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Effect of Zolpidem, Zaleplon, and Ramelton on Cognitive Functioning after Awakening from Napping

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Effect of Zolpidem, Zaleplon, and Ramelton on Cognitive Functioning after Awakening from Napping

by

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Dedication

This is dedicated to my supportive, compassionate wife, Sarah, who always accomplishes anything she sets her mind to. Thank you for setting your mind to care for our family. I also dedicate this to my one year old son, Thomas, who spent many enjoyable hours with me at the keyboard.

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Non-benzodiazepine sedative hypnotics and melatonin receptor agonist hypnotics induce the onset of sleep and are primarily prescribed for the treatment of insomnia. Although, non-benzodiazepine sedative hypnotic drugs zaleplon (Sonata) and zolpidem (Ambien) are not chemically like benzodiazepines, they induce sleep by binding to the same gamma-aminobutyric acid (GABA) receptors in the central nervous system. They may be less likely than benzodiazepine medications to disrupt natural sleep rhythm and patterns which may make sleep more restful. Ramelteon (Rozerem) is a new category of sleep medications that bind to the melatonin receptor in the suprachiasmatic nucleus.

Cognitive performance following a "full night's" rest after taking these medications has been more thoroughly studied than performance decrements should return to duty be required. These hypnotics may be used to induce sleep in circumstances not ideal for rest (shift work, noisy environment, short period available during the day,

etc.). Because these three drugs have a rapid onset and short half-life (one hour for zaleplon, 2.5 hours for zolpidem and 2.5 hours for ramelteon), they have the potential to be utilized in individuals that need assistance with sleep latency, but might need to wake up before a “full night’s” rest to perform critical tasks.

This project reviews the literature regarding the effectiveness of zaleplon, zolpidem, or ramelteon in inducing sleep and the effects on cognitive functioning and performance decrements within eight hours after use.

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Chapter 1: Introduction

Many professional occupations (military, pilots, law enforcement, firemen, EMS, astronauts, physicians, nurses, etc.) require continuous 24 hour operations. One in seven American workers are employed outside the normal daytime schedule (Bureau of Labor Statistics, 2002, 2004). A review of the Texas Workers' Compensation Commission shows that the Texas work injury rate is higher at night as compared to the day time (Fortson, 2004). In this review, the author felt Texas represents the United States as a whole. The increased accident rate is thought to be primarily from sleepiness and fatigue-related performance decrements that these late-night workers experience.

Napping strategies during potential rest periods could improve performance during nighttime circadian lows or make up for the shortfalls of total sleep time (Rosa et al., 1990). Studies of naps at work show improvements in fatigue, sleepiness, vigilance, satisfaction, and general quality of life. Nurses napping for 2 hours during a 16 hour night shift complained of less sleepiness and fatigue than non-napping nurses working only 8 hours (Takahashi et al., 1999). Industrial plant night workers allowed a 1 hour nap during their shift over the course of a year reported increased vigilance, satisfaction, and general quality of life (Bonnefond et al., 2001). General medical interns allowed to nap while on call slept more and reported less fatigue than the control group (Arora et al., 2006). Poor environmental conditions and abnormal sleep times often interfere with sleep quality and/or duration during potential rest opportunities. Pharmaceutical sleep

aids can hasten sleep onset and improve quality of sleep. Zaleplon, zolpidem, and ramelteon have relatively short half lives and may be useful in this population.

Many professionals allowed to nap must perform critical tasks upon scheduled or sudden awakening from sleep and cannot afford medication induced performance constraints. Most studies of side effects from sleep medications concentrate on insomnia and look at cognitive performance the morning after the medication was taken. The purpose of this capstone is to investigate the effectiveness of zaleplon, zolpidem, and ramelteon in inducing sleep and performance decrements within eight hours of taking these drugs. This project will describe the prevalence of the problem in the population and the impact on the individual's health, family, and community. This capstone will synthesize the current literature on cognitive performance decrements in the first eight hours after taking these hypnotics. Using the results of this information, this capstone will provide recommendations for the use of zaleplon, zolpidem, or ramelteon in the targeted professional populations.

Chapter 2: Fatigue and Health Detriments

Circadian rhythm produces a fluctuating twenty-four hour influence on almost every physiological and psychological process. Environmental signals (light/dark) from adverse work times conflict with the natural circadian rhythm confusing the body's sleep/wake rhythm. Sleepiness and fatigue at work can be caused by sleep deprivation or working during the circadian nadir (Leger & Pandi-Perumal, 2007). The biological clock also disturbs day time sleep because this is the body's natural period of alertness. Night shifts force workers to work during their circadian nadir and periods of greater sleepiness and reduced performance. It is extremely difficult for a night worker to adapt to night time activities. Sleep behavior during workdays is different than that on days off (Tepas & Carvalhais, 1990). Family and social obligations require night workers to resume daytime activities during non-work days. Night nurses regularly shift to daytime schedules on days not working (Quera-Salva et al., 1997). Long term exposure to night work may lead to adverse health outcomes if individuals fail to adapt to working at night. Night shifts also alter both the duration of wakefulness (average of sixteen hours for day workers) and circumstances for the most favorable sleep (Akerstedt, 2007). On average, shift workers get two to four hours less sleep than the recommended eight hours a day (Lamond et al., 2003).

Occupational requirements during periods of normal sleep times may result in insomnia or excessive sleepiness (Institute of Medicine, 2006). This sleep problem is a

result of the increasing twenty-four hour society meeting the demands for a global economy and living in an industrialized nation. In fact, one out of every five workers in industrialized countries works at night and displaces sleep to daytime (Basner, 2005). It is estimated that 10% of shift workers meet the criteria for shift work sleep disorder (SWSD) (Drake et al., 2004). SWSD is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM IV)(Francis et al., 1994) as:

> *'report of difficulty falling asleep, staying asleep, or non-restorative sleep for at least 1 month'* with '*a work period that occurs during the habitual sleep phase'*

Military, health care providers, transportation, food services, security personnel, hotel clerks, phone operators, astronauts, police, firefighters are all occupations that are targeted by abnormal work times or adverse sleep environments.

The detrimental health effects of SWSD have been well documented. Shift work has been shown to be associated with an increased risk of endometriosis (Marino et al., 2008), endometrial cancer (Viswanathan et al., 2007), breast cancer (Davis et al., 2001; Hansen, 2001, 2006; Schernhammer et al., 2001; Kloog et al., 2008), prostate cancer (Kubo, et al., 2006), coronary heart disease (Kawachi et al., 1995), metabolic syndrome (Karlsson et al., 2001), and type II diabetes (Kroenke et al., 2007).

SWSD can cause fatigue leading to compromised safety practices and operational decreased performance and productivity that might affect the worker or the general public (Akerstedt et al., 2007; Leger & Pandi-Perumal, 2007). Some of the world's worst environmental disasters have occurred during night shifts, including the Bhopal Union Carbide accident, the Exxon *Valdez* oil tanker leak, and the nuclear accidents at Three

Mile Island and Chernobyl. Subsequent formal inquires concluded that these accidents were at least partially due to human error and fatigue (Folkard & Lombardi, 2006). In health care, the Institute of Medicine estimated that 98,000 deaths occur a year in the United States from medical errors (Institute of Medicine, 2000). Fatigue associated with being on call was the second highest self-reported cause of resident medical errors (Wu et al., 1991). Medical errors occurred at alarming rate among interns on call prior to requirements to limit working hours (Landrigan et al., 2004). After investigators limited duty hours (60 hours a week and 16 consecutive hours a day) the medical error rate remarkably improved.

The unfavorable effects of night time shift work also affect the community outside of the work place. Shift work is one of the most common causes of sleep-related motor vehicle accidents (Connor et al., 2002). Sleepiness induced automobile accidents in the United States resulted in $29.2 to $37.9 billion dollars of cost in 1988 (Leger, 1994). Simulated driving after a night shift has shown a greatly increased risk of accidents (Akerstedt et al., 2005). After adjusting for alcohol and other cofounders in a population based case control study, acute driver-reported sleepiness accounted for an 11 fold increased risk of having a motor vehicle accident that resulted in hospitalization or death (Connor et al., 2002). Motor vehicle accidents are more likely to occur early in the morning between 0200 and 0600 (Connor et al., 2002; Horne & Reyner, 1995) and during the middle afternoon (Horne & Reyner, 1995) which corresponds with circadian related times of sleepiness. Sleep deprived drivers operate vehicles as poorly as those who are intoxicated (Powell et al., 2001).

The quality of life, well-being, and functioning of individuals working night shifts is affected by working during the circadian nadir (Baldwin & Daugherty, 2004; Strine & Chapman, 2005). Normal daytime activities such as shopping are achieved by sacrificing sleep. Poor sleep quality and health can affect family duties such as caring for children or ill family members and can lead to family friction and divorce (Institute of Medicine, 2006).

Chapter 3: Napping as a Countermeasure

A number of studies have investigated napping as a strategy to improve performance, productivity and safety during night shifts and prolonged working hours. Most studies have been performed in healthy young adults. Napping countermeasures have been implemented by positioning naps shortly before (prophylactic) and during (operational) duty hours.

Operational naps are usually taken at the workplace in-between duty hours. Controlled laboratory studies show nighttime napping improves fatigue-related performance decrements. Salline and colleagues (1998) showed an improved reaction time 50 minutes after awakening after napping for either 50 or 30 minutes at 0100 or 0400 hours. Similarly, a one hour nap at 2100 and 0430 showed performance improvements compared to not napping (Gillberg, 1984).

Field studies further support napping as an effective countermeasure against fatigue related performance decrements. Health care workers napping for 30 minutes during their break between 0200 and 0300 demonstrated improved reaction times compared to the control group. (Smith et al., 2007). In a randomized control trial involving physicians and nurses working 12 hour shifts, a 40 minute nap at 0300 hours was shown to improve intravenous insertion and subjective performance at the end of the shifts (Smith-Coggins et al., 2006). Similarly, napping has been shown to improve performance measurements in the aerospace industry. Aircraft maintenance personnel

improved response speed after a 20 minute nap compared those not napping (Purnell et al., 2002). Pilots demonstrated better performance and alertness after a 40 minute in-flight nap taken during a long haul flight (Rosekind et al., 1995).

Field studies are limited by the inability to obtain objective measurements such as polysomnography and the failure to control workplace environmental factors. However, these operational restraints represent actual impediments that workers must overcome to achieve sleep. Purnell and colleagues (2002) reported that approximately half of their subjects did not fall asleep during a scheduled 20 minute nap. Excessive noise was given as the reason that these night workers could not sleep. In the military, a deployment to a remote Southwest Asia location resulted in worse sleep efficiency and increased sleep onset latency (Peterson et al., 2008). Loud noises, uncomfortable bedding, and situational worry were given as the top reasons for difficulty falling sleep. Furthermore, sleep patterns of deployed night shift workers were significantly worse than those working day shifts (Peterson et al., 2008).

Prophylactic naps are usually taken at home shortly before leaving for work. One study showed that prophylactic naps could have prevented about 38% of car accidents in Italian shift working police drivers (Garbarino et al., 2004). A randomized, double-blind, crossover study showed subjects that received a 30 minute nap prior to driving at 2 AM drove better than those that did not nap (Philip et al., 2006).

Sleep inertia may increase sleepiness and hinder performance immediately after awakening from a nap. Sleep inertia persisted for 10 to 15 minutes after awakening from a 50 or 30 minute nap before performance benefits were seen (Sallinen et al., 1998).

Sleep inertia can be minimized by avoiding arousal during deep non-rapid eye movement sleep (Takahashi, 2003). Strategies to evade sleep inertia include avoiding long naps, circadian placed naps, and shortening the period without sleep before naps (Balkin, 1988; Naitoh et al., 1993; Matchock & Mordkoff, 2007). The effects of sleep inertia were seen after a 20 minute nap during the first night shift, but not after naps on the following night shift (Purnell et al., 2002). This finding could be a result of a longer period of wakefulness before napping during the first night shift as compared to the second night shift. Sleep inertia did not hinder performance following a mean nap duration of 13 minutes (Smith et al., 2007). The authors suggest that the brief duration of the nap prevented any measurable effects from sleep inertia.

The duration of a nighttime nap might be an important determinant of the efficacy of napping. One hour naps including both slow-wave sleep and rapid eye movement have shown the same learning performance benefits as sleeping 8 hours at night (Mednick et al., 2003). Short naps have shown benefits upon fatigue-related performance decrements. Naps of 10 and 20 minutes have been shown to improve cognitive performance compared to not napping (Brooks & Lack, 2006).

Studies disagree on the optimum nap time to reduce fatigue related performance detriments. One study investigated the effect of a 2 hour nap at one of five times near circadian peak and trough over a 56 hour period (Dinges et al., 1987). All nap times improved reaction time, but naps placed during the circadian nadir did not significantly affect the results compared to other napping times. In contrast, another study supported placing 2 hour naps at the nadir of circadian rhythms to improve performance

(Matsumoto, 1981). Sleep inertia was found to be similar when subjects were awakened from a 20 minute nap at various times throughout a 64 hour continuous work period (Naitoh et al., 1993).

Some authors report night time napping shortens subsequent day time sleeping (Rogers et al., 1989; Matsumoto & Hanada, 1994), but the total hours of daytime sleep are roughly equal between napping and non-napping individuals (Matsumoto & Hanada, 1994). However, another study found that day time sleep duration is about the same between napping and non-napping employees, giving napping workers additional total hours of sleep (Ribeiro-Silva, 2006).

Chapter 4: Hypnotics

Non-benzodiazepine Sedative Hypnotics

Non-benzodiazepine sedative hypnotics are an improvement compared to the older benzodiazepine class of drugs. Similar to benzodiazepines, they induce sleep by binding to benzodiazepine receptors which potentiates the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). However, they have affinity to specific GABA subunits resulting in improved effectiveness with fewer side effects. Non-benzodiazepine sedative hypnotics do not reduce the seizure potential, relax muscles, or display any anti-anxiety properties. Furthermore, they do not have any REM rebound effect and only minimally alter the stages of sleep as compared to benzodiazepines (Ramakrishnan & Scheid, 2007). The pharmacokinetics of each non-benzodiazepine sedative hypnotic determines the timing and duration of action. Both zolpidem and zaleplon have a rapid onset (C_{max} 27.1 ng·mL^{-1} and T_{max} 84.5 minutes for 10 mg zaleplon and C_{max} 120 ng·mL^{-1} and Tmax 81.8 minutes for 10 mg zolpidem) and extensive first pass effect resulting in a short half-life (one hour for zaleplon and 2.5 hours for zolpidem) (Drover et al., 2000; Ramakrishnan & Scheid, 2007).

Sleep latency in young patients with insomnia was shown to be similar between zaleplon and zolpidem when comparing 10 mg doses in an outpatient setting where polysomnography (PSG) was not performed (Elie et al., 1999). Zolpidem was more effective at increasing sleep duration (Elie et al., 1999) probably because of its longer

half-life and elimination time. A systematic review and meta-analysis found only two studies that directly compared sleep onset latency between zaleplon and zolpidem (Dundar et al., 2004). In the first study, zaleplon had significantly shorter sleep latency in elderly insomnia outpatients in a parallel-group study. (Ancoli-Israel et al., 1999). However, in the second study subjects preferred zolpidem in a double-blind, randomized, cross-over study (Allain et al., 2003). The recommended dose of zolpidem and zaleplon are similar despite the fact that zolpidem has a much lower bioavailability (30%) compared to zaleplon (70%) (Drover et al., 2000). Zaleplon was shown to have increased potency than zolpidem and a lower side effect profile when similar plasma concentrations were compared (Drover et al., 2000). This difference suggests that the two drugs may differ in their selective attraction to the GABA subunits (Drover, 2004).

Melatonin Receptor Agonist

Several studies have shown that increasing age is associated with decreased day time sleep in night shift workers (Matsumoto & Morita, 1987; Tepas et al., 1993). Furthermore, Tepas and colleagues (1993) showed significantly decreased age adjusted sleep length in female night shift workers compared to male night shift workers in the 18-49 age range. Quera-Salva and colleagues (1997) provide a possible explanation for differences between an individual's ability to adjust to working nights. In this study 10 permanent day shift and 10 permanent night shift nurses matched for age, sex, and socio-

familial responsibilities were placed on a shift schedule rotating from days to nights. Fourteen nurses had a peak melatonin level at 0718 AM on days off with no peak during night work. However, six nurses had peak melatonin on both days off and during night work. These dual melatonin shifting nurses scored significantly better on performance testing while at work. These results point out that the ability to quickly produce a melatonin shift might be a key to tolerating abrupt changes in sleep/awake cycles and suggests a possible countermeasure.

Ramelteon (Rozerem) is a new category of sleep medications that bind to melatonin receptors in the suprachiasmatic nucleus of the hypothalamus instead of binding to GABA receptors in the central nervous system. The suprachiasmatic nucleus regulates circadian physiological processes by serving as the body's sleep-wake cycle clock. The suprachiasmatic nucleus resets through the influence of the light-dark cycle. Melatonin produced by the pineal gland can acutely inhibit suprachiasmatic nucleus neuronal firing which is likely important for phase shifting (Stehle et al., 1989) and due to light exposure, entrains mammalian circadian rhythms with the existing environment (Lewy et al., 1992).

Several laboratory studies have shown ramelteon to be effective in decreasing sleep latency in young healthy subjects (Roth et al., 2005; Zammit et al., 2005), young insomnia patients (Erman et al., 2006), and elderly insomnia patients (Seiden et al., 2006; Roth et al., 2007). However, studies performed in outpatient insomnia patients showed efficacy in the elderly (Roth et al., 2005, 2006; Seiden et al., 2005), but not in younger subjects (Takeda Pharmaceuticals America, 2006). The lack of efficacy found in young

patients may be secondary to the more subjective measurements found in the outpatient setting. However, these findings may point to an association between melatonin and the age-related disturbance on circadian rhythm. Daytime melatonin levels decline with increasing age resulting in half of the normal melatonin level at age 50 compared to age 15 (Brown et al., 1979).

Chapter 5: Methods

In a previous chapter, the impact of night work on the individual's health, family, and community was addressed. Subsequent chapters reviewed napping as a strategy to prevent fatigue and improve work place performance and the potential use of the short acting hypnotics zolpidem, zaleplon, and ramelteon to promote the onset of sleep. This chapter describes the literature synthesis process utilized to accomplish the aim of this capstone.

The literature on cognitive functioning within eight hours of taking zolpidem, zaleplon, and ramelteon was identified by performing a literature search utilizing OVID that contained the keyword for 'zolpidem' (search #1), 'ambien' (search #2), 'zaleplon' (search #3), 'sonata' (search #4), 'ramelteon' (search #5), and 'rozerem' (search #6). Another search utilized the search list for 'performance' (search #7) with the subheadings of 'task performance and analysis' and 'athletic performance.' Furthermore, the keyword 'cognition disorders' (search #8) was searched for with the subheadings of 'chemically induced' and 'drug therapy'. The terms 'cognition' (search #9), 'psychomotor performance' (search #10) and 'memory' (search #11) were searched for with the subheading of 'drug effects'. Final searches included standard measurements for cognitive function such as 'neuropsychological tests,' 'psychological tests,' 'reaction time,' 'digit symbol substitution test,' 'flicker fusion,' 'synthetic work task,' 'math processing,' 'grammatical reasoning,' 'psychomotor vigilance test,' and 'CogScreen.'

The remainder of the literature search results is summarized in Table 1. The articles then had the OVID title and brief description reviewed utilizing the inclusion criteria of cognition measurements measured after drug intake. If any article met the inclusion criteria, the article's abstract content was then closer reviewed. If the article had contributions, the entire article was obtained and its content reviewed. The majority of the articles were excluded due to cognitive function measurements starting beyond eight hours of drug ingestion.

TABLES

Table 1: Literature search

Search #	Terms/Keywords	Results
1	zolpidem	1183
2	ambien	19
3	zaleplon	214
4	sonata	121
5	ramelteon	77
6	rozerem	2
7	performance or athletic performance or task performance and analysis	343724
8	cognition disorders (chemically induced, drug therapy)	4345
9	cognition (drug effects)	6648
10	psychomotor performance (drug effects)	7051

11	memory (drug effects)	11150
12	neuropsychological tests (standards, statistics & numerical data)	5245
13	psychological tests (drug effects)	5
14	reaction time (drug effects)	9220
15	digit symbol substitution test	387
16	flicker fusion (drug effects)	494
17	speech reception threshold test or synthetic work task	744
18	mathematics or math processing	1411777
19	grammatical reasoning	26
20	psychomotor vigilance test	26
21	Cog Screen	6
22	1 or 2 or 3 or 4 or 5 or 6	1444
23	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	1703055

24	22 and 23	379
25	limit 24 to English language and humans	289

Chapter 6: Results

The effects of zaleplon, zolpidem, and ramelteon on cognitive functioning within eight hours of administration have been compared to placebo and other sleep medications in small but well designed studies. The non-benzodiazepines sedative hypnotics zaleplon and zolpidem have been directly compared in several investigations.

Cognitive functioning was consistently not impaired after three hours of zaleplon ingestion by healthy individuals, even in doses as high as six times the recommended standard dose (Allen et al., 1993; Beer et al., 1994; Greenblatt et al., 1998; Vermeeren et al., 1998; Danjou et al., 1999; Troy et al., 2000; Hindmarch et al., 2001; Stone et al., 2002; Verster et al., 2002; Paul et al., 2003, 2004; Whitmore et al., 2004, 2004; Simons et al., 2006; Zammit et al., 2006). However, zaleplon showed some significant effects on cognitive functioning in healthy subjects at time periods between ingestion and three hours, especially in doses higher than the standard recommended 10 mg dose (Allen et al., 1993; Beer et al., 1994; Hindmarch et al., 2001; Paul et al., 2003, 2004; Whitmore et al., 2004). In one study, zaleplon was effective in inducing sleep in healthy individuals exposed to a noisy environment and no differences in cognitive impairments were found following middle of the night awakening after four hours of sleep as compared to placebo (Stone et al., 2002). In another study, a 10 or 20 mg middle of the night dose of zaleplon was administered to healthy individuals before performing a standardized driving test for

fatigue 5 hours later, and there was no differences in driving performance between either dose or placebo (Vermeeren et al., 1998).

Zolpidem did not affect cognitive functioning after five hours of ingestion in healthy subjects (Wesensten et al., 1991, 1996, 2005; Balkin et al., 1992; Sicard et al., 1992, 1993; Berlin et al., 1993; Allain et al., 1995, 2001, 2003; Greenblatt et al., 1998; Danjou et al., 1999; Troy et al., 2000; Hindmarch et al., 2001; Verster et al., 2002; Zammit et al., 2006; Storm, et al. 2007). Effects on cognitive performance within 5 hours of taking zolpidem were regularly time and dose dependent in healthy individuals (Berlin et al., 1993; Wesensten, et al., 1996; Greenblatt et al., 1998; Verster et al., 2002; Storm et al., 2007). In one study, no residual effects of 10 mg zolpidem were observed 7 hours after administration during a 40 minute simulated flight by navy fighter pilots (Sicard et al., 1992, 1993).

Zaleplon was observed to have less effect on memory and psychomotor performance than zolpidem in head-to-head comparative studies in the first three hours after ingestion (Greenblatt et al., 1998; Danjou et al., 1999; Drover et al., 2000; Troy et al., 2000; Hindmarch et al., 2001; Zammit et al., 2006). Similarly, middle of the night administration of zolpidem impacted healthy subject's actual driving performance four hours after drug ingestion while there was no effect with zaleplon (Verster et al., 2002). Psychomotor performance was found to correlate with the plasma concentration of each medication and zaleplon had less effect on psychomotor results than a similar plasma concentration of zolpidem (Drover et al., 2000).

No detriments in cognitive performance have been found with ramelteon (Johnson et al., 2006; Karim et al., 2006). Cognitive functioning was tested as soon as one hour after drug ingestion (Johnson et al., 2006; Karim et al., 2006) and at doses as high as 160 mg (Johnson et al., 2006), 20 times the recommended standard dose. Ramelteon has not been compared to zaleplon or zolpidem in controlled trials.

Chapter 7: Conclusion and Recommendations

Working during times normally reserved for sleep can result in fatigue related accidents, illness, work interference, and poorer quality of life for affected personnel. Short naps during night shifts or prolonged operations could reduce the impact of nighttime circadian lows or make up for the shortfalls of daytime sleep (Rosa et al., 1990).

Sleep inertia's potential effect on performance should be considered before instituting napping strategies. Prophylactic naps should not be affected by sleep inertia since the effects should have worn off by the time the worker reports for duty. Stimulating environments may mitigate the effects of sleep inertia upon awakening. For example, an intense continuous noise upon awaking from a one hour night time nap eliminated the effects of sleep inertia (Tassi et al., 1992).

Hypnotics have been found to have positive effects on sleep in abnormal sleep/wake cycles or adverse sleeping environments. Professionals may have difficulty napping due to situational insomnia caused by constant noise on an aircraft carrier. Zaleplon has been shown to reduce the time to persistent sleep despite a continuous loud intermittent noise (Stone et al., 2002). Mountaineers given zolpidem or zaleplon at altitude were found to have improved sleep patterns and Acute Mountain Sickness (AMS) scores decreased (Beaumont et al., 2007). Zolpidem has been shown to improve nap efficiency during a two hour period of otherwise continuous wakefulness (Caldwell

& Caldwell, 2005). This supports the use of hypnotics in occupations like the military that may have a limited time dedicated to sleep during prolonged operations. Shortening the sleep latency with a hypnotic would result in a longer duration of total sleep time.

Medications should only be considered to induce napping if needed. Personnel may not have difficulties falling asleep despite the time of day or the environmental conditions. Non-pharmaceutical strategies should be employed before relying on a pharmaceutical sleep aid. These strategies include stimulus control therapy, relaxation therapy, cognitive behavior therapy, and sleep hygiene education (Petit et al., 2003; Morin et al., 2007). Individual napping situations should be considered before recommending a treatment plan. Prescribers should closely monitor the use of any hypnotic drug for potential known and unknown side effects.

Ramelteon was approved for the treatment of insomnia by the FDA in July 2005 (Pandi-Perumal et al., 2007). The results show it does not impair cognitive performance. However, ramelteon has not been studied in night shift workers or jet lag (Srinivasan et al., 2008). Studies need to be conducted before considering ramelteon in the treatment of situational insomnia experienced by professionals trying to nap during abnormal sleep/wake times or adverse sleeping conditions. Side effects such as vivid dreams, increased prolactin, altered cortisol levels, and suicidal ideation should be considered before usage (Owen, 2006; Takeda Pharmaceuticals America, 2006; Ramakrishnan & Scheid, 2007).

Non-benzodiazepine sedative hypnotic drugs zaleplon and zolpidem have significant cognitive effects at estimated peak plasma concentrations. The FDA has

issued a warning to consumers and healthcare professionals that sedative hypnotics have potential risks for allergic reactions and complex sleep-related behaviors, like sleep-driving (United States Food and Drug Administration, 2007). Further serious side effects include sleep eating (Porterfield, 2006) and depression (Kripke, 2007). Zaleplon is preferred over zolpidem for workplace situational insomnia because it has less cognitive impairment and a shorter half-life. The rapid elimination of zaleplon allows its deleterious effects upon cognitive performance to resolve in 3 hours, 2 hours earlier than with zolpidem. Therefore, zaleplon should only be considered when napping personnel will not be required to awake and perform a critical task for 3 or more hours after drug ingestion. Likewise, zolpidem should only be considered when 5 or more hours are dedicated to sleep.

Individuals unexpectedly awakened from napping who need to perform critical tasks could possibly be administered flumazenil to counteract the cognitive impairment of non-benzodiazepine sedative hypnotics. In one study, flumazenil was administered 90 minutes after a 20 mg ingestion of zolpidem and rapidly reversed memory impairment (Wesensten et al., 1995). This novel use of flumazenil should only be recommended during emergent conditions, such an astronaut being suddenly awakened to pilot the space shuttle.

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Vita

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