements rapides dans d'autres fuseaux horaires et assurera l'efficacité opérationnelle des équipages d'aéronefs à leur arrivée à destination. Dans le cas des équipages au sol et du personnel de contrôle, l'utilisation de la resynchronisation du rythme circadien pour contrer le décalage lié au travail par roulement facilitera le passage des quarts de jour aux quarts de nuit, et vice versa. Les protocoles de resynchronisation du rythme circadien peuvent également améliorer le rendement à destination chez tout militaire des Forces Canadiennes (FC) devant traverser plusieurs fuseaux horaires, par exemple les cadres supérieurs du Ministere de Defence Nationale (MND) qui doivent assister à des réunions internationales.

Recherches futures : La prochaine étape consistera à mettre en pratique la science de la resynchronisation du rythme circadien dans les protocoles aéromédicaux et opérationnels. Sous la direction de la collectivité opérationnelle, les collectivités scientifique, aéromédicale et opérationnelle doivent travailler ensemble à l'élaboration de plans de mise en œuvre opérationnelle de gestion de la fatigue en y intégrant la science du rythme circadien. La collectivité aéromédicale doit établir une doctrine aéromédicale précise (par exemple, une directive à l'intention des médecins de l'air) relative aux produits pharmaceutiques et aux

luminothérapies destinés à la resynchronisation du rythme circadien. Les éléments clés de cette mise en œuvre comprendront l'instruction du personnel responsable des horaires concernant l'utilisation des outils d'établissement des horaires pour la gestion de la fatigue et l'instruction du personnel Médical/des Biosciences concernant l'élaboration de protocoles de traitement circadien. Nous recommandons également au médecin-chef ajoute au formulaire des Forces Canadiennes (FC) plusieurs préparations différentes de mélatonine, de même que des dispositifs de luminothérapie qui seront utilisés à l'échelle des escadrons/escadres.

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Table of contents

List of figures

Acknowledgements

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1 Background

In December 2003, the first author was deployed to Camp Mirage (eight time zones to the east) to assess the possibility that the increased operational tempo of the Tactical AirLift (TAL) in support of our troops in Afghanistan might be responsible for a series of flight safety incidents. That assessment was provided as a technical report which included models of aircrew performance for all participating aircrew (Paul and Miller 2004). Aircrew performance was modelled with FAST^{TM} (Fatigue Avoidance Scheduling Tool), a proprietary software program into which daily sleep and work times are entered into the program which then provides estimates of cognitive effectiveness. These models indicated that the elevated operational tempo did not result in attrition of modeled performance over time in circadian-acclimatized aircrew who had been in theatre for a month. However, the then standard operational procedure of engaging newly-arrived aircrew in TAL operations within 36 hours of arrival in-theatre (i.e., when the cognitive effectiveness of the aircrews was still severely impacted by jetlag) was a significant problem. The technical report concluded that newly arrived aircrew needed more time in theatre to recover from jetlag prior to engaging in TAL operations. In the event it was not possible to allow the crews to get over the worst of the jetlag prior to flying these missions, crews could undergo a circadian phase advancing protocol commencing at home during the last 4 days prior to deployment.

The Air Force response to these findings was the drafting of new orders to allow newly-arrived aircrew to recover from the worst of the jetlag over 5 days prior to commencing TAL operations. The Air Force also commissioned a 4-year project to conduct research to optimize Canadian Forces (CF) ability to advance and retard circadian rhythms with appropriately-timed ingestion of melatonin and/or appropriately timed light treatment (which suppresses the body’s ability to manufacture melatonin). This project was successfully completed and all 7 studies of this project have been published in the scientific literature.

The purpose of this report is to highlight the key findings of the project and to provide recommendations for optimizing circadian phase shifting across a spectrum of operational scenarios, in order to ameliorate jetlag and shiftlag and therefore sustain operational readiness.

2 Overview of jetlag and shiftlag

The body's internal clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus and receives non-image-forming signals from the retina. The SCN controls the body's synthesis and release of melatonin, a hormone with a marked circadian rhythm, normally high at night and suppressed by bright light. It helps to regulate other circadian rhythms (Arendt 2009; 2010; Eastman and Burgess 2009; Paul et al. 2009; Sack 2010). During daylight, melatonin production by the pineal gland is normally low and is barely detectable in serum or saliva. However, shortly after sunset, based on the absence of signals from the retina to the SCN indicating the absence of daylight, melatonin is released into the circulation, thus signaling the transition to night. It acts as a photoneuroendocrine transducer molecule conveying photic information as a humoral output. Since melatonin is normally released during the night, some researchers refer to melatonin as "the darkness hormone" or as "a biochemical expression of darkness".

Increasing melatonin levels induces sleepiness (Paul et al. 2004a) and enhances the diurnal decrease in core body temperature (Cagnacci et al. 1996) thereby facilitating sleep onset. When individuals have regular repeatable daily sleep patterns, the timing of the initial release of melatonin into the circulation (called Dim Light Melatonin Onset or DLMO) is quite repeatable from day-to-day (typically around 21:00 h (Lewy et al. 1992). In situations where there are no light-cues (or "Zeitgebers"), the SCN generates free-running circadian rhythms in melatonin and other variables with a periodicity called "*tau*" which for most people is slightly greater than 24 hours.

Jetlag is encountered after transmeridian travel due to a temporary misalignment of the internal clock with the new photoperiod (i.e., in internal misalignment with the sun-rise/sunset times in the new destination). Jetlag results in a recognized sleep disorder of daytime sleepiness and nocturnal insomnia since the body's propensity for sleep is out of phase with the new time zone. Other jetlag symptoms can include cognitive impairment, reduced physical performance, mood disturbance and gastrointestinal disorders (Sack 2010). On average, after eastward travel the body takes approximately one day to recover for each time zone crossed. After westward travel, the body recovers slightly faster since for most persons, *tau* is usually slightly in excess of 24 hours (i.e., 24.2 to 24.5 hours) (Burgess and Eastman 2008; Czeisler et al. 1999; Middleton et al. 1996) although some people have a tau of less than 24 hours. When tau is slightly in excess of 24 hours, adaptation to westward travel occurs faster than after eastward travel. The opposite may be true for those with a tau less than 24 hours.

Shiftlag is a result of rapid transitions between different work schedules within the same time zone, and produces similar sleep hygiene and daytime alertness difficulties to those encountered in jetlag. The circadian stress inherent in shifting quickly from day work to night work is similar to jetlag caused by flying half-way around the world. Individuals suffering from shiftlag can experience symptoms similar to those caused by jetlag. There is some evidence to suggest that those who do shift-work for their entire careers may be at increased risk for health problems such as heart disease or cancer (Stevens 2005).

Manipulation of circadian rhythms in the appropriate direction (forwards/phase advance to counter jetlag from eastward travel or backwards/phase delay to counter jetlag from westward travel) can reduce, if not eliminate the circadian desynchrony inherent in jetlag (Arendt et al.

1986; Arendt and Skene 2005; Eastman and Burgess 2009; Paul et al. 2010c; Paul et al. 2009; Revell and Eastman 2005; Smith et al. 2009). Similarly, appropriate manipulations of circadian rhythms can reduce, if not largely eliminate, the stresses inherent in shiftlag (Baehr et al. 1999; Deacon and Arendt 1996; Sharkey and Eastman 2002). Manipulation of the intrinsic circadian rhythm may be accomplished in several ways, including the use of sunlight and/or artificial light, avoidance of light at certain key times, ingestion of exogenous melatonin, and reprogramming by changing sleep/wake times.[1] The recent reluctance of colleagues from the United States of America (USA) (Caldwell et al. 2009) to recommend melatonin as a fatigue countermeasures (either to facilitate day-time sleep or to counter jetlag and shiftlag by phase shifting circadian rhythms) is based on the fact the in the USA, melatonin is not regulated and is therefore not of pharmaceutical grade. As a result, melatonin preparations in the USA can vary widely in purity and stability. Further, in the USA actual dose size can vary significantly from the stated dose. In Canada, regulatory control of melatonin falls under the Natural Health Products Directorate of Health Canada. Therefore, melatonin preparations in Canada are of pharmaceutical grade and are therefore, pure, stable, and the actual dose is consistent with the stated dose.

[1] Phase advance means shifting of the body clock towards an earlier time on the local clock. Conversely, phase delay means shifting the body clock toward a later time on the local clock.

3 Overview of 4-year DRDC Toronto Circadian Entrainment Project

The Air Force-sponsored circadian entrainment project consisted of 7 studies resulting in 4 scientific literature publications; one publication to determine which of 4 commercial light treatment devices provides the best phase shifting (Paul et al. 2007c), a publication based on 3 studies aimed at optimizing shifting of circadian rhythms forwards and backwards using the best light treatment device (Paul et al. 2009), a publication based on 2 studies comparing the phase shifting efficacy of three 3 mg melatonin formulations (regular release, sustained release, and surge-sustained release (Paul et al. 2010c), and a publication which confirmed that the net phase advancing benefit of combining afternoon melatonin with next morning light treatment is the sum of both treatment modalities (Paul et al. 2010a).

Circadian phase shifting is achieved by appropriately timed ingestion of melatonin (called exogenous melatonin), and/or by appropriately timed light treatment and by avoidance of light when light would compromise the desired phase shift. The following 6 figures and their captions illustrate the methods used to phase shift circadian rhythms.

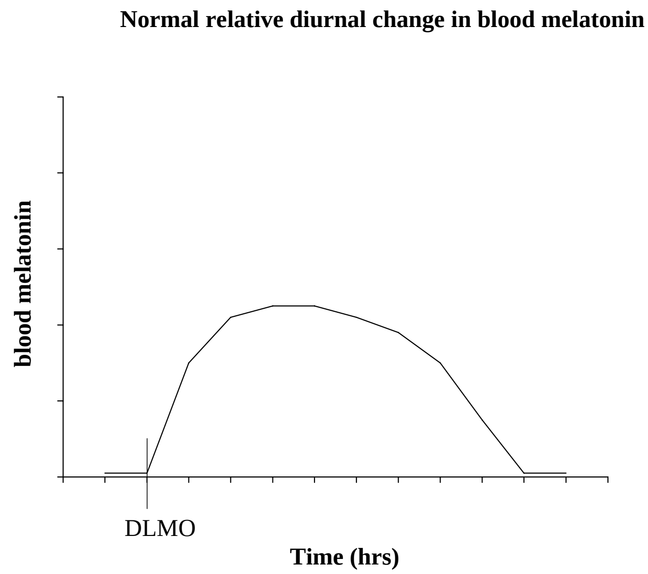

Figure 1: Normal relative diurnal changes in blood melatonin.

Illustrates the normal relative daily changes in blood melatonin. Note that Dim Light Melatonin onset (DLMO) occurs on average at about 2100 hours for those who maintain normal sleep patterns, i.e., going to bed around 2300 hours and arising from bed around 0700 hours. Melatonin Offset, when nocturnal melatonin production ceases is often called DLMOff or MelOff. The amplitude and duration of the melatonin rhythm varies between individuals but is quite consistent within an individual. Day-time levels of melatonin are barely detectable.

Circadian phase advance using supplementary melatonin

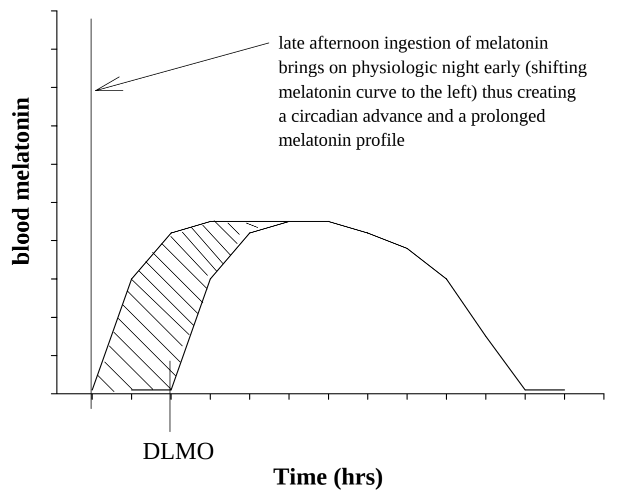

Figure 2: Phase advancing with melatonin.

We confirmed (Paul et al. 2010c) that the phase advances for each of 3 mg regular release, 3 mg sustained release (8-hour linear release profile) and surge-sustained formulation (made up of 1 mg regular release and 2 mg sustained release) were 1.23 hours, 1.44-hours, and 1.16 hours respectively, when given at 1600 hours in normally entrained individuals (i.e,. DLMO at 2100 hours).

Circadian phase delay using supplementary melatonin

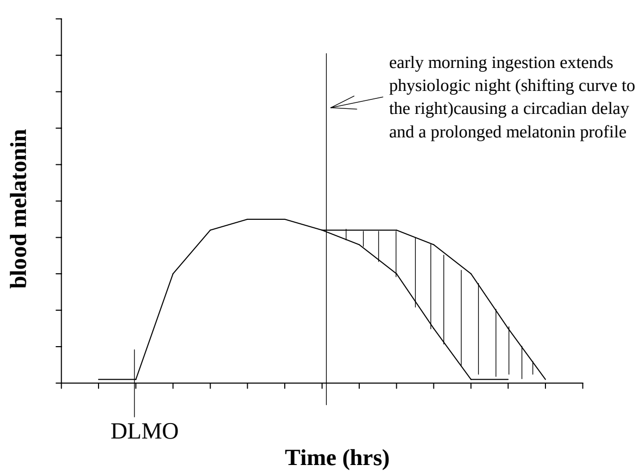

Figure 3: Phase delaying with melatonin.

We have confirmed (Paul et al. 2010c) that a regular release melatonin formulation works best for phase delay and achieved a 1.12 hour phase delay with a 3 mg regular release when given at 0600 hours in normally entrained individuals (i.e., DLMO at 2100 hours).

Circadian phase advance with light treatment

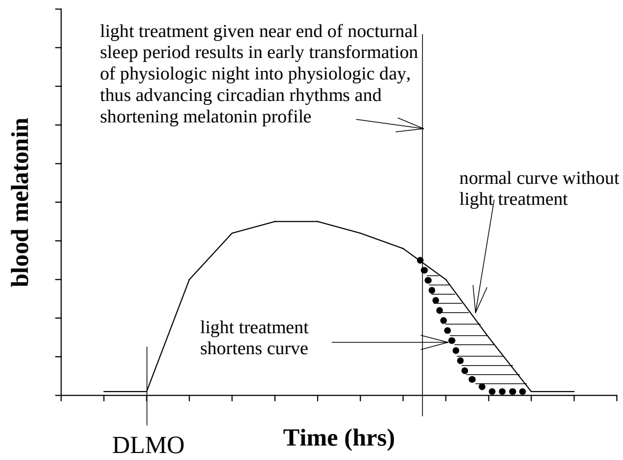

Figure 4: Phase advancing with light treatment.

Using the best of 4 phototherapy devices (Light Tower, Sunnex Biotechnologies, Winnipeg) we achieved a 0.44 hour phase advance (Paul et al. 2009) when light treatment was administered between 0700 hours and 0800 hours in subjects who are normally entrained (i.e., DLMO at 2100 hours).

Circadian phase delay with light treatment

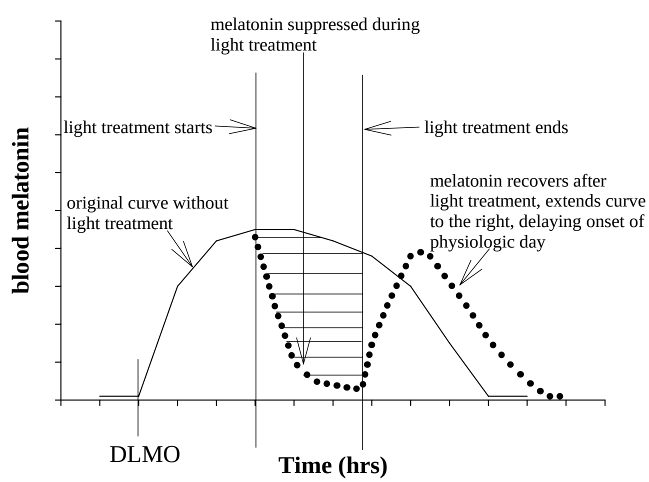

Figure 5: Phase delaying with light treatment.

Using the light tower we achieved a 0.55 hour phase delay (Paul et al 2009) when light treatment was administered between 0200 hours and 0300 hours or between 0230 hours and 0330 hours in subjects who are normally entrained (i.e., DLMO at 2100 hours).

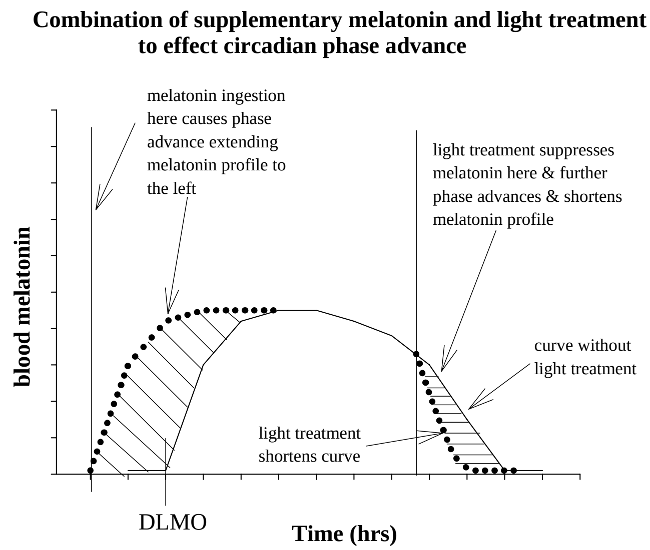

Figure 6: Phase advancing with afternoon melatonin plus next morning light treatment.

We determined that the combination of afternoon melatonin with next morning light treatment is additive in terms of net entrainment benefit (Paul et al. 2010a).

4 Light and melatonin phase response curves

Light and melatonin phase response curves illustrate the ideal treatment times (with light or melatonin) to achieve optimum circadian phase advance and delay. Further, the light phase response curve (PRC) can be used to determine when it is important to avoid light. For example, if phase advance is the goal, one would want to avoid light at a time when exposure to light would induce a phase delay. Figure 7, used here with permission from the publisher of Eastman and Burgess (2009) shows a 3.0 mg regular release melatonin PRC and a light PRC.

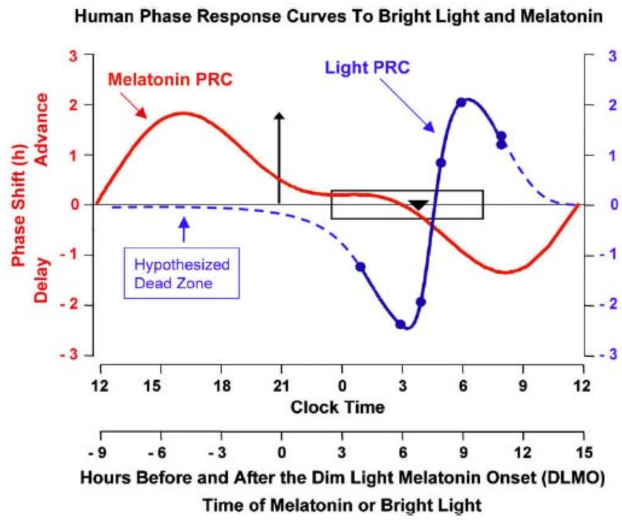

Figure 7: Light and melatonin phase response curves superimpose (Eastman and Burgess 2009).

PRCs were generated with data from subjects who were free-running during an ultradian Light/Dark (L/D) cycle (2.5:1.5) for three 24-hour days. Melatonin pills (3.0 mg) or bright light pulses (2 hours of ~ 3500 lux) were given each day, with different subjects receiving the treatment at different times of day. Phase shifts were calculated by the difference pre-and post- treatment DLMO. The X-axis shows the time the pill was given or the time the light treatment was commenced, relative to each subject's DLMO, represented by zero on the bottom time line and the upward arrow. For convenience, a clock time axis was added to the figure for a subject with a DLMO at 2100 hours. The rectangle shows a typical entrained sleep start time (starting 2.5 hours after the DLMO and lasting for 7.5 hours). The triangle 7 hours after the DLMO shows the typical core temperature minimum (T_{min}). This melatonin PRC was a curve fit to the data from 27 subjects. This bright light PRC should be considered preliminary because it is based on data from only 7 subjects. The dashed sections correspond to times with no data points. The 2.5-hour interval from the DLMO to sleep onset is based on averages from studies done in the Eastman and Burgess laboratory.

In Figure 7, the Y-axis represents the magnitude of the phase shift caused by the administration of a given treatment at the time indicated on the X-axis. Thus the maximal phase shift efficacy of a given treatment is indicated by the highest (phase advance) and the lowest (phase delay) points on the respective treatment curve.

Phase advance with melatonin and light

For optimal phase advance, the melatonin PRC indicates when a *3.0 mg regular release melatonin dose* is administered, it should be taken 5 hours before DLMO (i.e., at 16:00 hours in a normally entrained individual with a DLMO at 2100 hours) (Figure 7). *This phase advance can be improved by light treatment* 9 to 10 hours after the DLMO (Figure 7).

Phase delay with melatonin and light

For optimal phase delay, light treatment should occur approximately 5 - 6 hours after DLMO (i.e., about 0200 hours to 0300 hours in an individual with a DLMO at 2100 hours) (Figure 7). The phase delay can be improved by ingestion of a 3 mg dose of melatonin taken about 11 hours after the DLMO (i.e., about 08:00 hours in an individual with a DLMO at 21:00 hours (Figure 7).

A more recent light PRC based on data from 43 subjects (Paul et al. 2009) is presented in Figure 8.

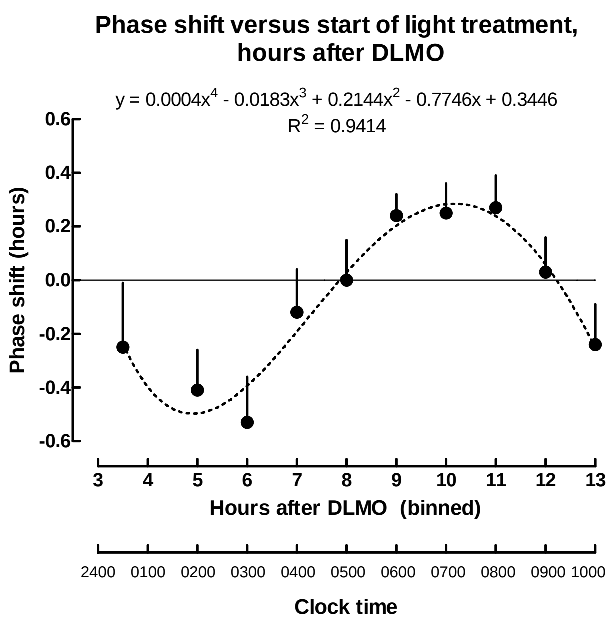

Figure 8: Recent light phase response curve from Paul et al. 2009.

Relationship of phase shift (mean + Standard Error of the Mean (SEM)) to the timing of the start of light treatment (hours after DLMO). Average N per point = 11.With DLMO at 2100 hours, 6 *hours after DLMO corresponds to 0300 hours clock time, etc. The 4th order polynomial equation above, $p<0.001$, has a correlation coefficient of $R^2 = 0.9414$ and therefore accounts for over 94% of the variance in this relationship.*

The light PRC illustrated in Figure 8 indicates that maximum phase delay is attained with light treatment commencing approximately 5 to 6 hours after DLMO or between 02:00 and 03:00 hours in an individual with a DLMO at 2100 hours. This PRC also indicates that maximal phase advance is attained with light treatment starting 9 to 11 hours after DLMO or between 06:00 and 08:00 hours in an individual with a DLMO at 2100 hours.

The 3.0 mg melatonin PRC (from Figure 7) is superimposed on a 0.5 mg melatonin PRC in Figure 9 (used here with permission of the publisher of Eastman and Burgess 2009). Humans normally produce from 25 to 35 micrograms of melatonin per 24-hour period (Fourtillan et al. 2001; Lane and Moss 1985), however Deacon and Arendt (1995) determined that a 0.5 mg dose of exogenous melatonin had to be administered to achieve physiologic levels of plasma melatonin. Two studies have demonstrated the efficacy of 0.5 mg doses of melatonin in entraining free-running blind individuals (Hack et al. 2003; Lewy et al. 2001). Two other studies have demonstrated the efficacy of 0.5 mg melatonin for phase advances (Deacon and Arendt 1995; Sharkey and Eastman 2002). Recent recommendations for preflight treatment of jetlag have suggested 0.5 mg (Arendt 2009), which may be the most appropriate dose. Most recently, Burgess et al. (2010) established that when a 0.5 mg dose is taken 2 hours before DLMO it produces a similar phase advance to a 3.0 mg melatonin dose taken 5 hours before DLMO.. In general, we believe the smallest effective dose should be used for phase changes, although there may be instances where are 3.0 mg dose would be appropriate in situations where there is a secondary goal of sleep facilitation since a 3.0 mg dose can induce sleepiness whereas it is unlikely that a 0.5 mg dose will induce sleepiness.

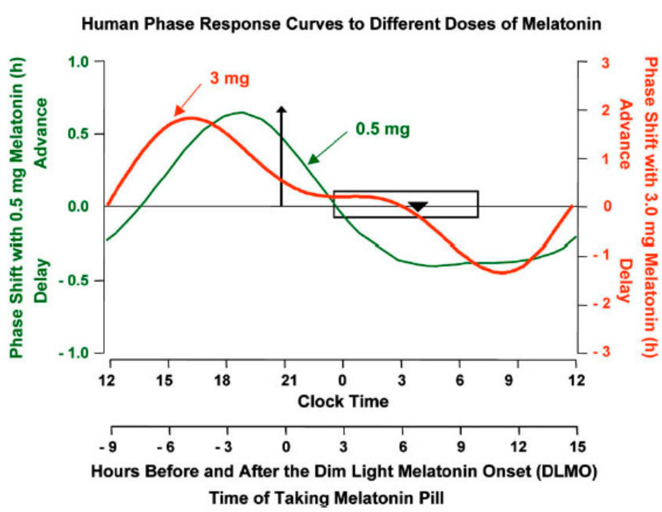

Figure 9: 3.0 and 0.5 mg melatonin phase response curves.

The melatonin PRC from Figure 7 is superimposed on a melatonin PRC for a 0.5 mg dose. The curve for 0.5 mg was fit to the data reported by Lewy and coworkers (Lewy et al. 1998). Note the different Y-axes for the different doses. Eastman and Burgess (2009) opine that this difference is *probably not due to the difference in dose but rather to the difference in protocols (i.e., free-running subjects for 3.0 mg and entrained subjects for 0.5 mg. These PRCs show that the 3.0 mg dose needs to be taken earlier than the 0.5 mg dose to produce the maximum phase advance.*

5 Circadian Synchronization Protocols for CF Operations

Using the data from melatonin and light phase response curves (Section **4**), it is possible to develop specific treatment-grid protocols to optimize circadian adjustment for individuals (or crews) travelling east or west. These particular treatment grids were developed in collaboration with Dr. Charmane Eastman from Biological Rhythms Research Laboratory, Rush University Medical Center, Chicago. The format for Figures 10, 11, and 12 is based on those previously published (Eastman and Burgess 2009). These treatment-grids include recommendations for melatonin and light-therapy timing prior to and during travel, and at destination, to optimize circadian adjustment. The specific examples below illustrate optimization of phase shifting between Trenton and Camp Mirage (CM) which is 8 time zones east during daylight savings time and 9 time zones east during standard time. Similar treatment-grids can be generated for any trans-meridian travel, as well as shift-work circadian changes.

These treatment grids were built based on actual flight timings used in 2010. However, in some cases, flight timings are not optimal from a jetlag perspective.

Pre-adapt to Camp Mirage by circadian phase advance

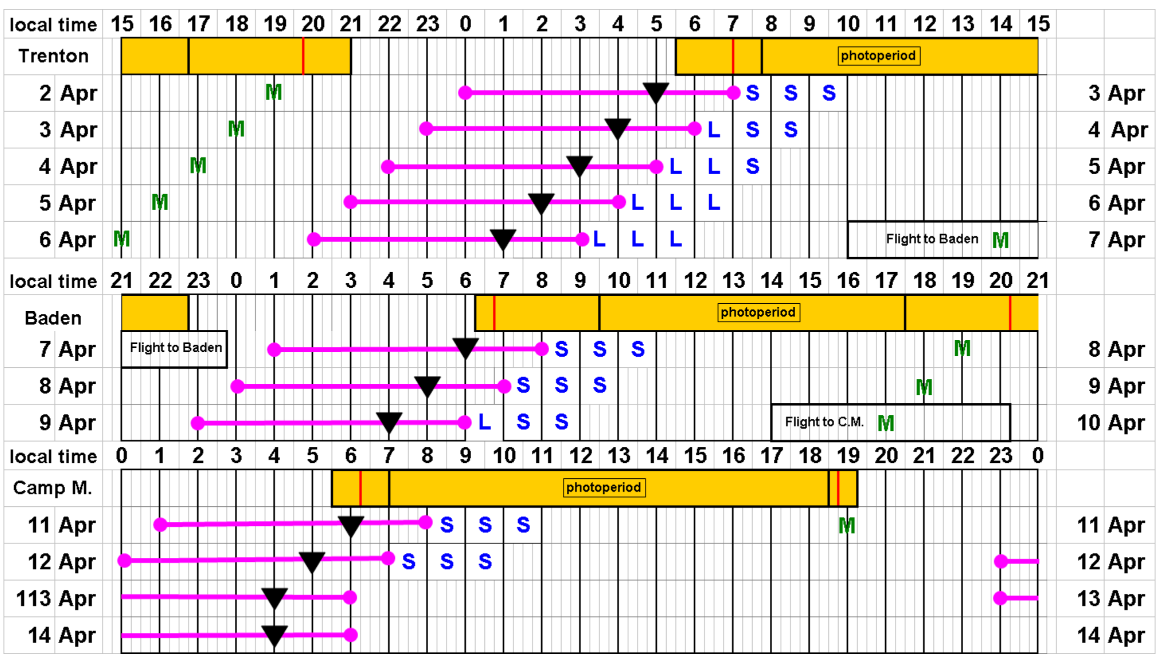

Figure 10: *Treatment grid for pre-adaption to Camp Mirage. by circadian phase advance*

A) Horizontal yellow bars illustrate maximum photoperiod (sun-rise to sun-set) at summer solstice for each of the cities on this itinerary. The vertical bold black lines in the yellow horizontal bars illustrate the minimal photoperiod at winter solstice. Vertical red lines in the horizontal yellow bars illustrate the current photoperiod.

B) The pink bars with a circle on each end represent times in bed.

C) The black triangles represent the body's core temperature minimum (T_{min}) during phase advance treatments, where T_{min} is a phase marker for the circadian clock, the sleepiest circadian time.The body generally advances 1.0 hour per day with appropriate light and melatonin treatment. Hence, during advance treatments, the T_{min} advances by an hour a day.
D) The blue "S" indicates sunlight exposure, whereas the blue "L" indicates use of a light treatment device which is typically used when treatment is given during a time of darkness where there is no sunlight in the local area.
E) The green "M' indicate ingestion timings for a 0.5 mg dose of melatonin.

Pre-adapt from Trenton to Camp Mirage by circadian phase delay

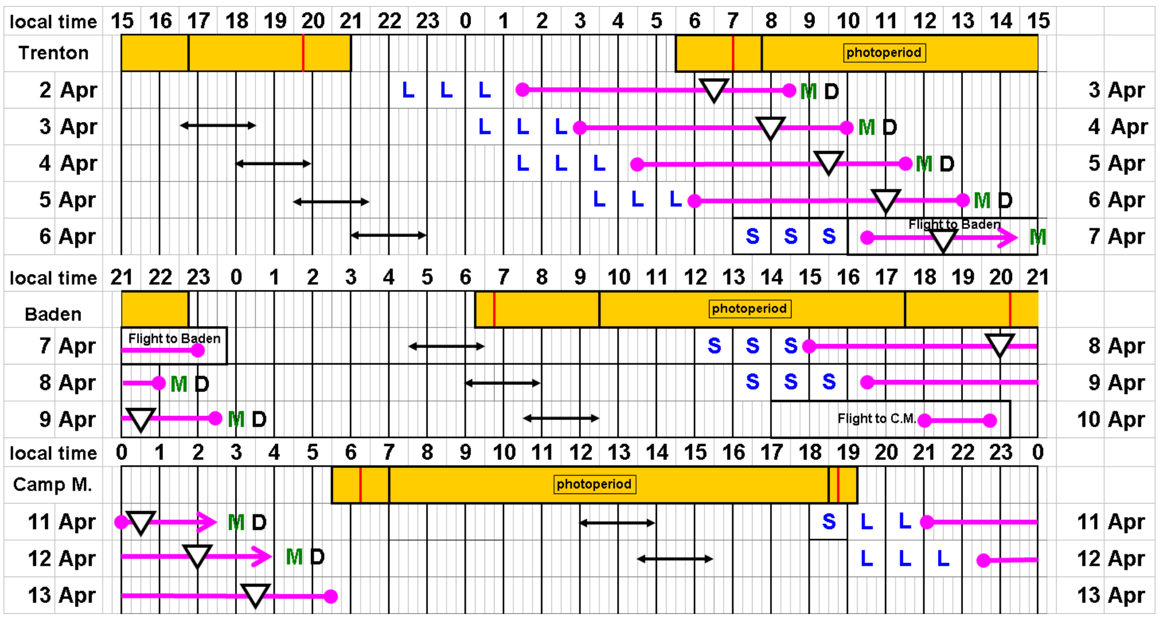

Figure 11: Treatment grid for pre-adaption from Trenton *to Camp Mirage. by circadian phase delay*

A) Horizontal yellow bars illustrate maximal photoperiod (at summer solstice) for each of the cities on this itinerary. The vertical bold black lines in the yellow horizontal bars illustrate the minimum photoperiod (at winter solstice). Vertical red lines in the yellow horizontal bars illustrate current photoperiod.
B) The pink bars with a circle on each end represent times in bed for major sleep periods.
C) The arrow on the right end of the pink bar within the flight to Baden and at the beginning of the rows on April 11 and 12 indicates that this is a good time to sleep and that remaining asleep longer is encouraged, as it is whenever the sleep schedule is gradually delayed.
D) The black bars with an arrow on each end represent ideal times for naps.
E) The open triangles represent core temperature minimum (T_{min}) during phase delay treatments., T_{min} is a phase marker for the circadian clock, the sleepiest circadian time. The human body generally delays about 1.5 hours per with appropriate light and melatonin treatment. Hence, during delay treatments, the T_{min} is delayed by 1.5 hours per day.

F) The blue "S" indicates sunlight exposure, whereas the blue "L" indicates use of a light treatment device which is typically used when treatment is given during a time of darkness where there is no sunlight in the local area.
G) The green "M" indicates ingestion timings for a 0.5 mg dose of melatonin.
H) The black "D" indicates the need to stay indoors in dim light or wear very dark glasses if obliged to go outdoors during daylight.
Note that the flight from Trenton to Baden would be better if it occurred at a different time because it interferes with sleep on April 7.
Note also that the flight from Baden to Camp Mirage. would be better if it started earlier in the day, e.g., 0800 hours, because it interferes with sleep on April 10.

Pre-adapt from Camp Mirage to Trenton by circadian phase delay

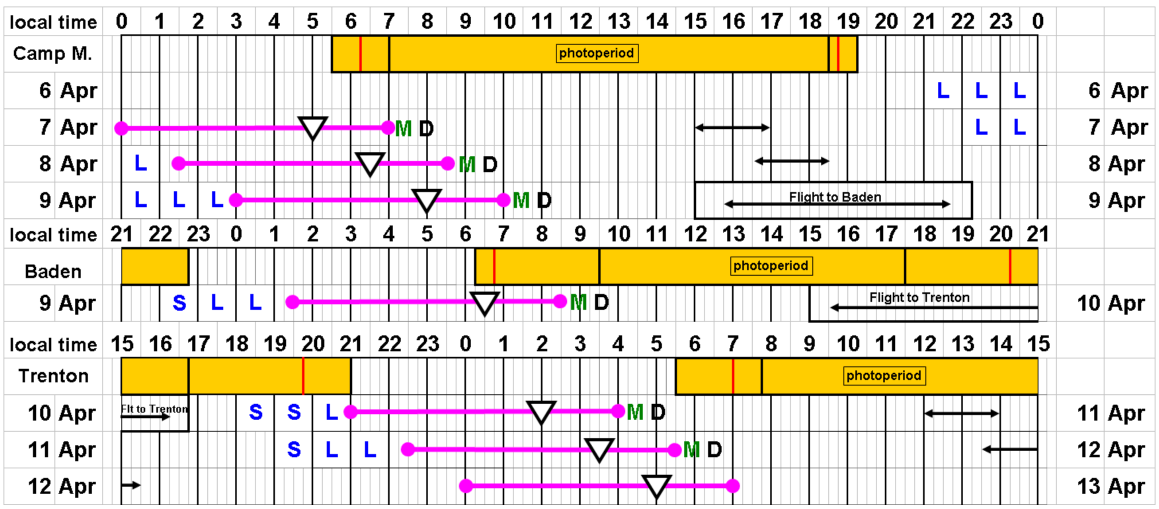

Figure 12: Treatment grid for pre-adaption from Camp Mirage to Trenton by circadian phase delay

A) Horizontal yellow bars illustrate maximal photoperiod (at summer solstice) for each of the cities on this itinerary. The vertical bold black lines in the yellow horizontal bars illustrate the minimal photoperiod (at winter solstice). Vertical red linesin the yellow horizontal bars illustrate current photoperiod.
B) The pink bars with a circle on each end represent times in bed.
C) The black bars with an arrow on each end represent ideal time for a nap.
D) The open triangles represent core temperature minimum (T_{min}) during phase delay treaments. T_{min} is a phase marker for the circadian clock, the sleepiest circadian time.. The body generally delays about 1.5 hours per day with appropriate light and melatonin treatment. Hence, during during delay treatments, the T_{min} is delayed by 1.5 hours per day.
E) The blue "S" indicates sunlight exposure, whereas the blue "L" indicates use of a light treatment device which is typically used when treatment is given during a time of darkness where there is no sunlight in the local area.
F) The green "M' indicate ingestion timings for a 0.5 mg dose of melatonin.

H) The black "D" indicates the need to stay indoors in dim light or wear very dark glasses if obliged to go outdoors during daylight.

6 Circadian Desynchrony Management as a Fatigue Countermeasure Tool

Circadian planning should be an integral part of an overall fatigue management plan for CF Air Operations, both for transmeridian operations, where jetlag is an issue, and for sustained operations, where night operations can pose a problem. Night operations can make it difficult to obtain sufficient sleep and impair operational performance of aircrew involved in night flying, personnel working in air operations centres, and groundcrew who must service aircraft overnight (shiftlag).

An overall Fatigue Management program should include the following tools:

6.1 Scheduling

To the extent possible, operations should be scheduled to limit circadian desynchrony whether due to jetlag or shiftlag. The FAST™, which predicts cognitive performance based on sleep and duty times, is a useful software tool which can be used by schedulers to assess the probable impact on performance effectiveness of an operations schedule before promulgation. FAST ™ (Eddy and Hursh 2001; Hursh 1998; Hursh et al. 2004; Hursh et al. 2003) would be helpful in developing optimum flight schedules or refining the timings for shift work schedule changes. DRDC Toronto has a single-licence application which could be used to provide feedback to schedulers for particular operations. In the future, the Air Force should acquire multiple-user FAST ™ licenses, a potentially very helpful tool for Division and Squadron schedulers.

6.2 Circadian Sychronization

If optimal scheduling is implemented and there is still the potential for circadian desynchrony, the use of appropriate Circadian Synchronization protocols (as discussed in Sections **4** and **5**) provide the potential for reducing or eliminating circadian desynchrony related to either jetlag or shiftlag. Circadian Synchronization protocols may include some or all of the following measures:

- Shifting of bedtimes and wake times in advance of travel

- Use of appropriately timed melatonin administration for phase advance or phase delay. The results of the studies supported by our research program indicate that 3 mg sustained melatonin taken approximately 5 hours before DLMO provides the best phase advance, while 3 mg regular release melatonin taken approximately 9 hours after DLMO provides the best phase delay. Subsequent to our research program, it has been demonstrated that a 0.5 mg regular release melatonin dose can provide similar phase shifts to the 3 mg dose (Eastman and Burgess, 2009), but the 0.5 mg dose should be taken 3 hours later (i.e., about 2 hours before DLMO) in order to optimize a phase advance (see Figure 9)

- Use of light exposure, through natural light when available or light devices at other times, to facilitate phase advance or delay as desired. The best light device examined in these studies was the Light Tower (Sunnex Biotechnologies, Winnipeg). Similar phase shifts were attained with the Feel Bright Light visor (Physician Engineered Products, Bangor, Maine), but it was deemed more intrusive by subjects. However, it does have the advantage of being easily portable.

- Avoidance of light at times which would be counterproductive and result in phase shifts in the wrong direction. Recent research (Rahman et al. 2010) has indicated that dark sunglasses, or sunglasses with appropriate wavelength filters may accomplish the same effect as avoiding outdoor light.

6.3 Assisted Sleep

For some types of operations, it is desirable to remain sychronized to home time, and yet there is a requirement for sleep at off-nominal circadian times. This occurs, for example, for turnaround flights across multiple times zones with a limited layover. In this case, it is counterproductive to try to synchronize with the destination time zone. In such situations, the limited use of sleep medications may be appropriate. There is already aeromedical policy in the CF which provides for flight surgeon-supervised use of selected sleeping medications during missions that are known to impact crew sleep. Currently approved medications include zopiclone and temazepam. Both of these medications have relatively long half-lives and require a minimum of 8 hours after ingestion before report-for-duty. However, melatonin can also facilitate sleep at off-nominal times (Paul et al. 2001), and has the advantage of not causing a performance decrement if sleep has to be interrupted (Paul et al. 2003). Melatonin is currently approved by Health Canada, but is not available in the CF formulary. Our experience indicates that for phase shifting, 3 mg regular release and sustained release formulations are most effective, although as mentioned earlier, subsequent to our project, it has been demonstrated that 0.5 mg, taken 3 hours later than a 3 mg dose (i.e., 2 hours before DLMO as opposed to 5 hours before DLMO) can provide similar phase advance to a 3 mg dose. For assisting sleep at off-nominal times, the first option should be melatonin. We believe that 1 mg or 2 mg sustained release may be most appropriate for facilitation of day-time sleep (Paul et al. 2004b; Rajaratnam et al. 2004), and if necessary, then hypnotics such as zaleplon, zopiclone or temazepam may be considered. We previously evaluated zaleplon (marketed as Starnoc™ in Canada and as Sonata™ in the USA) and found it to be a very effective short-acting hypnotic (1-hour half-life) which caused a modest but significant impairment in psychomotor performance for up to 2 hours after ingestion (Paul et al. 2003; Paul et al. 2004a). Unfortunately, the pharmaceutical company that imported this medication from France decided to discontinue sales in Canada due to insufficient demand. Serious consideration should be given to the acquisition of this medication direct from the manufacturer (for the CF formulary).

6.4 Stimulants

In fatigued aircrew (or other CF personnel) where there is still substantial fatigue in spite of the previous 3 types of interventions listed above (e.g., sustained operations), caffeine (either in coffee or caffeinated gum) or modafinil can be helpful.

- Caffeine from coffee (which can take from 15 – 30 minutes after drinking on an empty stomach before alertness is increased or an hour longer if coffee is ingested after a meal)

- Caffeine from caffeinated chewing gum (Stay Alert Gum) was developed by Walter Reid Army Institute of Research, Silver Spring, MD USA (Kamimori et al. 2005). One dose of gum contains 100 mg of caffeine (similar to one cup of coffee). However, the advantage of caffeinated gum over coffee is that the caffeine is absorbed by the capillary-rich mucosal lining of the mouth, thus by-passing the stomach and providing an alertness benefit within 5 to 10 minutes of commencing to chew on it.

- Modafinil, an alertness-inducing medication initially designed to treat narcolepsy (a pathological tendency to fall asleep at any time) has been shown to maintain alertness as effectively as amphetamines, but does not produce an addictive amphetamine “high” (and therefore has no abuse liability). However, in studies at DRDC Toronto, there was concern about the possibility of modafinil-induced overconfidence (Pigeau et al. 1995). More recently, overconfidence was investigated and not detected (Eddy et al. 2005). Currently, the C F policy does not permit the use of pharmacological stimulants.

7 Discussion

These Air Force-commissioned studies and resulting scientific, peer-reviewed publications have clearly demonstrated that the integrated use of melatonin and light along with avoidance of light at certain times can minimize or eliminate jetlag.

Prior to using circadian phase shifting to counter jetlag or shiftlag, every effort should be made to ensure that missions are scheduled to facilitate minimal fatigue. We have extensive experience with FAST™ using this software to estimate the impact of various operational schedules on fatigue (Paul et al. 2007a; b; Paul et al. 2008; Paul and Miller 2004) or optimized military work schedules (Paul and Miller 2005) and developed a new CF Submarine Watch Schedule (Paul et al. 2010b). We are available to assist Air Force schedulers in implementing FAST™ if licenses are purchased.

7.1 Implementation of Circadian Synchronization for Air Operations

7.1.1 Circadian Synchronization Treatment Grids

Treatment-grid protocols, as discussed in Section **5**, integrate and present visually the optimal timing of the various strategies used for circadian shifting, including sleep shifting, melatonin, and exposure to/avoidance of light. A Circadian Treatment Grid should become part of an Operations Briefing package for all operations where jetlag or shiftlag may be an issue. Currently, DRDC Toronto has the software model to generate such protocols. To implement circadian synchronization as part of an Air Force-wide fatigue management program, other individuals (e.g., Bioscience Officers) will need to be trained to generate such treatment-grids. Another option would be to produce an automated software tool which would generate such treatment grids based on inputs of certain parameters such as dates, latitude and longitude for point of origin and destination, etc.

7.1.2 Melatonin Formulations

Melatonin preparations have been approved by Health Canada for use in Canada as food supplements, and are available over-the-counter at health food stores, supermarkets and other outlets. The melatonin preparations used for these studies were all pharmaceutical-grade and produced under contract by a local pharmaceutical company. To effectively use melatonin as a circadian synchronization tool in CF Air Operations, it would be highly desirable to contract a Canadian pharmaceutical company to produce the required melatonin preparations, and to incorporate these in the CF formulary. The desired formulations would include, for phase shifting, 0.5 mg regular release, 3.0 mg sustained release, and for facilitation of sleep, 1.0 and 2.0 mg sustained release.

7.1.3 Light Devices

Of the 4 light treatment devices we evaluated in this project, the best two devices are the Light Tower (Sunnex Biotechnologies, Winnipeg, Manitoba, Canada; http://www.sunnexbiotech.com) and the Feel Bright Light (a light visor manufactured by Physician Engineered Products, Fryeburg, ME; www.feelbrightlight.com). Both of these lights emit monochromatic green light in the 500 - 505 nm. band. The Light Tower has towers with two fluorescent light tubes/tower. The towers are mounted on a base-plate and merged to focus on the eyes (60 cm in front of the tower) emitting light energy at 350 lux. The light visor is mounted under the bill of a visor (similar to a visor worn while playing tennis). This device has an array of three Light Emitting Diode (LED) lights in front of each eye. The arrays are about 10 cm from eyes and light energy output is selectable to either 8,000 or 12,000 lux. In spite of the differential in emitted light intensity (i.e., 350 lux vs. 8,000 or 12,000 lux) between these two devices, they both produced similar circadian phase changes.

While the sun (which produces 40,000 to 100,000 lux depending on time of day and cloud cover) remains the very best light treatment, when light treatment is necessary during local night, a light treatment device is the only option for such treatment. Early light treatment devices produce high intensity white (polychromatic) light. Of the devices we evaluated, we recommend the Light Tower for in-garrison or home phase shifting before travel. For light treatment during travel where 110 volt electricity is not available, the Feel Bright Light visor (which operates on a re-chargeable lithium battery pack) is more convenient. Since our evaluation of light treatment devices, there has been progress in the development of more convenient, portable, monochromatic devices which may be more applicable in the operational environment.

7.1.4 Light avoidance

Exposure to light at inappropriate times on the light phase response curve can adversely affect circadian entrainment by suppression of endogenous melatonin. Essentially, while exposure to light at optimal times is necessary for optimal circadian phase shifting, it is just as important to avoid light at certain critical times to avoid compromising the desired phase shift.

Zircadian ™ glasses are an optical product which are undergoing research to identify appropriate lens filters to eliminate or minimize this effect, and allow personnel to go out into daylight or operate in a well lit environment without suppression of endogenous melatonin. One such study has to evaluate these glasses during operations from Canada to Afghanistan has been proposed for CF transport aircrew. Support for such research is recommended. Suitable sunglasses with dark lenses can also provide a protective effect in terms of protecting the circadian rhythm from light modulation.

7.1.5 Sleep Assist Medications

The current Flight Surgeon Guideline 1900-01 Medications and Aircrew includes a section on the use of sedative/hypnotics for transport operations. Both zopiclone up to 7.5 mg and temazepam 15 mg are recommended for short-term use to facilitate sleep at off-nominal times e.g., during stop-overs or sleep shifts, for a maximum of 5 consecutive days. Both are included in the CF formulary. Zopiclone requires special authorization, and temazepam is designated as an

"Exception". Apart from triazolam, which is not recommended for aircrew because of the potential for anterograde amnesia and hallucinations, there are no very short acting hypnotics in the CF formulary. Zolpidem (Ambien™) and zaleplon (Starnoc™) are both short acting non-benzodiazepine sedatives with half-lives of approximately 1 hour. Zaleplon, as previously mentioned is approved in Canada but is no longer imported into Canada due to lack of sales. Ambien is the preferred hypnotic used by the National Aeornautics and Space Administratiopn (NASA) for assisting sleep in astronauts (personal communication, Dr. Smith Johnson, NASA Flight Surgeon). Because of the potential for overuse and abuse, the use of sedative/hypnotics in CF aircrew requires further explicit policy direction from the CF aeromedical community.

7.2 Specific Air Operations in Which Circadian Synchronization May Play a Role

7.2.1 Deployment to Camp Mirage for TAL Operations

Under the **Background** heading **(**Section **1**)**,** we refer to the impact of jetlag on aircrew arriving in Afghanistan (Paul and Miller 2004). Figure 13, a model of cognitive effectiveness created with FAST™ software, illustrates the effects of jetlag on aircrew performance.

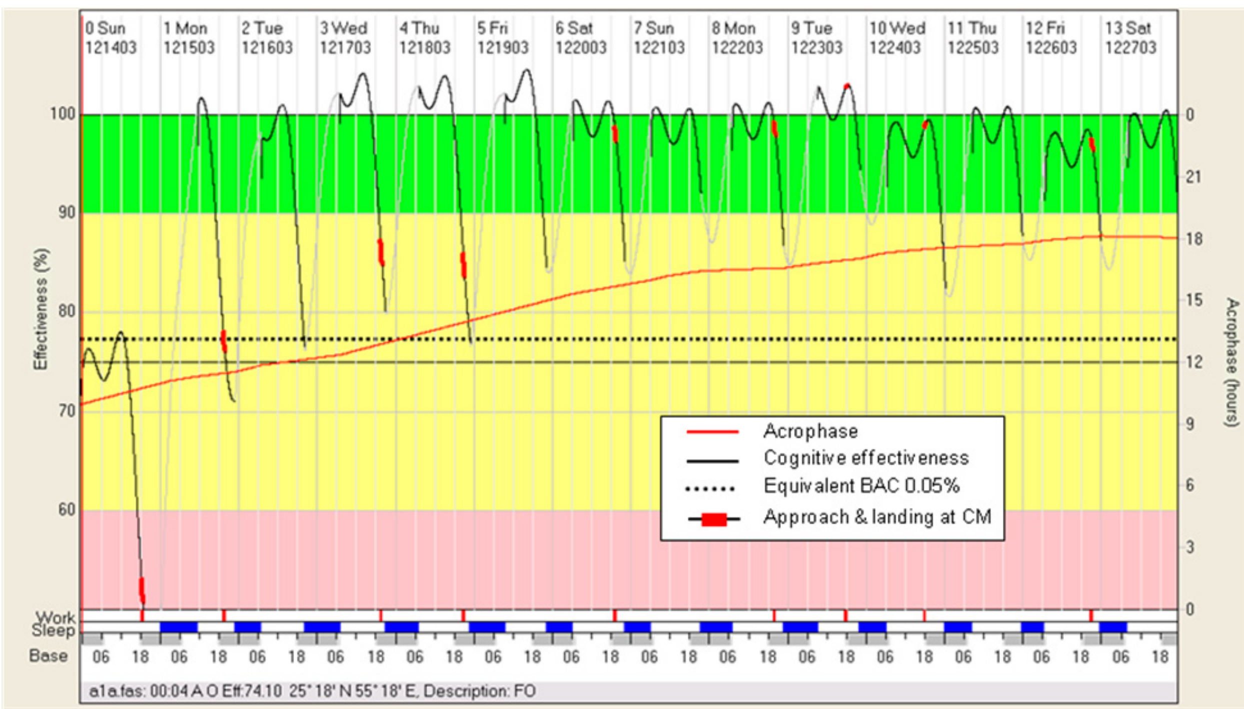

Figure 13: Example of jetlag in CF Air Transport Crews deployed to Camp Mirage.

The vertical axis on the left side of the FAST™ graphs represents modeled human cognitive performance effectiveness as a percentage of optimal performance (100%). The oscillating line in the diagram represents average performance (cognitive effectiveness) as determined by time of day, biological rhythms, time spent awake, and amount of sleep. The green band (from 90% to 100%) represents acceptable cognitive effectiveness for workers conducting safety sensitive jobs (flying, driving, weapons operations, command and control, etc.). The yellow band from 60% to 90% cognitive effectiveness indicates caution. Personnel engaged in skilled performance activities such as aviation should not be allowed to operate in this performance band without fatigue countermeasures. The area from the dotted line to the pink area represents the cognitive effectiveness equivalent to the circadian nadir and a 2nd day without sleep. The pink performance band (below 60%) represents performance effectiveness after 2 days and nights of sleep deprivation. Under these conditions, personnel cannot be expected to perform any cognitive task adequately. The vertical axis on the right side of this graph represents the acrophase (i.e., the time of day at which peak cognitive effectiveness occurs; normally, in the late afternoon or early evening). Acrophase is easily disturbed by night work, shift rotation (shift lag) and time zone changes (jet-lag). The dotted line at 77.5% cognitive effectiveness corresponds to estimated performance equivalent to a blood alcohol content (BAC) of 0.05% (legally impaired in some jurisdictions). A value of 70% cognitive effectiveness corresponds to performance equivalent to a BAC of 0.08% (legally impaired in most jurisdictions). The abscissa (X-axis) illustrates periods of work (short red bars, in this graph indicate the last 30 minutes of crew day during approach and landing back at Camp Mirage), sleep (blue bars), darkness (gray bars) and time of day in hours.

This 14-day FAST™ model shows dangerously low performance on Day 1, where the pilot was functioning at BAC equivalent of 0.05% at his best performance of the day, whereas during approach and landing he was performing at about 53% cognitive effectiveness (indicated by the short red thickening of the cognitive effectiveness line immediately above the first narrow red bar on the X-axis). The following day, this pilot's performance improved but during approach and landing he was functioning at a BAC equivalent of 0.05%. For the following 3 days, performance was still below the acceptable 90% for flying. From day 7 to the last day of the model (Day 14) performance during approach and landing was above 90%. The red acrophase line advances from 0900 hours reaching stability at 1800 hours (theatre time) over about 10 days. This indicates that full recovery from this jetlag takes 10 days, however performance for flying duties is within acceptable limits at about Day 7.

Since no deployment scheduling adjustments can eliminate jetlag, especially for travel across 8 or more time zones, aircrew should be given the opportunity and guidance/flight surgeon support to pursue circadian phase shifting treatments immediately prior to deployment. The first two circadian phase shifting treatments in Section **5** are designed for phase shifting to the Camp Mirage time zone. The first of these treatments uses phase advance for phase shifting (Figure 10), whereas the second treatment uses phase delay (Figure 11). The number of days of treatment for an 8-hour phase advance is similar to the number of treatment days for a 16-hour phase delay. This is largely due to the fact that phase delay treatments generally result in larger daily phase shifts than phase advance treatments. Since the phase advance treatment (Figure 10) involves progressively earlier melatonin dosing, earlier sleep times, and earlier arise times, we believe that some aircrew might prefer to adapt to the Camp Mirage photoperiod by the phase delay method (Figure 11), since this would optimize pre-deployment time with their families.

If aircrew who deploy to Camp Mirage follow the circadian phase shifting treatments (either Figure 10 for phase advance or Figure 11 phase delay) they should arrive in theatre with no jetlag. In this case, modeled performance upon arrival in theatre would be completely acceptable for flying operations after a single rest period (to recover from the deployment flight) as illustrated in Figure 14.

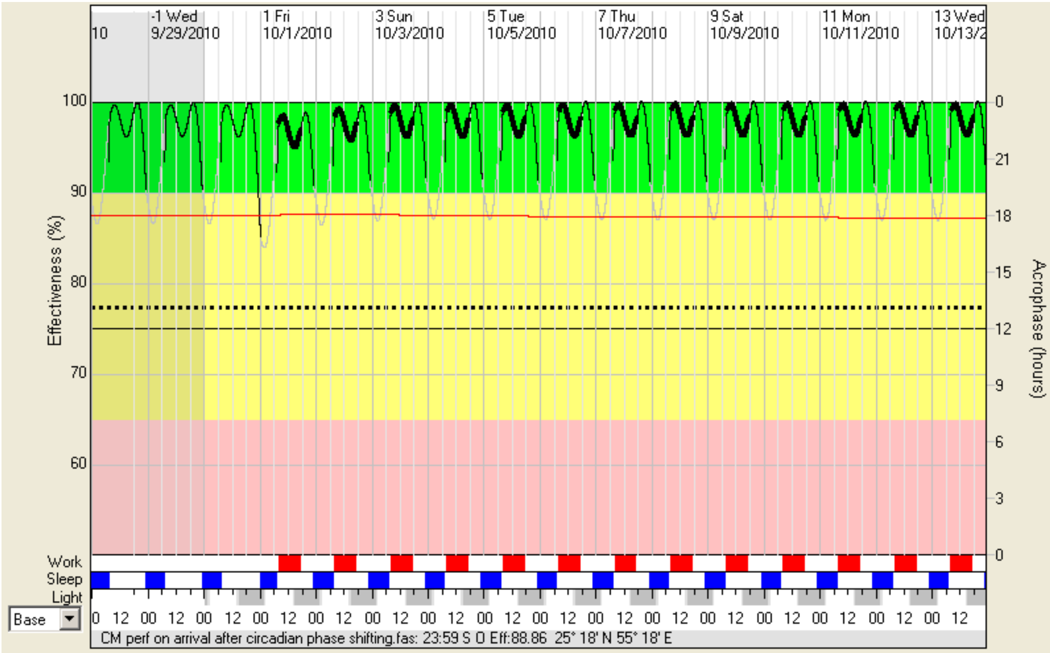

Figure 14: Examples of the efficacy of circadian phase shifting to eliminate jetlag in aircrew deploying to Camp Mirage.

This FAST™ model demonstrates when aircrew pre-adapt to theatre time (either by circadian phase advance or delay), performance for flying operations is excellent. There are no changes in the red acrophase line showing circadian rhythms are in synchrony with theatre time. The red bars in the abscissa of this graph correspond to the entire flight/work period.

DRDC Toronto is available to draft additional circadian phase shifting treatment grids whenever the need arises to counter circadian desynchrony whether due to a new transmeridian air transport mission or to accommodate changing work times from day to night work, or the reverse. In addition DRDC Toronto will work to develop a computer application to allow this to be done at the wing level.

At times, an individual will not be able to follow a circadian phase shifting treatment for the full pre-deployment treatment time. This could occur when an individual, for example, is tasked late for an unplanned deployment and there is insufficient time to undergo a full treatment prior to deployment. In such cases, hypnotics can be used to facilitate sleep for several days after arrival in theatre during which time phase shifting continues until they adapt to the theatre time zone.

7.2.2 Fighter Operations

Fighter missions are generally one to two hours long unless air-to-air refuelling is used to extend the range or endurance of the mission. Fatigue can be a factor if fighter aircrew are tasked with two or three missions per day. Such fatigue can be exacerbated when some or all of these multiple daily missions occur at night. Fatigue can be even greater when our fighter aircrew are called upon to deliver their fighters across time zones to a new theatre of operations (such as Kosovo) where they meet air-to-air refuelling aircraft at pre-set way points and pre-set times to extend their range. For any of these fighter aviation scenarios, squadron schedulers should be vigilant for opportunities to sustain performance by optimal scheduling with FAST™ modeling**.** Similarly**,** flight surgeons should be vigilant for opportunities to improve Air Force operational readiness by the use of circadian phase shifting, sleep facilitation, and pharmaceutical intervention for alertness management (using modafinil) although currently there is no CF policy for alertness management.

7.2.3 Transport Operations

Air transport missions can be relatively short (i.e., 2 to 5 hour flights) in-theatre TAL Operations or long-range (often transmeridian) Strategic Operations (i.e., 8 to 12 hour flights). FAST™ modeling should be used to optimize mission schedules in support of both Tactical and Strategic airlift operations.

For in-theatre TAL operations, to the extent possible, mission schedules should be as consistent as possible from day to day to allow aircrew to adapt to a steady work/rest rhythm (Miller 2005). If operational imperatives dictate frequent changes to mission schedules, flight surgeons should offer pharmaceutical support for sleep at off-nominal times with the first option being sleep facilitation with 1 mg or 2 mg doses of sustained release melatonin, and if necessary, then hypnotics such as zaleplon, zopiclone or temazepam.

For transmeridian strategic airlift operations, where the crews will return directly to home base in Canada after their delivery of personnel or cargo, flight surgeons can prescribe sustained release melatonin (1 mg or 2 mg doses) to facilitate off nominal sleep times. To stay on home-based time, whenever these crews are exposed to light (either day light or room light at times which would sabotage their desire to stay on home based time), they should use special eye-glasses to filter out the blue/green light wavelengths that are responsible for suppression of the body's daily manufacture and release of melatonin. Otherwise, exposure to such light could lead to their adaptation to non-home schedules.

For deployment of crews conducting night-time operations from Camp Mirage, the crews arrive in theatre well-adapted to conduct night operations (after a suitable rest to recover from the deployment flight) as long as they can remain on home-based time (i.e., avoid adapting to the in-theatre photoperiod. These aircrew need to avoid exposure to daylight or even normal room light between sunrise and 1600 hours theatre time. At 1600 hours they should seek out light for about 2 hours to anchor their circadian rhythms (i.e., avoid free-running circadian rhythms). In the event that during the in-theatre light sensitive time (i.e., between sun-rise and 1600 hours) the crews have to be exposed to either sunlight or normal room light, they should wear glasses designed to protect their "physiologic night" (which occurs during local day) by filtering out the blue/green light energy wavelengths that suppress nocturnal melatonin and initiate the undesirable process of adapting to the local photoperiod. We are prepared to conduct an operational evaluation of the efficacy of such glasses pending Air Force interest/support for this work.

7.2.4 Ground Crew

Ground crew are called on to service/repair aircraft around the clock. Since any errors they make could results in loss of life and loss of aircraft, they need to be as alert as aircrew. Their work schedules should be optimized through the use of FAST™ and their schedules should facilitate sufficient time for relaxation and an eight-hour-sleep period.

In general, personnel should be scheduled for shiftwork in accord with research-based principles (Miller 2006). When this is not possible due to personnel shortages, personnel should be left on any given work schedule for as long as possible to allow adaptation to that watch schedule. Extremes of shifting from one work schedule to another (such as day work to night work or the reverse) can cause excessive circadian stress. Frequent shifting of work schedules can undermine operational readiness since personnel who have to frequently switch work schedules always suffer from circadian stress and are never able to adapt to any given work schedule. Recent modeling of alternative submarine watch schedules demonstrated what is already common knowledge; i.e., that the worst diurnal performance occurs between midnight and 0800 hours. Therefore, a watch schedule was developed to split the performance liability of this midnight to 0800 hours period over 2 watches by having a watch change at the half-way mark; i.e., at 0400 hours (Paul et al. 2010b). This same approach could be used to optimize shift work for ground crew.

When personnel work nights they have an imperative to sleep during daylight hours. Sleeping during the day is difficult since the body doesn't produce melatonin during daylight hours, unless the individuals in question have adapted to night work and day sleep (Lavie and Zvulini 1992). For personnel with a day-time sleep obligation who are not yet adapted to this schedule, sustained release melatonin can facilitate day-time sleep. If a trial of sustained melatonin for day-time sleep is not successful, then hypnotics could be used.

7.2.5 Air Operations Centre or ATC Personnel

While the work of personnel in an Air Operations Centre and Air Traffic Control (ATC) personnel is very different from the work of ground crew, the sleep hygiene imperatives and fatigue management issues are similar to those of ground crew.

Figure 15 illustrates a CF ATC schedule (from CFB Cold Lake) where controllers work from 0800 - 1600 hours for 2 days, then work from 1600 - 0800 hours for the next 2 days and then have 4 days off.

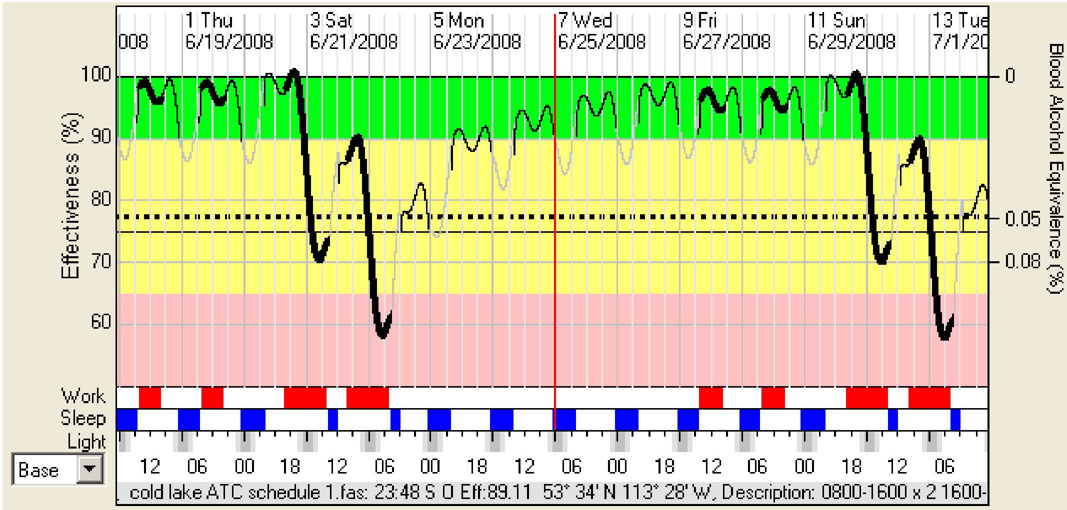

Figure 15: Example of the impact of a CF ATC schedule on cognitive effectiveness on ATC controllers.

The right vertical axis on this graph is set to BAC. The red bars on the abscissa of this graph reflect the full daily work periods. About ¾ of the way through the 1st 1600 - 0800 hour shift, the nadir of cognitive effectiveness reaches 70% (i.e., performance impairment associated with a BAC of 0.08%). The next night on this shift, the performance nadir drops even further to 58% (off scale for BAC impairment). Almost complete recovery occurs during the 4 days off. However, during the next iteration of this shift, performance during the 1600 - 0800 hour shifts are similar to the first iteration.

It is quite evident that 16-hour, 1600 - 0800 hour shifts are far too long, especially when they occur during the overnight period when performance is ordinarily impaired even during more optimal work schedules. In the interest of flight safety such a schedule (Figure 15) needs to be optimized. Figure 16 illustrates what happens when we reverse the work pattern of Figure 15 to 16-hour days and 8-hour nights, followed by 4 days off.

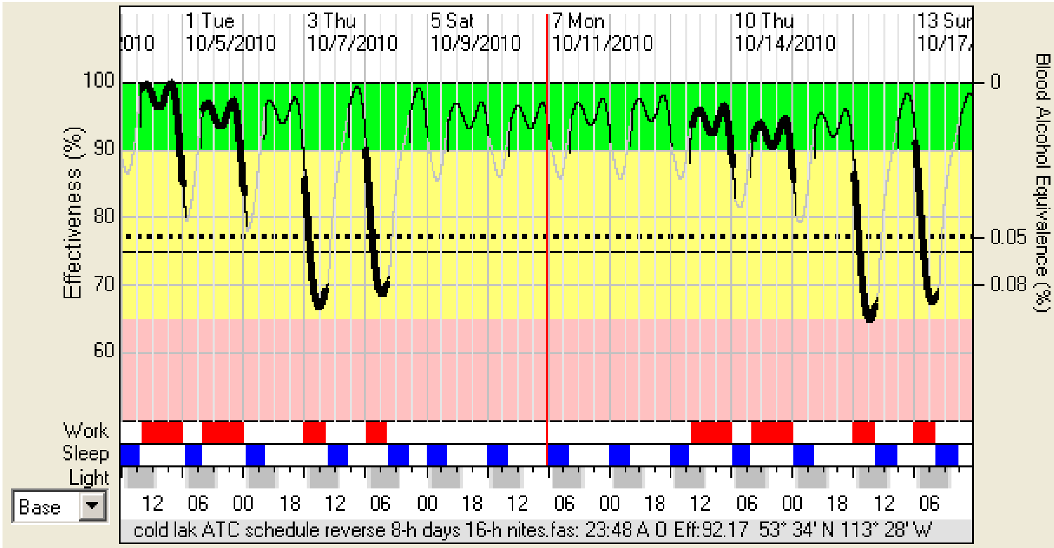

Figure 16. Example of the effect of reversal of ATC work shift pattern seen in Figure 15.

This models a reversal of the work pattern used in Figure 15, where 16-hour shifts are worked from 0800 hours to 2400 hours for 2 days followed by 8-hour shifts from 2400 hours to 0800 hours for 2 days followed by 4 days off. Similar to Figure 15, cognitive effectiveness during the first 0800 hours to 2400 hours shift averages about 97%. During the next shift, cognitive effectiveness drops to about 85% reflecting that impact of minimal rest between these 2 shifts. During the performance nadir on the first night shift, cognitive effectiveness drops to about 66% (well below performance impairment associated with a the BAC of 0.08%). During the 2nd night shift, cognitive effectiveness improves slightly to about 68% but still reflects a performance worse than BAC equivalent of 0.08%. After 4 days of rest, cognitive effectiveness essentially recovers back to normal, but cognitive effectiveness in the next 2 day shifts and follow-on 2 night shifts are lower than the first shifts, suggesting that on this schedule, cognitive effectiveness would deteriorate over time.

A more conventional solution is to use 12-hour shifts in the sequence DDNNOOO where D = day work, N = night work and O= off work (Miller 2006). Figure 17 shows this schedule.

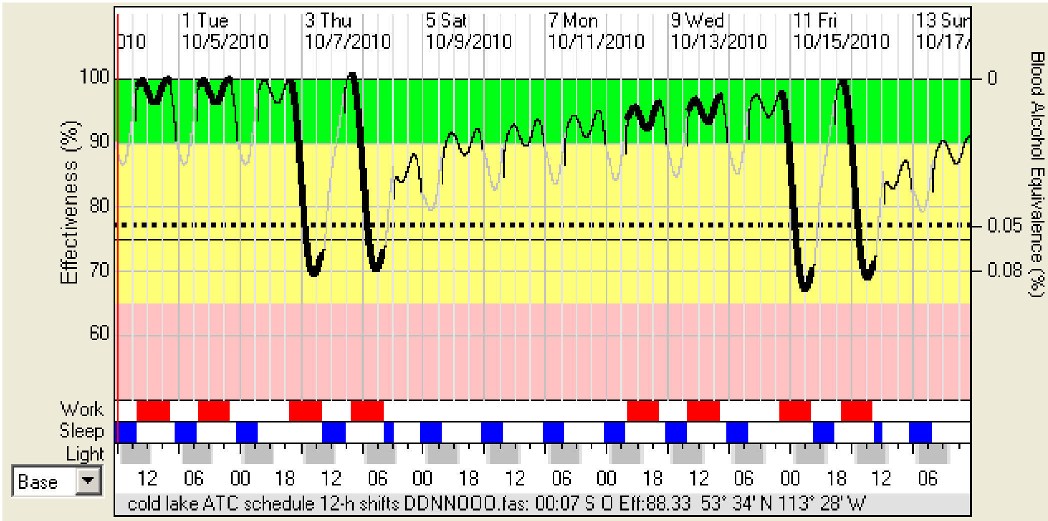

Figure 17: The effect of straight 12-h ATC work shifts.

The night shift here is no better here than in Figure 16.

There is no way to avoid the night-time performance trough. Thus, FAST™ is used in this case to point out the need for extraordinary fatigue countermeasures during the latter portions of the night shifts. Examples of countermeasures are minimization of sleep debt, running checklists twice instead of once, or rotating personnel among workstations more often, or implementation of on-duty napping, or the tactical use of caffeine (i.e., in the form of coffee, pills or chewing gum).

7.2.6 Non-aircrew travel

These circadian phase shifting protocols, although designed for air crew, can be used for anyone that requires a more rapid time zone adjustment. For example, often our senior DND staff are required to participate in many international meetings with little or no opportunity to adjust to a new time zone, yet are asked to not only represent DND at these meetings, but in some cases make significant decisions. These circadian phase shifting protocols are ideal in such circumstances.

For Special Forces operations which involve deployment across multiple time zones for immediate operational activities, circadian phase shifting can minimize the effects of jetlag and greatly enhance the performance on arrival in theatre. Thought should be given to the notion of maintaining Special Forces personnel on a home duty schedule that would facilitate rapid deployment to an operational theatre such as Afghanistan.

8 Recommendations

1. That the information in this Technical Report be translated into an operational implementation plan for Air Force operations.

2. That sufficient software user licenses for FAST™ models be purchased to ensure that squadron operations schedulers have access to and are trained to use FAST™ with a view to optimizing mission timings to keep fatigue to a minimum. A training program on the importance of scheduling as a fatigue countermeasure, assisted by utilization of FAST™ software, will be required for squadron scheduling personnel. DRDC Toronto in collaboration with the Institute of Behavior Resources (who market FAST™) could provide such a course for minimum cost.

3. That one or more Bioscience Officers be trained to generate circadian phase-shift protocols. A special, dedicated training program should be organized (e.g., at DRDC Toronto).

4. That a medical doctrine document (e.g., a Flight Surgeon Guideline) be developed to guide Flight Surgeons on the use circadian interventions to counter jet lag and shift lag using appropriate melatonin formulations, sedative/hypnotic medications, and light treatment devices.

5. That DRDC develop a software application automating the calculation of circadian interventions.

6. That the use of circadian phase shift pharmaceuticals (e.g., different melatonin formulations and hypnotics) be managed by Wing Flight Surgeons. An educational component needs to be incorporated in the Flight Surgeons Course, in conjunction with a Flight Surgeon Guideline.

7. That the Director General Health Services (DGHS) acquire the following melatonin formulations; for circadian phase shifting, 0.5 mg and 3.0 mg regular release, and for facilitation of sleep at off-nominal sleep times 1.0 and 2.0 mg sustained release.

8. That the DGHS acquire zaleplon (Starnoc™) in 5 mg and 10 mg doses.

9. That Canadian Forces Health Services (CFHS) (e.g., through logistics directorate, G4 medical equipment) be tasked to acquire appropriate light treatment devices for each air wing. These devices can be signed out by each squadron for treating squadron aircrew.

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List of symbols/abbreviations/acronyms/initialisms

ATC	Air Traffic Control
BAC	Blood Alcohol Content
CF	Canadian Forces
CFEME	Canadian Forces Environmental Medical Establishment
CFHS	Canadian Forces Health Services
CM	Camp Mirage
DGHS	Director General Health Services
DLMO	Dim Light Melatonin Onset
DND	Department of National Defence
DRDC	Defence Research & Development Canada
FAST™	Fatigue Avoidance Scheduling Tool
hrs	hours
L/D	Light/Dark
LED	Light Emitting Diode
NASA	National Aeronautics and Space Administration
PRC	Phase Response Curve
SCN	suprachiasmatic nucleus
SEM	Standard Error of the Mean
TAL	Tactical AirLift
T_{min}	daily human core body temperature minimum
USA	United States of America

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(U) Background: In response to operational difficulties resulting from the effects of fatigue (secondary to jetlag and shiftlag) on performance of Air Force personnel, the Air Force funded a 4−year project to optimize CF ability to manipulate circadian rhythms forwards or backwards to counter jetlag and shiftlag. This report presents the highlights of that work and offers recommendation for exploitation of this new capability to sustain operational readiness. Methods. The project consisted of 7 studies. Four studies involved light treatment, 2 studies involved efficacy comparisons of 3 melatonin formulations to produce a phase advance and a phase delay and the final study involved a combination of melatonin and light treatment. Results. We identified the best 2 of 4 light treatment devices, confirmed optimal melatonin doses and determined the correct treatment times with light and melatonin for circadian phase advance and phase delay. Discussion. We can now develop circadian treatments using light and melatonin along with shifting sleep/wake times and avoidance of light at key times across a broad range of operational scenarios. We are therefore in a position to exploit our new circadian phase shifting capability to counter jetlag and shiftlag. Recommendations. 1. That the Director General Health Services acquire several different melatonin dose sizes and formulations for the CF formulary, along with light treatment devices for use at squadron/wing level ; 2. that the Air Force develop medical doctrine to guide Flight Surgeons in overseeing circadian interventions to improve/sustain operational readiness and 3. that the Air Force operational community develop specific directives to assist aircrew and groundcrew in dealing with jetlag and shiftlag based on current knowledge as detailed in this report.

(U) Contexte : À la suite des difficultés opérationnelles découlant des effets de la fatigue (causée par le décalage horaire et par le décalage lié au travail par roulement) sur le rendement de son personnel, la Force aérienne a financé un projet échelonné sur quatre ans visant à tirer avantage au maximum de la capacité de manipulation du rythme circadien (avance ou retard de phase) en vue de contrer les effets du décalage horaire et du décalage lié au travail par roulement. Le présent rapport expose les faits saillants de ce projet et contient des recommandations relatives à la mise à profit de cette nouvelle façon de maintenir l’état de préparation opérationnelle. Méthodologie : Le projet comprenait 7 études. Quatre études portaient sur la luminothérapie, deux comparaient l’efficacité de trois préparations de mélatonine pour l’avance et le retard de phase du rythme circadien et la dernière portait sur l’administration de mélatonine associée à la luminothérapie. Résultats : Nous avons déterminé les deux meilleurs des quatre dispositifs de luminothérapie, nous avons confirmé les meilleures doses de mélatonine et nous avons établi le moment opportun des luminothérapies et des administrations de mélatonine pour l’avance et le retard de phase du rythme circadien. Analyse : Nous pouvons maintenant élaborer des traitements circadiens qui font appel à la lumière et à la mélatonine en plus de la resynchronisation des heures de sommeil/d’éveil et de l’évitement de la lumière à certaines heures en vue d’un large éventail de contextes opérationnels. Nous sommes donc en mesure d’utiliser la resynchronisation du rythme circadien pour contrer les effets du décalage horaire et du décalage lié au travail par roulement. Recommandations : 1. Cette base de connaissances doit être intégrée dans un plan de mise en œuvre opérationnelle par l’intermédiaire d’une interface avec le personnel opérationnel de la Force aérienne. Elle doit être utilisée dans l’élaboration de directives appropriées et dans l’instruction du personnel de l’escadron concernant l’utilisation des outils d’établissement des horaires (tels que FASTMC) pour la gestion de la fatigue. 2. La collectivité de la

médecine aérospatiale de la Force aérienne doit établir une doctrine médicale relative à l'utilisation des interventions circadiennes destinées à améliorer et à maintenir l'état de préparation opérationnelle. L'instruction doit comprendre l'éducation des officiers des sciences biologiques sur la physiologie circadienne et sur la préparation de protocoles de resynchronisation du rythme circadien et l'éducation des médecins de l'air sur la gestion pharmaceutique de la manipulation du rythme circadien par la mélatonine, la luminothérapie et les somnifères. 3. Le médecin chef doit ajouter plusieurs préparations et doses de mélatonine au formulaire des FC, de même que des dispositifs de luminothérapie qui seront utilisés à l'échelle des escadrons/escadres.

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(U) management of jetlag and shiftlag; melatonin; light treatment; circadian phase shifting; circadian phase advance; circadian phase delay