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Effects of Late Partial Sleep Deprivation on Major Depression in Women

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Geoffry William McEnany

DISSERTATION

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Dedication

This work is dedicated to Robert J. Thyken, Jr., who offered unconditional support and patience with my academic preoccupations over the last four years. His belief in both me and the importance of this work for nursing science offered a steady and sustaining influence that was and will continue to be greatly appreciated and remembered. It is with great warmth and appreciation that I express my immeasurable gratitude for the number of sacrifices made.

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And finally, I want to thank the women who participated in this research. Their willingness to engage in a rigorous protocol for the sake of learning more about nonpharmacologic strategies in depression was impressive. These women demonstrated a passion for learning about their illnesses and new means of coping with the concurrent challenges of living with a serious mood disorder. In doing so, they made a valuable contribution to women's health research.

Geoffry McEnany

10 June 1994

Effects of Late Partial Sleep Deprivation on Major Depression in Women
Geoffry W. McEnany

The purpose of this study was to examine the effect of late partial sleep deprivation in women diagnosed with major depressive disorder (non-seasonal, non-bipolar). Women were randomized to begin the study with either a placebo intervention or late partial sleep deprivation. Late partial sleep deprivation consisted of two consecutive nights of sleeping from 10PM to 2AM, and remaining awake until the following night at 10PM. The placebo intervention involved wearing a special pair of glasses (circadian adaptation glasses) designed to filter out daylight. These glasses were worn between 7PM and bedtime, and on any occasion when the women arose during the night or until 6AM.

This study utilized a quasi-experimental cross over design with two six-day periods of data collection for each subject to obtain data on mood, sleep patterns and circadian temperature rhythm before and after nonpharmacologic treatment. The subjects were 18 unmedicated women between the ages of 21 and 50 years. All data were collected during the follicular phase of the menstrual cycle.

Data collection was accomplished by home monitoring of sleep electroencephalography with the Medilog 9000-II system using standardized techniques. All sleep tapes were scored by a registered sleep technologist who was blind to the study protocol. Continuous core body temperature monitoring was accomplished with the use of the CorTemp telemetry system, using precalibrated ingestible sensors. Depression was measured with the Beck Depression Inventory and the Symptom Checklist 90-R. Diagnosis was confirmed by the use of the *Structured Clinical Interview for the DSM-IIIR (SCID)*. Prior to intervention, subject's urine was screened for substances that could potentially alter mood, sleep and rhythm patterns (e.g., drugs of abuse). During both six day periods of data collection, the participants maintained structured diaries which examined patterns of daily activity and self reports of sleep. Prior to each intervention, women participated in two consecutive nights of EEG with forty eight hours of concurrent temperature monitoring, and during this period completed morning and evening measures of mood. Days three and four were for intervention. Post intervention evaluation using the same measures as pre-intervention assessment occurred on days five and six.

Analysis of the data reveals that the placebo yielded no significant differences in depression ($t=0.32$, $p<.74$) or fatigue ($t=0.46$, $p<.64$). No significant differences were noted between pre & post active intervention. However, 67% of the sample reported a 25-75% improvement in depression at some point in the two post-active intervention days. When the data from responders were compared to those who did not respond, three significant differences emerged: 1) There was a significant difference in REM latency pre-LPSD, but this was not evident post-LPSD; 2) There was a significant increase in SOL to SW in responders; and 3) There was a significant phase delay in core body temperature among responders post-LPSD, that was not evident in non-responders.

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Abstract: Effects of Late Partial Sleep Deprivation on Major Depression in Women

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CHAPTER 1

INTRODUCTION TO THE PROBLEM

Depression comprises a constellation of mood disturbances whose conceptual and psychobiological dimensions have been greatly illuminated and defined over the last twenty years (Kandel, Schwartz & Jessell, 1991). What has fueled the evolution of new knowledge of various dimensions of mood is an ongoing revolution in science, particularly in psychiatry and the neurosciences. Such a revolution continues to challenge the traditionally held theories, perspectives and beliefs about human behavior, and is evident in new directions in research, clinical practice and teaching.

Historically, disciplines involved in the care and treatment of the mentally ill have endeavored to use a holistic lens on clinical practice, appreciating multifaceted exchanges between a person and the environment. New knowledge generated from the biological revolution in psychiatry and the neurosciences has forced a reconsideration of holistic principles across all disciplines, and nursing is no exception. For example, in the past some may have viewed *psychological* experience as a phenomenon more clearly of the *mind*, but not necessarily of the *brain*. Many of the strategies used to deal with problems of the mind were often psychological in nature, and implemented as if psychological tactics were divorced from biological processes. What such a dichotomy has highlighted is the dualistic mind/brain split. Such fragmentation is plausibly a reflection of clinical training and unquestionably an indication of Western culture's conceptualization and thought.

Commonly, perspectives from science reduce an individual to parts for the purpose of learning. Once the parts are understood however, traditionally there has been a failure to conceptually reintegrate the components to facilitate an understanding of the whole. This is particularly true in the study of, and clinical approaches to, what have been traditionally referred to as the *mental* illnesses. Goodman (1991) points out that a significant contributing factor to this fragmentation is language. Concepts and words to clearly describe the interconnectedness of the mind and body are rare, if at all existent in Western ways of thinking. This inadequacy of language and shortcoming in clinical pedagogy sometimes leaves clinicians in an unresolved quandary as to how to reduce dualistic trends in clinical practice.

In this day of neuroscience revolution, clinical perspectives that ignore psychobiologic dimensions of human experience are likely to do several things. First, such viewpoints are liable to perpetuate a dualistic standpoint on "mental" illness, acknowledging that the problem exists in the mind while ignoring the body. Secondly, ignoring the psychobiological aspects of an illness may perpetuate stigmatization. From a perspective that acknowledges the interplay between stressors and individual vulnerabilities, many mental illnesses are no different than other types of illness.

A model originally used to explain the interface between stressors and the emergence of symptoms in persons diagnosed with schizophrenia was called the *stress diathesis model* (Kaplan & Saddock, 1991). It proposes that an individual has a given vulnerability or diathesis, and in the presence of a sufficiently large stressor will develop symptoms. Generally speaking, the stressor can be biological, environmental or both. Similarly, the biology of the diathesis may also be shaped by other influences

such as drugs, alcohol, trauma or additional stressors. Presumably, this model can be applied to many illnesses, whether the pathology occurs in some dimension of the central nervous system or in another physiological system. What determines the difference between types of diseases whose symptoms surface in relation to a given stressor may be the individual's locus of vulnerability. Recognizing such vulnerability as a universal facet of all illnesses facilitates an appreciation of "mental" illness as being no different than other types of illness. However, the bias of new psychobiological knowledge requires that clinical phenomena be examined in a new light, and one that includes an understanding of both the biological dimensions of the phenomena that are concurrent with the lived experience, as well as the interface between the environment and the person. This trend is a compelling reason for clinicians and researchers to retool their perspectives on mental illnesses, and continue efforts at integrating the more established *psychological* knowledge with newer *psychobiological* perspectives. Such efforts may result in clinical practice that more closely approximates a multidimensional view of the person in a given environment.

Statement of the Problem

The treatment of depression has evidenced incredible advances over the last two decades, both in the areas of pharmacologic and nonpharmacologic interventions, based on an understanding of the psychobiologic dimensions of the illness. As a consequence of these developments, new nonpharmacologic interventions such as the sleep deprivation therapies have been generated. While testing of the sleep

deprivation strategies continues, there are several methodologic issues in the existing studies which hamper the interpretation of the findings. Issues such as diagnostic heterogeneity of samples, as well as the concurrent use of psychotropic medications clouds the perspective on *who responds* to the various forms of the sleep deprivation interventions.

The issue of diagnostic heterogeneity is a complex one which is likely to unfold in the future. What is apt to emerge is a useful template for understanding conceptually distinct subcategorizations of depressive illness not fully recognized today. This trend toward a more refined lens on the illness of depression is evolving, but is as of yet incomplete. This is evident, for example in the addition of new and valid course specifiers in depression-related diagnoses (APA, 1994). However, in the present this uncategorized divergence can act as a confounding influence in understanding the conceptual dimensions of an illness like depression. The disparate responses of similarly diagnosed persons to a given treatment may point to psychobiologically distinct subtypes of depression that are not discernable from a purely behavioral point of view. Such an argument supports an appreciation for the gaps in understanding depression itself, despite recent knowledge gains. This is not to minimize the prevailing advances made in understanding depression. Rather, it is intended to highlight the need for examining treatment effects in groups of persons diagnosed with analogous disorders in an effort to detect differences that would be lost in a diagnostically heterogeneous sample of individuals. Hopefully, what will emerge are data to support the conceptual separateness of depressive subtypes, and eventually a model of predicting treatment response based on these data.

This study offers data to the existing body of literature focused on nonpharmacologic intervention strategies in depression. While psychopharmacologic advances in the area of drug treatment of depression have recently advanced significantly, there are subsets of persons for whom these advances are inconsequential: those not wanting medications as a treatment alternative and those for whom medication has proven either to be intolerable due to side effects, or has yielded unsatisfactory results in terms of effective symptom management.

The issue of *who responds* to an intervention such as late partial sleep deprivation remains unclear. The disclarity stems from issues related to insufficient physiological data to support discussion of the biological differences between responders and nonresponders. While this study is unlikely to offer definitive predictors of response, it certainly allows for distinction between responders and nonresponders from a variety of physiologic and self report indices.

Germane to understanding treatment efficacy, which has not been adequately addressed in the current literature, is the issue of gender. Many intervention studies examining the effectiveness of a given treatment make no accommodation for the differences in response between men and women (Nadelson, 1993). Sleep and mood are directly correlated, as are sleep and temperature (Bonegio et al, 1988). In women who ovulate, the variables of temperature and sleep are directly affected by the different phases of the menstrual cycle. Lee (1988) points out that the average temperature acrophase may occur approximately two hours earlier and REM latency is earlier when temperature is higher in females after ovulation. These findings carry significant implications for the interpretation of results of existing research. For

example, if the variables under study include temperature or sleep, as is often the case in sleep deprivation research, and women are included as participants in the given research protocol, controls for menstrual phase are critical to the effects of the intervention.

How circadian rhythms shift in women with a homogeneous disorder such as major (non-seasonal, non-bipolar) depression, and the effect of treatment on these shifts has yet to be fully identified. There is a strong need for research that explores outcomes of interventions, controlling for those confounding variables such as fluctuating hormone secretion during the menstrual cycle, which potentially impact intervention effects.

A clinical trial of one form of sleep deprivation in a group of persons with a homogeneous form of major depressive disorder is needed to determine the extent to which it is effective. The investigator chose to study late partial sleep deprivation in this study for the reasons of previously reported effectiveness (Sack et al, 1988) and utility. These two factors play a critical role in the choice of a sleep deprivation strategy. If the type of sleep manipulation is overly fatiguing, or if its effects are marginalized by other factors, it is unlikely that they will be utilized by depressed persons. This is not to say that studying the other forms of sleep deprivation is not important, rather it was not feasible for the scope of this study.

Purpose of the Study

The primary purpose of this study was to contribute data to the body of knowledge on the use of sleep deprivation therapy in a homogeneous form of

depression, namely major depression. Because of methodologic difficulties in the existing literature, this study attempted to contribute clarity to the question of *who responds* to the nonpharmacologic intervention of late partial sleep deprivation. This was accomplished by building controls into the study's design which addressed some of the methodologic shortcomings of other studies. These controls included age, gender, concurrent use of mood and rhythm altering medications, menstrual phase and environment, as all participants were studied in their own homes.

Embedded in this main purpose, this study aimed to describe sleep patterns, body temperature rhythms, depression and fatigue variables in a group of young women diagnosed with major (non-seasonal, non-bipolar) depression before and after late partial sleep deprivation. Second, this study examined relationships between complaints of fatigue, depression and physiologic variables related to sleep and circadian rhythm. Third, this study tested the effect of late partial sleep deprivation on depression/fatigue states in women diagnosed with major (non-seasonal, non-bipolar) depression.

For the purpose of this study, depression was conceptualized as a human experience comprised of concomitant psychological phenomena and psychobiological events. These changes involved sleep patterns and other circadian rhythms such as temperature (Tsujimoto et al, 1990), various neurochemicals (Hasey & Hanin, 1991), and several hormones such as cortisol (Reus, 1985; Wolkowitz et al, 1993), thyroid stimulating hormone (Reus, 1989), and melatonin (Demitrack et al, 1990; Baumgartner et al, 1990), of which the first two from this list of possibilities were investigated as part of this study.

Hypotheses

The three main aims and related hypotheses of this study are:

Aim #1: to describe sleep, temperature, fatigue and mood patterns of young women diagnosed with a major (non-seasonal, non-bipolar) depressive episode.

Aim #2: to determine relationships between complaints of fatigue, depression and physiologic variables related to sleep and circadian rhythm. The specific aim was to test the following hypotheses:

2.1. There will be significant relationships between depression and fatigue scores, sleep, and circadian rhythm variables at baseline, prior to intervention.

2.2. There will be no significant relationships among depression scores, fatigue, sleep and circadian rhythm variables after the late partial sleep deprivation intervention.

Aim #3: to test the effect of late partial sleep deprivation (LPSD) and placebo on mood state in young women diagnosed with major (non-seasonal, non-bipolar) depression. The specific aim was to test the following hypotheses:

3.1. There will be a statistically significant difference between pre-intervention and post-intervention on four sleep variables (sleep onset latency, REM latency, percentage of sleep period time spent in sleep stages, and sleep efficiency index) for late partial sleep deprivation but no differences between baseline and post-intervention scores for placebo.

3.2. There will be a statistically significant difference between pre-intervention and post-intervention data on three circadian temperature rhythm variables (mesor, amplitude, acrophase) for late partial sleep deprivation but no

differences between baseline and post-intervention scores for placebo.

3.3. There will be a statistically significant difference between pre-intervention and post-intervention self rating scores of depression (Beck Depression Inventory) and fatigue severity (Visual Analogue Scale-Fatigue) for late partial sleep deprivation but no differences between baseline and post-intervention scores for placebo.

Significance of the Problem

According to recent statistics released by the Agency for Health Care Policy and Research (1993), one in eight individuals is likely to require some form of treatment for depression at some point during their lives. The point prevalence for major depressive disorder in the Western industrialized nations is 2.3% for men and 4.5 to 9.3% for women. The statistics describing the life time risk for a major depressive episode are even more alarming as the percentages increase upwards of 7 to 12% for men and 20 to 25% for women (AHCPR, 1993). It is clear from these estimates that women are at a greater risk for the development of a depressive episode than men. However, well-designed and controlled research on treatment specific outcomes with women diagnosed with major depression is sadly lacking.

The reasons cited for lack of studies focusing on the gender differences between women and men diagnosed with major depression are plentiful, but perhaps not fully defensible. Nadelson (1993) addresses the most commonly cited rationales for the exclusion or the underrepresentation of women in research protocols. Cost is a recurrent justification cited for *not* controlling for gender effects. The complexity of a

given research protocol is likely to be greater when variables such as menstrual phase and pregnancy need to be accounted for in both the study design and discussion of the results. Additionally, it seems both ethically sound and scientifically parsimonious to balance the research trends of the past with study efforts which specifically enhance the understanding of women and depression, as well as gender-bound responses to given treatments.

Across the spectrum of nursing practice, nurses continually deal with sleep related phenomena. Particularly germane to the practice of psychiatric nursing is the interface between the onset of sleep disturbance and the emergence of symptoms related to a variety of disorders, including depressive mood disorders. While it was recognized in early nursing research (Felton, 1975), it is only recently that concepts related to circadian rhythmicity and its concurrent psychobiology have begun to be more fully explored for their potential application to clinical nursing practice (Lee, 1988; Shaver et al, 1988), and in particular psychiatric nursing practice (Plumlee, 1986; Ryan, Montgomery & Meyers, 1987; McBride, 1990; McEnany, 1990; McEnany, 1991). However, to date, there have been no nursing studies that explore nonpharmacologic, yet psychobiologically based intervention strategies for depression.

This study will offer new data to nurses in practice, education and research. For those nurses in practice, the data from this study will help in the understanding of the sleep and rhythm disturbances of young women with depression. Additionally, it offers a new lens to examine behavioral phenomena such as depression and fatigue, from a biological rhythm perspective. Such information facilitates nurse's understanding of depression-related sleep disturbances and behavioral manifestations

of phase advance or delay. This information can be used as the basis for not only care planning, but for client teaching in an effort to demystify depression-related symptom patterns.

For nurses in education, this study offers data that may be used in reshaping pedagogical approaches to depression and its related symptoms. For example, while a phenomenologic perspective or a psychodynamic viewpoint are both important to the understanding of depression, they present an incomplete picture. Data from this study will help psychiatric nurse educators to reframe traditional perspectives, and to teach using a framework that accounts for both the lived experience and its concurrent biology.

Lastly, for nurse researchers, the data from this study underscore the importance of the use of appropriate methods and design to understand patterns of response among study participants. Biological rhythm data require rigor in their collection, as data of this type may be easily confounded by a variety of factors from both the internal and external environments.

CHAPTER TWO

CONCEPTUAL FRAMEWORK & REVIEW OF THE LITERATURE

Conceptual Framework

The conceptual face of depression is changing as a result of advances discussed here, and there are cogent examples of how these changes are reflected in diagnostic nomenclature, as well as in assessment and intervention strategies. For example, in the deliberations involved in the development of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (APA, 1994), several salient changes were made with regard to the assessment of depressive disorders. Specifically, among some of the more striking additions include greater attention to what are referred to as *course specifiers*. In DSM-IV, three subtypes related to the course of mood disorders are identified, and two of them are new (First et al, 1993). The specifier which is not new refers to seasonal pattern, but it has been made significantly more precise to facilitate its use in both research and clinical work. One of the new course specifiers refers to rapid cycling, and may point to treatment options as well as prognosis. The other new course specifier refers to postpartum depression, and as with the rapid cycling specifier, there are potential ramifications for both assessment and treatment. Given recent exponential advancements in the understanding of depression from a psychobiological perspective, it is likely that more precise descriptions of distinct subtypes of depressive illness will emerge. Concurrent with the confirmation of the existence of such subtypes will be more exacting and

reliable strategies for intervention.

Scientific advancements in the understanding of depression have been made in several areas: neurophysiology, particularly in the domain of neuroregulators and receptor mechanisms (Post, 1992); in neuroendocrinology, including dysregulation of thyroid hormones (Hall et al, 1979; Reus, 1985; Souetre et al, 1989), cortisol (Wolkowitz et al, 1993; Ribeiro et al, 1993), melatonin (Rosenthal et al, 1984; Rao et al, 1992) and others; in molecular genetics (Ezzell, 1993); and in the influence of circadian rhythmicity as an overarching construct whose influence transects all of the previously mentioned areas (Healy, 1987; Tsujimoto et al, 1990). These advancements have contributed support to the conceptual framework for this study, namely that depression is a phenomenon replete with concomitants of circadian rhythm disruption. To pursue a line of logic that argues which came first, the *depression* or the *biological rhythm disturbance*, courts a dualism that is antithetical to the framework presented here. It is the bias of the investigator that the experience of depression has concurrent biological rhythm disturbances perhaps even before the individual *labels the experience as depression.* If this is the case, then the prodromal symptoms discussed here are indeed a dimension of the whole experience of depression, much in the same way that shortness of breath may be a prodromal symptom of congestive heart failure (CHF). Because the shortness of breath has not yet been labeled as CHF does not mean that the experience is not one of cardiac dysfunction. This example highlights the line of reasoning which recognizes depression as no different than any other illness.

Discussion of the conceptual framework will be guided by the various

dimensions of the human circadian timing system. Elements of the framework to be reviewed here include: constructs germane to circadian rhythm theory; current theoretical perspectives on the neuroanatomic basis of the circadian timing system in humans; and a review of select neuroregulators significant to circadian rhythmicity in humans. With this foundation, the discussion will then shift to the application of these concepts to the understanding of circadian rhythm dysregulation in depression and an argument for using selected circadian variables as the basis for intervention in rhythm dysregulated conditions such as major depression.

Given the interconnectedness of the person and the environment, the role of the social environment must be addressed as well. Recognizing that the social environment directly impacts the individual's internal environment, discussion of the conceptual framework will conclude with attention to the social environment as a factor interacting with an individual's biology.

Circadian Rhythms

The focus on circadian rhythms in depression has been the subject of significant investigation, and carries with it a rich history of study, beginning with early scientific attempts to understand the nature of rhythmicity and its application to human experience. Challenging the early beliefs that daily variations in activity cycles of both plants and animals were more than just passive responses to environmental stimuli, the works of de Mairan (1729) and De Candolle (1832) demonstrated that certain rhythms in plants persisted without routinized environmental cues. DeCandolle (1832) illustrated that under controlled and constant conditions,

organisms will either gain or lose time according to the environment and are considered to be *free running* from the ±24 - hour clock. Some of the early investigations of free running rhythms in humans involved the use of time-free environments, that is, isolation from all cues of time. Just as with other mammals tested in time-free environments, humans demonstrated a persistent rhythmicity in cycles related to rest/activity and temperature (Aschoff, 1965). Studies indicated that the free running period in humans is approximately 25 hours. Providing that there is no resetting of the circadian clock via environmental means, referred to as environmental *entrainment*, the rhythm would delay about one hour each day in relation to clock time (Weaver, 1979).

In the natural light/dark environment provided by the earth's diurnal rotation, the rhythm delays are not apparent, pointing to an environmentally-based influence on the synchronization of rhythms, and this potent influence is natural light (Richter, 1965). Given that an environmental influence is evident in the regulation of rhythms, subsequent research focused on isolation of an anatomic transducer of light which demonstrated capacity to regulate rhythms. Richter (1967) conducted a variety of experiments on blinded rats, and sequentially destroyed neurologic and endocrine tissues that may confound the tracking of a free running rhythm. His results demonstrated that the hypothalamus was the only place where lesions affected the free-running rhythms. With the collaborative work of other researchers (Moore & Lenn, 1972; Rusak & Zucker, 1979), a retinohypothalamic projection was identified, which terminated in the suprachiasmatic nuclei of the anterior hypothalamus. Destruction of these nuclei yielded loss of rhythm capacity (Moore & Eichler, 1972).

Given that there is a >24 hour rhythm propensity in humans, the presence of light is critical in maintaining synchrony with a light/dark environment (Moore-Ede et al, 1983), and such a mechanism is the result of a functioning retinohypothalamic projection and suprachiasmatic nuclei in the hypothalamus. Providing intact physiologic substrates of the circadian system, then rhythm entrainment is possible with the influence of environmental timekeepers, referred to as *zeitgebers*. Light, although the most powerful, is not the *only* zeitgeber. Researchers have demonstrated the sources of nonphotic entrainment such as food (Boulos & Terman, 1980), states of arousal (Richter, 1979) and social cues (Miles et al, 1977). However, the most powerful source of entrainment is light, and this has become the source of a variety of applications for light across diverse conditions and illness states (Lin et al, 1990; Avery et al, 1991; Mackert et al, 1991; Parry et al, 1993; Lam, 1994).

The variance around a 24 hour periodicity for different individuals raises some important questions about the understanding of disorders which arise from circadian rhythm dysregulation. The normal range of entrainment for a synchronized human being is 23.5 to 26.5 hours. If one's internal "clock" is forced to advance more than approximately one half hour (or delay more than 2.5 hours), it is generally not well tolerated in one whose internal "clock" >24 hours (Moore-Ede et al, 1983). These rhythms can be modified by influences such as light intensity and hormones (Mistlberger & Rusak, 1989) and have significant implications for changes in circadian rhythmicity in major depression.

Given the evidence of free-running and entrained rhythms, the question of whether or not more than one clock exists within the human timing system gave rise

to the development of several chronobiological models. Of those models, a commonly accepted model is the *two oscillator model* developed by Weaver (1979). This model postulates that of the two oscillators, one is stronger than the other, and they are responsible for different functions. This model has received support over time inasmuch as repeated studies have demonstrated the persistence of weaker circadian rhythms subsequent to the destruction of the suprachiasmatic nuclei (Rusak, 1982). Normally, in light/dark environments, the two oscillators are coupled or linked. However, the two oscillators become free running in conditions of constant light (Kupferman, 1991). The weaker oscillator is believed to be more easily influenced by the presence of zeitgebers, and is alleged to regulate slow wave sleep, calcium excretion and plasma growth hormone. The stronger oscillator controls rapid eye movement (REM) sleep, core body temperature and corticosteroid secretion and potassium excretion (von Zerssen, 1987). According to Schulz and Lavie (1985), the notion of whether the 'master clock' for the body's rhythmicity is in the suprachiasmatic nucleus (SCN) is supported when those nuclei are surgically isolated, and the neural rhythms outside of the SCN island cease.

Circadian Rhythm Disruption in Depression

Some of the earliest investigations into circadian phenomena related to major depression date to the latter part of the 19th century with the works of Kraft-Ebing (1874). This area of knowledge development is of particular interest here for its applicability to understanding dimensions of depression that span from cellular mechanisms to behavioral manifestations of depressive illness. Clusters of data exist

which examine prominent and interrelated biological markers in depression, and include temperature, sleep, and various neuroregulators and their metabolites (Soutre et al, 1989). Part of the challenge embedded in this body of literature is the determination of the main chronobiological abnormalities that are concurrent with the illness of depression. The issue of which circadian variables are involved in the etiology of the illness of depression has yet to be fully understood.

Temperature. It is clear that core body temperature is an entrained circadian rhythm, but the mechanism for that entrainment is unclear (Mistlberger & Rusak, 1989). Temperature regulation is a cumulative response to input from a variety of body systems including the central nervous system, endocrine system and muscle responses to ambient temperature. The seat of the body's temperature regulation is the hypothalamus, which is also involved in the endocrine indices of temperature, eg, thyroid-related regulation of heat production (Kupferman, 1991).

Temperature plays an important role in sleep-wake periods. It has been long documented that humans have a daily variance in temperature that spans approximately 1.5°F with a peak in the late morning or early afternoon and a nadir at some point in the night (Hobson, 1989). The fact that there is a low point in temperature during sleep is critically important for the smooth enactment of sleep architecture and a restful experience.

Changes in temperature in sleep are influenced in three different ways. First, the circadian rhythm for core body temperature is as described above. Influences on the circadian rhythm include the propensity for morningness or eveningness in rhythm strength. This factor is responsible for whether an individual is considered to be a

morning type, evening type or neither (Drennan et al, 1991). Additionally, there is a gender effect on temperature rhythm in both women who are ovulating or perimenopausal. The work of Lee (1988) has shown that there is an increase in core body temperature mesor, along with a dampening of the temperature amplitude post ovulation. Second, temperature varies within the sleep period time. Part of this is related to the circadian influence on temperature rhythm in sleep, but the other component is an artifact of sleep stage changes. For example, thermoregulation is inhibited in REM sleep and conversely, the mechanisms for thermoregulation remain intact in non-REM sleep (Goltzbach & Heller, 1989). Third, there is an influence from the environment in which an individual sleeps, namely ambient or room temperature. With warm ambient temperatures, studies have noted reductions in REM and non-REM stages 3 and 4 , whereas cold ambient temperatures yielded more time awake, more movement time, longer sleep latencies, diminished REM and non-REM stage 2 (Karacan et al, 1978; Sewitch et al, 1986).

In depression, several events may occur and include either a phase advance (Czeisler et al., 1987) or phase delay of the body's rhythm for temperature or a blunting of the circadian rhythm for temperature (Rosenthal et al, 1990). Behaviorally, these influences include difficulties initiating and maintaining sleep, and varying levels of daytime fatigue.

Given the fact that temperature is such a reliable indicator of circadian rhythm strength and phase, it is an excellent index of the circadian timing system functioning in an illness such as depression. The monitoring of circadian rhythm related to temperature requires frequent data points over a twenty four to forty eight hour period

to be able to fully examine the dimensions of the rhythm; for example, the highest (acrophase) point and the lowest (nadir) point in the temperature rhythm as benchmarks of rhythm phase. Equally important is the rhythm strength. Lastly, the mean (mesor) temperature is a critical index in understanding both daytime fatigue and night time sleep disturbances (Campbell & Gillin, 1987; Lee, 1988).

Sleep. A variety of factors may alter or modify sleep stage distribution, and include age (Hoch, Buysse & Reynolds, 1989; Reynolds et al, 1987), prior history of sleep disturbance (Carskadon & Dement, 1989), disruption of circadian rhythms (Czeisler et al, 1987), core body temperature (Bonegio et al, 1988; Tsujimoto et al, 1990), menstrual cycle (Shaver et al., 1988; Lee et al, 1990), drug ingestion (Nicholson & Pascoe, 1989) and disease (Moore-Ede, Czeisler & Richardson, 1983).

The process of sleeping and remaining awake is expressed in a circadian pattern; this pattern varies from individual to individual, but generally reflects the basic adaptation of the person to a given environment (Moore, 1990). Sleep has both homeostatic and biorhythmic properties. The homeostatic features of sleep are juxtaposed on some very powerful biorhythmic fluctuations that are not only circadian (daily), but also infradian (less than daily) and ultradian (more than daily) throughout the sleep period (Broughton, Koninck, Gagnon, Dunham & Stampi, 1990).

Two types of sleep alternate rhythmically throughout the entire sleep period and these types are REM (rapid eye movement) and non-REM (non rapid eye movement). REM sleep is considered to be active sleep. In REM, the sleeping person is generally immobile with paralysis of the large muscles. Characteristically, the person's eyes dart back and forth. Most dreaming occurs in REM sleep.

REM is further delineated as phasic REM and tonic REM. In phasic REM, the person who sleeps is generally immobile, but minute twitches of the face, fingers or body are common. Snoring ceases and respirations become irregular. Cerebral blood flow increases and the metabolic activity of the brain increases; concurrently, the brain's temperature also increases (Hauri, 1982). Dement (1976) points out that in this phasic activity there exists evidence of short lived contractions of the middle ear muscles which occur only in REM. These contractions also mimic those that occur in waking states in response to various pitches of sound.

Tonic REM seems to be far less complex in its presentation. Tonic REM is a state within REM sleep which is characterized by similar brain activity but the absence of twitching small muscles. Dement (1976) speculates whether this state of tonic REM is actually sleep at all; he questions the perception of other researchers that tonic REM may possibly be a state of wakefulness with commensurate paralysis and hallucinations. It seems evident that if that were the case, sleep would be something to be avoided for its psychotic dimensions.

The other phase of sleep is called non-REM and is often described as an idling brain in an active, moving body. Non-REM consists of four stages, with stage 1 and 2 being lighter sleep, and stages 3 and 4 being deep sleep. Very little dreaming occurs within this type of sleep. Throughout the night, REM and non-REM cycles alternate to produce what is referred to as a typical *sleep architecture* for that person. Normally, non-REM/REM cycles vary from 70 to 110 minutes in duration, but the average is 90 minutes, and the first appearance of REM sleep (ie, REM latency) at about 90 minutes after sleep onset. Early night sleep is characteristically non-REM, particularly

stages 3 and 4, but as the night progresses, REM periods can last 60 minutes or longer, and the interspersed non-REM is nearly all light sleep (Moore-Ede, Sulzman & Fuller, 1982).

Several changes in sleep patterns of those who suffer with depression distinguish them from those classified as normal. Approximately 90% of persons diagnosed with major depressive disorder show some form of electroencephalography (EEG) verified alteration in sleep (Reynolds, 1989). More specifically, the changes noted in the sleep of persons with major depression include: a shortened REM latency and sleep discontinuity disturbances, e.g., prolonged sleep latency, middle of the night awakenings and early morning awakening. Other EEG verifiable changes include a diminished slow wave (delta) sleep, with a notable shift of delta activity from the first non-REM period to the second non-REM sleep period. Finally, there is altered temporal distribution of REM sleep within the night and an overall increase in the amount of REM sleep in a given night (Benca et al, 1992). These factors combined yield sleep that is more fragmented and less efficient, often leaving the depressed person feeling unrested and fatigued upon awakening (Campbell & Gillin, 1987).

Fleming (1989) raises the question of the relevance and clinical applicability of sleep architecture findings in depression, especially when several observable variables may contaminate the data. The concern of confounding influences is particularly noteworthy in relation to REM findings. For example, Fleming (1989) points out that short REM latencies have been found in persons recovering from alcoholism, withdrawal from tricyclic antidepressants, primary insomnia, narcolepsy, and the elderly. Lee and colleagues(1990) postulate that the shorter REM latencies in

women in the luteal phase of the menstrual cycle may be due to characteristic increases in the temperature mesor post ovulation. The issue of the stability of REM changes in depression merits consideration here as the fact that several influences, both normative and pathologic can influence the position and progression of REM sleep within the context of an overarching sleep architecture.

The stability of REM changes both from night to night within and after a depressive episode has become an issue for study since the early works of Gillin and colleagues (1984) noted short REM latencies in depression and other psychiatric conditions. Simons and Thase (1991) examined the course of biological markers and treatment outcome of a sample of 53 persons diagnosed with endogenous depression. Of the 53 participants, 20 had shortened REM latency. The investigators found no significant differences in REM latency between pre- and post treatment, even though self report depression scores showed significant improvement. Given the 20 subjects noted to have a reduced REM latency, this finding may be more an artifact of inadequate power than of stability of the variable across time. Such findings fall into the category of conceptual and methodologic issues germane to the diagnostic and research applications of EEG sleep patterns in depression. Buysse and Kupfer (1990) point out that while the definitions of many sleep EEG variables have been standardized, many, including phasic REM activity and REM latency have varied considerably in research studies. This trend, coupled with the practices of using group means in research findings as well as using different standards for study participants within the same sample (eg, for age), may cloud the results considerably. More consistent attention needs to be given to issues of sensitivity and specificity in

consideration of REM-related findings.

The issue of REM latency abnormalities may be evaluated from a variety of perspectives, and according to the various hypotheses to be addressed here. Findings from various researchers differ on the significance and meaning of REM latency changes in depression. For example, Kupfer and colleagues (1988) studied a group of 19 persons diagnosed with major depression of less than four weeks duration, and compared electroencephalographic data with data from a previous depressive episode. They found that early in the depressive episode REM sleep findings were more pathological, (e.g., shortened REM latency, increased REM sleep percent and REM activity) when compared to the previous episode. Non-REM variables were not significantly different. The investigators claim that their findings are not explainable on the basis of clinical severity or number of prior episodes, and suggest that potential relationships exist between electroencephalographic patterns, duration and course of a depressive episode.

Kupfer and colleagues (1991) continued their investigation of REM abnormalities in depression with a particular focus on the effect of timing within a depressive episode as a possible determinant of reduced REM latency. In this study, the investigators essentially replicated the finding of the previous study, using a larger sample of 32 participants. One methodologic problem that requires close examination in both of these studies is a potential gender effect. Across these two studies, 77% of the subjects were women and 22% were men. In either study, there were no controls for menstrual phase or menopausal status. Given the fact that the temperature acrophase is higher in women in the luteal phase of the menstrual cycle (Lee, 1988),

REM periods may occur earlier in these women, confounding the findings significantly (Lee et al, 1990).

Campbell and Gillin (1987) point out that the characteristic sleep architecture changes noted in depression, especially loss of slow wave sleep and problems with sleep continuity, are also found in other disorders such as generalized anxiety disorders and obsessive compulsive disorder. Kerkhofs and colleagues (1988) examined the effects of four subtypes of major depressive disorder on four sleep EEG variables, taking into account the effects of age, gender, severity of depression and dexamethasone suppression test results. What the investigators found was that slow wave sleep was significantly affected by age while total sleep time and sleep efficiency varied with severity of depression and age. REM latencies were modulated by the presence of endogenous depressive illness as well as gender, but surprisingly not by age. Further research is likely to offer clarification of these issues and offer direction to facilitate the inclusion of greater precision in research methods in the future. Nonetheless, four meta-analyses of sleep architecture changes in depression have consistently demonstrated short REM latency with increased REM density, difficulties with sleep continuity and diminished NREM stages 3 and 4 (Knowles & MacLean, 1990; Obermeyer et al, 1991; Benca et al, 1992; Hudson et al, 1992).

Given sleep architecture changes in depression, and the well accepted shortened REM latency marker as an indicator of major depression, polysomnography becomes a crucial measure in depression studies dealing with circadian variables. Recognizing the connection between core body temperature and sleep variables normatively, the issue of these two measures become exponentially more important

when used in combination. Sleep and temperature are excellent markers of rhythm function. In an illness state such as depression, abounding with concomitant indicators of rhythm dysregulation, these markers can serve to plot the course of a depressive episode. Additionally, these indicators provide a physiologic corollary to self report measures, enriching the dimensions of the data.

Issues of Sleep Episode Placement in the Circadian Day

While many studies use electroencephalographic studies of sleep in depression, they often examine night time sleep only, leaving the issue of potential effects of daytime sleep uncontrolled. Recognizing sleep as one dimension of circadian phenomena involved in the enactment of sleep/wake cycles, utilizing a perspective that excludes the influence of daytime sleep on the complete cycle can produce serious distortions in the appraisal of the overall cycle. Some of the work of Monk and colleagues (1985; Moline and Monk, 1988) demonstrate the significant impact of napping on various functions, eg, cognition, generally considered to be under the control of the circadian timing system. What these investigators were able to demonstrate in study participants living in temporal isolation was that cognition can influence particular variables such as sleep/naps, and the frequency of temperature rhythm in relation to sleep/wake cycles. These are important findings, as they point to other influences in circadian timing phenomena related to sleep/wake states, previously thought to be under the control of the circadian timing system.

There are some shortcomings in this small body of research which examines the temporal placement of sleep episodes in the circadian day. These issues include

small numbers of subjects and the need for replication of these findings in diverse samples of individuals. Campbell and Zulley (1989) examined the presence of slow wave sleep in spontaneous daytime naps. The purpose of this study was to explore the relationship between prior wakefulness and circadian variables such as core body temperature. What their results demonstrated was that naps occurring within four hours of the daytime temperature acrophase contained significantly more slow wave sleep, than at other points in the circadian clock. Using multiple regression, the investigators found no relationship between prior wakefulness and slow wave sleep measures, but discuss the importance of their findings in relation to an approximate 12 hour rhythm in slow wave sleep. This is an important finding inasmuch as it underscores the effects of the circadian timing system and sleep/wake organization.

Other studies reveal conflicting findings concerning the effect of daytime napping on nocturnal sleep in persons diagnosed with depressive disorders. For example, Kerkhofs and colleagues (1991) examined the effects of daytime napping in a group of 12 hospitalized persons diagnosed with major depression, and compared them with a group of 10 normal controls. According to the study protocol, participants were free to sleep whenever they chose; sleep/wake was monitored with ambulatory EEG. The results of the study showed that 50% of the depressed participants and 60% of the controls napped. The control group napped mainly in the afternoon, whereas the depressed participants napped at various times during the day. Napping did not affect night time sleep in either the control group or the depressed group.

Conversely, Southmayd and colleagues (1991) hypothesize that daytime napping creates disturbances in nocturnal sleep patterns, and presented a model to

explain these changes. In their work, they recognize that the two major hypotheses used to describe sleep in depression have been the *phase advance hypothesis* and the *S-deficiency hypothesis*. Their model is based on a review of descriptive studies in the literature focusing on sleep in depressed persons. Basically, their model recognizes the reciprocal interaction of non-REM and REM cycles normally, but in depressed persons there is a reduction in the night time non-REM sleep due to a release or discharge of delta waves, slow wave (stages 3 & 4) sleep. This part of the model is in keeping with the S-deficiency hypothesis, which will be addressed in more detail in the discussion which follows. However, according to the model put forth by Southmayd and colleagues (1991), the issue is not the discharge of a particular *type* of sleep, but more so is a dampening of the circadian rhythm for sleep. What results, according to this model is a greater likelihood for daytime sleep, and consequently, a disturbance in the overall regulation of the entire sleep-wake cycle. While the model merits attention for recognizing the impact of daytime sleep on overall sleep/wake cycles, there is no empirical evidence to support its claims. Such a lack points to the need for testing and verification.

What these studies collectively point to is the need for study designs that examine both night time sleep, and the potential of napping during the day. This can be accomplished with a combination of objective measures such as polysomnography for night time sleep periods, and self report measures of daytime napping. With a combination of these two types of measures, unexpected findings in one measurement can be scrutinized with data from the other, offering a multifaceted perspective on the sleep/wake experience of the individual under study.

Hypotheses of Sleep Pattern Disturbance in Depression

The question of etiology arises: what might be the underlying causes of the sleep pattern disturbances in depression, and are these patterns stable across a given type of depression? To answer the etiologic question, four major hypotheses have been proposed to account for salient sleep pattern disturbances in depression. Three hypotheses include the S-deficiency hypothesis, the phase advance hypothesis and the cholinergic-aminergic balance hypothesis. Another hypothesis involves melatonin secretion regulated by the circadian pacemaker in the suprachiasmatic nucleus in the anterior hypothalamus (Lewy et al, 1980; Rosenthal et al, 1985; Rosenthal et al, 1988).

S-deficiency hypothesis. The S-deficiency hypothesis states that the aforementioned sleep disturbances in depression result from a dual process model of sleep regulation (Borbely & Wirz-Justice, 1982). According to the model, which assumes the existence of a sleep-wake dependent component (Process S) and a circadian component (Process C), the two components interact to determine the duration and placement of sleep episodes within a 24 hour day, as well as to influence non-REM sleep. Process S and process C interact to create sleep organization; process S normally inhibits the onset of REM sleep. However, in depression, there is a hypothesized deficiency of process S, which in turn disturbs the circadian rhythm of sleep regulation. The results of this disturbed process are the patterns of sleep disturbance as previously described.

The works of van den Hoofdakker and colleagues (1986, 1990, 1992) have long

supported the S-deficiency hypothesis. In their most recent work (1992) they pose the question of whether non-REM sleep is responsible for the emergence of depressive symptoms in vulnerable individuals. The hypothesis put forth in their work assumes that the antidepressant effects of interventions such as various forms of sleep deprivation and temporal shifts in sleeping patterns are wrought in the suppression of non-REM sleep. Such a perspective is currently controversial, as the more well established belief is that REM suppression is the effective mechanism in ameliorating depressive symptoms.

The basis for the claim that the antidepressant action of sleep manipulation is based in non-REM mechanisms is believed to be related to homeostatic controls of non-REM sleep intensity. According to Beersma and colleagues (1992), if arousals from sleep are present in the earlier part of the night, then non-REM sleep intensity will be increased later in the night. Such a finding becomes a pivotal concept in the emergence of their hypothesis. The hypothesis put forth by Beersma and colleagues has been critiqued by a variety of scientists recently.

Gillin (1994) recognizes the merit of the non-REM hypothesis, but questions why other methods of non-REM suppression, eg, benzodiazepines, scopolamine or other drugs do not produce a similar antidepressant effect. Vogel (1994), a strong proponent of hypotheses in keeping with the phase advance hypothesis, questions the viability of the van den Hoofdakker group's hypothesis on several points. First, there is a recognition that not all pharmacologic interventions have been known to demonstrate a strong suppressive effect on non-REM sleep intensity. Second, that among the various forms of sleep deprivation in use at present (total sleep

deprivation, REM sleep deprivation, partial sleep deprivation, sleep schedule shifting), no support is given to assumptions put forth by van den Hoofdakker and colleagues that REM sleep deprivation decreases non-REM intensity.

As more empirical data are gathered in relation to the commonly shared psychobiological pathways for sleep and depression, some clarity is likely to surface as to the strength of the current hypotheses addressed by Beersma and colleagues, as well as their place in explaining phenomena related to REM and non-REM variables common to mood and sleep. Alternative hypotheses to explain sleep disturbance in depression glean eclectic perspectives, and are addressed below.

Phase advance hypothesis. This hypothesis is based on data that REM latency is earlier after sleep onset than predicted from healthy, non depressed persons. This hypothesis assumes that sleep/wake cycles are the result of interaction between two circadian regulators, known as oscillators. According to Gillin and Borbely (1985), one of the oscillators is responsible for regulation of circadian rhythms such as REM sleep, temperature and cortisol. The other oscillator determines the rhythm of non-REM sleep. While variations in cortisol and temperature are evident in depression (Avery, 1982; Gillin, 1989; Souetre et al, 1989; Baumgartner et al, 1990), REM disturbances can also be seen in those who shift their hours of sleep (e.g., shift workers or rapid travel across time zones) (Infante-Rivard, Dumont & Montplasir, 1989). According to several investigators, (Lewy et al, 1982; Lewy et al, 1983), abnormalities of circadian acrophase (time of trough and peak in the rhythm) or amplitude have been suspected also to be etiologic in fatigue severity as well as seasonal mood disorder.

The works of Vogel and colleagues (1980, 1983) have contributed significantly to the knowledge gains in understanding the interface of REM pressure and altered REM architecture in sleep, especially in depression. The hypothesis by Vogel and colleagues is in accordance with the phase advance hypothesis, and merits some discussion here. What their work demonstrated was that there are differences in the REM sleep of persons diagnosed with 'endogenous' depression when compared to non-depressed controls. What Vogel and colleagues found was that depressed persons had higher REM densities, yet their REM periods became shorter over the course of a given night.

Such findings pointed to the possibility of an underlying circadian rhythm disturbance. Interestingly, however, when Vogel and colleagues (1980) studied the sleep of those with depression as compared to normals, they found that the sleep of the depressives is comparable to the extended sleep of normals. In other words, the nocturnal non-REM/REM cycles of a person who is depressed appear very similar to the non-REM/REM cycles of a non-depressed person when deprived of nocturnal sleep and allowed to sleep through the next day. Such findings correspond with the notion of short REM latencies in depression, but it is not clear that short REM latency equates with phase *advance* for the circadian timing system (Gillin, 1989). For example, the work of Avery (1982) demonstrates that core body temperature mesor is elevated in depression, but not necessarily phase shifted. Other investigators have found phase advances of temperature in depressed persons, in relation to the consolidated sleep period (Wehr & Gillin, 1983).

More recently, Tsujimoto and colleagues (1990) found that phase *variability* is

more common than solely phase *advance* in depression, and that reduced temperature rhythm amplitude was significantly more common among depressed persons than those with non-depression psychiatric diagnoses. Other areas of current investigation may demonstrate important trends for understanding thermodysregulation in depressed states.

Thase and colleagues (1992) examined the patterns of REM sleep after nocturnal awakenings in depressed young male outpatients, and compared these data to healthy controls. What the investigators found was that depressives returned to REM sleep significantly more rapidly than did the normals. The rapidity of return to REM in depressed individuals corresponded significantly with depressive severity, but not with deficit of slow wave sleep. Such a finding may indicate that return to REM is a correlate of REM pressure, as discussed by Vogel (1983).

The findings of Souetre and colleagues (1989) report that depression may represent a weakening of the coupling mechanisms of circadian pacemakers, yielding reduced rhythm amplitude, as well as a supersensitivity of environmental stimuli. The environmental dimension of the data results from an examination of circadian variables of those who are in remission from depression versus those who are depressed: those with depression yield data which resembles that of persons living in temporal isolation. The investigators also report that circadian profiles normalize when rhythm amplitude is corrected. What these disparate findings may indicate is that depression is by far a less homogeneous disorder than previously thought. If this assumption is true, than it stands to reason that closer examination of groups of individuals with an analogous diagnosis may help to reveal patterns/trends in circadian data distinctive to

that diagnostic category.

Melatonin hypothesis. According to the melatonin hypothesis of depression, there is increasing evidence that hormones have a regulatory influence on circadian rhythms (Monk, 1989). This is likely to be related to modulation of coupling relationships between oscillators and oscillator-driven processes. One neuroendocrine marker of depression is believed to be an altered nocturnal secretion of melatonin. According to Rosenthal and colleagues (1984), light exerts an effect on the suprachiasmatic nucleus, regulating multiple rhythms, including the rhythmic output of melatonin, which in turn affects reproductive hormone secretion as well as eating and sleeping patterns. Release of melatonin is inhibited by light and stimulated by darkness. This hypothesis serves as the basis for intervention with light in persons suffering from certain forms of depression: suppress melatonin, thus reverse the hypothesized biological foundation of a depressive episode in a nonpharmacologic fashion (Lewy, Wehr, Goodwin et al, 1980).

While generally well accepted, the melatonin hypothesis has not received unequivocal empirical support. In a recent study, Checkley and colleagues (1993) examined the 24 hour melatonin rhythms from 20 persons diagnosed with seasonal affective disorder, compared with 20 normals. The study utilized matched controls on the variables of age and gender. All data were collected between November and March. Plasma samples were drawn at hourly intervals, and were radioimmunoassayed for melatonin. No significant differences in melatonin levels were found between the two groups. Several issues potentially impact on the finding of *no differences*, especially when the study involves fragile measures of hormones such as

melatonin. Other possible explanations may include issues of diagnosis of study participants, as the concerns over diagnostic equability resurface for examination and evaluation of findings such as those presented by Checkley's research group.

Melatonin and Mood

The notion of melatonin's role as a neurochemical contributor to mood states is an interesting one from several perspectives. Examples of such viewpoints include examining the functions of melatonin in nonseasonal disturbances of mood, the effects of thymoleptic treatment of mood disorders on the rhythm of melatonin, and the shared relationships between melatonin and other indices of neuroendocrine functioning. These certainly are important issues to examine in attempting to understand the various facets of a complex phenomenon such as depression.

In an attempt to understand the effects of melatonin suppression in bipolar and unipolar mood disorders, Lam and colleagues (1990) examined the effects of light (500 lux) on nocturnal suppression of melatonin. Study participants included 15 acutely ill individuals: (8 persons with bipolar depression and 7 with unipolar depression) and were 15 age and gender matched healthy controls. Participants were taking neither psychotropic nor ß-blocking medications. The protocol was conducted in conditions of very low lux (15 lux). Three pre-light exposure melatonin levels were taken at 15 minute intervals, starting at 0030 hours to 0100 hours. At 0100 hours, each participant was exposed to 1.25 hours of 500 lux intensity. Melatonin measures were taken at 15 minute intervals throughout the light exposure. Results indicated that those with unipolar depression and the normal controls did not differ in melatonin suppression.

While baseline melatonin concentration was lower in those diagnosed with bipolar disorder, normal controls showed greater melatonin suppression than the bipolar group.

The issue emerges of lux intensity and melatonin suppression, and this must be considered with caution when interpreting study results. On the one hand, as reflected in the Lam et al (1990) study, 500 lux may appear to be inadequate to suppress melatonin. On the other hand, the study conditions need to be carefully considered when understanding effects of light. For example, in a recent study (Teicher et al, 1994), different light intensities were examined for their effectiveness in seasonal affective disorder. In this study, participants were randomized to either an active (600 lux white light) or sham (30 lux red light) treatments and results yielded significant findings for both groups. Participants were instructed to wear light restriction glasses *whenever in daylight* during the treatment period. This daytime light restriction severely confounds the effects of a light exposure treatment, by creating an artificial night for study participants. Design sensitivity issues such as the one discussed here need to be carefully considered when drawing conclusions about light intensity effects.

The findings of Lam et al (1990) are in contradiction to the findings of Lewy and colleagues (1981, 1985), who demonstrated what appeared to be a light *supersensitivity* with melatonin in persons diagnosed with bipolar disorder. What confounds the study by Lam and colleagues (1990), and possibly the studies of Lewy and colleagues is that study participants were both kept *awake* into the night for the melatonin measures, and at least in the case of the Lam study, participants were

instructed to minimize their exposure to daytime light on the day of the study.

Melatonin and cortisol share a reciprocal relationship in depression (Kennedy et al, 1989). Spath-Schwalbe and colleagues (1991) have documented that either being awakened from sleep or remaining awake into the night may precipitate an arousal-induced cortisol 'burst' that is followed by transient inhibition of cortisol secretion, which is also coupled with ultradian rhythms within sleep, particularly non-REM sleep. Given the fact that norepinephrine (NE) is a regulator of melatonin synthesis, and NE is found in high cortical concentrations in waking states, it is reasonable to speculate that nocturnal arousals or wakefulness will influence the complementary relationship between cortisol and melatonin.

The issue of psychotropic medication's influence on both neuroendocrine and central neurochemical indices, eg, norepinephrine, brings this discussion to a point where the lines between what is *neurologic* in nature, and what is fundamentally mediated through *endocrine* mechanisms highlights a false dualism. The integrated functioning of these mechanisms is becoming clearer as more is learned about the interface of fundamental psychobiology and psychotropic pharmacokinetics. For example, Stewart and Halbreich (1989) examined plasma melatonin levels in persons diagnosed with depression before and after treatment with antidepressant drugs. This study was based on the premise that in some subtypes of depression, there is likely to be abnormalities in pineal functioning as well as in the hypothalamic-pituitary-adrenal axis. The investigators recognize that ß-adrenergic (norepinephrine) mechanisms play an important role in both the release of corticotropin releasing hormone (CRH) as a result, alterations in central catecholamine functions may be

commensurately altered. The connection between CRH and noradrenergic functioning was described by Gold and colleagues (1988).

It is the assumption of Stewart and Halbreich (1989) that since antidepressant medication effect changes in noradrenergic functioning, they must also affect melatonin. The investigators compared the effects of three different antidepressants and a placebo on melatonin levels before and after a six week trial of medication. The results of the study demonstrated that melatonin levels were lowered in persons taking imipramine, mianserin and placebo, but increased in persons taking a monoamine oxidase inhibitor (MAOI), phenelzine. There were significant differences in melatonin levels for those taking phenelzine as compared to all other groups. Given that there is no discussion of pre-treatment melatonin levels, it is difficult to interpret the findings of this study. However, given the significant differences between the MAOI and the other groups, it is important to question the mechanism of this result. The investigators point out that it could represent increases in the substrate (serotonin) or increases in melatonin due to intracellular norepinephrine.

Other influences can create changes in melatonin levels. It has been established that certain drugs, particularly the ß-adrenergic antagonists such as propranolol and atenolol (Rosenthal et al, 1988; Demitrack et al, 1990) are able to suppress nocturnal melatonin release. However, issues such as gender play an important role in endocrine functioning. Of special interest here are the interactions between the hypothalamic-pituitary-adrenal-gonadal (HPAG) axes. Tandon and colleagues (1990) note significant differences in cortisol secretion patterns between the follicular and luteal phases of the menstrual cycle in women diagnosed with major

depressive disorder. These changes may stem from a variety of sources, and merit consideration in the interpretation of findings related to endocrine shifts in major depression.

A variety of behavioral and mood disturbances have been documented in relation to endocrine disorders (Reus, 1986, 1989)and merit attention insofar as they are often assessed as fundamental disturbances of mood, when in fact the mood symptoms are secondary to a primary endocrine disorder. Cogent examples exist in the evaluation of thyroid disorders, particularly those which present in subclinical forms, as the symptoms may mimic those of dysthymia, atypical depression or major depression.

Cholinergic-aminergic hypothesis. In this hypothesis, it is argued that there are shifts in the neurotransmitter systems (acetylcholine and noradrenaline) involved in the enactment of sleep and arousal. Concurrent with these neurochemical alterations are characteristic pathognomic changes in sleep architecture among depressed individuals (Machowski, Annsseau & Charles, 1989). Acetylcholine and noradrenaline are found in groups of cells in the substantia nigra/ventral tegmentum and reticular formation, respectively. The neurons containing both of these neurotransmitters have projections to the cerebral cortex, and contribute significantly to the experience of responsiveness, arousal and activation. As with other advancements in science, the understanding of catecholamine implications in wakefulness were advanced by phenomenologic data related to use of particular drugs. Medications such as reserpine, known to yield states of idleness and calmness, act by depletion of monoamines, which can be pharmacologically reversed with the

administration of a catecholamine precursor such as l-dopa. Similarly, drugs which affect states of activation, such as amphetamines or cocaine, act by catecholamine mechanisms (Jones, 1989).

Other neurochemicals contribute to the experience of wakefulness and cortical activation, and included in this group are acetylcholine, histamine, glutamate, aspartate and many peptides. Acetylcholine, one of the earliest neurotransmitters to be discovered acts mainly as an excitatory neurotransmitter. However, as Risch and Janowsky (1984) point out, that while acetylcholine plays a critical role in the reticular activating system's mechanisms in wakefulness, it is also critical in both REM and non-REM sleep. It is a generally well accepted fact that both the limbic system and the hypothalamus play major roles in mood-related experience. Given extensive cholinergic innervation of both of these brain areas, acetylcholine is considered to be an important operative chemical in the regulation of mood states (Kandel, 1991). In the early 1970's, Janowsky and colleagues (1972) put forth a hypothesis that mood states may represent a functional balance between the central cholinergic and adrenergic mechanisms, and that depression was essentially a disease of cholinergic dysregulation.

The roles of histamine, glutamate, aspartate and other peptides are still under considerable investigation. For example, histamine is alleged to have an activating influence on the central nervous system, hence wakefulness, and this has been evidenced pharmacologically with the concurrent sedation that accompanies the administration of antihistamine compounds. Glutamate and aspartate are excitatory amino acids that are released in wakefulness (Mendelson, 1987). Additionally, there

are a variety of peptides such as thyrotropin releasing factor, corticotropin releasing factor and vasoactive intestinal peptide which are believed to function as neurochemical determinants of cortical activation and wakefulness (Jones, 1989). Other hormones play a role in states of wakefulness, and include substances such as adrenocorticotropin hormone, epinephrine or thyrotropin stimulating hormone (Inoue, 1989).

The cholinergic-aminergic hypothesis has been tested in animal models. Hasey and Hanin (1991) examined the role of acetylcholine and noradrenaline in conjunction with hypothalamic-pituitary-adrenal axis (HPA) hyperactivity in an animal model of depression. In their study, these investigators identified immobility as the analog of depression in rats. The basis of this study is wrought in the pharmacologic research literature using human subjects. The investigators review documented reports of the effects of cholinergic agonists such as physostigmine on the course of mania, depression and its effects in normal persons; the underlying hypothesis being that depressed persons represent a state of cholinergic supersensitivity. Coupled with evidence of down regulation of ß-adrenergic receptors with the use of antidepressant drugs, these investigators designed their study to examine the cholinergic-aminergic hypothesis via pharmacologic manipulation of acetylcholine and noradrenaline systems on behavioral and glucocorticoid indices. Plasma corticosterone was used as the index of HPA activity. Central and peripheral cholinergic activation was tested in 2 separate experiments, using physostigmine and neostigmine respectively, the latter compound not crossing the blood-brain barrier and acting peripherally only. The investigators tested the null hypothesis that pharmacologically blocking the effects of physostigmine

and neostigmine will have a no effect on the dependent variable, immobility, the analog of depression. Clonidine, an α_2 agonist, or metoprolol, a β_1 antagonist were used as the pharmacologic pretreatments to physostigmine and neostigmine. Results of the study showed that the effects of physostigmine were blocked by metoprolol and partially blocked with clonidine. However, the physostigmine increased central acetylcholine. Physostigmine also significantly increased immobility in the animal subjects, but neostigmine did not. Physostigmine also elevated plasma corticosterone levels. The investigators note that these data suggest that there is a linkage among the variables of central cholinergic stimulation, increased activity of the HPA and evidence of behavioral analogs of depression, relevant to the cholinergic-aminergic hypothesis of depression. Of course the limitations of this study exist inasmuch as it is conducted within an animal model, and its generalizability to humans has yet to be fully tested.

Several studies have examined the cholinergic-aminergic hypothesis through metabolites of noradrenergic functions, namely 3-methoxy-4-hydroxyphenylglycol (MHPG) (Nishihara & Mori, 1988; Lauer et al, 1988). In keeping with the cholinergic-aminergic hypothesis, MHPG excretion is reduced in those with certain types of depression as compared to normals (Gwirstman et al, 1989). Some researchers test this hypothesis with the use of a pharmacologically induced period of REM sleep. The test is known as the *cholinergic REM induction test*, and consists of the administration of a cholinergic agent such as physostigmine or other experimental compounds, which leads to a more rapid onset of REM sleep. In persons with depression, the REM onset is even faster (Sitarem et al., 1984). Increased MHPG

levels are related to REM sleep reduction and possibly arousals, pointing to support for an inverse relationship between REM sleep and norepinephrine metabolism (Salin-Pascual et al, 1989). Such findings are important to both the understanding of neuroregulatory mechanism dysfunction in depression as well as appreciation of the possible mechanisms for interventions such as various forms of sleep deprivation therapy.

Influences in Major Depression

Several influences transect the understanding of depression and interpretation of findings, refracted through the perspectives of the four major hypotheses discussed here. Such influences include age, gender and the presence of phenomena related to diurnal variation of depressive symptomatology. Each of these phenomena potentially impacts not only the nature of the experience of depression, but responses to interventions aimed at amelioration of symptoms.

Age. It has been a well established fact that life stage directly affects variables such as sleep stage distribution and circadian rhythms. This is evident in examining the sleep patterns of infants compared to young adults, compared to elders. Sleep quantity drops significantly from childhood to old age, and this is evident in sleep stage changes. For example, a young child may have as many as eight hours of REM sleep, whereas an elderly person may have as little as one hour per night. Similarly, looking at non-REM sleep, there is less of a drastic change, but from youth to senescence, the reduction is approximately from eight to five hours (Carskadon & Dement, 1989).

Czeisler and colleagues (1987) address the common sleep abnormalities that are not bound to depression, but are common across the life span. In the elderly, certain types of sleep disturbances may reflect circadian disturbances. Behaviorally, these changes manifest as earlier sleep onset, more frequent awakenings during the night, early morning awakening (terminal insomnia) and these factors are offset by more common daytime napping. These variables certainly correspond with alterations in sleep architecture. Hoch and colleagues (1989) note that there is an increase in wakefulness after sleep onset and diminished slow wave sleep among the elderly. It is not uncommon to see shortened REM latencies among elders, and these findings combined probably represent some phase advancing of circadian temperature rhythms, and an overall reduction in the elder's *tau*, or length of circadian day (Czeisler et al, 1987). Conversely, the sleep of younger persons demonstrates the reverse condition seen among the elderly, eg, delayed sleep phase insomnia, in which the younger person stays up later into the night and has difficulty getting up at early hours in the morning. Both of these conditions, delays and advances may potentially represent outermost examples of morningness and eveningness as discussed by Horne and Ostberg (1976).

In depression, there are also changes in sleep architecture that seem to be bound by age. Kupfer and colleagues (1989) examined EEG measures of sleep for two nights in 3 men and 5 women with depression whose mean age was 23.5 years. Compared to age-matched controls, depressed persons showed a longer sleep onset latency, reduced delta sleep and diminished sleep efficiency. There were no significant differences in REM latency noted between the depressed and control groups, but the

REM finding of decreased REM latency was replicated in a study of EEG sleep in young adults diagnosed with major depression (Goetz et al, 1991). Other studies of young depressed adults show similar findings to those of Kupfer and colleagues (1989), except for the reduced REM latency (Pailhous et al, 1988). There were no controls for gender-bound effects in any of these studies, which confounds interpretation of these results. However, given the trend in these data toward the common findings of prolonged sleep onset latencies, reduced delta sleep and low sleep efficiencies, there may be cause for identifying an age-bound effect among younger people.

Hoch and colleagues (1989) note that the sleep of depressed elderly persons demonstrates short REM latencies, prolongation of the first REM period and extreme difficulty in maintaining sleep. Sleep onset REM periods are not uncommon. The EEG findings of sleep in depressed elderly may potentially be confounded by other influences such as medical illness. Sleep disturbance has become an important target symptom in the distinction of depressive disorders from other neuropsychiatric disorders such as dementia (Jarvik & Wiseman, 1991) or pseudodementia (Buysse et al, 1988; Ramsdell et al, 1990).

Gender. One variable that merits careful consideration in understanding rhythm disturbances as reflected in sleep pattern changes in depression is that of gender. Many studies examining sleep and rhythm disturbances in depression make no accommodation for the differences between women and men (Nadelson, 1993). This trend of nondifferentiation is carried even further by making no distinction between ovulating and non-ovulating women. Ignoring critical differences in

physiologic functioning related to gender and life-stage serves only to bias findings with erroneous assumptions.

Current knowledge from women's health research can be applied to investigations relevant to major depression in women who are pre- and post menopausal, facilitating clarification of differences between the two groups in at least two areas. Descriptive data are needed to characterize variance in circadian rhythm disruption in ovulating and non-ovulating women diagnosed with major depression.

A few studies exist which contrast temperature circadian rhythm between youthful and elderly males and females (Prinz et al, 1992), but not between these two groups when depressed. Other normative data have been available for some time, namely differences in temperature rhythms between follicular and luteal phases of the menstrual cycle (Lee, 1988). The intervening variable of depression creates changes in the normal pattern of rhythm amplitude across a variety of thermoregulatory and neuroendocrine indices (Healy, 1988); the specifics of these shifts are not well understood between ovulating and non-ovulating women. Reynolds and colleagues (1990) examined the effects of gender on EEG variables with 151 pairs of men and women diagnosed with depression. The participants were matched for age and severity of depression. Ages of the participants spanned from 21-69 years. The major finding from this study was that depressed men had less slow wave sleep than did women. The investigators noted that according to the visually scored measures of sleep, gender differences were small with respect to slow wave sleep time and percent.

In terms of other EEG variables, the investigators noted that REM variables,

sleep efficiency, and early morning awakening demonstrated observable signs of age-bound effect, but not gender. Fearing occult use of alcohol by some of the outpatient participants, the researchers examined covariance for alcohol use, but noted no statistically significant differences. Unfortunately, the investigators demonstrated no controls for menstrual phase or menopausal status of the women participants, which threatens external validity of findings. The consequences of this threat are serious, but are not uncommon in the sleep and biological rhythm literature. Clearly, this study represents a large and expensive project, examining an issue that needs attention from an empirical standpoint. Application of such findings in practice may yield unfortunate consequences.

How circadian rhythms shift in women with a homogeneous disorder such as major depression, and the effect of treatment on these shifts have yet to be fully identified. Some investigators have used circadian rhythm variables as a basis for nonpharmacologic intervention in women with disturbances of mood related to menstrual cycle phase, rather than an illness such as major depression (Parry & Wehr, 1988; Parry et al, 1993). Many researchers acknowledge the mediating effect of hormones such as estrogen, on both mood and sleep (Thomson & Oswald, 1977; Schiff et al, 1979), and these findings carry strong implications for the treatment of depressed women. The work of Shaver and colleagues (1988) has demonstrated that variables such as sleep efficiency and REM latency may be affected by menopausal status. Such findings point to a sound rationale for expecting differences in the basic sleep architecture as well as outcome variables of a mood treatment in pre- and post menopausal women. There is a strong need for research that explores outcomes of

interventions, controlling for those confounding variables such as fluctuating hormone secretion during the menstrual cycle or during perimenopause, which may impact the intervention effects. The consequences of disregarding gonadal hormone effects on circadian variables in major depression is likely to yield invalid findings and potential error when such findings are applied to clinical practice.

Diurnal variation. The issue of daily variations in mood, whether feeling worse in the morning and better in the evening or vice versa have been long detected both in depression as well as in normal mood states (Fahndrich & Haug, 1988), and carries significant implications for the treatment of conditions such as depression. Diurnal variations have been estimated to occur in approximately 50% of persons diagnosed with major depression (Stieglitz et al, 1988). Several issues impact the evaluation of diurnality of symptoms in depression, and include stability of the pattern, its relation to underlying disturbances in circadian rhythm, and discernment of masking of the underlying pattern. Masking refers to the effect of an external factor that potentially may modify the shape, amplitude or timing of a rhythm that is being measured. Examples of masking influences include relational variables such as sleep and temperature, light and melatonin as well as stress and activation of the hypothalamic-pituitary-adrenal axis (Haug & Wirz-Justice, 1993).

In terms of the stability of the diurnal pattern, not all persons who demonstrate a diurnal pattern of mood express the pattern everyday (Tolle & Goetze, 1987). Perhaps the reason for this unpredictability rests with the fact that the assumption of a *circadian* pattern is erroneous; it may be ultradian in nature, or some other configuration of rhythm. It may be a dangerous to assume that because the diurnal

pattern is not apparent everyday that there has been failure in an underlying circadian mechanism. Perhaps the underlying pattern is influenced by subtypes of depression that have yet to be clearly delineated. Certainly the deliberations surrounding the development of the 4th edition of psychiatry's Diagnostic and Statistical Manual (DSM-IV) have focused attention on the diagnostic importance of diurnal variation. However, in the absence of both a framework through which to understand the significance of the phenomenon, as well as empirical evidence to support the meaning of diurnal variation, it is difficult to consider full application of this new knowledge to practice. There is an assumption in the literature that points to a belief that positive and negative diurnality eg, feeling better in the evening versus the morning, are wrought in one underlying mechanism, but these assumptions are based almost exclusively on phenomenologic ratings of mood (Reinink et al, 1993).

What acts as the biological underpinnings of diurnal variations is not well understood at present. Haug and Wirz-Justice (1993) speculate that diurnal variation is likely to be strongly connected with some dimension of the circadian timing system, given the cyclicity of the phenomenon itself, and the similarity to the endogenous circadian rhythm of core body temperature. If, indeed this assumption is true, then there are clear implications of such a finding in relation to concepts of fatigue, and environmental influences on diurnality. The investigators speculate that this may be the connection between masking and diurnal variation.

Recently, diurnal variation has been studied from the perspective of its predictive capacity to determine some dimensions of treatment outcome, particularly with sleep deprivation therapy (Haug, 1992). The findings of Riemann and colleagues

(1990) indicate that depressed persons whose mood improved in the evening prior to total sleep deprivation responded more favorably to the intervention than those whose mood improved in the morning or who had no diurnality in mood. Other investigators have examined the effects of partial sleep deprivation on the diurnality of mood symptoms and activity in major depression (Szuba et al, 1991). What these investigators found was that persons with bipolar illness responded more favorably with mood and measures of diurnality than other groups. Whether this was simply an expected response from bipolar participants, a possible predictor of response for persons with bipolar illness or a very early sign of hypomania is not clear from the report. It has been established that in persons with bipolar illness, while sleep reduction may improve depression, it may also play an important role in the inception of mania (Wehr et al, 1987; Wehr, 1992).

More data are needed to describe the various dimensions of diurnal phenomena, especially data which accurately reflect physiologic dimensions of the circadian timing system. When these data are available, then clear and fuller descriptions of the diurnal patterns will be available, allowing for further testing and refinement of ideas and concepts related to diurnality both normatively and in mood disturbances.

Social Environment. One of the perceived shortcomings of research that focuses on purely psychobiologic phenomena is that it fails to place biologic events in a larger context such as the social environment. The difficulties in bridging molecular or cellular environments to what is occurring in the social milieu has in the past been the purview of sociobiologists. The work of the sociobiologists has mainly been to

examine *mental* disorder from the perspective of evolutionary *biology* (Wenegrat, 1984). However, as technologies have evolved, and access to the internal environment has become more available and grossly more precise, the realm of sociobiology has changed as well. In many ways, sociobiology and psychobiology are merging to form a branch of science that works to understand and quantify the interplay between the internal and external environments.

Gortner and Schultz (1988) address the effect of framing research questions solely through a biological versus psychological perspective. They warn that questions that questions that recognize biological dimensions to the exclusion of other facets of the human experience are destined to miss the meaning of the biology for individuals. Such meaning calls forth issues related to the interpretation of the self, health and illness experiences. Conversely, questions that solely address social or psychological realities run the risk of inattention to biological phenomena. These issues are particularly relevant to research related to concepts dealing with sleep, rhythm and mood as these indices are particularly sensitive to changes in the psychosocial milieu. Sleep pattern changes may be among the very first signs of depression (Gillin, 1989), even before the individual labels the experience as *depression.*

Depression is a multifaceted phenomenon whose enactment is largely dependent on a broad number of variables, both internal and external to the individual. An examination of the various influences addressed in this discussion provides a basis for understanding the rationale for and appreciation of complex intervention, aimed at amelioration of symptoms related to a depressive episode.

Interventions for Depression

Medications & Electroconvulsive Therapies. Currently, a variety of pharmacologic and other somatic therapies are used in the treatment of depression. To determine the effectiveness of these treatments, a variety of meta-analytic findings will be discussed here. To appreciate the meaning of an effect size, Cohen (1988) discusses the importance of a numerical value that is free from the original measurement unit, one that allows a determination of degree of departure from the null hypothesis or *effect size (ES), and is referred to as the d score*. Determination of the size of an effect is determined by recognizing *d* as a score that expresses score distances in units of variability. Cohen (1988) points out that if the common within-population standard deviation is σ=100 scale points, then d=.1. What this refers to is that the means of two different groups differ by a tenth of a standard deviation. If σ=5, then d=2.0, indicating a difference of two standard deviations, which is certainly a much larger difference or effect than .1. The calculation for the *d score* for two independent samples is as follows: $d=m_A - m_B/\sigma$, and for the one tailed case, $d= |m_A - m_B|/\sigma$, where d=ES for t tests of means in standard unit, m_A, m_B=population means expressed in raw units, and σ=the standard deviation of either population since they are assumed to be equal.

Interpreting the meaning of effect sizes is an important issue, but relative to the phenomenon under study. For example, the greater the researcher's ability to control for confounding variables, the more likely it is that effect sizes will truly reflect the experimental condition. However, when the phenomenon under study is either not well understood, or confounding influences are not known, effect sizes are likely to be

small. Cohen (1988) refers to these effects in the range of d=.2, and effects of this size are often hard to detect outside of study conditions. Moderate effects are considered in the vicinity of d=.5, and large effect sizes are those over d=.8 (Cohen, 1988).

In terms of Parker and colleagues' (1992) meta-analysis of physical treatments for psychotic (delusional) depression, the authors caution the reader that the effect sizes in the analysis were dependent on the information about outcome measures available in the studies. Using 44 studies that examined single and combination treatments, Parker and colleagues examined the literature for trends that would suggest which of the physical treatments under study were most effective for psychotic depression. The investigators state that the literature anecdotally suggests that combination antidepressant/antipsychotic drug therapy and electroconvulsive therapy (ECT) are of comparable efficacy in treating psychotic depression, and are directly superior to either antidepressant or antipsychotic drugs alone. For the single treatments, effect sizes were reported as follows: ECT 2.30 (21 studies); antipsychotic drugs 1.37 (8 studies); tricyclic antidepressants 1.16 (28 studies); monoamine oxidase inhibitor antidepressants 0.69 (3 studies); amoxapine 1.68 (2 studies). With regard to combination treatments, the investigators report the following effect sizes: antipsychotic drugs + monoamine oxidase inhibitor antidepressants 3.13 (1 study); tricyclic + monoamine oxidase inhibitor antidepressants 1.41 (1 study); and tricyclic + antipsychotic drugs 1.56 (12 studies).

What these findings indicate is that for the three key treatment classes, ECT was ranked in terms of mean effect size as superior to the tricyclic/antipsychotic drug combination, which in turn was superior to tricyclic antidepressants alone. Statistical

evaluation of the combinations confirmed ECT as being more effective than tricyclic antidepressants alone and tending to be more effective than tricyclic antidepressant/antipsychotic combinations in treating psychotic depression. These findings, too, need to be evaluated carefully, as the investigators point out that despite attempts at diagnostic homogeneity, all of the studies used did not specify diagnostic classification criteria.

One dimension of treatment effectiveness that is not directly addressed in any of the studies discussed here is the impact of potential side effect on adherence to the prescribed regimen. This factor could potentially alter effect sizes, and consequently promote a distorted perspective on treatment effect. Whether the side effects consist of anticholinergic effects of some classes of psychotropic drugs, or memory loss associated with electroconvulsive therapy, these issues bear a potential impact on treatment course and outcome.

Psychotherapy. Svarthberg & Stiles (1991) analyzed 19 outcome studies to examine the effect sizes of short term psychodynamic psychotherapy (STPP) from studies published between 1978 and 1988. The investigators compared STPP in terms of overall effects, differential effects and moderating effects in no treatment controls (NT) compared to alternative psychotherapies (AP). Calculation of Cohen's *d* (1988) revealed an overall effect size of d=.20 for STPP versus no treatment and d=.24 STPP versus AP. The investigators report that 12 month follow-up studies with the same subjects revealed d= .72. The data from the 12 month follow up points to a trend that suggests a greater effect from therapy when longer the person is engaged in it for longer time periods.

Examining the effect sizes in the two cited meta analyses related to depression, Dobson (1989) examined the efficacy of cognitive therapy versus other treatments such as pharmacotherapy, no therapy controls, behavior therapy and other forms of psychotherapy. In terms of cognitive therapy versus no treatment, the mean effect size over 10 studies was 2.15, indicating that the average cognitive therapy patient did better than 98% (2 standard deviations) of the controls. Nine studies were used to determine the effect of cognitive versus behavioral therapies; the mean effect size was 0.46, pointing to a superior outcome compared to 67% of the behavior therapy clients. Comparing drug therapy to cognitive therapy, Dobson (1989) reports an effect size of 0.53, suggesting therapeutic superiority among cognitive therapy clients over those receiving medications. These results should be reviewed with caution as the investigator did not have a heterogeneous sample by age. Since there are no indicators of the diagnostic heterogeneity of the sample, it is unclear as to *who* is being included in this analysis and such an issue carries significant implications for the validity of the analysis.

A Meta Analysis of the Sleep Deprivation Therapy Literature

Types of Sleep Deprivation Therapies. Despite the advances in the realm of understanding the interface between depression and biological rhythm disturbances, no attempt to examine the effectiveness of treatment strategies aimed at rhythm adjustment and concurrent symptom amelioration has been conducted. Given the potential impact of these emerging strategies on future treatment of depression, it seems parsimonious to conduct such an analysis to facilitate interpretation of the

complexities inherent in this type of research. Additionally, a meta-analysis of this sort may facilitate a broader understanding of the conceptual gaps or methodologic challenges that exist in the current literature.

Understanding normal biological rhythms and the influence of illnesses on these rhythms opens the door to exploring new avenues for the clinical application of this very specialized knowledge. One area in clinical sciences where such applications are being tested is with the biological foundation of antidepressant response to specified forms of sleep deprivation. Wu and Bunney (1990) reviewed sixty one papers involving over 1,700 subjects where sleep deprivation has been applied to the treatment of those diagnosed with depressive disorders. What they report in their review of the literature is that over half of the depressed persons studied experienced an antidepressant response to sleep deprivation therapy. Such findings fall within a range of approximations, rather than a formal meta analytic evaluation of the sleep deprivation literature. As such, there are several confounding influences that cloud the findings, and such muddling may cause the reader to misconstrue the actual results. Such a trend is potentially dangerous, especially when these research findings are destined to be applied to ill persons in clinical settings.

Total Sleep Deprivation. In order to appreciate the findings within the sleep deprivation literature, it becomes important to critically examine some of the various dimensions of this emerging literature. For example, sleep deprivation is not a homogeneous intervention. The initial research on sleep deprivation as an intervention in depression used *total sleep deprivation* (TSD) as the exclusive approach (Pflug & Tölle, 1971). Results of this initial research highlighted that remission of depressive

symptoms indeed occurred in relation to TSD, but that the effect dissipated after a night of normal sleep.

Rapid Eye Movement Sleep Deprivation. Since 1971, other approaches to sleep deprivation have emerged and include at least three other forms of the intervention. First, there is a sleep deprivation that is sleep stage-specific, known as REM (rapid eye movement) sleep deprivation (Beersma, Dijk, Blok & Everhardus, 1990). This type of sleep deprivation requires that the sleeping person be constantly monitored on electroencephalography (EEG), and every time the person enters REM sleep, s/he is awakened by the monitoring technician. The drawbacks to such an intervention strategy seem obvious, but include the use of extensive monitoring equipment as well as the need for constant surveillance by trained personnel. In addition to being a work-intensive strategy, it is also expensive.

Early Partial Sleep Deprivation. The second type of sleep deprivation requires that the depressed person remain awake until approximately 2 AM, then sleep for roughly four and a half hours. This form of sleep deprivation is known as *early partial sleep deprivation* (EPSD), as the person is deprived of sleep in the early part of the night (Brunner, Dijk, Tobler & Borbely, 1990). This form of intervention has been less thoroughly researched, and as such is less frequently the subject of discussion in the sleep deprivation literature.

Late Partial Sleep Deprivation. The third form of sleep deprivation therapy is akin to EPSD, but the deprivation occurs in a different part of the night. Specifically, the depressed person goes to bed at their normal time and sleeps for approximately four and a half hours; this is referred to as *late partial sleep deprivation* (LPSD), as

the person is deprived of sleep that occurs in the latter part of the night (Wehr, 1990). This category of sleep deprivation has become more popular as it can be done without the use of equipment and personnel, once a clinical evaluation has been done to determine the state of the circadian timing system. This intervention will be the focus of this meta analysis.

The presence of different forms of sleep deprivation speaks to the influence of sleep manipulation on the functioning of the circadian clock. In certain forms of depression, there is evidence of disturbances within the circadian timing system. Examples of such problems are seen in variables such as the daily rhythms for temperature (Lee, 1988) or the progression of sleep stages throughout the sleep cycle, known as sleep architecture (Goetz, Puig-Antich, Dahl et al., 1991). The hypothesized difference between one form of sleep deprivation and another is found in the control that it exerts at given points in the circadian clock, and how it serves to correct the concurrently disturbed rhythms in depression.

Given the large number of studies from the international literature to which Wu & Bunney (1990) refer, one might speculate that a valid and reliable overall effect size could be derived from these different sleep deprivation intervention strategies. However, this is not the case. Across the sleep deprivation literature, certain patterns exist that obfuscate the findings of the available studies. Examples of these trends include diagnostically heterogeneous samples of subjects, concurrent use of psychotropic medications (e.g., antidepressants, antipsychotics, anxiolytics) that are known to alter biological rhythms and sleep, and inadequate measures of shifts in the circadian timing system as a result of sleep deprivation interventions. The lattermost

trend is evident in studies which *exclusively* use paper and pencil measures such as depression scales/instruments to determine the effectiveness of such a complex intervention as one of the sleep deprivation therapies.

The idea of determining an effect size for what have been traditionally referred to as *psychiatric* interventions is a relatively novel approach. Until very recently, most interventions in psychiatry were either interpersonal, psychopharmacologic or both depending on, among other things, the condition and resources of the person seeking help. Early attempts to quantify effect sizes of psychiatric intervention is seen in the group of meta analytic studies that explores the effectiveness of what has been loosely termed *psychotherapy* (Matt, 1989; Svartberg & Stiles, 1991). While these studies have dealt mainly with adult populations, other studies have exclusively examined the child psychotherapy outcome research (Weiss & Weisz, 1990). Germane to the issue of effect size of intervention strategies in mood disturbance, several meta-analyses exist . One renowned study examines the effectiveness of cognitive therapy for depression (Dobson, 1989) while another commonly cited studies examine a meta analytic evaluation of the effectiveness of *physical* treatments used in psychotic or delusional depression (Parker, Roy, Hadzi-Pavlovic & Pedic, 1992). The physical therapies in the Parker and colleagues (1992) study were limited to electroconvulsive therapy and combinations of antidepressant and antipsychotic drugs. There is no single recognition of nonpharmacologic interventions, such as sleep deprivation therapies, aimed at correction of biological rhythm disturbance in depression in either of the distinguished meta analyses dealing with depression.

Criteria for inclusion in this meta analysis are: (1) published studies only; (2) English language; (3) use of late partial sleep deprivation (LPSD) only or in comparison with other forms of sleep deprivation; and (4) use of LPSD as an intervention strategy in depression. A literature review generated 10 studies between 1980 and 1993 that dealt with the use of late partial sleep deprivation in the treatment of depression. Two of the 10 studies were eliminated. The first of these two (Höchli, Trachsler, Luckner & Woggon, 1985) was eliminated because while it dealt with LPSD and depression, its main focus was on depressive syndromes in schizophrenic disorders. It was thought that the focus of this study truly focused on schizophrenics, rather than those with a primary depressive disorder. The second study to be eliminated was by Holsboer-Trachsler, Weidemann & Holsboer (1988). The reason for eliminating this study was that it was believed to be the exact same study that was published earlier (Holsboer-Trachsler & Ernst, 1986) under a different title. Data from the two studies matched identically, and hence as a repeat of an already included study in the meta analysis, it was disqualified. Table 2.1 lists all studies included in this meta analysis, and offers descriptions of the study's characteristics.

The computations for this meta analysis were done using the DSTAT software program for meta analytic reviews of research literature (Johnson, 1989). Johnson worked with Hodges and Olkin (1985) at Stanford University while developing this program, which computes effect sizes on appropriate data as outlined by Cohen (1988). Table 2.2 presents information concerning the effect sizes derived through this analysis. Effect sizes approximating zero indicate no differential advantage for LPSD over the control or comparison treatment strategy.

Table 2.1 - Characteristics of Partial Sleep Deprivation Studies (Page 1)

Study	*Sample*	*N*	*Design*
Schilgen & Tölle (1980)	"Endogenous" depressives (25 unipolar, 5 bipolar)	30 † (18 Females, 12 Males)	Quasi-experimental
Holsboer-Trachsler & Ernst (1986)	Depressives (10 unipolar, 4 bipolar, 7 schizoaffective, 6 neurotic depressives, 2 schizophrenics, 1 personality disorder)	30 † (25 Females, 5 Males)	'Naturalistic clinical trial'
Elsenga, Beersma, Van den Hoofdakker (1990)	"Endogenous" depressives (Unclear as to % bipolar vs unipolar)	30 § (19 Females, 11 Males)	Quasi-experimental
Szuba, Baxter, Fairbanks, Guze & Schwartz (1991)	"Mixed" depressives (24 unipolar, 9 bipolar I, 4 bipolar II)	37 † (24 Females, 13 Males)	Quasi-experimental
Sack, Duncan, Rosenthal, Mendelson & Wehr (1988)	"Mixed" depressives (8 unipolar, 10 bipolar)	18 § (14 Females, 4 Males)	Balanced order crossover
Giedke, Geilenkirchen & Hause (1992)	"Mixed" depressives (26 major depressives, 4 schizoaffectives)	30 § (18 Females, 12 Males)	Balanced order crossover
Dessauer & Tölle (1985)	"Mixed" depressives (26 unipolar, 6 bipolar)	32 § (23 Females, 11 Males)	Quasi-experimental
Baxter, Liston, Schwartz, Altschuler, Wilkins, Richeimer & Guze (1986)	"Mixed" depressives (7 unipolar, 5 bipolar)	12 § (7 Females, 4 Males)	Quasi-experimental

† - Voluntary sample § - Voluntary sample with randomization to groups

The details of the treatment comparison designs are as follows: 4 studies

Table 2.1 - Characteristics of Partial Sleep Deprivation Studies (Page 2)

Study	*Duration of Intervention*	*Measures Used*
Schilgen et al. (1980)	1 night Slept 9PM to 130AM	Bojanovsky & Chloupkova (a 'derivation' of the HAM-D)
Holsboer-Trachsler & Ernst (1986)	3 nights w/i 1 week Slept 9PM to 130AM	HAM-D (sleep items were omitted) VonZerssen Depression, DST - 2 days before and 1 day after PSD
Elsenga et al. (1990)	Sleep schedule as follows: TSD-Recovery-TSD-Recovery followed by random assignment to TSD, EPSD or LPSD	HAM-D at baseline VonZerssen Depression, Sleep EEG Rectal temperatures
Szuba et al. (1991)	1 night Slept 9PM to 2AM	HAM-D POMS
Sack et al. (1988)	2 nights PSD in 1 week with balanced randomization to 2 nights PSD in week 2 [early vs late]	Bunney-Hamburg GAS VAS-D Sleep EEG
Giedke et al. (1992)	1 night PSD followed by one night recovery; crossover to alternate treatment with same schedule	AMS BRMS GVA
Dessauer & Tölle (1985)	5 LPSD Tx's at 5 day intervals. 2 groups: antidepressants alone or antidepressants and partial sleep deprivation	Bojanovsky & Chloupkova Luria's VAS - Mood
Baxter et al. (1986)	Ss randomized to 1 of 3 groups: PSD + lithium PSD + placebo or lithium alone. 1 night of LPSD in all groups	BDI (short version) SCRS HAM-D (augmented)

BDI - Beck Depression Inventory
HAM-D - Hamilton Rating Scale for Depression
SCRS - Short Clinical Rating Scale
VAS-D - Visual Analogue Scale - Depression
POMS - Profile of Mood State
AMS - Adjective Mood Scale
GVA - Global Vigor & Affect (a visual analogue scale)
DST - Dexamethasone Suppression Test
LPSD - Late Partial Sleep Deprivation
EPSD - Early Partial Sleep Deprivation
TSD - Total Sleep Deprivation

Table 2.2

Derived Effect Sizes in Studies in Present Meta Analysis

Statistic Used: $d = | X_{con} - X_{tx} | \ / \ SD_p$

Study	Effect Size	Source of Effect
Schilgen & Tölle (1980)	0.87 (p=.002) 0.78 (p=.005)	Pre/post AM HAM-D scores Pre/post PM HAM-D scores
Halsboer-Traschler & Ernst (1986)	1.15 (p=.045) 0.55 (p=.31)	Δ in HAM-D nights 1 & 3 of PSD Overall effect
Elsenga, Beersma & Van den Hoofdakker (1990)	0.68 (p=.01) 0.19 (p=.48)	Sleep efficiency change between TSD & EPSD. Sleep efficiency change [NB: LPSD & EPSD labels are opposite of what is reported in all other studies]
Szuba, Baxter, Fairbanks, Guze & Schwartz (1991)	0.64 (p=.09)[1] 0.9 (p=.79)[2]	Pre/post 6 item HAM-D scores with LPSD in responders (1) and nonresponders (2)
Sack, Duncan, Rosenthal, Mendelsen & Wehr (1988)	1.6 (p<.001)	Pre/post Global Depression Ratings with LPSD
Giedke, Geilenkirchen & Hauser (1992)	0.42 (p=.139)[1] 0.66 (p=.02)[2]	1-Pre/post BMRS score with LPSD 2-Difference in sleep efficiency between LPSD and EPSD
Dessauer, Goetze & Tölle (1985)	0.07 (p=.85)	Post intervention [LPSD] score between group rx'd with antidepressant drugs alone vs drugs + LPSD
Baxter, Liston, Schwartz, Altschuler, Richeimer & Guze (1986)	1.5 (p=.045)	Depression scores from LPSD vs lithium alone groups on day 2 of intervention

The details of the treatment comparison designs are as follows: 4 studies reported LPSD as the sole treatment condition; 2 studies compared LPSD to early partial sleep deprivation (EPSD); 2 studies reported three treatment conditions. In the lattermost category, one study had subjects go through two nights of total sleep deprivation (TSD), interspersed with a night of recovery sleep before randomizing the subjects to either EPSD or LPSD (Elsenga, Beersma, VandenHoofdakker, 1990). The other study in this category randomized subjects to one of three treatments: LPSD + lithium; LPSD + placebo; and lithium alone. Discussion of results will be according to the aforementioned categories. Included in the discussion of results will be a critique of methodologic concerns germane to each category of studies.

The calculation of the effect sizes was fully dependent on the data available in each of the studies. When there were means and standard deviations available, the effect sizes were equal to *d*, the formula for which is located in Table 2.2. When *t* values were presented, needed data were estimated from $t = Mean_{Pre - Post}/(SD_{Pre - Post}/\sqrt{N})$. Since $SD^2_{Pre - Post} = (SD^2_{Pre} - SD^2_{Post} - 2r_{Pre - Post} SD_{Pre} - SD_{Post})$. This was done by DSTAT, which also makes assumptions about the correlation between pre and post scores as well as the standard deviations. For the sake of calculations, the assumption was made that SD_{Pre} was equal to SD_{Post}. Given these calculations, *d* was calculated, allowing for a common metric across the eight studies.

Late Partial Sleep Deprivation Alone. The mean effect size for these studies was .676, indicating a moderately strong effect. Findings across these four studies showed that in endogenous depressives, LPSD yielded a greater effect on depression in the morning than in the evening, based on evaluation with psychometric

instrumentation designed to measure depression (Schilgen & Tölle, 1980). When examining the effect of repeated LPSD treatments, the effect was significantly greater after three nights of LPSD than one night (p=.045) in those who initially responded to one night. The overall effect however, was not significant (Holsboer-Trachsler & Ernst, 1986). Other studies showed that the effect of LPSD was either not significantly evident or absent (Szuba et al., 1991; Dessauer, Goetz & Tölle, 1985). These findings are in direct contradiction with the anecdotal report by Szuba and colleagues (1991) that LPSD produces an acute mood improvement in 60% of patients with major depression. The reason for the dissonance in findings may be explainable by examining methodologic issues.

Across these four studies, several threats to validity exist, which may help to understand the calculated effect sizes. First, all of these studies used diagnostically heterogeneous samples, some consisting exclusively of subjects who were diagnosed with mood disorders. Within the mood disordered group, however, there still exists considerable diversity. Subjects with bipolar disorder who are depressed are treated in the same fashion as non-bipolar subjects who also are depressed. This is a major conceptual flaw in the ways depression is understood and creates difficulties in research designs that treat such diversity uniformly. One study, however, used subjects from five distinct diagnostic categories. In attempting to determine the effect of LPSD on a diagnostically homogeneous group such as those with major (unipolar) depressive disorder from the existing literature, the diagnostic heterogeneity of the subjects surely obscures findings for a specific subgroup such as those with major depression. This is a clear circumstance where interaction of selection and treatment

present problems to the external validity of the findings.

The reliability of measures comes into question as many of the depression instruments have been altered to meet the needs of the investigator. Such arbitrary adjustments to research instrumentation disturbs the psychometric properties of the instruments. In terms of construct validity, there is evidence of mono method bias and inadequate preoperational explication of constructs. Such trends are evident in the lack of measures to evaluate the depressed person's chronotype, or to examine other indices of depression such as altered sleep architecture.

Aside from the above noted issues, not one study in this group discussed reliability or validity of the measures used. In some cases, there was evidence of using statistics inappropriately, e.g., use of repeated t tests when ANOVA may have been a more appropriate test. These issues contribute to a larger set of concerns related to the adequacy of the findings of these studies.

Comparisons of EPSD with LPSD. The mean effect size for this group of two studies was 0.89, indicating a difference of less than one standard deviation between the means of the two groups in these studies, a strong effect. However, the findings in this category are conflicting. On the one hand, there is evidence of a significant improvement in sleep efficiency between EPSD and LPSD (Giedke et al., 1992). One could speculate that since there is improvement in sleep efficiency, there is likely to be underlying sleep architecture changes that correspond to this improvement. Given the belief that abatement or amelioration of depressive symptoms correspond to improvements in sleep architecture, it is perplexing to also see an insignificant change in depression scores between pre and post LPSD intervention. Findings of another

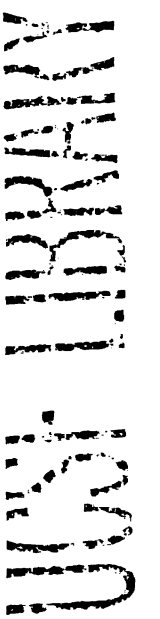
study in this grouping yield a significant effect size with LPSD but not with EPSD (Sack et al., 1988). The data comes into question here as there is a marked trend towards improvement in mood before any intervention is initiated! The basis for such a trend is unclear, but brings the results into question for further evaluation of placebo effects.

In terms of the evaluation of methodologic concerns from these studies, they share similar trends as noted in the group of studies on *LPSD alone*. The threats to conclusion validity, internal validity, construct validity and external validity previously noted are repeated in this set of studies.

Comparison of Three Treatment Conditions. The mean effect size for this group of two studies is 0.79 There is a significant trend in this group of studies that demonstrates improvement in sleep stages 3 & 4 in EPSD compared to TSD (Elsenga et al., 1990). The perplexing issue here is that Elsenga and colleagues (1990) refer to EPSD as LPSD is described in the rest of the literature. That technicality aside, there is a possibility that the findings of Giedke and colleagues (1992) concerning sleep stage improvement following sleep deprivation intervention are replicated in the work of Elsenga and colleagues (1990). Because the investigators in both of these studies do not distinguish responders versus nonresponders by diagnostic category, it is difficult to precisely determine who is responding to which intervention. Additionally, the findings of both of these studies are muddled by the addition of psychotropic drugs.

For example, in one study Baxter and colleagues (1986) are specifically testing the effectiveness of lithium in its ability to augment partial sleep deprivation. The investigators control for extraneous effects from medications by keeping subjects off

all psychotropics for five days prior to the start of the study. However, they then permit the use of a hypnotic to facilitate sleep during the data collection period. The use of a hypnotic drug is likely to cloud the effect of the lithium, albeit for a short period of time, as it may effect the subject's self perception of mood. Given that Baxter and colleagues (1986) exclusively use depression rating instruments as their indicators of mood change, the use of a hypnotic contributes a confounding influence. What Baxter and colleagues (1986) did find was a significant effect (d=1.5) between the LPSD group (LPSD + placebo and LPSD + lithium) and the lithium alone group on the second day of sleep deprivation. In other words, the group receiving LPSD demonstrated a significant reduction in depression when compared to those receiving lithium alone. Such a finding may correspond to the finding in the Holsboer & Ernst (1986) study which demonstrated significant improvement with three nights of LPSD compared to one night. Again, it is difficult to discern who is responding to what intervention, given the diagnostic heterogeneity of the samples.



Issues of Design Validity in Studies of Sleep Deprivation in Depression

Addressing the Construct Validity of Depression. Within the body of literature addressing effectiveness of sleep deprivation therapies in depression, several threats to construct validity are evident. Select studies are reviewed here, and a summary of the study's features are located in Table 2.3. Confounding influences abound in this type of research, and many investigators have failed to address these issues in their work. For example, many investigators exploring the effectiveness of sleep deprivation or phototherapy in depression tend to treat depression as if it were a

Table 2.3

Select Studies of Sleep Deprivation in Depression (Page 1)

Study	*Design*	*Sample*	*Focus*
Souetre, Salvati, Pringuey, Plasse, Savelli, Darcourt (1987)	Quasi-experimental	N=5 (Bipolar Ss)	Phase advance biological rhythms using sleep deprivation
Sack, Duncan, Rosenthal, Mendelson and Wehr (1988)	Balanced order crossover	N=16 (Depressed Ss)	To test the effectiveness of early (PSD-E) versus late (PSD-L) partial sleep deprivation in med free inpatient subjects.
Post, Kotin & Goodwin (1976)	Quasi-experimental	N=19 (Depressed, bipolar and 'atypical' mood sx)	To test the effect of one night of total sleep deprivation on depression and central amine metabolism.
Dessauer, Goetze & Tolle (1985)	Quasi-experimental Repeated treatment Non-equivalent group	N=32 (Depressed Ss)	To examine differences between drug tx alone and drug tx with an adjunct of PSD-L
Knowles, Southmayd, Delva, Prowse, MacLean, Cairns, Letemendia & Waldron (1981)	Controlled single cases; repeated measures	N=6 (Uni & bipolar)	To examine the effects of TSD on the course of major depression
Halsboer-Trachsler, Wiedemann & Halsboer (1988)	Quasi-experimental Repeated treatment	N=30 (Ss from 6 different dx clusters related to various forms of depression)	To examine the clinical effects of serial PSD-L in a heterogeneous group of depressed individuals

Table 2.3

Select Studies of Sleep Deprivation in Depression (page 2)

Study	*Interventions/Measures*	*Data Analysis*	*Findings*
Souetre et al. (1987)	One night of late partial sleep deprivation (PSD) No EEG measures HAM-D	Descriptive t tests Correlations	All subjects improved with PSD; 4 of 5 Ss had sustained remission.
Sack et al. (1988)	2 nights PSD-E followed by 7 day washout then 2 nights of PSD-L Sleep EEG monitoring Bunney/ Hamburg Global Assessment Scale	Paired t tests Spectral analysis of EEG	Negative correlation between response to PSD and sleep duration in the PSD-L situation.
Post et al. (1976)	Total sleep deprivation (TSD)for one night; bioassay measures of circadian functioning EEG Monitoring; Nurse's depression ratings	Descriptive Student t tests for independent samples	Effects of TSD were confined to the day following TSD; one subject became hypomanic w/ TSD.
Dessauer et al. (1985)	Drugs only or drugs plus 5 PSD-L treatments done at 5 day intervals AMS-Luria BCRS	Descriptive t tests Multiple regression	Tx with PSD-L and anti-depressant drugs is useful in drug refractory depressed states, and more effective than either treatment alone.
Knowles et al. (1981)	Two cycles of TSD three days apart; Clinical interviews	Multivariate ANOVA	First TSD was effective but transient in effect; Second TSD was less effective than the first.
Halsboer-Trachsler et al. (1988)	PSD-L three times within one week Monitoring of dexamethasone suppression tests during PSD-L intervention HRS	Descriptive, 2 tailed t tests, Multiple regression of biological assays	Difficult to determine, given that some of the Ss were medicated while others were not. Of the medicated Ss, 37% responded favorably.

HAM-D - Hamilton Rating Scale for Depression
AMS-L - Analogue Mood Scale - Luria
BCRS - Bojanovsky and Chluopkova's Ratinng Scale for depression
HRS - Hamilton Rating Scale

homogeneous phenomenon. In many of the samples from studies in this area of research, persons with different types of depression are included in studies, and are treated as if their depressions were uniform. From a psychobiologic perspective, depression in bipolar disease is likely to be a very different phenomenon than depression in a post partum mother. However, the literature does not make such a distinction; many forms of depression are dealt with as if they were conceptually and psychobiologically consistent. Such inattention to potential complicating influences may in part be a direct result of not understanding the multidimensionality of the construct under study, and hence falling victim to inadequate preoperational explication of the construct itself, failing to fully explain the concept under investigation before applying appropriate study methods to examine and/or test it. Mono-operation and mono-method biases are common in these studies. Mono-operational bias refers to the operationalization of one dimension of a concept or construct under investigation. Such a problem could be remedied with multiple measures of the same construct. Mono-method bias is similar to mono-operational bias inasmuch as it is the mistake of measuring only one dimension of a construct under study. Sleep is a particularly sensitive phenomenon which is likely to be affected by anything that intervenes in usual established sleep/wake patterns; the risk of interaction and treatment in sleep deprivation therapy research is quite high.

The issue of inadequate preoperational explication of constructs is evident in the works of Dessauer, Goetze & Tolle (1985), as well as Post, Kotin and Goodwin (1976). In the Dessauer et al (1985) study, the investigators attempted to evaluate the effect of periodic sleep deprivation in drug refractory depression. Given their lack of

an explicit definition of sleep deprivation, it is not clear what actually occurred with the subjects during sleep deprivation nights. For example, the investigators vaguely described sleep deprivation as *second half of the night from 01.30 hours*, but if subjects slept from 19.00 hours until 01.30 hours, no true sleep deprivation occurred; the subjects simply phase shifted their sleep hours to an earlier period. Post et al (1976) demonstrate a pattern of some of the earlier sleep researchers which truly illustrates the issue of inadequate preoperational explication of constructs. These investigators examined the effects of sleep deprivation on mood and central amine metabolism in depressed patients without ever defining sleep or its measurement. The researchers relied totally on a combination of patient self report, biological assays of amine metabolism and nurse's ratings based on observation. Such an oversight greatly undermines the validity of the study, but perhaps serves as an index of the under representation of the construct at that point in time.

The issue of mono-operation bias is one that was more common to the early sleep studies than to contemporary investigations. For example, as more has been learned about the complexity of sleep disturbance in depression, it has become clear that singular operationalizations of sleep are inadequate to understand the fuller dimensions of the construct. In the past it was common to see sleep operationalized under electroencephalographic (EEG) parameters alone. Today it is more common to see sleep *architecture* (e.g., stages of sleep) operationalized with EEG, and other circadian dimensions of sleep disturbance operationalized through temperature monitoring (Lee, 1988; Elsenga & Van den Hoofdakker, 1988) or other biobehavioral, circadian based indices such as neurohormones (Baumgartner, Graf, Kurten et al,

1990). Pflug (1976) as well as Dessauer, Goetze and Tolle (1985) demonstrate mono-operation bias in their work by using only paper and pencil measures of depression in their studies which examine the effect of periodic sleep deprivation in drug refractory depression.

Interaction of testing and treatment presents a particularly challenging task to the sleep researcher investigating an intervention strategy such as sleep deprivation therapy. For example, when an investigator studies a subject's sleep using routine measures such as sleep EEG and temperature monitoring, there are inherent tactile changes for the subject as a result of the equipment being in place. The presence of the equipment is likely to alter the subject's perceptions, and potentially yield some anxiety or apprehension, both of which are generally antithetical to quality sleep. In the case of sleep deprivation studies, such a shift in internal state can greatly affect the validity of the measures being utilized. The potential disturbance as a result of the placement of sleep monitoring equipment is known as *first night effect* (Kupfer, Frank & Elhers, 1989) and is often corrected by a second night of data collection and recognizing the potential confounding influences from the first night's data during its interpretation.

This issue of interaction of testing and treatment merits consideration from the perspective of clinical versus research demands; it courts issues germane to sensitivity and specificity of measures utilized in the course of the research. For example, in addition to the studies already partially critiqued, Sack et al, (1988), Halsboer-Trachsler, Wiedemann & Halsboer (1988) and Souetre et al (1987) all explore various dimensions of sleep deprivation techniques with depressed subjects.

These subjects however, are also *patients* and none of the investigators address the issue of results from the perspective of empirical noteworthiness versus clinical effectiveness. These examples are given to substantiate the impression that little effort has been made to create distinctions in the arenas of testing treatment interventions in the sleep deprivation literature. Clinicians need to utilize clinical schemata which permit broad categories of behavior to be funnelled into diagnostic classifications. Researchers often seek homogeneous groups, and attempt to determine the differences within such groups, whereas clinicians aim to understand a given person, the *patient.* Such distinctions carry clear implications for construct validity.

Statistical Conclusion Validity

A variety of statistical techniques have been used across the sleep deprivation literature, but the examples which follow characterize the most common trends in analysis. Many of the studies suffer from low statistical power, violated assumptions of statistical tests, unreliability of treatment implementation and most importantly, random heterogeneity of respondents. In sleep deprivation therapy several variables become important for analysis, e.g., sleep architecture variables, indices of mood change and other indicators of underlying or concurrent shifts in the circadian timing system. Many studies choose one or two of these measures. For example, in the Dessauer, Goetze and Tolle (1985) study, the investigators attempt to explore the effects of sleep deprivation on depression. Depression is measured by two separate instruments, a visual analogue scale completed by the subject as well as a depression

rating scale, completed by a rater who is not blind to the research questions. Reliability data are not reported on either instrument. The investigators removed three items from the depression rating scale, which likely diminished the stability of the instrument, and possibly disturbed validity and reliability. The statistical analysis of this study consisted of repeated t tests which examined the differences between the means of the depression rating scale and the visual analogue scale at several different data collection points. One of the major problems with repeated t tests is that they inevitably multiply the overall alpha rate, and yield a Type 1 error. Because researchers are looking at the individual t tests, they sometimes fail to recognize the difficulty created by the repeated use of the t test, and blindly make the error.

An example of low statistical power is found in a variety of the studies, and in no study reviewed were there any indications that power analyses were done. The number of subjects is often in the range of 5 to 16 per study (Sack et al, 1988; Knowles, Southmayd et al, 1981; Souetre et al, 1987). The issue of a small *n* might be corrected with repeated measures, but many of the investigators utilize one or two data collection periods. In the case of the Knowles et al (1981) study, the investigators have 6 subjects and utilize what they call *controlled single case design* whereby the subjects act as their own controls. This design is common in a time series strategy. The methodologic flaw in the Knowles et al (1981) study, however is that the investigators utilize ANOVA across various sleep parameters. Not only are the assumptions of the test violated, but the tests are incongruent with the study's design. With many repeated measures of multiple variables, a more appropriate approach may have been to use MANCOVA. In such an instance an example of the

covariates might be some dimension of sleep architecture (e.g., REM latency) and severity of depression. Other common trends include the use of t tests as the sole analytic strategy when there is the potential to use more appropriate tests. For example, Halsboer-Traschler, Weidemann & Halsboer (1988) examined the effects of serial partial sleep deprivation on depression and dexamethasone suppression test results. They had 30 subjects in the study, and could easily have utilized a two way analysis of variance. Instead, however, they relied exclusively on t tests, which truly diminished the strength of their results with the risk of a galloping alpha rate. Such inclinations are common in this body of literature.

Two remaining threats to statistical conclusion validity exist in this body of literature and include the reliability of treatment implementation and random heterogeneity of respondents. In terms of treatment implementation issues, one problem that exists in all studies reviewed is that of the conditions of data collection. All subjects in these studies were hospitalized, but there is no indication of whether they spent nights in sleep laboratories or if data were collected using ambulatory systems of monitoring. This presents a major threat inasmuch as subjects asked to sleep in a lab are subjected to sleeping in (usually) a small space, surrounded by a variety of equipment and usually a research assistant or two to watch them throughout the entire night. Such conditions certainly produce the *first night effects* previously discussed, but may also yield comparable effects on subsequent nights of testing. On the other hand, ambulatory monitoring allows a greater range of freedom while minimizing the discomforts of the equipment. Its main drawback includes an inability to draw from as many channels of EEG data than might be possible in a sleep laboratory

setting. Other disadvantages include less control within the data collection environment that might effect sleep and the subsequent EEG findings, e.g., snoring bed partners or other noise in the sleeping environment. It becomes imperative to screen for such confounding influences before the EEG is done, in an effort to guard the validity of the findings from the EEG evaluation. Whichever strategy is selected by the investigators, it would be helpful for the reader to know, to facilitate critique of the study findings.

One major issue that transects all studies reviewed here includes random heterogeneity of respondents. Out of all the potential influences in this category, the one that is most prominent is that of gender. All investigators but two (Sack et al, 1988; Dessauer, Goetze & Tolle, 1985) cited the gender of study participants. In those studies where gender of subjects was noted, there was approximately 75% female and 25% male participation (Souetre et al, 1987; Halsboer-Trachsler et al, 1988; Post et al, 1976). In no instance in the studies which mentioned the gender of the subjects was there any discussion of menstrual phase of the women participants. It is known that significant shifts in both temperature and sleep patterns occur in women who are in the luteal phase of the menstrual cycle (Lee, 1988), and no known corollary exists in males. Such a gender-bound characteristic can easily be controlled by studying women during the follicular phase of the menstrual cycle where such shifts are rare, or recognizing these circadian shifts in temperature as normal in women during the luteal phase.

Internal Validity

There are three main threats to internal validity in the literature reviewed for this paper. The threats are history, instrumentation and selection. Each will be reviewed separately.

History. History presents a particularly strong threat to internal validity in the sleep deprivation literature and occurs as a result of various psychotropic medications being started or adjusted to the regimens of the subjects/patients. The inherent difficulty presented by the introduction of new medications or adjustments in existing treatment is that these substances affect the covariance of the variables under study. The Sack et al (1988) and Post et al (1976) studies were the only two of the six studies being critiqued here whose subjects were medication-free throughout the entire investigation. The other four studies either had subjects on varying medication regimens which included antidepressants from several classes and/or neuroleptic drugs (Halsboer-Trachsler et al, 1988; Knowles et al, 1981; Souetre et al, 1987). In these latter studies, it is difficult to discern whether the post intervention results are due to sleep deprivation therapies or simply shifts caused by the psychotropic drugs.

Instrumentation. Instrumentation presents a challenge to the stability of internal validity in several of the studies reviewed. Given the large number of measuring instrument systems, there is a large berth for variance in the sensitivity of measures across studies. While there may be universally accepted calibration factors for EEG equipment and standardized procedures for the interpretation of EEG data, no such parameters exist for other types of instruments used in conjunction with the sleep deprivation studies. A good example of this variance is seen in temperature

monitoring systems, or in laboratory calibrations for biological tests such as the dexamethasone suppression test. In none of the investigations under critique here do the researchers discuss issues of standardization or calibration of their equipment, again pointing to questions of how to interpret the findings.

Selection. The issue of selection is raised in the diagnostic diversity of the subjects participating in the studies. While all of the investigators purported to study depression, a closer look at the diagnostic classifications of the subjects revealed some interesting differences. For example, Souetre et al (1987) exclusively studied persons with bipolar (manic depressive) illness, but called them *endogenous depressives* at several different points in the report. Halsboer-Trachler et al, (1988) had 30 *depressed* subjects in their study who came from six different diagnostic categories including bipolar disorder, schizoaffective psychosis and others from the Research Diagnostic Criteria. The difficulty that such diversity presents is in the distinction of the underlying disorders. For example a person suffering with bipolar mood disorder who is in a depressed phase of the illness may actually be dealing with a different illness than one who carries the diagnosis of major (endogenous) depression; psychobiologically speaking, these are likely to be very different illnesses. The problem in the literature is that the investigators use a variety of diagnostic classification systems whose criteria for a given diagnosis may vary widely. Such an issue raises the question of *who* is actually being studied in these different investigations.

External Validity

When dealing with external validity, one asks questions related to the generalizability of findings across various settings, persons, and time. The threats to external validity in this body of literature include interaction of selection and treatment and interaction of setting and treatment.

Selection. In dealing with interaction of selection and treatment, some of the inherent issues were initially discussed in examining the issue of selection alone. If the persons selected for participation in a study on the effects of a certain type of sleep deprivation on the course of a depressive episode, the group should be diagnostically homogeneous. However, diversity in the subjects who suffer with a homogeneous type of depression is important. In other words, if there is a group of subjects who meet Research Diagnostic Criteria for major depression, and they have no other confounding factors, such as bipolar disease, it will be important to look at women, men, persons of varying ages, various cultural and ethnic backgrounds and disparate geographical locations. Such divergence within a group of persons diagnosed with the same illness is likely to yield very important data on the nature and effectiveness of the intervention strategy on the dependent variable.

Selection and Treatment. The second issue to address here is that of interaction of setting and treatment. While all of the subjects in studies discussed in this review were obtained from inpatient settings, accommodation for confounding influences, such as first night effect were not made. The question comes forth about whether or not first night effects are carried into second and third night effects (or perhaps even longer) if subjects are studied in an environment that is unfamiliar and

filled with equipment and unknown individuals. Given the ready availability of ambulatory monitoring, it seems that collecting data in a familiar and comfortable environment is in the interest of parsimony and convenience for the subjects involved. What such a shift away from the laboratory setting is likely to do is to offer a naturalistic perspective on the data, which could not be replicated if the data were collected in a lab setting.

Trends in the Sleep Deprivation Literature

The findings of this meta-analysis and discussion of design validity bring to light some issues that merit serious attention in the literature related to sleep deprivation intervention in depression. First, it seems clear that investigations are needed to explore the effectiveness of all types of sleep deprivation therapies in diagnostically homogeneous samples. What such research is likely to offer is increased conceptual clarity on who responds to what type of intervention.

Second, there needs to be significant attention paid to issues affecting validity and reliability of the findings. Examples of the trends that merit correction in future research are common in the current literature and include the need for routine use of power analyses, careful attention not to violate assumptions of statistical tests and use of valid and reliable measures. Apropos to the issue of instrumentation, it becomes critical not to disturb the psychometric stability of the instrument by adding or subtracting items to suit the needs of the particular study. This issue of instrument stability is particularly important to the internal validity of the study, as is selection of subjects, resounding the need for homogeneous samples.

The third matter that merits attention for research on sleep deprivation therapies in depression is the need to adequately operationalize the constructs under study. Mood disorders such as depression are not unidimensional experiences, and as such cannot be fully understood with singular measures. There needs to be a broadened understanding and application of principles from the psychobiologic realm to corroborate findings from basic science research with those from the clinical setting. Examples of broadened operationalized constructs in depression include routine assessment of chronotype, and use of biological markers of depression such as alterations in sleep architecture. Efforts in this direction will not only broaden the conceptual understanding of depression, but will also make advances in the efforts to destigmatize mental illness as something *in the mind* but not *in the brain.*

The last point that merits attention of future research is likely to be the source of great challenge to those studying persons diagnosed with psychobiologic illnesses. This issue deals with the interaction of selection of subject and concurrent treatment, particularly psychotropic drugs. While the use of medications is central to the symptom management of many persons diagnosed with various mental illnesses, the presence of such medications obscures the clear perspective on the illness offered by unmedicated persons. This raises ethical issues that need to be seriously considered. However, in the case of depression, there may be those persons who, for one reason or another, are not medicated or are intolerant of the medication's side effects, and for whom there are fewer options. Individuals such as these need to be vigorously recruited into studies that explore the multidimensionality of the depression experience without the potentially confounding influence of psychotropic medications.

The contribution that their participation offers is critical, and opens the door to new understanding of the phenomenon in a way not known before this time.

Given all of the data presented in this section on treatment alternatives in depression, several questions arise. The first question deals with what, among all of these different options for the treatment of depression is the most efficacious. The answer to this question is confounded by a number of variables, the first of which is evaluation of the current research findings. Because of the methodologic issues in the existing literature, the results may appear deceiving, or at least conflicting. The clouding of these results raises the next level of questions.

Appreciating the obfuscated picture presented by the findings, questions dealing with pragmatic dimensions of treatment emerge. What treatment option best suits the needs of the individual, and which approach will be most effective in relieving symptoms? If a person opts for one of the various forms of psychotherapy, and the therapy is effective in relieving the symptoms, then no other option may need to be explored. One of a variety of thymoleptic drugs may be considered. If it is effective and the individual is able to get relief from the symptoms while minimally dealing with potential side effects, then no other option may need to be considered.

However, in clinical work, the fit between need, resource, acceptability of available resource and intervention efficacy often require repeated trials before an effective strategy is determined. Recognizing the potential complexity in meeting all of the aforementioned requirements of a given treatment, it is imperative to expand the available options for intervention to include a range of biologically active and therefore potentially effective treatments. Given the current boom in understanding

pharmacokinetics of the thymoleptics, there has been an increased awareness the biological correlates of both depression and treatment effects. Given these new gains, it is becoming more clear that biologically traceable, therapeutically effective treatment strategies are becoming available which are not pharmacologically based.

Of these treatments, sleep deprivation therapies hold significant promise as viable treatment options when *appropriately* applied. Of course, the issue of *when* and *which* sleep deprivation therapy to use have yet to be fully answered because of the current state of the existing research literature, as previously described. What is clearly needed are well designed studies that control for variables which potentially muddle the perspective on *who responds*. Such designs are likely to include placebo controls, measures to control for medications and drugs of abuse, and controls for potential differences in response related to gender. Additionally, these future studies need to use a variety of self-report and physiologic measures, to provide more data and to contribute to framework through which to better understand the phenomena under study.

CHAPTER THREE

METHODOLOGY

Research Design

This proposed quasi-experimental clinical trial utilized a pretest/post test crossover design to obtain data on depression, fatigue, sleep patterns and circadian temperature rhythm before and after nonpharmacologic treatment for major (nonseasonal, non-bipolar) depression. Participants were randomized to either late partial sleep deprivation or placebo, and whichever intervention was not received during the first phase was done during phase two. Participants were studied in their own homes on nights 1 and 2 pre-intervention followed by nights 3 and 4 of randomized intervention (i.e., placebo or late partial sleep deprivation). Subsequent to the intervention, participants were again studied on nights 5 and 6. While the home environment yields data that is more generalizable to the population of persons with endogenous depression, there are environmental factors that required attention to avoid problems with validity. Examples of such factors include snoring bed partners, environmental noise or children and pets in the household. While those who reported disturbed sleep due to noisy environments were excluded from participating, all participants were asked to keep a six-day sleep diary for the periods during which data were collected, (e.g, baseline, intervention and post intervention). These diaries began two days prior to the two days of intervention in each phase, and continued for the two days following intervention.

All data were collected from participants during the follicular phase of the menstrual cycle to control for variation in circadian rhythm variables altered by ovulation. All participants were medication-free during the study. Before both the placebo and late partial sleep deprivation interventions, all participants gave a urine sample for toxicology to assure drug-free status.

Assumptions

The investigator believes that the following assumptions underlie this research:

1. Circadian adaptation glasses worn during evening hours have no effect on any variable related to mood, fatigue or circadian rhythmicity.

2. Two consecutive nights of late partial sleep deprivation is adequate to demonstrate an antidepressant response in those persons who are likely to have a positive response to the intervention.

3. Fourteen to 21 days is an adequate washout period between active intervention and placebo.

4. Fatigue is conceptually distinct from depression, but may covary with the depressive experience.

Sample

Nature and size of sample. Over 150 women were screened for this study. Of the 150 women who inquired about the protocol, 115 were not eligible. The most common reasons for ineligibility included concurrent use of thymoleptic or rhythm

altering medications, evidence of perimenopausal symptoms or significant concurrent medical illness. The remaining 35 women met inclusion criteria. Of these 35, 26 enrolled and 18 completed the protocol. Reasons cited for either not starting or not completing the protocol included participant concerns that the protocol was too labor intensive, that the idea of a two month commitment was too great, or that the monitoring equipment was not acceptable.

Complete demographic data on the 18 women are located in Appendix I. All participants were women who met DSM-IIIR (APA, 1987) criteria for major depressive disorder. Seventy-two per cent of the participants were medication naive, while the remaining 27% had been through one or more antidepressant medication trials. All of the women who had taken medication in the past had been off medication for at least three months. Only one woman who completed the protocol was a tobacco smoker. Each participant underwent urine toxicology screens for drugs of abuse at both phases of the study. Of the 36 toxicology screens done, four were positive. Two were from the same participant, and were positive for cannabis at both phases. One participant tested positive for amphetamines, but withdrew from the study. The other person tested positive for morphine in the placebo phase, but given the sleep and rhythm-altering effects of this class of drug, these data were not used in the final analysis.

The sample was ethnically diverse, but probably not fully reflective of the diversity in the San Francisco community. This is evidenced by the lack of any participants of Asian heritage. While several women of Asian descent inquired about the study, none of them were interested in pursuing the study beyond the initial phone

contact.

The majority of participants had either some college education or a degree. The mean age was 38.6 years, with a range between 23 to 50 years old. Sixty-five percent of the participants were either single or divorced. Of those who were married or partnered, 75% of them felt mixed emotion about the relationship. Of those who responded to items concerning employment (n=18), 61% were employed. Twenty-eight percent were either suspended from work as a result of their depression, or were unemployed. Forty-four percent of the participants were in some form of psychotherapy.

Power Analysis. The goal of this power analysis is the determination of a sample size given an acceptable level of power (ß) at a given alpha (α) for comparing pre and post measures in this diagnostically homogeneous sample. Calculation of an effect size based on depression rating scales is difficult, given the large number of various scales used in the literature. In many cases, the instruments have been altered to meet the needs of a given study, thus disturbing the psychometric properties of the instrument. Wu and Bunney (1990) reviewed 61 papers from the last 21 years involving 1700 subjects undergoing sleep deprivation. They document a 59% reduction in depressive symptoms across the various depression instruments used. From the literature on nonseasonal depression, pre and post-intervention data using depression scales are available. Pre-intervention data are 19.5 ± 4.1 and post-intervention data are 15.3 ± 5.0, yielding an effect size of .90. Given 1-ß = .80 and α = .05, Cohen (1988) states that the number of subjects needed for adequate power to detect a statistically significant difference would be 25 participants.

Criteria for sample selection. All women who were pre-menopausal and met diagnostic criteria for major depressive disorder (unipolar) were invited to participate in the study. Those interested in participating met with the applicant to discuss the protocol, answer questions and secure subject consent to participate. To maximize homogeneity, participants included younger women with regular menstrual cycles diagnosed with a major depressive disorder only: other forms of mood disorders such as bipolar disorder, depressed, or seasonal depression were excluded. The diagnosis of major depressive disorder was made according to criteria set forth in the Diagnostic and Statistical Manual, 3rd edition, revised (APA, 1987). Potential participants were also screened with the Beck Depression Inventory (Beck et al, 1961) and the Structured Clinical Interview for the DSM-IIIR (Spitzer et al, 1990). Potential participants who were dually diagnosed with major depressive disorder and an active substance abuse disorder were excluded. If dually diagnosed persons have abstained from the substance of abuse for six months, they were eligible for inclusion in this study. It was advantageous to obtain a homogenous sample in terms of age, gender, concurrent medical illnesses and medication since these can influence data related to sleep patterns and circadian rhythms. Participants were ovulating women between the ages of 21-50, diagnosed with a major depressive episode and no concurrent medical illnesses. In no instance were potential participants excluded on the basis of culture or ethnicity. Given the confounding influence of medications on both the course of depression and concurrent circadian variables, all participants were free of psychotropic drugs during the data collection period. In order to control for variance in temperature and sleep data related to the menstrual cycle and the possibility of a

superimposed premenstrual syndrome, sleep and temperature data were collected only during the follicular phase of the menstrual cycle. Lee (1988) points out that the average acrophase may occur approximately two hours earlier and REM latency is earlier when temperature is higher in females after ovulation. Given the potential impact of rotating work schedules on sleep/wake cycles, persons working rotating schedules were excluded from this study.

Human subjects assurance and consent process. This study received approval from the Committee on Human Research at the Office of Research Affairs at the University of California, San Francisco as of 1 July 1992.

Potential participants either self referred as a result of having seen an advertisement for the study, or were referred to the investigator from an outpatient psychiatric nursing practice that specializes in the care and treatment of persons diagnosed with depressive and panic disorders. For new clients diagnosed with a major depressive disorder at the outpatient practice, clinical nurse specialist staff informed the client of this study, and determined the level of interest of the individual in participating in this study. At that time, potential participants were screened according to inclusion/exclusion criteria. For those self-referring, the investigator talked with them over the phone initially, to screen according to the inclusion criteria. If a potential participant met inclusion criteria and was interested in participating, the investigator scheduled an appointment to meet the person at a convenient location and time. At that time, the consent form was reviewed and the data collection instruments were explained. If the individual agreed to participate, the consent form was signed and dates for data collection were scheduled. Both participant and investigator kept a

signed copy of the consent form. Participants were assured that they could decline to answer any question that made them feel uncomfortable, and that they could withdraw from the study at any time. In light of the content of this study and the need to protect participant's confidentiality, the investigator assigned each participant a code number. All data collection instruments were marked with this code. The investigator kept a record of the participant's names and corresponding codes until the end of the study. At that time, the record of names/codes were destroyed, fully protecting the individual's identity in the final analysis. In no instance did any participant's name appear in any form or any written document except for the consent form and the investigator's name/code book.

The number of potentially hazardous procedures related to this study were nominal, but included a possibility of skin irritation from the collodion used to attach EEG leads to the skin. Persons undergoing the sleep deprivation intervention were likely to have a transient increase in fatigue as a result of the intervention. Additionally, there was a possibility of some minor sensory deprivation if a participant awakened during the placebo phase of the study, and had to wear the circadian adaptation glasses for any period of time.

The most important benefit was to the subjects and included the possible amelioration of depressive symptoms and restoration of well being. A second important benefit was to the knowledge base related to non-pharmacologic intervention in depression. A randomized clinical trial as was conducted here was nonexistent in the literature. The data from this study offered new and important information on alternative approaches to depressive illness and the care of those

suffering with such a disorder.

Data Collection Methods

Aim #1: to describe sleep, temperature, fatigue and mood patterns of women diagnosed with a major (unipolar) depressive episode prior to intervention (baseline).

Aim #2: to determine relationships between complaints of fatigue, depression and physiologic variables related to sleep and circadian rhythm.

Measurement of Sleep Stages. Sleep patterns were monitored for two consecutive nights by electroencephalogram (EEG) and electooculogram (EOG), using standardized techniques (Rechtschaffen & Kales, 1968). The EEG were recorded from the C3 and C4 electrode placement of the International 10-20 System. Electrooculogram were recorded from electrodes placed at the outer canthus of each eye. These four EEG/EOG sites were referenced to the ipsilateral mastoid (A1 or A2). The Medilog 9000 9-channel ambulatory monitoring system was used to record these four channels on C-120 cassette tapes at a rate of 2mm/second. The signals were calibrated using the Medilog XC-90-B calibrator unit to obtain a sine wave of 100 microvolts.

Scoring of the EEG and EOG data resulted in data reduction to include the following sleep parameters: a. Sleep onset latency (SOL) from lights out to first full minute of Stage 2; b.Total sleep time (TST) and sleep period time (SPT); c. Sleep disturbance (fragmentation) index (Stage 0 [wake]as a percentage of SPT), and Sleep efficiency index (ratio of TST to SPT); d. Light sleep (Stages 1 and 2 as a percentage of SPT); e. Delta sleep (Deep sleep stages 3 and 4 as a percentage of SPT); f. Rapid

eye movement sleep (REM), scored as minutes from SOL to first REM period and REM sleep as a percentage of SPT. The second night of data was used in analysis to control for any *first night effect* or to assure that the participant had adapted to the presence of the sleep recording equipment.

Measurement of Chronotype. Core temperature was recorded using a CorTemp telemetry system to monitor temperature continuously with precalibrated ingestible sensors. The sensors are 22.6 mm in length and 10.7 mm in diameter. These sensors, encapsulated in an FDA-approved coating of dimethyl polysiloxane, contain an oscillating quartz crystal, similar to a quartz wrist watch. The sensor oscillates at a frequency of 262 kH; a frequency lower than a doppler or a radio signal. There is no heat, no radiation, and no magnetism from the sensor. The signal is detected by a magnetic antenna and transduced into a temperature measure. The FDA has classified the device as a Class II medical device. The device is contraindicated for any person with a history of swallowing or gastrointestinal problems. In current research using women subjects of childbearing age (Kathryn Lee, P.I.), there has been no difficulty swallowing the sensor. Subjects were supervised by the researcher while swallowing the sensor. Recording began on the first morning of each data collection point, and continued for 48 hours or until sensor was passed. Temperature was measured continuously, recorded in five minute intervals, and fitted to a cosinusoidal wave using the methods of least squares and assuming a 24 hour period length. The mesor (24 hour rhythm adjusted mean), amplitude, and acrophase (clock time of the peak) for temperature was determined from the fitted rhythm which met minimum criteria of $R^2 > .55$.

Measurement of Depression. In order to estimate diurnal changes in mood, the Beck Depression Inventory (BDI) were used prior to sleep onset and upon awakening during the two consecutive days of sleep and circadian rhythm monitoring at each of the *two* data collection points. The BDI is a 13-item instrument designed to measure depression. The response alternatives for each item can range from zero (no depression) to three (severe depression). The items correspond to a specific manifestation of depression. The BDI takes approximately 5 minutes to complete, and is scored by summing the individual responses for a total score range of 0-39. Internal consistency has been evaluated with more than 200 patients. Spearman-Brown reliability coefficient was noted to be 0.93. Content validity was tested by correlating scores with other measures of depression. The BDI correlates at 0.75 with the Minnesota Multiphasic Personality Inventory (MMPI) subscale for depression (Beck et al, 1961). Categorization of scores is according to severity of depression on the BDI. On the 13 item BDI, the scores are interpreted as follows: 0-4 none to minimal depression; 5-7 mild depression; 8-15 moderate depression; 16-39 severe depression.

Measurement of Fatigue. Because fatigue is a common confounding complaint associated with depression, and because the sleep deprivation interventions may exacerbate fatigue, the Visual Analogue Scale - Fatigue (Lee et al, 1990) was administered with the depression measures. This instrument consists of 18 items developed to measure perceived fatigue severity. It contains two subscales: fatigue (13 items) and energy (5 items). The instrument has been tested on 75 healthy subjects and 57 sleep disorder patients. Internal consistency reliability ranges between 0.91-0.96. There is concurrent validity of the VAS-F with the Stanford

Sleepiness Scale and the Profile of Mood States subscales score for fatigue and vigor, and divergent validity with depression, anger and anxiety subscales. The VAS-F is easy to complete in less than two minutes. In order to assess diurnal variation, study participants completed the VAS-F prior to sleep onset and upon awakening during the two consecutive days of sleep and circadian rhythm monitoring at each of the four data collection points.

Aim #3: to test the effect of partial sleep deprivation (LPSD) and placebo on mood state in ovulating women diagnosed with major (unipolar) depression.

Measurement of Intervention Effects. For the purpose of this study, intervention was narrowed to late partial sleep deprivation (LPSD) compared to placebo. In order to examine the effect of LPSD on depression, the previously mentioned measurements of sleep, chronotype, mood and fatigue were assessed at four different data collection points, pre- and post random assignment to active intervention and placebo.

The sleep deprivation intervention was in the form of LPSD, in which participants were instructed to sleep from their normal bedtime to four hours later, at which time they were awakened with a phone call from the investigator and instructed to begin their day. In addition to being awake after four hours of sleep, they were instructed not to nap during the day. This pattern was repeated for two days following pre-intervention assessment, and prior to the two day post -intervention assessment.

In addition to LPSD, the alternate intervention involved a placebo. The placebo consisted of wearing a pair of "circadian adaptation glasses", designed to block out sunlight. These glasses were worn in the evening from 7 PM until bedtime, and at any

point when the participant awakened during the night (eg, to use the bathroom, etc). The glasses were removed during sleep and were no longer required once the person was awake in the morning, or after 6 AM, whichever came first. The placebo provided an inactive intervention to compare with the psychobiologically active intervention of LPSD. From these data, the investigator analyzed the effect of the interventions on the dependent mood variable, depression, as well as sleep, fatigue and circadian variables.

Procedure

The data collection period for each participant was six days during the follicular phase of the menstrual cycle during two consecutive months, to allow for both the active and placebo interventions. A random urine toxicology screen was taken prior to both the active intervention and the placebo. Within the two-six day data collection periods, participants underwent two days of pre-intervention data collection consisting of two consecutive nights of polysomnography and concurrently, 48 hours of core body temperature monitoring. The first night of sleep data at each point was necessary for adaptation to the presence of recording equipment; the second night of data was used for actual analysis. There were pre and post intervention measures for each variable of sleep, core temperature and mood (depression and fatigue). Additionally, participants were asked to keep continuous diaries of sleep, naps, exercise and food intake, including alcohol and caffeine during the six day data collection periods. On days three and four of the first phase of the study, subjects were randomized to one of two intervention groups: placebo or late partial sleep deprivation. On the last two days of

the data collection periods, participants had a post intervention evaluation which is exactly the same sequence as the pre-intervention evaluation. Whichever intervention was not done during the first month, was done in the second month of data collection.

Data Analysis

Appropriate data analysis for this study included descriptive techniques such as visual plots of individual subjects over time, and means/standard deviations, medians, and ranges for the group before and after intervention and placebo. Outlying data for individual subjects were scrutinized for possible confounding variables. A two tailed alpha of $p < .05$ was indicative of statistical significance for rejecting or failing to reject the hypotheses.

Aim # 1: Descriptive data were used to examine pre-intervention characteristics of the sample. Appropriate data analysis for descriptive measures included measures of central tendency (means, standard deviations, medians and ranges) and frequency percentages for the group.

Aim # 2: Pearson product moment coefficients were used to measure relationships between the continuous variables of sleep and temperature rhythm parameters, depression and fatigue severity scores.

Aim # 3: In order to analyze outcome variables, Mann-Whitney U tests were used to examine pre- and post intervention differences.

CHAPTER FOUR

RESULTS

Introduction

This chapter presents the results of a study which examined the effectiveness of late partial sleep deprivation (LPSD) as compared with placebo on depression and fatigue in a sample of young women diagnosed with major depressive disorder. The first section of this chapter examines data related to participant acceptance into the study in addition to descriptive data depicting the characteristics of the participants. Second, the strategy used to deal with missing data is presented. In the third section, there is discussion of reliability testing of the instrumentation used in this study. In the last section, there is a presentation of data related to each of the six hypotheses under three major aims.

Acceptance Rates

Participants were recruited through two main mechanisms: self referral from posters placed throughout the San Francisco community and referral from Turning Point Center, a clinical center for the care and treatment of persons diagnosed with mood disorders. One hundred and fifty women either responded to the flyers or were referred for initial screening for possible inclusion into the study.

Of the 150 women who inquired about the protocol, 115 were not eligible. The most common reasons for ineligibility included concurrent use of thymoleptic or rhythm

Table 4.1

Demographic Characteristics of Respondents (n=18)

	N	*(%)*
Ethnicity:		
African American	3	(17)
Caucasian	14	(78)
Hispanic	1	(6)
Marital Status		
Never married	4	(22)
First marriage	1	(6)
Second marriage	2	(11)
Living with partner	4	(22)
Separated or divorced	5	(28)
Missing data	2	(11)
Employment		
Employed	11	(61)
Laid off	1	(6)
Unemployed	4	(22)
Part time	2	(11)
Education		
High school	1	(6)
Some college	5	(28)
Completed college	5	(28)
Some graduate work	4	(22)
A graduate degree	3	(17)
Income ($)		
9,000 - 10,999	1	(6)
11,000 - 12,999	2	(11)
13,000 - 15,999	2	(11)
20,000 - 24,999	7	(39)
25,000 - 29,999	1	(6)
40,000 - 44,999	1	(6)
45,000 - 49,999	1	(6)
Over 50,000	3	(6)

altering medications, evidence of perimenopausal symptoms or significant concurrent medical illness. The remaining 35 women met inclusion criteria. Of these 35, 26

enrolled and 18 completed the protocol. Of the 26 who enrolled, 22 actually began the study with participation in one phase of the study; the other 4 out of the 26 decided not to participate after having been accepted into the study, but before data collection began. Two of the 22 who began the study reported remission of symptoms between phases, and left the study. Two additional participants decided to exit the study just prior to the post intervention assessment of the second phase, leaving the 18 who completed the protocol. Reasons cited for either not starting or not completing the protocol included participant concerns that the protocol was too labor intensive, that the idea of a two month commitment was too great, or that the monitoring equipment was not acceptable. The demographic characteristics of the women in the sample are located in table 4.1. Their ages ranged from 23 to 50 years with a mean age of 36.8 years ± 7.04 (S.D.).

Missing Data

Missing data are noted with polysomnography, core body temperature monitoring, and to a lesser degree, measures of self report of depression, fatigue, and measures of morningness/eveningness.

With polysomnography two consecutive nights of data were collected pre and post both the placebo and LPSD protocols. Data from night two were used in the analysis because of a possible first night effect of adapting to the equipment. There were no significant differences between first and second night polysomnography data, pointing to the fact that there was no *first night effect.* Lack of first night effect may be an artifact of participants being studied in their own homes, and has been

demonstrated in the study participants in the study *Fatigue and Sleep Patterns in Childbearing Women* (Kathryn Lee, PI), where women were also studied in their own homes. Since there were no significant differences between nights 1 and 2, where night 2 sleep data were missing (there were 8 such nights), data from night 1 were substituted for analysis.

There were no substitutions for missing temperature data. The reasons for missing temperature data included participant's unexpectedly passing the sensor through the gastrointestinal tract at an unexpectedly fast rate or in fewer cases, equipment failure.

Because of the sensitivity of measures of fatigue and depression, and the possibility of changes resulting from interventions, missing data were not substituted. Very few missing points exist among self report measures.

Table 4.2

Reliability Testing

Cronbach Coefficient Alpha Results

Instrument	Range of alpha
Beck Depression Inventory (pre and post; morning and evening)	.85 - .91
Visual Analog Scale - Fatigue (morning and evening)	.80 - .86
Morningness/Eveningness Questionnaire	.92
Symptom Checklist 90-R	.98

Internal consistency/reliability is both sample specific, as well as an intrinsic

property of a given instrument. For this study, alpha coefficients were determined for the Beck Depression Inventory (BDI), the Visual Analogue Scale - Fatigue (VAS-F), the Horne-Ostberg Morningness/Eveningness Scale and the Symptom Checklist 90-R (SCL-90R). Results of these tests are located in table 4.2. Additional data concerning alpha coefficient reliabilities are located in Appendix A.

Hypothesis Testing

In the section that follows, data will be presented according to the aims and hypotheses tested in this study. After each aim/hypothesis, supporting data will be presented.

Aim #1 was to describe sleep, temperature, fatigue and mood patterns of young women diagnosed with a major (non-seasonal, non-bipolar) depression. Tables 4.3 - 4.6 present descriptive sleep, temperature, mood and fatigue data, respectively. These data reflect pre-intervention conditions in both phases of the study.

The descriptive sleep data for the groups are located in Table 4.3. Additional descriptive sleep data by individual are located in Appendix B. What these data show are no significant differences between baseline data for pre/post placebo and baseline pre-LPSD interventions on four major sleep variables. These data demonstrate no change resulting from the placebo intervention. The variables noted in Table 4.3 were selected for analysis because they are commonly cited in the sleep literature as indices of sleep disturbance related to depression. Compared to women who are not depressed but are from the same age bracket as the participants in this study, there are some differences to be noted. The women in this study demonstrated longer sleep

onset latencies, shorter REM latencies and more slow wave sleep and higher sleep efficiency indexes when compared to non-depressed women (Williams et al, 1974). Mann-Whitney U's were calculated to demonstrate *no difference* between pre-and post placebo data, as well as *no difference* between baseline data from the two phases of the study.

Table 4.3

Baseline Descriptive Sleep Data

		Pre-placebo	*Post-placebo*	*Pre-LPSD*	*U*
Sleep onset latency (Minutes)	N	16	16	18	
	Mean	14.75	15.00	18.40	NS
	SD	15.10	20.29	10.31	
REM latency (Minutes)	N	16	16	18	
	Mean	63.7	67.27	57.7	NS
	SD	10.0	41.47	12.9	
Total slow wave (% Stages 3 & 4)	N	16	16	17	
	Mean	15.77	17.51	14.77	NS
	SD	4.13	9.45	6.72	
Sleep efficiency index (%)	N	16	16	17	
	Mean	95.1	95.93	95.2	NS
	SD	3.17	2.24	2.73	

NS=Not significant, using the Mann-Whitney *U*, $p<0.05$

The baseline group temperature data from this study are located in Table 4.4. Summary tables of individual temperature data are located in Appendix C. There were no significant differences (Mann-Whitney *U*) between pre and post placebo and pre-LPSD variables related to circadian rhythm.

Table 4.4

Baseline Descriptive Temperature Data

		Pre-placebo	*Post-placebo*	*Pre-LPSD*	*U*
R^2	N	15	17	13	
	Mean	0.67	0.73	0.75	NS
	SD	0.17	0.14	0.10	
Mesor	N	15	17	13	
(°C)	Mean	36.8	36.8	36.8	NS
	SD	0.16	0.31	0.16	
Amplitude	N	15	17	13	
	Mean	0.84	0.99	1.04	NS
	SD	0.25	0.37	0.34	
Acrophase	N	15	17	12	
(Clock)	Mean	1494	1499	1403	NS
	SD	138.13	113.18	90.37	

NS=Not significant; Mann-Whitney *U*, $p<0.05$

Table 4.5 presents the women's baseline data from the Beck Depression Inventory (BDI). Additional data on individual BDI scores are located in Appendix D.

The data from the BDI collected on the second morning at each time point were used in the analysis. The BDI has a possible range of scores from 1 - 39, and is divided into four categories for clinical interpretation: 1 = no symptoms or minimum symptoms with scores ranging from 0 to 4; 2 = mild symptoms with scores ranging from 5 to 7; 3 = moderate symptoms with scores from 8 to 15; and 4 = severe symptoms with scores above 15.

Table 4.5

Baseline Beck Depression Inventory

	Pre-placebo	*Post-placebo*	*Pre-LPSD*	*U*
N	18	18	19	
Mean Score (±S.D.)	12.8 (1.4)	14.9 (7.4)	12.8 (1.4)	NS
Mean Category (± S.D.)	3.22 (0.80)	3.27 (0.57)	3.10 (0.80)	NS

NS = Not significant; Mann-Whitney *U*, $p<0.05$

These data show that the participants were experiencing moderate to high moderate depressive symptoms, and that there were no significant changes from baseline of the first phase to baseline of the second phase. These data point to an adequate washout period between the two phases of this study.

Table 4.6

Baseline Fatigue Scores (2nd Evening)
mean ± (S.D.)

	Pre-placebo	*Post-placebo*	*Pre-LPSD*
N	18	15	16
Energy subscale (5 items)	24.37 (12.76)	22.42 (16.15)	24.97 (12.68)
Fatigue subscale (13 items)	62.27 (16.85)	65.05 (16.27)	68.15 (12.56)

Table 4.6 presents group data from the Visual Analogue Scale-Fatigue (VAS-F) (Lee, 1991). Additional VAS-F data for individuals are located in Appendix E. This instrument contains two subclasses: fatigue and energy. Mean data are presented according to the two subscales. With scores ranging from 0 mm to 100 mm, what these

data show are moderate degrees of fatigue and low energy at both phases pre-intervention.

Aim #2 was to determine relationships between complaints of fatigue, depression and physiologic variables related to sleep and circadian rhythm. The specific aim was to test two separate hypotheses. The hypotheses are presented below with corresponding data.

Hypothesis 2.1 stated that there will be significant relationships between depression and fatigue scores, and between sleep and circadian rhythm variables at baseline, prior to intervention. Tables 4.7 and 4.8 present the data for this hypothesis. Additional data are located in Appendix F. In general, these data support the hypothesis as it is presented here.

The data in table 4.7 address the relationship between mood and fatigue variables pre-placebo, and reveal several trends. First, there are moderate to strong correlations between morning and evening measures of depression on both days prior to the placebo intervention.

Unexpectedly, the correlation between Beck depression and SCL 90R depression subscale was moderate. There was a significant positive relationship between depression and fatigue, indicating that the more intense the level of depression, the greater the fatigue. The relationship trend between depression and energy was negative, indicating that the greater the depression, the lower the energy.

Table 4.7

Correlation Matrix of Mood & Fatigue Variables

(n = 18)

	Beck AM 2		
	Pre-placebo	*Post-placebo*	*Pre-LPSD*
Beck AM 1	.84	.89	.83
Beck PM 1	.86	.83	.93
Beck AM 2			
Beck PM 2	.77	.87	.75
SCL 90R Depression Subscale	.67	.71	.71
Fatigue AM 2	.53	.55	.50
Energy AM 2	-.54	-.71	-.63

All correlations are significant at $p<0.05$

Relationships between sleep and the circadian rhythm variables were examined pre-placebo, post-placebo and pre-LPSD, and the significant correlations between these variables at all time points are shown in Appendix G. Table 4.8 contains significant correlations between sleep and circadian rhythm. There were no correlations that were consistent at these three time points.

Significant correlations exist in the pre-LPSD data as well. However, none of the statistically significant correlations in the pre-placebo data are significant in the pre-LPSD data. This may be explainable by the small sample size and the lack of statistical power.

Table 4.8

Correlations of Sleep & Circadian Rhythm Variables

	Pre-placebo r	*Post-placebo r*	*Pre-LPSD r*
REM latency and rhythm strength	*-0.01* (p=.95) n=13	-0.58 (p<.03) n=15	*-0.11* (p=.70) n=13
% wake time and morningness/ eveningness score	0.51 (p<.05) n=16	*0.15* (p=.55) n=16	*0.03* (p=.90) n=17
% stage 2 and acrophase	0.70 (p<.01) n=13	*0.21* (p=.45) n=15	*-0.46* (p=.15) n=11
% REM and acrophase	-0.58 (p<.04) n=13	*-0.03* (p=.90) n=15	*0.37* (p=.23) n=12
Rhythm amplitude and sleep onset latency to 10 minutes of sleep	*-0.23* (p=.45) n=13	*0.01* (p=.94) n=16	0.62 (p<0.03) n=13
Temperature mesor and total sleep time	*-0.01* (p=.97) n=13	*-0.09* (p=.73) n=15	-0.70 (p<0.01) n=12
Rhythm amplitude and total sleep time	*-0.40* (p=.17) n=13	*-0.09* (p=.74) n=15	0.60 (p<0.04) n=12

Hypothesis 2.2 states that there will be no significant relationships among depression scores, fatigue, sleep and circadian rhythm variables after LPSD. The data which follow reject this null hypothesis.

Table 4.9

Correlation Matrix of Mood Variables

(Post-Late Partial Sleep Deprivation Data) (n = 18)

	Beck AM 2
Beck PM 1	0.83
Beck PM 2	0.75
SCL 90R	0.63
Fatigue AM 2	0.50
Energy AM 2	-0.45
Energy PM 2	-0.50

All correlations are significant at $p<0.05$

Tables 4.9 presents data which examines the relationships between mood and fatigue variables. Examining these data, the majority of the correlations are significant, supporting the notion that, in the entire sample, measures of morning and evening depression correlated positively, ie, the greater the depression severity in the morning, the greater the symptom in the evening. Of note, on day 2 post-LPSD intervention, the correlations no longer are significant. This trend will be discussed more fully in the data presented under the third aim of this study. Furthermore, the higher the level of depression, the higher the level of fatigue. But they are not measuring the same aspect of mood as they are not multi-collinear (>0.70). An inverse relationship between depression and energy is noted.

Few significant correlations exist between sleep and temperature variables

post-LPSD, and these findings are presented in Table 4.10. All of these correlations speak to the relationship between temperature and sleep. The first correlation suggests that the weaker the rhythm strength, the longer the individual takes to enter stage 1 sleep. The second correlation suggests that the shorter the REM latency, the weaker the rhythm strength. The last correlation suggests that the lower the percentage of REM during the night, the lower the temperature mesor.

Table 4.10

Correlations between Circadian Rhythm & Sleep Variables (N=18)

Significant ($p<.05$)

(Post-LPSD)

•Rhythm strength and latency to stage 1 sleep	r=0.57
•Rhythm strength and REM latency	r=0.62
•Temperature mesor (mean) and REM percentage	r=0.54

The data with fatigue vary from those of energy. In the entire sample, there are significant negative relationships between energy and depression across all phases of the study. These data suggest that the greater the depression severity, the lower the person's level of energy.

Aim # 3 was to test the effect of late partial sleep deprivation (LPSD) on mood state in young women diagnosed with major (non-seasonal, non-bipolar) depression. Under this aim, three hypotheses were tested. The hypotheses and their supporting data are presented below.

Hypothesis 3.1 stated that there will be statistically significant differences between baseline and post-intervention on salient sleep variables (sleep onset latency, REM latency, % of sleep time spent in various stages, and sleep efficiency index) for late partial sleep deprivation but no differences between baseline and post-placebo.

Table 4.11

Data on Select Sleep Variables

(Pre-Post Late Partial Sleep Deprivation)

		Pre-LPSD	*Post-LPSD*	*U*
Sleep onset latency	N	18	16	NS
(Minutes)	Mean	9.52	12.34	
	SD	10.31	18.40	
REM latency	N	18	16	NS
(Minutes)	Mean	57.73	61.60	
	SD	12.92	12.22	
Percent slow wave	N	17	16	NS
(Stages 3 & 4)	Mean	14.77	17.30	
	SD	6.72	5.79	
Sleep efficiency	N	17	16	NS
index (%)	Mean	95.20	94.31	
	SD	2.73	4.78	

NS=Not significant

There are no significant differences on any of the sleep measures between pre- and post-placebo on the variables of temperature rhythm strength, mesor, amplitude and acrophase (see Appendix H). In addition, there were no statistically significant differences between baseline/pre and post LPSD (see Table 4.11) on any of the salient sleep measures when the entire sample was examined.

Hypothesis 3.2 stated that there would be a statistically significant difference between pre-intervention and post-intervention data on three circadian temperature rhythm variables (mesor, amplitude & acrophase) for LPSD but no differences between baseline and post-placebo. Examining the sample as a whole there were no temperature mesor, amplitude and acrophase.

Table 4.12

Data on Select Temperature Variables

(Pre-Post Late Partial Sleep Deprivation)

		Pre-LPSD	*Post-LPSD*	*U*
R^2	N	13	14	NS
	Mean	0.748	0.754	
	SD	0.106	0.092	
Mesor	N	13	14	NS
(°C)	Mean	36.81	36.79	
	SD	0.164	0.31	
Amplitude	N	13	14	NS
	Mean	1.045	0.945	
	SD	0.341	0.281	
Acrophase	N	12	14	NS
(Clock)	Mean	1403.5	1473.71	
	SD	90.37	148.42	

NS=Not significant (Mann-Whitney U)

Table 4.12 presents the data on temperature variables pre- and post LPSD. There were no significant differences between the pre- and post LPSD phases.

Hypothesis 3.3 stated that there will be a statistically significant difference between pre and post LPSD rating scores of depression (Beck Depression Inventory) (BDI) and fatigue severity (Visual Analogue Scale - Fatigue) (VAS-F) for LPSD but

no differences between pre and post-placebo scores. The data do not support this hypothesis, based on statistical analyses used here.

The data on BDI scores pre/post LPSD are presented in Table 4.13. Data for pre-post placebo are in Appendix I. Examining the BDI scores from the sample as a whole, there were no significant differences between pre and post LPSD. However, determination of responder and non-responder was based on differences in BDI scores

Table 4.13

Mean (± S.D.) Beck Depression Scores Pre and Post LPSD

(N=19)

	Pre-LPSD				*Post-LPSD*				*U*
	Raw Score		*Category*		*Raw Score*		*Category*		
Beck AM 2	13.78	(7.45)	3.10	(.80)	11.16	(9.34)	2.52	(1.12)	NS
Beck PM 2	14.05	(8.35)	3.05	(.98)	11.22	(8.90)	2.57	(1.07)	NS

NB: Scores calculated here utilized four categories for Beck responses: (0-4=**1** [None to very mild]); (5-7=**2** [Mild]); (8-15=**3** [Moderate]); (16-39=**4** [Severe]).

from day 2 morning pre-intervention and day 2 morning post-intervention. There was only one responder to placebo intervention. However her urine toxicology screen tested positive for morphine. Raw Beck scores for the second morning are located in Appendix J.

Tables 4.14 presents the data on pre/post LPSD fatigue and energy scores. Data on individual pre-post placebo scores for fatigue and energy are in Appendix K. Based on the entire sample, there were no significant differences between pre/post

placebo (see Appendix L).

Table 4.14

Fatigue and Energy Scores (mm) for Pre and Post Late Partial Sleep Deprivation

		Pre-LPSD	*Post-LPSD*	*U*
Fatigue AM 2	N	17	18	NS
	Mean	54.65	47.37	
	SD	21.73	20.05	
Fatigue PM 2	N	16	17	NS
	Mean	68.15	57.39	
	SD	12.56	22.64	
Energy AM 2	N	17	18	NS
	Mean	33.45	42.11	
	SD	20.57	22.26	
Energy PM 2	N	16	17	NS
	Mean	24.97	32.98	
	SD	12.68	18.58	

NS = Not significant

There are no significant differences between pre and post LPSD on fatigue and energy. However, the variance in scores increased in the post-LPSD results indicating more diversity in responses. This finding gave rise to the notion of reconsidering the data from the perspective of responder/non-responder subgroups.

Table 4.15

Responder/Non-responder Differences (LPSD)

(Pre-intervention)

		Responder	*Non-responder*	*U*
REM Latency	N	10	8	18.0 (p=0.05)
	Mean	63.82	52.86	
	SD	12.25	7.30	

Table 4.16

Responder/Non-responder Differences (LPSD)

(Post-intervention)

		Responder	*Non-responder*	*U*
SOL to Slow	N	9	7	13.5 (p=0.05)
Wave Sleep	Mean	23.38	15.57	
	SD	5.92	10.50	

When the sample is divided according to responder/non-responder to the LPSD intervention, some significant findings emerge, and are presented in tables 4.15-16. How this division of responder/non-responder was accomplished was by the comparison of day 2 data pre- and post LPSD according to BDI scores. The scores had been collapsed from the raw data range of 0-39 to four categories of depression severity. These categories are the same ones that are used to interpret BDI findings in clinical practice. The translation of raw scores into categorical scores is as follows: 0-4 = 1 [no symptoms or very mild]; 5-7 = 2 [mild symptoms]; 8-15 = 3 [moderate symptoms; 16-39 = 4 [severe symptoms]. What these data show is that the responders to LPSD had a significantly longer REM latency than did the non-

responders, even though the mean REM latencies for both groups are still well within the range expected in those with major depression. Post-intervention what distinguished the responders and non-responders was that the responders had a significantly longer period between sleep onset latency and the emergence of the first slow wave sleep epochs. But, when responders were compared with non-responders to LPSD, the data supported acceptance of the hypothesis tested here.

Considering the temperature data from the pre- and post LPSD phase from the perspective of who responded to LPSD, significant findings emerge from the data of the responders, and are presented in table 4.17.

Table 4.17

Significant Differences in Pre-Post Temperature Data (LPSD)

(Responders Only)

		Pre-LPSD	*Post-LPSD*	*U*
Temperature Acrophase	N	7	9	12.0 ($p<0.04$)
	Mean	1421.14 *	1518.77 **	
	SD	5.71	10.66	

* - 1:45 PM ** - 2:40 PM

What these data indicate is that the responders demonstrated a phase shift in their temperature acrophase from a mean of approximately 1:45 PM to 2:40 PM, nearly an entire hour. This phase shift was not evident in non-responders.

CHAPTER 5

DISCUSSION

Introduction

This last chapter includes four sections. The first section addresses the interpreted findings of the study, and discusses the significance of these results. Second, the strengths and limitations of the study are reviewed. The third section addresses the implications of these findings for nursing science; and lastly, directions for future research are discussed.

The main purpose of this study was to contribute to the body of knowledge on the use of one non-pharmacologic intervention, late partial sleep deprivation therapy, compared to placebo in young women diagnosed with major depression. Given the methodologic and design problems in the existing literature on sleep deprivation, this study attempted to contribute clarity to the question of *who responds* to the nonpharmacologic intervention of late partial sleep deprivation. This was accomplished by building controls into the study's design which addressed some of the methodologic shortcomings of other studies. These controls included age, gender, concurrent use of mood and rhythm-altering medications, menstrual phase and research environment.

Many of the studies exploring the effects of late partial sleep deprivation in depression have very mixed samples. Young and old, women and men, those taking medication and those off medicines, those with concurrent illnesses and those who have no evidence of comorbidity are all clustered together, and treated as if they were

a homogeneous group. Such diversity within the sample obfuscates the results, and consequently, there are problems in the categorizing responder and non-responder to the intervention. The design of this study attempted to control for some of these extraneous influences in such a way as to allow for a clarified picture. Given the markedly higher prevalence of depression in women, this study also attempted to examine the effectiveness of the intervention in a group of women alone. This was done for the same reason as discussed above, namely clarity in recognition of who responds.

This is the first study to the investigator's knowledge, of late partial sleep deprivation where the effects of the active intervention of late partial sleep deprivation are compared with data from placebo intervention. Developing a placebo for this type of study is difficult for several reasons, the most obvious one being credibility without any rhythm-shifting properties. Several different types of placebo were considered, but rejected because of their potential for shifting rhythm or because they were likely to be obvious sham procedures from the perspective of the participants.

What was finally selected as the placebo intervention were light-reduction glasses, similar to sunglasses. The actual eyeglass equipment were developed by UVEX Corporation of Rhode Island, and were officially called *circadian adaptation glasses*. Glasses of this sort were worn by astronauts upon re-entry into the earth's day/night environment to re-establish adaptation to the light/dark environment cycles. Since these glasses were worn during the night hours *only*, no apparent biological influence was noted. It could be argued that the ambient lighting in a given room may exert some influence on rhythm, but this is questionable in the findings from this study.

Inherent in the main purpose, this study aimed to describe sleep patterns, body temperature rhythms, depression and fatigue variables in a group of young women diagnosed with major (nonseasonal, non-bipolar) depression before and after late partial sleep deprivation. Second, this study examined relationships between complaints of fatigue, depression and physiologic variables related to sleep and circadian rhythm. Third, this study tested the effect of late partial sleep deprivation on depression/fatigue states in women diagnosed with major (nonseasonal, non-bipolar) depression. For the purpose of this study, depression was conceptualized as a human experience comprised of concomitant psychological phenomena and psychobiological events. These changes involved sleep and mood patterns, and circadian rhythms operationalized through temperature, polysomnography and other measures.

Interpretation and Significance of Results

The Sample. The sample consisted of 18 women from a pool of 150 women who were screened for possible inclusion in the study. The mean age of the participants was 36.8 years, with a range of 23 to 50 years. The sample was comprised predominantly of Caucasian women (77%), 17% were African-American and 6% were Hispanic. Oddly, this is not fully reflective of the population in San Francisco, as there are no women of Asian descent in the sample. Several women whose families were from China, Japan or the Philippines were screened for the study, but in each instance, they refused participation. Several of these women cited perceived intrusion in their homes by a stranger (investigator or research assistant), or concerns that would potentially be stirred by family members by their inclusion in the protocol. Privacy and

need for others not to know about their depression were commonly cited as reasons for refusal to participate, and this may reflect cultural norms and principles surrounding illness-appropriate behavior. Another explanation for this trend among the Asian women may have had to do with the gender of the investigator. Issues of appropriateness of having a male investigator visit their home may have been a concern for some of the potential participants, even though this was never directly stated as a reason for non-participation.

Of note, many of the women who called to inquire about the protocol were particularly interested in the nonpharmacologic interventions being tested. Many of the inquiries from potential participants were women who clustered into five major categories: 1) those who were currently taking medication, and wanted to explore non-drug intervention strategies; 2) those who were currently depressed, had taken medications in the past, but wanted to explore nonpharmacologic treatment strategies as they were drug-free at the time of inquiry; 3) those who had *only partial* symptom abatement or for whom side effects were a major problem with medications in the past; 4) those who were medication naive; and 5) those who were experiencing depressive symptoms and sleep disturbance while going through the perimenopausal experience. The number of women who called to inquire about participating in the study who were older than the inclusion criteria had specified were many. This is of interest because it may point to a trend in the need for research in this age group of women who are depressed.

Data were collected in a sample of women who were on no psychotropic medications, and who were tested for the presence of any rhythm-altering substances,

specifically drugs of abuse. Prior research has generally neglected to control for such confounding variables, or at least in the case of psychotropic medications, built the use of these substances into the study's design. Recognizing the potential effects of nicotine both on rhythm and its relation to depression (Hall et al, 1993), this study attempted controls for nicotine use. However, one participant was a known smoker, and these data were scrutinized for differences in sleep architecture, fatigue/energy variables, but none were distinguishingly evident.

This study contributed data to the understanding of sleep, fatigue and circadian rhythms of women diagnosed with major (non seasonal, non bipolar) depression, offering new data pertaining to gender-bound response to late partial sleep deprivation. Given the fact that only women who had not gone through menopause participated in this study and the data were collected during the follicular phase of the menstrual cycle only, these data offered a perspective on the sleep and affective experiences of depressed women, controlling for temperature, sleep, and mood changes related to hormonal variation during the menstrual cycle. Similarly, this study excluded women who were either peri- or post menopausal. In doing so, the data from this study contributed to the understanding of variance in circadian rhythm disruption in young women only, barring the rhythm-shifting effects common to the perimenopausal period.

Changes in Sleep. Interpretation of the sleep data from this study presents a challenge. While there are published data available on the sleep of women with major depression in an outpatient setting (Reynolds et al, 1990), these data lack controls for variables related to women, eg, menstrual phase or menopausal status. Alternatively,

Lee and colleagues (1990) have published data on the sleep of women according to the follicular and luteal phases of the menstrual cycle, but these study participants were not diagnosed with major depression. Given these issues, the variables discussed here are compared with both the data of Lee and colleagues (1990), as well as Reynolds and colleagues (1990). Data are presented here in parentheses, first those data of Lee and colleagues (1990) (n=13) for the follicular phase data, followed by those of Reynolds et al (n=151) as follows: [Lee/Reynolds].

The first variable is sleep onset latency (SOL), the time (minutes) between lights out and stage 1 sleep: [6.9 ± 3.9/23.3 ± 26.6]. Difficulty falling asleep is one of the three major categories of sleep continuity disturbances noted in major depression. However, given the variance in the data from both this study [14.75 ± 15.10] and that of Reynolds and colleagues [23.3 ± 26.6], it is clear that this variable differs greatly among those with depression. The second variable is REM latency: [109.8 ± 38.5/64.4 ± 30.3]. REM latency is considered to be a particularly sensitive marker of depression. In this study, the mean REM latency value across both phases of the study was 61.64 ± 21.03. However, as Lee (1988) points out, REM latency can be reduced in women in the luteal phase of the menstrual cycle, and this is likely to be related to a higher core body temperature mesor, as compared to data from women in the follicular phase. The third variable is that of sleep efficiency index. This is calculated by dividing the percent of total sleep time by the time in bed: [94.0 ± 0.5/87.7 ± 10.9]. In this study, the mean sleep efficiency index was 95.38% ± 2.78.

Comparing the sleep findings of this study to those of Reynolds and colleagues (1990), the data provide some interesting contrasts. However, given the fact that

there were few controls in the Reynolds and colleagues (1990) study, it is difficult to draw reliable conclusions as to the meanings of the comparisons. For example, Reynolds and colleagues (1990) aimed to examine sleep, gender and depression, but place no controls for menstrual phase or menopausal status of the women participants. Given such a drawback nonetheless, the women in this study appear to have a comparable mean REM latency, but the amount of slow wave sleep, as well as the sleep efficiency index, varied considerably from the Reynolds and colleagues (1990) data on persons diagnosed with depression.

Unexpected findings from the current data from this study include both the high percentage of slow wave sleep, and the propensity for highly efficient sleep among the women in the sample from this study. Reynolds (1989) reports that there is a minority of persons diagnosed with major depression who demonstrate high sleep efficiencies. He discusses the distinguishing factors between the sleep efficiencies of those with unipolar depression versus bipolar depression, stating that sleep efficiencies are generally better in those with bipolar disorder, and worse in those with unipolar depression. Given the composition of this sample, it raises the question of whether or not this is a gender-bound effect since none of the participants neither had been diagnosed with bipolar disorder, nor was this illness noted in their family histories. Perhaps the high sleep efficiencies relate to unipolar depression in women, but this is purely speculative. What would be the supportive physiologic evidence for such a finding in women versus men? This is unclear, as are many dimensions of subtypes of depressive illness, and as such seems to be something requiring further inquiry.

The third variable is percentage of time spent in slow wave sleep (non-REM

stages 3 & 4): [19.9 ± 4.0/8.5 ± 8.4]. In this study, % non-REM stages 3 & 4 across both phases of the study was 15.78 ± 6.26. The issue of slow wave sleep and its role in depression is a complex topic, and the source of some robust inquiry and debate today. This matter pertaining to slow wave sleep in depression brings the discussion in the literature back to theoretical perspectives underlying biological rhythm disturbances in depression (Beersma, 1992), particularly those focused on potential non-REM and REM mechanisms at play in depression. Additionally, the debate extends into which of these mechanisms is at play with the effectiveness of various forms of sleep deprivation therapies to treat depression (Liebenluft & Wehr, 1992). The amount of slow wave sleep experienced by the participants of this research was twice as much as those in the Reynolds and colleagues (1990) study, but comparable to the women studied by Lee and colleagues (1990). In Hudson and colleague's (1992) meta analysis of sleep in depression, the average percent of slow wave sleep in those with depression (n=595) was 13.78 ± 6.20, and this is comparable with those findings presented here. Again, it is difficult to reliably interpret the findings from a meta analysis on sleep and depression, because of the confounding effects of some of the variable discussed previously. What the inconsistencies in these data point to is the need for better controlled studies, in order to more reliably interpret findings in a way that allows for comparison of data across studies.

One issue related to slow wave sleep in all of the current studies in the depression literature is that all of the polysomnography has been done in the laboratory setting. Contrasted to this study where the participants were studied in their own homes, the question comes forth about whether or not the changes in slow

wave sleep are related to the research environment, rather than an artifact of the depressive illness which is evident in the sleep architecture. This is an area where further research is needed in order to clarify whether or not the slow wave sleep changes are a dimension of the illness or the setting in which the data are collected. It seems that the implications of such a finding could be incredibly important to the field of sleep research on a variety of counts.

First, current studies in the depression literature assume that the reduction in slow wave sleep is a marker for depressive illness. Given this assumption, many of the theorists who attempt to explain sleep-related phenomena struggle to make sense of this finding in a way that is congruent with the existing theories. Such an issue may be the basis of the current incompatibilities noted between theories of sleep architecture changes in depression, namely the S-deficiency hypothesis (Beersma & van den Hoofdakker, 1992) versus REM bound pathogenesis, as noted by Vogel (1975). If, in fact, the NREM anomalies are laboratory artifact, then it stands to reason that some of the underlying theory needs to be re-thought in light of this finding.

The other trend in the polysomnographic recording of sleep was the lack of *first night effect.* Traditionally, what first night effect refers to is the alteration of sleep architecture as a consequence of the use of extensive polysomnographic equipment and/or sleeping in an unfamiliar environment. Collecting data in the homes of the participants yielded some obvious differences in sleep findings when compared to data collected in laboratory settings. Testing for differences between nights 1 and 2, there were no significant differences at any phase of the study. This is probably an artifact

of home monitoring of sleep, but it needs to be explored more fully in other studies using ambulatory polysomnographic monitoring.

Circadian Rhythm. The problems in evaluating the circadian temperature rhythm data which follow are similar to those of sleep, and include recognition of confounding influences. The only comparison data on the temperatures of women in the follicular phase of the menstrual cycle are available from the work of Lee (1988). These data represent temperature variables in 11 non-depressed women in the follicular phase of the menstrual cycle, and are as follows: rhythm strength = .76 ± 0.13; mesor = 36.8°C ± .281; amplitude = .97 ± .280; acrophase (clock) = 1442. In this study, rhythm strength was slightly less [.72 ± .13], the mesor [36.8 ± .207] was the same, the amplitude was slightly less [.95 ± .311] and the acrophase (clock) was similar [1467 ± 122].

Avery and colleagues (1982) reported reduced amplitude of body temperature in persons diagnosed with major depression. The findings of this study are somewhat unexpected, given that rhythm strength has been documented to be reduced in certain forms of depression (Gillin, 1989). Additionally, temperature mesors in those with some types of depression have been noted to be higher (Avery et al, 1982). In the data from this study, however, rhythm strength and amplitude are both reduced, but in marginal ways. This may be an artifact of two separate influences: actual differences between the data set provided from Lee (1988) and the data from this study, or that the data from this study represent mean data from all phases of the study, and the differentiating trends are lost in the pre/post means.

Given that higher daytime temperature acrophases correspond with greater

levels of energy and stamina, and lower night time temperature nadirs are requisite for sound sleep, it stands to reason that altered temperature mesors and blunted amplitudes would coincide with complaints of daytime fatigue and night time sleep disturbance. Given the fact that the temperature data are *marginally* different in this sample, one could speculate that this is a possible consequence of having controlled for some of the confounding variables. For example, many psychotropic drugs shift rhythms, and as a result may influence or mask the underlying rhythm. Granted to completely avoid masking effects, constant routine is necessary. However, in a more naturalistic setting, trends in the data need to be interpreted in a way that facilitates understanding of the whole system under study.

In order to appreciate the preceding discussion on the dimensions of sleep, rhythm and mood, it is important to understand findings as they relate to the intervention of late partial sleep deprivation (LPSD). The initial testing of the effects of LPSD did not yield significant differences between pre- and post measures of mood, sleep and circadian rhythm of temperature. However, when the responders were examined in contrast to the non-responders, three trends in the data emerged, related to REM latency, sleep onset latency to the first slow wave period, and phase shifting of temperature. It is important to recognize that these are *trends*, and as such, deserve to be explored, but also need to be replicated in larger samples in order to be truly significant. Given the fact that the issue of slow wave sleep has been discussed previously, the discussion will focus on REM latency changes, and temperature phase delays.

Mean REM latencies between pre- and post LPSD intervention shifted from

52.86 to 65.05 minutes. Concurrent with this shift was a significant phase delay in temperature acrophase by nearly an hour ($u=12.0$, $p<0.04$). What these findings mean is difficult to determine, given that there are no samples of similar study participants to contrast data from this study. However, what is evident in these findings is that they are related to improvement post-LPSD, and demonstrate a significant phase shift as a result of the LPSD intervention. These changes were absent in the placebo condition, and have never been demonstrated in LPSD, as many of the studies of sleep deprivation and temperature have been with total sleep deprivation. One study by Elsenga and Van den Hoofdakker (1988) examined core body temperature and depression during total sleep deprivation, but all of the study participants were being simultaneously treated with clomipramine, which obfuscates the clarity of the findings. According to Elsenga and Van den Hoofdakker (1988), clomipramine suppresses non-REM intensity, which is in direct contradiction to the findings of Kupfer and colleagues (1989), whose finding support that clomipramine increases non-REM sleep intensity.

Given the fact that sleep architecture is affected by temperature, it seems reasonable that REM changes accompany temperature shifting as well. While the temperature acrophase delayed approximately one hour, so did the REM latency concurrently shift about an hour in the responders as compared with the non-responders as well. It is not certain as to how these two variables are related, but it is reasonable to anticipate that physiologically, a change in one dimension of the system will yield a change in another part of the same system.

The meaning of these findings needs to be more fully explored, and these explorations need to take several different directions. Examples of areas needing

further clarification include the mechanisms by which the brain generates the various stages of sleep, particularly REM and delta sleep. Moving from the electrical activity of the sleep stages, cellular and chemical mechanisms underlying sleep deserve further study in an attempt to understand both the physiology of sleep more clearly, and the cellular mechanisms of interventions such as LPSD.

One variable of interest in this study was that of morningness/eveningness rhythm propensity, and the impact of such biological inclinations on the course of depression. Only one significant finding emerged from these data in relation to morningness/eveningness, and was related to a sleep variable: sleep efficiency index (SEI) and wake time during the night. Since wake time during the night is reciprocal of SEI, only SEI will be discussed further. There was a negative correlation between SEI and morningness/eveningness propensity. What this meant is that the more efficient the sleep, the less likely it is that this individual was an evening person. In other words, the morning persons (or *larks* as they are sometimes referred to) are likely to be more efficient sleepers, based on the data from this study. This correlation points to the fact that evening types are likely to sleep less efficiently, and this is demonstrated in the amount of wake time they experience during the night. If the owls are sleeping less efficiently, and waking more during the night, it stands to reason that there are some underlying circadian markers, perhaps temperature, which demonstrate a particular type of pattern disturbance characteristic of depression. This notion is not unlike that of REM latency shifts in depression. In this study, the data were of interest, but inadequate to allow for drawing larger conclusions about the interconnectedness of rhythm propensity and depression.

Changes in Depression Resulting from LPSD. Aside from the significant REM latency and temperature shift discussed above, there were no other significant findings between the pre and post measures with LPSD for the group. However, it was clear from both observation and self-report measures that there were participants who indeed did respond to the LPSD intervention. A closer examination of changes from the Beck Depression Inventories from day 2 pre- and post intervention showed that 10 of the 18 participants responded favorably to LPSD. The improvement was demonstrated in changes in Beck scores which ranged from 25-75% in the responders. Given this finding, the data of responders versus non-responders were scrutinized for changes between the pre- and post LPSD phases. Significant findings emerged from the data in the areas of sleep and temperature in addition to the mood changes already discussed.

In terms of sleep, two significant findings distinguished the responders from the non-responders. The first finding involved latency to the first slow wave sleep period. Responders had a significantly longer latency to slow wave sleep post-LPSD than did non-responders ($t=2.29$, $p<0.03$). This could be considered a suppression of non-REM sleep intensity, in keeping with Vogel's (1983) REM sleep pressure hypothesis. Combining this finding with the high mean percentage of slow wave sleep experienced by the study participants pre-LPSD, not only did the slow wave sleep occur later in the first sleep cycle, but there was a lower, albeit statistically insignificant mean increase in percentage of slow wave sleep in responders. This finding would stand in contradiction to the S-deficiency hypothesis (Borbely & Wirz-Justice, 1982), which states that among persons with depression, the process of non-REM *pressure* is

directly linked with the course of depression.

The findings of this study contradict some of the data in the current literature concerning sleep architecture in persons diagnosed with depression, particularly findings pointing to consistently reduced slow wave sleep in depression (Kupfer et al, 1990). One issue that distinguishes the data from this study is that they were collected in the participant's own homes. Perhaps the reduced slow wave sleep reported by several investigators is an artifact of having the individual in an unfamiliar sleeping environment. However, a closer look at the work of Kupfer and colleagues (1990) revealed that 74% of their sample consisted of women with depression whose mean age was 40.8 years ± 10.9 years. It is likely that a proportion of these women in this study were perimenopausal. It is reasonable to assume that overall sleep architecture, including delta ratio would be influenced by thermodysregulation, and as such, the data of Kupfer and colleagues are difficult to compare with the data from this study.

Changes in Fatigue due to LPSD. Significant differences in fatigue were not evident in the pre/post LPSD data in those who responded to the intervention. There was only one significant difference in fatigue that was evident in the sample as a whole, but not in the responder subset. This finding demonstrated a moderate positive correlation between fatigue and depression scores, pre-LPSD intervention. What this indicates is that the greater the depression intensity, the greater the fatigue. This correlation became insignificant post intervention, indicating loss of relationship between depression and fatigue. While this loss of significance could be the result of a shift in fatigue, depression or both, it is impossible to say based on the correlational

data alone. However, referring to the t-test scores between pre- and post LPSD, the data indicate a trend that is close to significant ($p<0.07$). Although not significant, this finding may be clarified with the addition of more study participants to enhance statistical power.

As a component of fatigue, energy level was assessed using the energy subscale of the VAS-F (Lee et al, 1990). There were significant changes in energy level among LPSD responders between pre- and post LPSD intervention. What these data indicate is that energy and depression negatively correlate significantly post intervention, but not prior to LPSD or in the placebo phase. Interpreting these data, there is an indication that post intervention, the lower the depression, the higher the level of energy. Understanding more specifically how these variables relate to each other is an area for future research.

What the data from this study demonstrate are some newer findings between responders and non-responders to LPSD. The implications for these finding are discussed later in this chapter.

Study Strengths and Limitations

Participants in this study were diagnosed with a homogeneous form of depressive disorder, namely major (nonseasonal, non bipolar) depression. The need for diagnostic uniformity in the sample allowed for the unequivocal comparison of data within the sample. One of the difficulties in many of the existing studies which examine LPSD in depression is that the samples are grossly heterogeneous. Participants diagnosed with unipolar depression are included in samples with those

diagnosed with schizoaffective, bipolar or dysthymic disorders. These various disorders represent different illnesses, and as such have diverse psychobiological bases. The application of a homogeneous intervention strategy to a disparate diagnostic sample is likely to do one of two things. In a large enough sample, it may highlight the characteristics of those who respond to the intervention. However, this type of strategy requires a significantly large enough sample to have adequate statistical power to demonstrate these trends in the data. Alternatively, the issue of diagnostic heterogeneity more often serves to dilute the power of the findings, and as such obfuscates any trends that may point to understanding clinical responses to the intervention. Aside from the majority of research in the area of seasonal affective disorder (SAD), many of the studies in the depression literature do not report control of variables related to seasonality, and data are collected across all months of the year, regardless of geographic location. This trend may cause the inclusion of persons with either latent, atypical or undetected seasonal patterns to be included into research protocols, repeating the previously described patterns of diversity in sample composition. It is important to recognize that the issue of diagnostic diversity is not the same matter as variance within the sample. The latter concern points to having multiplicity within a given set, and this may address, for example, degrees of severity within a specific symptom cluster or individual differences due to personality or social environment.

This study examined the experience of fatigue as a conceptual dimension of the depressive experience. Estimates of the prevalence of fatigue vary, but it has been noted to be the seventh most common symptom in primary care, especially among

women (Lee & DeJoseph, 1992; Kroenke et al, 1988). While fatigue is often associated with neurochemical or neurohormone shifts associated with depression (Reus, 1986), it is often undifferentiated from depression, or perhaps even treated as a target symptom of the depressive disorder. The human response to fatigue is potentially similar to depression-related symptoms and needs to be distinguished as such for the purpose of accurate nursing intervention.

Additionally, this study offers data on the relationships between depression, fatigue and physiologic variables related to sleep and circadian rhythm. The discussion of fatigue as a distinct entity in depression has not been well delineated in the depression literature. In the sleep deprivation literature, there are no discrete quantitative measurements of fatigue, although there are anecdotal reports of the incidence of subjective arousal in relation to sleep deprivation therapy(Van den Hoofdakker et al, 1989). Where the discussion of fatigue is common is in the literature addressing chronic fatigue syndrome (Goodnick & Sandoval, 1993) and in the women's health literature (Shaver, Giblin, Lentz & Lee, 1988; Lee, Shaver, Giblin & Woods, 1990; Lee & Rittenhouse, 1991; Lee & DeJoseph, 1992). This study will make a significant contribution to understanding the course of fatigue from pre-intervention through to two days post intervention, using a valid and reliable measure of fatigue (Lee, Hicks & Nino-Murcia, 1990).

One last area where of strength of this study is in the recognition of responsiveness to late partial sleep deprivation according to two separate measures of rhythm: influences of circadian rhythm propensity for morningness or eveningness, and diurnal variation in symptoms of depression and fatigue. Study participants had

baseline measures of affinity for morningness or eveningness, and fatigue/depression measures were completed at intervals which allowed for the correlation of these two influences. The notion that rhythm propensity for morning or evening may potentially exert an effect on an intervention such as late partial sleep deprivation is neither well explored or understood. However, there are some indications in the literature about the influence of diurnal variation on the outcome of total sleep deprivation (Reinink et al, 1990; Riemann et al, 1990; Haug, 1992). One study looks at the issue conversely, examining the effect of late partial sleep deprivation on diurnal variation of mood (Szuba et al, 1991). To date, no studies have described the response of those with and without diurnal mood variations with regard to responsiveness to LPSD.

The limitations of this study are several, and are discussed below. The first area is the size of the sample. Although every attempt was made to engage more participants in the protocol, only 18 completed the protocol. Despite the limitation of small sample, the power of the study was .77, based on a recalculation of the power analysis using study findings.

One issue that merits attention in this section is the impact of illness trajectory on the effectiveness of intervention strategy. For example, while all of the participants were screened using a structured interview for the DSM-IIIR diagnostic categories, there were lack of controls for issues such as prior treatment (medication or otherwise) or history of depressive illness. While there was screening used to check for personality disorder, there were no controls for a variety of personality factors. Examples of such influences include motivation, coping skills or perceived helplessness or hopelessness. This study made no attempt to control for the various

dimensions of the social environment including the presence of family or other social supports. There was no examination of the impact of these influences on treatment responsivity. All of these issues may potentially and significantly influence the outcome of an intervention strategy such as the one tested here, and this needs to be acknowledged as a limitation of this study.

The second area of limitation of this study is minor, and in part corrected by the study design. The issue is one of randomization. While participants were not randomly selected, the study design utilized random assignment to either placebo or LPSD in an effort to control for effects related to the sequencing of interventions. No effect from the sequencing of the two phases could be detected.

Implications for Nursing Science

The disciplines involved in the care and treatment of those who live with mental illnesses have been forced to reconsider the ways in which they view the phenomena of concern in their work. In the arena of mental health and illness, this reconceptualization has taken the shape of a revolution in scientific ideology, especially in the normative understanding of the psychobiological dimensions of behavior in general, and of psychiatric illnesses in particular.

The psychobiologic revolution of the last several years has forced a reconceptualization of mind as a process of the brain in interaction with the environment. Such a new perspective suggests a paradigm shift in psychiatry which negates biologic or structural reductionism, and which in turn triggers a rethinking of the existing dominant psychological paradigm. This shift requires the assimilation of

new perceptions, awareness and knowledge into the existing paradigm, or the development of a new paradigm altogether. The psychobiological revolution offers nursing an opportunity to operationalize a new form of holism which can potentially advance holism toward true paradigmatic status. Nursing can utilize new knowledge gained from psychobiology to more fully understand the spectrum of human experience from a holistic perspective. Assimilating this new psychobiologic knowledge into the nursing perspective would recognize that concepts such as mind have biological concomitants, and as such are processes of brain in communication with the environment. This perspective is truly holistic and is congruent with the tenets, assumptions and propositions of holism; it allows for the integration of the biological, psychological, social and spiritual realms to yield what humans have come to know as their experience.

One area of knowledge gain reflected in the psychobiological revolution is in the interface between biological rhythms and mood disorders, particularly depression. Manifest behaviors that are reflective of biological rhythmicity include sleep/wake patterns, diurnal patterns of mood and fatigue, and variables such as stamina, concentration capacity or alertness. All of these examples reflect phenomena of concern for nurses.

Nursing science has begun to explore the dimensions of biological rhythms and their application to practice. What these explorations are likely to do is to broaden the perspective of nurses on behaviors encountered in practice. For example, it is the bias of this writer that sleep is not a very well understood phenomena by many nurses. While nurses recognize the importance of balance between rest and activity, they may

not use a psychobiologic *lens* on the phenomenon. Consequently, they may not be aware of the interplay between patterns of temperature regulation and sleep/wake patterns. Without such understanding, difficulty falling asleep, staying asleep or early morning awakening may be viewed as something under the volitional control of the individual. While cognitive influences play an important role in some dimensions of sleep and alertness, not including an understanding of biological rhythms in one's perception of sleep behavior is certainly inadequate, if not precarious for clinical assessment and intervention. Lack of this type of knowledge may lead to a more common use of biomedical strategy, rather than psychobiological nursing strategy.

Continuing with the sleep example at hand, if nurses were to understand sleep/wake patterns as refracted through a biological rhythm lens, they may be more amenable to, and competent in, the use of sleep manipulation, phototherapy, or intervening with patterns which evidence circadian rhythmicity dysregulation as their base. Given nursing's domains of person and environment, new and potentially more effective strategies for clinical care would include means of shaping rhythm-based disturbances in health and illness across the life span. This study provides an example of the use of one strategy that needs development for its application to nursing practice. New knowledge such as may be generated through study such as this one holds not only valuable information for psychiatric nursing, but for nurses across all specialties within the discipline.

What do the findings from this study mean to the practice of nursing? In addition to the above noted discussion, the findings from this study speak to a different perspective on major depression, and its behavioral implications. For example, the

presence of shifts in sleep architecture (REM and non-REM slow wave sleep) as well as temperature shifts in depression affirm the physiologic dimensions of depression. As such, it is no longer reasonable or acceptable to view depression as a psychological phenomenon that is disconnected from a person's physiology in connection with a given environment.

Just from the researcher's experience in dealing with the women who participated in this study, there are several implications for practice. For example, upon completion of the protocol, the investigator met with each participant individually to review the participants findings. Many of the women were amazed to see physiologically based data that pointed to markers of depression that were not purely subjective in nature. Actually, several of the participants voiced relief at having some evidence that the depression was not "just a figment of my imagination". One of the first implications from these responses may be in the ways nurses approach teaching about depressive illness. Linking the physiologic dimensions of depressive illness to behaviors evident persons suffering from these disorders will help to make better sense of phenomena such as loss of dreaming, difficulty falling or staying asleep or even early morning awakening. Helping persons to understand the connection between slow wave sleep and feeling rested or fatigued, or helping a person understand the interface between temperature and sleep will only serve to demystify the illness of depression. This process of demystification will facilitate recognition of depression as no different than any other illness.

Other implications need development, but are nonetheless very important to the future practice of psychiatric nursing. One main area for development is the use of

various technologies in psychiatric nursing to better understand the course of illnesses such as depression. A nurse in a cardiac ICU would no more think of delivering care to a person with life-threatening arrhythmias without the use of some sort of monitoring equipment. Similarly, this study demonstrates the need for technologies such as polysomnography or core body temperature monitoring in the evaluation of an illness such as depression. When this occurs, perhaps there will be a heightened understanding of the individual patterns a person with depression demonstrates. For example, a phase advance or phase delay in core body temperature will certainly explain some dimensions of sleep disturbance in depression. Recognizing the phase delay as such will permit the development and implementation of intervention strategies to correct the phase disturbance, rather than implicating the person's volition as the *cause* of the concurrent sleep-disturbed behavior. Trends in the use of newer technologies in nursing will hopefully serve to update and enrich the practice of psychiatric nursing, not displace it.

The implications addressed here go beyond the scope of the specialty of psychiatric nursing. As previously discussed, depression is a common experience, and the illness of major depression is not rare. The Agency for Health Care Policy and Research (AHCPR) (1993) has documented that depression is a commonly encountered condition in primary care. It seems that while psychiatric nursing may benefit greatly by the implications discussed here, the practice of nursing across specialty areas will be equally enhanced.

Directions for Future Research

Evaluation of the data from this study has highlighted the directions for future research, and these directions fractionate into four main categories: need for replication of this study in older women as compared to the sample of younger women who participated in this protocol; need for screening of participants for neuroendocrinologic conditions such as thyroid dysfunction; and lastly, need for a more precise evaluation of *who responds* to LPSD, perhaps according to chronotype, REM latency or temperature mesor/acrophase. Lastly, this study needs to be replicated using a larger sample, and with a sample that includes men as participants.

This study was conducted with a sample of younger women in an attempt to control for variables related to menstrual phase and menopausal status. Given the large number of inquiries from women who were either experiencing perimenopausal symptoms or who had gone through menopause, it seems obvious that there may be a need among women of these age groups for this type of intervention. However, no studies have been conducted exclusively with women of these age groups. Consequently, as was the case prior to this study, no data exist in this area.

It is critical to recognize that the same sorts of controls need to be built into the study designs. The number of potentially confounding variables on this sort of research are many, and given the sensitive nature of the data, precautions need to be taken to assure that the data are as free of extraneous influence as possible. Such precision requires ardor of the investigator, because the number of potential participants who meet inclusion criteria are likely to be few in relation to the larger pool of those to be screened. Additional variables to be considered in future research include those

previously discussed in the section addressing the limitations of this study. Among those variables are influences such as history of previous depressive episodes, previous treatment strategies both pharmacologic and non-pharmacologic, treatment responsiveness, personality and social supports. All of these influences potentially impact the effectiveness of a given intervention, and merit consideration in future studies.

The second direction for research involves securing a perspective on some neuroendocrinologic variables that may cloud the assessment of mood. Of particular note are thyroid disorders. While overt manifestations of conditions such as hypothyroidism may be easier to detect, other occult types of thyroid dysfunction can appear indistinguishable from depression, from a behavioral standpoint. An excellent example exists with subclinical hypothyroidism. One of the concerns generated from this study is the notion that perhaps some of the women who did not respond may have had some modicum of thyroid or other neuroendocrinologic dysfunction. Because the protocol did not use serologic measures of thyroid screening, these data are missing from the profile of responders. In future research, this would be an important variable to objectively explore for inclusion/exclusion.

The last issue is that of *who responds* to LPSD, particularly from the perspective of chronotype. This study explored the issue of morningness/eveningness with the use of a single paper and pencil measure which was validated with temperature data. Questions retrospectively were raised by the investigator about understanding the interface of chronotype and particular subtypes of depression, as manifest in particular symptom clusters. For example, is morningness more clearly

associated with a propensity for phase advance in depression? Is eveningness more clearly related to a phase delay? Are those categorized as neither morning nor evening types on a measure such as the Horne-Ostberg (1976) scale more likely *not* to phase shift circadian rhythm in depression, but to demonstrate greater rhythm amplitude deterioration as a dimension of a depressive episode? These relationships are not clearly understood. Where some advances are being made is in the area of understanding the circadian variable of diurnal variation in depressive symptom presentation (Liebenluft et al, 1992). From this study, only one self report measure of morningness/eveningness was used. Additionally, temperature acrophase acted as a circadian marker of rhythm propensity. Other measures are currently being refined (Smith et al, 1989), and it may be helpful to examine two separate measures for the sake of correlation. Use of varied measures will permit the exploration of different dimensions of the construct of morningness/eveningness propensity in circadian rhythm, and potentially contribute to the question of who is likely to respond to the LPSD intervention.

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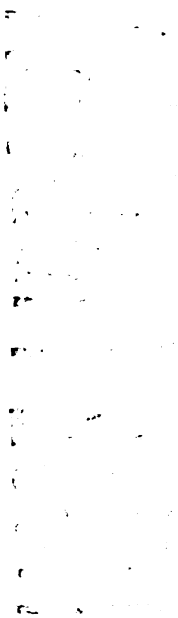

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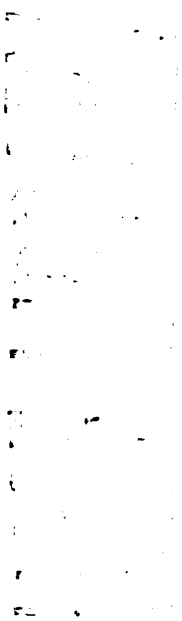

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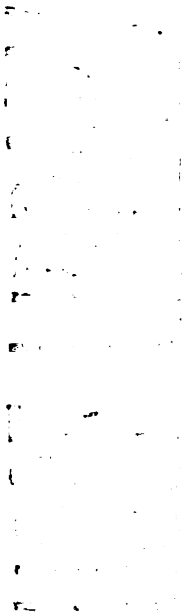
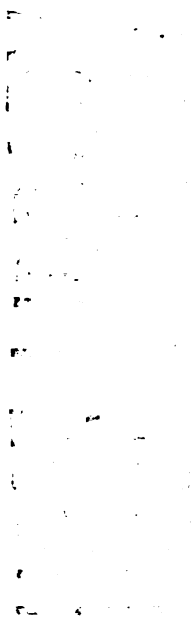


APPENDIX A

Appendix A

Internal Consistency Reliabilities (Alpha Coefficients) (n = 18)

	Subscales		*Total Scale*	
Instrument/Subscale	*#Items*	*Reliability*	*#Items*	*Reliability*
Beck Depression Scale (Morning/evening)			13	.84/.91
Visual Analog Scale-Fatigue (Morning/evening)			18	.86/.80
Fatigue	13	.95		
Energy	5	.89		
Morningness/ Eveningness Scale			19	.91
Symptom Checklist 90-R			90	.98
Depression	13	.95		

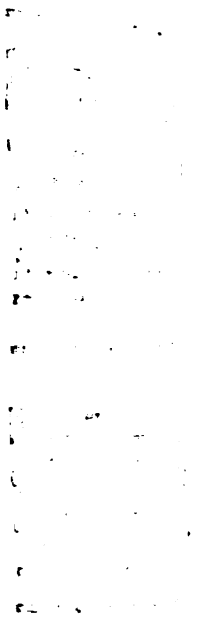


APPENDIX B

Appendix B

Descriptive Data
Sleep Variables

Variable	*Pre-placebo*	*Post-placebo*	*Pre-active*	*Post-active*
Sleep efficiency index				
(Mean)	94.7%	95.08%	94.7%	95.21%
(SD)	3.20	6.30	2.96	1.54
(Range)	88.4-97.5%	79.7-99.4%	90.9-98.4%	93.5-97.3%
REM latency (minutes)				
(Mean)	58.60	50.5	53.1	61.5
(SD)	16.48	12.92	13.6	14.13
(Range)	53.5-63.7	44.5-56.0	34-74.1	37.5-74.1
Total Sleep Time (minutes)				
(Mean)	397.83	405.3	411.8	382.1
(SD)	73.08	112.4	59.8	53.84
(Range)	376.4-419.2	198.6-571.4	345.3-536.4	314.7-463.8
Percent Slow Wave Sleep (NREM Stages 3 & 4)				
(Mean)	13.35%	20.45%	12.63%	15.84%
(SD)	4.11	12.17	6.51	7.31
(Range)	5.90-20%	7.40-46%	5.70-22.50%	7.30-26.9%



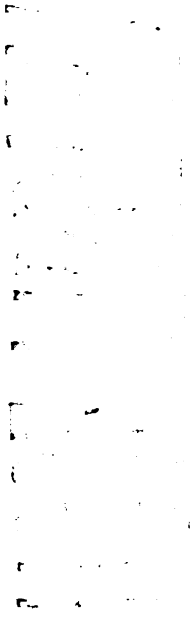
APPENDIX C

Appendix C
Temperature Data
(page 1)

		Placebo		*Active*	
		Pre	*Post*	*Pre*	*Post*
1	Mesor	36.77°	36.85°	Missing	36.58°
	Amplitude	1.107	0.864	Missing	0.742
	Acrophase	5:00PM	2:56PM	Missing	3:05PM
3	Mesor	36.92°	37.14°	Missing	Missing
	Amplitude	1.099	1.094	Missing	Missing
	Acrophase	3:07PM	3:25PM	Missing	Missing
4	Mesor	36.77°	Missing	36.84°	37.05°
	Amplitude	1.033	0.451	0.829	0.344
	Acrophase	1:37PM	Missing	2:40PM	1:25PM
5	Mesor	36.96°	37.21°	37.08°	Missing
	Amplitude	0.306	0.631	1.726	Missing
	Acrophase	1:04PM	3:35PM	4:49PM	Missing
6	Mesor	36.64°	36.69°	36.56°	36.71°
	Amplitude	0.651	1.141	0.599	0.581
	Acrophase	4:36PM	2:33PM	2:47PM	5:19PM
7	Mesor	36.88°	36.93°	36.58°	36.63°
	Amplitude	0.990	1.057	1.032	1.128
	Acrophase	5:09PM	4:12PM	1:28PM	4:30PM
8	Mesor	Missing	36.81°	36.86°	36.79°
	Amplitude	Missing	0.980	1.290	1.158
	Acrophase	Missing	3:37PM	2:17PM	3:37PM
9	Mesor	37.00°	37.15°	37.00°	37.15°
	Amplitude	0.929	1.449	1.164	1.057
	Acrophase	2:30PM	2:18PM	1:43PM	2:42PM
10	Mesor	36.69°	36.66°	36.95°	36.68°
	Amplitude	0.733	0.793	0.902	0.666
	Acrophase	2:31PM	3:07PM	2:36PM	2:00PM
11	Mesor	37.23°	36.88°	Missing	Missing
	Amplitude	1.148	1.128	Missing	Missing
	Acrophase	2:46PM	2:19PM	Missing	Missing

Appendix C
Temperature Data
(page 2)

		Placebo		*Active*	
		Pre	*Post*	*Pre*	*Post*
13	Mesor	36.91°	36.81°	36.70°	36.72°
	Amplitude	0.704	1.101	0.900	0.728
	Acrophase	3:11PM	1:27PM	2:31PM	12:17PM
15	Mesor	36.81°	36.72°	36.90°	Missing
	Amplitude	0.794	0.935	1.084	Missing
	Acrophase	4:47PM	5:46PM	4:34PM	Missing
16	Mesor	Missing	36.77°	Missing	36.79°
	Amplitude	Missing	1.089	Missing	0.944
	Acrophase	Missing	4:06PM	Missing	4:06PM
18	Mesor	Missing	36.63°	36.72°	36.79°
	Amplitude	Missing	0.579	0.781	1.183
	Acrophase	Missing	3:59PM	13:43PM	12:03PM
19	Mesor	36.97°	36.84°	36.68°	36.87°
	Amplitude	1.003	1.126	0.987	0.935
	Acrophase	3:45PM	2:56PM	1:55PM	2:43PM
20	Mesor	36.83°	36.60°	36.73°	36.46°
	Amplitude	0.952	1.040	1.078	1.132
	Acrophase	12:55PM	13:03PM	12:46PM	15:06PM
21	Mesor	36.73°	36.75°	36.92°	36.82°
	Amplitude	0.754	0.400	1.531	1.379
	Acrophase	3:20PM	4:58PM	2:46PM	3:12PM
22	Mesor	36.93°	36.78°	36.61°	37.11°
	Amplitude	1.080	1.187	0.825	1.925
	Acrophase	4:09PM	3:56PM	2:45PM	2:22PM



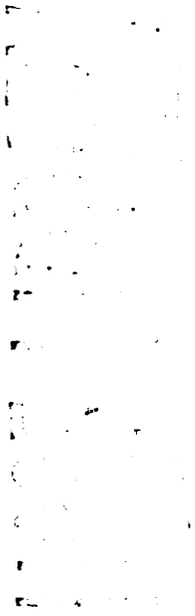
APPENDIX D

Appendix D

Beck Depression Ratings (Pre/Post Placebo only)

Dependent variable	*Pre-placebo*	*Post-placebo*	
Beck AM 1			
N	18	18	t=1.54, df=34, p<0.131
Mean	3.44	3.05	
SD	.78	.72	
Beck PM 1			
N	18	18	t=.465, df=34, p<0.644
Mean	3.05	3.16	
SD	.72	.70	
Beck AM 2			
N	18	18	t=.238, df=34, p<0.813
Mean	3.22	3.27	
SD	.80	.57	
Beck PM 2			
N	18	18	t=.776, df=34, p<0.443
Mean	3.00	3.22	
SD	.90	.80	

NB: Scores calculated here utilized four categories for Beck responses, and are as follows: (0-4=1 [None to very mild]); (5-7=2 [Mild]); (8-15=3 [Moderate]); (16-39=4 [Severe]).



APPENDIX E

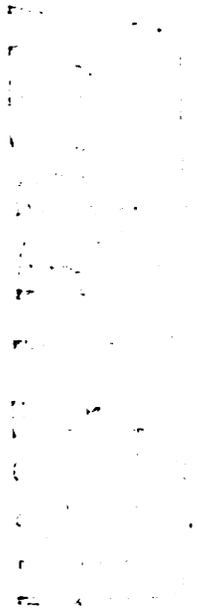
Appendix E

VASF Data (Individual)

	Post Placebo		*Post LPSD*	
Subject ID	*Fatigue Mean*	*Energy Mean*	*Fatigue Mean*	*Energy Mean*
1	*	11.8	*	50.2
3	56.1	19.6	67.3	4.4
4	84.7	12.6	71.9	11.2
5	44.0	48.6	49.6	35.2
6	36.2	52.6	38.0	23.6
7	51.9	36.4	63.6	15.6
8	11.0	72.0	3.3	80.6
9	24.9	71.0	54.2	51.4
10	28.9	68.0	56.9	57.0
11	66.4	30.2	44.8	44.2
13	74.8	9.0	62.1	39.6
15	56.2	30.0	29.7	41.6
16	31.2	59.4	49.0	50.0
18	*	*	37.6	64.8
19	34.1	41.8	46.2	51.6
20	25.9	17.0	20.1	71.0
21	66.7	31.4	85.5	14.8
22	54.2	46.0	58.1	32.0

* - Missing Data

APPENDIX F



Appendix F
(Page 1)

Correlational Matrix of Sleep, Rhythm & Mood Variables
By Sample and Responder Subset

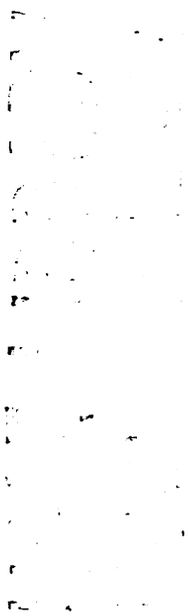
	Pre-placebo *Beck AM 2* *[S]*	*[R]*	*Post-placebo* *Beck AM 2* *[S]*	*[R]*	*Pre-LPSD* *Beck AM 2* *[S]*	*[R]*	*Post-LPSD* *Beck AM 2* *[S]*	*[R]*
SOL 3					.70 (.90)	-.02	-.31 (.23)	.54
SOL SW					.45 (.11)	.38	-.27 (.30)	.71
SOL 10					.47 (.49)	-.17		
SOL REM					.09 (.72)	-.54		
SWS 1	.26 (.32)	-.62			-.28 (.26)	-.37 (.12)	.18	-.54 (.48)
SWS 2	-.52	-.27 (.30)						
REM 1								
REM 2	.51	-.50						

All correlations are $p<0.05$ unless otherwise specified in (parentheses).
[S] refers to overall sample data; [R] refers to data from responders to LPSD.
All sleep data are from night 2 of the phases specified here.

Appendix F
(Page 2)

Correlational Matrix of Sleep, Rhythm & Mood Variables
By Sample and Responder Subset

	Pre-placebo Beck AM 2		*Post-placebo Beck AM 2*		*Pre-LPSD Beck AM 2*		*Post-LPSD Beck AM 2*	
	[S]	*[R]*	*[S]*	*[R]*	*[S]*	*[R]*	*[S]*	*[R]*
REM LAT					.14 (.57)	-.60		
REM 1 TT			.48 (.68)	-.10				
REM 2 TT			.12 (.64)	-.55				
REM 1 REMT			.49 (.65)	-.12				
REM 2 REMT			.10 (.69)	-.50				
AMPLITUDE							-.54	.24 (.40)
FATIG AM2	.47	-.19 (.45)	.59	-.22 (.36)	.54	-.02 (.93)	.19 (.43)	-.30 (.21)
ENER AM2	-.56	.37 (.14)	-.69	.38 (.11)	-.67	.01 (.95)	-.45	.52
TST	.43 (.09)	-.58						



APPENDIX G

Appendix G - Correlation Matrix of Sleep, Rhythm and Mood Variables

		R2	*Mesor*	*AMP 2*	*Clock*
SOL 1	Pre-placebo	-0.48 p=0.10 n=13	-0.17 p=0.57 n=13	-0.28 p=0.35 n=13	0.21 p=0.49 n=13
	Post-placebo	-0.03 p=0.90 n=16	0.18 p=0.50 n=16	0.08 p=0.77 n=16	0.32 p=0.23 n=16
	Pre-LPSD	-0.08 p=0.80 n=13	0.23 p=0.46 n=13	0.51 p=0.07 n=13	-0.16 p=0.61 n=12
REM Latency	Pre-placebo	-0.02 p=0.95 n=13	-0.33 p=0.27 n=13	0.12 p=0.71 n=13	-0.26 p=0.40 n=13
	Post-placebo	-0.58 p<.03 n=15	0.00 p=0.99 n=15	-0.44 p=0.11 n=15	0.44 p=0.10 n=15
	Pre-LPSD	-0.11 p=0.71 n=13	0.01 p=0.97 n=13	0.00 p=0.99 n=13	-0.20 p=0.53 n=12
STG 34	Pre-placebo	-0.38 p=0.19 n=13	0.03 p=0.93 n=13	-0.32 p=0.29 n=13	-0.10 p=0.74 n=13
	Post-placebo	0.19 p=0.50 n=15	0.04 p=0.89 n=15	-0.01 p=0.98 n=15	-0.14 p=0.62 n=15
	Pre-LPSD	-0.06 p=0.85 n=12	-0.03 p=0.92 n=12	-0.08 p=0.80 n=12	0.48 p=0.14 n=11
SEI	Pre-placebo	-0.17 p=0.57 n=13	-0.12 p=0.71 n=13	-0.12 p=0.71 n=13	0.14 p=0.64 n=13
	Post-placebo	-0.18 p=0.51 n=15	-0.15 p=0.60 n=15	-0.03 p=0.92 n=15	0.23 p=0.40 n=15
	Pre-LPSD	0.39 p=0.21 n=12	0.09 p=0.77 n=12	-0.26 p=0.42 n=12	0.43 p=0.18 n=11

APPENDIX H

Appendix H

Data on Select Temperature Variables

(Pre-Post Placebo)

		Pre-placebo	*Post-Placebo*	*U*
R^2	N	15	17	NS
	Mean	0.667	0.737	
	SD	0.174	0.149	
Mesor (°C)	N	15	17	NS
	Mean	36.85	36.8	
	SD	0.164	0.31	
Amplitude	N	15	17	NS
	Mean	0.841	0.998	
	SD	0.253	0.372	
Acrophase (Clock)	N	15	17	NS
	Mean	1494.53	1499.41	
	SD	138.13	113.18	

NS=Not significant

APPENDIX I

Appendix I

Data on Beck Depression Scores

(Pre-Post Placebo)

		Pre-Placebo	*Post-Placebo*	*U*
Beck AM 1	N	18	18	NS
	Mean	3.44	3.05	
	SD	0.784	0.725	
Beck PM 1	N	18	18	NS
	Mean	3.05	3.16	
	SD	0.72	0.70	
Beck AM 2	N	18	18	NS
	Mean	3.22	3.27	
	SD	0.80	0.57	
Beck PM 2	N	18	18	NS
	Mean	3.00	3.22	
	SD	0.90	0.80	

NB: Scores calculated here utilized four categories for Beck responses, and are as follows:
(0-4=**1** [None to very mild]); (5-7=**2** [Mild]); (8-15=**3** [Moderate]); (16-39=**4** [Severe]).

APPENDIX J

Appendix J

Raw Beck Scores (Pre/Post LPSD)

		Pre-LPSD	*Post-LPSD*	*U*
Beck AM 2	N	19	18	126.0
	Mean	13.79	11.17	p<0.18
	SD	7.45	9.345	
Beck PM 2	N	19	18	123.5
	Mean	14.05	11.22	p<0.16
	SD	8.35	8.90	

APPENDIX K

Appendix K

Data on Fatigue Scores

(Pre-Post Placebo)

		Pre-Placebo	*Post-Placebo*	*U*
Fatigue AM 2	N	18	17	NS
	Mean	53.06	49.89	
	SD	20.00	19.94	
Fatigue PM 2	N	18	15	NS
	Mean	62.27	65.05	
	SD	16.85	17.33	
Energy AM 2	N	18	17	NS
	Mean	33.84	37.54	
	SD	18.70	19.78	
Energy PM 2	N	18	15	NS
	Mean	24.36	22.42	
	SD	12.76	16.20	

NS = Not significant

APPENDIX L

Appendix L
(page 1)

Correlation Matrix of Mood & Fatigue Variables
(All correlations are significant at p<.05)

Pre-Placebo Data Only (n = 18)

	Beck AM 1	*Beck PM 1*	*Beck AM 2*	*Beck PM 2*	*SCL90 Depression*
Beck AM 1	1.00	.82	.84	.77	.79
Beck PM 1	.82	1.00	.86	.88	.50
Beck AM 2	.84	.86	1.00	.91	.67
Beck PM 2	.77	.88	.91	1.00	.54
SCL Depression	.79	.50	.67	.54	1.00
Fatigue AM 1	NSC				
Energy AM 1	NSC				
Fatigue PM 1	NSC				
Energy PM 1	NSC				
Fatigue AM 2			.53		.46
Energy AM 2			-0.54		-0.53
Fatigue PM 2	NSC				
Energy PM 2	NSC				

NSC: No significant correlations

Appendix L
(page 2)

Correlation Matrix of Mood & Fatigue Variables
(All correlations are significant at p<.05)

Post-Placebo Data Only (n = 18)

	Beck AM 1	*Beck PM 1*	*Beck AM 2*	*Beck PM 2*	*SCL90 Depression*
Beck AM 1	1.00	.89	.89	.83	.73
Beck PM 1	.89	1.00	.83	.78	.66
Beck AM 2	.89	.83	1.00	.87	.71
Beck PM 2	.83	.78	.87	1.00	.77
SCL Depression	.73	.66	.71	.77	1.00
Fatigue AM 1	NSC				
Energy AM 1	NSC				
Fatigue PM 1	NSC				
Energy PM 1	NSC				
Fatigue AM 2			.55		.46
Energy AM 2	-0.62		-0.71		
Fatigue PM 2	NSC				
Energy PM 2	NSC				

NSC: No significant correlations

Appendix L
(page 3)

Correlation Matrix of Mood & Fatigue Variables
(All correlations are significant at p<.05)

Pre-Active Intervention Data Only (n = 18)

	Beck AM 1	*Beck PM 1*	*Beck AM 2*	*Beck PM 2*	*SCL90 Depression*
Beck AM 1	1.00	.74	.83	.91	.77
Beck PM 1	.74	1.00	.92	.67	
Beck AM 2	.83	.92	1.00	.77	.71
Beck PM 2	.91	.67	.77	1.00	.72
SCL Depression	.77		.63	.72	1.00
Fatigue AM 1	NSC				
Energy AM 1	-0.55				
Fatigue PM 1	NSC				
Energy PM 1		-0.46			
Fatigue AM 2			.50		.46
Energy AM 2	-0.65	-0.58	-0.63		
Fatigue PM 2	NSC				
Energy PM 2		-0.48			

NSC: No significant correlations

Appendix L
(page 4)

Correlation Matrix of Mood & Fatigue Variables
(All correlations are significant at p<.05)

Post-Active Intervention Data Only (n = 18)

	Beck AM 1	*Beck PM 1*	*Beck AM 2*	*Beck PM 2*	*SCL90 Depression*
Beck AM 1	1.00	.50		.91	.57
Beck PM 1	.50	1.00	.83		.73
Beck AM 2		.83	1.00	.75	.63
Beck PM 2			.75	1.00	.56
SCL Depression	.57	.73	.63	.56	1.00
Fatigue AM 1	.46				
Energy AM 1	NSC				
Fatigue PM 1	NSC				
Energy PM 1		-0.45			
Fatigue AM 2			.50		.46
Energy AM 2			-0.45		
Fatigue PM 2	NSC				
Energy PM 2	.48			-0.50	

NSC: No significant correlations