

# Influence of sleep–wake and circadian rhythm disturbances in psychiatric disorders

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Recent evidence shows that the temporal alignment between the sleep–wake cycle and the circadian pacemaker affects self-assessment of mood in healthy subjects. Despite the differences in affective state between healthy subjects and patients with psychiatric disorders, these results have implications for analyzing diurnal variation of mood in unipolar and bipolar affective disorders and sleep disturbances in other major psychiatric conditions such as chronic schizophrenia. In a good proportion of patients with depression, mood often improves over the course of the day; an extension of waking often has an antidepressant effect. Sleep deprivation has been described as a treatment for depression for more than 30 years, and approximately 50% to 60% of patients with depression respond to this approach, especially those patients who report that their mood improves over the course of the day. The mechanisms by which sleep deprivation exerts its antidepressant effects are still controversial, but a reduction in rapid eye movement sleep (REM sleep), sleep pressure and slow-wave sleep (SWS), or a circadian phase disturbance, have been proposed. Although several studies support each of these hypotheses, none is sufficient to explain all observations reported to date. Unfortunately, the disturbed sleep–wake cycle or behavioural activities of depressed patients often explain several of the abnormalities reported in the diurnal rhythms of these patients. Thus, protocols that specifically manipulate the sleep–wake cycle to unmask the expression of the endogenous circadian pacemaker are greatly needed. In chronic schizophrenia, significant disturbances in sleep continuity, REM sleep, and SWS have been consistently reported. These disturbances are different from those observed in depression, especially with regard to REM sleep. Circadian phase abnormalities in schizophrenic patients have also been reported. Future research is expected to clarify the nature of these abnormalities.

Des données récentes démontrent que l'alignement temporel entre le cycle veille–sommeil et l'oscillateur circadien affecte les niveaux subjectifs d'humeur chez les sujets humains en bonne santé. Malgré les différences qui existent entre l'état affectif de sujets sains et de patients atteints de troubles psychiatriques, ces résultats ont des implications pour comprendre la variation diurne de l'humeur dans les troubles affectifs unipolaires et bipolaires de même que les troubles du sommeil chez des patients atteints d'autres désordres psychiatriques graves tels que la schizophrénie chronique. Chez bon nombre de patients atteints de dépression, l'humeur s'améliore souvent au cours de la journée, de sorte qu'une prolongation de la période d'éveil peut souvent entraîner un effet antidépresseur. La privation de sommeil a été décrite comme un traitement antidépresseur depuis plus de 30 ans et de 50 à 60 % environ des patients atteints de dépression répondent

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à cette approche, particulièrement ceux qui signalent une amélioration de l'humeur au cours de la journée. Les mécanismes par lesquels la privation de sommeil exerce son effet antidépresseur demeurent controversés, mais on suppose que cet effet pourrait résulter d'une réduction du sommeil paradoxal, de la pression à dormir et du sommeil lent profond (SLP), ou encore d'une perturbation de la phase circadienne. Bien que plusieurs études appuient ces hypothèses, aucune d'entre elles ne peut expliquer tous les résultats expérimentaux obtenus à ce jour. Malheureusement, les perturbations du cycle veille-sommeil ou des activités des patients dépressifs peuvent expliquer plusieurs des perturbations des rythmes diurnes rapportées dans les états dépressifs. Ainsi, des protocoles expérimentaux utilisant des modifications spécifiques du cycle veille-sommeil et capables de «démâser» l'expression de l'oscillateur circadien endogène sont requis. Dans la schizophrénie chronique, des perturbations significatives de la continuité du sommeil, du sommeil paradoxal et du SLP ont été systématiquement rapportées. Ces perturbations sont différentes de celles observées dans la dépression, en particulier en ce qui concerne le sommeil paradoxal. Des anomalies de phase circadienne furent également notées chez des patients schizophrènes. La recherche future continuera sans aucun doute à préciser la nature de ces anomalies.

There is mounting evidence to support a role for the sleep-wake cycle and the endogenous circadian system in the pathogenesis of major psychiatric disorders. Despite the fact that disturbances of affect and sleep are rarely specific to a given psychiatric condition, the magnitude of these disturbances are generally correlated with clinical severity, and conspicuous abnormalities persist even when the acute condition subsides. These phenomena have been hypothesized to reflect a disturbance of a circadian parameter, such as phase advance, phase delay, reduced amplitude, entrainment defect, or disturbance of a sleep-wake-dependent process, such as rapid eye movement (REM) sleep or slow-wave sleep (SWS). Or they may relate to a complex interaction of circadian and sleep-wake cycle-dependent-processes. This paper critically reviews the literature supporting these hypotheses in affective disorders and in chronic schizophrenia.

### Circadian modulation of mood in humans

It is well established that the overt rhythms of all behavioural variables studied to date, including sleep organization and propensity, subjective alertness, cognitive performance and short-term memory<sup>1,2</sup> have an endogenous circadian component and an evoked (e.g., sleep-wake-dependent) component. For all these parameters, the values reach their lowest point at a circadian phase corresponding to the nadir of the endogenous circadian temperature cycle. Similarly, scores are maximal at a circadian phase coinciding with the plateau phase of the endogenous circadian temperature cycle. These results suggest that an endogenous circadian pacemaker, presumably located in the suprachiasmatic nucleus of the hypothalamus, is a determinant of ob-

served daily variations in these variables. This notion is further supported by reports that, after phase shifts induced by exposure to bright or moderately bright light,<sup>3,4</sup> the circadian rhythms of subjective alertness and cognitive performance maintain similar temporal relations to other reliable circadian markers. Moreover, experimental manipulation of the timing of the sleep-wake cycle in healthy volunteers revealed that sleep latency, sleep efficiency and REM sleep propensity depend mainly on circadian phase, whereas the amount of SWS and slow-wave activity (SWA) depend mainly on the duration of prior waking.<sup>5-7</sup> SWS is the amount of Stage 3 and Stage 4 sleep measured by visual inspection based on a standardized scoring method,<sup>8</sup> whereas SWA is the power density in the slow range (0.75-4.5 Hz) determined digitally via a Fast Fourier transformation of the electroencephalograph (EEG) signal. Bright light exposure early in the morning can advance the time of appearance of REM sleep periods and reduce the duration of sleep episodes,<sup>9</sup> whereas bright light exposure late in the evening can increase sleep latency and delay the appearance of REM sleep.<sup>10</sup> These results are consistent with a phase shift in the underlying endogenous circadian pacemaker that modulates these sleep parameters.

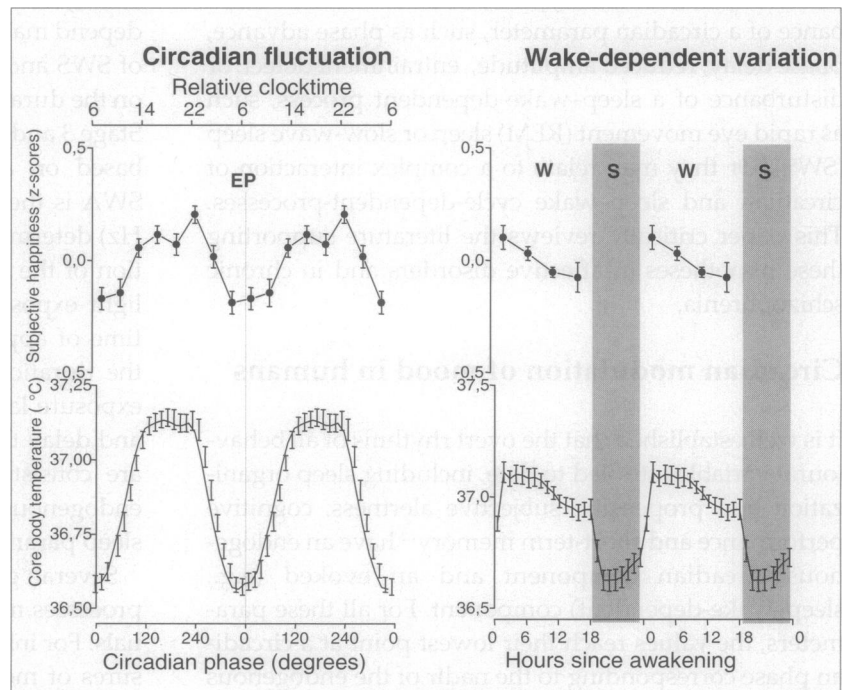
Several groups have reported evidence that these processes may also modulate mood in healthy individuals. For instance, a diurnal variation in subjective measures of mood in healthy volunteers has been reported.<sup>11,12</sup> Monk et al,<sup>11</sup> using the constant routine protocol, reported that subjective measures of mood reached their lowest values close to the minimum of the core body temperature cycle. However, sleep deprivation itself has been shown to result in a deterioration of mood in healthy subjects,<sup>13</sup> and sleep deprivation is an

unavoidable limitation of the constant routine procedure. Totterdell et al<sup>14</sup> and Taub et al<sup>15</sup> reported, in sleep displacement studies, that the timing of sleep had a significant impact on daily mean values of mood in healthy volunteers. However, in these earlier studies, the effects of extended wakefulness and circadian phase remained confounded. Given the deterioration of subjective mood rating with sleep deprivation in healthy subjects, an experimental protocol that separates the relative influences of time elapsed since awakening from circadian phase must be used to measure this interaction. In a recent collaborative research project,<sup>16</sup> we used a "forced desynchrony protocol," which is adapted from the pioneering studies by Kleitman and Kleitman.<sup>17</sup> In this study, 24 healthy young subjects (16 male, 8 female) spent between 19 and 33 days on a 28-hour or 30-hour sleep-wake schedule. Because entrainment of the endogenous circadian pacemaker to days much longer than 24 hours is not possible, these conditions induce desynchrony between the circadian timing system (which continues to oscillate according to its nearly 24-hour intrinsic period) and the imposed sleep-wake cycle. Subjective mood could then be assessed at a variety of circadian phases and times since waking. Subjective mood was assessed by 2 types of visual analogue scale administered either twice every 2 hours or 3 times per hour throughout all waking episodes. In the laboratory, subjects lived individually or in groups of 2 or 3 without knowledge of the time of day for several consecutive weeks. They maintained social contacts with staff members trained to avoid communicating the time of day and the nature of the experimental conditions.

Under these conditions, a significant variation in mood was observed with circadian phase. Subjective mood declined with the descending limb of the circadian temperature curve and reached its lowest value at a circadian phase corresponding to the nadir of the temperature cycle, which under entrained conditions would occur around 5:00 am to 07:00 am (Fig. 1, left panels). Subjective mood then improved with the ascending limb of the endogenous circadian component of the temperature cycle and reached its peak

around 220 to 240 circadian degrees, which under entrained conditions would occur around 10:00 pm. A statistically significant interaction of circadian and wake-dependent fluctuations was also evident. These results indicated for the first time that, in healthy young subjects, subjective mood is influenced by a complex and nonadditive interaction of circadian phase and duration of prior wakefulness. The nature of this interaction is such that moderate changes in the timing of the sleep-wake cycle may have significant effects on subsequent mood. These results indicate that the temporal alignment between the sleep-wake cycle and the endogenous circadian rhythms affects self-assessment of mood in healthy subjects. Under normal entrained conditions, subjects wake up approximately 1 to 2 hours after the endogenous minimum of the core body temperature rhythm, which occurs around 6:00 am. After 8 hours of wakefulness, the circadian phase is close to 120 to 130 degrees, a situation under which, according to the present analyses, means levels of mood will be high during the waking day.

When sleep is displaced, as it is in shiftworkers, the



**Fig. 1:** Circadian and wake-dependent variations in mood (upper panels) and educed waveform of core body temperature (lower panels) in 10 healthy men aged 21 to 30 years. The mean values (trend line) and standard error of the mean (error bars) were plotted at the midpoint of the bins and then double plotted. The mean values and SEM were plotted against circadian phase (left panel) or time since waking (right panel).<sup>16</sup>

phase relation between the sleep–wake cycle and the endogenous circadian pacemaker changes. This change may alter mood while awake. A high prevalence of anxious and depressive symptoms has been reported among shiftworkers;<sup>19</sup> our findings raise the question of whether a misalignment between the sleep–wake cycle and the endogenous circadian timing system may contribute to mood changes in that population. Our data also imply that the effects of sleep deprivation, sleep displacement and the diurnal variation of mood can no longer be attributed to a single process but need to be interpreted as a function of the simultaneous changes in circadian phase and earlier sleep–wake history. Further studies are thus needed to clarify how circadian and wake-dependent processes specifically interact in the regulation of sleep and mood in psychiatric disorders.

### Depressive disorders

Despite the difference in affective states in healthy subjects and patients with depression, our results in healthy volunteers bring a circadian perspective to the well-known phenomena of diurnal variation of mood and the effects of sleep deprivation on affect in patients with endogenous depression. However, the comparison of the diurnal variation in mood between patients with depression and healthy subjects is often limited by differences in the mood scales used across studies, medication and differences in sleep–wake schedules. Very few studies have compared diurnal variation of mood simultaneously in patients with depression and healthy controls. In one such study, patients with seasonal depression were enrolled in a 40-hour constant routine procedure.<sup>20</sup> An improvement in mood was observed with sleep deprivation in 52% of the patients versus 29% of the controls. This rate of improvement is in the range of that observed in nonseasonal depression.<sup>21</sup> Mood often improves over the course of the waking day in patients with depression, and, in contrast to healthy subjects, a further extension of wakefulness (i.e., sleep deprivation) often leads to a temporary alleviation of depressive symptoms,<sup>21</sup> although both the time course of diurnal variation and the response to sleep deprivation are highly variable. Interestingly, a relation has been observed between mood variability measures and the response to sleep deprivation.<sup>22</sup> No consistent relation has been reported between mood variability and the severity of the depressive syndrome,<sup>23</sup> or between the severity of depression and the response to sleep deprivation.<sup>22</sup>

These results imply that the relation between the daily variation of mood, the endogenous circadian pacemaker and the appearance of depressive symptoms is complex and not clearly understood. These phenomena have been hypothesized to reflect a disturbance of a circadian parameter, such as phase shift,<sup>24,25</sup> reduced amplitude<sup>26</sup> or a disturbance of a sleep–wake-dependent process (i.e., the S-deficiency,<sup>27</sup> non-REM sleep,<sup>28</sup> or REM sleep<sup>29</sup>), or to relate to a complex interaction of circadian and sleep–wake cycle-dependent processes<sup>30,31</sup> (reviewed in several recent articles<sup>32–37</sup>).

Most patients with depression present what has been called a “positive variation of mood,” which is characterized by depressive symptoms in the morning and improvement of mood at the end of the day.<sup>31</sup> Sleep deprivation, which is an extension of wakefulness, was described as a treatment for depression in the late 1960s.<sup>38</sup> Physiologically, the wakefulness experienced by patients with depression after sleep deprivation cannot be equated to the period of normal waking in healthy individuals. The antidepressant effect of sleep deprivation is mainly observed in patients presenting a positive variation of mood, whereas worsening of depression may occur in those presenting a negative variation of mood (e.g., better mood upon awakening).<sup>31</sup> The presence of a positive variation of mood the day preceding the night of sleep deprivation does not appear necessary for its antidepressant effect to occur. Intra-individual variability has also been reported, and sleep deprivation could be effective some days but not others.<sup>31</sup> For these reasons, the therapeutic effects of sleep deprivation should be evaluated over several consecutive days before a patient is categorized as a “responder” or a “nonresponder.” The precise quantification of the antidepressant effect of sleep deprivation is difficult, since variable diagnostic criteria, different mood scales and different psychotropic drugs have been used across studies.<sup>39</sup> Approximately 50% to 60% of patients with depression will respond to sleep deprivation, and recovery sleep will often induce a relapse of depression.<sup>21,38</sup> Indeed, a nap as short as 15 minutes has been reported to induce a relapse of depressive symptoms.<sup>40</sup> A fair number of patients also seem to develop tolerance to the antidepressant effect of sleep deprivation. Advancing the timing of sleep by several hours abruptly and returning it progressively to the habitual schedule has been reported to prevent responders to sleep deprivation from a relapse of depression.<sup>41,42</sup>

The mechanisms of action of sleep deprivation are

unclear. Several hypotheses have been proposed: a disturbance of REM sleep,<sup>29</sup> a disturbance of non-REM sleep,<sup>27,28</sup> a phase advance of circadian rhythms,<sup>24,42</sup> and a synergistic effect between sleep deprivation and light exposure.<sup>43</sup> Several authors reported that sleep deprivation during the latter part of the night was as effective as total sleep deprivation, and more effective than sleep deprivation during the first half of the night.<sup>39</sup> These observations have often been proposed as an additional piece of evidence for the role of REM sleep in the pathogenesis of depression. However, other evidence suggests that the inhibition of REM sleep is not sufficient to explain the antidepressant effects of sleep deprivation. REM sleep deprivation often takes several weeks to produce its antidepressant effects, whereas total or partial sleep deprivation act within the following days.<sup>44</sup> It was initially suggested that the therapeutic effect of antidepressant drugs depended on their ability to inhibit REM sleep.<sup>45-47</sup> However, several medications do not inhibit REM sleep expression and yet still exert a potent antidepressant effect. Such is the case for nefazodone,<sup>48</sup> amineptine<sup>45</sup> and bupropion.<sup>49</sup> These results suggest that the inhibition of REM sleep is not necessary for recovery from depression. Sleep deprivation also induces a substantial reduction of non-REM sleep, even when limited to the latter part of the night,<sup>28</sup> which suggests that other mechanisms than REM sleep reduction might be involved in its antidepressant effect. Despite our ignorance of its mechanisms of action, the clinical usefulness of sleep deprivation has been recognized (reviewed by Leibenluft and Wehr<sup>39</sup>). Combining sleep deprivation and pharmacological approaches has been proposed to hasten the antidepressant effects of antidepressants or lithium while concomitantly extending the benefits of sleep deprivation.<sup>39</sup>

The study of sleep in depression has been an intensive area of research. Indeed, depression is characterized by substantial changes in sleep. Increased sleep latency, early morning awakenings, and impaired sleep continuity have been reported and have been regarded as a state of "over-arousal." More interestingly, substantial modifications of REM sleep variables have been observed in patients with depression. These are characterized by reduced REM sleep latency, earlier distribution of REM sleep during the night, and increased eye movements during the first REM period.<sup>50</sup> These alterations of REM sleep appear to be more pronounced during depressive episodes and tend to normalize during recovery phases.<sup>51</sup> However, REM sleep abnormali-

ties persist during euthymic phases and have been proposed as a trait marker of depressive disorders in asymptomatic subjects and in relatives of patients with depression.<sup>52</sup> REM sleep alterations have also been proposed as a diagnostic probe to differentiate depression from dementia in elderly patients.<sup>53</sup> The temporal distribution of REM sleep earlier in the night was interpreted as resulting from a phase advance of the endogenous circadian system and from a state of abnormal phase relations between several diurnal rhythms. The phase advance hypothesis suggests that the endogenous circadian pacemaker is advanced to an earlier time relative to the sleep-wake cycle. This hypothesis is supported by several studies<sup>21,24,25,54</sup> and was conceptualized as what has been called the "internal coincidence model."<sup>55</sup> According to this model, the endogenous circadian system is advanced relative to the sleep schedule such that sleep occurs at critical circadian phases at the end of the night. During these phases, sleep exerts a depressogenic effect in susceptible individuals. Therapeutic success has been reported by scheduling sleep periods 5 to 6 hours earlier.<sup>24</sup> However, REM sleep latency and duration still remain abnormal after advancing the sleep period,<sup>56</sup> and it does not always produce an antidepressant effect.

Reduction of visually scored SWS and SWA has been reported in depression. SWS is affected more by the duration of prior waking than by circadian phase and is predominant during the first part of the night. Its reduction could thus provide an opportunity for REM sleep to express itself earlier in the night. Reduced REM latency could be interpreted as being the result of a faulty homeostatic process rather than a phase advance of the endogenous circadian system. This hypothesis, called the "S-deficiency" hypothesis of depression,<sup>27</sup> implies that sleep deprivation would exert its antidepressant effect by increasing the level of the homeostatic drive for sleep. This would result in increased levels of delta-wave activity during the recovery sleep episode. Even "pure" deprivation of REM sleep involves some reduction of SWS, which could be involved in its therapeutic effect. According to the S-deficiency model, an inappropriate rise of sleep pressure during wakefulness in depression would result in difficulties with sleep initiation and sleep maintenance, and in reduced SWS. Increases in SWS or SWA have been reported to result from antidepressant medications.<sup>57</sup> However, most antidepressant medications have no effect on visually scored SWS, and most selec-

tive serotonin re-uptake inhibitors (SSRIs), which are powerful antidepressant medications, even reduce SWS.<sup>52</sup> The S-deficiency model also hardly explains the advanced growth hormone secretion<sup>54</sup> peaking before bedtime or the abnormalities in the diurnal rhythms of plasma melatonin levels<sup>58</sup> and hormones of the hypothalamic–pituitary–adrenal (HPA) axis<sup>54</sup> observed in depression.

Decreased response to the dexamethasone test is recognized as an important clinical feature of endogenous depression. Increased plasma levels of cortisol and corticotropin-releasing hormone (CRH) have been consistently observed during the night in patients with depression,<sup>54,59</sup> and are consistent with a state of over-arousal. Interestingly, cortisol levels can be increased in humans by sleep deprivation.<sup>60</sup> Several animal studies have revealed that high plasma levels of cortisol can inhibit the secretion of melatonin by the pineal gland, and CRH inhibits melatonin secretion in healthy volunteers.<sup>61</sup> Thus, the higher cortisol levels in patients with depression may contribute to the reduction of melatonin levels reported in that population.<sup>58</sup> However, sleep disturbances are common in depression, and increased awakenings during the night may involve inappropriate exposure to light at that time of day characterized by increased sensitivity of the circadian system.<sup>18</sup> Since human subjects are much more sensitive to light than initially suspected,<sup>62</sup> this inappropriate timing of light exposure may contribute to the reduction of melatonin secretion by the pineal gland. Melatonin can also affect the functioning of the HPA axis, and a mutual interaction or positive feedback are not excluded. Besides unusual concentrations, abnormal timing in the secretion of various hormones has been reported in depression. For instance, the diurnal rhythms of plasma melatonin and plasma cortisol levels appeared abnormally advanced in patients with depression compared to those of healthy controls.<sup>26,54,59,63,64</sup> This would be consistent with a circadian hypothesis of depression and with the therapeutic effect of bright light exposure. Even though bright light exposure has been used successfully to treat patients with nonseasonal depression, the schedule of administration was not an important parameter.<sup>65–67</sup> Morning exposure to bright light, which should have induced a further phase advance shift according to the circadian hypothesis, should have further deteriorated mood. However, morning light exposure appears as effective as evening exposure.<sup>65</sup> A therapeutic effect was observed in about 50% of patients, but a placebo effect

cannot be ruled out. The actual studies are also insufficient to recommend phototherapy as a treatment for patients with nonseasonal depression. Further studies are thus needed to clarify the implication of endogenous circadian rhythms in the pathogenesis of depression. Unfortunately, the disturbed sleep–wake cycle or behavioral activities<sup>68</sup> could account for the abnormal diurnal rhythms<sup>69</sup> reported in endogenous depression. Therefore, protocols that use specific manipulations of the sleep–wake cycle to “unmask” the expression of the endogenous circadian system are needed.

### Seasonal affective disorder

In 1984, Rosenthal et al<sup>70</sup> described a disorder characterized by major depressive episodes occurring in fall/winter seasons with remission or hypomania the following spring/summer. The cause of seasonal affective disorder (SAD) is still unknown, but the shortening of the photoperiodic environment during fall/winter months has been implicated as a trigger. Despite the uncertainty concerning the role of light exposure in the pathogenesis of SAD, it is generally accepted that phototherapy is a clinically useful treatment for depression and is superior to placebo.<sup>71</sup> Overall, morning exposure was reported to be more effective than afternoon or evening exposures,<sup>72,73</sup> although this still remains a matter of debate.<sup>74</sup> This observation has served as the main argument for the phase delay shift hypothesis of SAD. In 1987, Lewy et al<sup>25</sup> proposed that the endogenous circadian system was phase delayed relative to the sleep–wake cycle and that morning phototherapy was effective by phase advancing the endogenous circadian rhythms of core body temperature and plasma melatonin levels. This hypothesis was either supported<sup>73,75–77</sup> or challenged<sup>74,78–80</sup> experimentally. If the phase-advance hypothesis were correct, patients' mood would deteriorate with evening exposure to bright light, due to the worsening of the phase delay shift it induces. On the contrary, evening phototherapy also produces an antidepressant effect and does not cause deterioration of mood. Exogenous melatonin, administered during the late afternoon or evening, should also be therapeutic, since it is known to induce a phase advance of the endogenous circadian system.<sup>81</sup> So far, exogenous melatonin has demonstrated no convincing therapeutic effects.<sup>82</sup> The phase-shift hypothesis and its latest variants, the phase-instability or impaired entrainment hypotheses,<sup>77</sup> can neither be ruled out nor confirmed at this stage. It has been proposed



that the circadian signal is weakened in SAD and that bright light exerts its antidepressant effect by enhancing circadian amplitude.<sup>83</sup> There is no convincing evidence to support this hypothesis.<sup>79</sup> Another circadian hypothesis of SAD involves the photic regulation of melatonin secretion. An abnormal sensitivity to light-induced inhibition of melatonin secretion has been hypothesized in SAD,<sup>84,85</sup> and melatonin could modulate the sensitivity of neurons to 5-HT stimulation.<sup>86</sup> However, controversial findings have been reported, and the baseline levels of melatonin between patients and control subjects have not always been comparable.<sup>78,87-91</sup>

A serious limitation of most previous studies is the masking effects of rest-activity cycles on the rhythms observed. A few studies<sup>20,75,76,92</sup> have used more sophisticated techniques, such as the constant routine procedure, to unravel the endogenous circadian phase of the core body temperature, plasma melatonin rhythms and plasma cortisol rhythms. Even with the use of the constant routine procedure, care must be taken to control for the length of sleep episodes between the experimental conditions. For instance, Avery et al<sup>75</sup> have reported a significant phase advance shift of the circadian rhythm of plasma cortisol after a week of morning phototherapy, compared with baseline and with control subjects. However, patients with SAD had a later rhythm at the start of the study compared with that of control subjects. Thus, an advance of the sleep schedule during the week of phototherapy might have contributed significantly to the between-group differences. This particular study is not a convincing demonstration of the phase advance hypothesis. In a recent and original study,<sup>93</sup> a 54-year-old man with SAD was enrolled in a forced desynchrony experiment in which he was scheduled to live on 20-hour days for 120 hours. He was studied during a depressive episode and after phototherapy. This study revealed the presence of a significant variation in mood levels, as measured by the Adjective Mood Scale. During the depressive episode, the circadian variation of mood was shifted earlier by about 2 hours compared with the recovery phase. Since the patient maintained a regular sleep schedule in the 4 days preceding his admission to the laboratory, this study suggests that the temporal relation between the circadian rhythm of mood and the sleep-wake cycle might be disturbed during depressive episodes. Extension of this particular study should clarify whether the circadian variation in other behavioural parameters — such as sleep organization, sleep propen-

sity and vigilance levels — is abnormal in winter depression.

## Bipolar disorder

Most studies looking at the relation between affective disorders and sleep have mixed patients with bipolar and unipolar depression. The disturbances of sleep and circadian rhythms described for unipolar patients were also reported for patients with bipolar disorder during their depressive phases. Sleep disturbances have been consistently observed in bipolar disorder and often precede relapses of depression or mania.<sup>94</sup> These disturbances consist of insomnia or hypersomnia, early morning awakenings, and polygraphically documented reduction of sleep efficiency and REM sleep latency. Moreover, a significant percentage of healthy subjects who are first-degree relatives of patients with bipolar disorder presented conspicuous sleep abnormalities, suggesting that sleep patterns may serve as a trait marker for vulnerability to psychiatric illnesses.<sup>95</sup> Indeed, the diurnal variation in mood, and the dramatic effect of sleep deprivation and sleep restoration on mood swings, are an important clinical feature of bipolar disorder.<sup>96-100</sup> Sleep disturbances are often seen as an important predictor of psychological deterioration. They can contribute to the escalation of mood levels in bipolar patients and to the triggering of manic episodes.<sup>97</sup> Independent investigators also reported that the switch from mania to depression and back to mania generally occurs during sleep in rapidly cycling mania,<sup>56,96,100</sup> suggesting that sleep disturbances may be of pathophysiologic relevance.

Over the last 20 years, the study of sleep patterns in patients with rapidly cycling manic-depression gained scientific attention because of its usefulness in elucidating the relation between circadian rhythms and affective disorders. Several groups have studied such patients in a time-free environment for several consecutive weeks. They observed that these patients typically experience one or more consecutive 48-hour or 72-hour sleep-wake cycle when they switch from depression to mania.<sup>56,100</sup> They compared this situation to that of healthy volunteers studied in extended time-free conditions, when their sleep-wake cycle spontaneously desynchronizes from their underlying endogenous circadian pacemaker. These observations suggest that an abnormal circadian control of sleep organization may be of pathophysiologic importance in patients with

bipolar disorder. Indeed, phase advances in the diurnal rhythm of melatonin secretion<sup>101</sup> have been reported in these patients. Several authors have also reported that exposure to bright light, a powerful synchronizer of endogenous circadian rhythms, can induce hypomania and mania in susceptible patients<sup>102,103</sup> and that relapses of mania tend to increase during spring.<sup>104</sup> Lengthening of the scotoperiod (the duration of the dark period) has been successful in stabilizing patients with rapidly cycling manic-depression who are resistant to treatment.<sup>105,106</sup> In a study conducted over a 4-year period, Linkowski et al<sup>107</sup> documented sleep patterns and diurnal rhythms of cortisol, prolactin and growth hormones in 8 patients with mania who were not receiving medication just admitted through the emergency department. They reported early timing of the nadir of the circadian curve of plasma cortisol and normal levels of growth hormone and prolactin. Unfortunately, these rhythms were expressed only relative to the time of sleep onset. Their results revealed that the sleep period was reduced, and awakening was earlier in the morning, in patients with mania than in control subjects. According to the phase-response curve of the endogenous circadian pacemaker to light exposure,<sup>18,108,109</sup> this sleep schedule should result in a net phase advance shift. The earlier timing of the diurnal rhythm of plasma cortisol, a reliable circadian marker, may thus be secondary to an altered sleep-wake cycle, rather than the reverse. The disturbance of daily rhythms of activities/social interactions has also been implicated in the deterioration of psychological state in patients with bipolar disorder<sup>110</sup> and even in healthy subjects.<sup>111,112</sup> In day-to-day life, the changes in activity levels and social interactions are indistinguishable from those of the cycle of sleep, darkness-wakefulness and light. Moreover, social interactions might have a direct effect on the psychological status of psychiatric patients, and this effect is most likely very different from its effect in healthy volunteers. It is thus very difficult to determine whether perturbations in the timing of nonphotic synchronizers have a direct effect on endogenous circadian rhythmicity or on the circadian regulation of mood in psychiatric conditions. This hypothesis will require further experimental exploration.

The reduction of REM sleep latency in patients with depression and mania<sup>94</sup> could also suggest that an abnormal phase advance of the endogenous circadian pacemaker, or an abnormal circadian control of sleep, could be present. However, the reduction of REM sleep

latency did not reach significant levels in Linkowski's study. Despite the presumed importance of circadian rhythms in the pathogenesis of mood and sleep disturbances, very little information is available concerning the circadian control of sleep organization in bipolar disorder. Most previous studies have been confounded by the masking effect of activity and light exposure on the rhythms studied. For instance, early morning awakening,<sup>94</sup> reduced sleep time,<sup>107</sup> and hypersensitivity to light<sup>113,114</sup> have all been observed in patients with mania, and raise the possibility that the observed phase advance of overt circadian rhythms may be the consequence of sleep disturbances. Finally, it is interesting to note that psychoactive treatments such as lithium, anxiolytics, antidepressants and even electroconvulsive therapy have all been reported to alter at least one circadian parameter, such as the amplitude, phase, period or entrainment of endogenous rhythms.<sup>56,115-119</sup>

### Chronic schizophrenia

Disturbed nocturnal sleep is a common observation among patients with chronic schizophrenia<sup>120-122</sup> and is exacerbated during psychotic relapses.<sup>123</sup> Although sleep architecture improves with long-term neuroleptic treatment, sleep still remains fragmented and does not return to a normal pattern,<sup>121</sup> suggesting that these abnormalities may be of pathophysiological relevance. Indeed, it was reported that sleep efficiency is inversely correlated with the level of psychosis in patients with chronic schizophrenia.<sup>122</sup> The most replicated finding across all studies is a significant reduction in sleep continuity associated with prolonged sleep latency, poorer sleep efficiency, reduced total sleep time, and increased wake-time after sleep onset.<sup>123-131</sup> Abnormal sleep continuity has been consistently reported in studies of patients with schizophrenia who have never received medication, those who had withdrawn from neuroleptic medications, and those receiving potent and numerous psychoactive drugs.<sup>121</sup> Sleep efficiency in patients with schizophrenia is poorer than that in healthy controls; this is true regardless of age, duration of the disorder, psychological state at the time of study, and pharmacological treatment.<sup>125</sup> Although robust, altered sleep continuity is not specific to chronic schizophrenia, since it is observed in a wide variety, if not most, psychiatric conditions, including anxiety or affective disorders.

Shortened REM sleep latency, higher REM sleep percentage during the first REM period, higher REM den-



sities and a failure of REM rebound after REM sleep deprivation<sup>120–122,127,132</sup> have been observed in patients with schizophrenia. However, several contradictory results have been reported, and REM sleep variables are not consistently affected.<sup>125,131</sup> Several pieces of evidence suggest that the most pronounced abnormalities of REM sleep could be attributed to neuroleptic treatment (for a review see Taylor et al<sup>121</sup>), withdrawal from earlier neuroleptic treatments,<sup>122,127</sup> tardive dyskinesia,<sup>129</sup> or unclear diagnostic criteria permissive to patients with the presence of depressive symptoms. The confounding effect of neuroleptic treatment is a serious limitation of most previous studies, although patients previously treated by depot neuroleptics in the past 6 months have been excluded. Indeed, prior neuroleptic drugs taken orally may continue to affect sleep structure even several months after their levels are undetectable in plasma.<sup>127</sup> An effect of age is also possible, since shortened REM sleep latency has been reported in older patients with schizophrenia who have never received neuroleptic treatments,<sup>133</sup> but not in younger ones.<sup>125</sup> The interest in studying REM sleep in chronic schizophrenia goes back to 1955, when Dement<sup>134</sup> correlated the paucity of dream recall in patients with schizophrenia with abnormal REM parameters. The similarity between psychosis and dream content seemed appealing to several investigators and has remained a preferential area of investigation in psychiatry for several years. However, further studies are needed to determine whether REM sleep variables are clinically important in chronic schizophrenia and to clarify which aspects of it are affected.

A few studies have looked at the spectral composition of electroencephalograms (EEGs) during REM sleep. This aspect is particularly important, since visually scored sleep may not reveal all the subtle changes of sleep structure in psychiatric conditions. This is true for all sleep stages, especially SWS. Reduced SWS<sup>124,126,135,136</sup> has been observed in schizophrenia. Several investigators have claimed that this reduction, especially of Stage 4 sleep, is the most consistent and clinically relevant observation in chronic schizophrenia.<sup>126,127,135</sup> However, contradictory results have been observed, especially in drug-free or never-medicated patients. Automated analysis of EEG, power amplitude analysis and spectral analysis of brain waves yielded more exciting results. Recent studies have revealed a substantial and consistent reduction of high-amplitude (> 35  $\mu$ V) low-frequency (0.33–1.0 Hz) delta waves in drug-free patients with schizophrenia, especially in anterior frontal areas.

Significant negative correlations were observed between reduced SWS or high-amplitude low-frequency delta waves and between negative symptoms<sup>125,137</sup> or neurocognitive impairment in schizophrenia.

Since the original attempt by Mills et al<sup>139</sup> to do a free-running study of two patients with schizophrenia, there have been very few in-depth circadian studies of schizophrenia. Irregular sleep–wake cycles<sup>140,141</sup> or abnormal diurnal rhythms of monoamines,<sup>142</sup> prolactin,<sup>143</sup> and melatonin,<sup>144,145</sup> have been reported in patients with schizophrenia. The study by Mills et al revealed the presence of robust circadian rhythms of core body temperature and urinary electrolytes, and a shorter-than-24-hour sleep–wake cycle in patients with pharmacologically treated schizophrenia. Although confounded by the presence of antidepressant and neuroleptic drugs, which could affect the rest–activity cycle and circadian rhythms,<sup>56,116,146,147</sup> these results are consistent with the early bedtimes often observed in these patients.<sup>139</sup> A recent report found a phase advance shift in the diurnal rhythms of plasma tryptophan (+2.9 hours), plasma melatonin (+1.2 hour) and plasma prolactin (+1.5 hour) in 90 drug-free patients with schizophrenia compared with healthy controls.<sup>142</sup> This raises the possibility that the abnormalities of sleep continuity reported by several investigators might be related to a phase advance of the endogenous circadian timing system. This phase advance could also explain the higher sleep latencies reported, since patients would try to fall asleep during the so-called “forbidden zone for sleep.”<sup>148</sup> This zone is characterized by higher waking propensity and occurs approximately 2 hours before regular bedtime, coinciding with the crest of the endogenous circadian curve of core body temperature. However, if the hypothesis of a circadian phase advance were true, one would also expect to observe consistent alterations of REM sleep, namely a reduction in its latency and a shift towards an earlier distribution within the sleep episode. This observation is supported by several studies, but is not consistently reported. Neuroleptic administration could also affect circadian physiology and retinal sensitivity to light,<sup>149</sup> which further complicates the interpretation of these results. More studies are needed to clarify this hypothesis.

## Conclusions

In psychiatry, sleep disturbances are an important cause of a diminished quality of life and frequently lead

to treatment with numerous drugs with unfortunate side effects. Since the start of the last century, sleep and circadian rhythms have been the focus of mounting scientific interest. Concomitantly, the chronobiological perspective of psychiatric disorders has fortunately opened new areas of investigation, and significant advances have led to innovative hypotheses and therapeutic interventions. It is imperative to continue this line of investigation despite its numerous methodological difficulties and to integrate the chronobiological perspective with future physiological and pharmacological studies of major psychiatric disorders.

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