At this time, both patients and professionals seem to have an unprecedented interest in circadian rhythms. We now know that the body's clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and that the SCN regulates the pineal gland's secretion of the hormone melatonin.

In humans as well as animals, light suppresses melatonin secretion; recent evidence shows that even ordinary room light can have this effect. Because light suppresses melatonin secretion, the hormone is typically secreted at night. Furthermore, the SCN can "remember" the day-length to which it has been recently exposed, so the timing of nocturnal melatonin secretion is determined by the "lights on" and "lights off" times of the preceding days. In 1994, scientists cloned genes regulating circadian rhythms in mice, making the circadian system the first complex behavioral system whose genetic underpinnings could begin to be unraveled in mammals (Vitaterna and coworkers).

In mood disorder research, interest in circadian rhythms is not new. For at least 50 years, investigators have questioned whether abnormalities in circadian rhythm regulation might be involved in the pathogenesis of mood disorders, including rapid-cycling bipolar disorder. These questions were motivated by three clinical observations. The first of these was that the sleep duration of patients often changes dramatically as they cycle between mania and depression, bipolar depression is typically associated with hypersomnia; while mania is characterized by extreme and sometimes total insomnia.

The second observation was that approximately 60 percent of depressed patients experience remission after a night of total or partial sleep deprivation (SD). In bipolar, patients, SD may actually cause a switch into hypomania or mania. However, this "upward" switch usually lasts only until the patient undergoes recovery sleep, leading to the formulation that SD, or extended wakefulness, is antidepressant, (or manicogenic), while sleep is depressogenic, (Wehr). The antidepressant effects of SD are conceptually important because they show that changes in sleep duration are more than just symptoms of the illness, and also play a pathogenic role.

Using a longitudinal analysis of mood and sleep in a sample of patients with rapid-cycling bipolar disorder, we recently demonstrated that decreased sleep duration precedes, rather than simply follows, a switch into hypomania; or mania (Leibenluft and coworkers, in press). Furthermore, in this sample, decreased sleep duration was more consistently associated with a shift to an earlier wake-up time than it was with a shift to a later bedtime. Pharmacologically, it is easier to manipulate the time a patient goes to sleep than to change the time he or she wakes up; perhaps for this reason, clinicians have generally attended less to wake-up time than to sleep-onset time. However, these data indicate that interventions designed to shift patients' wake-up time may deserve further study.

The third observation implicating abnormal circadian rhythms in the pathogenesis of mood disorders concerns diurnal variation. In its classic, typical form, diurnal variation is defined as a gradual improvement in the patient's depressed mood as the day wears on. Like sleep deprivation, typical diurnal variation demonstrates that extended wakefulness is associated with an antidepressant response. We recently extended the concept of diurnal variation to bipolar patients with data demonstrating that rapid-cycling patients are more likely to switch "up" (i.e., from depression or euthymia into hypomania) during the day, and to switch "down" (from hypomania or euthymia into...
depression) overnight, while they sleep (Susana Feldman-Naim, M.D., and coworkers, unpublished data). Thus, once again, extended wakefulness is associated with an antidepressant response, while sleep appears to be depressogenic.

Specific theories have been advanced as to how circadian rhythm dysfunction might lead to rapid-cycling bipolar disorder. In 1968, Halberg suggested that some, but not all, circadian rhythms in such patients were not synchronized with the 24-hour day-night cycle (Halberg). According to Halberg's hypothesis, the interaction between the unsynchronized, "free-running" rhythms and the normally synchronized (entrained) rhythms causes switches back and forth between mania and depression.

Kriple and colleagues then presented data demonstrating what appeared to be a free-running temperature rhythm in five of seven rapid-cycling patients. In these patients, the period (time taken to complete one cycle) was abnormally short, in essence showing that patients with rapid mood cycles had rapid physiological cycles. However, subsequent investigators have not generally found either free-running or unusually fast circadian rhythms in patients with rapid-cycling bipolar disorder.

In the 1970s and ‘80s Wehr and collaborators, working at the National Institute of Mental Health, continued to study biological rhythms in this patient population. Using both cross-sectional and longitudinal designs, they showed that the phase (timing) of patients’ sleep, temperature and motor activity rhythms varied systematically as they cycled between hypomania or mania and depression. Specifically, the timing of these rhythms appeared to be earlier in manic than in depressed patients, and earlier in depressed patients than in controls (Wehr and colleagues 1980). We now have preliminary data indicating a similar pattern in the time of onset of nocturnal melatonin secretion. These new data show that, in rapid-cycling bipolar patients, the time of nocturnal melatonin onset may be approximately 90 minutes earlier when they are hypomanic, compared to when they are depressed (Leibenluft and colleagues 1993). It is as if rapid-cycling patients might have an endogenous form of jet lag, internally traveling back and forth over one or two time zones as they cycle between hypomania and depression. Indeed, several studies show that bipolar patients are at risk to develop an affective episode when they travel across time zones (Young).

What might cause these phase shifts in the timing (phase) of nocturnal melatonin secretion? It is possible that phase shifts in nocturnal melatonin secretion precede patients’ mood switches and play a pathogenic role in mood cycling. However, it is also possible that the phase shifts are epiphenomena caused by the patient's symptoms. Specifically, the phase shifts may be secondary to the changes in the sleep-wake cycle; that occur with mood cycling. The phase of circadian rhythms is determined by zeitgebers (“time-givers”).

While light is the most potent zeitgeber, physical activity, eating and social routines can probably also affect the timing of circadian rhythms. The timing of these zeitgebers is often different when a patient is hypomanic, compared to when he or she is depressed, and shifts in the timing of zeitgebers would cause phase shifts in circadian rhythms.

However, a third possibility also exists. We suggest that phase shifts in melatonin secretion and other circadian rhythms are not the primary cause of mood cycling, but they are also not irrelevant epiphenomena. We hypothesize that phase shifts in melatonin secretion are secondary to the patient's symptoms or to more fundamental causes of bipolar illness, but they nonetheless have pathogenic significance and contribute to the development of a full-blown affective episode. This formulation is analogous to that of Wehr and coworkers (1987) in describing the contribution of sleep deprivation to the development of manic episodes. These authors suggested that insomnia, which is itself a symptom of mania, contributes to the development of a manic episode because it causes sleep deprivation. In other words, insomnia is both a symptom and a cause of mania. If one treats the insomnia early and aggressively, one can truncate an episode, or prevent mild or moderate symptoms from snowballing into a severe and destructive episode. Similarly, it is possible that the shifts in circadian rhythms, while not the initial cause of a mood switch, contribute to the severity and duration of an episode, and thus play a role in determining the course of illness.

We are currently testing this hypothesis by determining whether interventions designed to prevent phase shifts in nocturnal melatonin secretion have therapeutic effects in rapid-cycling bipolar patients. One such experimental treatment involves the use of phototherapy. Data indicate that midday bright light may increase the amplitude of nocturnal melatonin secretion. Since increasing the amplitude of a rhythm makes it more resistant to phase shifts, midday light might be expected to stabilize the time of nocturnal melatonin secretion. In other words, midday phototherapy administered to these patients might prevent the shifts in timing of nocturnal melatonin secretion that we believe have pathogenic significance. After encouraging results with a small number of patients, we are now conducting a formal, controlled trial of this intervention. Interestingly, morning
bright light, which shifts patients' circadian rhythms, may have caused several of our rapid-cycling bipolar patients to cycle more dramatically. Thus, even if circadian abnormalities are neither the sole nor the primary cause of bipolar illness, it is possible that circadian interventions can have therapeutic utility. Compared to psychotropic medications, circadian interventions are relatively flexible therapeutic modalities; they have a rapid onset and offset of action, and their clinical effects may be altered by changing the time that they are administered. This flexibility may be particularly useful in rapid-cycling bipolar patients, whose frequent mood cycles may require rapid alterations in their therapeutic regimen. Further research will indicate what, if any, role circadian dysfunction plays in the pathogenesis of rapid-cycling bipolar disorder, and whether circadian interventions can be helpful to these often treatment-resistant patients.

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