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The Effects of Melatonin on Sleep and Cognition in Cognitively Impaired Elderly Individuals:

A Chronobiological Perspective

by

Girardin Jean-Louis

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.

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2/14/97
Date

Chair of Examining Committee

2-14-97
Date

Executive Officer

Arthur J. Spielman, Ph.D.

Mony de Leon, Ed.D.

Jeffrey Fookson, Ph.D.

John Antrobus, Ph.D.

Susan K. Manning, Ph.D.

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

The Effects of Melatonin on Sleep and Cognition in Cognitively Impaired Elderly Individuals:
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by

Girardin Jean-Louis

Adviser: Professor Arthur Spielman

The purpose of this investigation was to assess the effects of melatonin on sleep and cognition of cognitively impaired patients. The results of this study favor the use of melatonin to ameliorate sleep/wake disturbances and possibly enhance cognitive abilities in the elderly. Although there is not yet a clear evidence that the level of melatonin in these participants was, in fact, elevated by exogenous melatonin, specific improvement in sleep/wake parameters indicates a possible link. In addition, melatonin enhanced the amplitude of the rest-activity rhythm and stabilized the period length of the rhythm. These observations relate directly to a positive and significant effect of melatonin on both cognitive and noncognitive abilities. The ability to remember previously learned items improved along with a significant reduction of observed depressed moods. This approach to understanding the role of melatonin in the elderly is strongly supported by the

available data and suggests that a longer treatment regimen may yield better results regarding cognitive abilities. Better results could also be obtained in a sample of more severe demented patients. Interestingly, these results indicate no detrimental effects associated with chronic administration of a pharmacological dose of melatonin. Additionally, no side effects or contraindications were reported by any of the participants during the trials for a period of ten days. The data obtained in this investigation are important from a chronobiological point of view. They offer support for a different experimental approach to studying changes that occur in aging individuals by placing them within the framework of circadian rhythm disorganization. They also propose a mechanism whereby some of these changes can be addressed with minimal intrusion into the life of the elderly.

Preface

> What does old age represent? The old offer us the fruit of their time.... The elderly are pictures of our future. Where they have preserved their faculties, we can sense the emergence of selfhood, the wealth of experience and trials overcome. Where they are senile, we can sense their return to simplicity and innocence; decrepitude itself confronts us with the reality of life and death and heightens our own "sense of path".
>
> William Bryant, The Veiled Pulse of Time

During a moment of respite granted by the festivities surrounding the coming of this new year, it occurred to me how much I have been immersed in the process of formulating a means to alleviate disturbances associated with circadian rhythm abnormalities in the elderly. Although a treatment strategy with the use of melatonin is hereby supported, the possibility of having overlooked some of the inherent implications of these findings remains quite intriguing. Nonetheless, the necessity for developing nonpharmacological interventions to address circadian-related abnormalities associated with aging becomes even more pertinent with this experience. This line of research is very important and merits further attention.

This respite has also allowed me to become cognizant that this endeavor would have been impossible without the selfless contribution and support of several persons. I desire, therefore, to salute them and extend my deepest gratitude to them all. First of all, I want to express my thanks and gratitude to my mentor, Arthur Spielman. From the very first course on the basics of sleep research to the most advanced courses on the intricacies involved in ascertaining the etiology of sleep disorders, Art has been very insightful and challenging. He has helped me develop the ideas which underlie this dissertation and has guided me through its

completion. Besides the teaching of the rudiments of sleep research and clinical management of sleep disorders, Art has also inspired me to be an independent researcher, mindful of the importance of a professional network.

I am grateful to Mony de Leon and Jeffrey Fookson for their willingness to help me design and structure this research. Their comments have been invaluable and their moral support priceless. My gratitude goes to Mony for his assistance in the recruitment of patients from New York University Medical Center and his teaching of neuroanatomy. My gratitude also goes to Jeff for his teaching on how to approach time series analysis in chronobiological studies. I am also grateful to John Antrobus and Susan Manning for their support and understanding in consenting to serve as outside readers at a very late stage of the development of this thesis.

I wish to thank Harvey Taub for his generosity and trust. Dr. Taub has made it possible to establish a sleep laboratory at the college of Staten Island, without which this dissertation would have been extremely difficult to undertake. Under his tutelage, Hans von Gizycki, Ferdinand Zizi, and I have developed and managed the laboratory with a staff of about fifteen undergraduate students for the last two years. This laboratory is now fully equipped to support basic sleep research and training with the use of state-of-the-art instruments and has already made a significant contribution to the field of sleep research. Warm thanks to Hans and Freddy for their unshakeable faith and friendship; they have been instrumental in maintaining the success of this new laboratory and in the completion of this project.

My special thanks to all of the students who participated in different aspects of this study. I am eternally grateful for their support and affection. We have come together for an important mission and it's happening. Keep up the good work all of you "...".

I have also received guidance and support from a number of collaborators from other institutions. My thanks go to Robert Fullilove for his wisdom and continuous guidance in data management and analysis. Thanks to Saul Rothenberg, Margaret Moline, and Deborah Hillman for their editorial comments on this document. Thanks to Joao Nunes for his moral support and medical assistance to the laboratory. Thanks to Bruce Johnson, Greg Falkin, and all the fellows at the National Development and Research Institute for their moral support and guidance throughout my graduate training. I would like to thank Vicky Tartter, Claudio Stampi, Daniel Kripke, Peter Hauri, Scott Campbell, Alan Kluger, Steve Ferris, Tom McRae, and Greg Hofeldt for their support and assistance.

Finally, I would like to thank all my family, friends, and significant others who have always believed in me and have supported me unwaveringly.

January 1997

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Chapter 5

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A Chronobiological Perspective

Introduction

The study of circadian rhythms has led to the recognition that many disorders have a circadian basis. It is now well documented that physiological as well as behavioral processes including sleep/wake patterns, rest-activity cycles, body temperature, and hormonal secretions all display rhythms of approximately 24 hours. Malfunctions of the circadian timekeeping mechanism, therefore, may result in an inability of the organism to adapt to different environmental conditions; thus, rendering the organism unable to ensure its survival. Evidence for this assertion comes from the animal literature revealing that when the circadian generator, the suprachiasmatic nucleus, is ablated, researchers observe a consequential loss of rhythmicity in several circadian parameters.

Similarly, the failure of the timekeeping generator to exert its synchronizing influence of its subordinate effector organs leads to a disorganization of the circadian rhythm as observed in jet-lag, night shift work, affective disorders, and

advanced or delayed sleep phase insomnia. Disorganization of circadian rhythms noted in the elderly and particularly in individuals with Alzheimer's disease (AD) indexes a dampening of the amplitudes of these rhythms which include rest-activity cycle, body temperature and hormonal regulations. Those alterations may also accompany changes in cognitive functioning and noncognitive manifestations. Recently, it has been observed that a deficit in the amplitude of melatonin, the most robust marker of circadian integrity, may underlie the noted disturbance of the sleep/wake cycle in the elderly and dementia. This observation has led to the understanding that mechanisms capable of enhancing the melatonin rhythm could potentially address circadian rhythm disturbances reported by aging individuals.

While it is important to study as vigorously as possible the corollaries of the aging brain and their influence on health, the present chronobiological investigation was conducted to document the changes that occur in several parameters as individuals age. These parameters included, sleep/wake cycles, circadian rhythm in rest-activity patterns, cognitive abilities, noncognitive behavioral manifestations, and subjective estimates of sleep, sleepiness, and mood.

Changes observed in the parameters that accompany aging can be addressed and remedied with a number of pharmacological and non-pharmacological interventions. However, drugs used in the elderly have undesired side effects which may exacerbate disturbances in the circadian rhythm. In keeping with a more effective treatment strategy, interventions with minimal distortion in the lives

of the elderly are preferable and some have proven very efficacious. Phototherapy, for instance, has shown remarkable improvement in elderly persons with circadian sleep/wake disturbance. When applied to individuals with Alzheimer's disease, it reduces sundowning behavior and ameliorates sleep/wake problems. However, issues related to compliance with the procedure and complications due to certain medical conditions such as the retinopathies, have made natural substances capable of combating sleep/wake problems a more favorable treatment strategy.

One such strategy currently in widespread use is melatonin, a natural hormone manufactured by the pineal gland. Although present knowledge on the workings of melatonin is limited, it seems certain that it possesses the virtue of eradicating sleep/wake complaints and restoring circadian amplitudes in the elderly; with the least intrusion into the lives of these individuals. Based on the available evidence supporting the efficacy of melatonin, an experimental manipulation was proposed to ascertain its role as a synchronizing hormone. The data gathered, heretofore, has led to the speculation that the manipulation used in this study may have produced an augmentation of circulating level of melatonin in cognitively impaired elderly persons; which comprised the target population. Consistent with previous research, this procedure has allowed the observation of a stabilization of the rest-activity cycle in this sample as determined by actigraphy. Additionally, the sleep of the participating individuals was improved under

melatonin along with a reduction in depressed states and an increase in memory function.

Overview of Chapters

In chapter 1, research evidence supporting the notion of a dampening of circadian rhythms and sleep/wake disturbance in elderly individuals is discussed. Given the consequences attributed to this phenomenon, the discussion involves the role of the suprachiasmatic nucleus (SCN), the putative biological clock responsible for the entrainment of internal rhythms. Sleep/wake disturbance in elderly and AD persons is considered as a byproduct of the failure of these rhythms to synchronize to the beat of the SCN. A discussion of the neuroanatomic correlates of sleep/wake disturbances in dementia is also included.

In chapter 2, melatonin is discussed as one of the factors associated with biological aging based on neuroendocrine investigations. The reduction of melatonin has been proposed as the best candidate to explain the noted disturbances in circadian rhythms. To date, the functional role of this neurohormone has not been definitively established. Nevertheless, based on preliminary evidence melatonin is discussed as a therapeutic agent capable of restoring lost circadian rhythm amplitudes and robustness associated with aging.

Several researchers have reported on the ability of melatonin to induce sleepiness and help maintain sleep in both normal and clinical populations, to entrain circadian rhythms, and to alleviate jet-lag symptoms among others. The biochemical pathway for the production and secretion of melatonin has been determined. Its possible modality of action on target organs has been discussed. The entrainment and sleep-promoting virtues of melatonin have been reviewed along with the available evidence.

In chapter 3, the methodology for the present investigation is presented. This methodology made use of several parameters to assess the effects of melatonin. A number of subjective scales were used including sleep/wake diaries, sleepiness, and moods (see appendix 3-A, 3-B, 3-C). The neuropsychological battery used to determine changes in cognition and performance in these studies is included in appendix 3-D. The diagnostic measures used by numerous aging and dementia research and clinical centers to assess dementia are presented in appendix 3-E.

Essentially, techniques used to diagnose Alzheimer's disease and dementia as a whole are discussed. The discussion here involves the global staging scales which furnish an overall clinical impression of disease severity and an estimate of clinical changes during the course of the illness. Tests used in the assessment of functional capacity and activity of daily living are also presented. They allow the

determination of a range of basic and complex activities necessary for personal self-maintenance and independent community residence.

Additionally, measures of cognitive functions which document cognitive impairment and measures of behavioral symptoms observed in AD are also discussed with supportive evidence. Further, the neuropsychological tests most widely used are described as they provide a basis for documenting objectively suspected brain organic deficits. Results of these tests are often, if not always, confirmed by neuroimaging examinations. Therefore, a brief presentation is also included concerning the procedures involved in neuroimaging, namely computerized tomography, magnetic resonance imaging, and positron emission tomography.

Polysomnography has been the instrument of choice for the determination of sleep/wake profiles. However, difficulty in the longitudinal assessment of sleep and the high costs involved in this kind of studies have led to the use of a relatively new methodology known as actigraphy. As a measure of sleep, the protocol in this study made use of the actigraph methodology which allows unobtrusive longitudinal documentation of sleep/wake activity. Though cost-effective and easy to use, this instrument has been questioned because of a number of methodological issues that have been raised. Therefore, a series of investigations were conducted to test the validity, reliability, sensitivity, placement, and its application in different clinical populations before it can be

used in elderly individuals. Due to the unavailability of a scoring method that reliably identifies sleep and wakefulness, a novel scoring system was developed. In appendix 3-F, 3-G, and 3-H, the development of a novel scoring method, the Actigraph Data Analysis Software (ADAS), is discussed and empirical support for its utilization is provided.

In the first part of chapter 4, statistical procedures used in this study are presented and details about procedures implemented to answer specific questions are provided. In the second part, the chronic effects of melatonin are reported. Data analysis showed that melatonin affects circadian rest-activity profile, sleep, mood, and memory in cognitively impaired individuals.

In chapter 5, the effects of melatonin in this sample of cognitively impaired individuals are discussed. The discussion also involves a presentation on the differences of actigraphic profile as a function of age. In addition, the discussion incorporates empirical support for the use of a two-hour interval for optimal soporific effects of melatonin. The possibility of interaction between melatonin and other substances is also considered as an important factor in melatonin usage. Finally, subjective reports of sleep, mood, and noncognitive behavior are considered with an observation of more negative moods in individuals with mild cognitive impairment.

Research data presented in this discourse favor the use of melatonin to ameliorate sleep/wake disturbance and enhance daytime cognitive performance in the elderly population. These data support the role of melatonin as a synchronizing hormone. Melatonin reentrained the rest-activity rhythm of the elderly patients with corresponding reduction in depressed moods and an improvement in memory function. Further, melatonin administration enhanced sleep quality by reducing sleep onset time and nocturnal transitions from sleep to wakefulness.

Chapter 1

Sleep and Circadian Rhythm in The Elderly

Sleep Disturbance in Elderly Patients

The literature offers ample evidence suggesting a direct association between aging and the occurrence of sleep/wake disturbance (Foley et al. 1995; Meguro et al. 1995, 1990; Bliwise 1993; van Someren et al. 1993b; Ancoli-Israel et al. 1981). Recently, an epidemiologic study was conducted investigating the most common sleep complaints among elderly persons based on three years follow-up data from the Established Populations for Epidemiologic Studies of the Elderly (Foley et al. 1995). These complaints included: trouble falling asleep, waking up, awaking too early, nap propensity, and restlessness.

The results of that study indicated that less than 20% of the individuals sampled rarely or never reported any complaints. However, over half had at least one of these complaints with a high frequency of occurrence. These investigators also reported that 23% to 34% of these individuals reported symptoms of insomnia and 7% to 15% were rarely or never felt rested upon awakening in the morning

(Foley et al. 1995). It is also important to note that these complaints were associated with a number of factors such as increasing respiratory symptoms, depressive symptoms, physical disabilities, nonprescription medications, and poor self-perceived health. A number of other medical conditions have been associated with sleep disturbance in the elderly. Those conditions include: nocturia, headache, bronchitis and asthma, cardiovascular disease, gastrointestinal disorders, diabetes, chronic pain (Bliwise 1993). In sum, it has been established that over half of the institutionalized population in the United States over 65 years old suffer from some form of chronic sleep disturbance associated with one or several factors. They include: disruptions of circadian rhythms, death of a spouse, close friends, or relatives, social changes, and side effects of medications (NIHCDCS, 1991)

Sleep architecture is notably affected by aging (Bliwise 1993; Vitiello et al. 1992, 1989). Those changes include an increase in:

1. wake time during the sleep period
2. number of nocturnal awakenings
3. nocturnal sleep latency
4. stage I percent

The amount of slow wave sleep and sleep efficiency, however, has been found to decrease substantially (Bliwise 1993; Anch et al. 1988). Sleep

fragmentation in the elderly has been linked to the incidence of periodic limb movements during sleep and sleep apnea (Ancoli-Israel et al. 1981). Circadian rhythmicity has also been reported as affected by aging, thus leading to the speculation that temporal disorganization of physiological processes may underlie the aging process. However, conflicting results have been reported with some investigators arguing that some elderly individuals display compromised rest-activity rhythm under entrained conditions, whereas others do not. Weitzman et al. (1982) have shown that the amplitude and period of the circadian rhythm are reduced in healthy elderly individuals. These conditions are accompanied by the observed increase in daytime somnolence and napping behavior of elderly people. Others suggest that elderly individuals exhibit a well-preserved rhythm (Prinz et al. 1982). It is believed that the resynchronization of the circadian rhythm in elderly individuals would eradicate frequent awakenings at night and consequently a reduction of nap episodes during the day (van Someren et al. 1993b).

In patients with moderate to severe senile dementia of the Alzheimer's type, the observed nighttime insomnia, along with nocturnal arousals involving disorientation and wandering, are crucial factors in determining hospitalization. Research findings have indicated significant changes in sleep/wake patterns of Alzheimer's disease patients, particularly loss of slow wave sleep, increased amount and frequency of nighttime wakefulness, daytime napping, and decreased sleep efficiency (Vitiello & Prinz 1989). Furthermore, Vitiello & Prinz (1989)

have reported that these disruptions of nighttime sleep coupled with disturbances of sleep/wake rhythms are detectable with polysomnography in the early stage of AD. Moreover, these disturbances increase in magnitude with progressive and increasing severity of dementia. Vitiello & Prinz (1989) have shown that patients with AD spend nearly 40% of their time in bed at night awake and 14% of the daytime is spent asleep. Witting (1990) has demonstrated with the use of rest-activity measures that circadian rhythms in AD patients are markedly disturbed. Those rest-activity measures tended to be correlated with the severity of dementia as well. A similar observation was made by van Someren et al. (1993a) in an actigraphic study. However, these authors noted that not all patients with AD displayed disturbances in their circadian rhythms. It is also important to remark that not all circadian rhythms are compromised in individuals with a mild/moderate form of the disease. Prinz et al. (1982) have demonstrated that core body temperature remains relatively unaffected by the global neuronal degeneration that characterizes Alzheimer's disease; at least in its moderate stages. These findings may be explained by the recognition that these processes may be controlled by two different pacemakers (see next chapter).

Neuroanatomic Markers of Sleep/Wake Disturbance

Investigators have observed an association between the degree of sleep problem and the degree of cognitive impairment (Vitiello & Prinz 1989). This observation has generated the hypothesis that disturbed sleep may index neuronal degeneration in demented patients (Prinz et al. 1982). Consistent with this hypothesis, several studies have been conducted in an effort to locate the neuroanatomic markers of sleep disturbances in AD. Investigators have shown that degeneration in cortical presynaptic cholinergic nerve terminal originating from the nucleus basalis of Meynart in the basal forebrain, which is believed to have sleep promoting properties, is severely affected in AD individuals (McKenney et al. 1982). Histopathologic investigations have revealed substantial neuronal degeneration in brainstem regions including the nuclei raphe dorsalis, locus coerelus, reticularis tegmenti, centralis superior, magnocellularis, alae cinereae and the reticular formation and the medulla (Ishino & Otrsuki 1975). The observed degenerations in these important pathways, regulating sleep, have been proposed as factors associated with sleep disturbances in AD patients.

To date laboratory tests that are noninvasive and usable in large scale clinical trials do not reliably yield diagnostic certainties for AD. Such tests are necessary in studies focusing on treatment and prevention. There is some evidence, however, suggesting that sleep/wake variables might be useful biomarkers for AD. Sleep variables (i.e., percentage wake, rapid eye movement

(REM), and slow wave sleep (SWS), and time in bed) can discriminate patients with AD from normal controls with 90 percent overall accuracy (Prinz et al. 1982). The degree of discrimination between AD volunteers and elderly normal persons was found to depend on stages of the disease. The discriminant model used by Vitiello yielded a classification rate of 63 percent suggesting that the model is not robust in detecting AD by simply relying on sleep/wake changes.

While Vitiello et al. (1989) could discriminate between mild/moderate AD patients and normal control volunteers using sleep/wake variables as determined by polysomnography, it is not clear if such discrimination is possible with other sleep/wake paradigms. In a study investigating differences between sleep/wake patterns of AD individuals and multi-infarct dementia patients, Aaron-Peretz et al. (1991) found no significant differences. They could not demonstrate sleep disintegration in AD individuals. The authors proposed that sleep disturbances may be detectable only in more advanced stages of the disease. Moreover, sleep patterns of patients in nursing home facilities may be affected by factors not directly related to their condition. One such factor relates to a lack of exposure to the light/dark (LD) cycle. This is particularly important because it represents the best synchronizer of circadian rhythm (Campbell et al. 1995; Czeisler et al. 1981). Chronobiological investigations have shown that LD exerts its influence on biological rhythms by acting on the suprachiasmatic nucleus.

Perspective on Circadian Rhythms

Historically, circadian rhythmicity has been recognized from the observation that certain plants seemed to exhibit a passive response to environmental periodicity. The heliotropic plant provided a good example of diurnal variations; this observation was incorporated in certain Greek mythology. Further, using the heliotropic plant, Jean-Jacques d' Ourtous de Mairain demonstrated that circadian rhythms did not passively respond to the environment as was previously conjectured. This plant, placed in isolation from diurnal variations, was able to show daily cycles similar to the ones displayed in constant environmental conditions (i.e., light, temperature, and others). This finding spawned several studies into the nature of plant circadian rhythms which led to the understanding that these rhythms were endogenous. One of the most important observations in this line of investigation is found in 1832 in the work of Augustin de Candolle. Essentially, he demonstrated that, under constant conditions, daily cycles in plant life were not precisely 24 hours (Moore-Ede et al. 1983).

Since these observations, it has been shown that different species have a period of less than 24 hours, while others have a period of a little more than 24 hours; both of which approximating 24 hours, hence the term circadian (with "circa" meaning about, and "dies" meaning day). The imprecision in the daily

cycles of organisms is shown in "free-running" conditions. Essentially, rhythms studied to date have shown an ability to synchronize to external stimuli. When placed in isolation from these stimuli, organisms still display their endogenous rhythm; albeit at a different period. Paradoxically, the ability of organisms to free-run is considered as an advantage. It allows organisms to maintain a stable phase relation with the environmental cycles and/or to adapt to seasonal variations in day length. Interestingly, studies have also shown that humans, when observed in isolation units, exhibited free-running rhythms as well (e.g, rest-activity, body temperature, cortisol, TSH, prolactin, melatonin) that can be entrained to the environmental light-dark cycle. Human free-running rhythms have been found to be about 25 hours. Therefore, were it not for the suprachiasmatic nucleus, a pacemaker with the capacity to maintain the proper phase relations with environmental zeitgebers, humans would actually lose about one hour each day (Ralph et al. 1990; Moore-Ede et al. 1983).

Location and Morphology of The Suprachiasmatic Nucleus

The suprachiasmatic nucleus is defined as a set of central neural structures which is primarily responsible for the generation and regulation of circadian rhythms in behavioral and physiological functions. Studies have localized the SCN in the anterior hypothalamus immediately above the optic chiasm (Swaab

1985). Anatomically, the SCN is seen as a small structure (0.25 mm^3), each of its two sets of nuclei containing 10,000 neurons.

The SCN is considered to be sexually dimorphic (i.e. more elongated in women and more spherical in men), with the vasopressin cell number and volume similar in both sexes. It is mainly composed of densely packed, parvocellular neurons and is nearly always clearly identifiable by cytoarchitectonic measures. It has been estimated that at birth, the SCN comprises 13% of the vasopressin-expressing neurons and 20% of the total cell number in adults. Cell numbers rise to maximum values 1 to 2 years postnatally and gradually decrease to about 50% during adulthood (Swaab et al. 1990).

Other studies undertaken to examine the pathways that may be involved in circadian entrainment have established two entraining pathways. The first one is a direct retinohypothalamic pathway which transmits photic information to the SCN and pineal (Cahill & Menaker 1989; Cahill & Menaker 1987; Ohi et al. 1991; Zatz and Herkenham, 1981). Recent anatomical research has yielded evidence for a secondary visual pathway referred to as the geniculohypothalamic tract stemming from the intergeniculate leaflet of the lateral hypothalamus (Rusak and Boulos, 1981; Pickard 1982; Rusak et al. 1989; Card & Moore 1982; Braak & Braak 1992; Rietveld 1992; Stephen et al. 1981; Mai et al. 1991)

Circadian Rhythms in Dementia

Neuropathologic studies in old age and in Alzheimer's disease have indicated selective deterioration of the SCN cell group [i.e., arginine-vasopressin cells] (Swaab et al. 1985; Swaab et al. 1987; Swaab et al. 1992b). These alterations are associated with changes in secretory outputs of the hormones manufactured by the pineal gland. One effect attributed to these changes is a phase-advance in hormonal secretions and reduced period and amplitude [e.g., melatonin, prolactin, TSH, and cortical] (van Coevorden et al. 1991), as well as an increased intradaily variability and a decreased interdaily stability of the circadian rhythm (van Someren et al 1993a; McGinty & Stern 1988). van Coevorden et al. (1991) also reported that, although sleep duration and architecture were disturbed, release of these hormones continues in old age. This finding seems consistent with other evidence suggesting an age-associated advance in the phase of body temperature and wrist activity. It is speculated that these changes may underlie the observation that in elderly persons, there is a reduction in sleep efficiency, SWS, and REM sleep (van Someren et al. 1993; Bliwise 1993; van Coevorden et al. 1991).

It has also been reported that both the retina and the optic nerve, which innervate the SCN, exhibit degenerative changes in AD (Katz et al. 1989). The deterioration of the SCN cell group, along with decreased melatonin secretion, have been proposed as a possible contributor of the reported sleep disturbances in

old age, particularly in people with AD (Swaab et al. 1987). The disruptions of circadian rhythms in AD patients are thought to be one of the factors contributing to mental decline (Fekete et al. 1985).

These observations have revealed the factors involved in circadian rhythm disturbances in old age and AD. They further suggest that a successful treatment strategy can be proposed since the entraining pathway is known and its modality of operation is somewhat defined. Such strategy should involve minimal intrusion into the life of volunteering patients while affecting directly the synchronizing mechanism.

Chapter 2

Therapeutic Management of Sleep and Circadian Rhythm Disturbances: A Case for The Use of Melatonin

Although several lines of pharmaceutical investigations have been systematically pursued leading to a vast literature documenting both the progression and course of AD, no cure has been found for Alzheimer's disease. Be that as it may, it is imperative that a good medical and social management be followed in order to ease the burden of the family caring for the AD patients. Clearly, medications can help ameliorate some of the symptoms exhibited by the Alzheimer's individual including agitation, anxiety, and sleep problems among others. To date, only one drug (i.e., Tacrine) has been approved by the FDA for the specific treatment of AD. However, medications prescribed to alleviate AD symptoms have been associated with a number of unwanted side effects (Ancoli-Israel et al. 1992; Witting et al. 1990). They include nervousness, dizziness, loss of appetite, daytime sedation, sleep disturbances, and psychomotor impairment.

Neuroleptic medications that have been prescribed to demented patients to treat behavioral disorders are not effective. Research findings have indicated that they are more effective than placebo in only 18 of 100 patients (Schneider et al. 1990). Evidence also suggests possible side effects associated with neuroleptics prescribed to treat behavioral domain symptomatology. Their consumption may lead to cognitive impairment and/or behavioral aggravations such as anticholinergic effects, gait and balance, hypersomnia, dry mouth, and extrapyramidal symptoms (Satlin et al. 1991; Reisberg et al. 1988; Reisberg et al. 1987). Though these side effects are highly undesirable, intervention strategies continue their course with a heavy reliance on pharmaceutical agents.

Recently, efforts have been deployed to investigate other strategies to manage behavioral symptoms documented in AD patients. It has been found that some of these behavioral symptoms may be a byproduct of a disturbance noted in the circadian rhythms of AD patients. Empirical evidence from the literature supporting the utilization of these modalities of treatment will be reviewed, with an emphasis placed on bright light and melatonin, two nonpharmacological strategies capable of improving circadian disturbances observed in demented patients. This presentation will, however, favor the use of melatonin as a preferred treatment strategy to treat behavioral, physiological, and cognitive symptomatology associated with disturbances in the circadian rhythms of demented persons.

Nonpharmacological Interventions in The Elderly

Nonpharmacological treatment modalities are preferred over pharmacological interventions which are accompanied by undesired daytime side effects, interactions with other medications, and tolerance. In addition, metabolism and rate of excretion of drugs are much slower in the elderly, leading to excessive sedation, confusion, cognitive impairment, and possible personality changes (Ancoli-Israel 1993). However, a number of nonpharmacological studies have indicated immediate effects on circadian parameters after phototherapy, vigorous exercise, and body heating with no apparent side effects (van Someren et al. 1993). Further, several investigators have suggested that these forms of brain stimulation might prevent or partially reverse brain atrophy (Swaab et al. 1991). Incidentally, it has been also suggested that exercise, which is naturally associated with an increase in sensory and proprioceptive stimuli, enhances stimulus sensitivity (Shearer et al. 1989).

These modalities present, nonetheless, some difficulty in the practicality of their implementation. Demented elderly patients, particularly in severe cases of dementia, may not comply with these procedures. Three other strategies have also been applied in sleep studies involving the elderly. They involve deprivation of daytime naps, curtailment of time in bed, and enforced social interaction.

Research relying on the notion that social interaction may serve as a potent zeitgeber has been equivocal. Evidence for a reduction in behavioral agitation, which accompanies dementia, has been found to be flawed by an increase in light exposure and daytime activity. Additionally, research findings indicated that enforced social interaction does not lead necessarily to the synchronization of circadian rhythms (Minors et al. 1989; Powell et al. 1974). One report has shown that elderly individuals who are imposed a sleep-restricted schedule exhibited better sleep continuity with possible daytime sleepiness experienced as is the case in sleep restriction therapy (Reynolds et al. 1987; Spielman et al. 1987; Rubenstein et al. 1987).

Moreover, correlation research investigating the relationship between naps and sleep problems is not yet convincing. It is of importance to note that this paradigm does not address the issue of reentraining the circadian rhythm nor does it suggest a strategy for preventing daytime nap episodes which would be exacerbated in the elderly. However, it is evident that in correlation studies, researchers have found that sleep/wake disturbance is associated with activity of daily living as well as cognitive impairment (Meguro et al. 1995, 1990; Prinz et al. 1982; Vitiello et al. 1990)

In contrast, the former treatment modalities namely: phototherapy (Campbell and Dawson 1990), body heating (Bunnell et al. 1985), and exercise (Powell et al. 1974) are practically more meritorious insofar as the reentrainment

of the circadian rhythm is concerned. There is some evidence suggesting that these modalities may be mediated by melatonin, whose rhythm in demented persons is severely attenuated. Consequently, there has been report of parallel decline in sleep quantity and quality (van Coevorden et al. 1991) and reduced 6-sulfatoxymelatonin (Haimov et al. 1994) associated with aging. Contrary to the decline in the observed amount of melatonin in infants which is thought to occur because of increasing body size, the cause of the age-related decline in melatonin has not been firmly established (Reiter 1992).

Several theories have been offered including the reduction in the population or metabolism of pinealocytes, decreased activity of pineal norepinephrine neurons, a decrease in response of β-receptors in pinealocytes, and possible alterations in the clearance rate of melatonin (Waldhauser et al. 1988). It is believed that the reentraining effect of these treatments was mediated by melatonin, thus supporting the notion that melatonin is a robust marker of circadian rhythm. Further, one explanation for these findings is that the endogenous melatonin rhythm must have been enhanced by these applications to effectuate a change in the circadian profile.

There is, however, a line of research evidencing the suppressive effect of melatonin production by light administration (Bunnell et al. 1992; Lewy et al. 1992). These observations suggest that, though melatonin is involved in the

entrainment of circadian rhythms, it may not be the final pathway for these treatments. van Someren et al. (1993) proposed that body temperature may be a better candidate for circadian entrainment since it increases with all three treatments. It is conceivable that these interventions may act on body temperature according to their unique mode of operation by manipulating the melatonin rhythm. It has been suggested that decrease in core temperature subsequent to melatonin ingestion may mediate an increase in sleepiness. Also, when melatonin was given to healthy normal volunteers, investigators observed a significant decrease in temperature along with an increase in the propensity to fall asleep (Reid et al. 1996; Deacon et al. 1995, 1994; Dollins et al. 1994).

Bright Light on Circadian Sleep/Wake Rhythms

The breakdown of the circadian sleep/wake rhythm, with significant amounts of wakefulness observed during the night with compensatory sleep occurring during the day, is one of the hallmarks of biological aging and may be associated with diminished exposure to bright light and a decrease in activity level (Campbell et al. 1993). Chronobiological studies in AD have revealed fragmented sleep/wake cycles and "sundowning", a syndrome of recurring confusion and increased agitation in the late afternoon or early evening (Vitiello et al. 1992). These findings are proposed to be a result of inappropriate timed rest and activity

(Satlin et al. 1992). In addition, it has been reported that AD individuals have a lower amplitude and delayed acrophase of circadian locomotor activity than healthy normal controls (Satlin 1991). This delayed acrophase has been proposed as a result of sundowning behavior late in the afternoon (van Someren et al. 1993b).

Several studies suggest that the human circadian sleep/wake patterns can be reset by exposure to bright light (Lewy 1987). The importance of light to human physiology was already evident in the work of Wever in 1979 who used fractional desynchronization of circadian rhythmicity by augmenting or diminishing artificial light/dark cycles, reinforced by "gong" signals, to entrain the circadian rhythm. It became also evident with subsequent chronobiological investigations that, in order for all circadian variables to remain entrained, the intensity of light exposure should be around 3500 lux (Arendt & Broadway 1987).

Scheduled bright light exposure as proposed by Daan & Lewy (1984) has been used in different treatment modalities. Exposure to light induces daily phase shifts [a shift to either an earlier or a later time of the day] (Pittendrigh 1974). The magnitude and direction of the phase shifts are contingent upon the timing of light exposure relative to the subjective circadian time (Lewy & Sack 1986). Generally, research evidence has led to the understanding that light exposure is most effective when presented in the vicinity of the core body temperature minimum; the closer the exposure time, the greater the magnitude of the phase-shifting response. If

light is presented before the temperature minimum, a phase-delay of the circadian rhythms is observed; whereas, when light is presented after the temperature minimum, a phase-advance is obtained (Campbell and Murphy 1996). In essence, morning exposure to bright light induces a phase advance in human circadian rhythms [shifts them to an earlier time] whereas evening bright light invokes a phase-delay [shifts them to a later time] (Campbell et al. 1993; Lewy et al. 1992, 1987, 1985; Czeisler 1989, 1986). This phase-shifting phenomenon with photic stimulation has been proposed using a phase-response curve (PRC) (Lewy et al. 1983).

According to Lewy et al. (1992, 1987), timing and duration of light exposure are two critical procedural elements determining the effectiveness of phototherapy. Recently, there has been a return to using low intensity light as a way of entraining the circadian rhythm. Light intensity, previously thought to be ineffective in resetting the biological clock in humans are now showing significant synchronizing effects when timed appropriately. Studies have shown that light intensity as low as 180 lux is capable of phase-shifting the circadian rhythm (Luke et al. 1996). Low level of illumination (i.e., 250 lux) has also been shown to completely inhibit the onset of melatonin secretion when administered over the initial secretory phase; as obtained through the dim light melatonin onset procedure (see below for discussion) [Trinder et al. 1996]. For optimal effect, individuals' circadian time may have to be determined according to a procedure

referred to as phase-typing, circadian time may vary from one person to another (Lewy et al. 1992). This procedure allows one to determine when during the course of a 24-hour day, maximal effect of a treatment strategy can be obtained. It is beneficial that phase-typing be done for other treatment strategies as well since there is a time of day effect associated with drug efficacy.

The advances made with bright light experiments have rendered this therapeutic approach a good treatment strategy for chronobiological disturbances because it is simple to administer and presents few side effects; which may be negligible in some instances. It has been utilized to treat patients with seasonal affective disorder (Lewy et al. 1995, 1992), shift workers (Tepas et al. 1981), jet-lagged travelers (Daan & Lewy 1984), and sleep/wake abnormalities (Czeisler et al. 1981). Preliminary observations have shown an improvement in sleep/wake rhythm disturbances and a diminution of nocturnal agitation and wandering in AD patients when exposed to bright light for 2 hours (Satlin et al. 1992). Although this strategy proves successful, certain difficulty inherent in its presentation limits its use in elderly demented persons.

Melatonin on Circadian Sleep/Wake Rhythms

Phototherapy is preferred over pharmacological interventions in managing behavioral problems associated with AD because it is less invasive and presents

less side effects than drug interventions. However, the protocol involved in phototherapy requires exposure to bright light boxes for some period of time; the duration is contingent upon research criteria used by the investigator. Although recent findings seem to indicate that light of low intensity can shift the circadian rhythm, investigators continue to use light of higher intensity to effect changes in circadian parameters (Trinder et al. 1995). In this type of investigations, compliance with instructions provided by the investigator and/or caregiver is a serious concern and determines who is likely to benefit from this therapeutic strategy. Because of a lack of compliance from AD patients and other issues related to possible degeneration of the photic entraining pathway, it is proposed that melatonin may be an excellent substitute in the management of circadian rhythms disturbances in AD patients (Lewy et al. 1995; Czeisler et al. 1990). Since its recent surge as a "miracle product", melatonin has been spoken about as a substance with potential medicinal values. To date, studies have shown an improvement in a number of conditions which include insomnia, jet lag, and shift work.

Melatonin: The Darkness Hormone

Melatonin (*N*-acetyl-5-methoxytryptamine) is the chief hormonal mediator of the pineal gland, a pea-sized structure nestled in the center of the brain. Several

decades of studies looking at the concentrations of melatonin in the blood have indicated that it follows a diurnal cycle. Melatonin is a derivative of the neurotransmitter, serotonin, which is made from an amino acid called tryptophan derived from foods consumed during the day. Administration of tryptophan has been found to increase circulating levels of melatonin. It is thought that serotonin and melatonin have a strong influence on homeostasis, metabolism, and immune functions. These two neurotransmitters control the basic rest-activity cycle; with high energy level experienced during the day as serotonin is released followed by a period of restful state with the secretion of melatonin at dusk (Reiter 1995; Krausse et al. 1990).

Melatonin is mainly secreted at night and is virtually undetected during the daytime hours. Research evidence suggests that melatonin is synthesized in photoreceptors of the retina and in the pinealocytes of the pineal gland (Reiter 1990). This secretion is controlled by neural inputs from the retina and a sympathetic input from the suprachiasmatic nuclei. It has been proposed that the level of melatonin traces found during the daytime hours have their origin in the retina. Nighttime levels of melatonin in plasma vary among species and have been found in values 5-10 times higher than daytime levels which are determined by activity observed in the pineal gland in accordance with its endogenous rhythm (Arendt 1987).

Research efforts have been made to delineate the regulatory sites in the melatonin system of mammals. These two systems identified seem to share certain morphological and developmental similarities; notably apparent in that both the pinealocytes and the retinal photoreceptors use the same pathway for converting serotonin to melatonin. To date, the synthesis of melatonin in the retina is not yet clear. However, it is believed that some intracellular mechanism in the form of cAMP and protein synthesis is involved. Additionally, it has been proposed that dopamine, and not norepinephrine, may be the neurotransmitter regulating its production in mammals and lower vertebrates (Krausse et al. 1990).

The role of the pineal in melatonin production is by contrast more established. At night, the SCN releases norepinephrine which interacts with β- and α-adrenergic receptors on the membranes of the pinealocytes; 85% of melatonin released at night comes from the activation of β-receptors whereas 15% is the result of α-adrenergic receptors (Reiter 1992). The interaction of norepinephrine and these receptor sites stimulates the production of cyclic AMP, an intracellular second messenger system triggering the subsequent activation of protein kinase (PKA). PKA activates CREBB protein which augments the transcription of arylalkylamine *N*-acetyltransferase (AA-NAT), the enzyme that catalyzes the rate-limiting step in the conversion of serotonin to melatonin (Reiter 1992; Krausse and Dubocovich 1990). There is a line of research pointing to a

circadian rhythm observed in NAT activity in its modality of response to environmental stimulation as determined by both in vitro and in vivo procedures (Binkly 1976). Interestingly, rhythmic changes in NAT output have been noted in the pineal gland as well as in the retina; with its corresponding synthesizing activity on serotonin (Binkly 1979).

Some studies have also shown that melatonin may be secreted directly into the bloodstream, metabolized by unique degradative pathways in the brain as well as in the liver (Hirata et al. 1974; Kopin et al. 1961). Contrary to other hormonal transmission systems, melatonin has no specific storage or release mechanism. Once synthesized, it is released into the blood and virtually accesses every fluid and/or cell in the organism by virtue of its highly lipophilic characteristic.

Evidence also indicates that the hormone acts on high affinity receptors in the retina, CNS, and the pituitary gland. Recently, researchers have identified three melatonin receptors. The first two receptors are 60 % identical in amino acid sequence; Mel_{1a} is found mostly in the brain, Mel_{1b} is located in the retina. The third receptor (i.e., Mel_{1c}) is found in frogs and birds, but not in mammals (Reppert et al. 1995).

The Pineal Gland and Aging

A comprehensive presentation on the potential therapeutic virtues of melatonin seems to require a discussion on the pineal gland, the "aging clock", and its physiological ramifications. One of the most important observations in melatonin research was made by Lerner (1959). Essentially, he extracted melatonin from the pineals of cattle which presumably shared with the retina the task of transducing light energy and determined its chemical structure. Another significant contribution was made by Axelrod et al. (1974). These investigators found that the pineal gland produces its hormone according to a regular oscillating system in a manner analogous to a circadian rhythm.

One of the key tasks of the pineal is to maintain phase relations within a multi-oscillator system; a phase coordinator for multiple biological rhythms. It has the ability to regulate the biochemistry of organism depending on what environmental rhythms it is exposed to. Further, it also detects subtle rhythms such as seasonal and lunar changes that are not readily observable by the naked eye (Wehr 1991; Binkly 1979).

The pineal gland is known for its role in entraining circadian rhythms, such as the sleep-wake cycle, body temperature, endocrine functions among others. It also governs seasonal rhythms lasting over weeks or months. By registering daily photoperiodic changes, for example, the pineal gland helps biological organisms to

anticipate seasonal changes (Wehr 1991). The pineal regulates a number of behavior exhibited by animals who respond to seasonal changes (Aldhous 1985). It signals when animals should mate, migrate, or hibernate (Swaab et al. 1985).

The regulatory or synchronizing role ascribed to the pineal is rendered possible by the release of its messenger hormone, namely melatonin. It is understood that changes in levels of melatonin signal to the body when to enter puberty and begin sexual development. Incidentally, neonates have not been found to display a functioning circadian melatonin rhythm. According to evidence gathered by Reiter et al. (1995), nighttime melatonin level peaks during childhood reaching on the average a peak of 125 picograms per milliliter (pg/ml). At age sixteen, melatonin levels experience the first sharp decline suggestive of the onset of puberty; showing an average of 85 pg/ml. The rhythm further declines indicating a level of 50 pg/ml at age forty-five. As we approach age 80, nighttime melatonin levels show about 25 pg/ml (Cowley 1995; Reiter 995, 1987; Reiter et al. 1990).

The seemingly inevitable progressive reduction of melatonin has led researchers to develop treatment strategies capable of restoring youthful levels of melatonin as a way of reestablishing the lost flexibility and vigor of organisms. In the elderly suffering from insomnia, evidence suggests that they exhibit a melatonin deficiency (Garfinkel et al. 1995; Haimov et al. 1994). This deficiency,

as exemplified by a dampening of the circadian amplitude, is believed to underlie sleep/wake disturbances in the elderly.

Based on the available evidence, it was thought that the pineal gland would continue to operate by providing signals commensurate with a young organism when furnished exogenous melatonin. This action would translate into more robust circadian rhythms. Consistent with this understanding, a number of studies have been performed to answer a multitude of questions surrounding the role of the pineal's messenger, melatonin.

Experimental Inquiries With Melatonin

The discovery that melatonin is suppressed by light exposure has led chronobiologists to the understanding that melatonin could be directly involved with the circadian timing of sleep mediated by the SCN (Lewy et al. 1980; Wurtman 1985; Lewy and Sack 1986). In fact, it has been speculated that one of the functions of melatonin is to regulate seasonal rhythms such as the breeding cycles of many photoperiodic animals, by the duration and/or phase of melatonin production corresponding to the annual change in photoperiod (Wehr et al. 1991). Changes in the duration of nocturnal melatonin production act as chemical signals mediating photoperiodic responses (Tamarkin et al. 1985). Many animal studies

with the administration of the hormone by infusion pump, injection, or feeding, have shown its synchronizing effect (Symons et al. 1983; Underwood 1977).

Melatonin and Phase-Shifting

The identification of melatonin receptors in the human suprachiasmatic nucleus has given the impetus for investigations with the administration of pineal melatonin in both blind and sighted individuals. Researchers have demonstrated circadian phase-shifting effects of exogenous melatonin in sighted humans (Wirz-Justice et al. 1996; Lewy et al. 1995; 1992; 1980; Deacon et al. 1994; Zaidan et al. 1994). Furthermore, they showed a significant relationship between time of administration and the magnitude of the phase-shift response. A phase response curve has also been found for melatonin which presents similar features with the shapes of PRCs for other stimuli such as the one described for light earlier. It has been found that the PRC for melatonin is nearly opposite in phase with the PRC for light (Lewy et al. 1995; Czeisler et al. 1989; Wever 1989).

The determination of a PRC for melatonin has important implications, hence deserves some attention in this context. The PRC for melatonin was derived after the observation that phase-shifting effects could be captured when the dim light melatonin onset (DLMO) is used as a marker. The DLMO is defined as the first interpolated point above 10 pg/ml as determined by specific gas chromatographic-negative chemical ionization mass spectrometric assay of blood

samples. This procedure allows the assessment of small changes in circadian phase position subsequent to melatonin ingestion for two weeks. The baseline level of DLMO can be used to assess circadian phase in response to light treatment and provides information about its own circadian pacemaker (Lewy et al. 1995, 1992).

The finding that melatonin has phase-shifting properties, controlling even its own endogenous production, coupled with the dim light melatonin onset, have provided the basis for assessing the optimal and proper scheduling for melatonin therapy in a variety of disorders. With proper scheduling, it is now possible to treat both advanced and delayed phase syndromes (Lewy et al. 1995, 1985, 1983; Deacon et al. 1994; Zaidan et al. 1994), sleep/wake maladaptation caused by shift work (Sack et al. 1992; Eastman 1986), seasonal affective disorders (Lewy et al. 1987), and sleep/wake disturbances induced by jet lag (Arendt 1995; Boulos & Rusak 1982). With precise phase typing, investigators can determine and avoid the "dead zone" in individuals' PRC and therefore correctly manipulate phase positions for desired effects.

Even very small doses of the hormone can phase shift the body's clock and affect sleep/wake parameters. Evidence for this assertion comes from a study conducted by Zhdanova et al. (1996). This double-blind, placebo controlled cross-over study provided volunteers with two doses (.3 mg and 1.0 mg) of melatonin and a placebo on three different nights over several weeks. The volunteers were

then monitored to determine their sleep onset latency and the quality of their sleep. It was found that both doses of melatonin reduced sleep onset latency, increased stage II, and increased sleep efficiency as measured by the percentage of time in bed spent sleeping, and reduced the number of awakenings after the onset of sleep. The study supported the hypothesis that melatonin even at low doses has hypnotic effects.

Melatonin and Jet Lag

According to a 1993 report by the National Commission on Sleep Disorders Research, frequent or chronic insomnia affects more than 60 million Americans, about one of every three adults, among which obviously is the elderly population. One such sleep problem is referred to as jet-lag; a temporary disturbance of biological rhythms caused by traveling across several time zones which results in insomnia and other symptoms including a lack of concentration and a feeling of disorientation. This circadian rhythm disturbance engenders a number of changes including blood pressure, blood sugar, mood, energy level, arousal, and hormonal levels (Arendt et al. 1995).

Although conventional sleeping pills may help induce sleep, patients have reported experiencing the other symptoms associated with jet lag. Several studies have shown that melatonin can combat symptoms commonly associated with jet lag; especially, when melatonin is administered to patients during the daytime.

Researchers have tested the effects of melatonin on 400 travelers and observed that those who received melatonin were able to reduce their jet lag by 50 percent (Nickelsen et al. 1991). In another study 30 volunteers who have experienced some difficulty with jet lag in the past were administered 8 mg of melatonin or placebo for four days starting on the day of the flight. The volunteers on melatonin were able to sleep and focus better and experienced fewer mood swings than those on placebo (Arendt et al. 1995).

Melatonin and Insomnia

The therapeutic effects of exogenous melatonin have also been investigated in a number of studies having for primary objective the restoration of a synchronized sleep/wake cycle in individuals with insomnia. As discussed earlier, the use of hypnotics in the management of sleep-related disturbances poses a serious challenge to clinicians involved in the search a quick "fix" for patients with a complaint of insomnia. Having learned about the side effects associated with such managements, the prospect of a natural substance with no known adverse effects has spawned studies yielding empirical evidence which strongly suggests its hypnotic properties.

Since the determination of the structure of melatonin, it has been found to be implicated in the regulation of a number of circadian markers and certain behavioral processes (Martini 1971, Gwiner 1978). Several lines of research

investigating the physiological effects of melatonin have shown an improvement in either sleep initiation or maintenance or both in normal individuals as well as patients with sleep disorders (Garfinkel et al. 1995; Haimov et al. 1995; Sack et al. 1994; Tzischinsky, et al. 1994; Haimov et al. 1993; McFarlane et al. 1991; Waldhauser et al. 1990).

Haimov et al. (1995) reported that melatonin, administered two hours before bedtime for a week, greatly improved sleep in melatonin-deficient elderly insomniac patients. Basically, when melatonin was administered in fast-release preparations, it significantly reduced sleep onset time. However, when melatonin was given in slow-release formula, it significantly improved sleep maintenance with no indication of tolerance over prolonged usage. In addition, sleep quality deteriorated after cessation of treatment. The findings of this study are important since they suggest that melatonin treatment may be effective only in melatonin-deficient insomniacs. Similar evidence has also been found in a parallel study conducted by Garfinkel et al. (1995). Essentially, they found that controlled-release melatonin administered for three weeks improved sleep quality as shown in a reduction of wake after sleep onset and an increase in sleep efficiency index. It is also important to note that this observation was made while participants in that study were taking other medications and were suffering from chronic diseases. However, no increase in sleep duration was found.

Melatonin is known to have a rapid absorption course, with peak levels occurring within 90 minutes. Using a supraphysiologic dosage, McFarlane et al. (1991) have found that melatonin increased the period length of subjective sleep and daytime alertness; with this effect noted on the second or third day of administration. The delayed effects of melatonin have also been reported in another study conducted by Arendt et al. (1984). In another study in which normal volunteers had an insomnia induced, researchers found that melatonin substantially reduced both sleep onset latency and the number of awakenings, thus increasing sleep efficiency (Waldhauser et al. 1990).

Melatonin in Dementia

Research evidence has led to the understanding that dementia is associated with circadian rhythm disturbances expressed in several axes including body temperature (Minors et al. 1989), hormonal levels [i.e., aldosterone, renin, testoterone, growth hormone, thyroid-stimulating hormone, estradiol, cortisol, and melatonin] (van Someren et al. 1993b; Bliwise 1993; van Gool and Mirmiran 1986), sleep/wake patterns (Vitiello et al. 1990; Prinz et al. 1982; van Gool and Mirmiran 1986, 1983), and rest/activity profiles (van Someren et al. 1993a; Bliwise 1993; Jacobs et al. 1989). These disturbances are believed to relate to a dampening in the amplitude of the circadian rhythm which is associated with reduced performance level and alertness (van Someren et al. 1993b). Several

researchers have proposed that these disturbances may be the result of an internal "phase drift" or a state of desynchrony in the rhythms driven by the X and Y pacemakers resembling the patterns of desynchronized rhythms observed in isolation studies (Sharma et al. 1989).

The X pacemaker has not been clearly defined anatomically; very little is known about its location and mode of operation. The Y pacemaker, on the other hand, has been extensively studied and is believed to be located in the SCN. Aging studies have linked the noted circadian rhythm disturbance to a failure of SCN cell groups to properly and timely gauge the manufacturing of melatonin (van Coevorden et al. 1991, Swaab et al. 1987). These findings suggest that chronobiological investigations in dementia may lead to empirical evidence supporting the reentrainment of the circadian rhythm.

To further examine the mechanisms regulating sleep/wake rhythms, assessments of plasma levels and urinary secretion of 6-sulfatoxymelatonin (aMT6s) have been conducted in various laboratory settings. Investigators have reported that melatonin secretion, not only exhibits an earlier timing but also, declines with age (van Coevorden et al. 1991; Skene et al. 1990). van Coevorden et al. (1991) have documented that neuroendocrine secretions (i.e., melatonin, prolactin, TSH, and cortisol) in a group of healthy elderly men were different from those of young normal volunteers. Daytime and nighttime circulating levels of TSH and GH were lower in old age. Additionally, the onset of melatonin, TSH,

and cortisol was earlier than normals. The authors concluded that these age-related differences were noted in the amplitude of these rhythms but not necessarily in the secretory output. These observations suggest a degeneration in the central mechanism responsible for the temporal organization of endocrine functions.

Support for these findings has been provided by another investigation conducted by Skene et al. (1990). These investigators have found that daily variation in the concentration of melatonin were particularly affected in AD patients. Marked daily variation in elderly individuals as well as in AD people virtually disappeared. Night-time melatonin concentration in AD individuals was found to be similar to their daytime levels. Evidence has been provided linking these observations to abnormal noreadrenergic axons in the pineals of elderly and AD persons. Further, this progressive attenuation of the melatonin rhythm may be associated with a gradual reduction of β-adrenergic receptor in the pinealocytes (Reiter 1995).

Rationale for The Present Study

A substantial body of literature suggests that disturbances observed in rest-activity data and sleep/wake cycles of elderly individuals may relate to alterations in the functional capacity of the suprachiasmatic nucleus. These disturbances may accompany cognitive impairment and noncognitive behavioral symptoms. As discussed in previous sections, several paradigms have been proposed to address these disturbances including pharmacological and nonpharmacological strategies. Recent evidence indicates that a direct application of exogenous melatonin may be more beneficial in addressing circadian rhythm disturbance than the other modalities. Haimov et al. (1995) have proposed that a nocturnal melatonin deficiency may be the factor responsible for disturbed sleep/wake patterns in the elderly; particularly when no medical conditions have been linked to disrupted sleep. Parallel observations have been made by other investigators (Garfinkel et al. 1995; Skene et al. (1990) suggesting a decline in the melatonin rhythm. Melatonin administration can, therefore, be used to address sleep complaints in these cases. Moreover, it is certainly more feasible than the other aforementioned treatment strategies and is not associated with known adverse effects in the populations studied to date. Anecdotal reports suggest, however, that individuals

who use large dosages may experience residual sleepiness upon awakening in the morning.

The effects of melatonin administration have been investigated in numerous research studies. Research findings have demonstrated an improvement in sleep initiation and maintenance in both normal individuals and patients with sleep disorders. However, most of these studies have been conducted with the use of polysomnography as the instrument to assess differences in sleep/wake parameters. Furthermore, since these studies were conducted in controlled environmental settings, the extent to which these findings are ecologically valid has always been controversial. With the fabrication of modern actigraph devices, several investigators have proposed the utilization of the actigraph methodology to assess sleep/wake activity unobtrusively in natural settings. In addition, it has been suggested that this methodology may be very useful in assessing possible differences in sleep/wake activity with the introduction of drug treatments.

Investigating the effects of different dosages on sleep parameters, it has been found that elderly insomniacs can tolerate both low and high doses of melatonin with reported improvement in sleep (Singer et al. 1994a; Singer et al. 1994b). Investigators have also observed that sustained release melatonin preparations can as well improve the sleep of elderly patients with insomnia when administered over a long time period (Garfinkel et al. 1995; Haimov et al. 1995). It remains unclear, however, if immediate release preparations have similar effects

on sleep. Based on current evidence, it is generally accepted that hypnotic effects of melatonin are noted when the regimen includes a chronic administration with relatively low dosage (Haimov et al. 1995; Arendt et al. 1984). Further, Sack et al. (1992) have shown that melatonin can improve the synchrony between endogenous circadian rhythms and daytime sleep in shift workers.

Other lines of research have led to the understanding that melatonin may be also involved in the control of certain types of behavior. Research findings suggest that melatonin may reduce anxiety (Golus and King 1981). Others have reported conflicting findings with regards to its efficacy when given to individuals with different types of depression. Improvement in sleep parameters is noted in patients with seasonal affective disorder, whereas, in severe depression sleep seems to worsen (Carmen et al. 1976).

Further, to determine if pharmacological doses of melatonin had any behavioral effects, healthy normal individuals were studied on a battery examining numerous neuropsychological indices including, memory, performance, and visual sensitivity. It was found that melatonin decreased self-reported alertness and increased sleepiness as measured by the profile of mood states (POMS) and the Stanford sleepiness scale (SSS). However, as reported by Lieberman et al. (1984) motor performance was not impaired when assessed with the digit symbol substitution test.

In a similar study, Jean-Louis et al. (in press) used several behavioral and cognitive measures to determine which ones were sensitive in detecting changes associated with melatonin manipulations (Spinweber et al. 1982; McNair et al. 1973). The results of this study have shown that acute melatonin administration is associated with a significant reduction in sadness (i.e., from the visual analog scale). These investigators also observed a significant decrease in activity, arousal and memory related to melatonin. However, performance on the digit symbol substitution test increased, while performance on the finger tapping decreased subsequent to melatonin administration.

Augmenting the circulating levels of melatonin with an exogenous preparation has been proposed as an efficacious mechanism for reentraining the circadian rhythm in cognitively impaired elderly individuals. Based on the available evidence for the therapeutic role of melatonin and valid and reliable measures that can be used in documenting its efficacy in the elderly, this study was undertaken in an attempt to remediate the observed cognitive and behavioral disturbances observed in the elderly. The purpose of this study was to investigate the effects of melatonin on the sleep/wake patterns and daytime functioning of cognitively impaired elderly patients. Data analysis was aimed at addressing the following issues:

1. Differences in rest-activity profiles as a function of age

2. Effects of melatonin on sleep/wake parameters (i.e., TST, SEI, WASO, and others)
3. Effects of melatonin on circadian profile (i.e., actigraphic amplitude)
4. Effects of melatonin on cognitive abilities (i.e., recall, recognition, psychomotor, and others)
5. Effects of melatonin on noncognitive behavior (i.e., depressed moods, concentration, attention, and others)

The study was approved by the Internal Review Board at the College of Staten Island, City College of New York, and New York University Medical Center. No procedure used in this study posed any significant risks to the participating individuals and all volunteers gave informed consent.

Melatonin As Used In This Study

Melatonin (5-Methoxy-N-Acetyl Tryptamine) used in this study was manufactured by Cardiovascular Research Ltd. Analysis conducted by ABCO Laboratories showed a level of purity of 99.62% when assayed. Melatonin obtained from this company has been reencapsulated with a slightly bigger capsule manufactured by Capsugel. The same capsules were utilized to produce placebo controls. These capsules were filled with an inert substance referred to as mannitol. Essentially, mannitol, as defined by Stedman's Medical Dictionary

(24th Ed), is a manna sugar, the hexahydric alcohol derived by reduction of fructose; widespread in plants.

Reencapsulation was done under the supervision of Dr. Joao Nunes. (Dr. Nunes is the program director of the Behavioral Science of the Sophie Davis School at City College New York). Melatonin and placebo have been encapsulated in a similar pink capsule. They were coded by Girardin Jean-Louis, the principal investigator in the study, who had the sole responsibility for code breaking in case of an emergency. Therefore, the principal investigator took no part in data acquisition to maintain the integrity of the study protocol. However, he supervised all aspects of data acquisition and management.

Chapter 3

Experimental Methods

Participants

Ten community-residing elderly persons with different level of cognitive and memory impairment volunteered to participate in the study (mean age = 73.82; SD = 4.64; men = 4; and women = 6; see also table 4-A-2). Nine were recruited from a sample of patients who were enrolled in the research registry at the Aging and Dementia Research Centers from New York University Medical Center. All patients participated in the standard diagnostic protocol at the center.

Diagnostic evaluations included medical history, radiological examination, psychiatric assessment, and neurological evaluation. Upon evaluation, patients were assigned a diagnostic classification based on the observed level of severity according to the GDS rating system. Patients received a diagnosis of Alzheimer's disease only if they met the diagnostic standards as established by the National Institute of Neurological and Communicative Disorders and Stroke, the Alzheimer's Disease and Related Disorders Association and the DSM-IV criteria. Seven patients had a GDS score from 1 to 3 and two patients were diagnosed with

Alzheimer's disease (i.e., GDS = 4 and 5). One participant did not undergo the diagnostic workup from New York University Medical Center. He was referred to the study coordinator from another source. The patient had a similar profile as the cognitively impaired patients. He was included because he was found to meet these study criteria (i.e., subjective report of sleep and memory complaints) [see table 4-A-2 for participant demographics].

The Global Deterioration Scale, the Clinical Dementia Rating scale, the Mini Mental Status Examination, and a neuropsychological battery were administered to determine the severity of intellectual and cognitive impairment in these patients. To rule out major affective impairment, the Hamilton scale was administered. Additionally, participants were rated with the Hachinski scale to determine neurological disorders. Those who met the Aging and Dementia Research Center diagnostic criteria received MRI scans to assess brain structural damage. Patients were selected for this study on the basis of self-reported sleep/wake disturbances. Patients reported difficulty initiating sleep and frequent nocturnal awakenings. They would be excluded if the following factors were present:

- Suspicion of apnea syndrome by history and/or periodic limb movement
- Current or past history of significant medical illness.
- Disturbance in consciousness or symptoms of other possible causes of dementia

- Neurological disorders including Parkinson's disease
- Metabolic or toxic disorders and severe sensory loss affecting cognitive assessment
- History of alcoholism and/or substance abuse
- Major psychiatric illness
- Evidence of infarction based on MRI scans

Procedure

This study investigated the effect of melatonin on elderly patients who reported sleep/wake disturbances and exhibited cognitive deficits, primarily at the level of memory. All participants were asked to wear an actigraph device for sleep/wake monitoring. In addition, participants were examined with a neuropsychological battery and urine samples were collected to determine the 24-hour profile of their aMT6s. Sleep behavior and daily activity of these patients were recorded in a sleep/wake log, the SSS, and the Visual Analog Scale (VAS). Information about patients whose level of dementia was more severe was provided by their caregivers along with their own sleep/wake activity. In addition, an investigator called the patient/caregiver every day to inquire on activities for that day and the night before.

Caregivers were told that the answers to the questions on daily activities should be based on their subjective approximations. It was also emphasized that

they should not try to monitor the patient's nocturnal awakenings but need only report their regular routine observations. During those phone calls, the investigator also tried to address any problem that arose during the course of daily rest-activity monitoring.

This study was a double-blind, placebo-controlled, crossover investigation consisting of five phases. The first four patients were entered in the protocol based on a counterbalanced procedure to control for the order of melatonin and placebo administration. However, given some of the difficulty encountered in patient management due to the demands of the protocol, the remaining patients were administered melatonin first followed by placebo. It was decided that in the event of attrition, at least data on the effects of melatonin would have been collected and could be compared to baseline subjective reports of sleep and mood. At the end of the study, two patients received placebo first whereas, eight patients were administered melatonin first followed by placebo.

Phase I

During the first phase of the study, participants who met the selection criteria were recruited for the study and were mailed an invitation letter and a prospectus describing the purpose of the study. A week later, prospective participants were phoned to determine if they desired more information about the

study and those that were interested in participating were enrolled. Interested participants were then sent a five-day sleep log, the sleepiness scale, and the mood scale to gather baseline data on their sleep/wake habits, sleepiness level, and mood. When the forms were returned, participants were scheduled for a semi structured interview assessing sleep/wake patterns. Both patients and caregivers were interviewed to ascertain sleep pathology (e.g., episodes of sleep apnea and/or periodic limb movement). The study protocol was fully explained to both patients and caregivers and thereafter consent forms were obtained. After this screening process, qualified participants received the following items.

1. Forms: Sleep/wake logs, temperature and urine sample form, sleepiness and mood scales, timeline for data acquisition [see appendix 3-A, 3-B, 3-C]
2. Actigraph device for continuous sleep/wake monitoring [see appendix 3-F, 3-G, 3-H]
3. Urine cups (4)
4. Thermoscan Instant Thermometer
5. Treatment (melatonin or placebo)

Phase II

During that phase of the study, participants were administered melatonin (6 mg) or an identical placebo for 10 days, two hours before bedtime based on their sleep log. Further, subjective reports on mood, sleepiness, and sleep were

collected for 10 days. Actigraphic data were collected for the last five days of that phase. On the last day, the 24-hour profile of their aMT6s were determined by collecting four urine samples for one day--the first sample was collected upon awakening on the tenth day. The second sample was collected at 3:00 P.M., the third at 8:00 P.M., and the last at 3:00 A.M. Tympanic temperature was recorded during each urine collection using a thermometer.

Caregivers were responsible for the collection of urine samples in moderate cases of dementia. During that day, participants were strongly encouraged to remain at home while engaging in their daily activities. They had a normal breakfast, lunch, and dinner. Urine samples were kept in the participant's refrigerator until collected by an investigator the following day. On that day, the investigator conducted a neuropsychological evaluation including the following tests:

1. Alzheimer's Disease Assessment Scale
2. Digit Span (Forward and Backward)
3. Digit Symbol Substitution
4. Finger Tapping
5. Mini Mental State

After the neuropsychological tests were conducted, the investigator collected all forms that have been completed by the patient/caregiver along with the actigraph and the urine samples [for details on these tests, see appendix 3-D].

Phase III

Phase III consisted of a washout period lasting five days; that is, participants were not asked to wear the actigraph nor were they administered any treatment. Additionally, they were not asked to provide urine samples and participate in a neuropsychological battery. However, sleepiness, mood, and sleep/wake data were collected.

Phase IV

During phase IV, procedures for sleep/wake diary and actigraphic monitoring for all participants were similar to phase II. However, throughout this 10-day experimental period the order of treatment was reversed; that is, participants who received melatonin first were administered placebo and vice versa. As in phase II, on the tenth day of that phase, temperature and urine samples were collected. The neuropsychological tests were administered as in phase II in the eleventh day. In addition, urine samples, the actigraph, and sleep/wake logs were obtained on the last day of this phase.

Phase V

Procedures for phase V were similar to phase I and III and served as a follow-up. Essentially, sleep/wake diary, sleepiness scale, and the visual analog scale were kept throughout that phase and collected by an investigator on the last day. Participants were debriefed after the completion of the study.

Instructions to Participants

Participants and caregivers were told that the purpose of the study was to investigate the therapeutic effect of melatonin on the circadian sleep/wake rhythm, cognitive, and noncognitive abilities in elderly individuals. The experimental protocol was described to participants and caregivers, including the techniques of sleep/wake monitoring with the use of wrist actigraph, neuropsychological assessment, the SSS, the VAS, and urine sampling for melatonin profiles. Participants were asked to keep their daily routines and light/dark cycle as constant as possible for the duration of the study. They were asked to refrain from administration of antidepressant, hypnotic, or neuroleptic medications during the course of the study. Additionally, they were required to abstain from heavy consumption of alcohol and caffeinated beverages during data acquisition. Some

participants were allowed to use certain medications only when it was absolutely necessary.

Participants and caregivers were asked to fill out logs which provided daily information regarding bedtime, estimated sleep latency, daytime sleepiness, estimated total sleep time for the 24-hour period, the number of nocturnal awakenings, and others (see sleep log in appendix 3-A). Informed consent was obtained from all participants or from either a spouse or a legal guardian. An informed consent was also obtained from the caregivers. Participants and caregivers were assured that their participation will be kept strictly confidential and used for research purposes only. They were advised to phone the laboratory if they wanted to know of the outcome of their participation in the study. After the completion of data acquisition, participants were debriefed and were told about preliminary analyses of the results. The study was approved by the Ethics Committee at New York University Center, City College of New York, and the College of Staten Island.

Instrumentation and Assessment Batteries

The Stanford Sleepiness Scale

The Stanford Sleepiness Scale (SSS) is a seven point self-rating instrument soliciting information on degrees of sleepiness ranging from items including

"feeling active and vital, alert, wide awake (1) to "almost in reverie, cannot stay awake, sleep onset appears imminent (7) [Hoddes et al. 1973] [see also appendix 3-B].

The Visual Analog Scale

The visual analog scale (VAS) was used for the quantification of volunteers' self-rated current moods on a 10 cm line scale, ranging from very little to very much. The moods assessed were: alert, sad, tense, effort, happy, energetic, fatigued, restless, hungry, weary, irritable, sleepy, angry, sexual desire, and overall feeling of well being [see also appendix 3-C].

Actigraphy

The actigraph methodology has been in use for several decades in monitoring changes in sleep/wake activities in both research and clinical studies. It has been shown to be highly concordant with polysomnography, the gold standard in the assessment of sleep/wake parameters. All actigraphic data were analyzed with the Actigraph Data Analysis Software (ADAS). The Actigraph Data Analysis Software was developed at the Psychophysiology Laboratory at the College of Staten Island by Hans Von Gizycki and Girardin Jean-Louis. It was written with the Microsoft Visual Basic software package.

ADAS allows visual inspection of patterns of individual's activity based on actigraphic data. ADAS uses a set of computer algorithms written to perform specific data manipulation yielding statistical values for a number of actigraphically derived variables including, total sleep time (TST), sleep efficiency index (SEI), wake after sleep onset (WASO), sleep onset latency (SOL), mean activity level (MAL), transition from sleep to wakefulness [i.e., number of periods of arousals] (TRANSITION), sleep latency post awakening (SLPA) and others.

Additionally, circadian rhythm in rest-activity patterns can be determined with smoothing and autocorrelation functions. The smoothing function uses a Fast Fourier Transform to low-pass filter the actigraphic data. It allows the user to select a specific amount of smoothing which is the number of points over which to smooth the raw data series. The autocorrelation of the data is executed in several steps. First, the data is set as $y(t) = x(t)$, with x and y representing the same variable. Using a constant amount, the function is then shifted and multiplied by an exact replicate of itself to obtain the covariance and then the correlation coefficient. This operation allows the determination of the relationship between x and y across the elapsed time involved. It is repeated several times shifting x(t) in time as a function of y(t); the time shifts are considered as lags. The correlation coefficients for each lag constitute the autocorrelation which can be plotted. This time-series analysis allows the determination of cyclic phenomena in the actigraphic data such as the occurrence of the predominant periodicity and the

amplitude which is a measure of the strength of the circadian rhythm. Frequency analysis and Pearson correlation coefficients can be obtained by automatic minute by minute comparison of the actigraphic and polysomnographic data.

ADAS has been optimized and tested thus far on a normal sample using actigraphs provided by Gaewiler Electronic and distributed by Sing-Medical and Associates from Switzerland (For technical details on these devices, see section 3-F, 3-G, 3-H in appendix). This software has been found to be reliable when applied to different actigraphs and more importantly when used to score actigraphic data from insomniacs. Furthermore, the use of ADAS has also led to the documentation of actigraphy as a reliable instrument for assessing rest-activity profiles by showing high correspondence between actigraphs when used in pairs and little discrepancy when two actigraphs were placed on different sites [For more details about validation of actigraphy with ADAS, see section 3-F, 3-G, 3-H in appendix].

Alzheimer's Disease Assessment Scale

The Alzheimer's Disease Assessment Scale (ADAS*) includes a number of subtests that have been shown to have high interrater reliability and have been used by several investigators mostly in aging and dementia studies (Mohs et al. 1984) [see also appendix 3-D, 3-E]. It comprises two parts. The cognitive part

includes word recall, word recognition, object and finger naming, commands, constructional and ideational praxis, remembering test instructions, orientation, word-finding difficulty, comprehension, and concentration. The non-cognitive items of that battery consisted of depressed mood, tearful, delusion, hallucination, pacing, increased motor activity, and cooperation to testing.

The Wechsler Adult Intelligence Scale-Revised

The other neuropsychological subtests composing the battery were selected from the Wechsler Adult Intelligence Scale-Revised (WAIS-R). They include digit span (forward and backward) and digit symbol substitution test. These subtests are widely used in studies assessing cognitive changes associated with drug therapy [see also appendix 3-D, 3-E].

Finger Tapper

The finger tapper is a widely used test of simple motor speed and/or simple manual dexterity. As used in the Halsted-Reitan neuropsychological battery, it consists of a tapping key attached to a counter that registers the number of taps completed using the index finger. It is administered in series of ten second trials for each hand (Psychological Assessment Resources) [see also appendix 3-D].

Thermoscan Instant Thermometer

The Thermoscan instant thermometer is an easy and accurate device commonly utilized to measure tympanic temperature (Thermoscan Inc.).

Control Baseline Profile for Group Comparison

Baseline data including sleep/wake diaries, mood, sleepiness, neuropsychological, and urinary samples were also acquired on three normal groups who agreed to participate in the study based on individual solicitation and advertising. Data were collected from elderly individuals with no major medical and/or psychiatric disorders (n = 9; mean age = 69.56; SD = 5.29). Data from young normal persons were also gathered (n = 12; mean age = 22.75; SD = 5.05) and adult normals (n = 11; mean age = 45.55; SD = 8.58). All participants were screened for sleep pathology with a questionnaire and were asked to provide informed consent after the protocol for data acquisition was explained to them. No major medical or psychiatric problem was reported by these individuals on initial interview.

Chapter 4

Statistical Analysis

Effects of Melatonin on Sleep/Wake Outcome Measures

In both phases (II and IV) of the study, sleep-wake activity was continuously monitored with an actigraph device during the last five days of the ten day protocol. The stored data was analyzed in three steps. The collected data was first visually inspected to ascertain actual time in bed. Time in bed was synchronized or adjusted by a trained scorer in cases where there was a discrepancy between reported bedtime and actigraphic counts; discrepancies were mostly noted for the reported time at which participants went to bed. Secondly, the data was analyzed with respect to derived sleep/wake parameters and activity level during the day. Bedtime actigraphic recordings were analyzed with the Actigraph Data Analysis Software to determine minutes of wakefulness and minutes of sleep as described in appendix 3-F and 3-G.

Thirdly, ADAS was also used to determine possible changes in circadian amplitude in rest-activity patterns, calculated over a lag of 1700 minutes to capture activity rhythm that may be more than 24 hours (1440 minutes).

Variables derived from the actigraphic data including TST, SEI, WASO, TWT, and TRANSITION were averaged over the five day-period to allow meaningful comparisons in repeated-measures MANOVA. Subsequent univariate F tests were performed to point out which variables showed a significant effect of melatonin.

Effects of Melatonin on Neuropsychological Outcome Measures

Cognition is a complex mental process that involves multiple factors and stages, some of which are more affected by the aging process than others. This study made use of a battery of neuropsychological tests designed to evaluate many of these subprocesses in various modalities, including memory indices and nonmemory tasks. Measures including memory, attention, concentration, and mood were compared across the two treatment conditions with a MANOVA procedure.

Activity Level After Melatonin Administration

Activity level subsequent to melatonin administration was determined with an ANOVA procedure. Univariate repeated-measures F tests were used to examine differences between the two experimental conditions for activity level during the two hours preceding actual bedtime subsequent to melatonin ingestion.

Repeated-Measures ANOVA Assessing Drug Interaction and Differences Between Patients (Gp A Vs Gp B) on The Basis of Drug Use

Participants were dichotomized on the basis of drug consumption throughout the study. Group A (n = 5) included persons who did not consume any drug besides melatonin during the study, whereas, participants in group B (n = 5) were allowed to use other substances (only when it was absolutely necessary and/or mandated by their physician) in combination with melatonin. These substances included: lanoxin, valium, amitriptyline, restoril, meprobromate, donnatol, fiorecet, zoloft, and others.

Comparison of Actigraphic Data Across Age

A MANOVA procedure was performed to determine group differences followed by a post hoc Duncan test. Differences between elderly normals, young normals, adult normals, and cognitively impaired patients were assessed with independent t-tests. Analyses were conducted for sleep/wake parameters, daytime activity level, and circadian profiles. Analysis was conducted for sleep parameters, daytime activity level, and amplitude of rest-activity rhythm. Comparisons of groups were made based on average data for all available days and nights.

Results

Effects of Melatonin on The Actigraphic Factors for The Cognitively Impaired Elderly (Gp 4) as Assessed With Repeated-Measures MANOVA

The results of the repeated-measures MANOVA for the actigraphic variables were significant for the factors indicated in table 4-A-3. The effects of melatonin on the actigraphic data were further examined with repeated-measures ANOVA showing significant differences for some of these factors (i.e., rest-activity amplitude, sleep onset latency, and transition from sleep to wakefulness).

Repeated-measures ANOVA has indicated a significant treatment effect on the circadian amplitude of rest-activity cycle, sleep onset latency, and transition [$F(1, 9) = 5.16$, $p = .049$; $F(1, 9) = 8.20$, $p = 018$; $F(1, 9) = 10.08$, $p = .011$, respectively]. Sleep quality as determined by sleep efficiency index was marginally significant between the two experimental conditions favoring an effect of melatonin on sleep maintenance [$F(1, 9) = 3.40$, $p = .098$]. In addition, during the placebo condition, patients showed a period of about 22.9 hrs whereas under the melatonin condition, they exhibited a period of about 24.7 hrs. However, statistical analysis showed no significant difference between these two observations

Effects of Melatonin on The Neuropsychological Factors for The Cognitively Impaired Elderly (Gp 4) as Determined With Repeated-Measures MANOVA

Repeated-measures MANOVA showed an overall significant difference for the factors indicated in table 4-A-4. Subsequent univariate repeated-measures ANOVA indicated significant differences between the conditions. It has been found that melatonin does not have an effect on all of the neuropsychological factors. However, it significantly reduced depressed moods and enhanced the ability to recall previously learned items from the Alzheimer's Disease Assessment Scale [$F(1, 7) = 7.36$, $p = .024$; $F(1, 9) = 9.75$, $p = .021$, respectively]. The ability to concentrate and perform the digit span backward marginally improved with melatonin [$F(1, 9) = 3.46$, $p = .096$, $F(1, 9) = 2.93$, $p = .121$; respectively].

Soporific Effects of Melatonin When Administered Two Hours Before Bedtime

Given the paucity of empirical data to support the soporific effects of melatonin when administered two hours before bedtime, a statistical analysis was conducted to examine possible differences between the melatonin and placebo conditions with an ANOVA procedure. This analysis assessed activity level

during two hours before actual bedtime after ingestion of the respective treatment. The result of this analysis showed no difference in activity level between these two conditions. However, once patients went to bed, they fell asleep much faster when they were given melatonin and were able to maintain sleep reasonably well (see table 4-A-3).

ANOVA for Differences Between Patients on The Basis of Drug Use and Repeated-Measures ANOVA Assessing Drug Interaction

Statistical analysis was conducted in two phases. First, baseline data including total sleep time, nap episode, fatigue level, sleepiness level, depressed moods, and rest-activity patterns of the participants were compared between the two groups by independent t test. The results of this analysis showed significant differences between these two groups. Individuals who consumed sleep medications showed more depressed moods ($t_8 = 2.08$, $p = 0.028$), took more naps ($t_8 = 3.28$, $p = 0.011$), and were more fatigued ($t_8 = 2.36$, $p = 0.014$) than those who did not (see table 4-A-5). Second, repeated-measures ANOVA controlling for medication use were performed indicating no interaction between melatonin and other medications used.

MANOVA for Group Actigraphic Characteristics (Gp 1 - 4)

As illustrated in table 4-A-6, the results of the MANOVA examining rest-activity differences among the four populations (Group 1 = Young Normal; Group 2 = Adult Normal; Group 3 = Elderly Normal; Group 4 = Cognitively Impaired Elderly) were strongly significant (see table 4-A-1 for group characteristics). Univariate F tests for these four factors were also strongly significant (see table 4-A-6).

Post hoc Duncan along with independent t tests showed significantly lower amplitude and daytime mean activity level (DMA) for individuals in group 1 Vs 2 (t_{21} = -2.33, p = .03; t_{21} = -2.14, p = .04, respectively). Group 1 also exhibited lower amplitude than group 3 (t_{19} = -3.80, p = .001) and was not significantly different from group 4 regarding circadian amplitude of activity. However, it showed significantly less wake after sleep onset than group 3 and 4 (t_{17} = -2.46, p = .02; t_{17} = -2.24, p = .04; respectively).

Though certain trends were noted, there was no significant difference between group 2 and 4. Group 2 showed much higher DMA and marginally higher amplitude than group 4 (t_{19} = 3.76, p = .002; t_{21} = 1.79, p = .09); respectively). DMA and amplitude were significantly higher for group 3 than 4 (t_{18} = 2.75, p = .01; t_{18} = 2.68, p = .02; respectively) [see also table 4-A-7].

Estimate of Sleep, Mood, and Noncognitive Behavior in The Elderly

A separate analysis was conducted to determine if symptoms of sundowning were present in the elderly individuals (normal and cognitively impaired patients). This analysis indicated no difference for the measures analyzed including pacing, delusion, increased motor activity, and others. The only consistent observation has been a report of increased depressed moods, which as presented earlier was significantly reduced with melatonin ($F(1, 9) = 7.36$, $p = .024$). One patient with probable AD exhibited delusional states which were associated with a compromised circadian rest-activity profile (see case vignette in chapter 5).

ANOVA showed significant differences between elderly normals and cognitively impaired patients for a number of factors. Elderly normals were less sleepy and depressed than the impaired elderly [$F(2, 18) = 9.09$, $p = .010$; $F(2, 18) = 6.43$, $p = .024$; respectively). Additionally, the cognitively impaired group showed more negative moods than elderly normals. They included feeling of well being, happy, and weary ($F(2, 18) = 22.21$, $p = .0004$; $F(2, 18) = 9.44$, $p = .009$; $F(2, 18) = 6.54$, $p = 024$; respectively) [see table 4-A-8]. Moreover, a strong inverse relationship was noted between feeling of well being and degree of sleepiness ($r = -.83$, $p = .0001$) [see figure 4-A-1].

Chapter 5

Discussion

Since the recent surge of melatonin in the market, many claims have been made about its potential virtue as a sleep-inducing and synchronizing hormone with possible effects on cognition and mood. This study examined the effects of melatonin on sleep/wake patterns, circadian rest-activity profile, cognition and behavior.

Consistent with the need to establish melatonin as a safe and effective therapy for sleep/wake disturbance associated with circadian abnormality, this study investigated the effects of melatonin on several parameters. They included: sleep/wake patterns, circadian rest-activity profile, cognition, and behavior. Control measures of actigraphic profile were also analyzed by examining differences as a function of age. It was thought that, as previously demonstrated with other research tools that rest-activity profile would be different across age groups; with more compromised circadian rhythm associated with the elderly group or more specifically, individuals with cognitive impairment.

The discussion that follows also incorporates empirical support for the use of a two-hour interval for melatonin administration. The discussion continues on the possibility of interaction between melatonin and other substances. Subjective reports of sleep, mood, and noncognitive behavior are also presented with an account of more negative moods observed in individuals with cognitive impairment.

Effects of Melatonin on Actigraphic Sleep/wake Profile of The Cognitively Impaired Elderly Individuals

It is not clear at this time if the attenuation of the amplitude of rest-activity cycles in these patients could be linked to a reduced melatonin output since the data of AMT6 profiles are not yet available. Nonetheless, a parallel may be drawn with the data of Witting (1990) and Haimov et al. (1995) who have demonstrated melatonin deficiency in elderly insomniacs and AD individuals. These observations were also corroborated by the findings of a phase advance and reduced amplitude of melatonin associated with aging (van Coevorden et al. 1993).

Although the present analyses were based on cognitively impaired individuals with no PSG diagnosed sleep disorders, significant changes in the rest-activity patterns of these patients were found. Essentially, their circadian rest-activity rhythm was reentrained as exemplified by an increase in the amplitude of

the rest-activity cycle and a possible stabilization of the periodicity of the rest-activity data approximating 24 hours. These results support previous reports indicating that sleep/wake disturbance noted in the elderly may be the by-product of a compromised circadian rhythm. According to earlier findings, reduction in the circadian amplitude of rest-activity data is one of the early observations in dementia (van Someren et al. 1993a, 1993b; Witting 1990). Other researchers have shown that early during the course of dementia, patients exhibit compromised sleep architecture which index can be used to differentiate them from elderly normal persons (Prinz et al. 1990).

Melatonin also significantly improved sleep quality in the elderly individuals by reducing their sleep onset time and number of transitions from sleep to wakefulness. Total time spent awake was significantly lower under melatonin and sleep quality as determined by SEI was marginally improved. The improvement observed in these sleep parameters is consistent with previous findings on the soporific effects of melatonin (Haimov et al. 1995; Garfinkel et al. 1995). The lack of statistical support for SEI may be explained by the high base level of SEI for this sample (average SEI = 90%). It further shows that participants in this sample did not have an objective sleep problem. The complaint of sleep disturbance may be reflective of their misperception of sleep (Foley et al. 1995; Hauri and Wisbey 1992).

Melatonin Effects on Cognition and Mood of Cognitively Impaired Elderly Individuals

Previous research has demonstrated some of the effects of melatonin. It has some effect on sleep/wake parameters (Haimov et al. 1995; Garfinkel. 1995). It phase-shifts endogenous melatonin rhythms in individuals with jet-lag (Arendt et al. 1987), night shift work (Sack et al. 1992) among others. It remains unclear, however, the extent to which certain cognitive and behavioral processes may be affected by melatonin administration. There is, however, some evidence indicating that melatonin may reduce anxiety level and worsen symptoms of depression in severe cases (Carmen 1976). Additionally, it increases fatigue based on the Profile of Mood States and augments reaction time on four-choice visual tasks (Lieberman et al. 1984).

The present analyses did not show significant improvement in all of the neuropsychological measures used in this study. However, a number of trends toward a positive effect on both cognitive and noncognitive parameters were noted; which may prove important and meaningful in a larger sample. Further, although the elderly patients showed some cognitive impairment based on the Global Deterioration Scale, baseline cognitive profile of these participants was within the range of cognitive ability exhibited by normal elderly persons based on Mini Mental State scores (see table 4-A-1). Hence, melatonin may not be that effective in this sample as a ceiling effect would be expected since these patients

exhibited a relative high level of cognitive functioning. At least, it is worth noting at this point that these two scales do not show a consistent profile of cognitive functioning for this sample.

Nevertheless, a significant improvement on memory has been found which warrants further probe into a possible role of melatonin regarding its effect on delayed recall. It is not clear why there was no significant variation in immediate recall and/or recognition. An improvement on these measures could have indicated a change in performance due to improved sleep under melatonin. It is speculated that melatonin may be acting on the mechanism responsible for memory consolidation as seen in an enhanced capacity to recall previously learned items.

The observation of a significant reduction in reported depressed moods is particularly interesting in view of the suggested role of melatonin as a synchronizing neurohormone with possible affective correlates. This finding supports the report of a decrease in sadness as noted with acute melatonin ingestion in the young normal sample in a previous study (Jean-Louis et al. 1997). In addition, analysis of sleep and mood diaries in this patient population has also indicated a trend toward a diminution in level of sadness as assessed from the VAS.

Case Vignette

The use of melatonin administration in this study proposes an interesting approach to investigate the well-being of the demented elderly by placing it within the framework of chronobiology. In that regard, a case analysis was conducted for the two participants with a diagnosis of Alzheimer's disease. The data acquired from these two patients are particularly interesting for they speak directly to the issue of an amplitude reduction in the circadian rhythm of elderly demented individuals. They also support the notion that not all AD patients exhibit a disturbed circadian rhythm (van Someren et al. 1993a).

van Someren et al. (1993a) have found a substantial inter-individual variability in the severity of circadian disturbance in their AD patients. They noted that more circadian disturbances were associated with greater severity of the disorder in institutionalized patients. These authors argue that baseline profile for patients selected for chronobiological investigations may have to be determined for optimal treatment effect. Ceiling effects may be found in patients exhibiting an intact circadian rhythm. This case analysis was conducted to examine if, in fact, melatonin could be used to address circadian rhythm disturbance in Alzheimer's disease. To that end, two AD patients with different circadian profile and yet similar cognitive abilities were studied.

The first patient (A) was a community-residing elderly woman cared for by her husband. At the time of the study, she was 72 years old with a cognitive profile as follows: GDS score = 4, MMS score = 20, and her score from the Alzheimer's Disease Assessment Scale (ADAS*) was 68.

Interestingly, the actigraphic data showed that she was very active while in the placebo condition. When she was given melatonin, patient A exhibited slightly less activity; the results were not, however, statistically significant. Consequently, the circadian amplitude of her rest-activity data was slightly attenuated while no changes were observed on the neuropsychological measures. Her actigraphic rest-activity rhythm was comparable to the rest of the sample at baseline.

The other patient (B) was a 75 year old woman, residing at home and cared for by her daughter. Baseline data showed that she had the following profile: GDS score = 5, MMS score = 15. However, her ADAS* score of 96 was much higher than most other patients in the sample, thus suggesting higher cognitive impairment. Incidentally, the discrepancy between MMS and ADAS* presents an interesting scenario insofar as the sensitivity of these instruments is concerned.

Although, no significant difference was noted for the sleep variables analyzed for the four days of actigraphic monitoring, considerable trends toward improvement of sleep quality were observed. An average of 10 minute reduction was found in sleep onset time. Further, a significant increase was found for

daytime arousal and a borderline increase in activity level between the two conditions (t_3 = 3.80, p = .019; t_3 = 2.48, p = .068, respectively). In addition, analysis of the Stanford Sleepiness Scale indicated a significant decrease in sleepiness level associated with melatonin ingestion (t_9 = 2.33, p = .045). These analyses are corroborated by the observation that the rest-activity cycle under the melatonin conditions seems to be better organized than that seen under the placebo condition. That is, activity counts were more prominent or consolidated during daytime hours when the patient was in the melatonin condition (see figures 4-A-2 and 4-A-3).

When the same data was analyzed with an autocorrelation function, it revealed other important features. As shown in figure 4-A-4, the rest-activity rhythm observed under placebo resembles the pattern of what has been proposed as an internal "phase drift" caused by alterations in the SCN pacemaker (van Someren et al. 1993a, 1993b; Witting et al. 1990; van Gool and Mirmiram 1986). No significant dominant periodicity was found in the rest-activity cycle. This observation supports the notion that demented patients suffer from a dampening in the amplitude of their circadian rhythm.

However, as exemplified in figure 4-A-5, a well defined circadian rhythm in rest-activity pattern was reestablished in the patient subsequent to exogenous melatonin. The data obtained from this patient shows the synchronizing role of melatonin as reported in previous studies (Arendt et al. 1995; Lewy et al 1992;

Lewy et al. 1989). Incidentally, this patient was the only one who exhibited delusional states at baseline. It could be argued that there may be a link between the manifestation of symptom-like sundowning and disturbance of the circadian rhythm; most of the participants were observed between 3:00 PM and 7:00 PM.

When patient B was administered melatonin, two clear observations were made. Besides the observed synchronization of the rest-activity rhythm (i.e., amplification of the amplitude and stabilization of the period length), the patient showed a reduction in delusional states and depressed moods. This finding seems consistent with the prediction of Lewy et al. (1992) that melatonin may improve mood disorders when administered at the appropriate circadian phase. It is of interest to determine if melatonin, given at specific time points of the PRC (i.e., using the phase-typing procedure) can eliminate symptoms of depression related to a circadian phase drift as it has been demonstrated with phototherapy.

Several reports have suggested that the amplitude of the melatonin rhythm is low in individuals with depression (Grasby and Cohen 1987). It is not clear if the attenuation observed in melatonin level in these cases was a direct reflection of pineal malfunction or an indirect effect of reduced serotonergic and noradrenergic function (Arendt 1988). The results of this observation, though preliminary, suggest that the stabilization of the rest-activity rhythm in the patient with Alzheimer's disease may have contributed to a diminution of noncognitive behavior. In fact, they support previous research showing a reduction of

sundowning symptoms in a nursing population when treated with phototherapy (Satlin et al. 1992).

The use of exogenous melatonin may prove very useful for understanding the role played by melatonin as a synchronizing hormone. Although a youthful rest-activity level was not fully restored, the ingestion of melatonin enhanced the amplitude of the rest-activity cycle. This finding points to the necessity for more chronobiological investigations in dementia. It is speculated that the entrainment of the rest-activity rhythm may facilitate the remediation of cognitive abilities and an amelioration of sleep/wake problem in the elderly.

Soporific Effects of Melatonin Administration

Evidence supporting the role of melatonin as a robust marker of biological rhythms has been discussed. However, research on melatonin administration has not been conclusive regarding the proper timing of its administration. Different schedules of administration have not yielded consistent results. A number of investigators have reported that melatonin has a sleep-inducing effect contingent upon the time of day at which it is ingested. It has been shown that low doses of melatonin taken at 5:00 PM can induce subjective fatigue later in the evening (Arendt et al. 1986). Earlier studies have suggested that oral and intranasal

preparations given in the afternoon or early evening could induce sleep (Anton-Tay et al. 1971; Vollrath et al. 1981).

Others have shown that melatonin operates according to a phase response curve and must also be administered at very specific time of the circadian cycle depending on desired effect (Lewy et al. 1992). Pharmarcokinetic properties of melatonin have been investigated demonstrating that melatonin has a half life of about 35 to 50 minutes and remains in circulation for up to 7 hours after ingestion (Aldhous et al. 1985). It remains unclear whether or not the physiological effects of melatonin are the same when patients self-administer melatonin in combination with other medications or when ingestion is done on a full stomach. It is important to note that some investigators have consistently administered melatonin 2 hours before bedtime and have found significant sleep-inducing effects (Haimov et al. 1995; Garfinkel et al. 1995).

To date, no empirical data has been provided to support the practice of a two-hour interval before actual bedtime for optimal soporific effects of melatonin. Although the present study did not systematically investigate the effects of melatonin administered at different times, an analysis was conducted to determine possible differences in activity level before actual bedtime. The result of this analysis offers the first actigraphic support for the administration of melatonin 2 hours before bedtime. Essentially, when activity level was analyzed two hours before bedtime, no difference was noted between the melatonin and placebo

conditions. This result suggests no sedative effects of melatonin during that time period. However, when the actigraphic data was analyzed for sleep/wake parameters for actual time in bed, two clear observations were made. Sleep initiation was facilitated and nocturnal sleep was better maintained.

These two observations demonstrate that melatonin has indeed sleep-promoting virtues. Further, they support the notion that a pharmacological dose of melatonin can be used for facilitating sleep onset as well as improving sleep continuity. Another point of interest relates to the possible undesired effects of melatonin reported in the past anecdotally. In this study, no patient has reported any side effects and/or drug interactions. In fact some participants reported feeling better under melatonin and some were able to determine when they were administered melatonin Vs placebo.

Interaction Between Melatonin and Other Substances?

The management of sleep-related disturbances in patients with a complaint of insomnia involved the use of hypnotics. Pharmacological interventions are often accompanied by undesired daytime side effects, interactions with other medications, and tolerance. In addition, metabolism and rate of excretion of drugs are much slower in the elderly, leading to excessive sedation, confusion, cognitive impairment, and possible personality changes (Ancoli-Israel 1993). In keeping

with the recognition that undesired side effects are associated with such management, a number of nonpharmacological studies have been undertaken. These studies indicate immediate effects on circadian parameters after phototherapy, vigorous exercise, and body heating with no apparent side effects (van Someren et al. 1993b).

Another line of nonpharmacological studies concerns the use of exogenous melatonin. As shown in these studies and previous ones, melatonin has sedative hypnotic properties when administered to animals and humans in pharmacological and supraphysiological dosages. The observation that circulating level of melatonin is significantly lower in old age has given rise to the notion that melatonin may be beneficial in alleviating numerous sleep problems in the elderly. With the prevalent use of melatonin, it has become a matter of great concern that caution be exercised when melatonin is used in combination with other medications or supplements. To date, no major study has looked at the effect of melatonin in combination with other medications. Therefore, the efficacy of melatonin was investigated when taken in combination with other sleep-inducing compounds used by the elderly.

Although participants in these two groups were different on certain baseline measures (i.e., fatigue level, depression, and nap episodes), melatonin was found to be effective in improving their sleep. The finding of no drug interaction with melatonin administration is very important and consistent with a previous report

by Garfinkel et al. (1995). However, the failure to detect a drug interaction in this analysis may be due to a lack of statistical power, given the size of the sample. In addition, no side effects were reported by participants in either group, suggesting that this pharmacological dosage of melatonin may not pose a significant risk in the elderly population

Sleep, Mood, and Noncognitive Behavior in The Elderly

Noncognitive behavioral symptoms and sleep disturbance have been well recognized concomitants of dementia. These symptoms include pacing, verbal aggression, wandering, hallucinations, combativeness, and delusions form the syndrome referred to as sundowning mostly observed in late afternoon or early evening (Reisberg et al. 1986, Vitiello et al. 1990). Research has shown that sundowning may be explained by specific ideological hypotheses. In Alzheimer's disease, these symptoms are believed to relate to either neurochemical changes and/or psychological effect of cognitive losses. Evidence suggests that the cholinergic system is the one most affected, followed by the noradrenergic and serotonergic neurotransmitter systems (Kolb and Whishaw 1990).

Explanation for this syndrome also comes from another line of studies pointing to the deterioration of the suprachiasmatic nucleus. Alterations in the SCN are mostly noted in the arginine-vasopressin cell group (Swaab et al. 1990).

The SCN is responsible for the synchronization of circadian rhythms which include sleep-wake cycle, body temperature, hormonal regulations, and others. A number of objective parameters have been identified to account for sleep disturbance observed in normal and demented elderly patients. Essentially, the quality of sleep of demented persons is more compromised than elderly normals as shown by both polysomnographic and actigraphic recordings (van Someren et al. 1993a, Bliwise 1993).

The findings of this study indicated no evidence of symptoms of sundowning in both elderly and cognitively impaired participants. Given the comparable mean age of the two groups and the exclusion of disorders capable of causing sleep and mood disturbance, the observed differences (i.e., in sleepiness, degree of happiness, overall level of well being, sadness, weary and depression) may be attributed to the onset of dementia. The noncognitive behavioral disturbances may be present only in late stages of the disease. In fact, delusional states were noted only in a person diagnosed with probable Alzheimer's disease. The findings of this study, therefore, support previous observations demonstrating the association between the severity of dementia and the manifestation of sundowning behavior. Interestingly, participants who reported a high level of well being did not exhibit substantial daytime sleepiness, thus suggesting that improving the feeling of well-being of the elderly might result in a reduction of daytime sleepiness or vice versa.

Application of Actigraphy

The prevalent use of actigraphy has been fostered by the development of state-of-the-art activity monitors along with demonstrably robust scoring methods. Methodological inquiries by research laboratories have documented the usefulness of actigraphy, thus enabling continuous and unobtrusive recording of rest-activity patterns. Besides a vast animal literature supporting its use in ascertaining locomotor activity in several species, investigators have found many applications for actigraphy in human studies. They include the determination of sleep/wake parameters, daytime activity level, circadian rhythm, internight variability, and drug effects on sleep and wakefulness. However, the mode of operation of actigraphy does not allow the characterization of sleep architecture since its sole unit of analysis is body movement recorded over time. Therefore, the application of actigraphy is limited insofar as assessing sleep architecture which is based on several indices.

Polysomnographic investigations have revealed different sleep architecture profiles contingent upon the age of the person examined. To date, only a few studies have attempted to examine differences in rest-activity patterns on the basis of age using actigraphy. Actigraphy in these three studies has been used as an important outcome variable in this study. With the pooled data from group one to

four, a separate set of analyses were performed to examine differences in rest-activity pattern as a function of age in this heterogeneous population.

Differences in Actigraphic Profile Across Age

The results of this analysis have demonstrated the parameters evidencing changes in rest-activity patterns associated with aging and the onset of dementia. Although elderly persons showed characteristic differences from the young and adult samples, the cognitively impaired elderly group showed the most compromised circadian rhythm and sleep/wake profile. The amplitude of the rest-activity rhythm was significantly attenuated relative to the adult and elderly normal samples, Additionally, they showed an earlier dominant diurnal amplitude than the other groups (e.g., group 3 = 24.14 hrs, group 4 = 22.82 hrs). These results support previous research showing a breakdown of sleep architecture as one of the early indicators of Alzheimer's disease (Vitiello et al. 1992).

This finding may index the onset of the observed dampening of circadian rhythms associated with AD. Interestingly, the amplitude of the rest-activity rhythm of the young persons was rather low and has not been found to be significantly different from the mildly cognitively impaired elderly. This observation may reflect the documented erratic sleep schedule that characterizes the life of young people. However, their rhythm was found to be well

synchronized to a circadian cycle, thus suggesting a healthy pacemaker with robust capacity for entrainment.

In sum, the Actigraph Data Analysis Software has allowed the determination of the usefulness of actigraphy in monitoring sleep/wake profiles with minimal intrusions in the daily life of the individuals participating in these studies. The application of ADAS has led to important experimental evidence demonstrating the reliability and sensitivity of actigraphy. ADAS has also shown that placement of the actigraph poses no risk to the validity of actigraphic data nor is there a first night effect associated with actigraphy.

With the use of specific algorithms incorporated in ADAS, it has been possible to document changes in rest-activity patterns across age groups. The results of the present investigations are consistent with previous studies performed with other instruments such as PSG. More importantly, when applied to monitor changes in sleep/wake patterns as a result of experimental manipulations, actigraphy has shown its ability to differentiate treatment conditions based on different dimensions including sleep/wake parameters, daytime activity level, and circadian profile.

Conclusion

The purpose of this chronobiological investigation was to document the changes that occur in several parameters as individuals age. The parameters studied included sleep/wake cycles, circadian rhythm in rest-activity patterns, cognitive and non-cognitive abilities, and subjective estimates of sleep, sleepiness, and mood. Changes observed in these parameters can be addressed and remedied with a number of pharmacological and non-pharmacological interventions. In this study the experimental protocol allowed for the augmentation of circulating level of an indoleamine, melatonin in cognitively impaired elderly persons; thus resynchronizing the observed circadian rhythm disturbances in these patients.

The data obtained in this investigation are important from a chronobiological point of view. They offer support for a different experimental approach to studying changes that occur in aging individuals by placing them within the framework of circadian rhythm disorganization. They also propose a mechanism whereby some of these changes can be addressed with minimal intrusion into the life of the elderly. This document adds to previous attempts by numerous fields to provide a comprehensive understanding of dementia by relying on state-of-the-art technology.

This documentation includes a summary of the instruments used by numerous aging and dementia research and clinical centers to diagnose

Alzheimer's disease and dementia of different severity level. The global staging scales furnishing an overall clinical impression of disease severity and an estimate of clinical changes during the course of the illness were presented. Tests used in the assessment of functional capacity and activity of daily living were also presented. Measures of cognitive evaluations and behavioral manifestations in AD are also discussed with supportive evidence. Further, the neuropsychological tests most widely used are described along with confirmatory support by neuroimaging examinations.

The research evidence supporting the notion of a dampening of circadian rhythms in elderly individuals was discussed with an emphasis on the role of the suprachiasmatic nucleus, the putative biological clock responsible for the entrainment of internal rhythms. Sleep/wake disturbance in elderly and AD was also considered as a byproduct of the failure of these rhythms to be entrained by the SCN. The discussion on the SCN was linked with its action on the pineal hormone, melatonin, which has been proposed as the marker accounting for the noted disturbances in circadian rhythms. Melatonin was discussed as a therapeutic agent capable of restoring circadian rhythm amplitudes and robustness attenuated in aging individuals.

Traditional polysomnographic studies in the elderly and dementia are limited insofar as providing the determination of their sleep/wake profiles. It became, therefore, necessary to use a different methodology for such

determinations. A number of studies have been conducted with the actigraph methodology to demonstrate its validity and reliability; thereby allowing precise and unobtrusive longitudinal documentation of sleep/wake activity. The software developed for actigraphic data, the Actigraphic Data Analysis Software, provided important outcome variables in this study. A discussion of its usefulness and empirical support for its utilization were thus provided.

The ability of melatonin to induce sleepiness and maintain sleep in both normal and clinical populations, to phase-shift circadian rhythms, and to alleviate jet-lag symptoms among others has been discussed. The present study made use of the available evidence to investigate the reentraining and sleep-promoting virtues of melatonin in a sample of individuals diagnosed with mild to moderate cognitive impairment and who reported sleep/wake disturbances. The data gathered in this protocol are in favor of the use of melatonin to ameliorate sleep/wake disturbance and enhance daytime cognitive performance in this population. Although there is not yet a clear evidence that the level of melatonin in these participants was, in fact, elevated by exogenous melatonin, specific changes in a number of parameters seem to indicate a possible link. The administration of melatonin has shown a clear reentraining capacity by enhancing the amplitude of the rest-activity rhythm. These observations were parallel to a positive and significant effect of melatonin on both cognitive and noncognitive

abilities. The ability to remember previously learned items improved along with a significant reduction of observed depressed moods.

This approach to understanding the role of melatonin in the elderly is strongly supported by the available data and suggests that a longer treatment regimen may yield better results in cognitive abilities. Better results could also be obtained in a more advanced sample of impaired participants. Interestingly, these results suggest that no detrimental effects associated with chronic administration of a pharmacological dose of melatonin. No side effects or contraindications were reported by any of our participants over a period of ten days.

Although the results of this study seem to demonstrate the role of melatonin in improving sleep and possibly cognition, there remains some uncertainty concerning the method used for determining circadian rhythm. For instance, it is not yet clear why the amplitude of the rhythm in the young normal group was similar to the cognitively impaired individuals while the period length was significantly different. Other parallel methods may have to be used in ascertaining circadian profile besides actigraphy. There may be certain factors that the actigraph cannot account for. Additionally, the actigraphic data obtained after the application of the autocorrelation function yielded a more compelling evidence for the synchronizing effects of melatonin than do the actigraphic raw data series. It is, therefore, suggested that both be taken into account when examining drug-induced effects on the profile of rest-activity data.

Future Studies

Though research with melatonin has been in progress for decades, it is only recently that it has become the substance most talked about and debated in many circles because of its therapeutic properties. While some of the claims on the virtues of the pineal hormone have not been entirely substantiated. melatonin researchers and others continue to make liberal predictions on its potential to treat several sleep disorders including jet lag and insomnia of diverse pathologies. The findings of these studies may lead to the development of new therapeutic strategies for not only improving sleep but also improving alertness and wakefulness and cognitive functioning.

One of the most exciting roles of the pineal melatonin concerns its therapeutic effects on individuals with a diagnosis of Alzheimer's disease. As argued in this discourse, AD patients are characterized by an attenuation of their melatonin circadian rhythm which may be in part responsible for a number of observations. They include disturbances in sleep/wake cycle, memory loss, and cognitive deficits. The advent of melatonin replacement therapy may prove particularly revolutionary insofar as the management of symptoms related to circadian rhythm disturbance is concerned. If in fact, a clear link between a compromised melatonin rhythm and some of the symptoms encountered in

dementia can be established, a wide range of treatment strategies can be adapted to address cognitive deficits as well as circadian disturbances in these patients.

A case for the anti-aging properties of melatonin has already been made, supported by animal experimental evidence. It is now important that research efforts be made to investigate if degenerative damages engendered by senile plaques and neurofibrillary tangles can be halted and possibly reversed. It is hypothesized that the pineal hormone could be upregulated by proper provision of a replacement strategy geared at reestablishing youthful levels of melatonin.

Ascertaining directly the health of the pineal gland may not be feasible. Nevertheless, its chief hormone, melatonin may be assessed to determine the strength of the endogenous regulator. It is hoped that the findings of this research along with previous reports will establish a solid foundation upon which others may build for the recognition of melatonin as a viable replacement therapy.

Appendix 3-A

Aging and Dementia Research Center (New York University)	The Psychophysiology Laboratory (College of Staten Island)

Sleep/Wake Log	Patient

Name:		DAY					
Age:	Gender:	DATE					
Last Night							
1. What time did the patient get into bed last night?							
2. What time did the patient turn the lights out or begin trying to fall asleep last night?							
3. How long did it take the patient to fall asleep?							
4. What time did the patient physically get out of bed in the morning?							
5. How much sleep did the patient get last night to the nearest quarter of an hour?							
6. How many times did the patient wake up last night?							
7. How long was the patient physically out of bed and awake during the night?							
8. What time did the patient wake up and did not go back to sleep last night?							
9. How difficult was it for the patient to wake up this morning? (Choose from 1 to 9) **(least difficult)** ①②③④⑤⑥⑦⑧⑨ **(most difficult)**							
10. How rested did the patient feel upon awakening this morning? (Choose from 1 to 9) **(least rested)** ①②③④⑤⑥⑦⑧⑨ **(most rested)**							
Yesterday							
1. How many naps did the patient take yesterday?							
2. How much time did the patient spend napping yesterday?							
3. How much time did the patient spend outdoors yesterday?							
4. Did the patient exercise yesterday? If YES, was it in the Morning (**M**), Afternoon (**A**), or Evening (**E**)?							
5. What time did the patient remove the actigraph yesterday?							
6. How would the patient rate his/her alertness yesterday? (Choose from 1 to 9) **(least alert)** ①②③④⑤⑥⑦⑧⑨ **(most alert)**							
7. How would the patient rate his/her fatigue yesterday? (Choose from 1 to 9) **(least fatigued)** ①②③④⑤⑥⑦⑧⑨ **(most fatigued)**							

Appendix 3-B

Psychophysiology Laboratory

The College of Staten Island

STANFORD SLEEPINESS SCALE

Name _____ Time: _____

Date:_____ Study_____

Tech:

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. Sleepy, prefer to lie down, woozy.

7. Almost in reverie, cannot stay awake, sleep onset appears imminent.

Appendix 3-C

The Psychophysiology Laboratory	**Visual Analog Scale**

Name_____ Date____/____/____ Time_____

Please put a vertical mark through each line at the place which best describes how you **feel right now** from very little to very much.

Example: Very Little ——|—— Very Much

1. How **alert** do you feel right now? _____
2. How **sad** do you feel right now? _____
3. How **tense** do you feel right now? _____
4. How much an **effort** is it to do anything right now? _____
5. How **happy** do you feel right now? _____
6. How **energetic** do you feel right now ? _____
7. How **fatigued** do you feel right now ? _____
8. How **restless** do you feel right now? _____
9. How **hungry** do you feel right now? _____
10. How **weary** do you feel right now? _____
11. How **irritable** do you feel right now? _____
12. How **sleepy** do you feel right now? _____
13. How **angry** do you feel right now? _____
14. How much **sexual desire** do you feel right now? _____
15. How much of yesterday's activities can you **remember** right now? _____
16. **Overall**, how do you feel right now? _____

Very Bad ⟷ Very Good

Appendix 3-D

The Psychophysiology Laboratory, CSI
Aging and Dementia Research Center, NYUMC

Name:_____
Date:_____
Examiner:_____

Neuropsychological Assessment Battery

_____ 1. Mini-Mental State

_____ 2. ADAS_Word Recall Task

_____ 3. ADAS_Naming Objects & Fingers

_____ 4. ADAS_Commands

_____ 5. ADAS_Constructional Praxis

_____ 6. ADAS_Ideational Praxis

_____ 7. ADAS_Word Recognition Task

_____ 8. Finger Tapping

_____ 9. WAIS-R Digit Span Subtest (Forward & Backward)

_____ 10. WAIS-R Digit Symbol Subtest

_____ 11. ADAS_Delayed Word Recall Task

Alzheimer's Disease Assessment Scale (ADAS)

Subject: _____ Date:_____ Rater: _____

1.Word Recall Task:
Mean Error Score over three trials _____

2.Naming Objects & Fingers:_____
___Flower ___Bed ___Whistle ___Pencil
___Rattle ___Mask ___Scissors ___Comb
___Wallet ___Harmonica ___Stethoscope ___Tongs
___Thumb ___Pinky ___Index ___Middle ___Ring
0=0-2 items named incorrectly
1=3-5 items named incorrectly
2=6-8 items named incorrectly
3=9-11 items named incorrectly
4=12-14 items named incorrectly
5=15-17 items named incorrectly

3.Commands:_____
Score = # of elements performed incorrectly.
___Make a fist.
___Point to the ceiling and then to the floor.
___Put the pencil on top of the card and then put it back.
___Put the watch on the other side of the pencil and turn over the card.
___Tap each shoulder twice with two fingers keeping your eyes shut.

4.Constructional Praxis:_____
0=all 4 drawings correct Closing In? Yes No
1=1 form incorrectly drawn
2=2 forms incorrectly drawn
3=3 forms incorrectly drawn
4=4 forms incorrectly drawn
5=no figures drawn; scribbles; parts of forms; words instead of forms

5.Ideational Praxis:_____
Score = # of elements incorrectly performed.
___Fold letter.
___Put letter in envelope.
___Seal envelope.
___Address envelope.
___Mark where stamp goes.

6.Orientation:_____
Score = # of incorrect elements.
____Person
____Day
____Date(+/- 1 day)
____Month
____Year
____Season (1wk before/2 wks after change)
____Time of Day (within 1 hour)
____Place (partial name acceptable)

7.Word Recognition Task:
Mean Error Score over three trials: _____

8.Remembering Test Instructions*:_____
0= None *from word recognition task
1= Very Mild: forgets once
2= Mild: must be reminded 2 times
3= Moderate: must be reminded 3-4 times
4= Moderately Severe: must be reminded 5-6 times
5= Severe: must be reminded 7 or more times

9.Spoken Language Ability: _____
0= None
1= Very Mild: one instance of lack of understandability
2= Mild: difficulty <25% of the time
3= Moderate: difficulty 25-50% of the time
4= Moderately severe: difficulty >50% of the time
5= Severe: one to two word utterances; fluent, but empty speech; mute

10.Word Finding Difficulty:_____
0= None
1= Very Mild: 1-2 instances, not clinically significant
2= Mild:noticeable circumlocution or synonym substitution
3= Moderate:loss of words without compensation on occasion
4= Moderately Severe: frequent loss of words without compensation
5= Severe: nearly total loss of content words; speech sounds empty; 1-2 word utterances

11.Comprehension Spoken Language:_____
0= None: patient understands
1= Very Mild: one instance of misunderstanding
2= Mild:3-5 instances of misunderstanding
3= Moderate: requires several repetitions and rephrasing
4= Moderately Severe: only occasionally responds correctly; i.e., yes/no answers
5= Severe: rarely responds to questions appropriately; not due to poverty of speech

12. Concentration: _____
0=None
1=Very Mild:one instance of poor concentration
2=Mild:2-3 instances;signs of restlessness/irritability/easy distractibleness
3=Moderate:4-5 times during interview
4=Moderately Severe:poor concentration/distractability throughout much of interview
5=Severe:extreme difficulty in concentration and extremely distractable;unable to complete tasks

Word Recall:	_____
Word Recognition:	_____
Other Cognitive Behaviors:	_____
Total Cognitive Score:	_____
Noncognitive Behaviors:	_____
Total ADAS Score:	_____

The Psychophysiology Laboratory | Aging and Dementia Research Center

Mini-Mental State

Name:_____ Date:___/___/___ Time:_____

Orientation

1 Score: (5)		
What is the:	a) year	d) date
	b) season	e) month
	c) day	

2 Score: (5)		
Where are we:	a) country	d) building
	b) state	e) floor
	c) city	

Registration

3 Score: (3)			
"I'd like to test your memory, Ok? I'll say some words for you to remember." (leave one second between words)	Rose	Battleship	Teacup
"Please repeat the words I just said"	Rose	Battleship	Teacup

If a client is unable to recall all three words begin again by repeating the three words and ask client to say the words. This may be repeated up to six times. Record trials to criterion.. **(Do not include this score in MMS total score)**	1	2	3	4	5	6

Attention and Calculation

4 Score: (5)	Do not add this score into MMS total.				
"Please begin with 100 and count backwards by sevens". If the client cannot understand the intructions, say: "Start with 100 and take away 7 from that, then take 7 away from your answer, and so forth". Stop at 5 response or if client shows stress.	93 (1)	86 (1)	79 (1)	72 (1)	65 (1)

5 Score: (5)					
"Spell WORLD backwards" (Score equals the numbers of letters in the correct position.)					
Position #	1	2	3	4	5
Letter	D	L	R	O	W
Response					
Score	(1)	(1)	(1)	(1)	(1)

6	Score: (3)		
"Earlier I asked you to say three words. What were they?"	Rose (1)	Battleship (1)	Teacup (1)

Language

7	Score: (2)	Naming
Show client a wrist wacth. Say, "What is this?"	(1)	
Show client a pencil. Say, "What is this?"	(1)	

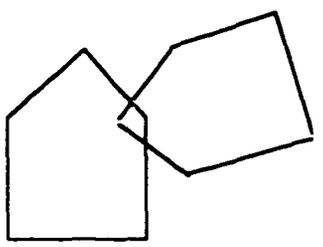
8	Score: (1)	Repetition
Say to client, "Say no if's, and's, or but's."	(1)	

9	Score: (3)	Three Stage Command Comprehension & Praxis
Hand client a sheet of plain paper. Say,	"Take the paper in your right hand,	(1)
	fold it in half,	(1)
	and put in on the floor".	(1)

10	Score: (1)	Reading
Show client the sheet with "close your eyes" written on it. Score 1 point for correct performance.	(1)	

11	Score: (1)	Spontaneous Writing
Say, "Write a sentence about today's weather." Sentence must be produced spontaneously, contain a subject and verb and make sense. Grammar and punctuation are not scored. Score 1 point if the above criteria are met.		(1)

12	Score: (1)	Construction
Ask client to copy the intersecting pentagons from sample onto unlined paper (1/2 sheet). Score I point if all 10 angles are seen and if both figures intersect. Ignore tremor and rotation in scoring.		



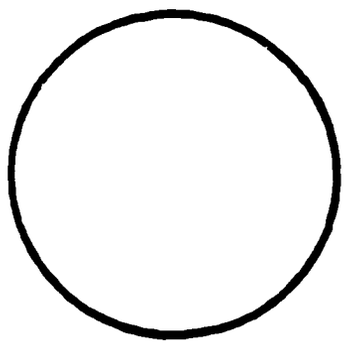
13	MMS TOTAL & MMS ADJUSTED	
Sum all scores and report the total score for Mini-Mental State	MMS TOTAL =	
Add score on A-5 to MMS TOTAL	MMS ADJUSTED =	

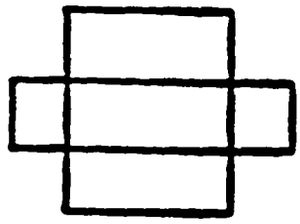
Check *each* word recalled *correctly*.

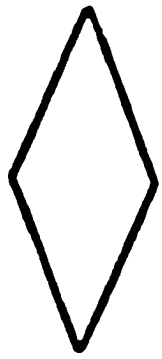
TRIAL 1	
BUTTER	
ARM	
SHORE	
LETTER	
QUEEN	
CABIN	
POLE	
TICKET	
GRASS	
ENGINE	
TOTAL	

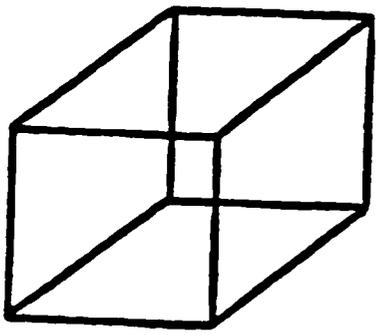
TRIAL 2	
POLE	
LETTER	
BUTTER	
QUEEN	
ARM	
SHORE	
GRASS	
CABIN	
TICKET	
ENGINE	
TOTAL	

TRIAL 3	
SHORE	
LETTER	
ARM	
CABIN	
POLE	
TICKET	
ENGINE	
GRASS	
BUTTER	
QUEEN	
TOTAL	









Check *each* word identified *correctly*. Words in the shaded regions are the *original* words and the patient should answer *"YES"* or *"OLD"*; words in the unshaded regions are new words and the patient should answer "NO" or "NEW".

TRIAL 1	
FRIEND	
EXCUSE	
OFFICER	
THOUGHT	
LAD	
CAMP	
FATE	
CUSTOM	
BANKER	
GOLF	
PERMISSION	
ABILITY	
BLISTER	
DIRT	
FIGMENT	
ICEBOX	
CONCEPT	
PIANIST	
NONSENSE	
TRIPOD	
FALLACY	
GENDER	
BULLET	
INTELLECT	
TOTAL	

TRIAL 2	
FRIEND	
EXCUSE	
PLANT	
LAD	
CUSTOM	
AMOUNT	
INDUSTRY	
BANKER	
ABILITY	
DIRT	
OCCASION	
CRADLE	
FIGMENT	
ICEBOX	
BANALITY	
SINGER	
HYPOTHESIS	
NONSENSE	
NOOSE	
DISTINCTION	
TANK	
TRIPOD	
DECREE	
FALLACY	
TOTAL	

TRIAL 3	
SEAL	
FRIEND	
EXCUSE	
LAD	
METHOD	
ENGINE	
CUSTOM	
SOUL	
BANKER	
JELLY	
ABILITY	
ORIGIN	
DIRT	
FIREPLACE	
FIGMENT	
JEOPARDY	
ALLIGATOR	
ICEBOX	
SURTAX	
VOLCANO	
ADAGE	
NONSENSE	
TRIPOD	
FALLACY	
TOTAL	

Sleep Disorders Center, City College of New York
Aging and Dementia Research Center, NYUMC
National Development and Research Institute, INC.

FINGER TAPPING TEST

1. RECORD NUMBER OF TAPS FOR EACH 10 SECOND TRIAL.
2. ALTERNATE BETWEEN HANDS.
3. MAKE SURE ALL FINGERS EXCEPT THE INDEX FINGER ARE ON THE BOARD.
4. MAKE SURE THERE ARE AT LEAST 3 TRIALS WITHIN 5 TAPS.

TRIAL	RIGHT	LEFT
1.	_____	_____
2.	_____	_____
3.	_____	_____
4.	_____	_____
5.	_____	_____

---------- continue only if necessary ----------

7.	_____	_____
8.	_____	_____
MEAN (3 trials) =	_____	_____
age-matched norms: mean =	_____	_____
s.d. =	_____	_____
Z-SCORE =	_____	_____

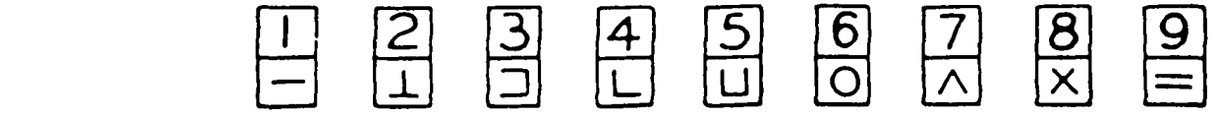
NOTES:

DIGIT SPAN Discontinue after failure on both trials of any item.
Administer both trials of each item, even if the first trial is passed.

DIGITS FORWARD					Score
Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0
1.	6-2-9		3-7-5		
2.	5-4-1-7		8-3-9-6		
3.	3-6-9-2-5		6-9-4-7-1		
4.	9-1-8-4-2-7		6-3-5-4-8-2		
5.	1-2-8-5-3-4-6		2-8-1-4-9-7-5		
6.	3-8-2-9-5-1-7-4		5-9-1-8-2-6-4-7		
				Max. = 12 Total Forward	

DIGITS BACKWARD Administer Digits Backward even if examinee scores 0 on Digits Forward.					Score	
Item	Trial I	Pass-Fail	Trial II	Pass-Fail	2, 1, or 0	
1.	5-1		3-8			
2.	4-9-3		5-2-6			
3.	3-8-1-4		1-7-9-5			
4.	6-2-9-7-2		4-8-5-2-7			
5.	7-1-5-2-8-6		8-3-1-9-6-4			
6.	4-7-3-9-1-2-8		8-1-2-9-3-6-5			
				Max. = 12 Total Backward		Max. Total = 24

Digit Symbol



SAMPLES																										
2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4
1	5	4	2	7	6	3	5	7	2	8	5	4	6	3	7	2	8	1	9	5	8	4	7	3
6	2	5	1	9	2	8	3	7	4	6	5	9	4	8	3	7	2	6	1	5	4	6	3	7
9	2	8	1	7	9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

Appendix 3-E

Comprehensive Profile and Assessment of Alzheimer's Disease

Diagnosis of Alzheimer's Disease

With the increase in the percentage of individuals with moderate or severe dementia, it became necessary to develop accurate diagnostic criteria. Consensus meetings by different organizations in different countries have led to a number of diagnostic entities for the classification of Alzheimer's disease. One of these criteria was published by Mc Khann et al. (1984) after the 1984 meeting organized by the NINCDS-ADRDA. They are still a cornerstone in establishing a clinical diagnosis of probable AD. The other widely used criteria are those of DSM-IV for primary degenerative dementia. These criteria were reformulated in what is now referred to as DSM-IV criteria for dementia of the Alzheimer's type (American Psychiatric Association 1994). More recently, attempts have been made by the consortium to establish a registry for Alzheimer's disease (CERAD) assessment battery.

According to the DSM-IV criteria, Alzheimer's disease is characterized by an insidious onset with uniformly progressive deteriorating course, and exclusion of all other specific causes of dementia by the history, physical examination, laboratory tests, psychometric, and other special investigations.

In addition to these diagnostic criteria, investigators use several other research criteria contingent upon their research modalities. Most research

protocols investigating some aspect of dementia of the Alzheimer's type are conducted using medical history, psychiatric evaluations, neurological examination, cognitive assessment, and laboratory tests to increase diagnostic certainties by carefully ruling out other possible causes of dementia. Other diseases can cause cognitive degeneration if left untreated (Scheck et al. 1982). They include:

1. toxic condition (e.g., barbiturate intoxication, alcohol abuse)
2. nutritional disorders (e.g., chronic malabsorption syndrome, vitamin B_{12} deficiency)
3. infections (e.g., tuberculosis, encephalitis)
4. endocrine disorders (e.g., myxedema, pituitary insufficiency)
5. cerebral disease (e.g., normal pressure hydrocephalus, slowly growing cerebral tumors).

To identify these reversible causes of dementia, the following ancillary tests have been used:

1. serum enzymes and electrolytes
2. complete blood cell count
3. urinalysis
4. chest X-ray
5. serological test for syphilis
6. serum thyroxin
7. vitamin B_{12} and folate level
8. CT/MRI scans.

Classification of Diagnostic Criteria in Dementia

This classification was adapted from the work done by Kluger et al. (1994) which presents some of the measures used in the diagnosis of AD. It includes the following:

1. global staging scales (furnish an overall clinical impression of disease severity and an estimate of clinical changes during the course of the illness)
2. assessments of functional capacity and ADL (range of basic and complex activities necessary for personal self-maintenance and independent community residence)
3. measures of cognitive evaluations (document primary cognitive symptoms of AD)
4. measures of behavioral symptoms (characterize behavioral symptoms observed in AD).

A number of diagnostic measures have been used in the evaluation of AD. These measures have been validated in numerous studies by different research groups and have been found to be reliable assessment tools. The following diagnostic measures will be briefly presented: the Global Deterioration Scale, Clinical Dementia Rating scale, Katz Activity of Daily Living, Physical Self Maintenance, Instrumental Activity of Daily Living, Functional Assessment Staging, the Brief Cognitive Rating Scale, the Blessed Dementia Rating Instruments, the Mini Mental Status Examination, Mattis Dementia Rating, Alzheimer's Disease Assessment Scale, the Behavioral Pathology in Alzheimer's Disease Rating Scale, Geriatric Depression Scale, Cornell Scale for Depression in Dementia, Dementia Behavior Disturbance, and a number of neuropsychological test batteries. Furthermore, during the past two decades, investigators have added

various neuroimaging techniques as a means of providing diagnostic confirmation. In this regard, the use of CT, MRI, and PET will be briefly mentioned.

Global Staging

1. A The Global Deterioration Scale

The Global Deterioration Scale (GDS) is 7-point rating instrument developed on the basis of systematic phenomenologic observations of the nature of symptomatology in age-associated memory impairment [AAMI] and primary degenerative dementia [PDD] (Reisberg et al. 1988; Reisberg et al. 1982). The scale is comprised of seven major clinically distinguishable stages of dementia. These criteria are broadly defined in table 1.

Table 1.

CLINICAL STAGE	DIAGNOSTIC	CHARACTERISTICS
Stage 1.	Normal	Normal cognitive capacity in the absence of either subjective and/or objective evidence of cognitive deficits.
Stage 2.	Very mild	Subjective complaints of cognitive functional impairment in the absence of clinically manifest deficit
Stage 3.	Mild	Mild cognitive impairment which may interfere with complex occupational or social tasks
Stage 4.	Moderate	Marked cognitive impairment which may interfere with performance in complex activities of daily life
Stage 5.	Moderately Severe	Severe cognitive impairment interfering with independent community survival
Stage 6.	Severe	Very severe cognitive impairment interfering with basic activities of daily life such as dressing and bathing
Stage 7	Very severe	Deficits sufficient to require continuous assistance with basic activities of daily life

1.B The Clinical Dementia Rating Scale

Essentially, this instrument is administered by a clinician in a semi-structured interview format involving both the patient and a collateral source. It describes five levels of observed impairment in performance on each of six categories of cognitive functioning. They include memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Hughes et al 1982; Berg et al 1988). Ratings for those levels of impairments are described below.

RATINGS	CHARACTERISTICS
CDR = 0	(none)
CDR = 1	(questionable)
CDR = 2	(mild)
CDR = 3	(moderate)
CDR = 4	(severe)

Assessment of Functional Capacity

2.A Katz Activities of Daily Living Scale

This instrument evaluates physical ADL based on a three-point scale rating the patient's ability to perform six unaided activities. They include:

RATING	CHARACTERISTICS
ADL = 1	can be done independently
ADL = 2	needs some assistance
ADL = 3	requires total assistance/can't do the activity

Activities assessed include: bathing, dressing, toileting transfer, feeding, and continence (Katz et al. 1983).

2.B Physical-Self Maintenance Scale

This instrument assesses six physical ADL functions, each with different level of impairment. The observer-rated version uses a five-point scale; from requiring no assistance at all to different level of needed assistance (Lawton and Brody, 1969). The self-rated version uses a three-point scale assessing each activity as necessitating no help, needing some help, or necessitating complete assistance (Lawton and Brody 1988b). Activities assessed include: bathing, dressing, toileting, grooming, feeding, and physical ambulance.

2.C Instrumental Activity of Daily Living

The observer-rated version of this instrument evaluates eight ADL functions according to a five-point scale. Functions assessed include: 1) use of telephone, 2) shop, 3) food preparation, 4) housekeeping chores, 5) laundry, 6) traveling, 7) administration of medications, 8) finance handling (Lawton and Brody 1988a). The self-rated version uses a three-point scale (Lawton and Brody 1988c).

2.D The Functional Assessment Staging

The Functional Assessment Staging is a 16-item scale which assesses in detail the progression of functional change in aging and AD. Like the BCRS, the FAST stages and substages were designed to be maximally concordant with the corresponding GDS stages. This scale is used in studies attempting to stage dementia patients exhibiting behavioral disturbances such as depression, anxiety, psychosis, and agitation (Reisberg 1988). The fact that FAST assesses 16 different stages of AD progression has enabled physicians to ascertain clinical changes even in late stages of dementia when traditional assessment instruments fail to detect any changes (e.g., because of floor effects). These tests are believed to contain tasks that are beyond the cognitive capacity of severely demented patients due to the homogenous multiple disintegration of higher nervous and mental functioning of AD individuals [Sclan et al. 1990]. Further, the ordinality of FAST is crucial in facilitating the determination of complicating factors in dementia. Clinicians can therefore identify possible reversible causes of dementia and anticipate disease progression until death. (For details concerning characteristics, diagnosis, estimated duration and approximate at which function is acquired see Reisberg 1985). [table from Reisberg 1985].

Cognitive Assessment

3.A The Brief Cognitive Rating Scale

The Brief Cognitive Rating Scale is a widely used instrument in the assessment of cognitive symptomatology in AAMI and PDD. It consists of 7-point hierarchical clinical axes which have been developed to maximally concordant across axes and with the corresponding GDS stages. The five major axes are as follows:

CLINICAL AXES	CHARACTERISTICS
Axis 1.	Concentration
Axis 2.	Recent memory
Axis 3.	Remote memory
Axis 4.	Orientation
Axis 5.	Functioning and self-care

The BCRS also includes three minor axes:

CLINICAL AXES	CHARACTERISTICS
Axis 6.	Language
Axis 7.	Motoric functioning
Axis 8.	Mood

3.B The Blessed Dementia Rating Scale

The Blessed Dementia Rating Scale is a 17-point scale developed to determine changes in individuals' capacity to perform daily activities and self-care task. It assesses memory, concentration, and functional and emotional status. Blessed et al. (1968) have shown a high degree of association between this instrument and severity of cortical implications. A score of 4 or more is indicative of advanced cortical deterioration.

3.C The Mini Mental State Exam

The Mini Mental State Exam is designed to screen organic impairment and provide a rapid assessment of global cognitive deficits. It measures a range of cognitive tasks, including orientation, verbal reasoning, language, memory, and visuoperceptual skills (Folstein 1975). The MMSE is comprised of scores ranging from 0 to 30, with score of 27 to 30 indicating normal to mild impairment, and score falling below 23 considered the threshold for organic disturbance. Patients with a GDS 3 may achieve perfect scores whereas volunteers with a GDS 5 may approach scores of zero.

3.D Mattis Dementia Rating Scale

This instrument is used as a screening tool to determine brain pathology in geriatric patients. A number of cognitive functions are assessed with this tool including, attention, praxis, verbal and nonverbal abstraction, recent memory, and perserveration, both verbal and nonverbal. Scores range from DRS = 0 (poorest performance) to DRS = 144 (perfect performance) (Mattis 1976).

3.E Alzheimer's Disease Assessment Scale (ADAS)*

This instrument evaluates both cognitive and noncognitive behavior in AD patients as well as in geriatric volunteers. The cognitive section (Scores from 0 to 70) uses eleven items derived from short neuropsychological subtests including, memory, praxis, and language. The noncognitive section (Scores from 0 to 50) comprises items including mood, vegetative functions, delusions and hallucination, agitation, tremor, and concentration/distractibility. The total score ranges from zero to 120, with higher scores indicating poorer performance (Rosen et al. 1984, Mohs and Cohen 1988)

Neuropsychology and Alzheimer's Disease

Since memory dysfunction has been shown to be the earliest indicator of incipient AD (Jacobs 1994) and is required for the diagnosis of dementia according to DSM-IV. Memory has been the province of a multitude of research endeavors since the inadvertent groundbreaking discovery of William Scoville in 1953. Scoville, a neurosurgeon, had performed a bilateral resection of the hippocampus in H.M. which had resulted in an anterograde amnesia. Though, stored memories were not affected, the ability to store and/or retrieve new memories was hindered. This discovery could not have been predicted from the efforts of Karl Lashley in 1915 in his failed attempts to identify the neural locations of learned habits and/or memories.

Scoville's findings on the H.M. case have spurred a lot of investigations into the process of memory storage. Investigators have since reported that only bilateral resection of the hyppocampus leads to loss of virtually all information after the operation; unilateral resection results in severe deficits in memory; uncharacteristic of that of H.M. (Kolb and Whishaw 1990). Along the same line of research, lesions of the right temporal lobe affect only nonverbal material, whereas, lesions of the left temporal lobe result in memory impairment for verbal material.

It has also been observed that though individuals lose declarative memories subsequent to a bilateral resection of the hyppocampus, procedural memories have been spared. After the hippocampal lobectomy, H. M. was able to learn the skills necessary to perform new tasks. This finding has led to the understanding that these two types of memories may be housed in two different locations: one location would be in the system that executes the behavior, the other in the system that stores relevant details concerning time, place, and success in the execution of

that behavior. Another approach has been to view amnesia as caused by a dissociation between the systems necessary for declarative memories and the motor system. Further, it has also been shown that neocortical lesions do not result in amnesia (Kolb and Whishaw 1990).

These early findings are particularly relevant in the understanding of the neuropsychological correlates of brain dysfunction in the case of Alzheimer's disease as the case of H.M. presents an interesting homology. With the onset of senile dementia of the Alzheimer's type, individuals report memory disturbances affecting declarative memories while procedural memories are intact. As will be discussed later, neuroradiological studies have evidenced cellular degeneration at the level of the hippocampal formation as the earliest neuroanatomical marker for AD; neocortical degeneration appears later as the disease progresses and increases in severity.

It bears indicating at this point clearly in normal aging acquisition seems to decline, but recall of previously learned information is preserved (Petersen 1994). Delayed recall and forgetting are thought to be the best indicators of dementia. The rate of forgetting of verbal and nonverbal material noted in AD patients has not been found to be significantly different than elderly normal individuals (Becker et al. 1987.). Although memory is a sensitive indicator of early dementia, this measure seems to be less reliable as the disease increases in severity.

Neuropsychological Tests

Neuropsychological assessment has played an essential role in recent investigations undertaken to better understand the nature of Alzheimer's disease. It serves a number of functions including the identification and severity of deficits, the distinction of Alzheimer's disease from other degenerative diseases, the

determination of disease progression, and the application of cognitive measures to answer research questions about the functioning of the brain. In fact, it is now known that drugs with therapeutic effects on the central nervous system will impact on certain aspects of behavior such as language, perception, attention, affect, and motoric functions.

Below is a list of some of the neuropsychological measures used in the evaluation of Alzheimer's disease. The measures listed in the next table represent subtests of different neuropsychological batteries that have been developed to assess a variety of cognitive functions. They are derived from tests including the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Wechsler Memory Scale-Revised (WMS-R), Finger Tapping, Bushke Selective Reminding Test, Trail Making Test, Boston Naming, Benton Visual Retention Test, Token Test, and Guild Memory Test.

CATEGORIES	MEASURES
Verbal Recall	Paragraph recall Shopping list task Brown-Peterson Distractor Task
Associative Recall	Paired associates Design recall First-Last name task
Language	Vocabulary Category retrieval Object naming

Immediate Memory	Digit span forward Logical memory I Visual reproduction I
Delayed Memory	Logical memory II Visual reproduction II
Visuospatial Praxis	Digit symbol substitution
Visual Recognition Memory	Facial recognition memory
Psychomotor Speed	Finger tapping speed Driving test

These measures have been extensively used in different investigative inquiries into the nature of cognitive deficits in Alzheimer's disease. Using IQ subtests, Fuld (1983) has reported that AD patients are characterized by the striking deficits they exhibit on similarities and digit span, information and vocabulary, object assembly, digit symbol and block design of the WAIS-R. These patients also do poorly on other tests including backward digits, object naming, and telling time on clocks without numbers (Kolb & Whishaw 1990). In a cross-sectional study assessing cognitive functions in Alzheimer's patients, investigators reported cognitive deficits on tests of recent memory, psychomotor speed, concept formation, visuospatial praxis, remote memory, and language (Flicker et al. 1991). Additional cognitive impairments were found in more advanced forms of the disease. Patients showed impairment on tests of immediate memory, language abilities, and visual-perceptual skills.

Besides the known cognitive impairments considered the defining feature of AD, patients that carry a diagnosis of primary degenerative dementia also manifest prominent affective and behavioral disturbances. Generally, it has been reported that the number of behavioral problems increases as cognitive functioning deteriorates and the types of problems reported seem to vary with level of cognitive impairment (Teri et al. 1988). As the disease progresses, AD individuals become confused, disoriented, and unaware of their surroundings or behavior.

Disorientation leading to a general confusional state is thought to result from the patient's inability to perceptually process environmental stimuli (Merriam 1988). They lose their ability to do basic daily activities and exhibit disruptive behavior such as wandering, aggression, irritability, pacing, fear, withdrawal, and anxiety (Patterson et al. 1990; Terri et al. 1988). Attempts to explain behavior problems such as those characterized by ideational manifestations have led to the understanding that AD patients exhibit an inability to discern their subjective mental impressions from actual external representations of people or objects (Merriam 1988).

Behavioral Assessment

4.A The Behavioral Pathology in Alzheimer's Disease Rating Scale

The Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). This scale has been developed on the basis of phenomenologic and pharmacologic treatment data from studies conducted by Reisberg et al. (1989). It consists of 25 items which fall within 7 categories as indicated below. Each item is rated on a 4-point scale. (See Reisberg et al. 1987 for description of each item).

1. Paranoid and delusional ideation

2. Hallucination
3. Activity disturbances
4. Agressivity
5. Diurnal rhythm disturbances
6. Affective disturbance
7. Anxiety and phobias

4.B Geriatric Depression Scale

This instrument was designed to assess depression in the elderly and comprises two versions. The first one consists of 30 items (Yesavage and Brink 1983) and the second one has 15 items (Yesavage and Brink 1988). They can be self-rated or observer-rated using a yes/no format to each item.

4.C Cornell Scale for Depression in Dementia

This instrument was designed to rate or monitor depression in demented patients. Information is gathered by a clinician in an interview with both the patient and caregiver. This scale has 19 items with five broad categories: 1)mood, 2) behavioral disturbances, 3) physical signs, 4) cyclic functions, 5) ideational disturbances (Alexopoulos et al 1988). Ratings are as indicated below:

RATINGS	CHARACTERISTICS
CS =1	(absent)
CS =2	(mild or intermediate)
CS =3	(severe).

4.D Dementia Behavior Disturbance

Administered by a clinician in an interview format with the caregiver, this instrument measures behavioral phenomena associated with dementia. It contains 28 items rated on a 5-point scale ranging from: DBD = 0 (never occurs), to DBD = 4 (occurs all the time) (Baumgarten et al. 1990).

4.E ADAS Noncognitive Scale*

This instrument uses a 5-point rating system assessing the following noncognitive items: 1) depression, 2) tearful, 3) delusions, 4) hallucinations, 5) pacing, 6) motor activity, 7) tremors, 8) concentration/distractibility, 9) cooperativeness, 10) appetite (Mohs and Cohen 1988).

Neuroimaging and Alzheimer's Disease

With the advent of noninvasive neuroimaging techniques [e.g. Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET)], it is now possible to visualize structures in and around the brain and measure local chemical and physiologic functions in neurodegenerative brain regions. Information gained from these morphologic and functional imaging studies provides insight into the pathologic and pathophysiologic changes associated with brain diseases.

Among many suspected brain regions that have been studied, the hippocampus has been found to be the earliest brain structure to exhibit neurodegenerative changes associated with Alzheimer's disease. The observed structural hippocampal atrophies include neurofibrillary tangles, neuritic plaques, granulovacuolar degeneration and neuronal loss (de Leon et al. 1992). Also, a number of neurotransmitter deficits in the hippocampal structures have been documented including depletions of acetylcholinesterase, choline

acetyltransferase, norepinephrine, somatostatin, and glutamate (Kemper et al. 1984; Powers et al. 1988). A discussion on the procedures involved in MRI and PET and their contribution in the diagnosis of Alzheimer's disease is presented in the following section.

Magnetic Resonance Imaging

Computerized Tomography (CT) studies have certainly contributed to our understanding of AD and ultimately its diagnosis. However, due to beam-hardening artifacts by bony tissue, visualization of the temporal lobe, especially at the level of the entorhinal cortex and hippocampal formation has been limited. Hence, this structural brain imaging technique has been utilized primarily for purposes of excluding other brain abnormalities (Erkinjuntti et al. 1993). With the advent of MRI procedures it is possible to reliably study structural damage manifested in the brain of AD patients. To date a number of studies have been conducted indicating selective atrophies of the temporal lobe gray matter and the hippocampal formation (de Leon et al. 1988). In addition, the development of new MRI techniques has made it possible to differentiate patients with AD from normal controls (Seab 1988).

In vivo examination of the hippocampal formation is believed to be of diagnostic and predictive value in the clinical study of AD. There is a line of research indicating hippocampal deterioration as the earliest marker of AD. Though, the noted deterioration is not necessarily coupled with large neocortical metabolic brain changes, nonetheless, investigations have demonstrated that, in fact, the early hippocampal degeneration is correlated with cognitive deficits that are considered as characteristic of AD (de Leon et al. 1992). Longitudinal data acquired by this work group confirm that hippocampal atrophy as determined by MRI measurements is indeed predictive of the clinical dementia associated with

Alzheimer's disease. Based on these findings, it is now clear that MRI can be used to identify individuals that are at risk for developing AD and may be helpful in providing guides to relatives and caregivers about possible consequences and available treatment modalities if clinical investigations confirm the MRI findings.

In vivo MRI procedures are important considering that in late stages of AD, the observed diffuse degeneration changes makes it impossible to ascertain the location of the earliest markers of AD at post-mortem examinations. Moreover, in standard clinical practice, the presence of objective cognitive deficits does not lead directly to a diagnosis of AD. These patients may have a score greater than 23 based on Mini Mental State Exam, a measure assessing global intellectual impairment (Reisberg et al. 1982). Evidently, a number of neuropsychological parameters including remote memory, recent memory and others can be utilized to demonstrate cognitive deficit in AD patients. However, their language abilities are relatively unimpaired. They tend to perform at the same level as normal elderly controls on tests of visuoperceptual tasks, immediate memory, and psychomotor speed (Flicker et al. 1991).

The application of MRI procedures to individuals who are at risk for AD is important because it may provide clinicians a tool to assess certain variables of interest. Such applications allow the observation that the neuropsychological data are in good accord with the neuroradiological findings as described earlier. Additionally, hippocampal atrophy, as detected by MRI as the earliest neuroradiological marker for AD, is well associated with recent memory deficits observed in AD (Zola-Morgan et al. 1986).

Damage to the temporal cortex, on the other hand, appears much later in the course of AD and, therefore, is not considered as an early marker of AD onset. This finding explains the failure to distinguish AD Patients from normal controls on measures assessing language deficits in AD (de Leon et al. 1992). Language

dysfunction is associated with more global cortical degeneration and is likely to advance to more severe level of cognitive deterioration.

Positron Emission Tomography

Positron Emission Tomography (PET) has been used extensively in research on normal and pathological brain function. Given the subtlety of morphological changes as depicted with the utilization of MRI scanning, several investigators have opted for the use of PET procedures to assess early functional alterations in the brain.

Using PET as a diagnostic tool, several investigators have demonstrated that glucose metabolic deficits at the level of the temporal and parietal association cortices reliably distinguish AD patients from age-matched normal controls (de Leon et al. 1988). In fact, there is a line of research evidencing a greater sensitivity for functional imaging techniques in identifying brain pathology that are specific to Alzheimer's disease as opposed to structural imaging techniques. (de Leon et al. 1983).

In general, PET investigations have revealed an inverse correlation between absolute metabolic rates and the severity of dementia; the more severe the dementia, the lower the global glucose and oxygen metabolic rates and the cerebral blood flow. A number of regional deficits have been reported in the association neocortices (e.g., parietotemporal, prefrontal) (de Leon et al. 1988; de Leon et al. 1992).

Another issue of concern along these lines of inquiry is the finding of asymmetric metabolic deficits in AD. Investigators have reported that in AD asymmetric metabolic deficits appear early in the disease process and the side of predominant involvement correlates with the dominant neuropsychologic deficit

observed in individuals with AD. Patients with predominant language deficits exhibit predominant left side metabolic deficits whereas individuals with dominant visuoconstructive deficits exhibit predominant right side deficits (Foster et al. 1983; Haxby et al. 1985).

In another study conducted by Nyback et al. (1991), patients were examined with the use of PET and neuropsychological tests. Patients with AD, relative to controls, exhibited up to a 60% reduction in glucose metabolism in posterior parietal and superior temporal cortex. Several other cortical areas showed similar changes, whereas no changes were revealed at the level of the pre- and postcentral area, the cerebellum, and the basal ganglia. The neuroradiological data correlated with the neuropsychological findings. The authors reported a positive correlation between the rate of glucose metabolism and the neuropsychological test performance. The findings indicated an association between verbal and memory measures with greater left hemisphere metabolism in patients but not in normal controls. Non-verbal abilities, on the other hand, were found to be associated with right hemisphere metabolic dominance.

The Hachinski Ischemia Scale

The Hachinski scale is a rating instrument which is used in assessing risk factors associated with multi-infarct dementia. A score of 4 or greater indicates the likelihood of vascular basis for the observed cognitive deficit.

Appendix 3

The Actigraph Methodology Revisited

After almost a century of research and clinical application, polysomnography (PSG) remains the gold standard in the assessment of sleep/wake patterns. For purposes of documenting sleep architecture, it is imperative that the sleep investigator makes use of PSG because it allows the determination of a number of physiological parameters. These parameters include electroencephalography (EEG), electrooculography (EOG), electrocardiography (ECG), and others. However, given some of the difficulties inherent in the use of this technology, researchers have been looking for alternative measures to document sleep/wake patterns.

One such measure in current use has been the actigraph methodology. In this section, some of the studies that have been conducted to investigate a number of potential methodological artifacts associated with the utilization of this methodology will be discussed. Some of these issues include validation in normal persons (section 3-F) as well as in a clinical population (section 3-G). Actigraph reliability when used over time and in combination, actigraph placement, and first night effect will also be discussed (section 3-H).

The first two studies dealing with validation in a normal population and in insomnia will be presented. The other studies will be presented together by discussing each one sequentially. Together, these studies have offered a novel approach to the scoring and interpretation of actigraphic data. A new model for

identifying sleep and wakefulness based upon actigraphic data has been proposed, tested, and optimized.

The background rationale for these three papers overlaps somewhat because the issues involved are very closely related and were intended for journal submission. They have been inserted to offer a comprehensive determination of the advantage of the Actigraph Data Analysis Software. Moreover, they also show the necessity for its development before undertaking the assessment of the efficacy of melatonin as done in the three studies consisting the subject of this document.

Appendix 3-7

Validation of Actigraphy on Normals

Determination of Sleep and wakefulness with the actigraph data analysis software (ADAS)

Introduction

Investigators have shown that the actigraph methodology is very useful in longitudinal assessment of sleep/wake activity (Cole et al. 1992; Sadeh et al. 1995). It is not only cost effective in comparison to traditional nocturnal polysomnography (PSG), it is also relatively unobtrusive. Additionally, there are reports suggesting that the actigraph (ACT) provides more accurate information about sleep/wake patterns than the sleep/wake diaries (Brooks et al. 1993; Webster et al. 1982). Though these findings have rendered actigraphy more acceptable among sleep researchers, there remain certain methodological issues that need be resolved to warrant its use in clinical population.

The validity of actigraphic assessment of sleep and wakefulness has been questioned because of the potential confounding effects of artifacts related to the device placement and sensitivity, breathing movement, and wrist positioning during sleep (Alster et al. 1990). In light of these artifacts, scoring methods must be carefully tested to minimize erroneous interpretation of actigraph-derived sleep/wake data . Moreover, systematic actigraphic investigations with different

threshold values for activity counts are necessary to help distinguish actual body movement from mere artifacts due to breathing movement and nocturnal wrist positioning.

Investigators have attempted to address issues regarding the sensitivity and placement of the actigraph on nondominant vs. dominant wrist (Sadeh et al. 1994). Internight and intravolunteer variability have also been investigated in healthy persons (van Hilten et al. 1993). Present scoring methods have demonstrated good overall correspondence for normal individuals between total sleep time as determined by polysomnography and total sleep time derived from actigraphy (i.e., 89% to 98% agreement with a mean discrepancy value in one study of about 19 minutes) [Cole et al. 1992; Kripke et al. 1978; Mullaney et al. 1980; Webster et al. 1982]. However, it is understood that, for individuals who are motorically restless while asleep and those who lie still in bed while awake, existing scoring methods are less successful.

Determination of sleep and wakefulness with actigraphy in patients with insomnia has proven very difficult because insomniac patients often lie in bed awake with no actigraphically registered movement. Assessment of total sleep time (TST) in this type of patients has shown an agreement between the two methodologies of 78% to 88%, with a mean discrepancy value of about 49 minutes (Hauri and Wisbey 1992; Verbeek et al. 1994). TST derived from actigraphy is overestimated in patients with psychophysiologic insomnia whereas in patients with sleep state misperception, TST is underestimated (Hauri and Wisbey 1992; Hauri and Wisbey 1994).

To investigate methodological issues related to the use of actigraphy, we have conducted a series of studies using a new actigraph data analysis software (ADAS) developed in the Psychophysiology Laboratory. Here, we report the results of our first study evaluating the validity of actigraphy in assessing

sleep/wake activity with ADAS. According to this method, two criteria for sleep/wake identification were established. The first criterion comprised an actigraphic sleep threshold indicating arousals from sleep and the second consisted of a wake interval post arousal which identifies true awakenings. Used in conjunction, these two criteria represent a novel approach allowing accurate discrimination of periods of sleep from wakefulness.

Method

Participants

Twenty normal volunteers (male = 11, female = 9) with ages ranging from 21 to 53 years participated in the study (mean age = 29.95 and SD = 8.98). Each person was screened for major sleep pathology with a questionnaire and volunteered to participate in the study. All volunteers in this study were attending college during data acquisition.

Procedure

Participants in both phases of the study (i.e., the calibration sample [n = 6] and the validation sample [n = 14]) reported to the laboratory between 9:00 P.M. and 12:00 midnight for an overnight polysomnographic recording using a standard sleep recording montage along with an actigraphic recording. While in the lab, volunteers answered a questionnaire assessing mood and activity for the day, as well as a bedtime and a morning questionnaires. Volunteers were allowed to sleep contingent upon their own schedule. Some volunteers spent less than their habitual time in bed because of academically-related activities.

The actigraph (Gaewiler Electronic) was placed on the dominant wrist to record sleep/wake activity during the recording night. Additional EMG electrodes were placed on the dominant forearm to record phasic arm electromyographic events (PAEMG). For optimal synchronization between actigraphy and polysomnography, the designated bedtime was marked on the polysomnogram according to the time indicated by the internal timer of the computer from which the actigraph was initialized. Additionally, every PAEMG movement was recorded in a night log by a technician at the time they occurred for verification while manually scoring polysomnographic records. All PSG records were scored according to standard criteria (Rechstchaffen and Kales 1968). All sleep stages (i.e., 1, 2, 3, 4, and REM) were tabulated for each volunteer yielding the total value of sleep time used in statistical analysis. PSG records were scored by an investigator other than the one who performed the actigraph data analysis.

Instrumentation

The actigraphs used in this study were provided by Gaewiler Electronic (CH-8634 Hombrechtikon, Switzerland). Actigraphic data represented wrist movement which was translated into an electric signal via a piezoelectric element. Suprathreshold movements (i.e., accelerations > 0.1 g with a band pass filter of 0.25 - 3.00 Hz over 60-second epochs), were stored in the actigraph memory every minute. Stored data including volunteer's ID, start time and stop time, sampling interval, and actigraphic counts were downloaded via an IBM-compatible computer. All actigraphs were initialized with one minute sampling interval.

All actigraphic data were analyzed with the Actigraph Data Analysis Software (ADAS). This software was developed at the Psychophysiology Laboratory at the College of Staten Island by Hans von Gizycki and Girardin Jean-

Louis. It was written using the Microsoft Visual Basics software package; hence, at this time it is only operational in IBM-compatible computers. This software allows for visual inspection of patterns of activity based on actigraphic data. Data can be manipulated to yield statistical values for a number of actigraphically derived variables including, total sleep time (TST), sleep efficiency index (SEI), wake after sleep onset (WASO), sleep onset latency (SOL), and others. Additionally, amplitude and periodicity of circadian rhythm in activity patterns can be determined with the added smoothing and autocorrelation functions. Frequency analysis and Pearson correlation coefficients can be obtained by direct comparison of the actigraphic and polysomnographic data (von Gizycki et al. 1995).

Phase 1. Determination of The Actigraphic Sleep Threshold

The objective of the first phase of the study was to determine an actigraphic sleep threshold (AST) based on the number of activity counts reflecting wakefulness and those representing sleep. The first step in the analysis of the actigraph data in phase 1 comprised a visual identification of a window of activity designated as time in bed (TIB). This window of activity data was analyzed by scoring activity counts above threshold values as wake and those below threshold were scored as sleep. This analysis was conducted for each volunteer in the calibration sample using each actigraphic count (i.e., 252 counts). Using total sleep time as an index of comparison, the threshold value that yielded the best possible match between actigraphy and polysomnography was selected as the AST for each volunteer. The obtained ASTs were averaged across volunteers and determination of sleep and wakefulness for each volunteer was repeated using the mean value of actigraphic sleep thresholds.

Phase 2. Application of Actigraphic Sleep Threshold and Wake Interval Post Arousal

The assignment of a specific actigraphic count as a threshold for sleep yielded good TST values for volunteers in the calibration sample. However, subsequent analyses applied to that sample have led to the understanding that sleep latency subsequent to an arousal is not accounted for by this procedure, nor is sleep fragmentation assessed; two crucial measures in cases where individuals exhibit severe sleep disturbances. We, therefore, added to the scoring software an algorithm which allowed statistical computations based not only on the AST but also on an adjustable wake interval post arousal (WIPA). Arousals were defined in terms of actigraphic counts that were above the AST but less than the ascribed criterion value for WIPA.

The second criterion, the wake interval post arousal allows only those arousals (i.e., activity counts that were above the AST) that were less than or equal to the criterion value to be scored as sleep. Arousals of a longer duration than the criterion were scored as wake. Accordingly, a WIPA of 3 minutes permitted the automatic scoring of arousals equal or less than 3 minutes as sleep (see figure 4-F-1). Successive arousals greater than three minutes were score as wake. This three minute criterion was selected based on a previous research demonstrating that an average latency of three minutes is necessary for volunteers to return to sleep after nocturnal awakenings determined by PSG recordings (Jean-Louis et al. 1995). These criteria, when combined, provide a way of identifying epochs of sleep fragmentation and also a sleep latency post awakening indicator during the night.

Results

After the inclusion of the second criterion, the calibration sample was rescored with a WIPA of 3 minutes using all the actigraphic counts for all

volunteers. The computed threshold values after the application of both criteria were averaged across volunteers and the mean value of actigraphic sleep thresholds (i.e., an AST of 10 counts) was used to determine sleep and wakefulness in the final analysis. Using Pearson r analysis, a high correlation coefficient was obtained between actigraph-derived total sleep time and polysomnographic total sleep time (i.e., $r = 0.93$, $p = 0.008$) [see table 3-F-1]. The optimal scoring method was then applied to the validation sample to identify actual sleep time derived from actigraphy. This prospective analysis revealed a higher correlation coefficient for total sleep time (i.e., $r = 0.97$, $p = 0.0001$) [see table 3-F-2]. When pooled, the calibration and validation samples yielded a very strong correlation coefficient (see figure 3-F-2). Sleep onset latency was also highly correlated for the validation sample ($r = 0.78$, $p = 0.001$).

Discussion

This study has further demonstrated the validity of the actigraph methodology. Based on our findings and earlier reports, it is clear that, overall, actigraphy is an excellent tool for unobtrusive documentation of sleep/wake activity in normal individuals. Our analyses have indicated an overall agreement between the two methodologies of 97% with an average discrepancy of 12 minutes in total sleep time for the validation sample.

Using the optimal method of sleep/wake actigraphic determination in a prospective analysis of the validation sample, we have obtained a significant correlation coefficient for total sleep time (i.e., $r = 0.97$, $p = 0.0001$). Our results have demonstrated a threshold of 10 actigraphic counts to be a reliable criterion for sleep in normal volunteers. However, since our analyses involved volunteers with no severe sleep disturbances, it is important that this threshold for sleep be

investigated in other populations such as those that are characterized by individuals who are motorically restless when sleeping and/or insomniacs.

By allowing a three minute period to fall asleep besides the actigraph threshold for sleep, we have reduced the likelihood of misscoring activity counts. It is also postulated that this method might increase the sensitivity of our software to detect brief arousals during the night and correctly score them. Efforts are now being deployed in our laboratory to investigate which actigraphic thresholds can best serve at identifying events such as breathing movement, wrist positioning, and others. In this study, nocturnal arousals were scored as either awakenings or transition time between an awakening and an actual sleep onset. This method has made it possible to measure sleepiness level subsequent to nocturnal awakenings. It was found that normal individuals return to sleep rather quickly (mean = 1.43 minutes, SD = .65). This finding is believed to be in agreement with the results of an earlier study we conducted investigating sleep latency subsequent to REM awakenings in a REM deprivation protocol (Jean-Louis et al. 1995).

The application of this new scoring software has led to similar findings with other existing scoring methods. It is also clear that though the actigraphs in this study were placed on the dominant wrist, a very high degree of correspondence was established between the two methodologies, suggesting that perhaps sensitivity of the actigraph rather than placement is crucial in sleep/wake monitoring with actigraphy. In effect, preliminary observations on an ongoing study in our laboratory, investigating possible differences between dominant Vs nondominant wrist placement of the actigraph, have indicated very little discrepancy in the measures analyzed. For total sleep time and sleep efficiency index, Pearson Product Moment coefficients were 0.99, $p = 0.0001$ and 0.97, $p = 0.0001$, respectively ($n = 18$).

Appendix 3-G

Validation of Actigraphy in Insomnia

Actigraphy in Insomnia Revisited: Determination of Sleep and Wakefulness With The Actigraph Data Analysis Software (ADAS)

Introduction

Technological advances have given rise to diverse miniaturized ambulatory monitoring devices now in use by many investigators. The use of these devices stems from their ability to accurately document sleep/wake activity in a cost-effective manner in both research and clinical settings. Considerable interest in the utilization of actigraphy (ACT) has emerged as an alternative to polysomnography (PSG), the gold standard in the assessment of sleep/wake patterns. Because of the potential benefits offered by the actigraph methodology (e.g., continuous unobtrusive recording of sleep/wake activity), efforts have been made to determine its validity and reliability in normal persons as well as in individuals with sleep problems of different etiologies.

To date, scoring methods used to validate actigraph devices, have demonstrated good overall correspondence for normal individuals between total sleep time (TST) as determined by polysomnography and total sleep time derived from actigraphy [i.e., 89% to 98% agreement with a mean discrepancy value in one study of about 19 minutes] (Cole et al. 1992; Kripke et al, 1978; Mullaney et al 1980; Webster et al. 1982). Further, using normal individuals, potential

methodological problems have been addressed systematically. In a series of methodological studies conducted in our laboratory, it has been demonstrated that placement of the actigraph poses no serious challenge to the reliability of TST in the actigraphic data (see next section on appendix 3-H). In addition, the actigraph has been found to be reliable when used over time. When used in pairs, high reliability coefficients have been observed (see next section on appendix 3-H).

However, for individuals who are motorically restless while asleep and for those who lie still in bed while awake, existing scoring methods may be less successful (Verbeek et al. 1994). In fact, lower correlation coefficients between ACT and PSG have been found for persons with those characteristics. It is said that as the quality of sleep diminishes, the effectiveness of scoring methods becomes questionable (Levine et al. 1986); or that the actigraph does not yield meaningful data for such individuals. Disagreement between PSG and ACT has been noted mostly in periods of transition between sleep and wakefulness but not when individuals are fully alert or in deep sleep (Hauri 1991; Pollmaecher et al. 1988). Evidently, scoring methods have to incorporate a mechanism for discriminating true wake periods from episodes of mere inactivity, if they are to reliably account for moments of sleep and wakefulness.

One clinical application of actigraph has been in the assessment of sleep in insomnia. This is necessary because it allows naturalistic documentation of large night to night variability that characterizes the sleep of insomniacs (Hauri and Wisbey 1992). There is thus a consensus that more than one night of PSG recording is needed to obtain a good profile of insomniac's sleep/wake patterns. Also, the sleep of insomniacs may be severely affected by the environment they sleep in; with better or worse nights experienced in the laboratory (Hauri et al. 1989). Hauri and Wisbey (1992) have reported that one-third of the patients they have diagnosed slept better in the laboratory whereas two-thirds had better sleep at

home. The use of actigraphy potentially eliminates this confound known as the "first night effect" by allowing patients to maintain their bedtime ritualistic activities leading to sleep in their habitual environment. Research findings on normal individuals have indicated that there is no first night effect associated with actigraphy when used at home (see next section in appendix 3-H).

Determination of sleep and wakefulness with actigraphy in insomnia patients, nevertheless, has proven very difficult. These individuals may lie in bed awake with no actigraphically registered movement. Others may be very active in their sleep (e.g., periodic limb movement). This may in part explain why lower coefficients are found in insomnia validation studies. Assessment of total sleep time in this population has shown an agreement between ACT and PSG of 78% to 88% (Hauri and Wisbey 1992; Verbeek et al. 1994). Two other difficulties inherent in actigraph research involving insomnia deserve some research effort.

The first one concerns its inability to provide an exact representation of sleep/wake activity with different diagnostic classification for insomniacs. Differences have been noted in actigraphic sleep/wake profile suggesting that diagnostic category is an important covariate that is worthy of some consideration. TST derived from actigraphy is overestimated in patients with psychophysiologic insomnia whereas in patients with sleep state misperception, TST is underestimated (Hauri and Wisbey 1992; Hauri et al. 1994). The other issue of importance in developing a profile of sleep/wake patterns in insomnia relates to whether actigraphy is, in effect, a better instrument than sleep diaries which rely primarily on the patient's subjective estimates.

To our knowledge, few studies have been conducted to document the validity of actigraphy in the insomnia population. Two independent investigations have, thus far, revealed average discrepancies of 48 and 49 minutes in total sleep time between ACT and PSG (Hauri and Wisbey 1992; Verbeek et al. 1994). The

validity of actigraphy is, consequently, questioned in insomnia because of the considerable discrepancy that has been reported between the two methodologies. The present study sought to determine the applicability of a new scoring method, the Actigraph Data Analysis Software [ADAS] by further exploring the correspondence between ACT and PSG in insomnia. This investigation was undertaken by conducting a reanalysis of a subsample of the Mayo Clinic Insomnia database.

Method

Participants

In this investigation, a subsample of 24 insomniac participants from an insomnia database was reanalyzed (mean age = 45.38, SD = 11.11; male = 8, female = 16). Participants were screened and interviewed to ascertain sleep/wake patterns and daytime functioning. To be included in the study, participants had to report sleeping poorly on at least 3 nights weekly and suffered from insomnia for a minimum of 6 months. Additionally, they reported impairment of daytime functioning resulting from insomnia which was, however, not caused by chronic pain, medical conditions, and alcohol and drug use. On initial interview, those who reported a sleep latency of more than one hour or more than 90 minutes of wakefulness during the night on at least 3 nights weekly were accepted in the study. None of the participants used hypnotics, sedatives, anxiolytics and other sleep inducing medications for at least 2 weeks before beginning the study.

Procedure

Participants in the study reported to the laboratory at 8:30 P.M. for three consecutive overnight polysomnographic recordings upon completion of a one-week actigraphic recording along with sleep/wake diaries and Stanford sleepiness scale. While in the laboratory, standard sleep recording montage along with the ambulatory monitoring device were used to monitor patients' sleep/wake patterns. At the end of night three, they all received a diagnosis of insomnia based on the International Classification of Sleep Disorders (Hauri and Wisbey 1992). Patients were diagnosed with psychophysiologic insomnia (PI), sleep state misperception (SSM), and insomnia associated with a psychiatric disturbance (IPD).

PSG records were scored according to standard criteria (Rechstchaffen and Kales 1968). Originally, the actigraph records were scored by the Actigraphic Scoring Analysis of Sadeh et al. (1989), an automatic program developed through stepwise discriminant analysis techniques of actigraphic data. The present analysis was performed on actigraphic data recorded during the first night with the Actigraph Data Analysis Software. Of the original sample of thirty-six volunteers from the Mayo Clinic, a total of twenty-four were used in this reanalysis because of missing data. Twenty of the available participants had complete ACT and PSG data for the first night; complete recordings were performed on two of the three nights spent in the laboratory. The first night was chosen for analysis because more data points were available for that night.

Instrumentation

The Actigraph Data Analysis Software was developed in the Psychophysiology Laboratory at the College of Staten Island by Hans Von Gizycki

and Girardin Jean-Louis. It was written with the Microsoft Visual Basic software package. ADAS allows visual inspection of patterns of individual's activity based on actigraphic data (see figure 3-G-1). ADAS uses a set of computer algorithms written to perform specific data manipulation yielding statistical values for a number of actigraphically derived variables. They include, total sleep time (TST), sleep efficiency index (SEI), wake after sleep onset (WASO), sleep onset latency (SOL), mean activity level (MAL), transition from sleep to wakefulness (TRANSITION), sleep latency post awakening (SLPA) and others.

Additionally, amplitude and periodicity of circadian rhythm in sleep/wake patterns can be determined with smoothing and autocorrelation functions. Smoothed data can be further analyzed by interfacing with MATLAB; an interactive, matrix-based system for scientific and engineering calculations available in Sun/Apollo/PC/Apple Macintosh and others. Frequency analysis and Pearson correlation coefficients can be obtained by automatic minute by minute comparison of the actigraphic and polysomnographic data (von Gizycki et al. 1995).

ADAS has been optimized and tested thus far on a normal sample using actigraphs provided by Gaewiler Electronic and distributed by Sing-Medical and Associates from Switzerland (For technical details on these devices, see previous section in appendix 3-F). These actigraphs are considerably different from the ones used in the insomnia validation study reported by Hauri and Wisbey (1992). In their original study, actigraphs from Ambulatory Monitoring, Inc. Ardsley, NY were used with initialization for zero-crossing at 30-second intervals. Because these two systems have a different modality of actigraphic data initialization, storage, and transfer, data obtained from the insomnia database had to be converted into a format that could be processed by ADAS; since the software was initially developed based of the Gaewiler actigraph system. Besides this

conversion, no further programming manipulation was necessary to score the actigraphic data.

Data analysis was performed based on the criteria used in the earlier validation study on normal individuals. According to the procedures used in that study, the software was calibrated by implementing two criteria for sleep/wake scoring. These criteria consisted of an actigraphic sleep threshold, and a wake interval post arousal that showed the best match between ACT and PSG. Second, this software was subsequently tested on a validation sample showing little discrepancy between ACT and PSG (see previous section in appendix 3-F). These criteria are described in the following section.

Determination of The Actigraphic Sleep Threshold and The Wake Interval Post Arousal

As previously argued, problems inherent in scoring actigraphic data resulted from an inability to precisely discriminate true wake episodes from periods of mere inactivity. To address this problem two criteria were implemented. The first criterion comprised an actigraphic sleep threshold indicating arousals from sleep and the second one involved a wake interval post arousal which identifies true awakenings.

The first criterion, the actigraphic sleep threshold (AST), was determined based on the number of activity counts reflecting wakefulness and those representing sleep. The first step in this process comprised a visual identification of a window of activity designated as time in bed for all actigraphic data in the calibration sample. This window of activity data was analyzed by scoring activity counts above threshold values as wake and those below threshold were scored as sleep. This automatic minute-by-minute analysis was conducted for each person in the calibration sample using each actigraphic count (i.e., 1-252 counts) with a

sleep latency interval of 15 minutes of consecutive sleep. Using total sleep time as an index of comparison, the threshold value that yielded the best possible match between actigraphy and polysomnography was selected as the AST for each person. The AST value obtained for each person was then averaged yielding a final AST of 12 counts.

In the original study, an AST of 10 counts was chosen because it provided a correlation coefficient slightly higher than the one found for an AST of 12 counts. However, further analysis examining the discrepancy between ACT and PSG for that sample has shown a lower discrepancy for an AST of 12 counts. This observation along with the need to establish standard criteria for sleep/wake identification provided the rationale for the application of the same criteria to the insomnia sample.

The second step concerned the addition of a second criterion, a sub-routine which permits the inclusion of a wake interval post arousal (WIPA). According to this method a wake interval post arousal of 3 minutes allows those arousals (i.e., activity counts that were above the AST of 12 counts) that lasted 3 minutes or less to be scored as sleep. Arousals greater than three minutes were scored as wake. This three-minute criterion was selected based on our previous research demonstrating that an average latency of three minutes is necessary for normal and narcoleptic individuals to return to sleep after experimental nocturnal awakenings determined by PSG recordings (Jean-Louis et al. 1995). This criterion has found some support from the preliminary results reported by Gorny et al. (1996). These investigators have shown that when a 2-minute rule was applied to their actigraphic data, more precise sleep/wake determinations were made.

This method provided a way of identifying epochs of transition, sleep fragmentation, and sleep latency post awakening during the night. Since actigraphy relies only on activity counts, this approach to sleep fragmentation may

not be maximally concordant with fragmentation as understood from PSG data. Nevertheless, it offers another avenue whereby nocturnal activity patterns can be meaningfully assessed with actigraphy. After comparisons with total sleep time obtained from PSG, the optimal criteria for application to the validation sample were determined to be an AST of 12 counts and a WIPA of 3 minutes. The reanalysis of the insomnia actigraphic data was conducted by adapting this standardization, thus allowing meaningful comparisons between normal and insomniac sleep/wake activity data.

Results

The optimal scoring method derived from the actigraphic data of normal individuals was applied to the insomniac actigraphic data to identify actual sleep and wake periods. The obtained actigraphic value for each person was then compared to their prescored PSG data to determine possible discrepancies between ACT and PSG. Using Pearson correlation analysis, we have found a high correlation coefficient for total sleep time ($r = 0.85$, $p = 0.0001$). Sleep efficiency index and sleep onset latency were also highly correlated for that sample ($r = 0.74$, $p = 0.001$; $r = 0.56$, $p = 0.007$; respectively) [see table 3-G-1]. Examination of wake after sleep onset did not show a significant correlation between ACT and PSG. Further, comparison of the mean values of these measures between actigraphy and polysomnography has shown little discrepancy. Using total sleep time as an index of comparison, an average discrepancy value of 7 minutes was observed [see table 3-G-1].

By contrast, the same statistical analysis was conducted to determine the correspondence between ACT and PSG when only the first criterion, the actigraphic sleep threshold, was used. The application of the AST without the second criterion, the wake interval post arousal, is an automatic minute-by-minute

approach to determine actigraphic sleep/wake epochs. As described earlier, each minute was scored as sleep if it was below the AST of 12 counts and wake if it was above the criterion. Analysis with this criterion has shown a significantly lower correlation coefficient for TST and SEI when compared to the values obtained when both criteria were implemented ($t = 6.69$, df(23), $p = 0.0001$; $t = 6.55$, df(23), $p = 0.0001$; respectively) [see table 3-G-2].

Additionally, the application of the AST by itself produced a larger average discrepancy value than the two criteria combined. For the AST only, our analysis has demonstrated a correlation coefficient of 0.78, $p = 0.0001$, with an average discrepancy of 24.08 minutes between ACT and PSG. Whereas, as reported above, the combination of AST and WIPA (i.e., the optimal scoring method) yielded a coefficient of 0.85, $p = 0.0001$, with a discrepancy value of 7.18 minutes) [see table 3-G-3]. We have also observed that actigraphy overestimated sleep duration and sleep efficiency when the AST was used separately ($t(19) = 2.60$, $p = 0.02$; $t(19) = 2.11$, $p = 0.05$; respectively, whereas a trend toward underestimation of sleep duration and efficiency was noted when both the AST and WIPA were used.

Discussion

The scrutinization of actigraphy is necessary since current attempts are aimed at its establishment as a reliable adjunct to polysomnography in research as well as clinical practice. Controversy surrounding the use of this methodology has been mostly related to its utilization in clinical populations. In insomnia, in particular, actigraphy has been found to be useful only in the assessment of internight variability as a within-subject coefficient of .81 was noted (Chambers 1994). Its accuracy in determining precise sleep/wake patterns has not been supported due to reported high discrepancy between ACT and PSG.

The finding of this reanalysis is very important for research as well as clinical application since it offers a paradigm supporting the usefulness of actigraphy in insomnia. The results of this reanalysis have demonstrated that a threshold of 12 actigraphic counts along with a wake interval post arousal of 3 minutes can be used as reliable criteria for discriminating sleep from wakefulness in insomnia. We have obtained high correlation coefficients for total sleep time, sleep efficiency index, and sleep onset latency ($r = 0.85$, $p = 0.0001$, $r = 0.74$, $p = 0.001$; $r = 0.56$, $p = 0.007$, respectively).

Contrary to previous reports, our findings have clearly demonstrated that overall actigraphy is an excellent tool for unobtrusive documentation of sleep/wake activity in normal individuals as well as persons diagnosed with insomnia. The observed discrepancy of 7 minutes compared favorably with the earlier report of 49 minutes discrepancy. This observation may be an indication of the advantage of this scoring method. However, further applications of ADAS are necessary to determine its sensitivity in identifying sleep/wake activity in other clinical subpopulations.

Additionally, this reanalysis was based on more than half of the original database for which we had complete actigraphic and polysomnographic data. Therefore, an inference can be made that ADAS could be fairly robust in identifying actual sleep from the actigraphic data for the remaining patients if it were processed. Further, a more direct comparison with the earlier results of Hauri and Wisbey would entail a reanalysis of all available nights and the average data would be the basis for comparison between ACT and PSG. This reanalysis was based on the first night for the available 20 patients because it was determined that the sample represented a sizable proportion of the original sample.

Traditionally, algorithms have been found to yield some discrepancies when used to score actigraphic data from a device for which they were not

originally optimized. Using Cole's algorithm, Verbeek et al. (1994) have reported an agreement of 84% for their insomnia data while Cole found an agreement of 88% for his normal population. Sadeh's scoring formula has produced an agreement of 91.8% when normal volunteers were used. Using the same formula, Hauri and Wisbey have obtained an agreement of 82% in their analysis of insomniac actigraphic data. These observations further indicate the exigency of a more precise demonstration of interdevice reliability and sensitivity of scoring methods. In effect, such an investigation would require that pairs of actigraphs from different manufacturers be used on the same wrist to monitor changes in activity level. It is understood that a robust scoring method would yield similar output for two different actigraph devices. Moreover, scoring methods should also show the ability to perform equally well when applied to a different population on which they were not optimized. This test is needed to determine its sensitivity to account for subtle differences inherent in each population examined.

Consistent with the need to establish a software applicable to different actigraphs and various populations, the compatibility of ADAS was assessed. This assessment was based on an examination of the visual output of data derived from two devices with a different mode of operation. This comparison involved data from subjects who were different in their patterns of sleep/wake activity. One group had no complaint of sleep problem (see previous section in appendix 3-F), while the other was diagnosed with insomnia (Hauri and Wisbey 1992). This attempt has led to two important observations. First, the results of the actigraphic data were highly concordant with these individuals' PSG records. Second, although the devices used were different, ADAS was, nevertheless, able to distinguish the patterns of sleep/wake activity in normal persons from individuals with insomnia (see figure 3-F-2). This illustration is typical of a larger data set characterized by significant differences between normal and insomniac sleep/wake actigraphic patterns (Jean-Louis et al., unpublished results).

While these methodological questions merit further experimental consideration, it seems plausible to assume that, based upon the present findings, sleep/wake data derived from different actigraphs are comparable. However, comparisons should be made with the same scoring method with accurate scoring criteria as proposed by the Actigraph Data Analysis Software. ADAS offers a new and comprehensive approach to the scoring and interpretation of actigraphic data. The findings of this reanalysis further document the validity of actigraphy in assessing sleep and wakefulness in insomnia.

In sum, this reanalysis and our previous work in documenting the validity and reliability of actigraphy have provided a mechanism to address some of the methodological challenges encountered in actigraph research. However, whether sleep diaries can be relied upon to establish an accurate profile of sleep in insomnia remains an important question that can not be addressed in this study. Future effort to systematically answer this question would be much appreciated.

Appendix 3-H

Reliability, Sensitivity, Placement, and First-Night Effect

(Section H-Study 1-5):

Methodological consideration in actigraphic assessment of sleep-wake activity: Application of the Actigraph Data Analysis Software (ADAS)

Introduction

Rest-activity data have been in use in both animal and human research investigations as a behavioral measure and/or a marker for physiological processes (Lieberman and Wurtman 1989; Richter 1922) . However, documenting this type of behavioral and physiological indicator has been met with a measure of skepticism, particularly, when the claim would be to supplant polysomnography (PSG) with actigraphy (ACT). The argument for a widespread recognition of actigraphy gains more ground with the fabrication of a number of state-of-the-art ambulatory monitoring devices currently used in research and clinical assessment of sleep; a physiological as well as a behavioral phenomenon. Contrary to the limitations imposed by PSG in long term assessment of sleep and wakefulness, the advent of actigraphy has made it possible to record sleep/wake patterns unobtrusively on a longitudinal basis.

Decades of research with the use of the actigraph methodology have given rise to a body of literature on the establishment of the validity and the reliability of this methodology. Using a variety of actigraph systems with unique features and different modes of operation, researchers have developed a number of algorithms specifically calibrated and tested for the analysis of actigraphic data. We are, however, cautioned that many softwares that have been developed are limited to the actigraph for which it was not optimized (Sadeh et al. 1995). In fact, when used to analyze actigraphic data from other devices, considerable discrepancies have been noted between the predictions made from different algorithms (Cole et al. 1992).

Several investigations, particularly in presumed normal volunteers have demonstrated remarkably high reliability coefficients, with values ranging from 89% to 98% when comparing ACT and PSG; with TST as index of comparison (Kripke et al. 1978; Sadeh et al. 1989; Webster et al. 1982). In clinical populations, however, lower values have been observed, ranging from 78% to 88% (Brooks et al. 1993; Hauri and Wisbey 1992). Given the heterogeneity of the populations studied and the diversity of research settings that have been utilized in these investigations, the findings of these studies have added a degree of convergent validity to the actigraph methodology.

These findings notwithstanding, a number of methodological artifacts inherent in the use of actigraphy have been reported (Alster and Sadeh 1990). Actigraphic artifacts include interdevice reliability and diminution of sensitivity over time, placement of the actigraph on nondominant versus dominant wrist and wrist versus ankle placement, breathing movement, and wrist positioning during sleep (Alster and Sadeh 1990; Sadeh et al. 1995). As previously argued, some of these artifacts may have led to equivocal interpretations of actigraphic data (Sadeh et al. 1994). Others evoke the formulations of the possible limitations of actigraph

devices in assessing sleep and wakefulness in certain sleep disorders. Clearly, a large scale adoption of the actigraph methodology, if exigent, entails that a concentrated effort be deployed in order to systematically document these potential artifacts (Sadeh et al. 1995). To date, few investigators have attempted to delineate and/or investigate some of these artifacts (Alster and Sadeh 1990, Sadeh et al. 1994).

Sadeh et al. (1994) have shown no significant differences between actigraphically determined sleep/wake measures between pairs of actigraphs placed on the dominant and nondominant wrist. This finding is supported by Chung et al. (1995) who have also shown no differences in sleep duration derived between devices placed on both wrists. However, significant differences have been reported for activity level (Sadeh et al. 1994). A possible explanation for the observed difference in activity level was that the actigraphs used in that study may not have been sensitive enough or that some variability in sensitivity caused the discrepancy. Significant interdevice differences have also been reported, indicating low reliability of the actigraph (Sadeh et al. 1994). Using an elderly population, other researchers have reported that there are no first night effects associated with the use of actigraphy. However, significant internight and intraindividual variability have been found (van Hilten et al. 1993).

To further document the usefulness of actigraphy in research and clinical practices, some of the methodological studies conducted in our laboratory to systematically address these artifacts are reviewed. Issues addressed in these studies include, dominant and nondominant placement of the actigraph, ankle and wrist placement, interdevice variability, possible attenuation of device sensitivity over time, and "first night effect" and/or internight variability with actigraphy.

Method

Participants

A series of four studies were conducted, each investigating a specific methodological issue. A total of 39 healthy volunteers (male = 15, female = 24) with ages ranging from 19 to 57 participated in these studies (mean age = 29.46, SD = 10.16). Each volunteer was screened for major sleep pathology with a questionnaire and was assigned to one or more studies.

Procedure

The purpose of study 1 was to assess possible difference that might exist between devices when worn at the same time. A pair of actigraphs were placed on the dominant wrist to record sleep/wake activity during a period of twenty-four hours. Volunteers (n=18 mean age =30.06, SD =13.06) were asked to record in a log the time at which they went to bed and their wake up time.

The purpose of study 2 was to determine difference in old versus new devices as a way of examining their sensitivity over time. Normal volunteers (n=10 mean age =28, SD =10) were given a pair of actigraphs to wear on the dominant wrist for a 24 hour period. Actigraphs were categorized as old and new. The old actigraphs have been used in a number of studies in our laboratory for at least eighteen months. The new ones have been recently purchased.

The purpose of study 3 was to assess difference in placement of the actigraph on the dominant versus the nondominant wrist. Volunteers (n=11, mean age =34, SD =10) were each asked to wear a pair of actigraphs for one night: one on the dominant wrist, and the other on the nondominant wrist and record in a log the time at which they went to sleep, their wake up time, daytime sleep periods, and the time the actigraph was removed for bathing.

The procedures for study 4 (n=14, mean age =29, SD =14) were similar to study II, except that actigraphs were placed on the dominant wrist and the dominant ankle. Finally, in study 5 (n=22, mean age =25,73, SD =5.03) volunteers wore the actigraph for two or more nights on the dominant wrist for continuous sleep/wake monitoring, and a sleep/wake diary was kept to assess night to night variability.

The procedures used to derive actigraphic sleep/wake variables have been described earlier in our validation studies. It must be noted that, since our volunteer population was considered normal, we used the criteria reported earlier in our validation study that is, an actigraphic sleep threshold (AST) of 10 counts, a wake interval post arousal (WIPA) of 3 minutes, and a sleep latency threshold of 3 minutes observed after lights out. Actigraphic data in all four studies were analyzed with the actigraph data analysis software (ADAS) developed in our laboratory. Analyses were based on designated TIB which was examined on a minute by minute basis to derive nocturnal sleep/wake measures for each device. Data analysis was conducted in two stages. First, subjective estimates of time in bed (TIB) were visually examined by a trained scorer for possible discrepancies. Second, TIB was statistically analyzed, yielding a value for each actigraph-based variable (see table 3-H-1).

Instrumentation

All actigraphic data were analyzed with the Actigraph Data Analysis Software. This software has been optimized and tested thus far on both normal and insomnia samples. The validation study with normal persons was conducted using actigraphs provided by Gaewiler Electronic and distributed by Sing-Medical and Associates from Switzerland (see section 3-F). The validation study with insomniac individuals was conducted using actigraphs manufactured by

Ambulatory Monitoring Inc. (see section 3-G). The results in both studies have shown high correspondence between actigraphy and polysomnography.

Results

Study 1:

In study 1, the sensitivity of the actigraph was investigated. Actigraphically determined sleep/wake measures were compared using Pearson correlations. Strong correlation coefficients were observed for most of the variables analyzed (e.g., a coefficient of 0.99, $p = 0.0001$ was found for total sleep time). Dependent t-tests were also performed yielding no significant differences between pairs of actigraphs for all the variables measured (see table 3-H-1.a).

Study 2:

One presumption in actigraph research has been that once the actigraph is calibrated by the manufacturer, it remains reliable over time. In this study we explored this methodological issue by examining the possible attenuation in sensitivity over prolonged utilization of actigraphs placed on the dominant wrist. Pearson Product Moment Correlation analyses were conducted to assess the interdevice reliability using all the actigraphically derived sleep/wake measures. These results have shown strong correlation coefficients (e.g., $r = 0.99$ $p = 0.0001$), suggesting a low interdevice variability. Dependent t-tests were performed for these variables, which revealed no significant differences between devices (see table 3-H-1.b).

Study 3:

To examine possible differences between dominant and nondominant wrist placement, Pearson Product Moment Correlation analyses were conducted for all the actigraphic sleep/wake measures. Firstly, these analyses were performed for the self-reported TIB, which demonstrated strong correlation coefficients for all of the sleep/wake variables (see table 3-H-2.a). Secondly, analyses were also conducted for the daytime actigraphic data. These results have also shown strong correlation coefficients (e.g., for our activity measure, $r = 0.99$, $p = 0.0001$), suggesting no significant differences between dominant and nondominant wrist placement during the day as well.

Study 4:

This study was conducted to assess possible differences between wrist and ankle placement of actigraphy. Comparisons were made using Pearson Correlation analyses. These analyses have revealed no significant differences for all the actigraphic sleep/wake measures (for TST, $r = .99$, $p < .0001$) [see table 3-H- 2.b].

Study 5:

The aim of the study V was to determine if there is a first-night effect associated with actigraphy as it is the case with polysomnography (Kader and Griffin 1983, Webb and Campbell 1979). Using dependent t-test, these analyses have shown no significant differences between night 1 and night 2 for the variables analyzed (see table 3-H-3). Pearson correlations analyses were also conducted which revealed strong correlation coefficients for most of the variables examined (e.g., a coefficient of 0.76, $p = 0.001$ was found for the fragmentation measure).

Discussion

These methodological studies were conducted in our laboratory to systematically address some of the methodological artifacts previously reported in the literature. The results of our first study support the earlier report by Sadeh et al. (1994). The finding of a high correlation coefficient for TST ($r = 0.99$, $p = 0.0001$) between pairs of actigraphs placed on the dominant wrist, clearly demonstrates a significantly strong interdevice reliability. Though the observed variability between the devices was very low, it was considerable enough to reflect lower coefficient values for measures such as arousal and fragmentation. Care must, therefore, be taken when scoring and interpreting actigraph sleep/wake measures derived from non-zero counts.

It bears remarking that certain factors (e.g., body positions and breathing) have not been systematically ascertained in this study. Thus, these artifacts may have slightly confounded the sensitivity of the actigraph; however, given our results this confounding is probably negligible. Since individual participants were studied at home, no observation of body positions nor breathing artifacts could be made. Other studies are necessary to rule out the potential confounding effects of these artifacts on the reliability of nocturnal actigraphic data. By allowing certain arousals to be scored as sleep, it is believed that the probability of scoring as wake activities that result from breathing artifacts or body positions has been reduced. It is highly unlikely that movements resulted from these two activities will produce activity counts above an AST of 10. Nonetheless, more than one night of sleep monitoring are recommended for a more accurate assessment of sleep/wake activity patterns.

Along the same line of investigation on interdevice sensitivity, another study was undertaken to determine if, in fact, actigraphs devices are subject to

mechanical changes in sensitivity due to prolonged utilization and/ or when used over time. Based on these findings, the actigraphs seem to be quite robust in withstanding prolonged use as no differences were found between twin actigraphs placed on the dominant wrist (i.e., old versus new; for TST, $r = 0.99$, $p < 0.0001$). These findings suggest that the actigraph may be used reliably over long periods of sleep/wake monitoring without any significant mechanical sensitivity changes. Clearly, this finding may not be generalizable to other actigraph devices since each device has its unique features and mode of operation. Furthermore, the reliability of the actigraph may have to be evaluated over certain time interval. Future studies are necessary to determine the actual time interval when mechanical changes, if any, are likely to occur. In this study, we have shown, at least for our actigraphs, that they are highly reliable even after over eighteen months of utilization.

Consistent with the finding of Sadeh et al. (1994), no difference has been observed for any of the sleep/wake variables analyzed in the third study. Interestingly, this observation was consistent across volunteers. However, no significance difference was found in activity level as reported by Sadeh et al. (1994). Further, these results showed a slight difference between the coefficient values derived at night and the one observed during the day for activity level. The finding of a higher correlation coefficient for the daytime activity level may be an indication of more mobility while awake reflecting a wider range of activity values, hence resulting in more covariation between activity counts on both actigraphs. However, during the night there exists virtually no difference between dominant and nondominant wrist movement (for TST, $r = 0.99$, $p < 0.0001$). This study further corroborates earlier reports and suggests that the placement of the actigraph poses no risks with regards to the reliability of the actigraphic data (Chung et al. 1995; Webster et al. 1982).

The results of the fourth study indicate that there are no noticeable differences relative to device placement on the wrist versus the ankle (for TST, $r = 0.99$, $p < 0.0001$). These findings further support ankle placement in studies involving infants, since it has been found to be a convenient and effective way of monitoring sleep/wake activity in that population. The observation of no differences in the third and the fourth study clearly offers no basis for a preferential choice of dominant versus nondominant and wrist versus ankle actigraph placement. The data seem to indicate that actigraphic placement is irrelevant so long as it is placed on the wrist or on the ankle. But, where optimal precision is desired, wrist placement may be preferred since higher reliability coefficients were observed for some of the actigraphic variables between dominant and nondominant than wrist and ankle.

Discrepancies reported in earlier studies may be due to variability in device sensitivity and not necessarily to an actual difference in device placement. Since each activity monitor has its unique features and mode of operation, specific reliability tests may have to be conducted to ascertain possible sensitivity changes in the monitor one wishes to utilize. Future research studies should investigate possible differences between ankle and wrist placement of the actigraph in individuals with certain types of sleep disorders, particularly, those characterized by periodic limb movement and restless leg syndrome.

Though a different scoring method and younger volunteers in our assessment of night to night variability were used, these results are consistent with the findings of van Hilten et al. (1993). No first-night effect was observed for any of the actigraph-derived variables. The results of this study further suggest that an adaptation night is not required with the actigraph methodology. Moreover, the low variability noted in our fragmentation measure from night 1 to night 2 may be an indication of the stability of intravolunteer nocturnal activity.

These studies have addressed some of the methodological problems inherent in the use of the actigraph methodology. Based on our findings and earlier reports, it is clear that, overall, actigraphy is an excellent tool for unobtrusive documentation of sleep/wake activity in normal individuals. Clearly, the results of these studies have elucidated some of the potential methodological artifacts in actigraphy and have offered a novel approach to systematically address them. Rigorous testing procedures with the virtue of ascertaining potential confounding artifacts in the development of scoring methods are recommended to ensure precise identification of sleep and wakefulness from actigraphic data.

Behavioral and physiological phenomena can be reliably assessed with the use of the actigraph methodology even in cases of severe sleep disturbances, provided that the proper model of sleep/wake identification is utilized. It is believed that the scoring software (i.e., ADAS) used in the analysis of our actigraphic data can be optimized to accurately identify sleep/wake patterns in different sleep disorders subpopulations by establishing the correct actigraphic sleep/wake criteria.

Appendix 3

Tables and Figures For Actigraphic Studies

Scoring Criteria: AST and WIPA

Correspondence Between Actigraphy and Polysomnography in Normals

Calibration Sample,(n=6)

Methodology	Mean	SD
PSG	380 mn	32 mn
ACT	370 mn	27 mn

Mean Discrepancy = 10 minutes

$r = 0.93$ $p < 0.008$

Table 3-F-1: Comparison between actigraphic Total Sleep Time (TST) and polysomnographic TST as reflected by mean, standard deviation (SD), Pearson r and corresponding significance level, and discrepancy value; using the optimal method of Sleep/Wake determination on the calibration sample. (AST = Actigraphic Sleep Threshold, WIPA = Wake Interval Post Arousal).

Scoring Criteria: AST and WIPA

Correspondence Between Actigraphy and Polysomnography in Normals

Validation Sample,(n=14)

Methodology	Mean	SD
PSG	391 mn	57 mn
ACT	403 mn	60 mn

Mean Discrepancy = 12 minutes

$r = 0.97$ $p < 0.0001$

Table 3-F-2: Comparison between actigraphic TST and polysomnographic TST as reflected by mean, SD, Pearson r and corresponding significance level, and discrepancy value; using the optimal method of Sleep/Wake determination on the validation sample.

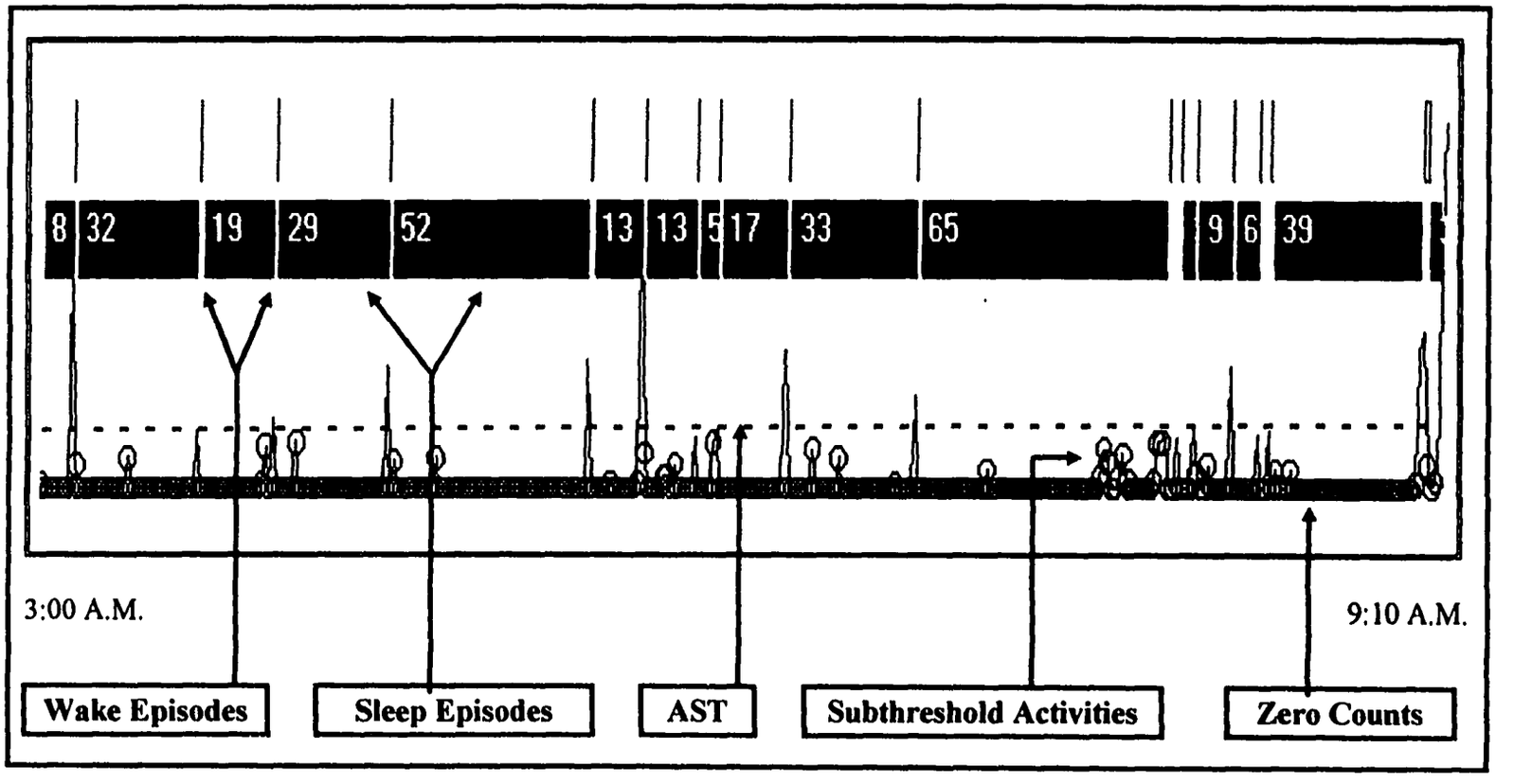


Figure 4-F-1: Illustration of nocturnal sleep/wake activity of a young normal individual as determined by the application of the final protocol of ADAS to his actigraphic data (i.e., with an Actigraphic Sleep Threshold (AST) of 10 activity counts and a Wake Interval Post Arousal (WIPA) of 3 minutes as criteria for sleep). Intersperced white lines represent periods of wakefulness. Shaded rectangles represent periods of sleep with total number of minutes indicated. Circles indicate subthreshold activities. The base of the graph shows zero counts with overlapping circles. The horizontal dotted line corresponds to the actigraphic sleep threshold.

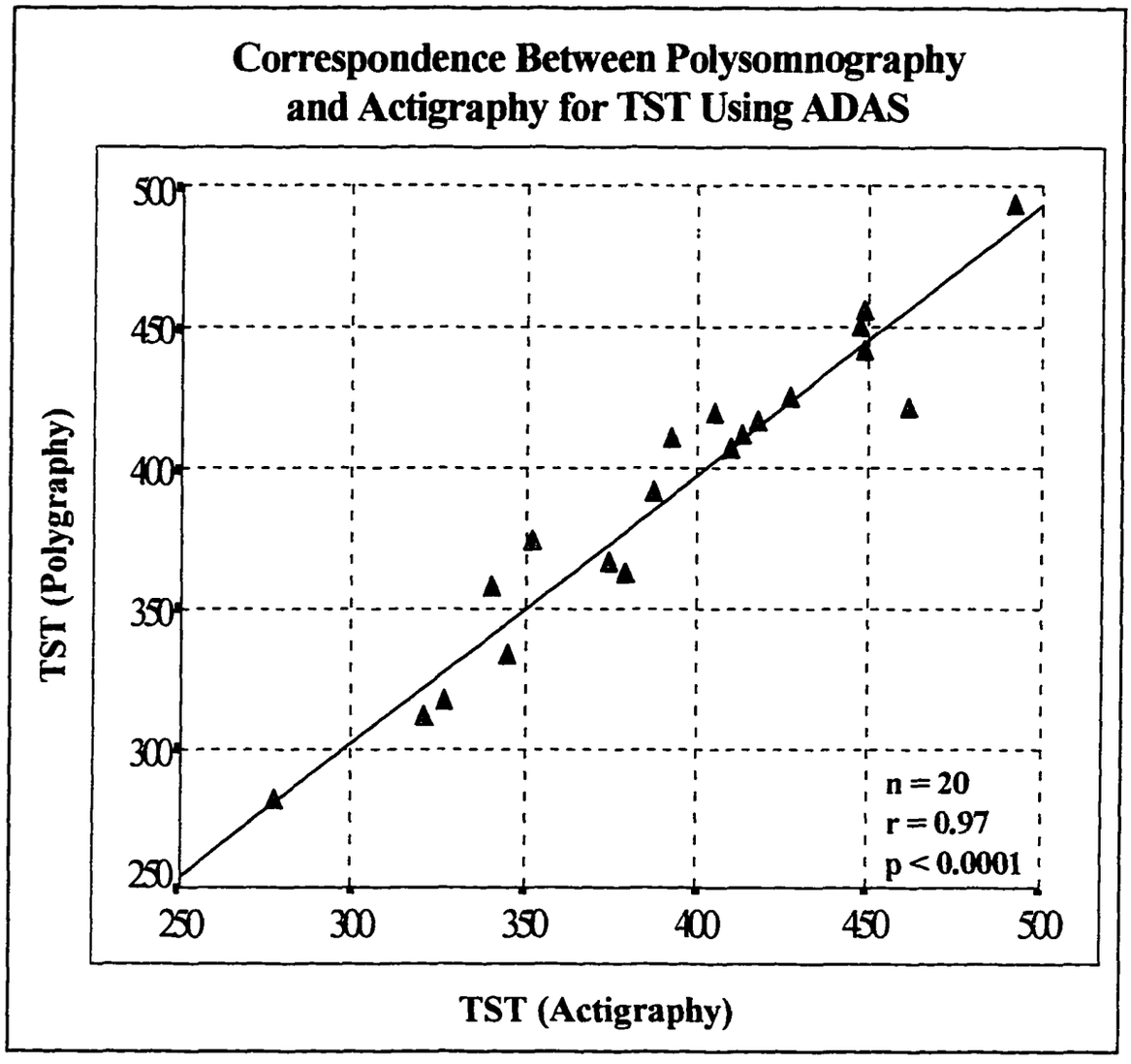


Figure 3-F-2: Correspondence between polysomnography and actigraphy for one night using TST as an index of comparison. P and r values were obtained from a bivariate correlation with 20 volunteers; the calibration and validation samples were pooled.

Correspondence Between Actigraphy and Polysomnography in Insomnia

Actigraphy	Mean	SD	Polygraphy	Mean	SD
TST	325 mn	77 mn	TST	332 mn	61 mn
SEI	.77 %	.14 %	SEI	.80 %	.12 %
SOL	37 mn	39 mn	SOL	27 mn	20 mn

Mean Discrepancy for TST = 7 minutes	r = 0.86	p < 0.0001
Mean Discrepancy for SEI = .03 %	r = 0.74	p < 0.001
Mean Discrepancy for SOL = 10 minutes	r = 0.56	p < 0.007

TST = total sleep time
SEI = sleep efficiency index
SOL = sleep onset latency

Table 3-G-1: Comparison between actigraphic TST, SEI, and SOL and polysomnographic TST, SEI, and SOL using ADAS.

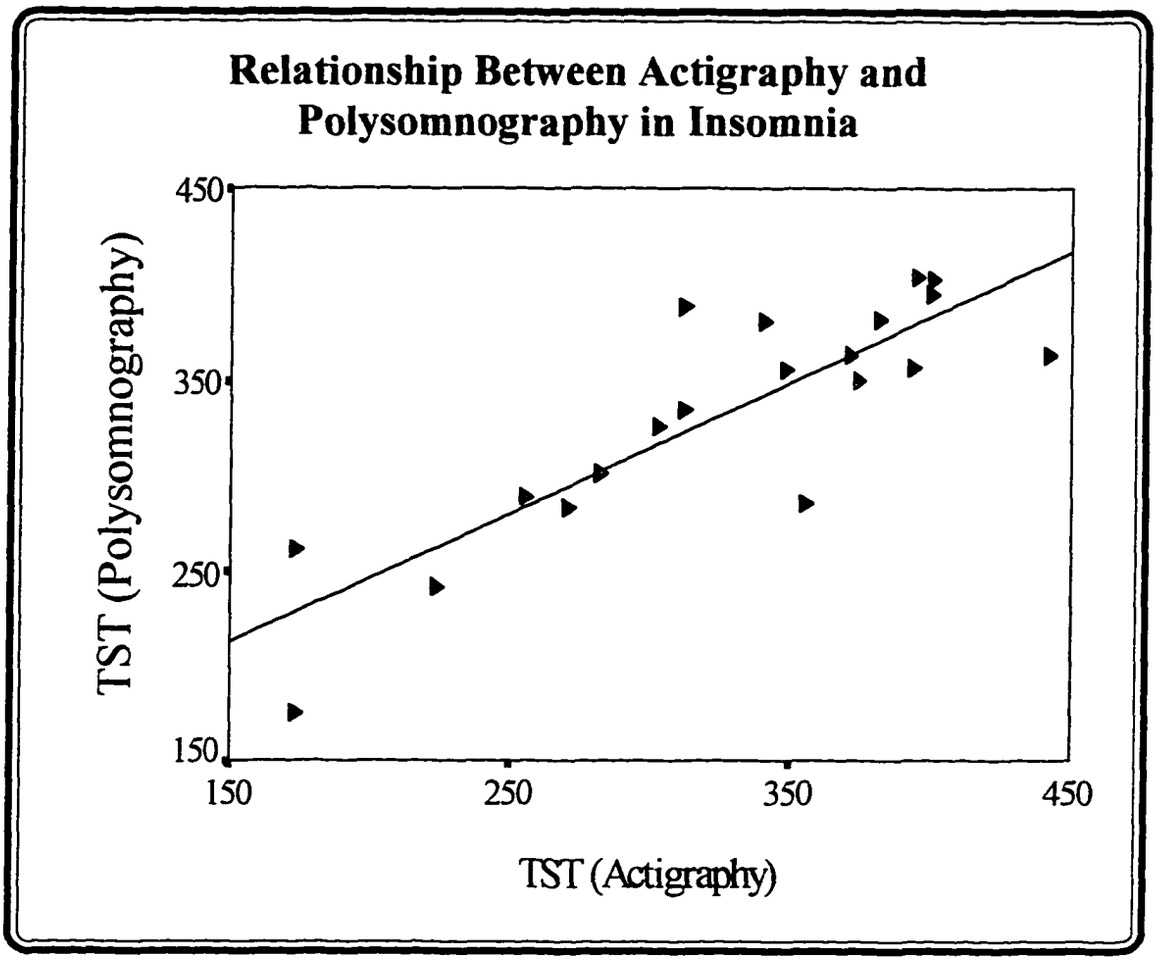


Figure 3-G-1: Diagramatic illustration of the relationship between actigraphy and polysomnography with respect to total sleep time expressed in minutes. Pearson r and p values were obtained from a bivariate correlation analysis.

Correspondence Between Actigraphy and Polysomnography Using AST and AST Combined With WIPA

Criterion	Factor	r	p	Average Discrepancy
AST	TST	.78	.0001	24.07 mn
AST	SEI	.59	.007	.05 %
AST + WIPA	TST	.85	.0001	7.18 mn
AST + WIPA	SEI	.74	.0001	.03 %

Table 3-G-2: Relationship between actigraphy and polysomnography as determined by the application of the Actigraphic Sleep Threshold (AST) alone and the combination of AST and Wake Interval Post Arousal (WIPA).

Identification of Sleep and Wakefulness: Difference Between AST and AST Combined With WIPA					
AST			**AST and WIPA**		
Factor	**Mean**	**SD**	**Factor**	**Mean**	**SD**
TST	308 mn	85 mn	TST	342 mn	72 mn
SEI	.73 %	.17 %	SEI	.80 %	.14 %
TST: $t(23) = 6.69$, $p < 0.0001$			SEI: $t(23) = 6.55$, $p < 0.0001$		

Table3-G-3: Difference between actigraphic TST and SEI obtained by the application of the Actigraphic Sleep Threshold (AST) separately and the combination of AST and Wake Interval Post Arousal (WIPA).

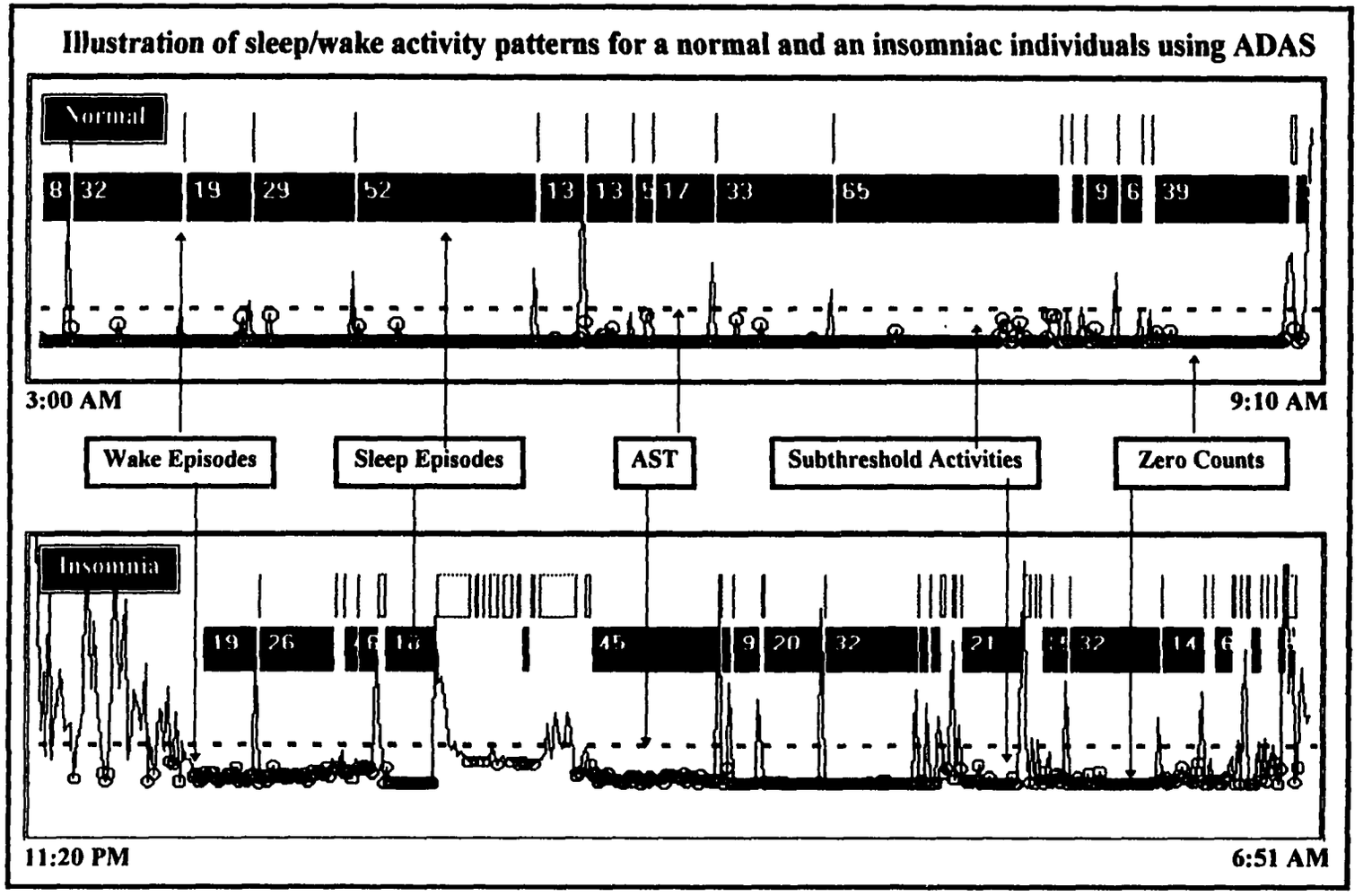


Figure 3-G-2: Comparison of sleep/wake activity patterns between a normal and an insomniac individuals. Data was processed based on actual bedtime using an AST of 12 counts, a WIPA of 3 minutes and a sleep latency criterion of 3 consecutive minutes.

Interdevice Reliability Analysis

Interdevice Sensitivity (1a)

Variables	r	p	t	p
1. Activity	.70	.001	-.97	NS
2. Arousal	.89	.0001	1.17	NS
3. Fragmentation	.78	.001	.29	NS
4. TST	.99	.0001	-.77	NS
5. SEI	.92	.0001	-.88	NS
6. SOL	.94	.0001	-.36	NS
7. WASO	.91	.0001	-.88	NS
8. Transition	.92	.0001	-.53	NS

Interdevice Sensitivity (1b)

Variables	r	p	t	p
1. Activity	.83	.006	-1.29	NS
2. Arousal	.92	.0001	-1.94	NS
3. Fragmentation	.88	.002	-1.07	NS
4. TST	.99	.0001	1.92	NS
5. SEI	.85	.003	2.01	NS
6. SOL	.73	.03	-1.48	NS
7. WASO	.88	.002	-.37	NS
8. Transition	.85	.003	-1.79	NS

Actigraph Variable Definition

Activity = sum of 1-mn epochs with non-zerocounts
Arousal = activity count above threshold for sleep (i. e., count > 10)
Fragmentation= number of arousal periods > 3 min
TST = TIB - wake (i.e., total number of minutes in each fragmentation period + minutes of transition)
SEI = sleep efficiency index
SOL = sleep onset latency
WASO = wake after sleep onset
SLPA = sleep latency post awakening
Transition = transition time between sleep and wakefulness

Table 3- H-1: Actigraph nocturnal sleep/wake variables for interdevice variability, describing the relationship of pairs of actigraphs placed on the dominant wrist for one night. In interdevice sensitivity I, pairs of contemporaneous actigraphs were used (1.a). In interdevice sensitivity II, actigraphs that have been in use for over a year were compared to newly acquired actigraphs of the same model (1.b).

Actigraphic Placement			
Dominant Vs. Nondominant (2a)	**Variables**	**r**	**p**
	1. SOL	.812	.002
	2. Activity	.903	.0001
	3. Arousal	.919	.0001
	4. Fragmentation	.860	.001
	5. TST	.997	.0001
	6. SEI	.919	.0001
	7. SLPA	.908	.0001
	8. WASO	.920	.0001
	9. Transition	.922	.0001
Wrist Vs Ankle (2b)	**Variables**	**r**	**p**
	1. SOL	.859	0001
	2. Activity	.951	.0001
	3. Arousal	.891	.0001
	4. Fragmentation	.734	.007
	5. TST	.998	.0001
	6. SEI	.894	.0001
	7. SLPA	.782	.003
	8. WASO	.792	.002
	9. Transition	.936	.0001

Table 3-H-2: Investigation of possible differences relative to actigraphic placement. Reliability coefficients and corresponding p values are provided for actigraphs placed on the dominant versus the nondominant wrist (2.a), and on the wrist versus the ankle (2.b). P and r values were obtained from a bivariate correlation.

Internight Variability				
	Night 1	Night 2		
Variables	Mean ± SD	Mean ± SD	t	p
1. Activity	1092.75 ± 742.79	1025.04 ± 615.40	1.23	NS
2. Arousal	30.88 ± 19.47	29.86 ± 17.66	-.35	NS
3. Fragmentation	14.67 ± 8.2	15.38 ± 7.38	-.53	NS
4. TST	416.21 ± 77.20	428.08 ± 89.97	-.62	NS
5. SEI	.92 ± .04	.93 ± .04	-.81	NS
6. SOL	5.17 ± 8.38	4.25 ± 5.67	.61	NS
7. WASO	31.83 ± 22.61	30.67 ± 19.46	.42	NS
8. SLPA	2.05 ± .69	1.96 ±.70	.54	NS
9. Transition	11.71 ± 10.56	9.42 ± 7.42	1.23	NS

Table 3-H-3: Difference between the first night and the second night as assessed by actigraphy. Numbers represent mean values, standard deviation (SD), and matched t-tests and p values for ten actigraph-derived measures.

Appendix 4

Tables and Figures For The Melatonin Study

Baseline Group Characteristics

	Factor	Mean (SD)	Min	Max	N
Gp 1	AGE	22.75 (5.05)	18	35	12
	MMS	28.00 (2.98)	20	30	12
	ADAS*	4.44 (2.99)	1.0	12.3	12
Gp 2	AGE	45.55 (8.58)	36	57	11
	MMS	29.00 (1.41)	27	30	4
	ADAS*	5.83 (1.93)	3.3	8	4
Gp 3	AGE	69.56 (5.29)	59	76	10
	MMS	25.80 (1.64)	23	27	5
	ADAS*	8.44 (2.8)	4.7	11.9	5
Gp 4	AGE	73.50 (4.77)	65	79	10
	MMS	26.70 (4.85)	15	30	10
	ADAS*	22.53 (23.41)	5.7	68	10

Table 4-A-1: Group description reflecting age, mini mental state (MMS) score, and Alzheimer's Disease Assessment Scale (ADAS*) score for Gp 1 = Young normal, Gp 2= Adult normal, Gp 3 = Elderly normal, and Gp 4 = Cognitively impaired elderly. Participants in group 3 and 4 were comparable cognitively regarding their MMS score. However, group 4 was more impaired than group 3 based on ADAS*. According to this scale, the higher the rating, the more impairment is observed. The variability noted in ADAS* scores for group 4 may reflect the heterogeneity of the sample relative to their GDS rating (see table 4-A-2).

Baseline Patient Characteristics

Patient	Age	GDS	ADAS	MMS	Sex	SEI
1.	73	4	68.00	21	0	.91
2.	75	4	58.96	15	0	.88
3.	65	-	7.30	29	1	.89
4.	79	3	10.67	30	0	.94
5.	79	3	8.99	28	1	.92
6.	76	3	12.33	28	0	.92
7.	68	2	5.66	28	1	.90
8.	69	2	6.67	30	0	.89
9.	74	3	9.00	29	1	.85
10.	77	3	12.99	29	0	.91

Table 4-A-2: Characteristics of the cognitively impaired elderly group as reflected by age, global deterioration scale (GDS), Alzheimer's Disease Assessment Scale (ADAS*), mini mental state (MMS), sex, and actigraphic sleep efficiency index (SEI).

Omnibus Repeated-Measures F-Test for Actigraphic Factors

Test	Value	F	p
Hotelling	2.003	4.674	.043

Univariate F-Test for Actigraphic Data

Factor	Melatonin [$\bar{X}$(SD)]	Placebo [$\bar{X}$(SD)]	F	p
Amplitude(%)	.54(.21)	.41(.24)	5.16	.045
SOL(mn)	14.70(7.21)	26.08(10.97)	8.20	.018
Transition(mn)	17.75(7.79)	31.20(11.37)	10.08	.011

Table 4-A-3: MANOVA procedure demonstrating differences between the two experimental conditions. Among the variables entered rest-activity amplitude was significanrly higher whereas, sleep onset latency and transition between sleep and wakefulness were significantly lower under melatonin administration.

Omnibus Repeated-Measures F-Test For Neuropsychological Factors

Test	Value	F	p
Hotelling	15.946	11.960	.035

Univariate F-Test For Neuropsychological Data

Factors	Melatonin[$\bar{X}$(SD)]	Placebo[$\bar{X}$(SD)]	F	p
Delayed Recall	5.14 (2.73)	3.10 (2.47)	9.75	.021
Depression	.60 (.70)	1.20 (.92)	7.36	.024

Table 4-A-4: MANOVA procedure illustrating differences between placebo and melatonin. Among the variables entered delayed recall and depressive states showed a significant effect of melatonin. Patients expressed less depressed moods and more items were recalled under the melatonin condition. Scores for delayed recall ranged from 0 to 10, with a score of 0 indicating a poor ability to remember. Depression was rated on a scale from 0 to 5, with a value of 0 representing the absence of depressed moods.

Independent t-Test				
Factor	**Group A[$\bar{X}$(SD)]**	**Group B [$\bar{X}$(SD)]**	**t**	**p**
Depression	1.80 (.84)	.60 (.55)	-2.08	.028
Nap	.65 (2.27)	.17 (.18)	-3.28	.011
Fatigue	4.39 (1.10)	2.36 (.93)	-3.15	.014

Table 4-A-5: Independent t-tests for group A Vs. group B showing differences in depressed moods rated on a sale from 0 to 5, average daily nap, and fatigue level ranging from 0 to 10; a score of 0 indicated no fatigue. Group A included patients who used sleep medications and group B did not use any.

Overall MANOVA (group)

Test	Value	F	p
Hotelling	.98467	92.00	.007

Univariate F-Test By Group (1, 2, 3, 4)

Factor	F	p
Day Mean Activity	4.47741	.009
Amplitude	4.18071	.012
WASO	2.64746	.054

Table 4-A-6: MANOVA procedure showing overall group differences as determined by Hotelling. Univariate F test for amplitude of rest-activity rhythm, daytime mean activity level, and wake after sleep onet (WASO) were significantly different.

Post Hoc Independent t Test for Group (1,2,3,4)				
Daytime Mean Activity Level				
	Group1	Group 2	Group 3	Group 4
Group 1		t=-2.14*		
Group 2				t=3.76**
Group 3				t=2.75**
Rest-Activity Amplitude				
	Group1	Group 2	Group 3	Group 4
Group 1		t=-2.33*	t=-3.80**	
Group 2				t=1.79~
Group 3				t=2.68*
Wake After Sleep Onset				
	Group1	Group 2	Group 3	Group 4
Group 1			t=-2.46*	t=-2.24*
Group 2				
Group 3				
* => p < .05; **=> p <.01; ~ =>marginally significant				

Table 4-A-7: Differences in sleep/wake parameters and circadian profile across age group using the actigraph methodology. Results were based on average data obtained over a period of five days of activity monitoring.

ANOVA for Independent Groups				
Factor	**Group 3 [$\bar{X}$(SD)]**	**Group 4 [$\bar{X}$(SD)]**	**F**	**p**
Sleepy	1.57 (.55)	2.83 (.84)	9.09	.010
Depression	.0 (0)	1.09 (.94)	6.43	.024
Well Being	7.85 (.74)	4.90 (1.28)	22.21	.0004
Happy	6.22 (1.81)	4.13 (1.33)	9.44	.009
Weary	1.04 (.34)	3.46 (3.46)	6.54	.024

Table 4-A-8: ANOVA procedure showing group differences as determined by Hotelling. Univariate F test for subjective report of sleepiness, feeling of well being, happiness, weary, and observed depressed moods were significantly different. These factors are part of the VAS and were rated on a ten-point scale.

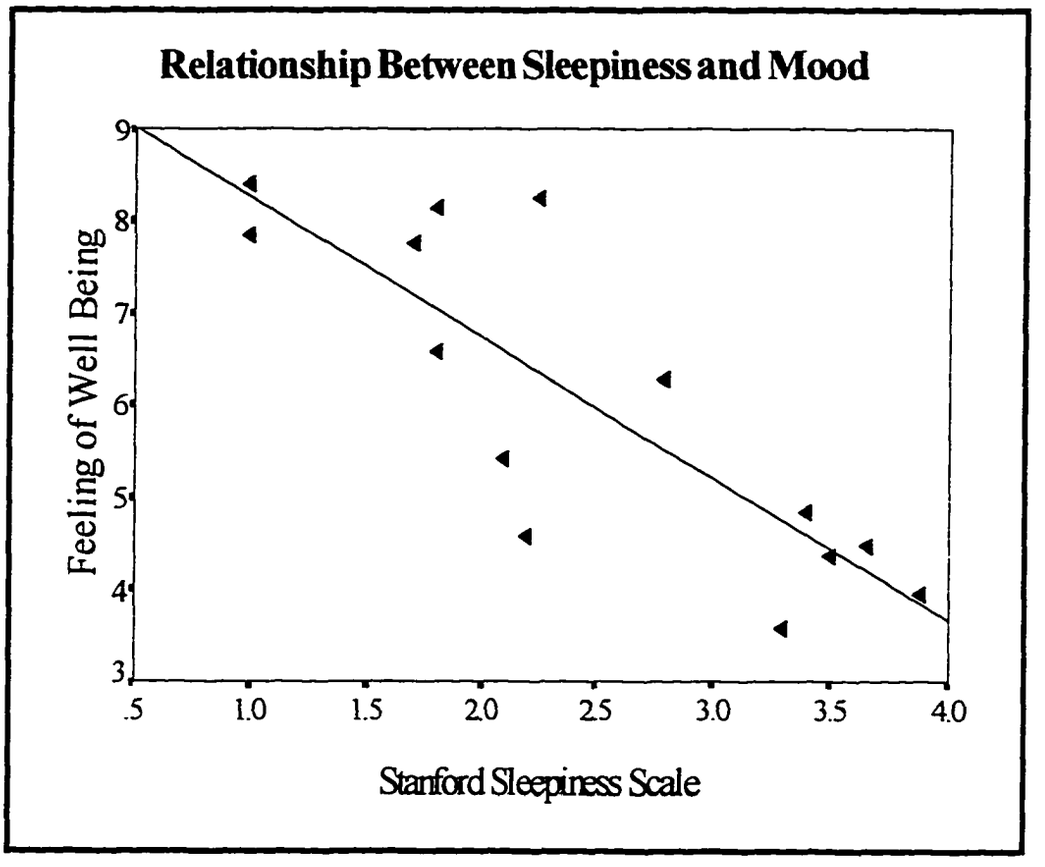


Figure 4-A-1: Illustration of the relationship between Stanford Sleepiness Scale and Feeling of Well Being in the elderly.

Actigraphic Rest-Activity Data For An Alzheimer's Disease Patient (Placebo)

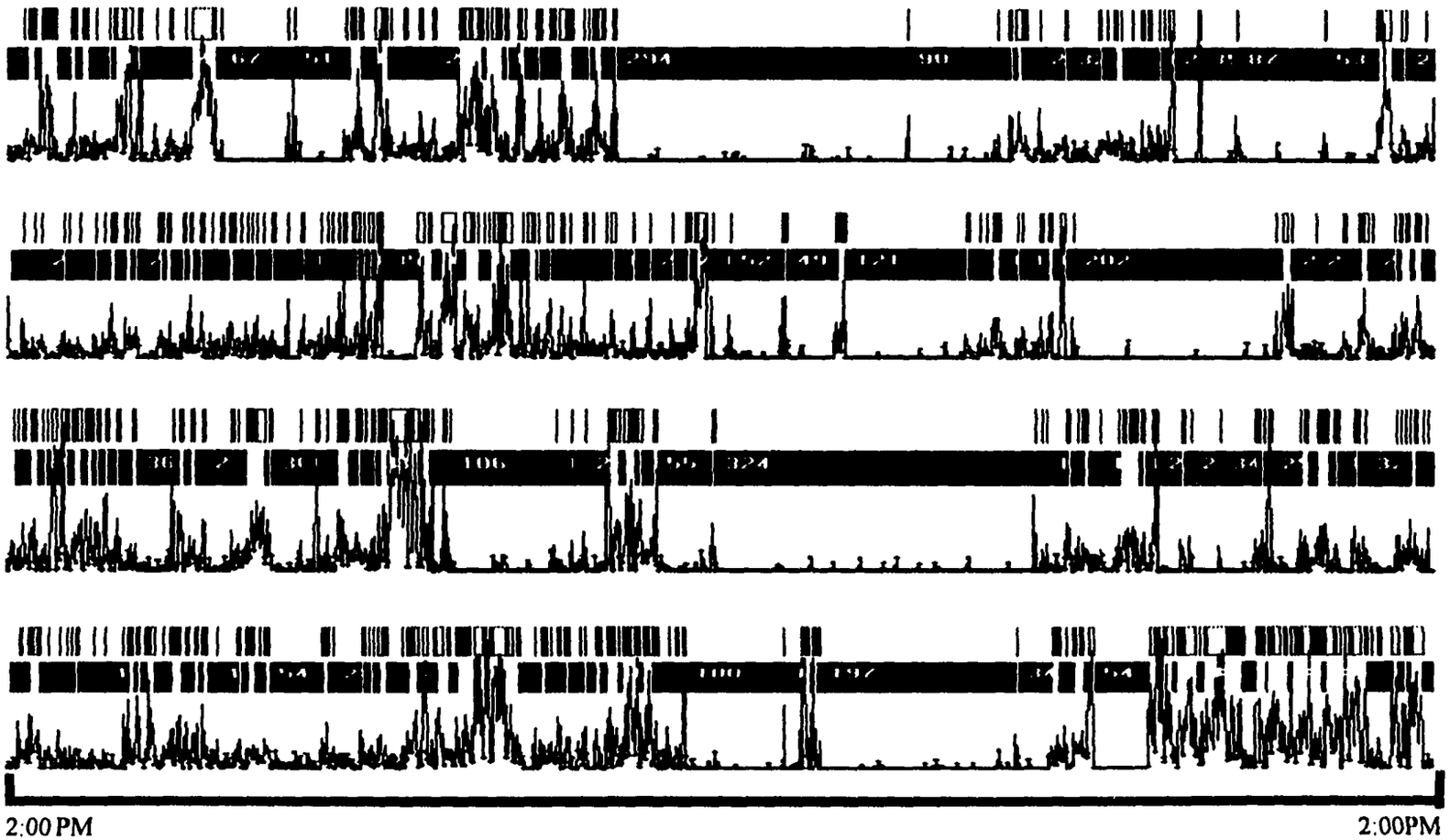


Figure 3-A-2: Illustration of sleep/wake activity patterns derived from actigraphic data obtained from an AD individual. Data was processed for a period of 24 hours over four days using ADAS. Each plot illustrates activity level from 2:00PM to 2:00PM. Interspersed white lines or spaces in the shaded bar represent periods of high activity level whereas the shaded areas represent periods of inactivity.

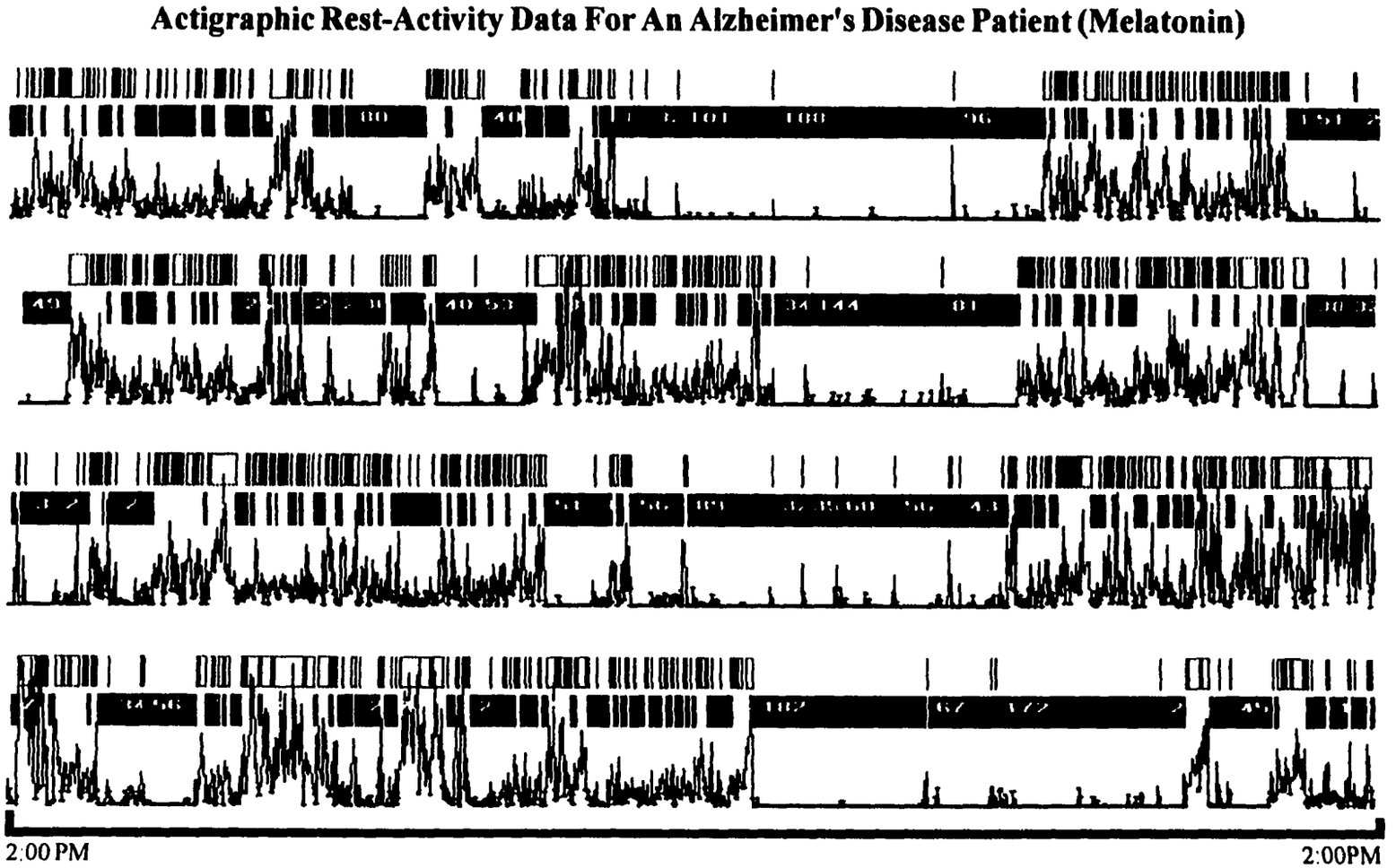


Figure 3-A-3: Illustration of sleep/wake activity patterns derived from actigraphic data obtained from an AD individual. Data was processed for a period of 24 hours over four days using ADAS. Each plot illustrates activity level from 2:00PM to 2:00PM. Interspersed white lines or spaces in the shaded bar represent periods of high activity level whereas the shaded areas represent periods of inactivity.

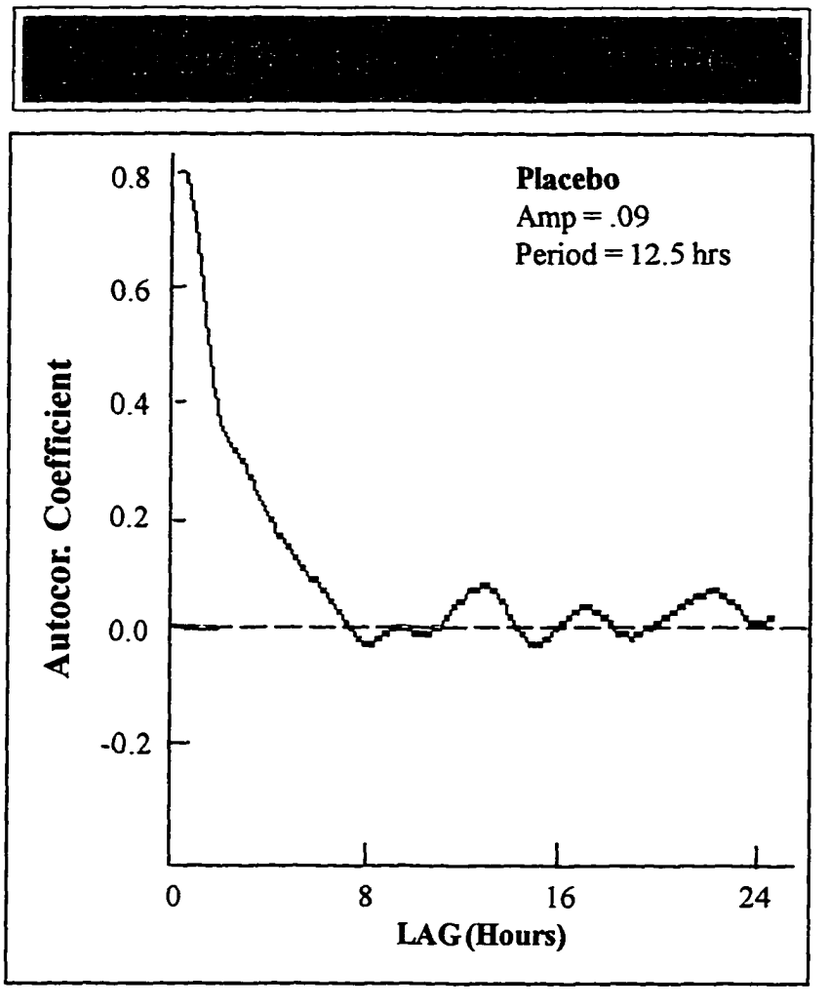


Figure 4-A-4: Illustration of a blunted rest-activity rhythm in an Alzheimer's patient (B). Autocorrelation of the activity data was processed at a lag of 26 hours using ADAS.

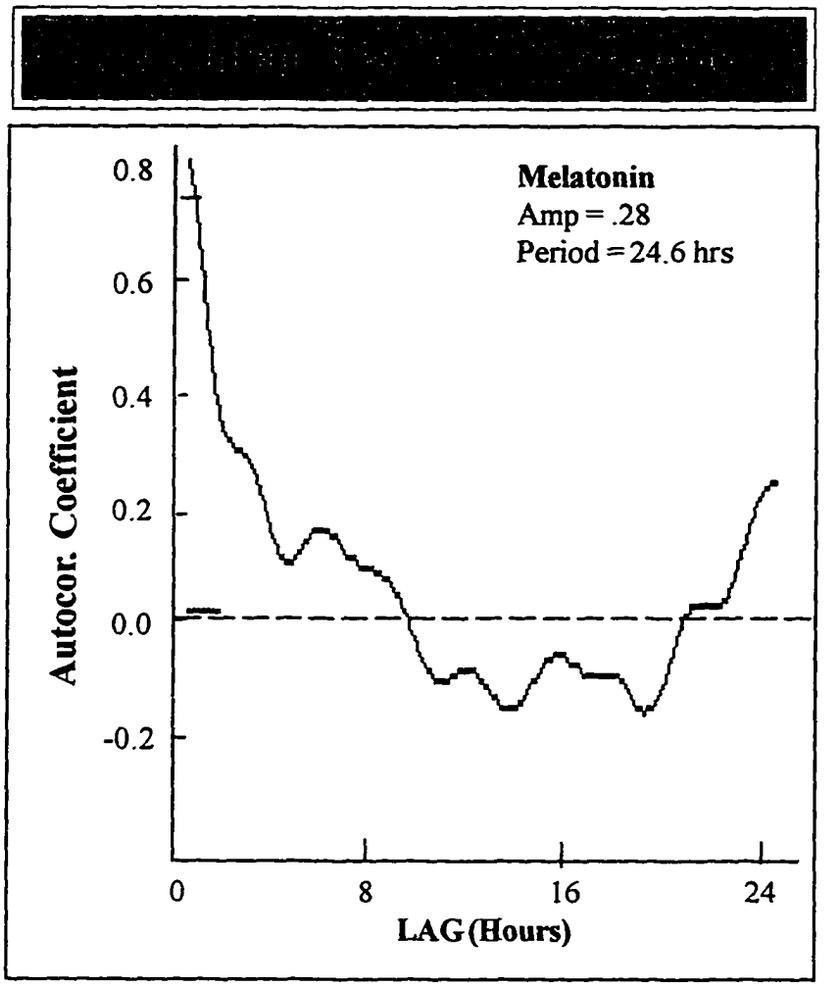


Figure 4-A-5: Illustration of the resynchronized rest-activity rhythm in the same Alzheimer's patient (B) under melatonin. Autocorrelation of the activity data was processed at a lag of 26 hours using ADAS.

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