Sleep-Wake Cycle, Sleep-Related Disturbances, and Sleep Disorders: A Chronobiological Approach

Dieter Kunz and Werner Martin Herrmann

There is convincing evidence that the functions of sleep include restoration of brain energy storage and memory consolidation. The circadian timing system (CTS) is involved in the daily variation of almost any physiological and psychological variable evaluated thus far. Disturbances of the CTS can be clinically observed by their influence on the sleep-wake cycle, hormones, body temperature, and locomotor activity. This article reviews the basic mechanisms of circadian rhythm sleep disturbances, names the applicable diagnostic tools and specific therapeutic strategies, and thereby hints at the impact of circadian rhythm sleep disturbance on psychiatric disorders, especially disorders of affect and cognition. In light of the preventive, diagnostic, and therapeutic tools now available, a new round of chronobiological studies in psychiatry seems justified, promising, and necessary.

THERE IS A growing body of evidence that non–rapid eye movement (NREM) sleep restores the brain, sleep deprivation leads to neuronal degeneration, and selective rapid eye movement (REM) sleep deprivation leads to cognitive impairment.[1-4] Thus, proper sleep seems to be of particular importance to daytime brain functioning.

In epidemiological studies, the reported incidence of sleep-related complaints varies between 20% and 40% in the general population.[5-7] Using standardized interviews to allow a diagnosis according to DSM-IV, 6% of the general population meet criteria for primary insomnia alone.[8] Three percent to 10% of the general population use substances to facilitate sleep on a daily basis, be they classic hypnotics, antidepressants, phytopharmaca, or alcohol.[5-7] Estimations of the intent-to-treat population are 10% to 15% of the general population, of which about 80% suffer from sleep disorders generated by or primarily affecting the brain. For example, in Germany, of 10 million people suffering from neuropsychiatric sleep-related disturbances, two thirds never consult a physician for insomnia.[8,9] Most of the patients who seek treatment consult physicians other than neuropsychiatrists or sleep specialists because of other concomitant symptoms.[8,10]

The individual consequences of sleep disorders have to be considered severe in terms of reduced socialization, higher morbidity, less productivity, and higher risk of accidents as a consequence of performance deficits.[11-16] Chronic insomnia is the best single predictor for developing major depression.[5,17,18] The calculated direct cost of sleep disorders in the United States for 1995 was 14 billion dollars.[19,20] The indirect costs, derived from illness-related morbidity and mortality borne by the patient and the employer in the form of ambulatory care, sick days, decreased work productivity, and industrial and motor vehicle accidents, were estimated to be about 100 billion dollars.[21] Altogether, sleep disturbances represent some of the most common neuropsychiatric disorders with severe distress for the patients themselves and substantial socioeconomic consequences.

Sleep disturbances are a part of any psychiatric disorder.[22] Whereas many sleep disorders (e.g., narcolepsy, restless-legs syndrome, obstructive sleep apnea, etc.) represent clinical entities by themselves, most of the basic features in circadian rhythm sleep disorders are also typical for sleep disturbances in psychiatric disorders.[22,23] Still, there are only scant epidemiological data available as to the incidence of circadian rhythm sleep disorders. In the present review, we summarize the hypothesized functions of sleep, cite the basic mechanisms assumed to comprise sleep-wake regulation with an emphasis on the circadian component, review circadian rhythm sleep disorders as clinical entities, predictors, symptoms, or causes of psychiatric disorders, and name possible preventive, diagnostic, and therapeutic approaches.

FUNCTION OF SLEEP

Although humans spend one third of their lives sleeping, the functions of sleep still seem to be not fully elucidated. Sleep research over the last few years has provided a good body of evidence for the

From the Interdisciplinary Sleep Clinic, Department of Psychiatry, Freie Universität Berlin, Berlin; and Department of Psychiatry and Psychotherapy, Universitätsklinikum Lübeck, Lübeck, Germany.

Address reprint requests to Dieter Kunz, M.D., Department of Psychiatry and Psychotherapy, Universitätsklinikum Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany.

0010-440X/00/4102-1016$10.00/0

rather old hypothesis that the 2 major functions of sleep are restoration of the brain and memory consolidation.[1,24] The question as to whether the brain rather than the body is restored is generally debated as follows[25]: (1) sleep is best distinguished from quiet waking by changes in neuronal activity patterns (manifested in the electroencephalogram [EEG]) and by loss of responsiveness; (2) quiet waking rests the body but does not satisfy the sleep need; (3) sleep deprivation affects cognitive functioning more than body functioning; and (4) the most reliable quantitative response to sleep deprivation concerns the amplitude of slow-wave EEG patterns.

The 2 most acknowledged current hypotheses with respect to the function of sleep are (1) the restoration of brain energy metabolism in NREM sleep introduced by Bennington and Heller in 1995[1] and (2) the reversed learning theory introduced by Crick and Mitchinson in 1983.[26] Bennington and Heller presented a model in which NREM sleep is essential for replenishment of cerebral glycogen stores that are depleted during waking. This model integrates the key phenomena of NREM sleep, such as a reduction in neuronal responsiveness, an inattention to sensory stimuli, and a loss of consciousness, into data concerning the regulation of cerebral glycogen levels and the homeostatic regulation of sleep expression. Another hint of the restorative function of sleep is the recent startling finding of neuronal degeneration as a consequence of sleep deprivation in rats.[2]

Today, with regard to REM sleep, there is not much evidence in favor of Freud's psychoanalytic dream theory.[27] Among the many theories that have been proposed with respect to the function of REM sleep, the restoration of cognitive capabilities such as attention and the enhancement of learning processes such as memory consolidation are now being favored.[28] An increase of REM sleep has been observed in numerous studies following acquisition in formal tasks and following exposure to enriched environments,[4] whereas selective REM sleep deprivation has proven to lead to cognitive impairments.[3,29,30] Here, cognitive procedural tasks seem to be more sensitive to REM sleep deprivation than declarative memory.

PROCESSES UNDERLYING THE SLEEP-WAKE CYCLE

Three basic processes underlie sleep-wake regulation[31]: (1) a homeostatic process mediating the increase in sleep pressure during waking and the dissipation of sleep pressure during sleep; (2) a circadian process, a clock-like mechanism defining the alteration of periods with high and low sleep propensity and being basically independent of prior sleep and waking; and (3) an ultradian process occurring within sleep and represented by the alternation of the 2 basic sleep states, NREM sleep and REM sleep. Various mathematical models have been proposed to account for circadian, ultradian, and homeostatic aspects of sleep regulation. The most acknowledged one is the 2-process model introduced by Borbély[32] in 1982, which was modified later.[33]

In this model, the timing, duration,and architecture of sleep are considered to be determined by the interaction of the circadian pacemaker process, C, with a homeostatic process, S, dependent solely on prior wakefulness. The level of process S increases during waking and declines exponentially during sleep. Process C, independently of process S, represents the circadian-driven sleep propensity, with a sleep propensity almost opposite in phase to the homeostatic process S. Under entrained conditions (synchronized to the environmental light-dark cycle), circadian sleep propensity is low in the evening at a time when homeostatic sleep pressure is high, allowing one to stay awake with proper daytime brain functioning. On the other hand, circadian sleep propensity is high in the early morning while the level of homeostatic sleep pressure is low, facilitating the ability to maintain a consolidated bout of sleep at night.[34] In the hypnogram, process C is represented by the timing and duration of REM sleep, which is under strong circadian control.[35,36] Therefore, REM sleep propensity is high at the nadir of body temperature, which leads to long bouts of REM sleep in the early morning.[37]

In mammals, the circadian timing system (CTS) has proven to be involved in the daily variation of almost any physiological and psychological variable evaluated thus far.[38-42] Circadian rhythms in humans are driven by a central pacemaker located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus,[43,44] and persist in the absence of environmental factors.[45] The endogenous rhythms generated by the SCN (whose periodicity is close to 25 hours) are entrained to the 24-hour day by "zeitgebers," with light being the principle zeitgeber.[43,46-50]

The daily variation of melatonin secretion is driven by the SCN. Whereas the main function of melatonin is considered to be hormonal transduction of the light-dark cycle to the rest of the organism, it also provides feedback via high-density and high-affinity melatonin receptors to the SCN.[44,51] In principle, such a positive-feedback mechanism amplifies the SCN circadian signal and increases the coherence (presumably by increasing the amplitude) of the circadian system. Thus, melatonin may function as a potent zeitgeber, as well.[52]

Circadian rhythm sleep disorders are thought to be the consequence of disturbances in process C leading to circadian rhythms that are (1) entrained but out of phase with the light-dark cycle (phase-delay and phase-advance syndrome), (2) uncoupled from the external environment, i.e., "external desynchronization" (non–24-hour sleep-wake pattern), (3) acutely dissociated (jet lag), or (4) chronically "internally desynchronized" (shift work or an irregular sleep-wake pattern).[23,52,53]

CIRCADIAN RHYTHM SLEEP DISORDERS

Diagnostic Methods

The SCN are very small regions located in the hypothalamus and containing about 10,000 neurons each.[44] Thus, a visualization by today's imaging techniques is not possible. A distinctive regulation of the daily variations in melatonin receptor density and affinity of rat SCN has been elegantly shown by melatonin receptor autoradiography studies.[54] Still, in humans, this might only be a future approach.

While the activity of the circadian pacemaker itself cannot be studied in the clinical routine, more attention might be given to its output. Circadian rhythms in hormones, core body temperature, and locomotor activity may be described by the phase, period, and amplitude of their daily variation.

To evaluate the circadian rhythmicity of hormones, continuous blood sampling is necessary. Although this is an awkward, distressing, and expensive procedure, it may contribute much to our current knowledge of the chronobiological factors in neuropsychiatric diseases.[55]

The easily applicable tools in circadian rhythm research are actigraphy devices, which can monitor the daily variation in locomotor activity and measure continuous rectal temperature, as well as confounding influences such as light exposure. The major drawback in these studies of circadian rhythms is the confounding influence of "masking" effects; e.g., sleep, meals, posture, ambient temperature, and physical activity all influence the deep body temperature.[56,57] Several strategies have been used to eliminate masking effects in human studies, such as "constant routine protocols,"[58] the "7/13 paradigm,"[59] or "forced desynchrony."[60] These studies have contributed substantially to the understanding of circadian rhythms in humans. Unfortunately, the study conditions are artificial and more or less strenuous and distressing. Thus, they are useful in studies with healthy subjects, but can hardly be applied in patients who are impaired with respect to their ability to cooperate. Mathematical procedures are now available for "demasking" the temperature rhythm for exogenous influences.[61,62] Even though these procedures do not eliminate all confounding influences, they do allow one to obtain some valid data for this important marker of circadian rhythmicity in patients.

The most robust known circadian rhythm with low intraindividual variation is the one of melatonin, which can be estimated by measuring 6-sulfatoxymelatonin (aMT6s) in urine. About 90% of secreted melatonin is excreted in urine as aMT6s with a plasma half-life of 10 to 45 minutes.[51,63] Thus, measuring the 24-hour aMT6s level in urine seems to be an appropriate method for evaluating the secretory activity of the pineal gland to produce melatonin.

The "dim-light melatonin onset" (DLMO), obtained with saliva, is known as the most reliable phase marker of the CTS in humans.[64] Polysomnography may contribute in that some of the microstructure features such as spindles, REM density, sleep continuity, and REM sleep episode length are at least circadian-modulated.[41]

Since melatonin plays a key role in maintaining the coherence of the CTS, low endogenous melatonin was expected to predict both the occurrence of circadian rhythm disturbances and the response to melatonin treatment. In contrast, in only 1 of the clinical studies[65] in which exogenous melatonin showed usefulness did low or high endogenous melatonin excretion predict response.[66-69] Furthermore, no clinical phenomenon could be associated to either high or low melatonin secretion.

The adult shape and size of the pineal gland, as well as the amount of melatonin secretion, are, presumably genetically, determined early in life.[70]

With respect to these 3 parameters, there is a 20-fold interindividual variability, prohibiting normative data.[70-72] A preliminary finding stated that a high degree of pineal calcification (DOC), as measured using conventional computed tomography (CT), indicates disturbances with respect to the sleep-wake cycle.[73] The basic assumption in that study has now been confirmed, i.e., a decrease in melatonin excretion is associated with an increase in pineal calcification in humans.[74] Thus, the DOC may prove to be an intraindividual vulnerability marker of the CTS, maybe for circadian rhythm disturbances, with implications for replacement therapy, e.g., in the elderly. Of course, this needs to be established before adding the measurement of DOC to routine examination of the CTS.

Altogether, actigraphy in combination with rectal temperature monitoring are easily applicable tools to evaluate circadian rhythm disturbances in outpatients or psychiatric inpatients over long intervals. Polysomnography in combination with the measurement of body temperature, aMT6s in urine, and DLMO in saliva is a noninvasive and less distressing procedure which seems feasible with respect to compliance or ethics even in psychiatric inpatients. The introduction of continuous blood sampling for the evaluation of neuroendocrine parameters may be an additional useful method for state-dependent variables, and the DOC as calculated by CT might prove to be a trait-like marker with implications for replacement therapy.

Therapeutic Approaches

Since pharmacokinetic parameters are known to vary with the time of day, it is not surprising that the outcome of many medical treatments partially depends on the time of application. Besides, psychotropic drugs can influence the output of the CTS. Thus, controlling for the phase, amplitude, and period of the CTS may firstly increase efficacy and secondly attenuate some of the side effects of psychotropic drugs, especially with respect to the sleep-wake cycle.[74a]

As to the general therapy of circadian rhythm sleep disorders, the term "chronobiotic" has been introduced. It is defined as a substance capable of therapeutically shifting the phase, re-entraining acutely dissociated or chronically desynchronized circadian rhythms.[52] As to this definition, the potential of a drug to modulate the perception of a zeitgeber and alter the entraining drive, or to feedback onto the pacemaker, is a chronobiotic property. For example, vitamin B_{12} seems to increase the sensitivity of retinal photoreceptors to light and therefore may be considered a chronobiotic.[52] On the other hand, β-blockers, which abolish melatonin secretion, might be considered "antichronobiotics."[75]

The 2 strongest chronobiotics known so far are light and melatonin. Melatonin delays circadian rhythms when administered in the morning and advances them when administered in the afternoon or early evening according to a phase-response curve (PRC), which is nearly opposite in phase to the PRCs for light exposure.[47,76] In general, bright light is more suited to situations where a large phase-shift is required in a relatively short time (e.g., in shift work or jet lag). Exogenous melatonin may be easier to apply, thus improving compliance in long-term administration.

The phase-shifting properties of both light and melatonin are well established, but there are only scant data available with respect to the influence of melatonin on the amplitude of the CTS. It has been hypothesized that melatonin increases the amplitude of the CTS.[52,77] The first clinical evidence for the hypothesis is from an exploratory study in which exogenous melatonin administered to patients with REM sleep behavior disorder (RBD) quantitatively and qualitatively restored REM sleep.[78] REM sleep, of course, is under strong circadian control.[35,36] RBD was thought to be a state of internal desynchrony. It was hypothesized that exogenous melatonin, administered to patients with internal desynchrony at the time of the maximal increase of melatonin secretion, might increase the overall amplitude of the circadian pacemaker by re-entraining the SCN and thereby restore circadian-driven rhythms, one of them being the circadian modulation of REM sleep.[78]

Today, the toxicity of exogenous melatonin is considered to be low.[79] Still, the time sensitivity of the action and the subtlety of the effects suggest that unless it is administered in the correct patient populations at the appropriate time and individually titrated using an appropriate dose and delivery system, melatonin may prove ineffective or perhaps even countertherapeutic.

In conclusion, (1) psychotropic therapy needs to consider the time of administration and mode of action with respect to the influence on the CTS, and (2) in the treatment of circadian rhythm sleep

disorders, chronobiotics such as light and melatonin administered at the appropriate time of day seem to be the therapy of choice.

Phase-Delay/Advance Syndrome

Circadian rhythm sleep disorders are special in that sleep mechanisms per se are functionally intact but there is a temporal misalignment between the timing of the sleep-wake cycle, the timing of the individual's CTS, and/or social conventions about the appropriate time for sleep.[23,52,53]

Phase-advance (advanced sleep-phase syndrome [ASPS]) and phase-delay (DSPS) syndromes seem to represent the extremes of morning- and evening-type individuals who feel best in the morning and worse in the evening or vice versa. The endogenous nature of chronotypes has been independently proven in adolescents and adults.[80,81] Although there is some influence of social time cues in a delayed circadian phase, the common belief that symptoms are due to voluntary habitually late bedtimes and are generally relieved by improved sleep hygiene has not been substantiated.

DSPS has been defined as initial insomnia combined with difficult morning awakening, and yet also as undisturbed late sleep of normal length and quality when there is no conflicting schedule.[82] It has been reported to be associated with psychopathology leading to major social and work problems in as many as 60% to 75% of affected individuals.[82] The prevalence is estimated to be 7% in adolescents and 0.7% in the elderly.[83,84] Most patients report the occurrence of the first symptoms during childhood or adolescence. In a study of 33 patients with DSPS, two thirds were presently or formerly depressed. Depression in all of these patients was refractory to treatment.[83] The possible reasons for the etiology or aggravation of symptoms are that (1) the endogenous circadian period may be particularly long, which explains the high prevalence in adolescents, since the length of the endogenous circadian period normally shortens over the lifespan; and (2) there is a paucity of time cues if daylight becomes too dim (e.g., in living closer to polar latitudes), if there is insufficient time spent in outdoor light due to lifestyle, or if there is a subsensitivity of the SCN to light.[85,86]

The therapy of choice is either bright light in the morning or melatonin in the early evening for a phase advance, which is known to improve daytime well-being.[87-89] Of course, substances which may have contributed to the altered phase, such as caffeine, ethanol, theophylline, L-dopa, steroids, and antidepressants, should be considered with respect to their properties to lengthen or shorten the endogenous circadian period.[90,91]

In many respects, ASPS mirrors features of DSPS. Patients report difficulty in staying awake in the early evening and maintaining sleep in the early morning even when their total sleep time, due to a desired bedtime of 11 PM, has been as short as 4 hours. Due to sleep deprivation, patients usually report midafternoon fatigue and/or excessive sleepiness. When patients can sleep ad libitum, their sleep is normal in quality and length without daytime impairments.

ASPS is more often found in the elderly, and may reflect a lack of sensitivity in the delay portion of the PRC for light.[92] There are no representative studies available with respect to the incidence of ASPS, but the incidence of its key feature, early morning awakening, has been estimated at 3% to 22% in the general population.[93] The incidence of depressive symptoms irrespective of sleep complaints is estimated to be 40%.[94] Bright evening light has proven highly effective in delaying the circadian phase, including the individual sleep-wake cycle.[94,95] Of course, in major depressive disorder, early morning awakening is one of the characteristic features.

Another unanswered question is the impact of long-term part-time sleep deprivation that is most likely to occur in DSPS patients who are forced to awaken before their individual arising time. Nighttime sleep is shortened and daytime functioning is impaired in children as young as fifth-grade level when school starts at an individually inappropriate early time, in combination with an inability to initiate sleep at the desired bedtime.[96] "Shifted evening types," defined as those whose daily activity forces them to arise before 8 AM despite their chronotype classification as evening types, have the lowest total sleep time of all chronotypes, suggesting a state of continuously ongoing sleep deprivation.[97]

Non–24-Hour Sleep-Wake Pattern

When people are deprived of environmental time cues as in temporal isolation studies, the endogenous circadian pacemaker "free-runs" with a period close to 25 hours.[45] Some 60% to 70% of a large group of blind subjects reported sleep-related

complaints.[98] Survey data indicate that a high percentage of symptoms in these subjects are cyclic in nature with recurring asymptomatic periods every 4 weeks, indicating the typical non–24-hour sleep-wake pattern with "moving-around-the-clock."[99] Using the endogenous plasma melatonin rhythm as a phase marker of the CTS, up to 50% of totally blind subjects have atypical (mostly free-running) circadian rhythms.[100,101]

It is presumed that individuals who are not blind but exhibit the symptoms of the non–24-hour sleep-wake syndrome lack the retinohypothalamic tract (RHT).[102] Cortically blind patients in whom the RHT was intact showed a normal suppression of peak melatonin levels by light and no sleep-related complaints, indicating a regular retinohypothalamic phototransduction.[101] Thus, bilateral enucleation, e.g., for cosmetic reasons in the blind, needs to be reconsidered given its potential for disrupting the photic entrainment of the circadian pacemaker.

The most potent drug known to stabilize the free-running endogenous rhythm in blind people to the environmental light-dark cycle is melatonin.[103,104] In addition to re-entrainment, mood was enhanced and learning capacity improved in a disabled child.[104] Still, there are not many data on this subject.

Irregular Sleep-Wake Pattern

The irregular sleep-wake pattern syndrome is a disorder associated with the dysfunction of the pacemaker itself. It occurs in patients with impaired SCN, e.g., by a tumor,[105] or in patients with diminished or inactive SCN neurons, leading to lower pacemaker output. These patients, being under stronger homeostatic control, develop a polycyclic sleep pattern with unpredictable, multiple sleeping and waking periods throughout the 24-hour day.[57,106,107] Since entrainment of circadian rhythms by melatonin depends on intact hypothalamic SCN,[108] there is no specific treatment available for patients with destroyed or lesioned SCN. In studies treating children with multiple brain damage that yielded an irregular sleep-wake pattern, both light in the morning and melatonin in the evening restored a regular 24-hour sleep-wake cycle, improving mood and cognitive functioning besides greatly alleviating the parents' exhaustion.[109]

The strength of the CTS as indicated by the number of SCN cells and by the output amplitude (e.g., temperature and hormones) is dampened in elderly people and more pronounced in patients suffering from Alzheimer dementia (AD).[55,57,110,111] The circadian amplitude of melatonin and temperature as an indicator of circadian strength is positively related to sleep duration ($r = .87$).[112-114] Most interestingly, in very healthy elderly subjects, circadian amplitude was not altered as compared with healthy young controls, including an unaltered sleep-wake cycle.[115] Moreover, there are data indicating that a higher amplitude of the circadian-driven rest-activity rhythm is positively correlated with the survival time in rats.[116]

The irregular sleep-wake pattern syndrome necessitates the reorganization or strengthening of the circadian pacemaker by zeitgebers or chronobiotics. Such a reversal appears possible by increasing endogenous melatonin levels with either photic stimulation or exogenous melatonin. Direct and even indirect bright light improves circadian rest-activity rhythm disturbances in demented patients.[107,117] It remains to be established whether cognitive functioning improves with this treatment as well. Still, this is an important finding since the patient's restlessness during the evening or night is strongly associated with stress for the caregiver and is a major factor in the decision to place a demented relative in a nursing home.[118,119] Yet preliminary results suggest that melatonin may increase nocturnal sleep as effectively in AD patients[120] as in elderly insomniacs.[65,121]

In animal studies, exogenous melatonin increased the amplitude of the circadian rhythm of body temperature.[77] In a pilot study, there was an increase of the circadian modulation of REM sleep and an increase of the amplitude of the circadian rhythms of melatonin excretion and temperature in humans[78] (Kunz D, Bes F, 1998, unpublished observation). Thus, future studies need to address whether exogenous melatonin can attenuate the age-dependent decrease in the amplitude of the CTS, thereby possibly reversing some of the age-dependent changes.

Jet Lag

The jet lag syndrome is a disorder of modern life. It occurs when an individual crosses several time zones by flight and the endogenous circadian rhythms are rendered out of phase with the new environment. Circadian rhythms, including the

sleep-wake cycle, temperature, and hormone secretion, gradually synchronize with the new environment over several days, changing by about 1.5 hours per day. Due to the endogenous 25-hour rhythm, the adaptation is easier after westbound flights compared with eastbound flights. Typical symptoms include sleep disruption, fatigue, difficulty concentrating, gastrointestinal distress, impaired psychomotor coordination, reduced cognitive skills, and alterations of mood.[53] All of these were ameliorated by melatonin administration in various studies.[122,123] Bright light treatment may be similarly effective, but this has not been studied.

The impairments caused by jet lag are mostly difficult to substantiate. But due to their rapid onset, affected subjects do notice the symptoms and some consider them disabling. It remains to be established as to how slow-developing but long-lasting desynchronization as a result of shift work or diminished circadian amplitude affects well-being.

Shift Work

In contrast to jet lag, in which the CTS tries to catch up with the change in the environmental light-dark cycle, shift workers are forced to compete against normal entraining zeitgebers. Due to the homeostatic and circadian influence on sleep, many individuals find their sleep truncated when it is initiated at an inappropriate circadian phase, e.g., the late morning hours following a nightshift. According to EEG studies, the ensuing sleep is reduced by 2 to 4 hours.[124] Sleep length is maximal when initiated immediately following the core body temperature maximum, and minimal when initiated shortly after the temperature minimum.[125,126] Thus, many of the health and safety problems reported by shift workers result from the sleep deprivation associated with shorter, fragmented daytime sleep.[127,128] Since REM sleep is strongly circadian-modulated,[35,36] REM sleep deficit accounts for most of the sleep deficit in shift workers.[129] The cognitive deficits expected in the long run need to be established.

Since 20% of the working population is on regular shift work, it seems useless to propose a total avoidance of shift work as the therapy of choice.[12] A therapeutic decision has to be made as to whether an adaptation to the working schedule is desired. In the case of short-term (e.g., 2 to 4 days) nightshifts, the phase of the CTS should be kept stable in phase with the environmental light-dark cycle.[130] The duration of daytime sleep may be increased by administration of short-acting benzodiazepines. On the other hand, in long-term shift transition, it may be more appropriate to phase-shift the CTS accordingly by the application of bright light during the night, avoidance of bright light during the off-time day, and administration of melatonin at the desired bedtime.[131,132] It needs to be emphasized that melatonin in the short-term nightshift condition should not be administered prior to daytime sleep. It has proven ineffective,[133] thus corroborating that melatonin has only small hypnotic effects independent of the time of administration. Moreover, side effects may be expected as a result from dissociating circadian rhythms.

In contrast to jet lag with short-term dissociation, shift workers tend to externally desynchronize continuously over long time intervals. Thus, it is likely that they do not synchronize at all over long time intervals.[134] Besides, with age, there is a reduced ability to adapt to rapid phase-shifts.[135,136] Referring to the "use it or lose it" theory,[137] this long-term desynchronization may lead to a decreased amplitude (or output) of the circadian pacemaker even after discontinuation of shift work, and could easily explain the long-lasting sleep problems and impaired well-being in former shift workers.[138]

CONCLUSIONS

Sleep disturbances, especially the so-called physiological ones, are in many instances an integral feature of psychiatric disorders.[22] Like most of the disorders themselves, the associated sleep disturbances are heterogeneous. Some of the disturbances are state-dependent, and others have trait-like characteristics. It was beyond the scope of this article to review or discuss the old "chicken or egg" question as to whether psychiatric disorders are a consequence of chronic insomnia or vice versa. Psychiatric disorders are most likely caused by disturbances of interacting, nonlinear, dynamical systems. Thus, the introduction of a chronobiological approach probably will not clarify the causes of depression, e.g., depression, but may establish subgroups, lead to a better understanding and thereby avoidance of side effects caused by current treatment strategies, and help to develop symptomatic treatment strategies.[23,139] Besides, controlling for the phase, period, and amplitude of the CTS in neuroscientific studies may remove some of

the noise in results dealing with physiological or psychological variables known to be driven or modulated by the circadian pacemaker (e.g., mood, cognition, hormones, receptor density and affinity, gene expression, etc).[140]

Studying the basics of circadian rhythm sleep disorders and referring them to psychiatric disorders leaves many open questions. Even though many of them are not original or innovative, they are still unanswered. For instance, there has been much research on how the CTS is involved in the characteristic REM sleep features found in major depressive disorders.[141] Still, a comprehensive explanation remains to be found. Is early morning awakening caused by an attenuated circadian-driven sleep propensity in the morning? Are the diurnal variations in mood found in major depressive disorders due to circadian rhythm disturbances? Why does sleep deprivation influence mood?[142] Why does phase advancement of the sleep-wake cycle prove beneficial in major depressive disorders?[143] Is the increase of the circadian amplitude of core body temperature in depressed subjects after electroconvulsive therapy a marker for re-entrainment?[144] How does light improve symptoms in seasonal affective disorder?[145-147] Does chronic "low-dose" sleep deprivation or the "light-deprivation" of modern life contribute to, e.g., chronic fatigue syndrome, neurasthenia, or burnout syndrome? Is chronic REM sleep deprivation involved in the etiology of cognitive impairments or even dementia? Are age-related changes with respect to the sleep-wake cycle caused by an attenuated amplitude of the CTS and, moreover, is the age-related impairment of well-being induced by these changes? How does long-term shift work affect the CTS? Is the aging process in shift workers accelerated by a long-term internal desynchronization leading to a reduced amplitude of the CTS?

Although there is an obvious need for sleep research and sleep medical care, the number of diagnostic, therapeutic, and research sleep facilities is small. There are very few facilities which offer proper diagnostic procedures such as polysomnography. In Germany, for a target population of several million people, there are some 23 neuropsychiatric sleep laboratories accredited by the German Association of Sleep Research and Sleep Medicine with approximately 50 fully equipped sleeping places, resulting in a total technical and personal capacity of 5,000 recorded patients per year.

Besides cost arguments, which in most industrial countries prevent adequate payment for state-of-the-art diagnostic procedures in sleep disorders, the lack of interest in such facilities by neuropsychiatrists may be due to the lack of specific diagnostic and therapeutic consequences in the past. On the other hand, there has been a tremendous increase of basic knowledge with respect to the sleep-wake cycle and particularly circadian rhythm neuroscience in the last decade in animals and healthy human subjects. Thus, taking into account the functions of sleep, which presumably are brain restoration and memory consolidation, a new round of chronobiological studies in mental disorders, especially affective disorders, seems both promising and necessary.

REFERENCES

1. Bennington JH, Heller HC. Restoration of brain energy metabolism as the function of sleep. Prog Neurobiol 1995;45:347-360.

2. Eiland MM, Gilliland M, Bergmann BM, Rechtschaffen A, Siegel J. Neuronal degeneration in sleep deprived rats. Sleep 1998;21(Suppl 2).

3. Karni A, Tanne D, Rubenstein BS, Askenasy JJM, Sagi D. Dependence on REM sleep of overnight improvement of perceptual skills. Science 1994;265:679-682.

4. Smith C. Sleep states and memory process. Behav Brain Res 1995;69:137-145.

5. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders—an opportunity for prevention? JAMA 1989;262:1479-1484.

6. Foley DF, Monjan AA, Brown SL, Simonsick EM, Wallace RB, Blazer DG. Sleep complaints among elderly persons: an epidemiologic study of three communities. Sleep 1995;18:425-432.

7. Partinen M. Epidemiology of sleep disorders. In: Kryger MH, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine. Ed. 2. Philadelphia, PA: Saunders, 1994:437-450.

8. Zulley J, Ohayon M. Ergebnisse einer epidemiologischen Repräsentativstudie zur Insomnie in Deutschland: wer geht mit seinen Schlafstörungen zum Arzt? Somnologie 1998;2(1 Suppl, Abstr):6.

9. Welstein L, Dement WC, Redington D, Guilleminault C, Mitler MM. Insomnia in the San Francisco Bay area: a telephone survey. In: Guilleminault C, Lugaresi E (eds): Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution. New York, NY: Raven, 1983:73-85.

10. Dement WC. The proper use of sleeping pills in the primary care setting. J Clin Psychiatry 1992;53:50-56.

11. Coren S. Daylight savings time and traffic accidents. N Engl J Med 1996;334:924.

12. Dinges DF. An overview of sleepiness and accidents. J Sleep Res 1995;4(2 Suppl):4-14.

13. Horne JA, Reyner LA. Driver sleepiness. J Sleep Res 1995;4(2 Suppl):23-29.

14. Smith L, Folkard S, Poole CJM. Increased injuries on night shift. Lancet 1994;344:1137-1139.

15. Reynolds CF III, Buysse DJ, Kupfer DJ. Disordered sleep—developmental and biopsychosocial perspectives on the diagnosis and treatment of persistent insomnia. In: Bloom FE, Kupfer DJ (eds): Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven, 1995:1617-1629.

16. Mitler MM, Dinges DF, Dement WC. Sleep medicine, public policy, and public health. In: Kryger MH, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine. Ed. 2. Philadelphia, PA: Saunders, 1994:453-461.

17. Livingston G, Blizard B, Mann A. Does sleep disturbance predict depression in elderly people? A study in inner London. Br J Gen Pract 1993;43:445-448.

18. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. Am J Epidemiol 1997;146:105-114.

19. Walsh JK, Engelhardt CL, Hartmann PG. The direct economic cost of insomnia. In Nutt D, Mendelson W (eds): Hypnotics and Anxiolytics. Baillieres Clin Psychiatry 1995;369-381.

20. Chilcott LA, Shapiro CM. The socioeconomic impact of insomnia—an overview. Pharmacoeconomics 1996;10(1 Suppl): 1-14.

21. Stoller MK. Economic effects of insomnia. Clin Ther 1994;16:873-897.

22. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. Arch Gen Psychiatry 1992;49:651-668.

23. Wirz-Justice A. Biological rhythms in mood disorders. In: Bloom FE, Kupfer DJ (eds): Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven, 1995:999-1017.

24. Crick F, Mitchison G. REM sleep and neural nets. Behav Brain Res 1995;69:147-155.

25. Horne J (ed): Why We Sleep—The Functions of Sleep in Humans and Other Mammals. Oxford, UK: Oxford University Press, 1988.

26. Crick F, Mitchinson G. The function of dream sleep. Nature 1983;304:111-114.

27. Freud S. Project for a scientific psychology. In: Strachey J (ed): Complete Psychological Works. Vol. 1. London, UK: Hogarth, 1895:347-447.

28. Hobson JA, Stickgold R, Pace-Shott F. The neuropsychology of REM sleep dreaming. Neuroreport 1998;9:R1-R14.

29. Stickgold R, Schirmer B, Patel V, Whidbee D, Hobson JL. Visual discrimination learning: both REM and NREM sleep are required. Sleep 1998;21:256.

30. Smith CT, Conway JM, Rose GM. Brief paradoxical sleep deprivation impairs reference, but not working, memory in the radial arm maze task. Neurobiol Learn Mem 1998;69:211-217.

31. Borbély AA, Achermann P. Concepts and models of sleep regulation: an overview. J Sleep Res 1992;1:63-79.

32. Borbély AA. A two-process model of sleep regulation. Hum Neurobiol 1982;1:195-204.

33. Daan S, Beersma DGM, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. Am J Physiol 1989;246:R161-R178.

34. Dijk DJ, Czeisler CA. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. Neurosci Lett 1994;166:63-68.

35. Czeisler CA, Zimmermann JC, Ronda JM, Moore-Ede MC, Weitzmann ED. Timing of REM sleep is coupled to the circadian rhythm of body temperature in man. Sleep 1980;2:329-346.

36. Zulley J. Distribution of REM sleep in entrained 24 hour and free-running sleep-wake cycles. Sleep 1980;2:377-389.

37. Bes FW, Jobert M, Müller LC, Schulz H. The diurnal distribution of sleep propensity: experimental data about the interaction of the propensities for slow-wave sleep and REM sleep. J Sleep Res 1996;5:90-98.

38. Weitzman ED, Czeisler CA, Moore-Ede MC. Sleep-wake, neuroendocrine and body temperature circadian rhythms under entrained and non-entrained (free-running) conditions in man. Acta Endocrinol (Copenh) 1978;89:25.

39. Wirz-Justice A. Circadian rhythms in mammalian neurotransmitter receptors. Prog Neurobiol 1987;29:219-259.

40. Johnson MP, Duffy JF, Dijk D-J, Ronda JM, Dyal CM, Czeisler CA. Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. J Sleep Res 1992;1:24-29.

41. Dijk D-J, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. J Neurosci 1995;15:3526-3538.

42. Boivin DB, Czeisler CA, Dijk DJ, Duffy JF, Folkard S, Minors D, et al. Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. Arch Gen Psychiatry 1997;54:145-152.

43. Rusak B, Zucker I. Neural regulation of circadian rhythms. Physiol Rev 1979;59:449-526.

44. Klein DC, Moore RY, Reppert SM (eds). Suprachiasmatic Nucleus: The Mind's Clock. New York, NY: Oxford University Press, 1991.

45. Wever RA. The circadian system of man: results of experiments under temporal isolation. In: Schaefer KE (ed): Topics in Environmental Physiology and Medicine. New York, NY: Springer-Verlag, 1979:256-265.

46. Jewett ME, Rimmer DW, Duffy JF, Klerman EB, Kronauer RE, Czeisler CA. Human circadian pacemaker is sensitive to light throughout subjective day without evidence of transients. Am J Physiol 1997;273:R1800-R1809.

47. Lewy AJ, Ahmed S, Jackson L, Sack RL. Melatonin shifts circadian rhythms according to a phase-response curve. Chronobiol Int 1992;9:380-392.

48. Lewy AJ, Sack RL, Miller S, Hoban TM. Antidepressant and circadian phase-shifting effects of light. Science 1987;235: 352-354.

49. Duffy JF, Kronauer RE, Czeisler CA. Phase-shifting circadian rhythms: influence of sleep timing, social contact and light exposure. J Physiol 1996;495:289-297.

50. Boivin DB, Duffy JF, Kronauer RE, Czeisler CA. Dose-response relationships for resetting of human circadian clock by light. Nature 1996;379:540-542.

51. Brown GM. Melatonin in psychiatric and sleep disorders—therapeutic implications. CNS Drugs 1995;3:209-226.

52. Dawson D, Armstrong SM. Chronobiotics—drugs that shift rhythms. Pharmacol Ther 1996;69:15-36.

53. Moore RY. Circadian rhythms: basic neurology and clinical applications. Annu Rev Med 1996;48:253-266.

54. Gauer F, Masson-Pevet M, Stehle J, Pevet P. Daily variations in melatonin receptor density of rat pars tuberalis and suprachiasmatic nuclei are distinctly regulated. Brain Res 1994;641:92-98.

55. van Coevorden A, Mockel J, Laurent E, Kerkhofs M, L'Hermite-Balériaux M, Decoster C, et al. Neuroendocrine rhythms and sleep in aging men. Am J Physiol 1991;360:E651-E661.

56. Buxton OM, Frank SA, L'Hermite-Balériaux M, Leproult R, Turek F, van Cauter E. Roles of intensity and duration of nocturnal exercise in causing phase delays of human circadian rhythms. Am J Physiol 1997;273:E536-E542.

57. Myers BL, Badia P. Changes in circadian rhythms and sleep quality with aging: mechanisms and interventions. Neurosci Biobehav Rev 1995;19:553-571.

58. Mills JN, Minors D, Waterhouse J. Adaptation to abrupt time shifts of the oscillator(s) controlling human circadian rhythms. J Physiol 1978;285:455-470.

59. Lavie P, Scherson A. Ultrashort sleep-waking schedule. I. Evidence of ultradian rhythmicity in "sleepability." Electroencephalogr Clin Neurophysiol 1981;52:163-174.

60. Kleitman N, Kleitman E. Effect of non–twenty-four-hour routines of living on oral temperature and heart rate. J Appl Physiol 1953;6:283-291.

61. Minors D, Waterhouse J. Masking in humans: the problem and some attempts to solve it. Chronobiol Int 1989;6:29-53.

62. Waterhouse J, Minors D, Weinert D, Atkinson G, Reilly T, Rietveld W. Seeing through the environment into the body clock in humans. In: Touitou Y (ed): Biological Clocks. Mechanisms and Applications. Amsterdam, The Netherlands: Elsevier Science, 1998:151-158.

63. Arendt J. Melatonin and the Mammalian Pineal Gland. London, UK: Chapman & Hall, 1995.

64. Lewy AJ, Sack RL. The dim light melatonin onset (DLMO) as a marker for circadian phase position. Chronobiol Int 1989;6:93-102.

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

66. Garfinkel D, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. Lancet 1995;346:541-544.

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

68. Lushington K, Lack L, Kennaway DJ, Rogers N, van den Heuvel C, Dawson D. 6-Sulfatoxymelatonin excretion and self-reported sleep in good sleeping controls and 55-80-year-old insomniacs. J Sleep Res 1998;7:75-83.

69. Youngstedt SD, Kripke DF, Elliot JA. Melatonin excretion is not related to sleep in the elderly. J Pineal Res 1998;24:142-145.

70. Wetterberg L, Iselius L, Lindsten J. Genetic regulation of melatonin excretion in urine. Clin Genet 1983;24:403-406.

71. Vollrath L. The pineal organ. In: Oksche A, Vollrath L (eds): Handbuch der mikroskopischen Anatomie des Menschen. Ed. 7. Berlin, Germany: Springer, 1981.

72. Bhatnagar KP. Comparative morphology of the pineal gland. In: Shafii M, Shafii SL (eds): Biological Rhythms, Mood Disorder, Light Therapy, and the Pineal Gland. Washington, DC: American Psychiatric Press, 1990:1-37.

73. Kunz D, Bes F, Schlattmann P, Herrmann WM. On pineal calcification and its relation to subjective sleep perception: a hypothesis-driven pilot study. Psychiatry Res 1998;82:187-191.

74. Kunz D, Schmitz S, Mahlberg R, Mohr A, Stoter C, Wolf KJ, et al. A new concept for melatonin deficit: on pineal calcification and melatonin excretion. Neuropsychopharmacol. In Press.

74a. Lemmer B, Bruguerolle B. Chronopharmacokinetics—are they clinically relevant? Clin Pharmacokinet 1994;26:419-427.

75. Cowen PJ, Bevan JS, Gosden B, Elliot SA. Treatment with beta-adrenoceptor blockers reduces plasma melatonin concentration. Br J Clin Pharmacol 1985;19:258-260.

76. Zaidan R, Geoffriau M, Brun J, Taillard J, Bureau C, Chazot G, et al. Melatonin is able to influence its secretion in humans: description of a phase-response curve. Neuroendocrinology 1994;60:105-112.

77. Koster-van Hoffen GC, Mirmiran M, Bos NP, Witting W, Delagrange P, Guardiola-Lemaitre B. Effects of a novel melatonin analog on circadian rhythms of body temperature and activity in young, middle-aged, and old rats. Neurobiol Aging 1993;14:565-569.

78. Kunz D, Bes F. Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM sleep regulation. Mov Disord. 1999;14:507-511.

79. Lamberg L. Melatonin potentially useful but safety, efficacy remain uncertain. JAMA 1996;276:1011.

80. Kerkhof GA, van Donge HPA. Morning-type and evening-type individuals differ in the phase position of their endogenous circadian oscillator. Neurosci Lett 1996;218:153-156.

81. Carskadon MA, Vieira C, Acebo C. Association between puberty and delayed phase preference. Sleep 1993;16:258-262.

82. Weitzmann ED, Czeisler CA, Coleman RM, Spielmann AJ, Zimmermann JC, Dement WC. Delayed sleep phase syndrome: a chronobiological disorder with sleep onset insomnia. Arch Gen Psychiatry 1981;38:737-746.

83. Regenstein QR, Monk TH. Delayed sleep phase syndrome: a review of its clinical aspects. Am J Psychiatry 1995;152:602-608.

84. Ando K, Kripke DF, Ancoli-Israel S. Estimated prevalence of delayed and advanced sleep phase syndromes. J Sleep Res 1995;24:509.

85. Lewy AJ, Sack R, Singer C. Immediate and delayed effects of bright light on human melatonin production: shifting "dawn" and "dark" shifts the dim light melatonin onset (DLMO). Ann NY Acad Sci 1985;453:253-259.

86. McArthur AJ, Lewy AJ, Sack RL. Non–24-hour sleep-wake syndrome in a sighted man: circadian rhythm studies and efficacy of melatonin treatment. Sleep 1996;19:544-553.

87. Rosenthal NE, Joseph-Vanderpool JR, Levendosky AA, Johnson SH, Allen R, Kelly KA, et al. Phase-shifting effects of bright morning light as treatment for delayed sleep phase syndrome. Sleep 1990;13:354-361.

88. Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes JD. Delayed sleep phase syndromes response to melatonin. Lancet 1991;337:1121-1124.

89. Nagtegaal JE, Kerkhof GA, Smits MG, Swart ACW, van der Meer YG. Delayed sleep phase syndrome: a placebo-controlled cross-over study on the effects of melatonin administered five hours before the individual dim light melatonin onset. Sleep 1998;7:135-143.

90. Feldmann JF. Circadian periodicity in neurospora: alteration by inhibitors of cyclic AMP phosphodiesterase. Science 1975;190:789-790.

91. Wirz-Justice A. Anti-depressant drugs: effects of the circadian system. In: Wehr TA, Goodwin EF (eds): Circadian Rhythms in Psychiatry. Pacific Grove, CA: Boxwood, 1983.

92. van Cauter E, Moreno-Reyes R, Akseki E, L'Hermite-Balériaux M, Hirschfeld U, Leproult R, et al. Rapid advance of the 24-h melatonin response to afternoon dark exposure. Am J Physiol 1998;275:E48-E54.

93. Karacan I, Thornby J, Williams R. Sleep disturbances: a community survey. In: Guilleminault C, Lugaresi E (eds): Sleep/Wake Disorders: Natural History, Epidemiology, and Long-Term Evolution. New York, NY: Raven, 1983:243-260.

94. Lack L, Wright H. The effect of evening bright light in delaying the circadian rhythms and lengthening the sleep of early morning awakening insomniacs. Sleep 1993;16:436-443.

95. Campbell SS, Dawson D, Anderson MW. Alleviation of sleep maintenance insomnia with timed exposure to bright light. J Am Geriatr Soc 1993;41:829-836.

96. Epstein R, Chillag N, Lavie P. Starting times of school: effects on daytime functioning of fifth-grade children in Israel. Sleep 1998;21:250-256.

97. LaJambe CM, Brown FM. Sleep and wakefulness disruption in shifted evening chronotypes (SETs). Chronobiol Int 1997;14(1 Suppl):92.

98. Leger D, Guilleminault C, Defrance R, Domomt A, Paillard M. Blindness and sleep patterns. Lancet 1996;348:830-831.

99. Klein T, Martens H, Dijk DJ, Kronauer RE, Seely EW, Czeisler CA. Circadian sleep regulation in the absence of light perception: chronic non–24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep-wake schedule. Sleep 1993;16:333-343.

100. Sack RL, Lewy AJ, Blood ML, Keith LD, Nakagawa H. Circadian rhythm abnormalities in totally blind people: incidence and clinical significance. J Clin Endocrinol Metab 1992;75:127.

101. Czeisler CA, Shanahan TL, Klerman EB, Martens H, Brotman DJ, Emens JS, et al. Suppression of melatonin secretion in some blind patients by exposure to bright light. N Engl J Med 1995;332:6-11.

102. McArthur AJ, Lewy AJ, Sack RL. Non–24-hour sleep-wake syndrome in a sighted man: circadian rhythm studies and efficacy of melatonin treatment. Sleep 1996;19:544-553.

103. Arendt J, Aldhous M, Wright J. Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment. Lancet 1988;8588:772-773.

104. Lapierre O, Dumont M. Melatonin treatment of a non–24-hour sleep-wake cycle in a blind retarded child. Biol Psychiatry 1995;38:119-122.

105. Cohen RA, Albers HE. Disruption of human circadian and cognitive function following a discrete hypothalamic lesion. Neurology 1991;41:726-728.

106. Bliwise DL. Sleep in normal aging and dementia. Sleep 1993;16:40-81.

107. van Someren EJW, Kessler A, Mirmiran M, Swaab DF. Indirect bright light improves circadian rest-activity rhythm disturbances in demented patients. Biol Psychiatry 1997;41:955-963.

108. Cassone VM, Chesworth MJ, Armstrong SM. Entrainment of rat circadian rhythms by daily injection of melatonin depends upon the hypothalamic suprachiasmatic nuclei. Physiol Behav 1986;36:1111-1121.

109. Jan JE, Espezel H, Appleton RE. The treatment of sleep disorder with melatonin. Dev Med Child Neurol 1994;36:97-107.

110. Prinz PN, Christie C, Smallwood R, Vitaliano P, Bokan Z, Vitiello MV, et al. Circadian temperature variation in healthy aged and Alzheimer's disease. J Gerontol 1984;39:30-35.

111. Swaab DF, Fliers E, Partiman TS. The suprachiasmatic nucleus of the human brain in relation to sex, age and senile dementia. Brain Res 1985;342:37-44.

112. Morris M, Lack L, Dawson D. Sleep onset insomniacs have delayed temperature rhythms. Sleep 1990;13:1-14.

113. Wever R. Order and disorder in human circadian rhythmicity: possible relations to mental disorders. In: Kupfer DJ, Monk TH, Barchas JD (eds): Biological Rhythms and Mental Disorders. New York, NY: Guilford, 1988:253-346.

114. Czeisler CA, Dumont M, Duffy JF, Steinberg JD, Richardson GS, Brown EN, et al. Association of sleep-wake habits in older people with changes in the output of circadian pacemaker. Lancet 1992;340:933-936.

115. Monk TH, Buysse DJ. Circadian rhythms in the elderly: a comparison of field, laboratory and unmasked conditions. Sleep Res 1989;18:433.

116. Martin JR, Fuchs A, Bender R, Harting J. Altered light-dark activity difference with aging in two rat strains. J Gerontol 1986;41:2-7.

117. Satlin A, Teicher MH, Liebermann HR, Baldessarini RJ, Volicer L, Rheame Y. Circadian locomotor activity rhythms in Alzheimer's disease. Neuropsychopharmacology 1991;5:115-126.

118. Pollack CP, Perlick D, Linsner JP, Wenston J, Hsieh F. Sleep problems in the community of elderly as predictor of death and nursing home placement. J Community Health 1990;15:123-135.

119. Pollack CP, Perlick D. Sleep problems and institutionalization of the elderly. J Geriatr Psychiatry Neurol 1991;4:204-210.

120. Singer C, Colling E, Moffit M, Cutler N, Sack R, Lewy AJ. Melatonin and sleep in patients with Alzheimer's disease. Sleep 1998;21(Suppl):248.

121. MacFarlane RJ, Cleghorn JM, Brown GM, Streiner DL. The effects of exogenous melatonin on the total sleep time and daytime alertness of chronic insomniacs: a preliminary study. Biol Psychiatry 1991;30:371-376.

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

123. Claustrat B, Brun J, David M, Sassolas G, Ghazot G. Melatonin and jet lag: confirmatory result using a simplified protocol. Biol Psychiatry 1992;32:705-711.

124. Akerstedt T. Work hours, sleepiness and the underlying mechanisms. J Sleep Res 1995;4(2 Suppl):15-22.

125. Czeisler CA, Weitzmann ED, Moore-Ede MC, Zimmermann JC, Knauer RS. Human sleep: its duration and organisation depend on its circadian phase. Science 1980;210:1264-1267.

126. Zulley J, Wever R, Aschoff J. The dependence of onset and duration of sleep on the circadian rhythm of rectal temperature. Pflugers Arch 1981;391:314-318.

127. Akerstedt T, Gillberg M. The circadian variation of experimentally displaced sleep. Sleep 1981;4:159-169.

128. Kecklund G, Akerstedt T. Effects of timing of shifts on sleepiness and sleep duration. J Sleep Res 1995;4(2 Suppl): 47-50.

129. Horne J. Human slow wave sleep: a review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness. Experientia 1992;48:941-954.

130. Goichot B, Chapotot F, Gronfier C, Piquard F, Brandenberger G. Effects of the shift of the sleep-wake cycle on three robust endocrine markers of the circadian clock. Am J Physiol 1998;275:E243-E248.

131. Czeisler CA, Dijk DJ. Use of bright light to treat maladaptation to night shift work and circadian rhythm sleep disorder. J Sleep Res 1995;4(2 Suppl):70-73.

132. Sack RL, Blood ML, Lewy AJ. Melatonin administration promotes circadian adaptation to night-shift work. Sleep Res 1994;23:509.

133. James M, Tremea MO, Jones JS, Krohmer JR. Can melatonin improve adaption to night shift? Am J Emerg Med 1998;16:367-370.

134. Weibel L, Spiegel K, Gronfier C, Follenius M, Brandenberger G. Twenty-four-hour melatonin and core body temperature rhythms: their adaption in night workers. Am J Physiol 1997;272:R948-R954.

135. Valentinuzzi VS, Scarbrough K, Takahashi JS, Turek FW. Effects of aging on the circadian rhythm of wheel-running activity in C57BL/mice. Am J Physiol 1997;273:R1957-R1964.

136. Quera-Salva MA, Defrance R, Claustrat B, De Lattre J, Guilleminault C. Rapid shift in sleep time and acrophase of melatonin secretion in short shift work schedule. Sleep 1996;19: 539-543.

137. Swaab DF. Brain aging and Alzheimer's disease, "wear and tear" versus "use it or lose it." Neurobiol Aging 1991;12: 317-324.

138. Dumont M, Montplaisir J, Invante-Rivard C. Sleep quality of former night shift workers. Int J Environ Health 1997;3:10-14.

139. Dolberg OT, Hirschmann S, Grunhaus L. Melatonin for the treatment of sleep disturbances in major depressive disorder. Am J Psychiatry 1998;155:1119-1121.

140. Turek FW. Circadian rhythms. Recent Prog Horm Res 1994;49:43-90.

141. Riemann D, Schnitzler M, Hohagen F, Berger M. Depression und Schlaf—der gegenwärtige Forschungsstand. Fortschr Neurol Psychiatr 1994;62:458-478.

142. Leibenluft E, Wehr TA. Is sleep deprivation useful in the treatment of depression? Am J Psychiatry 1992;149:159-168.

143. Wehr TA, Wirz-Justice A, Goodwin FK, Duncan W, Gillin JC. Phase advance of the circadian sleep-wake cycle as an antidepressant. Science 1979;206:710-713.

144. Szuba MP, Guze BH, Baxter LR. Electroconvulsive therapy increases circadian amplitude and core body temperature in depressed subjects. Biol Psychiatry 1997;42:1130-1137.

145. Rosenthal NE, Sack DA, Gillin JC. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry 1984;41:72-80.

146. Terman M, Terman JS, Quitkin FM, McGraph PJ, Stewart JW, Rafferty B. Light therapy for seasonal affective disorders: a review of efficacy. Neuropsychopharmacology 1989;2:1-22.

147. Wirz-Justice A, Graw P, Krauchi K, Gisin B, Jochum A, Arendt J, et al. Light therapy in seasonal affective disorder is independent of time of day or circadian phase. Arch Gen Psychiatry 1993;50:929-937.