INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

ProQuest Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI®

The Effects of Exogenously Administered Melatonin (MT)

on Sleep Maintenance Insomnia (SMI)

By

Paul D'Ambrosio

A dissertation submitted to the Graduate Faculty in Psychology
in partial fulfillment of the requirements for the degree of Doctor of Philosophy,
The City University of New York.

2001

UMI Number: 3024778

Bell & Howell Information and Learning Company
300 North Zeeb Road
P.O. Box 1346
Ann Arbor, MI 48106-1346

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor in Philosophy.

9/10/01
Date

Chair of Examining Committee

9/13/01
Date

Executive Officer

Arthur J. Spielman, Ph.D.

Paul B. Glovinsky, Ph.D.

Lissa Weinstein, Ph.D.
Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

The Effects of Exogenously Administered Melatonin (MT)

on Sleep Maintenance Insomnia (SMI)

By

Paul D'Ambrosio

Advisor: Arthur J. Spielman, Ph.D.

Two studies were conducted to clinically evaluate sleep maintenance insomnia (SMI). The first study was conducted to assess the efficacy of a new therapeutic strategy for SMI. SMI, characterized by poor sleep in the later half of the night, afflicts many mid-life and elderly adults. It has been suggested that this type of insomnia may in part reflect a phase advance in circadian rhythms (Lacks, et al., 1996). The goal of the first study was to assess whether exogenously administered daily physiological doses (0.3 mg.) of MT in the morning would induce an endogenous melatonin onset delay as a treatment for SMI. The study compared the effects of double-blind administration of MT (0.3 mg.) to placebo (PB) ingested in the morning at waketime in two groups of participants experiencing SMI. Outcome measures were: 1) Phase shift in endogenous salivary MT onset time (assessed via salivary DLMO); 2) PSG measures; 3) Subjective assessments of sleepiness; and 4) An insomnia scale.

In the second study, wrist actigraphy (ACT) was recorded simultaneously with polysomnography (PSG) to obtain 51 recordings from 15 subjects. Although overall ACT correlated well with PSG, we examined and scrutinized the reliability of epoch-by-epoch comparison. The main objective of the second study was to assess the accuracy of ACT sleep recording in SMI subjects, identify discordance by epoch-by-epoch comparisons

between ACT and PSG and develop correction factors based on baseline (BL) nights of PSG recordings that can be implemented to subsequent ACT recordings to improve ACT validity.

ACKNOWLEDGEMENTS

Words can not express my gratitude for the sacrifices and contributions my family, friends, colleagues and participants have made during my academic endeavors.

I would like to thank Dr. Albala for his guidance and for the introduction to my mentor, Arthur J. Spielman. Dr. Spielman nurtured my graduate education and taught the most valuable lesson one can acquire in education; the road to achieving your goal is far more rewarding than the goal itself. His advice, guidance, and didactic insights provided me with the inspiration necessary to complete this endeavor.

Accomplishments are often accompanied by great sacrifices. My family and friends set new standards for the sacrifices they have made over the years. Thank you Mom, Dad, Mary Jo, Nonno, Ma K., Pa K., John, Jeff, Grandma and my entire family for going beyond the call of duty and helping me to attain my goals. Your unwavering support through the years provided me with the strength, confidence, and encouragement I needed to "not only try, but to do."

Kristen, you have provided me with the greatest gift of all. Your love, patience, understanding and support helped me immensely and made every moment worthwhile. I could not have done this without you and I am confident that our life together will be filled with many more wonderful accomplishments.

I would also like to express my appreciation to all of the participants for their time and dedication in making this study a success. Special thanks to my colleagues who provided me with the resources to make this study possible, including those at The New York Methodist Sleep Disorders Center, St Agnes-Our Lady of Mercy Hospital, Pfizer Inc., Pharmaceutical Discovery Corporation, New York Presbyterian Hospital and the City College Sleep Disorders Center and its research administration, led by a team second to none. Thank you Chien-Ming Yang, Andrew Tucker, Deirdre Conroy, Becky Quattrucci, Andrew Scott, Jason Birnbaum, Masanori Nagata, Boris Dubrovsky, Matt Ebben, Jude Vallone, Shiro Sherizawa, Juliana Bates, Jean Remy and Joao Nunes. Your talents, dedication and support made this study a reality.

Table of Contents

Lists of Tables

Lists of Figures

Study 1: The Effects of Exogenously Administered Melatonin (MT) in the Morning on Sleep Maintenance Insomnia (SMI)

[1,2,3]Paul D'Ambrosio, [1,2]Arthur J. Spielman, [1,2]Chien-Ming Yang, [1]Deirdre Conroy, [1]Jason Birnbaum, [1]Masanori Nagata, [1]Boris Dubrovsky, & [1,4]Joao Nunes

[1]Sleep Disorders Center, The City College of The City University of New York

[2]Sleep Disorders Center, New York Methodist Hospital, Brooklyn, NY

[3]Pfizer, NY

[4]Behavioral Medicine Department, The Sophie Davis School of Biomedical Education, The City University of New York Medical School

Subtitle: Melatonin (MT) Effects on Sleep Maintenance Insomnia (SMI)

Financial support: This research was partially supported by:

1999 - 2000 Professional Staff Congress - City University of New York (PSC - CUNY 31) Research Award Grant Number 62711-00-31;

1998 - 1999 PSC - CUNY 30 Research Award Grant Number 61628-00-30;

National Institute of Aging, #AG05732.

Corresponding author: Paul D'Ambrosio, Sleep Disorders Center,

The City College of The City University of New York,

North Academic Center, Room 8/213,

Convent Avenue at 138th Street, New York, New York 10031,

Phone: 212-733-5021; Fax: 212-573-4446.

e-mail: Paul.D'Ambrosio@Pfizer.com

***** Manuscript to be submitted to the journal *Sleep*. *****

Abstract

Study Objectives: The present study was conducted to assess the efficacy of exogenously administered daily doses of melatonin (0.3 mg.) in the morning for the treatment of sleep maintenance insomnia (SMI).

Design: A factorial design with one between group factor (melatonin (MT) vs. placebo (PB) treatments) and one repeated measure factor (baseline (BL) vs. end-of-treatment (ET) assessments) was utilized to assess the effects of MT on SMI. After a preliminary screening phase, prospective subjects were simultaneously recorded with actigraphy (ACT) and polysomnography (PSG) on two successive nights for BL assessments. At the end of one month of ingesting either 0.3 mg of MT or PB upon awakening in the morning (double-blind), subjects returned to the lab for ET assessments. ET assessments consisted of two successive nights of ACT and PSG recordings, with subjects still taking their assigned treatment. In addition, salivary dim-light melatonin onset (DLMO) and dim-light melatonin offset (DLMOff) were collected the evening prior to and the morning after BL and ET assessments. Subjective assessments (Stanford Sleepiness Scale [SSS] and an Insomnia Scale) were also collected the evening prior to and the morning after BL and ET assessments.

Setting: Standard nocturnal PSGs were recorded at either the City College of New York Sleep Disorders Center or at the subject's home using an ambulatory polygraph system.

Participants: Seventeen participants, men (n = 8) and women (n = 9) ranging in age from 38 to 82 (mean age = 59.3, $\pm$SD = 12.3), completed the study. Fourteen subjects participated in all 4 PSG recordings (2 BL and 2 ET) and three subjects were recorded 3

times (two participated in 1 BL night and 2 ET nights and one participated in 2 BL nights and 1 ET night).

Measurements and Results: ANOVAs were performed on: 1) Endogenous salivary DLMO; 2) PSG measures of sleep; 3) Subjective assessments of sleepiness; and 4) An insomnia scale.

Following treatment, there was no significant difference between the salivary DLMO in MT subjects (mean phase shift = 28.2 minute delay) and PB subjects (mean phase shift = 1.1 minute advance, $F[1,15]=.49$, $p=.49$).

While there were no differences in sleep continuity measures (total sleep time, sleep efficiency and wake time), a significant interaction was present in sleep architecture. The results indicated a decrease in REM sleep in the first third of the night in MT subjects (BL mean=18.0 minutes, ET mean=12.8 minutes), while there was an increase in REM sleep in the first third of the night in PB subjects (BL mean=12.3, ET mean=16.2, $F[1,15]=6.18$, $p<.05$) following the treatment.

A significant interaction was present on an insomnia questionnaire item in which PB subjects were "experiencing brief awakenings during the night" more often at BL (PB mean = 80.3) and less often at ET (PB mean=61.5). While the opposite was present with MT subjects (BL MT mean = 54.9, ET MT mean=65.2, $F[1,15]=5.31$, $p<.05$).

Conclusion: Exogenous MT in the morning did not produce a significant phase delay in salivary DLMO in SMI. Failure to phase shift may be in part due to introducing exogenous MT based on waketime and not DLMO time. Results do not illustrate changes in PSG sleep continuity variables in subjects who were phase advanced, however, following treatment, MT subjects redistributed REM sleep to later parts of the

night, while subjects in the PB group demonstrated more REM sleep in earlier parts of the night. Future studies will require acquiring endogenous salivary DLMO levels as a circadian rhythm marker to determine the appropriate timing of MT administration.

Key words: Sleep maintenance insomnia, circadian rhythms, dim-light melatonin onset, melatonin.

Introduction

Sleep Maintenance Insomnia (SMI), characterized by frequent and/or extended nocturnal awakenings or premature awakenings in the morning (Morin and Kwentus, 1988), is often difficult to treat. Although pharmacological and behavioral approaches (Bootzin and Perlis, 1992) can be successful in addressing this form of insomnia, safer and more convenient alternative treatment modalities are needed. It has been proposed that a phase advance in circadian rhythms may contribute to awakenings in the later part of the sleep period because the rising body temperature rhythm promotes wakefulness (Lack, 1996; Sack, 1998). This notion is supported by the findings in one study where the core body temperature of SMI patients is phase advanced compared to controls (Lack, 1996). The general approach to the treatment of circadian sleep disorders is to resynchronize the circadian pacemaker with the desired sleep/wake schedule by shifting the phase of the circadian rhythm. Phase shifts can be produced by time cues such as bright light and exogenous doses of melatonin (MT; Czeisler, 1989; Lewy, 1998; Sack, 1998). The timing of the exposure to the time cues and the size and direction of the phase shift induced in the rhythm can be plotted as a phase response curve (PRC; see Pittendrigh, 1976). In order to address the phase advance purported to be contributing to SMI, bright light exposure would need to be scheduled in the late subjective day or early subjective night (Czeisler, 1995). In a study with SMIs, Campbell et al. (1993) demonstrated that evening exposure to 2 hours of bright light increased total sleep time in elderly insomniacs. However, this demonstration study did not evaluate the continued efficacy of evening bright light. A daily 2-hour light treatment regimen is time-

consuming and inconvenient, thus, an alternative form of treatment would be more desirable.

The PRC for MT describes and shows that exogenous MT of 0.5mgs. administered at specific times of the 24 hour day is capable of shifting circadian rhythms (Lewy et al., 1992). A phase delay, in endogenous circadian rhythm, is seen if exogenous MT is ingested in the early subjective morning, no later than 5 hours after habitual wake-up time, with the optimal phase delay occurring if MT is ingested just after sleep offset. This time of day corresponds to 07:00 (Lewy, 1998). The demonstrated phase delay shift provides the rationale for MT ingestion in the morning to treat SMI in the present proposal, since SMI is hypothesized to be characterized by an advance in endogenous circadian rhythm (Lacks et al., 1996). The present study assumes that in general, patients with SMI have an endogenous circadian phase that is advanced with respect to their habitual bedtime. The study aims to produce a phase delay in the sleep/wake cycle by the administration of MT in the morning in order to reset the phase relationship between their endogenous circadian rhythm and habitual bedtime. The resetting of the sleep/wake phase relationship is expected to produce important objective and subjective improvements in SMI.

Available over the counter as a sleeping aid, MT has shown promise for several types of sleep disturbances, including insomnia. It has been used in doses (0.1 to 0.3 mg.) that produce blood levels in the physiological range and doses (1 to 10 mg. and higher) that produce super physiological levels (Lewy et al., 1992). Evening administration of MT to patients with delayed sleep phase syndrome advanced sleep onset and wake times towards conventional times (Dahlitz, 1991). Other findings suggest

that MT has considerable therapeutic potential in many situations of disturbances of circadian rhythms such as jet lag, shift work, insomnia, blindness, and replacement therapy in the elderly (Cupp, 1997). Unlike benzodiazepines, which can become less effective as tolerance develops, MT does not lose its effectiveness over time (Reiter, 1995). In fact, MT can become a more effective treatment with chronic use. Haimov et al. (1995) gave 26 elderly insomniacs, 2 mg. doses of MT, for a 2-month period. At the end of the treatment, participants fell asleep at their desired time even more so than they did after one week of treatment. In addition, MT has a minute number of the negative side effects associated with traditional sleep medications such as benzodiazepines and anti-histamines (Reiter, 1995). These results are very appealing in treating the elderly, since their insomnia is often chronic.

Various experiments have been conducted to assess MT's safety profile on body temperature, sleepiness, mood and performance (Anton-Tay et al., 1971; Cramer et al., 1974; Lieberman et al., 1984; Deacon, 1994; Hughes et al., 1994). Exogenously administered MT doses that produce physiological levels of MT, have minimal effects on body temperature and behavior (e.g. sleepiness, mood, performance etc.; Van den Heuvel et al., 1998), while exogenously administered MT doses well above physiological levels have clinically significant effects on body temperature and behavior (Van den Heuvel et al., 1998; Dollins, 1993). Pharmacokinetic data indicate that a single near physiological dose of MT (0.5 mg.) has a half-life between 30 and 45 minutes, and is completely eliminated from circulation within 5 hours (Lewy et al., 1992; Sack, 1998).

The goal of the study was to assess whether exogenously administered daily physiological doses (0.3 mg.) of MT in the morning would induce an endogenous

melatonin onset delay as a treatment for SMI. The study compared the effects of double-blind administration of MT (0.3 mg.) to placebo (PB) ingested in the morning at waketime in two groups of participants experiencing SMI. Salivary dim-light MT onset (DLMO) was measured to assess the phase shift in endogenous MT onset time. PSG recordings and subjective ratings for sleepiness and insomnia symptoms were also conducted to evaluate the treatment effects.

Methods

Participants

Twenty-one sleep maintenance insomniacs were recruited from the 5 Boroughs of New York by flyers and public announcements. Four subjects either discontinued or were excluded during the study, thus, 17 subjects completed the study. They included men (n = 8) and women (n = 9) ranging in age from 38 to 82 (overall mean age = 59.3, [$\pm$SD] = $\pm$12.3; MT mean age=57.7$\pm$12.3; PB mean age=61.1$\pm$14.2, t=-.54, p=.60). They were screened and cleared of all other major sleep, medical, neurologic, and psychiatric disorders. Female subjects with a history of clinically significant premenstrual syndrome were excluded since the endogenous MT rhythm has been shown to vary at different stages of the menstrual cycle (McIntyre, 1987). The following inclusion criteria were met: Subjects were at least 35 years old with cognitive functioning indicated by a score $\geq$ 23 on the Mini-Mental State Examination; subjects had an insomnia complaint of $\geq$ 1 year, wake after sleep onset longer than 30 minutes at least three nights per week; non-shift worker and no travel across time zones during the study or during the month prior to the study; not currently pregnant and willing to avoid getting pregnant during the study; not currently using psychotropic or hypnotic medications and willing to refrain from

using these medications during the course of the study; limit caffeine consumption to one or less coffee serving or equivalent per day before noon; limit alcohol intake to 7 drinks per week and ≤ 2 drinks on any one night; and no napping. If a subject did not meet the final 3 inclusion criteria, they were given the opportunity to comply with these specific restrictions and were re-evaluated three weeks later. Prospective subjects were contacted by phone, prior to the first laboratory appointment, to assure that all criteria were met. The experimental protocol was approved by the Institutional Review Board at the City College of New York and by the Institutional Review Board at New York Methodist Hospital. Informed consent was obtained from each subject, and all written documentation was retained.

Procedure

Pre-Experimental Weeks

The study consisted of 3 pre-experimental weeks and 4 experimental weeks. During the pre-experimental weeks, subjects wore an ACT and filled out sleep logs to assist in confirming reported bedtime and waketime (time they woke up in the morning). They came to the lab once a week for a briefing about the study and to have their sleep/wake schedules, as depicted on the sleep logs, examined. A sleep/wake schedule was designated for each subject according to his or her reported habitual bedtime and waketime. Subjects were allowed to determine their own bedtime and waketime with the understanding that these times were going to be consistent throughout the study. During the 3 pre-experimental weeks, subjects slept at home and followed the designated sleep/wake schedule in an effort to stabilize their sleep/wake rhythm. If they could not abide by their bedtime and waketime, they were instructed to document the deviations on

the sleep log. Throughout the study, subjects were required to keep a daily sleep log, wear their ACT and to continue to abide by all inclusion criteria. Subjects with bedtime or waketime deviations greater than one hour, more than once a week, were not included in the study.

Experimental Weeks

Subjects first came to the lab for a screening PSG to rule out primary sleep pathologies. All subjects arrived at the lab 5 hours prior to habitual bedtime and were kept awake one and one-half hours past their habitual bedtime. Four individuals were excluded from the study since their screening PSGs showed excess amounts of periodic limb movements with arousals of > 15/hour and/or sleep disordered breathing with an apnea plus hypopnea index of > 15/hour. Eligible subjects returned to the lab approximately 5 days later for 2 baseline (BL) PSG assessments. After the 2 BL PSGs, subjects were randomly assigned to either a MT group or a PB group. The MT pill contained 0.3 mg of MT with lactose filler. The PB pill contained lactose only. The first dose of the treatment (either MT or PB) was ingested following BL assessments.

For the next month subjects ingested either 0.3 mg of MT or PB, double-blind, at their designated dose-time and were instructed to avoid bright light for at least two hours after MT or PB ingestion. Dose-time was defined as a time no earlier than their scheduled waketime, or up to one hour after their scheduled waketime if the subject slept late. If a subject woke up more than 1 hour after the scheduled waketime, he/she was instructed not to take a pill that day. This flexible designated dose-time was designed to allow participants to sleep late, which is a sign of improved sleep function. In addition, the criteria is a conservative constraint since the human MT Phase Response Curve

(PRC) has phase-delay capability during the subjective early morning hours (between 4 hours prior to habitual waketime and 5 hours after habitual waketime; Lewy et al., 1992).

Two end of treatment (ET) PSG assessments were collected approximately four weeks after BL assessments. During BL and ET assessments, subjects arrived at the lab 2 hours prior to their habitual bedtime and went to bed at their habitual bedtime. All subjects left two hours after their habitual waketime. Wrist ACT was recorded simultaneously with PSG for all the experimental nights. In addition, the Stanford Sleepiness Scale (SSS) was collected the evening prior and morning after BL and ET assessments while one insomnia scale was completed at BL and one completed at ET (see Figure 1). Following the study, all participants who still complained of SMI, were offered one month of free MT treatment.

Measurements

Salivary Dim-Light MT Onset (DLMO). The salivary DLMO test was conducted to determine endogenous MT phase position. Saliva was collected the evening prior to the screening PSG and the evening after ET PSG assessments. Subjects arrived at the sleep lab, which was illuminated at 50 lux or less, about five hours before their regular bedtime. They remained awake and inclined in order to avoid the effect of changing posture on MT level (McIntyre, 1987). They rinsed their mouths out with water ten minutes prior to the collection of the saliva samples and provided saliva (2 ml.) into a disposable plastic tube every 30 minutes starting from four and one-half hours prior to the participants' habitual bedtime and ending at one and one-half hours past their habitual bedtime. Saliva samples were centrifuged, stored at -20° C and later delivered to New York Presbyterian Hospital, Westchester Division, Biochemical Lab (White Plains, New

York) where all radioimmunoassays were performed following the procedures provided by American Laboratory Products Co. (Windham, NH). Samples were analyzed in duplicate. The amount of MT contained in each sample was measured by the Buhlmann Direct Saliva MT radioimmunoassay (RIA) kit which measures MT by a double-antibody RIA based on the Kennaway G280 anti-MT antibody (Vaughan, 1993). Undiluted human saliva samples and reconstituted standards and controls were incubated with the anti-MT antibody and ^{125}I-MT. ^{125}I-MT competes with MT present in samples, standards, and controls. After 20 hours of incubation, solid-phase second antibody was added in the mixture in order to precipitate the antibody bound fraction. After aspiration of the unbound fraction, the antibody bound fraction of ^{125}I-MT is counted.

Salivary DLMO was calculated as the first interpolated point above 4.0 pg/ml of MT that continued above the threshold level in later samples. The threshold criterion has been validated in previous studies (Carskadon, 1996a; Carskadon, 1996b).

Nocturnal Polysomnogram (PSG). The screening PSG was conducted on subjects at the City College Sleep Disorders Center (CCNY - SDC). The standard recording montage is as follows: four EEG channels (C3/C4 and O1/O2, ref 10-20), two horizontal eye movement channels (left and right outer canthus), and one bipolar chin muscle channel. EEG and eye movement placements were referenced to linked mastoids (A1 + A2). In addition to the standard electrode recording montage, there were sensors to measure respiratory effort (thoraco-abdominal strain gauges), respiratory airflow (nasal and oral thermistors) and oxygen saturation of the blood (finger pulse oximeter, [Ohmeda Co.]). In addition, bipolar electrodes were applied on the skin above the middle of the anterior tibialis muscle to record periodic limb movements. All electrophysiological

parameters were recorded using silver chloride disk electrodes filled with electrode gel or cream and affixed to the skin with either tape or cream-soaked gauze utilized in EEG placement. The international ten - twenty system was utilized for EEG electrode placement.

The BL and ET standard montage PSG recordings were collected at either the City College Sleep Disorders Center or at the participant's home on an ambulatory sleep-data acquisition computer system (H20 [Home-to-Office], Telefactor). If a subject chose to be studied at home, a technician went to the subject's home, prepared the subject, activated the ambulatory computer system, left the home and returned the following morning to retrieve the data. Subjects who chose to have recordings at the City College Sleep Disorders Center, slept in a sound attenuated room and PSG data was obtained (Model 7D, Grass Co.). PSGs were scored according to standard criteria of Rechtschaffen and Kales (1968). All subjects completed their screening PSG at the CCNY-SDC (total number of screening PSGs=17). Twelve subjects completed both BL and both ET assessments at the CCNY-SDC. Two BL PSGs were unscoreable due to technical difficulties (total number of CCNY-SDC PSGs=46). Four subjects completed both BL and both ET assessments via the ambulatory system. One ET PSG was unscoreable due to technical difficulties (total number of H2O PSGs=15). One subject completed both BL assessments via the ambulatory system and both ET assessments at the CCNY-SDC (number of PSGs=4).

Subjective Rating Scales. The Stanford Sleepiness Scale (SSS; Hoddes, 1973) is a 7-point subjective rating scale where each increment on the scale describes an increasing level of sleepiness (see Appendix 1). The SSS was collected every 30 minutes

the evening prior to and morning after BL and ET assessments. A modified procedure, which required subjects to sit quietly in a dark room with their eyes closed for one minute before each SSS rating, was implemented to eliminate the masking effects of behavioral arousal on subjective sleepiness. In addition to the SSS, subjects completed one modified insomnia scale (Spielman et al., 1987) at BL and one modified insomnia scale at ET. The insomnia scale (see Appendix 2) required subjects to rate their sleeping difficulties on 11 insomnia-related descriptions by placing a vertical mark along a 100 mm. horizontal line with the extreme left and right poles labeled "very little" and "very much", respectively.

Results

The mean (SD) "lights out" time for all PSGs was at 22:43 (+ 43.0 min.) for MT subjects and 23:06 (+ 39.0 min.) for PB subjects. The mean "lights on" time for all PSGs was 05:57 (+ 58.0 min.) for MT subjects and 06:38 (+ 64.0 min.) for PB subjects. In addition, the mean pill ingestion time, at ET assessments, was 06:11 (+ 62.0 min.) for MT subjects and 06:50 (+ 65.0 min.) for PB subjects. There were no significant differences in "lights out", "lights on" or pill "ingestion time" between the MT group and the PB group.

At BL, the mean (SD) salivary DLMO was at 21:55 (+ 83.0 min) for MT subjects, 48 minutes prior to mean habitual bedtime, and 21:34 (+ 126 min) for PB subjects, 92 minutes prior to mean habitual bedtime. At ET, salivary DLMO was at 22:23 (+ 101.0 min) for MT subjects, 20 (+ 96.3) minutes prior to mean habitual bedtime, and 21:32 (+ 84 min.) for PB subjects, 94 minutes prior to mean habitual bedtime. From BL to ET, MT subjects had a mean 28.2 minute salivary DLMO delay, while PB subjects had a mean 1.1 minute salivary DLMO advance.

Salivary DLMO

Table 1 illustrates the mean (±SD) salivary DLMO prior to treatment, following treatment and its respective phase shift. From BL to ET, the MT subjects had a mean 28.2 minute salivary DLMO delay, while the PB subjects had a mean 1.1 minute salivary DLMO advance. A 2 (Group: MT vs. PB) x 2 (Session: BL vs. ET) repeated measure ANOVA revealed neither main effects (Group: $F[1, 15]=2.38$, $p=.14$; Session: $F[1,15]=.42$, $p=.53$) nor interaction ($F[1,15]=.49$, $p=.49$).

The curves for BL and ET salivary MT levels are presented in Figure 2 and 3 for MT and PB subjects, respectively. Two MT subjects at BL, 4 MT subjects at ET, 2 PB subjects at BL and 1 PB subjects at ET never achieved the recognized DLMO threshold (4.0 pg/ml, Carskadon, 1996a; Carskadon, 1996b), therefore, their DLMO was identified as their last sample time collected at 0.5 hours past their habitual bedtime. In addition, 1 MT subject at ET and 1 PB subject at BL were above the recognized DLMO threshold beginning with their first sample collected at 4 hours before habitual bedtime, therefore, their DLMO was identified as their first sample time. Figure 4 presents salivary DLMO times for MT and PB subjects at BL and ET.

Since no significant difference in phase shift was present when comparing groups (MT vs. PB), a post-hoc analysis was conducted to determine if a specific ingestion time for MT could produce and optimize a phase shift. The MT and PB salivary DLMO phase changes from BL to ET, in relation to the timing of treatment administration, are presented in Figure 5. Six out of 7 subjects ingesting their respective pill less than 8.5 hours after salivary DLMO induced a phase advance, while 8 out of 10 subjects ingesting their respective pill greater than 8.5 hours after salivary DLMO induced a phase delay. A

2 (Ingestion time: less than 8.5 hrs. after salivary DLMO vs. greater than 8.5 hrs. after salivary DLMO) x 2 (Session: BL vs. ET) repeated measure ANOVA revealed an ingestion time main effect ($F[1,15]=5.37$, $p<.05$) and an interaction between ingestion time and session ($F[1,7]=14.08$, $p<.05$). A post-hoc t-test analysis with Bonferonni correction showed that, after treatment, no significant shift in salivary DLMO was present in subjects who ingested their respective pill less than 8.5 hrs. after salivary DLMO ($t[7]=2.04$, $p=.09$). However, a significant delay in salivary DLMO was present in subjects who ingested their respective pill greater than 8.5 hrs. after salivary DLMO ($t[10]=-3.42$, $p<.025$). The pattern occurred in both MT and PB group.

Polysomnography

PSG sleep variables were analyzed with 2 (Group: MT vs. PB) x 2 (Session: BL vs. ET) repeated measure ANOVAs and post-hoc analyses performed were t-tests with a Bonferonni correction. Comparing the MT group (n=9) with the PB group (n=8), there were group main effects in mean percent of slow wave sleep (SWS) (mean MT=6.6 [$\pm$7.9] vs. PB=16.6 [$\pm$9.5], $F[1,15]=6.96$, $p<.05$), SWS latency (mean MT=33.3 [$\pm$24.1] minutes vs. PB=14.1 [$\pm$8.9] minutes, $F[1,15]=8.08$, $p<.05$) and SWS present during the second-third of the night (mean MT=5.6 [$\pm$7.4] minutes vs. PB=15.5 [$\pm$10.7] minutes, $F[1,15]=7.37$, $p<.05$). All other comparisons were not significant.

One significant interaction, REM sleep during the first third of the night, was present ($F[1, 15]=6.18$, $p<.05$). Prior to treatment, the mean REM sleep during the first third of the night was 17.9 ($\pm$13.9) minutes for MT subjects and 12.3 ($\pm$8.0) minutes for

PB subjects. Following treatment, the mean REM sleep during the first third of the night was 12.8 (±9.8) minutes for MT subjects and 16.2 (±9.9) minutes for PB subjects.

Interaction effects for mean percent of stage 3 sleep ($F[1,15]=3.25$, $p=.09$) and REM sleep present during the third-third of the night ($F[1,15]=4.02$, $p=.06$) approached significance. Prior to treatment, the mean percent of stage 3 sleep was 4.3 (±4.1) for MT subjects and 9.3 (±5.2) for PB subjects. Following treatment, the mean percent of stage 3 sleep was 5.9 (±5.5) for MT subjects and 7.7 (±3.0) for PB subjects.

Prior to treatment, the mean REM sleep in the third-third of the night was 30.8 (±13.2) minutes for MT subjects and 31.7 (±9.9) minutes for PB subjects. Following treatment, the mean REM sleep in the third-third of the night was 34.9 (±17.2) minutes for MT subjects and 24.5 (±10.3) minutes for PB subjects. Post-hoc analysis showed no significant difference in MT subjects ($t[9]=-0.82$, $p=.43$), however, a significant decrease was revealed in PB subjects ($t[8]=3.62$, $p<.025$). The means and standard deviations are provided in Appendix 3. REM distribution during the night of MT (n=9) and PB (n=8) subjects is presented in Figure 6.

One of our hypotheses suggests that a circadian phase delay would improve PSG variables in SMI. Two (Salivary DLMO: advance vs. delay) x 2 (Session: BL vs. ET) repeated measure ANOVAs were performed to compare PSG variables between subjects with a phase advance (n=8) and subjects with a phase delay (n=9), irrespective of their treatment. All post-hoc analyses performed were t-tests with a Bonferonni correction. No main effects were present, however, significant interactions occurred in percent of

REM sleep ($F[1,15]=5.96$, $p<.05$), SWS latency ($F[1,15]=5.00$, $p<.05$) and SWS present in the second-third of the night ($F[1,15]=5.30$, $p<.05$).

Prior to treatment, the mean percent of REM sleep was 24.2 (±11.1) in advance subjects and 16.6 (±4.0) in delay subjects. Following treatment, the mean percent of REM sleep was 17.8 (±3.7) in advance subjects and 19.3 (±4.9) in delay subjects.

Prior to treatment, the mean SWS latency was 21.4 (±14.1) minutes in advance subjects and 26.2 (±27.8) minutes in delay subjects. Following treatment, the mean SWS latency was in 34.8 (±24.6) minutes in advance subjects and 15.5 (±7.3) minutes in delay subjects.

Finally, prior to treatment, the mean SWS in the second-third of the night was 4.9 (±5.9) minutes in advance subjects and 14.8 (±12.2) minutes in delay subjects. Following treatment, the mean SWS in the second-third of the night was 10.6 (±9.8) minutes in advance subjects and 10.2 (±10.4) minutes in delay subjects. Post-hoc analyses showed a significant increase in advance subjects ($t[8]=-3.21$, $p<.025$), but no significant difference in delay subjects ($t[9]=1.17$, $p=.28$). The means and standard deviations are provided in Appendix 4. SWS distribution during the night of advance (n=8) and delay subjects (n=9) is presented Figure 7.

Subjective Ratings: Stanford Sleepiness Scale (SSS) and insomnia scale

A 2 (Group: MT vs. PB) x 2 (Session: BL vs. ET) x 10 (Evening time: every 30 minutes starting at bedtime – 4.0 hrs. until bedtime + 0.5 hrs. or Morning time: every 30 minutes starting at waketime and ending at waketime + 4.5 hrs.) repeated measure ANOVA was performed on the SSS ratings.

The results for evening SSS assessments revealed a significant session main effect (mean BL=4.0 vs. ET=3.0, $F[1,12]=8.91$, $p<.05$) suggesting a decrease in sleepiness levels from BL to ET assessments. A significant time main effect ($F[9,108]=21.80$, $p<.05$) was also present. Results of a Scheffé post-hoc analysis indicated that subjects rated themselves significantly sleepier 1.5 hours before habitual bedtime compared to some of the previous ratings. The increased levels of "sleepiness" continued until 0.5 hours past their habitual bedtime, which is when subjects retired for the evening. No significant interaction ($F[9,108]=0.98$, $p=.46$) was present. Mean evening SSS rating ratings are presented in Figure 8.

The results for morning SSS assessments revealed a significant time main effect ($F[9,108]=7.12$, $p<.05$), however, no significant interaction ($F[9,108]=0.12$, $p=.99$) was present. Results of a Scheffé post-hoc analysis revealed that subjects rated themselves significantly less sleepy 1.0 hour after waketime. The decreased levels of sleepiness continued until 4.5 hours after waketime, which is when subjects left the lab. Mean morning SSS ratings are provided in Figure 9.

A 2 (Group: MT vs. PB) x 2 (Session: BL vs. ET) repeated measure ANOVA was performed on the insomnia questionnaire. Significant group main effects were present on questions 8 (mean MT=22.1 [$\pm$22.8] vs. PB=45.9 [$\pm$27.5], $F[1,15]=4.84$, $p<.05$) and 9 (mean MT=26.7 [$\pm$22.9] vs. PB=61.8 [$\pm$22.5], $F[1,15]=20.47$, $p<.05$) suggesting that subjects in the PB group were significantly sleepier than subjects in the MT group. Significant session main effects were present on questions 3 (mean BL=43.7 [$\pm$36.2] vs. ET=28.9 [$\pm$27.3], $F[1,15]=7.34$, $p<.05$), 6 (mean BL=53.6 [$\pm$31.4] vs. ET=33.7 [$\pm$32.3]

F[1,15]=5.54, p<.05) and 11 (mean BL=29.1 [±28.1] vs. ET mean=45.1 [±30.5], F[1,15]= 4.58, p<.05) suggesting an increase in the ability to sleep from BL to ET assessments.

One significant interaction was present on question 5 (F[1,15]=5.31, p<.05). Prior to treatment, more "brief awakenings during the night" were experienced by PB subjects (mean=80.3 [±24.2]) than by MT subjects (mean=54.9 [±27.8]). Following treatment, fewer "brief awakenings during the night" were experienced by PB subjects (mean=61.5 [±28.6]) than by MT subjects (mean=65.2 [±27.1]). The means and standard deviations for all insomnia questions are provided in Appendix 2.

Discussion

The chronobiotic phase shifting potential of exogenously administered MT was not convincingly demonstrated in the current study with clinical subjects. Although the mean salivary DLMO in the MT group showed a mild delay, the mean salivary DLMO in PB group remained essentially the same after treatment. However, these changes were not statistically significant and may be confounded due to inherent variability in sleep/wake endogenous cycles. The mild delay, following MT treatment, in circadian rhythmicity, accompanies the circadian characteristics of REM sleep. MT subjects redistributed REM sleep to later parts of the night, while PB subjects demonstrated more REM sleep in earlier parts of the night. The increase of REM sleep during the first third of the night and decrease during the last third of the night suggest that MT subjects redistributed REM sleep to later parts of the night, while PB subjects demonstrated more REM sleep in earlier parts of the night.

The salivary DLMO findings also purport that regardless of what treatment group subjects were in, ingesting their respective pill less than 8.5 hours after salivary DLMO

induced a phase advance, while ingesting their respective pill greater than 8.5 hours after salivary DLMO induced a phase delay. This implies that individuals with a late salivary DLMO gravitate towards a phase advance, while individuals with an early salivary DLMO tend to gravitate towards a delay in phase.

There are a number of possible explanations for the failure to produce a significant phase delay. Although ingestion time was assigned to take place at waketime, in retrospect, the time appears to be arbitrary. We recommend that it is imperative to determine the position of an individual's salivary DLMO prior to MT administration in order to promote appropriate phase changing treatment. A more appropriate dose time could be identified if the salivary DLMO, an accurate circadian marker, was assessed and determined prior to determining precise MT delivery. Of course, the dose time should continue to comply with the recognized PRC to MT (Lewy, 1998). One may also question the MT dosage (0.3mgs) and duration of MT delivery (approximately 3 weeks) as possible explanations for failure to produce a phase delay in salivary DLMO. Lewy's (1998) PRC to MT study provided empirical findings suggesting that 4 successive days of a physiological dose (0.5mg) induced a significant phase delay in salivary DLMO, therefore, the study's slightly lower physiological dose may not have been sufficient in creating the desired circadian phase delay. One may also consider the ongoing change in endogenous MT phase, overlapping with the duration of MT delivery, as an explanation that may have vitiated the phase shifting effects of MT. Finally, as with most studies, uncontrollable aspects, such as evening and morning light exposure and variability in subjects (e.g. age and lifestyles) as possible explanations for failure to produce a phase delay in salivary DLMO.

It has been suggested (Campbell et al., 1993) that inducing a circadian phase delay would improve SMI. Unlike findings in previous SMI studies (Campbell, 1993; Hughes, 1998), the present results do not illustrate changes in PSG sleep continuity variables, although, significant changes in sleep architecture occurred. As indicated earlier, one significant interaction, increased REM sleep during the first third of the night, was present in the MT group compared to the PB group. Prior to treatment, mean amount of REM sleep during the first third of the night was greater in MT subjects and less in PB subjects. Following treatment, mean amount of REM sleep during the first third of the night was less in MT subjects and greater in PB subjects. Thus, it is unclear whether the MT treatment or baseline difference in the amount of REM sleep between groups was responsible for the significant difference.

There are a number of possible explanations for the limited significant effects in objective PSG findings and subjective scale assessments. Considering the small sample size of the study, random group assignment may not have been appropriate. Rather, a future study, utilizing a similar sample size, may choose to match subjects for each group (e.g. age, gender, similar concomitant complaints). In addition, unlike Campbell (1993), who chose to include a specific sub-group of insomniacs (those that met the International Classification of Sleep Disorders (ICSD) diagnostic criteria for advanced sleep phase syndrome (ASPS) – intrinsic type), our study included all subjects who complained of experiencing wake after sleep onset longer than 30 minutes at least three nights per week. Unfortunately, our subject selection included a heterogeneous group in terms of endogenous circadian rhythms (subjects with advances, delays and normal endogenous circadian rhythms) which may not have been appropriate for assessing changes in

endogenous circadian rhythms. The subject selection should have been more selective. Only subjects who meet the ICSD criteria for ASPS (inability to stay awake until the desired bedtime or inability to remain asleep until desired waketime) should have been identified and included. This would have targeted a homogeneous subject sample at baseline, thus, providing a more appropriate deduction whether exogenously administered daily physiological doses of MT in the morning could induce a significant endogenous MT onset delay. In addition, a homogenous subject sample would also provide a better evaluation of treatment effect on PSG recordings and subjective ratings for sleepiness and insomnia symptoms. Future studies may choose to identify ASPS subjects via salivary DLMO. In conclusion, our study does not support the hypothesis that morning administration of MT would be an effective treatment in SMI. Suggestions for future studies assessing MT in SMI include determining salivary DLMO phase prior to treatment, conducting a mid-study salivary DLMO phase check and controlling for subject and environmental variability.

Acknowledgements: We would like to thank, Professor Keith Parrot, Pharm.D., College of Pharmacy (Oregon State University, Corvalis, Oregon) for preparing all of the double-blind pills.

Table 1

Salivary DLMO in relation to bedtime.

Group	Baseline (+SD)	End of Treatment (+SD)	Phase Shift (+SD)
Overall			
MT (n=9)	-48.0 (84.5) min.	-20.0 (96.3) min.	+28.0 min.
PB (n=8)	-92.0 (123.2) min.	-93.0 (70.5) min.	-1.0 min.
Pill administered < 8.5 hrs. after salivary DLMO			
MT (n=5)	+10.1 (62.1) min.	-21.6 (91.7) min.	-31.7 min.
PB (n=2)	+65.8 (34.2) min.	-43.4 (59.2) min.	-109.2 min.
Pill administered > 8.5 hrs. after salivary DLMO			
MT (n=4)	-97.5 (73.1) min.	+5.4 (113.9) min.	+102.9 min. *
PB (n=6)	-137.8 (92.5) min.	-102.9 (72.1) min.	+34.9 min. *

(*=significant phase shift, $p < .025$)

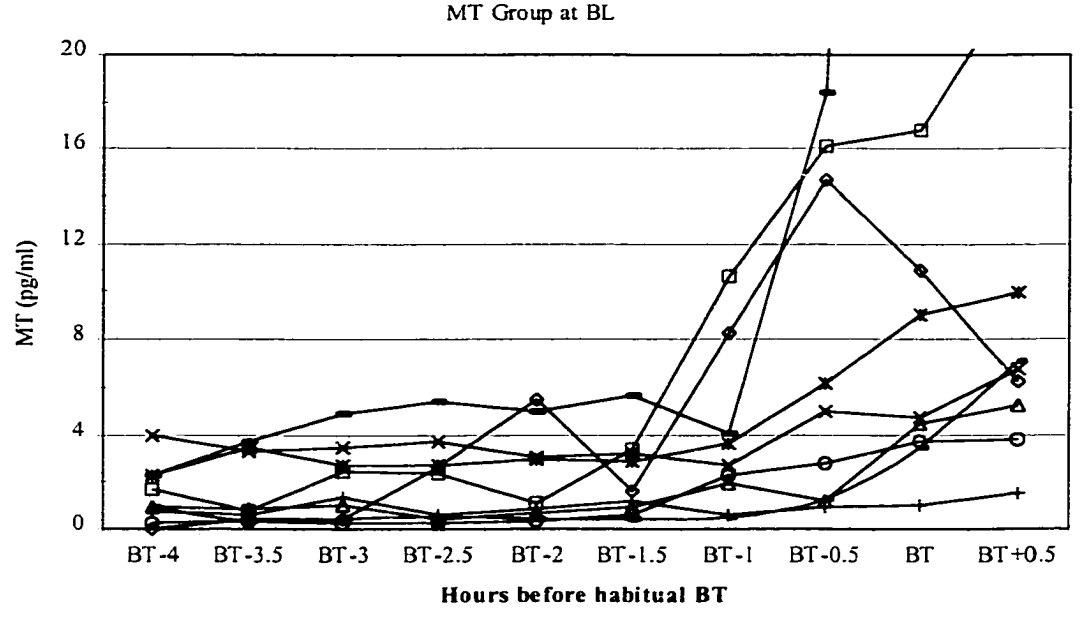
Figure 1

Schedule of assessments

Assessment	Pre-Experimental	Day 1	Day 2	Day 3 to 25	Day 26	Day 27	Day 28
Actigraphy and Sleep Logs	X	X	X	X	X	X	X
Pill Ingestion				X	X	X	
Baseline DLMO	X						
Baseline: PSG, SSS and Insomnia Scale (IS)		X	X				
End of Treatment: PSG, SSS and IS					X	X	
End of treatment DLMO							X

Figure 2

A. BL salivary MT levels for MT subjects in relation to bedtime (BT). Samples are plotted every 30 minutes beginning with 4.0 hours before habitual BT and ending 0.5 hrs after habitual BT



B. ET salivary MT levels for MT subjects in relation to bedtime (BT). Samples are plotted every 30 minutes beginning with 4.0 hours before habitual BT and ending 0.5 hrs after habitual BT

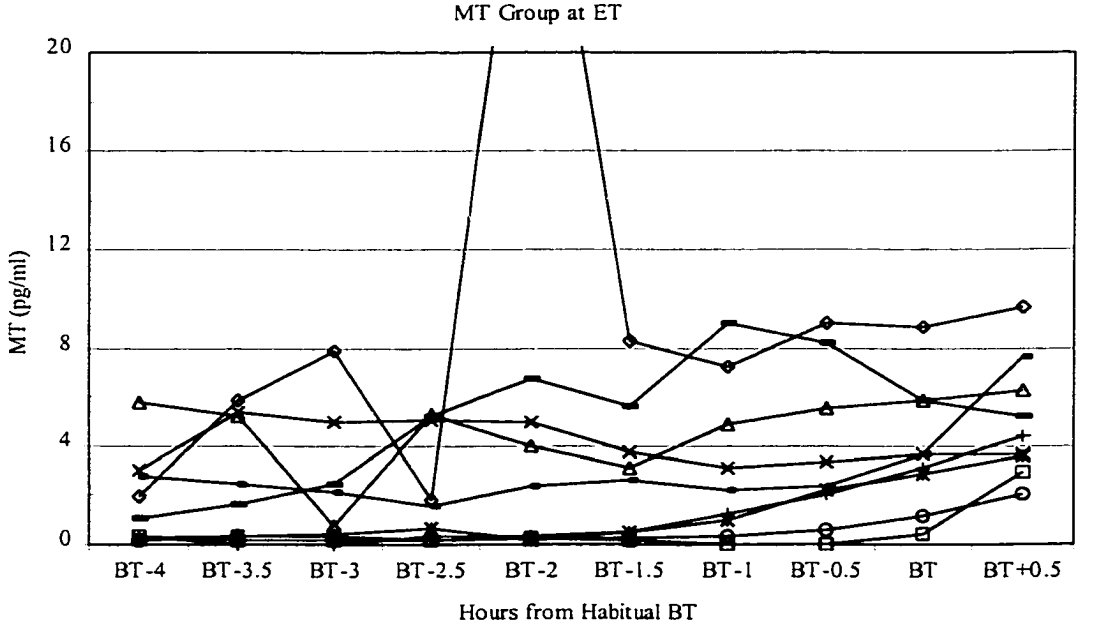
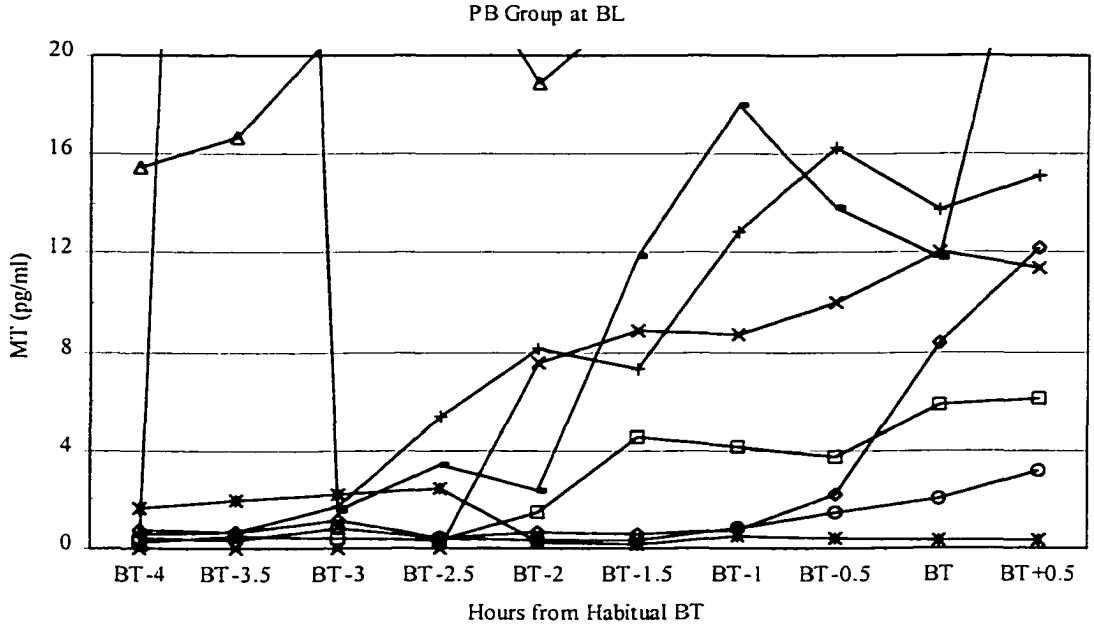


Figure 3

A. BL salivary MT levels for PB subjects in relation to bedtime (BT). Samples are plotted every 30 minutes beginning with 4.0 hours before habitual BT and ending 0.5 hrs after habitual BT



B. ET salivary MT levels for PB subjects in relation to bedtime (BT). Samples are plotted every 30 minutes beginning with 4.0 hours before habitual BT and ending 0.5 hrs after habitual BT

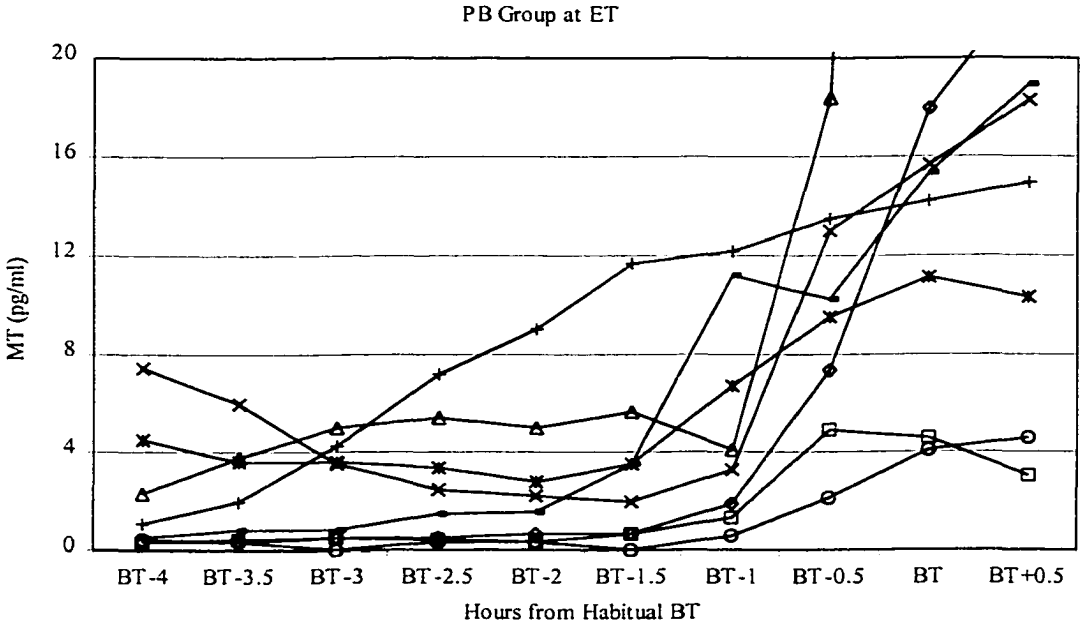
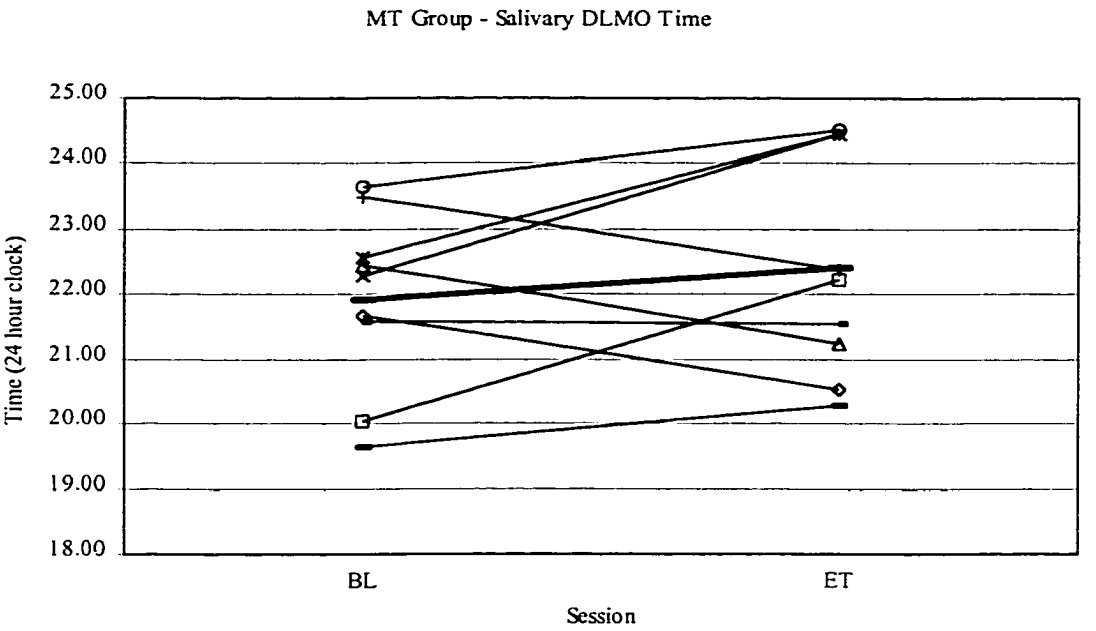


Figure 4

A. Salivary DLMO time for MT subjects at BL and ET with the mean represented by the dark line



B. Salivary DLMO time for PB subjects at BL and ET with the mean represented by the dark line

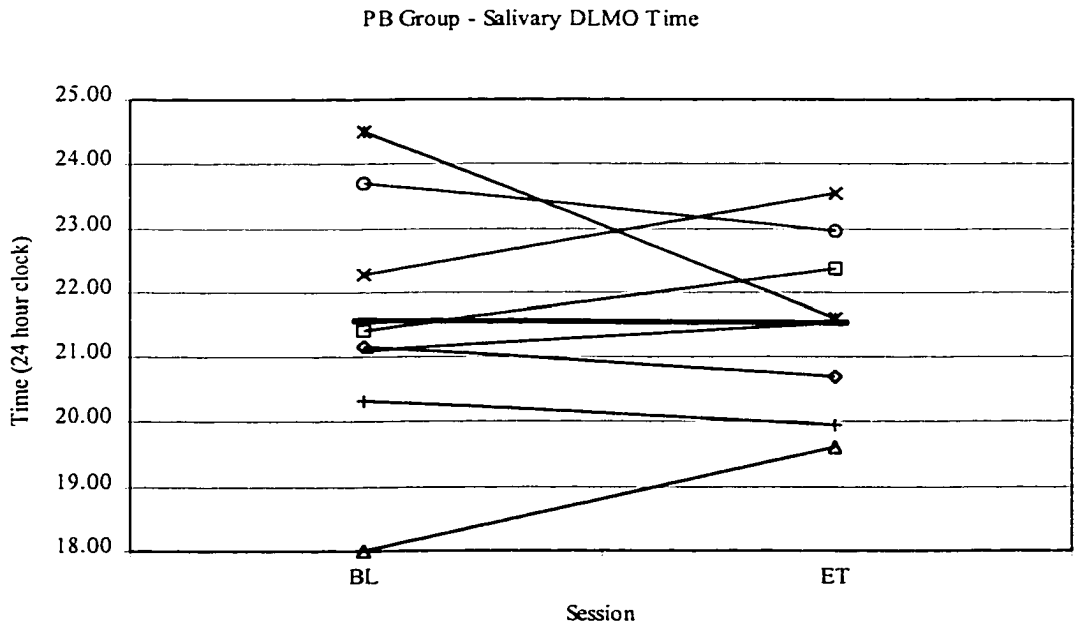
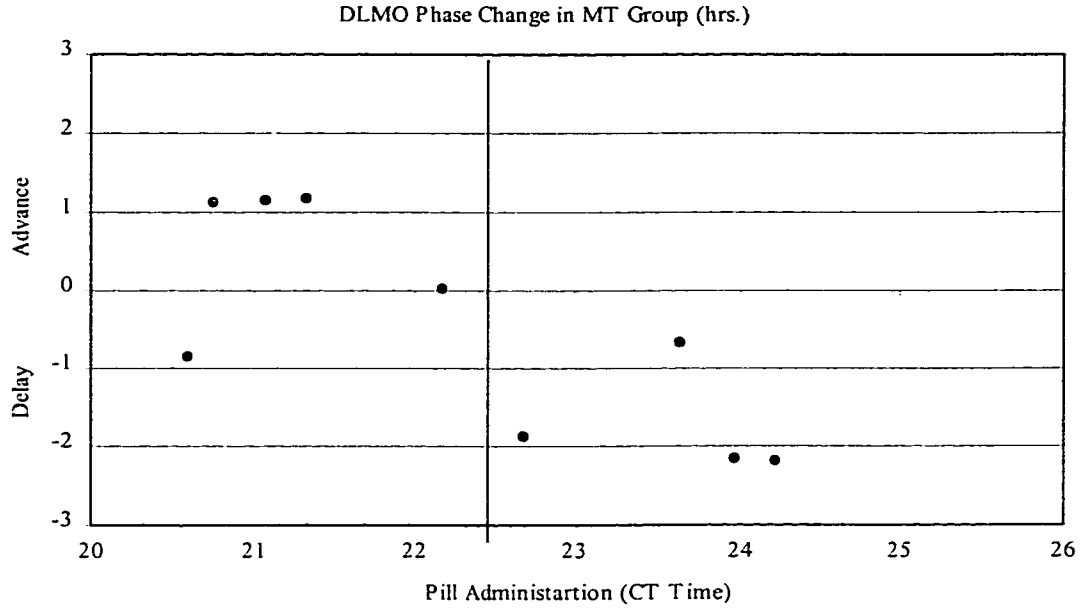


Figure 5

A. Salivary DLMO phase change in MT Group at ET. Samples are plotted at time of pill administration in reference to DLMO time (~CT 14:00)



B. Salivary DLMO phase change in PB Group at ET. Samples are plotted at time of pill administration in reference to DLMO time (~CT 14:00)

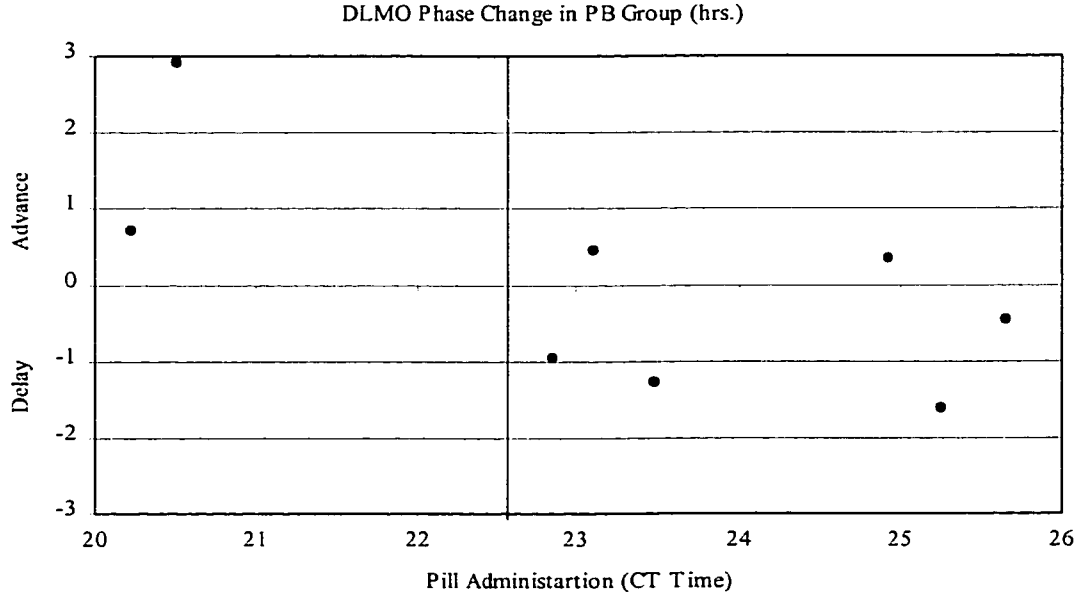
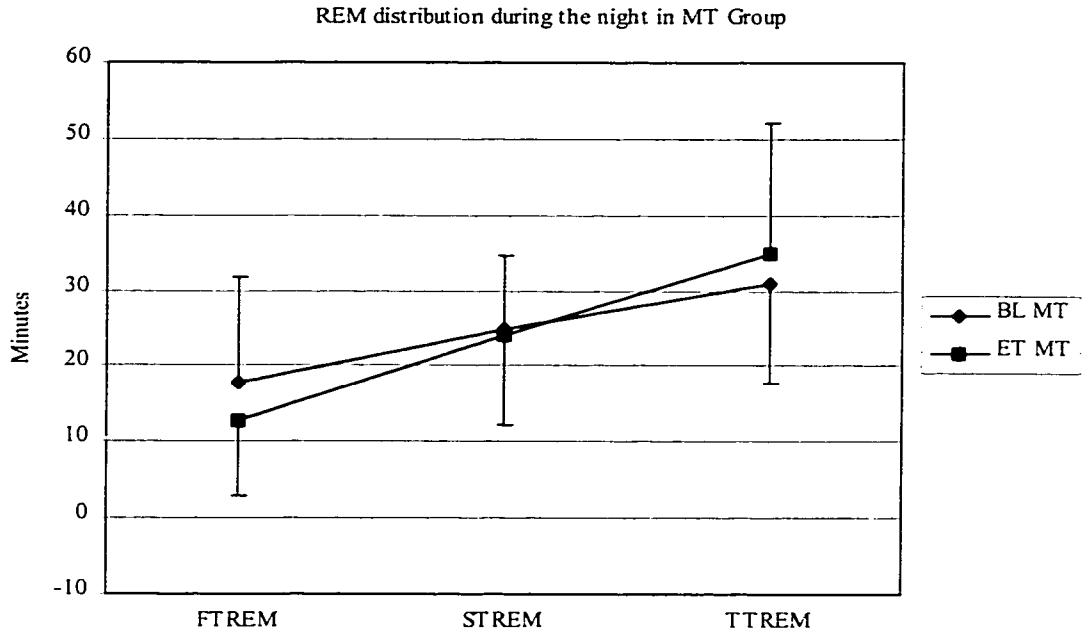


Figure 6

A. REM distribution (minutes) during the night in MT subjects (n=9)



B. REM distribution (minutes) during the night in PB subjects (n=8)

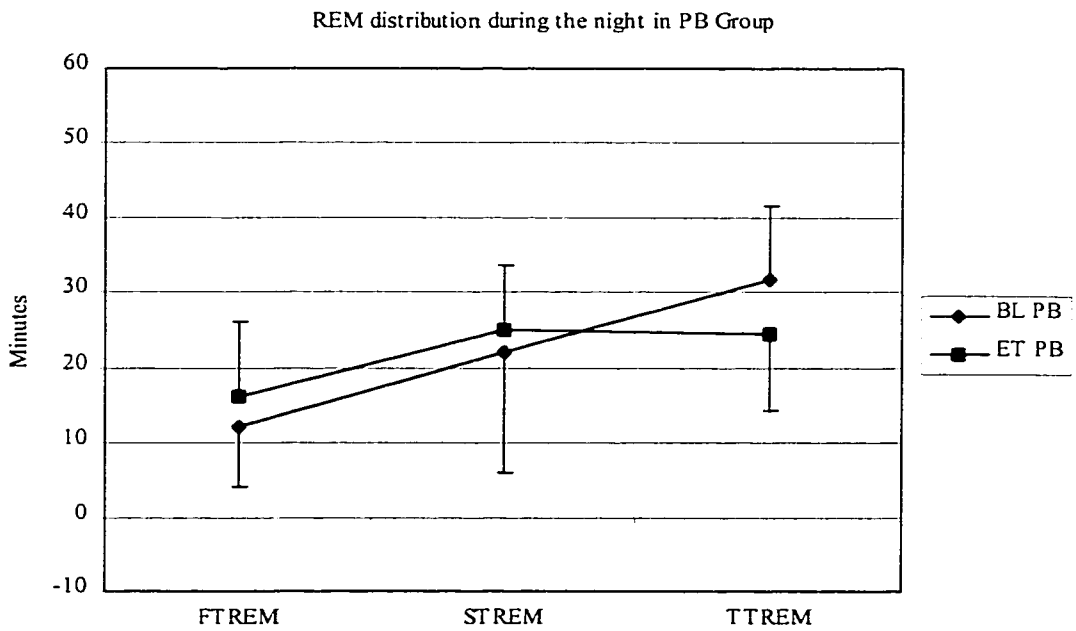
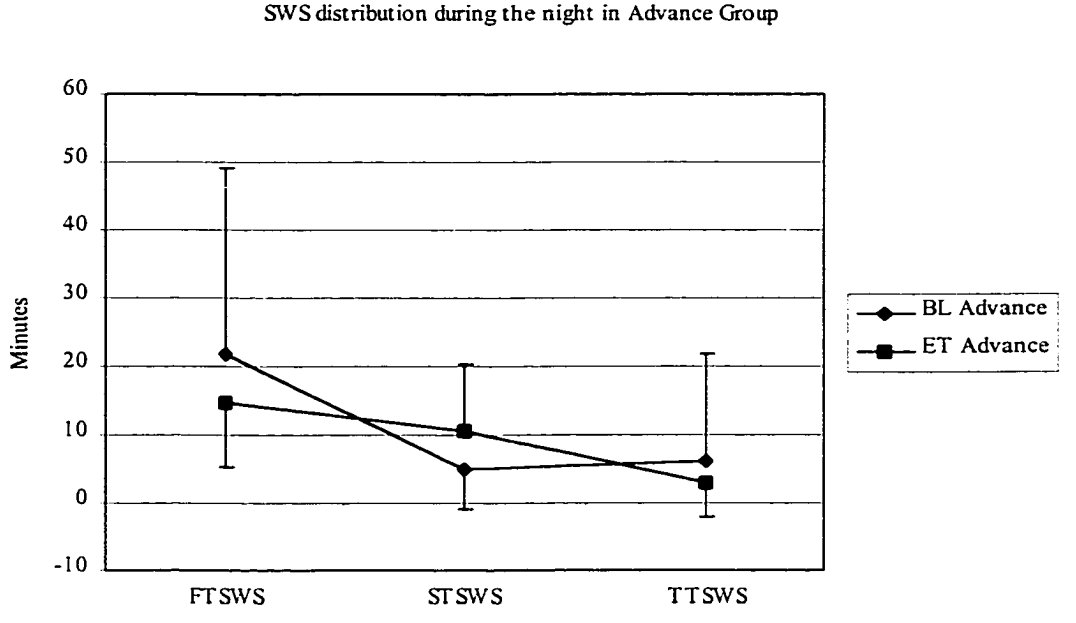


Figure 7

A. SWS distribution (minutes) during the night in advance subjects (n=8)



B. SWS distribution (minutes) during the night in delay subjects (n=9)

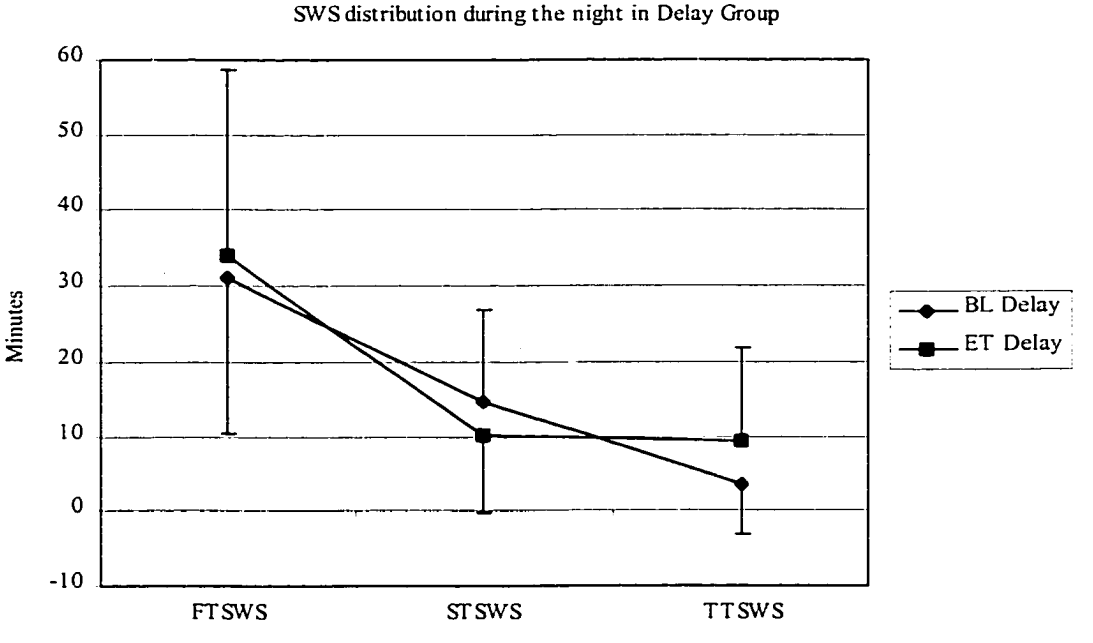
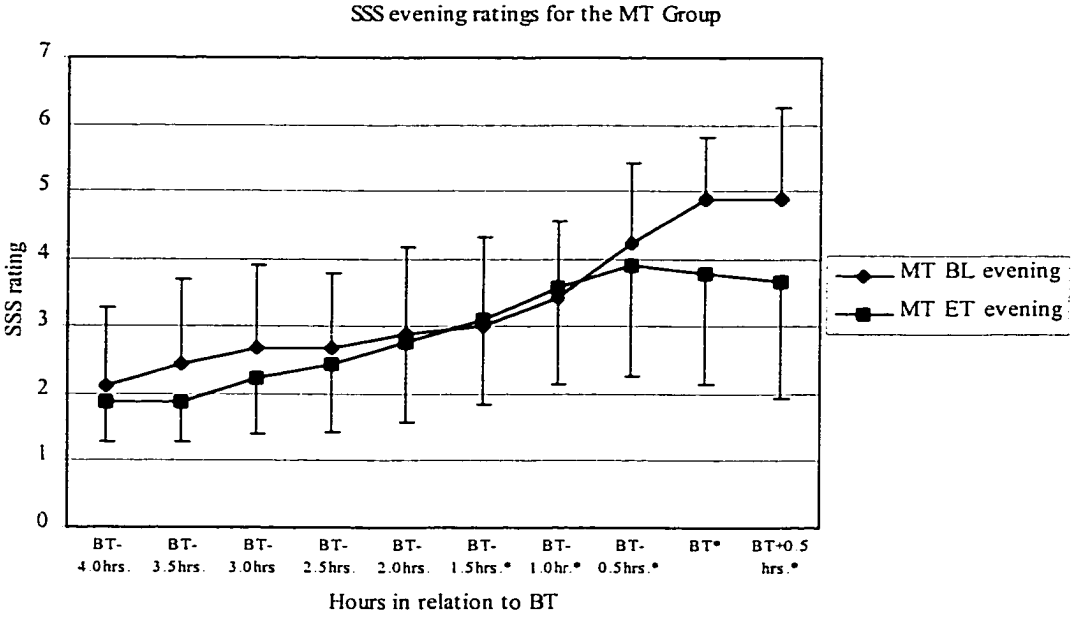


Figure 8

A. Mean (SD) Stanford Sleepiness Scale (SSS) evening ratings for the MT group (n=9). SSS is plotted every 30 minutes beginning with 4.0 hours before habitual BT and ending 0.5 hrs after habitual BT



B. Mean (SD) SSS evening ratings for the PB group (n=8). SSS is plotted every 30 minutes beginning with 4.0 hours before habitual BT and ending 0.5 hrs after habitual BT

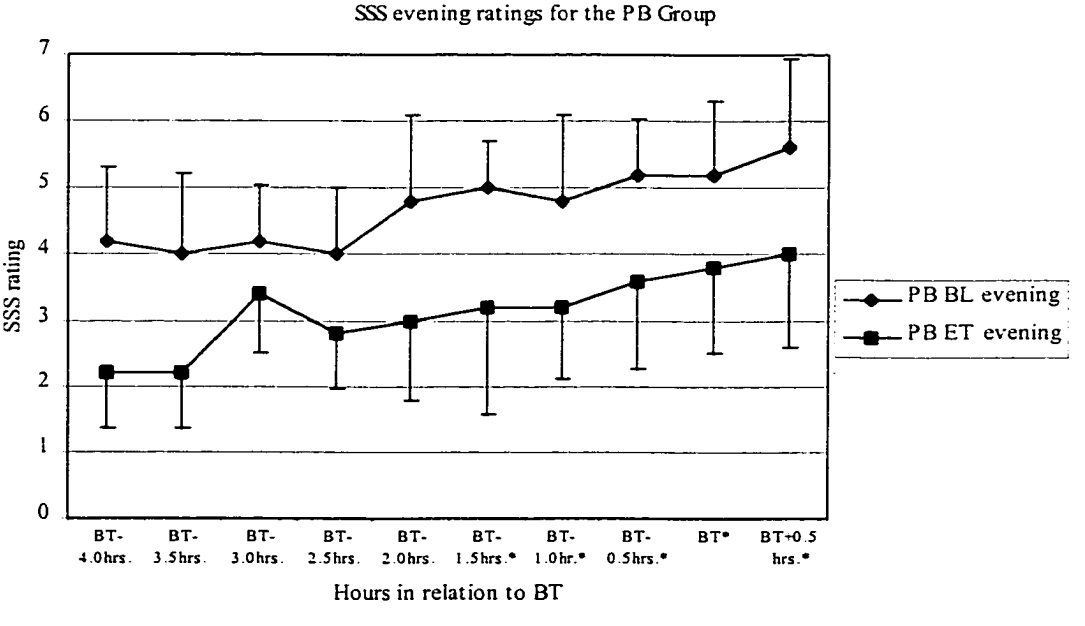
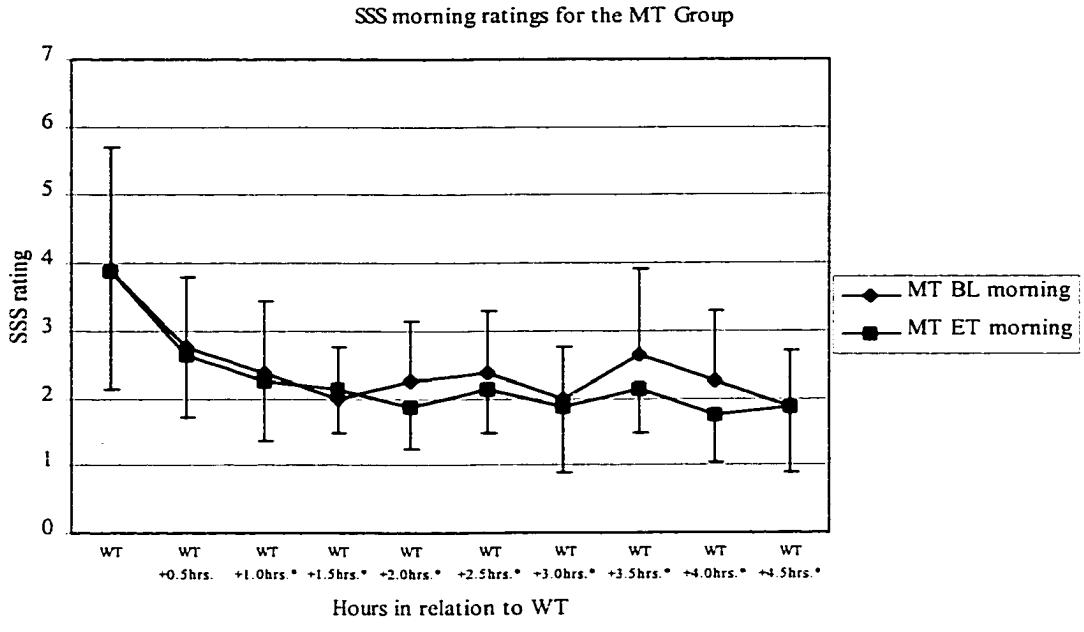
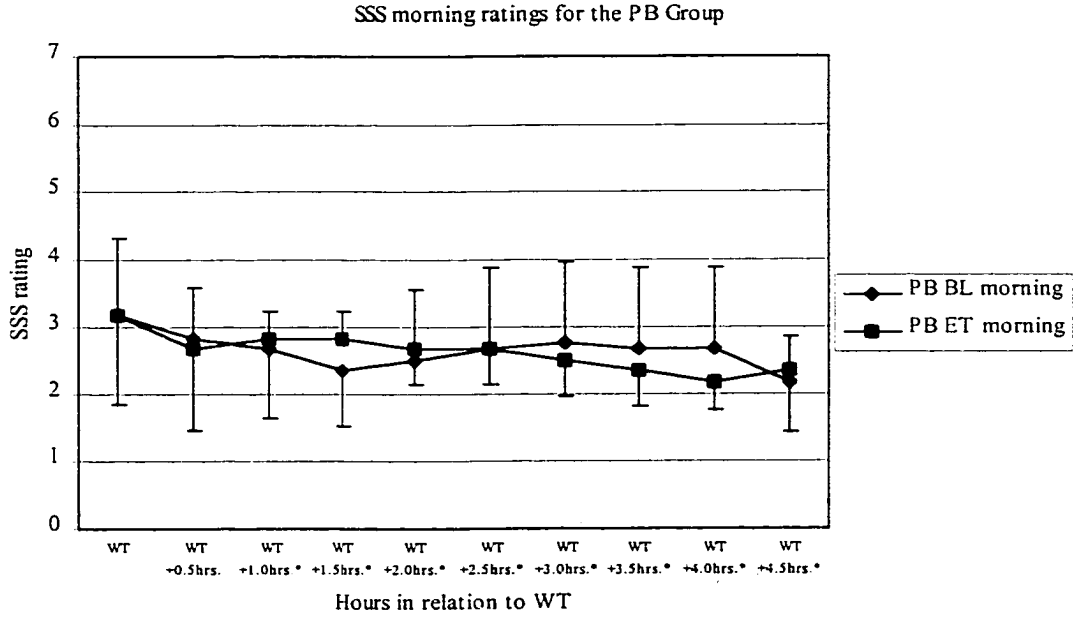


Figure 9

A. Mean (SD) Stanford Sleepiness Scale (SSS) morning ratings for MT group (n=9). SSS is plotted every 30 minutes beginning with waketime (WT) and ending 4.5 hrs after WT



B. Mean (SD) SSS morning ratings for PB group (n=8). SSS is plotted every 30 minutes beginning with WT and ending 4.5 hrs after WT



Appendix 1

Stanford Sleepiness Scale

Circle the *one* number that best describes your level of alertness or sleepiness right now.

1. Feeling active, vital, alert, wide awake.
2. Functioning at a high level but not at peak, able to concentrate.
3. Relaxed, awake but not fully alert, responsive.
4. A little foggy, let down.
5. Foggy, beginning to lose track, difficulty in staying awake.
6. Sleep, prefer to lie down, woozy.
7. Almost in reverie, cannot stay awake, sleep onset appears imminent.

Appendix 2

Means and standard deviations for Insomnia Scale questions on BL and ET assessments between MT (n=9) and PB (n=8)

Group	BL Mean (+SD)	ET Mean (+SD)
Q1 - Do you lie awake at night worried, anxious or distressed?		
MT	32.6 (35.6)	27.9 (34.2)
PB	42.0 (36.4)	32.3 (28.5)
Q2 - During the day, do you worry about how you will sleep at night?		
MT	25.1 (36.8)	24.7 (34.4)
PB	25.3 (31.5)	19.6 (28.7)
Q3 - Are you watching the clock or aware of time passing while lying awake in bed? [S]		
MT	45.9 (36.9)	27.4 (27.8)
PB	41.3 (37.7)	30.5 (28.5)
Q4 - Is your sleep restless?		
MT	53.0 (27.0)	44.2 (25.1)
PB	48.0 (39.7)	34.3 (30.4)
Q5 - Are you experiencing brief awakenings during the night? [I]		
MT	54.9 (27.8)	65.2 (27.1)
PB	80.3 (24.2)	61.5 (28.6)
Q6 – Are you experiencing long awakenings during the night? [S]		
MT	53.3 (34.8)	24.1 (20.9)
PB	53.9 (29.6)	44.4 (40.6)
Q7 – Do you feel tired or fatigued during the day or evening?		
MT	56.9 (27.6)	33.8 (23.9)
PB	49.9 (31.2)	51.1 (34.8)
Q8 – Do you take any naps or fall asleep briefly during the day or evening? [G]		
MT	27.9 (25.0)	16.2 (20.5)
PB	47.3 (19.1)	44.6 (36.0)
Q9 – Are you sleepy or drowsy during the day or evening? [G]		
MT	31.9 (21.2)	21.4 (24.7)
PB	58.3 (27.0)	65.4 (18.1)
Q10 – Do you feel you get an adequate amount of sleep?		
MT	38.9 (30.7)	43.4 (28.5)
PB	16.4 (16.5)	24.8 (31.6)
Q11 – Do you feel you get good quality of sleep? [S]		
MT	32.1 (28.9)	41.7 (28.9)
PB	25.8 (28.8)	49.0 (33.8)

[S] = Session (BL vs. ET) main effect ($p < .05$)

[I] = Interaction effect ($p < .05$)

[G] = Group (MT vs. PB) main effect ($p < .05$)

Appendix 3

Means and standard deviations of PSG variables in MT (n=9) and PB (n=8) subjects

PSG Variable	BL Mean (+SD)	ET Mean (+SD)
TST		
MT	329.5 (103.7)	372.7 (58.5)
PB	340.3 (77.0)	336.6 (68.4)
SE		
MT	74.9 (20.6)	85.1 (7.8)
PB	75.8 (15.1)	75.4 (16.0)
% of TWT		
MT	19.5 (16.8)	14.9 (7.8)
PB	17.9 (6.5)	18.3 (6.1)
% of WASO		
MT	13.6 (13.4)	11.6 (6.3)
PB	12.8 (5.0)	12.0 (3.2)
% of S1		
MT	12.4 (6.9)	13.3 (4.7)
PB	11.0 (7.0)	11.8 (5.3)
% of S2		
MT	54.0 (14.9)	60.4 (7.1)
PB	47.3 (13.3)	48.2 (18.8)
% of S3 [TR]		
MT	4.3 (4.1)	5.9 (5.5)
PB	9.3 (5.2)	7.7 (3.0)
% of S4		
MT	1.7 (3.9)	1.3 (3.2)
PB	8.2 (10.1)	8.0 (8.4)
% of SWS [G]		
MT	6.0 (7.3)	7.2 (8.5)
PB	17.5 (10.9)	15.7 (8.2)
% of Non-REM		
MT	72.4 (16.4)	80.8 (4.1)
PB	75.8 (14.6)	75.7 (16.3)
% of REM		
MT	22.1 (10.7)	19.2 (4.1)
PB	18.0 (5.9)	18.0 (4.8)
SOL		
MT	11.0 (9.8)	8.5 (4.9)
PB	15.1 (13.7)	17.9 (21.0)
S2L		
MT	13.5 (12.0)	11.2 (8.4)
PB	16.0 (13.7)	20.0 (25.1)
SWSL [G]		
MT	35.7 (24.2)	30.9 (24.0)
PB	10.7 (6.7)	17.4 (11.1)
REML		
MT	76.9 (32.0)	111.1 (80.6)
PB	72.6 (27.8)	67.2 (32.2)
FTW		
MT	17.3 (17.8)	16.4 (20.2)
PB	15.0 (8.2)	16.9 (9.2)

STW		
MT	21.9 (22.4)	19.3 (18.0)
PB	24.0 (17.6)	17.7 (15.6)
TTW		
MT	21.7 (22.6)	16.5 (10.8)
PB	19.9 (15.4)	20.8 (10.6)
FTSWS		
MT	14.6 (17.2)	20.0 (24.7)
PB	40.5 (23.3)	30.6 (15.5)
STSWS [G]		
MT	6.1 (9.3)	5.2 (5.5)
PB	14.7 (11.0)	16.3 (10.4)
TTSWS		
MT	0.7 (1.0)	2.1 (4.3)
PB	9.4 (15.8)	11.1 (12.5)
FTREM [I]		
MT	17.9 (13.9)	12.8 (9.8)
PB	12.3 (8.0)	16.2 (9.9)
STREM		
MT	24.9 (9.8)	24.0 (11.7)
PB	22.1 (16.1)	25.0 (8.6)
TTREM [TR]		
MT	30.8 (13.2)	34.9 (17.2)
PB	31.7 (9.9)	24.5 (10.3)

TST = total sleep time (min); SE = sleep efficiency (%); % of TWT = percentage of total wake time after light-out; % of WASO = percentage of wake time after sleep onset; % of Stage 1 = percentage of stage 1 sleep; % of Stage 2 = percentage of stage 2 sleep; % of Stage 3 = percentage of stage 3 sleep; % of Stage 4 = percentage of stage 4 sleep; % of SWS = percentage of slow wave sleep; % of Non-REM = percentage of Non-REM sleep; % of REM = percentage of REM sleep; SOL = sleep onset latency (min); S2L = stage 2 sleep onset latency (min); SWSL = SWS onset latency (min); REML = REM sleep onset latency (min); FTW = wake time during the first-third of the night (min); STW = wake time during the second-third of the night (min); TTW = wake time during the third-third of the night (min); FTSWS = slow wave sleep during the first-third of the night (min); STSWS = slow wave sleep during the second-third of the night (min); TTSWS = slow wave sleep time during the third-third of the night (min); FTREM = REM sleep during the first-third of the night (min); STREM = REM sleep during the second-third of the night (min); TTREM = REM sleep during the third-third of the night (min).

[TR] = Interaction trend approaching significance ($p < .10$)

[G] = Group (MT vs. PB) main effect ($p < .05$)

[I] = Interaction effect ($p < .05$)

Appendix 4

Means and standard deviations of PSG variables in subjects with a salivary DLMO phase advance (n=8) and subjects with a salivary DLMO phase delay (n=9)

PSG Variable	BL Mean (+SD)	ET Mean (+SD)
TST		
Advance	322.5 (110.6)	340.3 (82.0)
Delay	345.8 (70.8)	369.3 (43.4)
SE		
Advance	73.0 (21.1)	77.5 (16.7)
Delay	77.4 (15.0)	83.3 (8.5)
% of TWT		
Advance	14.7(17.3)	16.3 (5.7)
Delay	17.0 (7.2)	16.7 (8.5)
% of WASO		
Advance	13.2 (14.1)	14.7 (3.4)
Delay	13.2 (5.2)	12.1 (6.2)
% of S1		
Advance	12.3 (8.8)	14.7 (6.2)
Delay	11.2 (4.7)	12.1 (3.7)
% of S2		
Advance	48.1 (16.3)	54.9 (17.2)
Delay	53.3 (12.4)	54.4 (13.3)
% of S3		
Advance	5.0 (5.2)	14.7 (3.8)
Delay	8.2 (5.0)	8.2 (4.8)
% of S4		
Advance	4.2 (10.0)	2.8 (4.7)
Delay	5.3 (6.3)	6.0 (8.4)
% of SWS		
Advance	9.1 (12.6)	14.7(5.9)
Delay	13.4 (8.8)	14.2 (10.8)
% of Non-REM		
Advance	69.5 (14.5)	75.9 (16.1)
Delay	77.9 (15.5)	80.7 (4.9)
% of REM [1]		
Advance	24.2 (11.1)	17.8 (3.7)
Delay	16.6 (4.0)	19.3 (4.9)
SOL		
Advance	12.8 (10.6)	11.3 (11.6)
Delay	13.0 (13.1)	14.4 (18.2)
S2L		
Advance	15.2 (12.7)	12.4 (12.8)
Delay	14.2 (13.0)	18.0 (22.4)
SWSL [1]		
Advance	21.4 (14.1)	34.8 (24.6)
Delay	26.2 (27.8)	15.5 (7.3)
REML		
Advance	63.7 (26.1)	82.1 (57.1)
Delay	84.9 (29.6)	97.8 (73.1)

FTW		
Advance	14.7 (15.5)	14.7(8.7)
Delay	17.6 (12.8)	18.4 (20.2)
STW		
Advance	23.1 (24.3)	14.7 (16.3)
Delay	22.7 (16.0)	22.0 (16.7)
TTW		
Advance	20.5 (24.7)	21.3 (12.6)
Delay	21.2 (13.6)	16.1 (8.5)
FTSWS		
Advance	21.8 (27.2)	14.8 (9.6)
Delay	31.2 (20.8)	34.1 (24.5)
STSWS [1]		
Advance	4.9 (5.9)	10.6 (9.8)
Delay	14.8 (12.2)	10.2 (10.4)
TTSWS		
Advance	6.2 (15.5)	3.1 (5.0)
Delay	3.6 (6.6)	9.2 (12.5)
FTREM		
Advance	19.4 (13.9)	17.0 (9.5)
Delay	11.6 (8.2)	12.2 (9.8)
STREM		
Advance	26.6 (16.7)	18.9 (9.5)
Delay	20.9 (8.1)	29.4 (8.1)
TTREM		
Advance	33.7 (11.2)	28.9 (14.5)
Delay	29.0 (11.3)	31.0 (16.1)

TST = total sleep time (min); SE = sleep efficiency (%); % of TWT = percentage of total wake time after light-out; % of WASO = percentage of wake time after sleep onset; % of Stage 1 = percentage of stage 1 sleep; % of Stage 2 = percentage of stage 2 sleep; % of Stage 3 = percentage of stage 3 sleep; % of Stage 4 = percentage of stage 4 sleep; % of SWS = percentage of slow wave sleep; % of Non-REM = percentage of Non-REM sleep; % of REM = percentage of REM sleep; SOL = sleep onset latency (min); S2L = stage 2 sleep onset latency (min); SWSL = SWS onset latency (min); REML = REM sleep onset latency (min); FTW = wake time during the first-third of the night (min); STW = wake time during the second-third of the night (min); TTW = wake time during the third-third of the night (min); FTSWS = slow wave sleep during the first-third of the night (min); STSWS = slow wave sleep during the second-third of the night (min); TTSWS = slow wave sleep time during the third-third of the night (min); FTREM = REM sleep during the first-third of the night (min); STREM = REM sleep during the second-third of the night (min); TTREM = REM sleep during the third-third of the night (min).

[1] = Interaction effect ($p < .05$)

Study 2: Calibration of Actigraphy (ACT) by Polysomnography (PSG) to Improve the Validity of Subsequent Actigraph Recordings in Sleep Maintenance Insomnia (SMI)

[1,2,3]Paul D'Ambrosio, [1,2]Arthur J. Spielman, [1,2]Chien-Ming Yang, [1]Becky Quattrucci, Andrew Scott, [1]Matt Ebben & [2]Gerard Lombardo

[1]Sleep Disorders Center, The City College of The City University of New York

[2]Sleep Disorders Center, New York Methodist Hospital, Brooklyn, NY

[3]Pfizer, NY

Subtitle: Calibration of Actigraphy (ACT) by Polysomnography (PSG)

Financial support: This research was partially supported by:

1999 - 2000 Professional Staff Congress - City University of New York (PSC - CUNY 31) Research Award Grant Number 62711-00-31;

1998 - 1999 PSC - CUNY 30 Research Award Grant Number 61628-00-30;

National Institute of Aging, #AG05732.

Corresponding author: Paul D'Ambrosio, Sleep Disorders Center,

The City College of The City University of New York,

North Academic Center, Room 8/213,

Convent Avenue at 138th Street, New York, New York 10031,

Phone: 212-733-5021; Fax: 212-573-4446.

e-mail: Paul.D'Ambrosio@Pfizer.com

***** Manuscript to be submitted to the journal *Sleep*. *****

Abstract

Study Objectives: Our objective was to assess the accuracy of actigraphy (ACT) recordings in patients with sleep maintenance insomnia (SMI), and to develop correction factors based on one or two nights of simultaneous ACT and polysomnograhpy (PSG) recordings to improve the validity of ACT.

Design: After a preliminary screening phase, prospective subjects were simultaneously recorded with ACT and PSG, twice on successive nights, for baseline (BL) assessments. They were once again recorded for two successive nights with ACT and PSG for end of treatment (ET) assessments after one month of either melatonin (MT) or placebo (PB) treatment (the results of the treatment trial will be presented elsewhere).

Setting: Standard nocturnal PSG were recorded at either the City College of New York Sleep Disorders Center or at the subject's home using an ambulatory polygraph system.

Participants: Fifteen subjects, men ($n = 6$) and women ($n = 9$) ranging in age from 38 to 76 (mean age = 57.9, SD = 11.9), completed the study. A total of 51 recordings were assessed. Nine subjects participated in all 4 PSG recordings, 3 subjects were recorded 3 times (BL 1 night, ET 2 nights) and 3 subjects were only recorded for the 2 BL nights.

Measurements and Results: Comparison between ACT and PSG provided epoch-by-epoch agreement rate of 82.3%. Prior to applying correction factors, Pearson r analyses indicated significant correlations between ACT total sleep time (TST) and PSG TST for all recordings ($r = 0.69$, n=51, $p < .05$), excluding the first BL recording ($r = 0.67$, n=36, $p < .05$) and on ET recordings ($r = 0.64$, n=18, $p < .05$). Correction factors were developed based on discrepancy errors on baseline nights to estimate and correct the errors on subsequent recordings and improve ACT validity. None of the correction

factors improved the validity of ACT.

A median split demonstrated that 1 correction factor significantly improved ACT validity on TST from the original correlation between ACT TST and PSG TST (r=0.67) when ACT wake epochs $\geq$ 69.5 (r=0.89, p<.05). In addition 3 other correction factors significantly improved ACT validity on TST from the original correlation between ACT TST and PSG TST (r=0.64) when ACT's predictive value for wakefulness $\geq$ 63.9% (r=0.97, 0.96, 0.99, ps<.05, respectively) ACT sleep epochs < 405 (r=0.94, 0.94, 0.94, ps<.05, respectively).

Conclusion: ACT is not as accurate in estimating sleep and wake with SMI as it is in a normal population. Problematic areas of ACT use with SMI include individuals lying motionless in bed while awake or individuals being motorically restless while asleep. In addition, SMI present with unpredictable within subject (night-to-night) variability making it difficult to develop correction factors that utilize one or two recordings of baseline assessment that consistently improve ACT accuracy on subsequent recordings in SMI.

Key words: Sleep, wake, actigraphy, polysomnography and sleep maintenance insomnia

Introduction

The "gold standard" method for discriminating between sleep and wakefulness, polysomnography (PSG), is time consuming and expensive. Movement detection devices, or actigraphs (ACT), were introduced shortly after EEG based systems for the determination of sleep/wake state (Kleitman about 1949). Refinement of these devices has led to the hope that this inexpensive, technically simple means of detecting state, may replace or compliment PSG (Brooks et al., 1993). Empirical evidence has demonstrated good overall total sleep time (TST) correspondence between ACT and PSG in a normal population, with correlations ranging between .84 and .98 (Kupfer et al., 1972; Foster et al., 1972b; Kripke, et al., 1978; Mullaney, 1980; vanHilten et al., 1993).

Studies have addressed a variety of confounding effects which critics have suggested may disqualify ACT as a valid instrument (Alster et al., 1990). Device placement (Sadeh et al., 1994), breathing movement, nocturnal wrist positioning, immobility and internight and intravolunteer activity have all been investigated in healthy subjects and TST correlations between ACT and PSG have remained very good ranging between .91 and .93 (vanHilten et al., 1993). However, a growing concern regarding the reliability of ACT recordings, suggests that up to 28 percent of weekly recordings may be unacceptable (Acebo, 1999).

Empirical inconsistencies have been cited regarding ACT use within various populations. Early studies, in normal subjects, indicate that ACT was useful in assessing sleep patterns, while other empirical research suggest that ACT accuracy is significantly less when assessing sleep in a clinical population (Levine, 1986). In its limited use with insomniacs, ACT has been shown to be a successful screening instrument, a reliable

measure and a useful technique, when following the same insomniac over time (Sadeh et al., 1989; Hauri, PJ, Wisbey, J., 1994). However, given the various insomnia diagnoses and the sensitivity of ACT, significant variability can affect the level of TST agreement between ACT and PSG. ACT may overestimate TST in patients with psychophysiologic insomnia and in insomniacs associated with psychiatric illness (Mullaney et al., 1980; Hauri et al., 1989; Hauri and Wisbey, 1992) since these patients typically lie motionless in bed while awake. ACT may also underestimate sleep with patients experiencing sleep state misperception or difficulty initiating and maintaining sleep since these patients may be motorically restless while asleep. These reasons may help explain why TST agreement rates between ACT and PSG with insomniacs are lower, ranging between .78 and .88 (Hauri and Wisbey, 1992).

Various algorithms and scoring methods (Webster et al., 1982; Cole et al., 1992) attempt to minimize erroneous interpretations of ACT-derived sleep/wake data which have led to the development of several software programs (Sleepest, Actigraphic Scoring Analysis, SADED, and Actigraph Data Analysis Software) for the sleep/wake scoring of ACT data. Since it is much more convenient and less expensive to perform multi-night sleep recordings with ACT than with PSG, if a correction factor could be generated based on one or two nights of simultaneous ACT and PSG recordings, then subsequent recordings could be performed with ACT in lieu of the time consuming and expensive PSG method. The main objective of the study is to assess the accuracy of ACT sleep recording in SMI subjects, identify discordance by epoch-by-epoch comparisons between ACT and PSG and develop correction factors based on baseline (BL) nights of PSG recordings that can be implemented to subsequent ACT recordings to improve ACT

validity.

Method

Participants

As part of a larger study, 19 sleep maintenance insomniacs (SMI) were recruited from the 5 Boroughs of New York by flyers and public announcements. Four individuals were either discontinued or excluded from the study, thus, 15 subjects, which included men ($n = 6$) and women ($n = 9$) ranging in age from 38 to 76 (mean age = 57.9, SD = 11.9), completed the study. All 15 subjects were screened and cleared of all other major sleep, medical, neurologic and psychiatric disorders. In addition, female subjects with a history of clinically significant premenstrual syndrome were excluded since the endogenous melatonin (MT) rhythm has been shown to vary at different stages of the menstrual cycle (McIntyre, 1987). The exclusion criterion was necessary for an exogenous MT treatment study, which will be reported elsewhere. The following inclusion criteria were met: Subjects were at least 35 years old with cognitive functioning indicated by a score ≥ 23 on the Mini-Mental State Examination; subjects had an insomnia complaint of ≥ 1 year, wake after sleep onset longer than 30 minutes at least three nights per week; non-shift worker and no travel across time zones during the study or during the month prior to the study; not currently pregnant and willing to avoid getting pregnant during the study; not currently using psychotropic or hypnotic medications and willing to refrain from using these medications during the course of the study; limit caffeine consumption to one or less coffee serving or equivalent per day before noon; limit alcohol intake to 7 drinks per week and ≤ 2 drinks on any one night; and no napping. If a subject did not meet the final 3 inclusion criteria, they were given the

opportunity to comply with these specific restrictions and were re-evaluated three weeks later. Prospective subjects were contacted by phone, prior to the first laboratory appointment, to assure that all criteria were met. The experimental protocol was approved by the Institutional Review Board at the City College of New York and by the Institutional Review Board at New York Methodist Hospital. Informed consent was obtained from each subject, and all written documentation was retained.

Procedure

Pre-Experimental Weeks

The study consisted of 3 pre-experimental weeks and 4 experimental weeks. During the pre-experimental weeks, subjects filled out sleep logs and wore an ACT to assist in confirming reported bedtime and waketime (time they woke up in the morning). They came to the lab once a week for a briefing about the study and to have their sleep/wake schedules, as depicted on the sleep logs, examined. A sleep/wake schedule was designated for each subject according to his or her reported habitual bedtime and waketime. Subjects were allowed to determine their own bedtime and waketime with the understanding that these times were going to be consistent throughout the study. During the 3 pre-experimental weeks, subjects slept at home and followed their designated sleep/wake schedule in an effort to stabilize their sleep/wake rhythm. If they could not abide by their bedtime and waketime, they were instructed to document the deviations on the sleep log. Throughout the study, subjects were required to keep a daily sleep log, wear their ACT and to continue to abide by all inclusion criteria. Subjects with bedtime or waketime deviations greater than one hour, more than once a week,

were not included in the study.

Experimental Weeks

Subjects first came to the lab for a screening PSG to rule out primary sleep pathologies. All subjects arrived at the lab 5 hours prior to habitual bedtime and were kept awake one and one-half hours past their habitual bedtime. Four individuals were excluded from the study since their screening PSGs showed excess amounts of periodic limb movements with arousals of > 15/hour and/or sleep disordered breathing with an apnea plus hypopnea index of > 15/hour. Eligible subjects returned to the lab approximately 5 days later for two baseline (BL) PSG assessments. Two end of treatment (ET) PSG assessments were collected approximately four weeks after BL assessments. During BL and ET assessments, subjects arrived at the lab 2 hours prior to their habitual bedtime and went to bed at their habitual bedtime. All subjects left two hours after their habitual waketime. Wrist ACT was recorded simultaneously with PSG for all the experimental nights.

Measurements

Nocturnal Polysomnogram (PSG). The screening PSG was conducted on subjects at the City College Sleep Disorders Center (CCNY – SDC). The standard recording montage is as follows: four EEG channels (C3/C4 and O1/O2, ref 10-20), two horizontal eye movement channels (left and right outer canthus) and one bipolar chin muscle channel. EEG and eye movement placements were referenced to linked mastoids (A1 + A2). In addition to the standard electrode recording montage, there were sensors to measure respiratory effort (thoraco-abdominal strain gauges), respiratory airflow (nasal and oral thermistors) and oxygen saturation of the blood (finger pulse oximeter, [Ohmeda

Co.]). In addition, bipolar electrodes were applied on the skin above the middle of the anterior tibialis muscle to record periodic limb movements. All electrophysiological parameters were recorded using silver chloride disk electrodes filled with electrode gel or cream and affixed to the skin with either tape or cream-soaked gauze utilized in EEG placement. The international ten - twenty system was utilized for EEG electrode placement.

The BL and ET standard montage PSG recordings were collected at either the City College Sleep Disorders Center or at the subject's home on an ambulatory sleep-data acquisition computer system (H20 [Home-to-Office], Telefactor). If the subject chose to be studied at home, a technician went to the subject's home, prepared the subject, activated the ambulatory computer system, left the home and returned the following morning to retrieve the data. Subjects who chose to have recordings at the City College Sleep Disorders Center slept in a sound attenuated room and PSG data was obtained (Model 7D, Grass Co.). PSG was scored according to modified criteria (one minute epochs) of Rechtschaffen and Kales (1968) to compare ACT data to PSG data epoch by epoch. All subjects completed their screening PSG at the CCNY-SDC (total number of screening PSGs=15). Eleven subjects completed both BL and both ET assessments at the CCNY-SDC. Three BL PSGs and 4 ET PSGs were unscoreable due to technical difficulties (total number of CCNY-SDC PSGs=37). Three subjects completed both BL and both ET assessments via the ambulatory system. Two ET PSGs were unscoreable due to technical difficulties (total number of ambulatory PSGs=10). One subject completed both BL assessments via the ambulatory system and ET assessments at the CCNY-SDC (number of PSGs=4).

ACT. The ACT (Activity Monitor, Computer Science and Applications Inc.) is a small (5.1 cm x 3.8 cm x 1.5cm), lightweight (43 grams) device that was placed on the subjects' dominant wrist during the study. It uses a miniature accelerometer to sense and measure motion. An electronic filter rejects frequencies outside normal human movements. Accelerations were sampled by an 8-bit A/D processor at 10 kHz, sensitivity threshold was 0.05 G, with a resolution of 0.016 G. Its full scale is 2.13 G. ACT recorded and date/time stamped the data which was later downloaded to a standard home PC via a provided Reader Interface Unit (RIU). The signal was digitized and numerically integrated over one-minute epochs.

Data Analysis

A total of 60 recordings were conducted. Nine subjects participated in all 4 sleep recordings (2 BL, 2 ET), 3 subjects were recorded 3 times (1 BL 1, 2 ET) and 3 subjects were only recorded for the 2 BL nights. One BL recording was lost for 3 subjects and both ET recordings were lost for 3 subjects, therefore, a total of 51 successful recordings were obtained.

Concordance between ACT and PSG

In order to compare ACT data to PSG data, establishing a value of movement counts as an ACT sleep/wake threshold was required to differentiate ACT values as either sleep epochs (movement counts $\leq$ threshold) or wake epochs (movement counts > threshold). Establishing a threshold was based on acquiring an ACT value that provided the highest ACT sensitivity to sleep (correct identification of sleep epochs) concurrently with the highest ACT specificity to sleep (correct exclusion of wake epochs). The first BL recording for each subject was used to identify the peak ACT sensitivity to sleep and

the peak ACT specificity to sleep as the point to be utilized as the sleep/wake threshold. For all first BL recordings assessed, as the threshold value increased beyond ACT value of zero, ACT sensitivity to sleep steadily but only marginally increased, while ACT specificity to sleep steadily and sharply declined. In addition, ACT sensitivity to sleep was always greater than the ACT specificity to sleep (see Figure 1). Based on these characteristics of the ACT data, a threshold with ACT counts equal to zero was categorized as sleep (AS), while ACT counts greater than zero were categorized as wake (AW).

PSG data was scored following conventional sleep stage scoring (Rechtschaffen and Kales, 1968), except that epoch length was one minute. Epochs were categorized as either PSG sleep (PS; stages 1-4, and REM) or PSG wake (PW). Each one-minute segment of data was categorized by the conjunction of PSG and ACT scores. For example, if an epoch was scored as sleep by PSG and had an ACT count equal to zero, it was categorized as PSAS. All of the naming conventions are presented in Table 1.

Using PSG as the standard and ACT as the predictor, indices for ACT accuracy were calculated as follows:

ACT predictive value for sleep (PVS) = PS**AS**/[PS**AS** + PW**AS**] x 100%
Epochs correctly categorized as sleep by ACT as a percent of all epochs categorized as sleep by ACT.

ACT predictive value for wakefulness (PVW) = PW**AW**/[PW**AW** +PS**AW**] x 100%
Epochs correctly categorized as wake by ACT as a percent of all epochs categorized as wake by ACT.

ACT sensitivity to sleep = **PS**AS/[**PS**AS +**PS**AW] x 100%

Epochs correctly categorized as sleep by ACT as a percent of all epochs categorized as sleep by PSG.

ACT specificity to sleep = **PW**AW/[**PW**AW + **PW**AS] x 100%

Epochs correctly categorized as wake by ACT as a percent of all epochs categorized as wake by PSG.

Agreement rate (AR) = [PSAS + PWAW]/[PSAS+PWAW+PWAS+PSAW] x 100%

Total epochs correctly categorized by ACT as a percent of the total number of epochs in the recording.

Assessment of timing discrepancies between ACT and PSG

Any misalignment between the ACT and PSG epochs will result in degradation of concordance between the two measures. Sources for this type of error include different start times, different stop times and timing mechanisms. To assess differences in timing of the two methods, after each recording we compared the durations of the recording period of each device. The PSG start and stop times were determined by an electric clock. We then compared the electric clock time to the time of the internal clock of the ACT. To examine the extent to which different start times may have degraded concordance between the two measures, we shifted (advanced [+] and delayed [-]) the ACT data set by one minute increments, for up to five minutes, to determine the highest levels of agreement and the lowest levels of discrepancies.

Correction factors

The general strategy underlying the development of correction factors is based on the assumption that between subject variability is greater than within (night-to-night) subject variability for the validity of ACT. If this is the case then using a correction

factor that is based on an individual's baseline validity of ACT compared to PSG will be useful for correcting future ACT estimates. Since the degree of correction is individualized on the baseline night, if subsequent nights have a similar discrepancy between ACT and PSG, the correction will improve ACT predictions. Each of the following correction factors assumes that subject's sleep and awakening behaviors and patterns are consistent from night to night.

Algorithms were developed to estimate the PWAS and PSAW errors based on baseline nights, improve the overall correlations between ACT TST and PSG TST and ultimately further support the validity of ACT.

A. The first three correction factors attempt to remedy ACT overestimating TST by subtracting PWAS correction values (from ACT TST). These epochs, incorrectly identified by ACT as sleep (AS), are present in individuals who lie motionless in bed while awake. These correction factors also assume that each individual will display the same characteristics while asleep or while lying awake motionless and does not vary from night to night. The correction factors attempt to correct ACT overestimating TST by comparing minute by minute epochs of PSG and ACT BL data. Any time PSG identifies an epoch as wake and ACT identifies an epoch as sleep, a PWAS discrepancy is tallied. The total number of PWAS discrepancies is divided by the total number of wake periods, regardless of length. This PWAS average is then multiplied by the total number of PSG wake periods on subsequent nights and subtracted from ACT TST. For example, if a total of 100 PWAS epochs occur during 10 PSG wake periods on BL 1, an average of 10 PWAS discrepancies is calculated and then multiplied by the total number of PSG wake periods on subsequent nights. This calculated PWAS correction value is then subtracted

from ACT TST.

The correction factor is most useful in individuals who lie in bed awake while not moving either when they first fall to sleep or when they awaken. The correction factor calculates the average number of epochs ACT incorrectly identified as sleep, during each PSG wake period, based on the first BL night and is used to predict the number of epochs ACT incorrectly identifies as sleep, during each PSG wake period, for each subsequent night. The correction factor's accuracy and efficacy on subsequent nights is based on the subject awakening and lying still the same number of times from night to night.

1. Subtracting average number of PWAS errors per awakening period based on the first BL night (BL 1).

The first correction factor is based on the assumption that during each wake period throughout the night, there will be a number of epochs in which the subject is lying still but is awake. These epochs, scored as wake by PSG (PW), will be incorrectly identified by ACT as sleep (AS). Further, since the number of awakening periods with ACT errors (defined as the number of non-consecutive PWAS epochs) is likely to differ on different nights, the correction factor uses the average number of PWAS epochs per awakening period on BL 1 as an estimated number of PWAS epochs per awakening period for subsequent nights. The value is then multiplied by the number of awakening periods on subsequent nights and then subtracted from all ACT epochs of sleep to yield the predicted AS value for the subsequent nights.

Calculation of correction value based on BL 1:

Correction value =

(number of PWAS epochs on BL 1/number of PSG wake periods on BL1)

Application of the correction value:

Predicted number of AS epochs = Original number of AS epochs –

Correction value X number of PSG wake periods of subsequent night

2. Subtracting PWAS percentage of all ACT sleep epochs based on BL 1.

The second correction factor uses the number of epochs incorrectly identified as ACT sleep as a percentage of all ACT sleep epochs on BL 1 as a correction value for subsequent nights. The PWAS percentage is then multiplied by the number of ACT sleep epochs on subsequent nights. The value is then subtracted from the number of ACT sleep epochs to yield the predicted AS value.

The correction factor is also most useful in individuals who lie in bed awake while not moving either when they first fall to sleep or when they awaken. The correction factor adjusts for the average number of epochs ACT incorrectly identifies as sleep, as a portion of all epochs ACT identifies as sleep, based on the first baseline night and is used to predict the number of epochs ACT incorrectly identifies as sleep, as a portion of all epochs ACT identifies as sleep, for each subsequent night. Once again, the correction factor's accuracy and efficacy on subsequent nights is based on the subject awakening and lying still the same number of times from night to night.

Calculation of correction value based on BL 1:

Correction value =

(number of PWAS epochs/number of AS epochs) X *100%*

Application of the correction value:

Predicted number of AS epochs =

Original number of AS epochs – *Correction value* X number of AS epochs

3. Subtracting average number of PWAS errors per awakening period based on both BL nights.

Since the number of ACT errors and wake periods may differ on different nights, the third correction factor is based on the same principle of the first correction factor but uses the average number of discrepancies per wake period on two BL nights as the correction value to be applied to ET nights.

The correction factor is also most useful in individuals who lie in bed awake while not moving either when they first fall to sleep or when they awaken. The correction factor adjusts for the average number of epochs ACT incorrectly identifies as sleep, during each PSG wake period, based on the mean of both baseline nights and is used to predict the number of epochs ACT incorrectly identifies as sleep, during each PSG wake period, for each ET night. The correction factor's accuracy and efficacy on ET nights is based on the subject awakening and lying still the same number of times from night to night.

Calculation of correction value based on BL 1:

BL1 Correction value =

(number of PWAS epochs on BL 1/number of PSG wake periods on BL1)

Calculation of correction value based on BL 2:

BL2 Correction value =

(number of PWAS epochs on BL 2/number of PSG wake periods on BL 2)

Application of the correction value to ET night:

Predicted number of AS epochs =

Original number of AS epochs on ET night - ([*BL1 Correction value* + *BL2*

Correction value]/2) X number of PSG wake periods on ET night.

B. The following two correction factors attempt to remedy ACT underestimating TST by adding PSAW correction values (to ACT TST). These epochs, incorrectly identified by ACT as wake (AW), are present in individuals who may be motorically restless while asleep, patients experiencing sleep state misperception or individuals experiencing difficulty initiating and maintaining sleep. The correction factors attempt to correct ACT underestimating TST by comparing minute by minute epochs of PSG and ACT BL data. Any time PSG identifies an epoch as sleep and ACT identifies an epoch as wake, a PSAW discrepancy is tallied. The total number of PSAW discrepancies is divided by the total number of ACT wake epochs. This PSAW average is then multiplied by the total number of ACT wake epochs on subsequent nights and added to ACT TST. For example, if a total of 10 PSAW discrepancies and 100 ACT wake epochs are present on BL 1, an average of 10 PSAW discrepancies is then multiplied by the total number of ACT wake epochs on subsequent nights. This calculated PSAW correction value is then added to ACT TST.

4. Adding PSAW epoch percentage of all ACT wake epochs based on BL 1

The fourth correction factor uses the number of epochs incorrectly identified by ACT as wake on BL1 as a percentage of all ACT wake epochs as a correction factor for subsequent nights. The PSAW percentage is multiplied by the number of ACT wake epochs on subsequent nights. The value is then added to ACT sleep epochs to yield the predicted AS value.

Unlike the first three correction factors, this correction factor is most useful in individuals who are motorically restless while asleep. The correction factor adjusts for

the average number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, based on the first BL night and is used to predict the number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, for each subsequent night. The correction factor's accuracy and efficacy on subsequent nights is based on the subject sleeping with the same amount of restlessness from night to night.

Calculation of correction factor based on BL 1:

Correction value =

(*number of PSAW epochs/number of AW epochs*) *X 100%*

Application of the correction:

Predicted number of AS epochs =

Original number of AS + (*Correction Value* X number of AW epochs)

5. Adding average number of PSAW epoch errors based on both BL nights

Since the motor activity during sleep may vary across nights, the fifth correction factor is based on the same assumption of the forth correction factor but obtains the correction value based on both BL nights.

The correction factor is also most useful in individuals who are motorically restless while asleep. The correction factor adjusts for the average number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, based on the mean of both baseline nights and is used to predict the number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, for each ET night. The correction factor's accuracy and efficacy on ET nights is based on the subject sleeping with the same amount of restlessness from night to night.

Calculation of correction factor based on BL 1:

BL 1 correction value =

(number of PSAW epochs on BL 1/number of AW epochs on BL1)

Calculation of correction factor based on BL 2:

BL 2 correction value =

(number of PSAW epochs on BL 2/number of AW epochs on BL2)

Application of the correction to ET night:

Predicted number of AS epochs =

Original number of AS + ([*BL 1 correction value* + *BL 2 correction value*]/2) X number of ACT wake periods on ET night.

C. The first five correction factors attempt to predict ACT TST based upon adjusting either PWAS or PSAW. With the possibility of overcompensating AS epochs, we will attempt to minimize the error in ACT TST compensation by combining two correction values. The remaining three correction factors attempt to remedy ACT overestimating TST (individuals lying in bed awake) by subtracting PWAS correction values in conjunction with attempting to remedy ACT underestimating TST (individuals motorically restless while asleep), by adding PSAW correction values.

6. Subtracting average number of PWAS errors per awakening period based on BL 1 (correction factor #1 value) AND adding PSAW epoch percentage of all ACT wake epochs based on BL 1 (correction factor #4 value).

The correction factor attempts to correct both the PWAS errors and PSAW errors based on one BL night by combining correction factors #1 and #4. It adjusts for the average number of epochs ACT incorrectly identifies as sleep, during each PSG wake

period, based on the first BL night and is used to predict the number of epochs ACT incorrectly identifies as sleep, during each PSG wake period, for each subsequent night.

In addition, the correction factor also adjusts for the average number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, based on the first baseline night and is used to predict the number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, for each subsequent night. The correction factor's accuracy and efficacy on subsequent nights is based on the subject awakening and lying still the same number of times as well as the subject sleeping with the same amount of restlessness from night to night.

Predicted number of AS epochs =

Original number of AS epochs – *Correction value #1 + Correction value #4*

7. **Subtracting PWAS percentage of all ACT sleep epochs based on BL 1 (correction factor #2 value) AND adding PSAW epoch percentage of all ACT wake epochs based on BL 1 (correction factor #4 value).**

The correction factor again attempts to correct both the PWAS errors and PSAW errors based on one BL night by combining correction factors #2 and #4. It adjusts for the average number of epochs ACT incorrectly identifies as sleep, as a portion of all epochs ACT identifies as sleep, based on the first BL night and is used to predict the number of epochs ACT incorrectly identifies as sleep, as a portion of all epochs ACT identifies as sleep, for each subsequent night.

In addition, the correction factor also adjusts for the average number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, based on the first BL night and is used to predict the number of epochs ACT incorrectly

identifies as wake, as a portion of all epochs ACT identifies as wake, for each subsequent night. Once again, the correction factor's accuracy and efficacy on subsequent nights is based on the subject awakening and lying still the same number of times as well as the subject sleeping with the same amount of restlessness from night to night.

Predicted number of AS epochs =

Original number of AS epochs – *Correction value #2 + Correction value #4*

8. **Subtracting average number of PWAS errors per awakening period based on both BL nights (correction factor #3 value) AND adding average number of PSAW epoch errors based on both BL nights (correction factor #5 value).**

Our final correction factor combines the two adjustments (correction factors #3 and #5) based on both BL nights. It adjusts for the average number of epochs ACT incorrectly identifies as sleep, during each PSG wake period, based on the mean of both baseline nights and is used to predict the number of epochs ACT incorrectly identifies as sleep, during each PSG wake period, for each ET night.

In addition, the correction factor also adjusts for the average number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, based on the mean of both BL nights and is used to predict the number of epochs ACT incorrectly identifies as wake, as a portion of all epochs ACT identifies as wake, for each ET night. The correction factor's accuracy and efficacy on ET nights is based on the subject awakening and lying still the same number of times as well as the subject sleeping with the same amount of restlessness from night to night.

Predicted number of AS epochs =

Original number of AS epochs – *Correction value #3 + Correction value #5*

Median discrepancies

An early validation study suggests that ACT accuracy appears to be significantly compromised when sleep is fragmented (Levine, 1986), thus, medians were acquired from BL1 recordings and utilized to split the data on subsequent recordings (n=30). Median splits for ACT sleep efficiency (SE - amount of sleep time divided by the amount of time spent in bed, multiplied by 100%), PSG SE, PS, AS, PW, AW, PSAS, PWAW, PWAS, PSAW, PVS, PVW, ACT Sensitivity, ACT Specificity and AR were executed to determine whether correction factors were more useful for specific arrays of ACT or PSG data. Pearson *r* correlations were performed on both median halves prior to and after corrections factors were applied.

Results

Concordance and Discordance between ACT and PSG

Prior to applying correction factors, Pearson *r* analyses indicated significant correlations between ACT TST and PSG TST for all recordings ($r = 0.69$, n=51, $p < .05$), when excluding the first BL recording ($r = 0.67$, n=36, $p < .05$) and when including only ET recordings ($r = 0.64$, n=18, $p < .05$). These correlation, although significant, are not sufficient in clearly identifying the epoch-by-epoch concordance and discordance between ACT and PSG. An epoch-by-epoch comparison, utilizing a threshold cut-score of 0 counts to define sleep and > 0 counts to define wakefulness, between ACT and PSG is presented in percentages of concordance and discordance in Table 2 and 3.

When comparing the all night average scoring for each method separately, average nightly sleep/wake scoring only differs by 9 minutes, which at first may appear to certainly be acceptable. However, a closer look reveals that the standard deviation is

45.5 minutes and the range for PW-AW is –71 to 143 minutes. In addition, epoch-by-epoch comparisons also indicates a nightly discordance of 35.3 minutes for PSG defined sleep. The discrepancy is an ACT sensitivity of 90.3 percent or, viewed in a different way, a 9.7 percent error rate of ACT in identifying sleep. This is barely acceptable using the common criterion of 10 percent error rate permissible between two different scorers of the same PSG.

The epoch-by-epoch scoring yields a nightly discordance of 45.3 minutes for PSG defined wakefulness. The discrepancy is an ACT specificity of 49.2 percent or, viewed in a different way, is a 50.8 percent error rate between the two methods for wakefulness, which is unacceptable. Correction factors were developed, based on PWAS and PSAW errors on BL, to estimate and correct the errors on subsequent recordings, thus, improving the overall correlations between ACT TST and PSG TST and ultimately improving ACT validity.

Assessment of timing discrepancies between ACT and PSG

To examine the extent to which different start and run times between the clocks in the ACT and the PSG may have degraded the concordance between the ACT and PSG, we shifted (advanced [+] and delayed [-]) the ACT data set by one minute increments, for up to five minutes. The averages of ACT and PSG concordance and discordance with shifts of ACT timing from 51 recordings are presented in Table 4.

As Table 4 indicates, the "No lag" condition provides the highest levels of concordance between the two methods for sleep (PSAS) and wakefulness (PWAW) and the lowest level of PSAW discordance, while the "-1 min delay" has the lowest level of PWAS discordance. The "No lag" and the -1 min delay conditions are quite similar in

their concordance and discordance values. We therefore conclude that the timing of the ACT and PSG methods are close to equivalent and the discrepancy in the scoring of the two methods is not due to differences in ACT and PSG clock timing.

Correction factors

The objective of the correction factors was to estimate and correct the PWAS and PSAW errors on subsequent recordings, based on BL recordings, improving the overall correlations between ACT TST and PSG TST and ultimately further improving the validity of ACT. Once the correction factors were established, they were applied to subsequent recordings. Eight correction factors were developed. Five of the correction factors (1, 2, 4, 6 and 7) used the first recording of all 15 subjects to predict the subsequent 36 recordings, whereas the remaining three correction factors (3, 5 and 8) used subjects (n=9 subjects) who completed both baseline recordings (18 recordings) to predict the subsequent 18 end of treatment recordings. Fisher's z-transforming (as described in Snedecor & Cochran, 1980), indicated no statistical difference between TST correlations prior to and after applying the correction factors (see Table 5).

Fragmented Sleep

It has been suggested that ACT accuracy is compromised when sleep is fragmented (Levine, 1986). Sleep efficiency (SE) is a robust measure of sleep, and in SMI it is a good measure of sleep fragmentation. In the hope that poor ACT predictions could be improved on nights with fragmented sleep, we used PSG SE of 85 percent as the cut score to divide the nights into low SE nights (n=32) and high SE nights (n=19). We re-evaluated the concordance and discordance indices in these two groups of recordings. Table 6 illustrates that on recordings with low PSG SE, the PWAS discordance is nearly

36 minutes ($p<.05$) higher than on recordings with high PSG SE. Similarly, the ability of ACT to predict sleep (PVS) is nearly 10 percent ($p<.05$) greater on high PSG SE recordings. Striking is the reverse from the pattern with the ACT predictive value of wakefulness. In this case, on recordings with low PSG SE, the PVW is better by 28 percent ($p<.05$) compared to the high PSG SE recordings. However, the PVW of 62.4 percent in subjects with low PSG SE is still quite poor. In addition, the agreement rate, which is a ratio of total concordance over all epochs, is significantly better in subjects with high PSG SE ($p<.05$) (see Table 6).

Looking at a range of cut scores for SE between 60 percent and 95 percent revealed two linear trends for PVS and PVW as well as PSAW and PWAS (see Figure 2). As SE increases there is a direct increase in PVS. As first discussed by Levine (1986), ACT prediction of sleep improves on nights with higher SE. This is mainly due to a pronounced increase in PWAS errors as SE declines. Conversely, ACT prediction of wakefulness improves on nights with lower SE values. The seemingly paradoxical finding is due to a fairly constant level of PSAW errors over the range of SE values and increasing levels of PW epochs with lower SE. Therefore, with decreasing SE the ability of the ACT to predict sleep is lower and the ability to predict wakefulness is enhanced (see Figure 2).

Because the strategy of defining subgroups (post-hoc) by a cut score of PSG SE changed ACT validity, we decided to perform median splits on SE, concordance indices and discordance indices to assess if correction factors were more effective for either the top half or the bottom half of the data set. Subjects missing their BL1 or both BL1 and BL2 recordings were not used in the fragmented sleep analysis. Fisher's method of

transforming the correlations to z-scores was utilized to determine significant differences between correlations. The median split findings illustrate that correction factor 1 significantly improved ACT validity on TST compared to the original correlation between ACT TST and PSG TST (r=0.67) when AW epochs $\geq$ 69.5 (r=0.89, p<.05).

Correction factor 3, 5 and 8 significantly improved ACT validity on TST compared to the original correlation between ACT TST and PSG TST (r=0.64) when PVW $\geq$ 63.9 percent (r=0.97, 0.96, 0.99, ps<.05, respectively) and AS epochs < 405 (r=0.94, 0.94, 0.94, ps<.05, respectively). In addition, correction factor 5 significantly improved TST compare to the original correlation (r=0.64) when PWAS epochs < 40.5 (r=0.95, p<.05), PSAW epochs < 25 (r=0.94, p<.05), and ACT Sensitivity $\geq$ 91.9 percent (r=0.94, p<.05).

Discussion

Although our data, as reported in previous studies (Sadeh et al., 1989; Hauri and Wisbey, 1992; Brooks et al., 1993), indicates statistically significant correlations between ACT TST and PSG TST, the accuracy of ACT does not reach a satisfactory level to use as a reliable tool. The average overall agreement rate between ACT and PSG (82.3 percent) is below the conventional criteria (90 percent) used for inter-scorer reliability for PSG scoring. Only 15.7 percent of the recordings reach this standard.

By examining the data, epoch-by-epoch, we were able to identify where the errors existed. The discordance often occurred around sleep to wake or wake to sleep transitions. In addition, lying motionless in bed while awake or being motorically restlessness while asleep were significant sources for ACT/PSG discordance. Based on the errors identified, we developed several correction factors in an attempt to improve the

accuracy of ACT on sleep recordings.

Unfortunately, none of the correction factors developed improved the validity of ACT. It appears as if the within subject (night-to-night) variability (see Figure 3) interfered with the success of our correction factors. Studies have demonstrated that night-to-night variability (Hilten, 1993; Sadeh, 1991) was a significant problem for ACT in various populations. Our study is no exception. Internight sleep and wake variability prevented correction factors from accurately predicting ACT/PSG discordance on subsequent recordings.

Another important aspect, which may help explain the inability of our correction factors to improve ACT validity, may be the incompatibility of epoch scoring. According to standard PSG scoring, if less than 50 percent of a PSG epoch is wake activity, it may be scored as sleep, whereas, with ACT, movement is totaled and averaged across the epoch bin which may skew an epoch from "accurate" assessment. The fundamental differences in scoring methods leaves room for significant discordance between ACT and PSG and prevent the correction factors from accurately minimizing discordance indices.

Another approach we took to explore the usefulness of ACT was to identify the group of sleepers in whom the ACT may show better validity. Similar to previous empirical study suggestions, the more fragmented sleep is, as indicated by lower SE, the poorer the agreement between ACT and PSG (Levine, 1986). Recordings that fall below the 85 percent PSG SE cutoff demonstrate significantly more PWAS discordance, as well as significantly lower levels of ACT's predictability of sleep and wake. This may be a result of sleep maintenance insomniacs lying motionless in bed while awake. Results from the median splits further suggest that ACT is more reliable when ACT identifies

more waking or less sleep.

ACT and PSG essentially gather different types of information. ACT aims at collecting various levels of arousal and movement, whereas PSG aims at identifying tiers of sleep. ACT should be recognized as a useful instrument that may be used when we are concerned about movement in sleep. Clearly, the weakest aspect of ACT is its inability to accurately detect transition periods of sleep and wake. Our epoch-by-epoch indices depict the wake to sleep transitions (which may explain PWAS errors) and the sleep to wake transitions (which may explain PSAW errors). Although we were able to identify the error types, our efforts to correct for them on subsequent nights failed. It is our suggestion that more ACT research be conducted to have a better understanding of which specific clinical population is likely to benefit the most from ACT and how ACT and PSG discordance can be most efficiently minimized through the use of correction factors.

Acknowledgements: We would like to thank, John Cunningham for invaluable technical assistance and Computer Science and Applications Inc., Ambulatory Monitoring Applications Division (Shalimar, Florida) for providing the actigraphs.

Table 1

Naming convention for epoch categorization

Acronym	Definition
PS	An epoch categorized as sleep by PSG
AS	An epoch categorized as sleep by ACT
PW	An epoch categorized as wake by PSG
AW	An epoch categorized as wake by ACT
PSAS	An epoch categorized as sleep by both PSG and ACT
PWAW	An epoch categorized as wake by both PSG and ACT
PWAS	An epoch categorized as wake by PSG and sleep by ACT
PSAW	An epoch categorized as sleep by PSG and wake by ACT

Table 2

Overall average scoring (SD) of sleep and wakefulness for ACT and PSG and indices of epoch-by-epoch concordance and discordance between the two methods (n=51)

Description	Indices	Mean (SD)
Single Method Scoring	PS	366.6 (64.5)
	AS	375.5 (59.3)
	PW	89.2 (64.0)
	AW	80.6 (48.3)
Concordance Between Methods	PSAS	330.2 (61.3)
	PWAW	43.9 (43.4)
Discordance Between Methods	PWAS	45.3 (34.6)
	PSAW	35.3 (22.5)

Table 3

ACT's Mean (SD) predictive value for sleep (PVS) and wakefulness (PVW), as defined by PSG, ACT Sensitivity for sleep and specificity for sleep, and agreement rate (AR) between ACT and PSG (n=51)

Indices	Mean (SD)
PVS	87.9% (9.2%)
PVW	51.0% (23.6%)
ACT sensitivity	90.3% (5.9%)
ACT specificity	49.2% (19.4%)
AR	82.3% (7.5%)

Table 4

One minute advance (+ minutes) and delay (- minutes) increments to determine average ACT and PSG concordance and discordance from 51 recordings

Indices	Act +5 min.	Act +4 min.	Act +3 min.	Act +2 min.	Act +1 min.	**ACT No Lag**	Act -1 min.	Act -2 min.	Act -3 min.	Act -4 min.	Act -5 min.
PSAS	312	314	315	317	320	**330**	327	323	320	319	317
PWAW	30	31	32	34	37	**44**	43	39	37	35	33
PWAS	56	55	54	53	50	45	**44**	47	48	49	50
PSAW	50	48	48	47	44	**35**	37	41	43	45	46
PVS	85%	85%	85%	86%	87%	**88%**	**88%**	87%	87%	87%	86%
PVW	30%	33%	34%	35%	40%	**51%**	50%	45%	40%	38%	36%
ACT sensitivity to sleep	86%	86%	87%	87%	88%	**90%**	89%	88%	88%	87%	87%
ACT specificity for sleep	29%	31%	32%	33%	38%	49%	**51%**	44%	39%	38%	35%
AR	77%	77%	78%	78%	79%	**82%**	82%	81%	80%	79%	78%
Total epochs	447	448	449	450	451	**454**	451	450	449	448	447

Table 5

Means (SD) and correlations between PSG TST and ACT TST prior to and after applying correction factors (CF) and p-values comparing correlations

CF	N	PSG TST (SD)	ACT TST (SD) after CF	Pearson *r* Prior to CF	Pearson *r* after applying CF	p-values comparing correlations
1	36	365.3 (62.0)	328.1 (53.3)	0.67*	0.74*	0.28
2	36	365.3 (62.0)	329.6 (52.7)	0.67*	0.71*	0.38
3	18	384.2 (46.1)	338.0 (45.9)	0.64*	0.72*	0.34
4	36	365.3 (62.0)	408.8 (57.2)	0.67*	0.64*	0.42
5	18	384.2 (46.1)	423.5 (47.6)	0.64*	0.58*	0.40
6	36	365.3 (62.0)	363.8 (54.2)	0.67*	0.63*	0.39
7	36	365.2 (62.0)	365.4 (54.6)	0.67*	0.59*	0.29
8	18	384.2 (46.1)	376.1 (49.5)	0.64*	0.60*	0.43

* = $p < .05$

Table 6

Concordance and discordance indices between PSG SE < 85% (n=32) and PSG SE ≥ 85% (n=19) epoch indices

Indices	PSG SE < 85% 77.7 (10.4) Mean (SD) n=32	PSG SE > 85% 91.5 (3.3) Mean (SD) n=19	t-value	p-value
PWAS	**58.3 (35.8)**	**22.8 (16.2)**	**4.11**	**0.01***
PSAW	33.7 (22.6)	38.0 (22.7)	-0.65	0.52
PVS%	**84.3 (9.0)**	**94.1 (4.4)**	**-4.27**	**0.01***
PVW%	**62.4 (17.1)**	**34.4 (24.9)**	**4.78**	**0.01***
ACT sensitivity % to sleep	90.0 (6.1)	90.7 (5.7)	-0.39	0.70
ACT specificity % to sleep	49.8 (18.6)	39.5 (19.4)	1.89	0.07
Agreement Rate	**80.1 (6.9)**	**86.5 (6.8)**	**-3.25**	**0.01***

* = $p < .01$

Figure 1

ACT sensitivity and specificity to sleep (n=51)

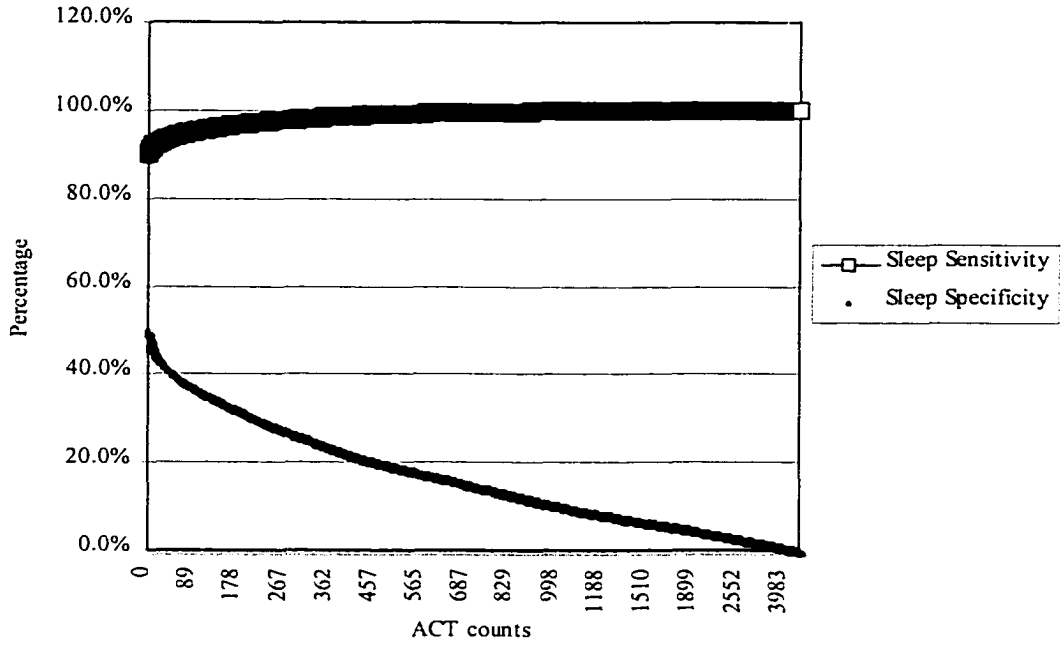
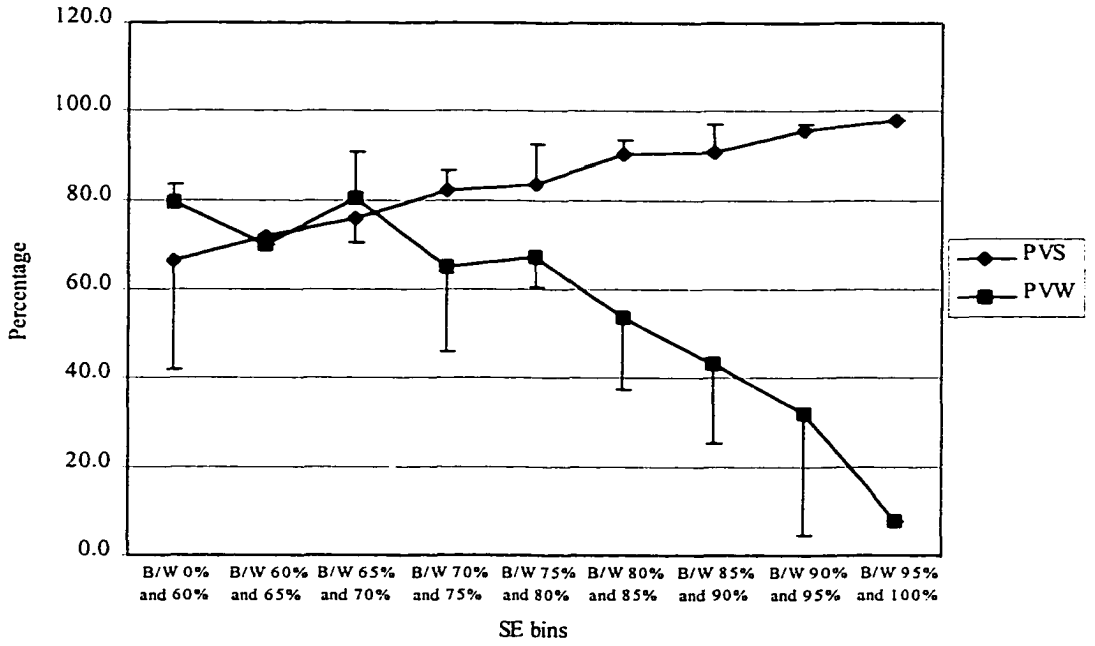


Figure 2

A. Mean PVS and PVW per PSG SE bin ranging from 0%-100%



B. Mean PSAW and PWAS errors per PSG SE bin ranging from 0%-100%.

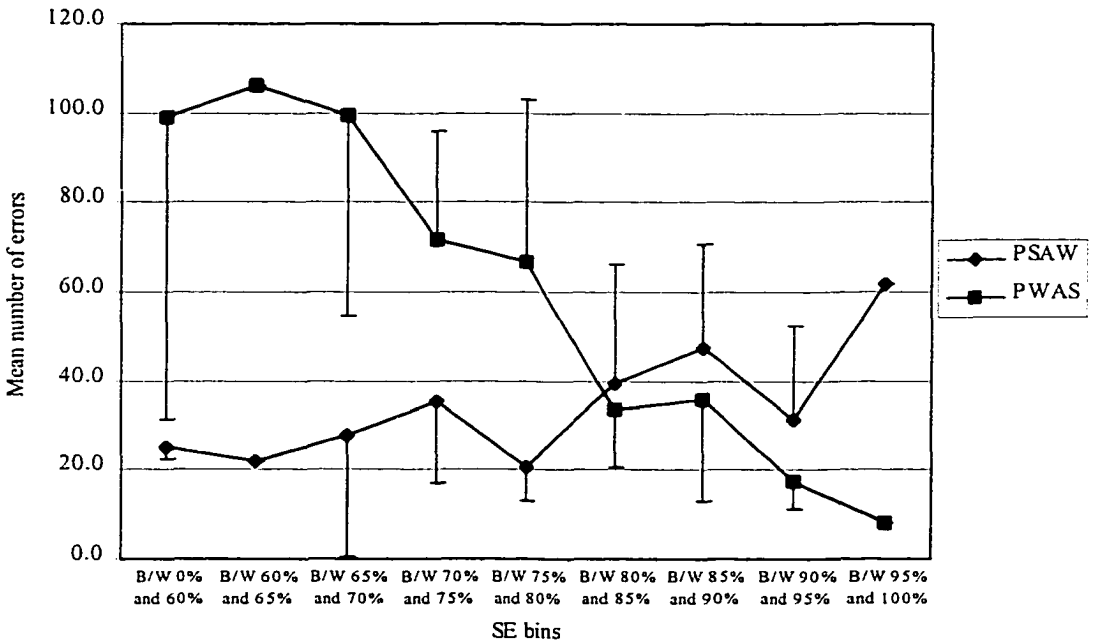
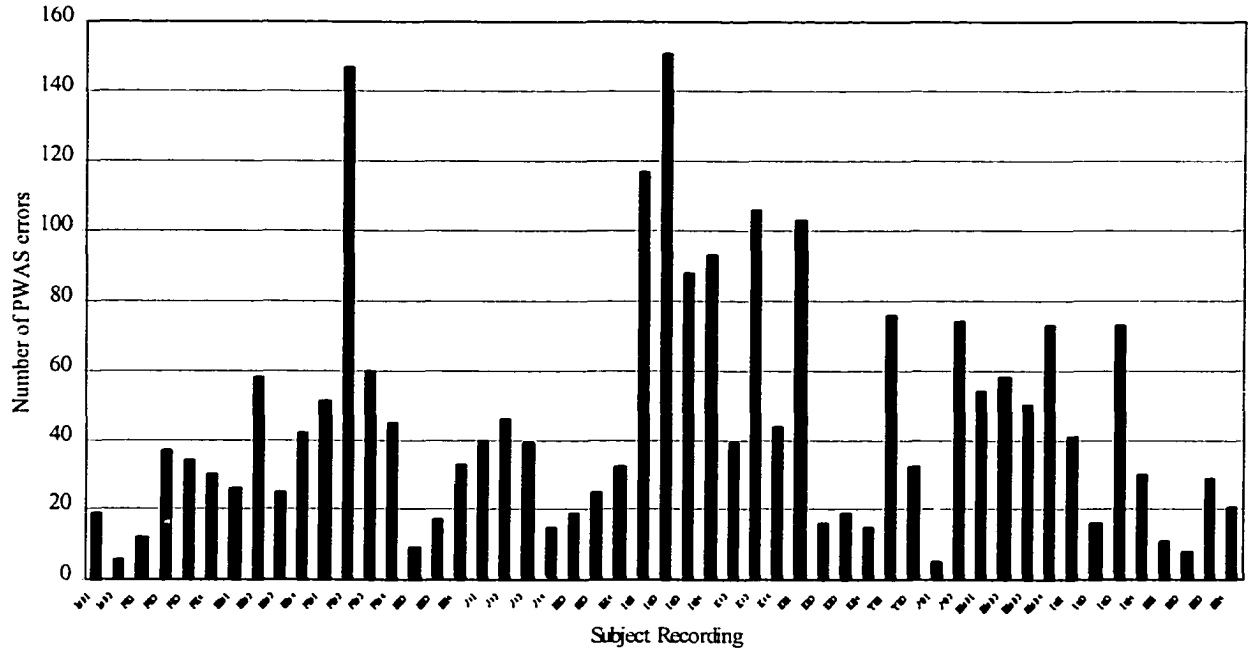
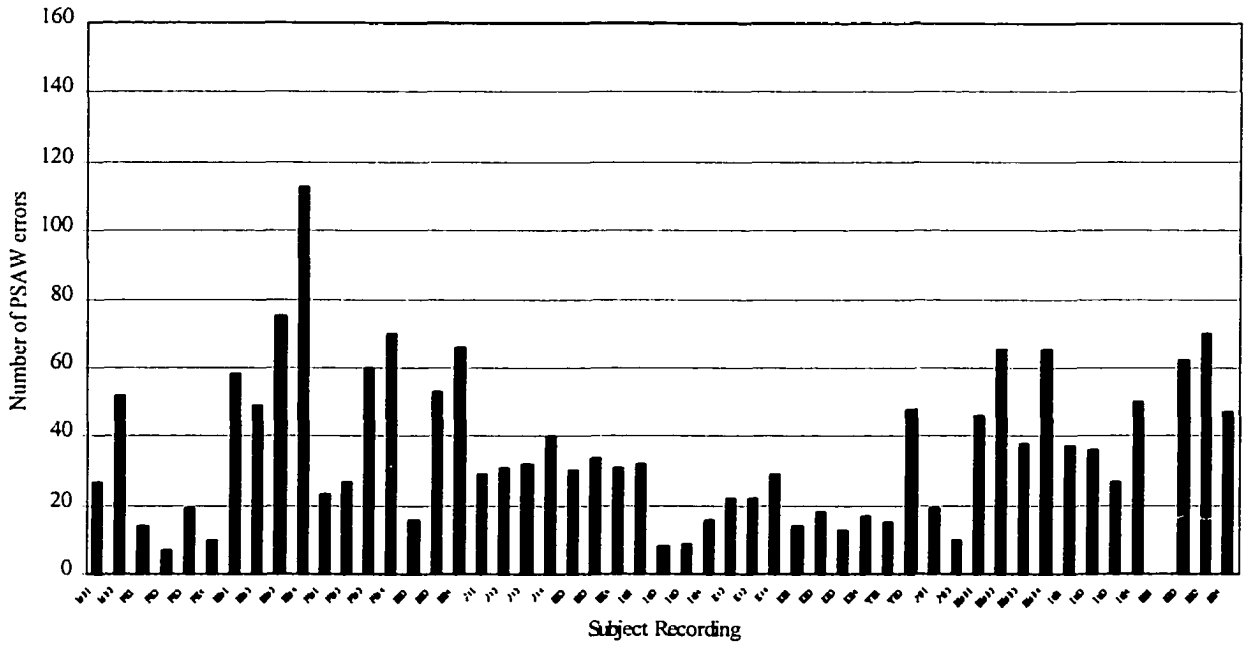


Figure 3

A. PWAS errors occurring on each ACT recording (n=51)



B. PSAW errors occurring on each ACT recording (n=51).



Appendix 1

Acronym Index

Acronym, Definition
ACT, actigraph or actigraphy
PSG, polysomnography
SMI, sleep maintenance insomnia
BL, baseline
ET, end of treatment
MT, melatonin
PB, placebo
TST, total sleep time
SE, sleep efficiency
PS, an epoch categorized as sleep by PSG
AS, an epoch categorized as sleep by ACT
PW, an epoch categorized as wake by PSG
AW, an epoch categorized as wake by ACT
PSAS, an epoch categorized as sleep by both PSG and ACT
PWAW, an epoch categorized as wake by both PSG and ACT
PWAS, an epoch categorized as wake by PSG and sleep by ACT
PSAW, an epoch categorized as sleep by PSG and wake by ACT
ACT predictive value for sleep (PVS) = PSAS/[PSAS + PWAS] x 100%
ACT predictive value for wakefulness (PVW) = PWAW/[PWAW +PSAW] x 100%
ACT sensitivity to sleep = PSAS/[PSAS +PSAW] x 100%
ACT specificity to sleep = PWAW/[PWAW + PWAS] x 100%
Agreement rate (AR) = PSAS + PWAW/[PSAS + PWAW + PWAS + PSAW] x 100%

References

1. Acebo C, Sadeh A, Seifer R, Tzischinsky O, Wolfson A. R., Hafer A, Carskadon MA. Estimating sleep patterns with activity monitoring in children and adolescents: How many nights are necessary for reliable measures? Sleep 1999; 22 (8): 95-103.

2. Aldhous M, Franey C, Wright J, and Arendt J. Plasma concentrations of melatonin in man following oral absorption of different preparations. British Journal of Clinical Pharmacology 1985; 19: 517-521.

3. Alster J, and Sadeh A. Artifact and pattern recognition in wrist actigraphy. Journal of Polysomnography Technology 1990; Spring/Summer: 27-30.

4. Anton-Tay F, Diaz JL, and Fernandez-Guardiola A. On the effect of melatonin upon human brain. Life Science 1971; 10: 841-850.

5. Arendt J, Deacon S, English J, Hampton S, and Morgan L. Melatonin and adjustment to phase shift. Journal of Sleep Research 1995; 4 (Suppl. 2): 74-79.

6. Axelrod J and Weissbach H. Enzymatic O-methylation of N-acetylserotonin to melatonin. Science 1960; 131: 1312-1313.

7. Bootzin RR, and Perlis MA. Nonpharmacologic treatments of insomnia. Journal of Clinical Psychiatry June 1992; 53 (Suppl. 6): 37-41.

8. Borbély AA. A two process model of sleep regulation. Human Neurobiology. 1982; 1: 195-204.

9. Brooks III JO, Friedman L, Bliwise DL, and Yesavage JA. Use of the wrist Actigraph to study insomnia in order adults. Sleep 1993; 16 (2): 151-155.

10. Brzezinski A. Melatonin in humans. The New England Journal of Medicine. 1997; 336 (3): 186-195.

11. Buhlmann melatonin radioimmunoassay (RIA) test kit RK-DSM. American Laboratory Products Company (ALPCO). PO box 451, Windham, NH, 03087, 603-893-8914.

12. Campbell S, Dawson D, and Anderson M. Alleviation of sleep maintenance insomnia with timed exposure to bright light. Journal of the American Geriatric Society 1993; 41: 829-836.

13. Cardarelli NF. The role of a thymus-pineal axis in an immune mechanism of aging. Journal of Theoretical Biology. 1990; 145: 397-405.

14. Carskadon MA, Acebo C, Richardson G, Tate B, and Seifer R. Entrainment of sleep and Dim-light salivary melatonin onset (DLMO) in young adolescents using a fixed schedule. Sleep Research Abstracts 1996a; 25: 544.

15. Carskadon MA, Richardson G, Tate B, Acebo C and Seifer R. Circadian parameters in adolescence: Preliminary results using the "long nights protocol". Sleep Research Abstracts 1996b; 25: 545.

16. Carskadon MA, Dement WC, Mitler MM, Guilleminault C, Zarcone VP, Spiegle R. Self-reports versus sleep laboratory findings in 122 drug-free participants with complaints of chronic insomnia. American Journal of Psychiatry 1976; 133: 1382-1388.

17. Cassone VM. Effects of melatonin on vertebrate circadian systems. Journal of 199X; Vol: 457-464.

18. Cavallo A and Ritschel WA. Pharmacokinetics of melatonin in human sexual maturation. Journal of Clinical Endocrinology and metabolism 1996; 81 (5): 1882-1886.

19. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. Sleep 1992; 15 (5): 461-469.

20. Cramer H, Rudolph J, and Kendel K. On the effects of melatonin on sleep and behavior in man. Advances in Biochemical Psychopharmacology 1974; 11: 187-191.

21. Cupp MJ. Melatonin. American Family Physician 1997; 56 (5): 1421-1425.

22. Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (type O) resetting of the human circadian pacemaker. Science 1989; 244: 1328-1333.

23. Czeisler CA. The effect of light on the human circadian pacemaker. Ciba foundation symposium 1995; 183: 254-302.

24. Czeisler CA, Shanahan T, Klerman E, Martens H, Daniel B, Emens J, Klein T and Rizzo J. Suppression of melatonin secretion in some blind patients by exposure to bright light. The England Journal of Medicine 1995; Jan.: 6-11.

25. Czeisler CA, Weitzman ED, Moore-Ede MC, Zimmerman JC, and Knauer RS. Human sleep: Its duration and organization depend on its circadian phase. Science 1980; 210: 1264-1267.

26. Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes JD. Delayed sleep phase syndrome response to melatonin. The Lancet 1991; 337: 1121-1123.

27. Deacon SJ and Arendt J. Adapting to phase shifts, II. Effects of melatonin and conflicting light treatment. Physiology and Behavior 1996; 59 (4/5): 675-682.

28. Deacon SJ and Arendt J. Acute phase-shifting effects of melatonin associated with suppression of body temperature in humans. Neuroscience Letters 1994; 178: 32-34.

29. Deacon SJ and Arendt J. Posture influences melatonin concentrations in plasma and saliva in humans. Neuroscience Letters 1994; 167: 191-194.

30. Deacon SJ, Arendt J, and English J. Posture: A possible making factor of the melatonin circadian rhythm. Melatonin and the pineal gland 1993; 387-390.

31. Diagnostic and statistical manual of mental disorders (4th ed.). American Psychiatric Association.

32. Dollins AB, Lynch HJ, Wurtman RJ, Deng MH, Kischka KU, Gleason RE, and Lieberman HR. Effect of pharmacological daytime doses of melatonin on human mood and performance. Psychopharmacology 1993; 112: 490-496.

33. Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal melatonin concentrations in daytime on sleep, mood, body temperature and performance. Proc. Natl. Acad. Sci 1994; 91: 1824-1828.

34. Folkard S, Arendt J, Aldhous M and Kennett H. Melatonin stabilizes sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. Neuroscience Letters 1990; 113: 193-198.

35. Foster FG, Kupfer D, Weiss G, Lipponen V, McPartland R, Delgado J. Mobility recording and cycle research in neuropsychiatry. Journal Indiscipl Cycle Res 1972b; 3 (1): 61-72.

36. Gallup Organization. Sleep in America. Princeton, NJ: 1995.

37. Gallup Organization. Sleep in America. Princeton, NJ: 1991.

38. Gillette MU, McArthur AJ. Circadian actions of melatonin at the suprachiasmatic nucleus. Behavioural Brain Research 1996; 73: 135-139.

39. Glovinsky PB and Spielman AJ. Sleep restriction therapy. In: Hauri, P. ed. Case studies in insomnia. New York: Plenum 1991:49-63.

40. Graw P, Werth E, Kräuchi K, Gutzwiller F, Cajochen C, Wirz-Justice A. Early morning melatonin administration impairs psychomotor vigilance. Behavioural Brain Research 2001; 121: 167-172.

41. Haimov I, Laudon M, Zisapel N, Souroujon M, Nof D, Shlitner A, Herer P, Tzischinsky O, and Lavie P. Sleep disorders and melatonin rhythms in elderly people. British Medical Research 1994; 309: 167.

42. Haimov I and Lavie P. Potential of melatonin replacement therapy in older patients with sleep disorders. Drugs and Aging 1995; 7 (2): 75-78.

43. Haimov I, Lavie P, Laudon M, Herer P, Vigder C, and Zisapel N. Melatonin replacement therapy of elderly insomniacs. Sleep 1995; 18 (7): 598-603.

44. Hauri PJ. Wrist actigraphy in insomniacs. Sleep Research 1989; 18: 239.

45. Hauri PJ and Wisbey J. Wrist actigraphy in insomnia. Sleep 1992; 15 (4): 293-301.

46. Hilten JJ van, Braat EAM, Velde EA van der, Middelkoop HAM, Kerkhof GA, Kamphuisen HAC. Ambulatory activity monitoring during sleep: an evaluation of internight and intrasubject variability in healthy persons aged 50-98. Sleep 1993;16:146-150.

47. Hirshkowitz, DeLaCueva, and Herman. (1993).

48. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: A new approach. Psychophysiology 1973;10:431-6.

49. Hughes RJ, Sack RL, Lewy AJ. The role of melatonin and circadian phase in age-related sleep-maintenance insomnia: Assessment in a clinical trial of melatonin replacement. Sleep 1998; 21 (1): 52-68.

50. Hughes RJ, Sack RL, Singer CM, and Lewy AJ. A comparison of the hypnotic efficacy of melatonin and temazepam on nocturnal sleep in healthy adults. Sleep Research 1994.

51. The international classification of sleep disorders, revised: Diagnostic and coding manual ((ICSD) 1997). American Sleep Disorders Association. ICSD - Rochester, Minnesota: American Sleep Disorders Association.

52. James SP, Sack DA, Rosenthal NE, and Mendelson WB. Melatonin administration in insomnia. Neuropsychopharmacology 1990; 3 (1): 19-23.

53. Jean-Louis G, von Gizycki H, Spielman AJ, Adler J, Fullilove R. Sleep latency post REM awakening: A new dimension of sleepiness. Sleep Research 1995; 24: 258.

54. Jean-Louis G, von Gizycki H, Zizi F, Spielman AJ, Hauri P, and Taub H. The actigraph data analysis software: I. A novel approach to scoring and interpreting sleep-wake activity. Perceptual and Motor Skills 1997; 85: 207-216.

55. Jean-Louis G, von Gizycki H, Zizi F, Spielman AJ, Hauri P, and Taub H. The actigraph data analysis software: II. A novel approach to scoring and interpreting sleep-wake activity. Perceptual and Motor Skills 1997; 85: 219-226.

56. Jean-Louis G, von Gizycki H, Zizi F, Fookson J, Spielman AJ, Nunes J, Fullilove R and Taub H. Determination of sleep and wakefulness with the actigraph data analysis software (ADAS). Sleep 1997; 19 (9): 739-743.

57. Kokkoris C, Weitzman ED, Pollak CP, Spielman AJ, Czeisler C, and Bradlow H. Long term ambulatory monitoring in a participant with a hypernycthemeral sleep-wake cycle disturbance. Sleep 1978; 1 (2): 177-190.

58. Kräuchi K, Cajochen C, and Wirz-Justice A. A relationship between heat loss and sleepiness: Effects of postural change and melatonin administration. Journal of Applied Physiology 1997; 83 (1): 134-139.

59. Kripke DF, Mullaney DJ, Messin S, and Wyborney VG. Wrist actigraphic measures of sleep and rhythms. Electroencephalogr Clin Neurophysiol 1978; 44: 674-676.

60. Kupfer DJ, Detre TP, Foster F, Tucker GJ, and Delgado J. The application of Delgado's telemetric mobility recorder for human sleep studies. Behavioral Biology 1972; 7: 585-590.

61. Laakso ML, et al. Correlation between salivary and serum melatonin: Dependence on serum melatonin levels. Journal of Pineal Research 1990; 9: 39-50.

62. Lacks LC, Mercer JD, and Wright H. Circadian rhythms of early morning awakening insomnia. Journal of Sleep Research 1996; 5 (4): 211-219.

63. Lerner AB, Case JD, Takahashi Y, Lee TH and Mori W. Isolation of melatonin, the pineal gland factor that lightens melanocytes. Journal of American Chemistry Society; 80: 2587.

64. Levine B, Moyles T, Roehrs T, Fortier J and Roth, T. Actigraphic monitoring and polygraphic recording in determination of sleep and wake. In: Chase MH, McGinty DJ, Crane G, eds. Sleep research. Los Angeles: UCLA Brain Information Service/Brain Research Institute 1986; 15:247.

65. Levitt RA. An activity measure of sleeping and waking behavior. Psychon Sci 1966; 5: 287-288.

66. Lewy AJ, Bauer VK, Ahmed S, Thomas KH, Cutler NL, Singer CM, Moffit MT, Sack RL. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiology International 1998; 15 (1): 71-83.

67. Lewy AJ, Ahmed S, Latham-Jackson JM, and Sack RL. Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiology International 1992; 9 (5): 380-392.

68. Lewy AJ, Ahmed S, and Sack RL. Phase shifting the human circadian clock using melatonin. Behavioral Brain Research 1996; 73: 131-134.

69. Lewy AJ and Sack RL. Use of melatonin to assess and treat circadian phase disorders. Melatonin and the pineal gland 1993; 205-210.

70. Lewy AJ and Sack RL. The dim light melatonin onset as a marker for circadian phase position. Chronobiology International 1989; 6 (1): 93-102.

71. Lewy AJ, Sack RL, Blood ML, Bauer VK, Cutler NL and Thomas KH. Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans. Circadian clocks and their adjustments 1995; 303-321.

72. Lezak MD. Neuropsychological assessment (3rd ed.). New York: Oxford University Press; 1995.

73. Lieberman HR, Waldhauser F, Garfield G, Lynch HJ and Wurtman RJ. Effects of melatonin on human mood and performance. Brain Research 1984; 323: 201-207.

74. McIntyre IM, Norman TR, Burrows GD, Armstrong SM. Human melatonin suppression by light is intensity dependent. Journal of Pineal Research 1987; 6: 149-56.

75. McIntyre IM, Norman TR, Burrows GD and Armstrong SM. Melatonin rhythm in human plasma and saliva. Journal of Pineal Research 1987; 4: 177-183.

76. Mellinger GD, Balter MB, and Uhlenhuth EH. Insomnia and its treatment. Prevalence and correlates. Archives of General Psychiatry 1985; 42 (3): 225-232.

77. Mendelson WB, Caine ED, Goyer P, Ebert M, and Gillin JC. Sleep in Gilles de la Tourette syndrome. Biological Psychiatry 1980; 15 (2): 339-343.

78. Miles A, Philbrick DRS, Thomas DR, and Grey J. Diagnostic and clinical implications of plasma and salivary melatonin assay. Clinical Chemistry 1987; 33 (7): 1295-1297.

79. Miles A, Philbrick DRS, Shaw DM, Tidmarsh SF, and Pugh AJ. Salivary melatonin estimation in clinical research. Clinical Chemistry 1985; 31 (12): 2041-2042.

80. Miles A, Philbrick DRS, Tidmarsh SF, and Shaw DM. Direct Radioimmunoassay of melatonin in saliva. Clinical Chemistry 1985; 31 (8): 1412-1413.

81. Miyazaki T, Hashimoto S, Masubuchi S, Honma S, and Honma KI. Phase-advance shifts of human circadian pacemaker are accelerated by daytime physical exercise. American Journal of Physiological Regulation Integr Comp Physiology 2001; 281 (1): R197-205.

82. Monane M. Insomnia in the elderly. Journal of Clinical Psychiatry June 1992; 53 (Suppl. 6): 23-28.

83. Monk TH, Moline ML, and Graeber RC. Inducing jet lag in the laboratory: Patterns of adjustment to an acute shift in routine. Aviation, Space, and Environmental Medicine, 1988; 59: 703-710.

84. Morin CM. Insomnia: Psychological assessment and management. New York: Guilford Press, 1993.

85. Morin CM, Colecchi C, Stone J, Sood R and Brink D. Behavioral and pharmacological therapies for late-life insomnia. A randomized controlled study. Journal of the American Medical Association 1999; 281 (11): 991-999.

86. Morin CM, Kowatch RA, Barry T, Walton E. Cognitive-behavior therapy for late-life insomnia. Journal of Consulting and Clinical Psychology 1993; 61 (1): 137-146.

87. Morin CM, Kwentus JA. Area review: Behavioral and pharmacological treatments for insomnia. Annals of behavioral medicine 1988; 10(3): 91-100.

88. Mullaney DJ, Kripke DF, and Messin S. Short report. Wrist-actigraphic estimation of sleep time. Sleep 1980; 3 (1): 83-92.

89. Parry BL, Berga SL, Mostofi N, Klauber MR and Resnick A. Plasma melatonin circadian rhythms during the menstrual cycle and after light therapy in premenstrual dysphoric disorder and normal control subjects. Journal of Biological Rhythms 1997; 12 (1): 47-64.

90. Pittendrigh CS and Daan S. A functional analysis of circadian pacemakers in nocturnal rodents; IV: entrainment: pacemaker as clock. Journal of Comparative Physiology [A]. 1976; 106: 291-331.

91. Roehrs T, Zorick F, Roth T. Transient and short-term insomnia. In: Kryger MH, Roth T, Dement WC, et al., eds. Principles and practice of sleep medicine. Philadelphia, WB Saunders Company, 1989.

92. Reber, AS. Dictionary of psychology. New York: Penguin Books, 1985.

93. Rechtschaffen A. and Kales A. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects, U. S. Department of Health, Education and Welfare Publication No. 204, U. S. Government Printing Office, Washington, D. C. 1968.

94. Regestein QR and Monk TH. Delayed sleep phase syndrome: A review of its clinical aspects. American Journal of Psychiatry 1995; 152 (4): 602-608.

95. Reiter RJ and Robinson J. Melatonin. New York: Bantom Books, 1995.

96. Richardson, Williams, Giesking, and Lubin. 1966.

97. Rusak B, Groos G. Suprachiasmatic stimulation phase shifts rodent circadian rhythms. Science 1982; 215: 1407-1409.

98. Sack RL, Lewy AJ, and Hughes RJ. Use of melatonin for sleep and circadian rhythm disorders. The Finnish Medical Society Duodecim 1998; 30: 115-121.

99. Sadeh A, Alster J, Urbach D and Lavie P. Actigraphically based automatic bedtime sleep-wake scoring: Validity and clinical applications. Journal Ambulatory Monitoring 1989; 2: 209-216.

100. Sadeh A, Hauri PJ, Kripke DF, and Lavie P. The role of actigraphy in the evaluation of sleep disorders. Sleep 1995; 18 (4): 288-302.

101. Sadeh A, Lavie P, Scher A, Tirosh E, Epstein R. Actigraphic home-monitoring sleep-disturbed and control infants and young children: a new method for pediatric assessment of sleep-wake patterns. Pediatrics 1991; 87:494-499.

102. Sadeh A, Sharkey M, Carskadon MA. Activity-based sleep-wake identification: An empirical test of methodological issues. Sleep 1994; 17 (3): 201-207.

103. Singer C, Wild K, Sack RL, and Lewy AJ. High dose melatonin is well tolerated by the elderly. Sleep Research 1994; 23: 86.

104. Snedecor GW and Cochran WG. Statistical Methods, Iowa State University Press 1980.

105. Spielman AJ. Assessment of insomnia. Clinical Psychology Reviews 1986; 6: 11-25.

106. Spielman AJ (Panel member). Sleep and arousal disorders. In: Guides to the Evaluation of Permanent Impairment. American Medical Association, revised edition, Appendix C 198; 229-239.

107. Spielman AJ and Anderson MW. The clinical interview and treatment planning as a guide to understanding the nature of insomnia: The CCNY insomnia interview. In Chokroverty ed. Sleep disorders medicine (2nd ed.). 1997.

108. Spielman AJ, Caruso L, and Glovinsky P. A behavioral perspective on insomnia treatment. Psychiatric Clinics of North America 1987; 10 (4): 541-553.

109. Spielman AJ and Glovinsky PB. The Evaluation and Differential Diagnosis of Insomnia. In: Pressman M and Orr W, eds. Sleep and Biological Rhythms in Health and Sickness, American Psychological Association, 1997: 125-160.

110. Spielman AJ and Glovinsky PB. The varied nature of insomnia. In: Hauri P ed. Case studies in insomnia. New York: Plenum, 1991: 1-15.

111. Spielman AJ, Nunes J, and Glovinsky PB. Insomnia. In: Aldrich M, ed. Neurologic Clinics. Philadelphia, PA: Saunders, 1996; 4 (3): 513-543.

112. Spielman AJ, Nunes J, and Yang CM. Chronobiology and Medicine. Medical Textbook. Association for the Behavioral Sciences and Medical Education and W. B. Saunders Co. (in press).

113. Spielman AJ, Saskin P, and Thorpy MJ. Treatment of chronic insomnia by restriction of time spent in bed. Sleep 1987; 10 (1): 45-56.

114. Susman JL. Insomnia in the elderly: A practical approach. Journal of Family Practice, 1989; 29: 528-533.

115. Takahashi JS and Zatz M. Regulation of circadian rhythmicity. Science 1982; 217: 1104-1111.

116. Thorpy MJ, Korman E, Spielman AJ, and Glovinsky PB. Delayed sleep phase syndrome in adolescents. Journal of Adolescent Health Care 1988; 9: 22-27.

117. van den Heuvel, Cameron J, Kennaway DJ, and Dawson D. Effects of daytime melatonin infusion in young adults. American Journal of Physiology 1998; 275: E19-E26.

118. van Hilten JJ, Braat EAM, van der Velde EA, Middelkoop HAM., Kerkhof GA, Kamphuisen HAC. Sleep medicine: Test and equipment validation studies. Ambulatory activity monitoring during sleep: An evaluation of internight and intrasubject variability in healthy persons aged 50-98 years. Sleep 1993; 16 (2): 146-150.

119. Vaughan GM. New sensitive serum melatonin radioimmunoassay employing the Kennaway G280 antibody: Syrian hamster morning adrenergic response. Journal of Pineal Research 1993; 15: 88-103.

120. Voultsios A, Kennaway DJ, and Dawson D. Salivary melatonin as a circadian phase marker: Validation and comparison to plasma melatonin. Journal of Biological Rhythms 1997; 12 (5): 457-466.

121. Waldhauser F, et al. In: Touitou Y, et al. eds. The physiological secretion pattern of melatonin in man. Melatonin and the pineal gland 1993: 331-338.

122. Waldhauser F and Steger H. Changes in melatonin secretion with age and pubescence 1985.

123. Webster JB, Kripke DF, Messin S, Mullaney DJ, and Wyborney G. An activity-based sleep monitor system for ambulatory use. Sleep 1982; 5 (4): 389-399.

124. Wurtman RJ and Waldhauser F. Melatonin in humans, proceedings of the first international congress on melatonin in humans, Vienna, November 7-9.

125. Waldhauser F, et al. The physiological secretion pattern of melatonin in man. In: Touitou Y et al. Melatonin and the pineal gland – From basic science to clinical application. Elsevier, 1993:331-338.

126. Waldhauser F, Waldhauser M, Lieberman HV, et al. Bioavailability of melatonin in humans. Neuroendocrinology 1984; 39: 307-313.

127. Weitzman ED, Czeisler C, Coleman R, Spielman AJ, Zimmerman J, Dement G and Polk, CP. Delayed sleep phase syndrome: A chronobiological disorder with sleep onset insomnia. Archives of General Psychiatry 1981; 38: 737-746.

128. Williams RL, Karacan I, Hursch CJ. Normative sleep values across age groups. EEG of human sleep: Clinical applications 1974.

129. Yang CM, Spielman AJ, D'Ambrosio, P, Serizawa, S, Nunes, J and Birnbaum J. A single dose of melatonin prevents the phase delay caused by a delayed weekend sleep pattern. Sleep 2001: 24 (3): 272-281.

130. Yang, CM and Spielman, AJ. Behavioral Treatment of Insomnia. Disease Management and Health Outcomes (in press).

131. Zaidan R, Geoffriau M, Brun J, Taillard J, Bureau C, Chazot G, and Claustrat B. Melatonin is able to influence its secretion in humans: Description of a phase response curve. Neuroendocrinology 1994: 105-112.

132. Zaidan R, Geoffriau, Claustrat B, Brun J, Taillard J, Bureau C and Chazot, G. A single afternoon or evening melatonin infusion advances the endogenous melatonin secretion in humans. Melatonin and the pineal gland 1993: 235-239.