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Commentary

# Mood Episode Recovery Changes Gear in the Intrinsic Clock

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Bipolar disorder, also known as manic-depressive illness, which affects three out of 200 people is a long-term disease, presents remittent depressive, hypomanic, manic or mixed episodes of illness, and bears a serious risk of death from suicide (Grande et al., 2016). About half of the time patients with bipolar disorder have symptoms impairing their work, social activities or relationships with others. Treatment focuses on preventing the recurrence of episodes and can clearly improve the outcome.

Circadian clocks are intrinsic pacemakers. They evolve their properties, when subjected to selection, but have remained conservative during evolution (Rosbash, 2009). These intrinsic clocks not only generate the oscillation in those physiological functions and behaviors that demonstrate the daily and seasonal fluctuations, but also maintain these oscillations in their adaptive response to the time-giving signals, such as exposure to light, which they receive from the habitat.

Dysfunction of the circadian clocks plays a role in mood disorders (Baron and Reid, 2014). It is not known, however, whether they have a causal role in the etiology or display their effects on mood later during the pathogenesis.

Basic research findings from mice recently pointed out that circadian rhythm abnormalities directly correlated with depression-like behavior following unpredictable chronic mild stress in wild-type mice (Logan et al., 2015), and that the genetic disruption of circadian rhythms by specific deletion of a key clock gene in the suprachiasmatic nucleus did cause helplessness, behavioral despair and anxiety-like behavior (Landgraf et al., 2016). Now, new pieces have been added to this puzzling picture.

Recently in *EBioMedicine*, Moon et al. (2016) reported a clinical study and suggested that abnormalities in the circadian clocks might be a key pathophysiological mechanism of bipolar disorder. They repeatedly measured biochemical circadian rhythms in patients with bipolar disorder during hospitalization from ill states at admission to euthymic states at discharge, and compared them with those of healthy controls.

Moon and colleagues found that the circadian rhythms had abnormal phases during acute mood episodes, and that these returned to normal after treatment. The way back to normal mood, however, took diverse routes, since the recovery of depressive episodes was through phase advances of 4 to 5 h and that of mixed episodes, which present depressive and manic states together, through phase advances of 6 to 7 h. In contrast, concerning manic episodes, the abnormal phases resolved on average through delays by 7 h or advances by 17 h to recover the normal rhythm after treatment.

Current clinical practice should next pay more attention to the assessment of the timing and regularity of bedtimes and wake-up calls, rather than just sleep duration and sleep quality. It appears that even after taking sleep disturbances into account, current depressive episodes tend to demonstrate a link to the timing of daily activities guided by the circadian clocks (Antypa et al., 2016). Therefore, abnormalities in the circadian clocks deserve clinical attention.

Significance of the report of Moon and colleagues to basic scientists lies in the possibility to develop of the assessment of circadian rhythms a biomarker for diagnosis and treatment monitoring in bipolar disorder. In this effort, the molecular characterization of the individual's schedule for the timing of daily activities is the first step. These schedules form a continuum, or chronotype, with the anchorage poles of "early birds" and "night owls". Some preliminary attempts to reach this goal have been made (Kasukawa et al., 2012).

This being said, there are naturally many unanswered questions that still need addressing. Questions such as, whether the findings of Moon and colleagues hold in mood disorders at large, or in other words, can they be replicated also in depressive disorders, await. On the other hand, a clinically hot question will be which one, if any, of the trajectories for recovery does hold in those mood disorders that follow a seasonal pattern (Partonen and Lönnqvist, 1998), since these patients are most likely to benefit from treatment options that influence the circadian clocks. All these need to be addressed with prospective trials.

There is a lot of work ahead in elucidating the pathogenic molecules and dissecting the pathways for causality. The question whether abnormalities in the circadian clock properties cause a mood episode, or whether emergence of a mood episode is not due to such abnormalities but other reasons driving the circadian clocks to abnormal phase orientations, is the golden key here. If they were causal, the next question will be whether there is a major "mood gene". If there were some, the hunt for mechanistic explanation will be on, etc.

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The take-home message from the report of Moon and colleagues in *EBioMedicine* is that it not only extends our understanding, but also opens a new view on clinical interventions that might be discovered useful for the treatment of bipolar disorder. Of course, it remains to be verified, whether such approach is productive in providing effective tools for secondary and tertiary prevention, and whether it can thereby improve the quality of everyday life and save lives.

## Disclosure

The author declared no conflicts of interest.

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