

# Circadian Rhythms and Mood Disorders: A Guide for the Perplexed

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Özdemir and coworkers' present contribution<sup>1</sup> to this journal invites the opportunity to outline some of the fundamentals concerning circadian rhythms and affective illness. Consensus or near-consensus has been reached on the tools for assessing and adjusting circadian rhythms, if not on the hypotheses for their role in seasonal affective disorder (SAD, typically winter depression), non-seasonal unipolar major depressive disorder (MDD), and bipolar disorder. First proposed in the 1980s,<sup>2,3</sup> the dim light melatonin onset (DLMO) is now acknowledged as the most accurate biomarker for circadian phase position.<sup>4,5</sup> It can be obtained at home in saliva,<sup>5</sup> conveniently occurring in most cases before habitual bedtime. The dim light requirement was one of many important developments<sup>6(p15)</sup> that have resulted from the discovery that intensity-dependent light suppresses nighttime melatonin production in humans.<sup>7</sup> This discovery continues to advance the field that now includes perhaps the first comprehensively useful laboratory test in psychiatry.

Two types of phase-resetting agents are used to shift circadian rhythms. Bright light (as in the present study<sup>1</sup>) and low-dose melatonin can be given as adjunctive therapy, because they have few contraindications. However, a phase shift in the wrong direction may result if they are not scheduled at the correct time. Patients should first be phase typed, as either advanced ("morning larks") or delayed ("night owls"). An early versus late DLMO is the best way to accomplish objective phase typing, even for circadian disorders in which adjusting the timing of sleep is the clinical goal.<sup>5</sup>

Phase-delayed disorders require bright light in the morning and/or low-dose melatonin in the afternoon/evening to provide a corrective phase advance; phase-advanced disorders require bright light in the evening and/or low-dose melatonin in the morning to provide a therapeutic phase delay.<sup>8,9</sup> Among individuals, optimal treatment times can differ greatly; these are phase-locked to the internal body clock, marked by the DLMO. The resulting shift in the DLMO monitors treatment efficacy and provides for further refinement of optimal treatment times. Thus, the DLMO is comprehensively useful in the diagnosis, and in all stages of treatment, of circadian rhythm disorders.

Over a wide range of intensities, the brighter the light, the greater is its phase-shifting effect. However, higher doses

of melatonin are not necessarily more effective than lower ones.<sup>10</sup> Although there is a dose-response relationship in the physiologic range,<sup>11</sup> higher doses do not confer any additional benefit and increase the risk of sleepiness immediately after taking melatonin (which occurs in approximately one-third of the population). High doses may also be less efficacious in causing phase shifts.<sup>10</sup> Burke and coworkers<sup>12</sup> recently reported that the effects of light and melatonin are equal and additive; however, while their choice of 3,000 lux may approximate the optimal light intensity, their 5-mg melatonin dose was probably an order of magnitude too high and they might have achieved greater phase-shifting effects with lower doses.

The phase shift hypothesis (PSH) is the leading<sup>6</sup> explanation of why SAD patients typically become depressed in the winter and how bright light is antidepressant.<sup>13,14</sup> Accordingly, as day length shortens, circadian rhythms drift out of phase with the sleep/wake cycle, creating a mismatch (internal misalignment) between the set of circadian rhythms tightly coupled to the body clock (cued to the light/dark cycle) and the less tightly coupled set encompassing the sleep/wake cycle and its evoked rhythms. The DLMO and the sleep midpoint, respectively, are the best phase markers for these two sets. The time interval between them, or phase angle difference (PAD), is the best marker for circadian misalignment.<sup>15</sup> Although an optimal alignment "sweet spot" of PAD 6 (an interval of 6 hours between the DLMO and midsleep) has been documented in SAD,<sup>15</sup> the jury is out as to the optimal PAD in MDD and bipolar disorder. PAD is also used for phase typing SAD patients: PAD ≤ 6 indicates phase-delayed circadian misalignment (a DLMO that is delayed with respect to midsleep) and requires treatment with bright light in the morning and/or low-dose melatonin in the afternoon/evening; PAD > 6 (up to one-third of SAD patients<sup>15</sup>) indicates phase-advanced circadian misalignment (a DLMO that is advanced with respect to midsleep) and requires treatment with bright light in the evening and/or low-dose melatonin in the morning. Monitoring PAD can be used to assess correction of circadian misalignment. Phase-delayed circadian misalignment appears to predominate in MDD,<sup>16-19</sup> although each patient may have his or her own ipsative<sup>14</sup> sweet spot, longer or even shorter than PAD 6. It is not known which specific rhythm(s) in the two sets marked by the DLMO and midsleep are pathogenic when misaligned (in an otherwise vulnerable individual); the endogenous melatonin rhythm is not likely to be one of them. It is also important to keep in mind that while the DLMO marks the phase of the circadian rhythm of sleep

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propensity, the rise in endogenous melatonin levels does not initiate or maintain sleep.

It was intended in the present study<sup>1</sup> to begin light exposure no later than 8.5 hours after DLMO, which was recommended by the Terman research group (Terman et al<sup>20</sup>), or 2.5 hours after sleep midpoint if the DLMO could not be determined (also recommended<sup>20(p69)</sup> [subsequently qualified<sup>20(p74)</sup>] by the Terman group in an article that has been previously critiqued<sup>8,9</sup>). This recommendation is problematic because it usually curtails sleep.<sup>20</sup> Accordingly, if patients in the present study<sup>1</sup> slept completely within the approximately 10:00 PM–6:30 AM window of opportunity, they would have had to have been awakened at 4:45 AM, 2.5 hours after their 2:15 AM midsleep time. This recommendation<sup>20</sup> also goes against a key requirement of the PSH, in that the requisite phase advance in the DLMO needs to be greater if wake time is concomitantly advanced, in order to correct phase-delayed circadian misalignment (a DLMO that is delayed with respect to the sleep/wake cycle).<sup>8,9</sup> In the present study,<sup>1</sup> patients were actually scheduled to start 7,000 lux light exposure at 7 AM. Although this is 30 minutes after the optimal time (immediately upon awakening), it is better than the Terman group's recommendation,<sup>20</sup> which would have required waking up 1.75 hours earlier than usual for the 1 hour of light exposure. It should also be noted that some SAD patients have phase-advanced circadian misalignment,<sup>15</sup> best treated with evening bright light (and/or morning low-dose melatonin).<sup>13,15</sup>

While the present article<sup>1</sup> is commendable for studying a population of inpatients with severe MDD, the authors acknowledge several limitations. Primary among these is the absence of a placebo control group, which is always a challenge for light treatment studies. Dim light is no longer (if it ever was<sup>21</sup>) a credible placebo. Altering the timing of bright light remains a way of controlling for the placebo effect, as when my colleagues and I<sup>13</sup> showed that morning light was superior to evening light and that the combination produced an intermediate antidepressant effect that was also not different from baseline ratings (evidence against the photoperiod hypothesis,<sup>22</sup> which posits that extension of day length in the morning and in the evening [to shorten nighttime melatonin duration] would be most antidepressant).

Low-dose melatonin is ideally suited for minimizing and controlling for—if not completely avoiding—the placebo effect. Patients usually do not become sleepy with low-dose melatonin and cannot distinguish it from placebo. The use of low-dose melatonin and concurrent measurement of PAD offers the opportunity for conducting rigorously controlled studies, at least with regard to establishing the PSH. Low-dose melatonin has also provided for concurrent testing of the photoperiod hypothesis, which failed another (serendipitous) test when patients did not do relatively worse after extending melatonin duration.<sup>15</sup>

The authors of the present study<sup>1</sup> correctly assumed that the circadian misalignment component of MDD is likely to be the phase-delayed type and thus appropriately

chose to schedule bright light in the morning. As mentioned above, most patients with SAD<sup>13,15</sup> and perhaps even a greater proportion of MDD patients<sup>16–19</sup> have phase-delayed circadian misalignment. Correction of circadian misalignment may be sufficient treatment in SAD, but it is probably a smaller component in MDD.

Bipolar patients figured prominently in the formulation of the phase advance hypothesis.<sup>23</sup> Because there are few, if any, studies of PAD in these patients (not to mention other psychiatric illnesses), the type and clinical meaningfulness of circadian misalignment in these disorders remain to be determined. Recent findings<sup>24</sup> relating the anxiety features of SAD to PAD invite studies of the circadian misalignment component of anxiety disorders.

Before closing, it is important to discuss the fact that their patients did not relapse after bright light treatment was discontinued,<sup>1</sup> which is not what usually happens in light treatment of typical SAD patients. Perhaps in MDD, in which the circadian rhythm component is less important than in SAD, once internal misalignment is corrected—albeit temporarily—other biological or behavioral factors are set on a course of improvement. Alternatively, perhaps venlafaxine maintains corrected alignment. Finally, it cannot be ruled out that bright light has an antidepressant mechanism unrelated to circadian phase-resetting that has an abiding benefit after discontinuation; if not shared by melatonin, this could be the one advantage of light therapy over melatonin treatment. All of these possible antidepressant mechanisms can be ruled in or out by measuring PAD.

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## REFERENCES

- Özdemir PG, Boysan M, Smolensky MH, et al. Comparison of venlafaxine alone versus venlafaxine plus bright light therapy combination for severe major depressive disorder. *J Clin Psychiatry*. 2015;76(5):e645–e654.
- Lewy AJ. Effects of light on human melatonin production and the human circadian system. *Prog Neuropsychopharmacol Biol Psychiatry*. 1983;7(4–6):551–556.
- Lewy AJ, Sack RL. The dim light melatonin onset as a marker for circadian phase position. *Chronobiol Int*. 1989;6(1):93–102.
- Klerman EB, Gershengorn HB, Duffy JF, et al. Comparisons of the variability of three markers of the human circadian pacemaker. *J Biol Rhythms*. 2002;17(2):181–193.
- Keijzer H, Smits MG, Duffy JF, et al. Why the dim light melatonin onset (DLMO) should be measured before treatment of patients with circadian rhythm sleep disorders. *Sleep Med Rev*. 2014;18(4):333–339.
- Overy C, Tansey EM, eds. *The Recent History of Seasonal Affective Disorder (SAD)*. London, UK: University of London; 2014. [http://www.histmodbiomed.org/sites/default/files/W51\\_LoRes.pdf](http://www.histmodbiomed.org/sites/default/files/W51_LoRes.pdf). Accessed December 4, 2014.
- Lewy AJ, Wehr TA, Goodwin FK, et al. Light suppresses melatonin secretion in humans. *Science*. 1980;210(4475):1267–1269.
- Lewy AJ. Melatonin and human chronobiology. *Cold Spring Harb Symp Quant Biol*. 2007;72(1):623–636.
- Lewy AJ. Endogenous and exogenous melatonin, the sleep/wake cycle and the circadian component of affective disorder. In: Kushida C, ed. *Encyclopedia of Sleep*. Vol 3. Oxford, UK: Oxford University Press; 2013:126–137.
- Lewy AJ, Emens JS, Sack RL, et al. Low, but not high, doses of melatonin entrained a free-running blind person with a long circadian period.

- Chronobiol Int.* 2002;19(3):649–658.
11. Lewy AJ, Emens JS, Lefler BJ, et al. Melatonin entrains free-running blind people according to a physiological dose-response curve. *Chronobiol Int.* 2005;22(6):1093–1106.
  12. Burke TM, Markwald RR, Chinoy ED, et al. Combination of light and melatonin time cues for phase advancing the human circadian clock. *Sleep.* 2013;36(11):1617–1624.
  13. Lewy AJ, Sack RL, Miller LS, et al. Antidepressant and circadian phase-shifting effects of light. *Science.* 1987;235(4786):352–354.
  14. Lewy AJ, Sack RL, Singer CM, et al. The phase shift hypothesis for bright light's therapeutic mechanism of action: theoretical considerations and experimental evidence. *Psychopharmacol Bull.* 1987;23(3):349–353.
  15. Lewy AJ, Lefler BJ, Emens JS, et al. The circadian basis of winter depression. *Proc Natl Acad Sci U S A.* 2006;103(19):7414–7419.
  16. Emens J, Lewy A, Kinzie JM, et al. Circadian misalignment in major depressive disorder. *Psychiatry Res.* 2009;168(3):259–261.
  17. Buckley TM, Schatzberg AF. A pilot study of the phase angle between cortisol and melatonin in major depression—a potential biomarker? *J Psychiatr Res.* 2010;44(2):69–74.
  18. Hasler BP, Buysse DJ, Kupfer DJ, et al. Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: further evidence for circadian misalignment in non-seasonal depression. *Psychiatry Res.* 2010;178(1):205–207.
  19. Rahman SA, Kayumov L, Shapiro CM. Antidepressant action of melatonin in the treatment of Delayed Sleep Phase Syndrome. *Sleep Med.* 2010;11(2):131–136.
  20. Terman JS, Terman M, Lo ES, et al. Circadian time of morning light administration and therapeutic response in winter depression. *Arch Gen Psychiatry.* 2001;58(1):69–75.
  21. Rosenthal NE, Sack DA, Gillin JC, et al. Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry.* 1984;41(1):72–80.
  22. Wehr TA, Duncan WC Jr, Sher L, et al. A circadian signal of change of season in patients with seasonal affective disorder. *Arch Gen Psychiatry.* 2001;58(12):1108–1114.
  23. Wehr TA, Wirz-Justice A, Goodwin FK, et al. Phase advance of the circadian sleep-wake cycle as an antidepressant. *Science.* 1979;206(4419):710–713.
  24. Lewy AJ, Tutek J, Havel L, et al. The role of circadian rhythms, light and melatonin in sad and nonseasonal affective and anxiety disorders. *Curr Psychiatry Rev.* 2014;10(3):214–222.