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To cite this article: Andrew N. Coogan & Johannes Thome (2011) Chronotherapeutics and psychiatry: Setting the clock to relieve the symptoms, The World Journal of Biological Psychiatry, 12:sup1, 40-43, DOI: [10.3109/15622975.2011.598389](https://doi.org/10.3109/15622975.2011.598389)

To link to this article: <https://doi.org/10.3109/15622975.2011.598389>



Published online: 12 Sep 2011.



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ORIGINAL INVESTIGATION

Chronotherapeutics and psychiatry: Setting the clock to relieve the symptoms

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Abstract

Circadian rhythms are near 24-h cycles in a number of physiological and behavioural parameters and the underpinning circadian timing systems is one of the key homeostatic regulatory systems in mammalian physiology. Many common psychiatric conditions are associated with disrupted sleep, including a common occurrence of delayed or advanced phase sleep syndromes, which in themselves may be indicative of dysregulated circadian timing in these disorders. In this article we discuss the evidence for abnormal circadian rhythms in seasonal affective disorder, bipolar disorder and attention deficit/hyperactivity disorder. Much of this evidence suggest that these conditions are associated with either phase delays or phase advances of core phase markers of the circadian clock such as melatonin or core body temperature, suggesting the presence of circadian desynchrony in these conditions. We also highlight findings that pharmacological and/or behavioural interventions that ameliorate circadian misalignments are efficacious in producing symptomatic relief, suggesting an intrinsic link between the circadian and affective systems that can be manipulated for clinical benefit.

Key words: *Circadian; depression; chronotherapeutics*

Introduction

Circadian rhythms are recurring near 24-h patterns that occur in a host of metabolic, physiological, behavioural and cognitive processes. These rhythms are generated by internal circadian timekeeping system which serves to impose a temporal architecture on an organism's physiology (Reppert and Weaver 2002). In constant environmental conditions, the internally generated circadian rhythm may deviate from 24 h exactly (circadian does indeed translate as about a day), but in any normal situation that an animal may find itself in, it will be exposed to a number of environmental time cues, such as sunrise/sunset, food availability, social interaction and ambient temperate fluctuations. These environmental factors may act as entraining, or synchronising inputs to the circadian clock (Zeitgebers) in order to ensure that the internally generated time is appropriate to environmental cycles. For humans, and other animals, the dominant Zeitgeber is light, and as the solar cycle is by definition 24 h, then normally the circadian clock is entrained

to this cycle so as to display a period of exactly 24 h. However, there is accumulating evidence that a number of factors, such as neurological and psychiatric disorders, medication, shift work and old age may weaken the entrainment of the central clock to environmental Zeitgebers, in turn leading to a circadian desynchrony between internal and external cycles (e.g., Beynon et al. 2009; Wulff et al. 2010; Coogan et al. 2011). Such desynchrony may in turn be detrimental to psychological and physiological processes. In this article I will explore the evidence that such circadian dysfunction may occur in psychiatric disorders, and explore the possibilities and applications of treatments that restore circadian synchrony being used for symptomatic relief in such conditions.

Evidence for abnormal circadian timekeeping in psychiatric disorders

Clock genes are the core molecular components that allow for the generation of circadian rhythmicity.

A number of genetic association studies have linked polymorphisms in a number of clock genes with a number of psychiatric disorders, such as major depression, bipolar disorder, attention-deficit/hyperactivity disorder, schizophrenia and seasonal-affective disorder (Lamont et al. 2007). Such associations are of interest, but care must always be taken in the interpretation of such results given the paucity of data on the influences on such polymorphisms on protein function and ultimately circadian function.

More direct evidence comes from the analysis of circadian rhythms in psychiatric patients cohorts when compared to well-matched healthy controls. Often the first signs of disordered circadian function become obvious when manifested through sleep disturbance, which in turn is a very common hallmark of many psychiatric conditions. Circadian abnormalities may present themselves as delayed or advanced sleep phase syndromes, and such disturbances are reported as being co-morbid with major depression, winter depression and ADHD, amongst others (Dagan 2002). Delayed or advanced sleep phase syndromes may be indicative of underlying phase-misalignment of the circadian system, as under the two process model of sleep regulation circadian time has a major influence on sleep onset (Borbély 1982).

A number of studies have directly assessed the functioning of the circadian systems in patients with affective and other psychiatric disorders, using a variety of endocrine, behavioural and molecular approaches. For example, in a seminal study by Lewy et al. (2006) it was reported that seasonal affective disorder (SAD) is associated with a phase-delay in the dim light melatonin onset (DLMO: one of the gold standards for phase-markers of the circadian rhythm) in about two-thirds of patients with SAD with the remaining one-third of patients demonstrating a phase advance of the DLMO. These data indicate that SAD is associated with a misalignment of the circadian clock to the shortening of the photoperiod and delayed light onset during winter. This circadian desynchrony may in turn help explain some of the atypical neurovegetative symptoms that also occur in SAD, such as hyperphagia and consequent weight gain, as the circadian system plays roles in not only in the affective system, but also in other key homeostatic systems such as energy balance and feeding regulation. Further evidence for the role of circadian misalignment in SAD comes from the findings that application of bright light therapy and melatonin treatment, at the appropriate time to counter either the phase delays or advances of the DLMO, alleviates the depression (Lewy et al. 2006).

Studies in patients with bipolar disorder also report changes in circadian parameters. Jones and Evershed (2005) report that euthymic patients display weakened stability and increased variability of circadian motor behaviour as assessed by actigraphy, with circadian variability being found to be predictive of diagnostic group. Ankers and Jones (2009) further report that individuals at high risk of bipolar disorder showed altered circadian patterns in motor activity compared to controls prior to illness onset. Melatonin levels are reported to be suppressed in bipolar disorder, with phase advances of the melatonin rhythm associated with mania and phase delays with depressive episodes or euthymia (Dallassezia and Benedetti 2009). Yang et al. (2009) utilised an *ex vivo* approach to examine circadian rhythms in clock gene expression profiles in fibroblasts either obtained from bipolar disorder patients or healthy controls, and report that *BMAL1*, *PER1*, *PER2*, *REV-ERB- α* and the clock controlled gene *DBP* all tended towards reduced amplitudes of circadian oscillation in bipolar disorder. Further, these authors show that in a sub-group of patient samples there is a significant underexpression of phosphorylated glycogen synthase kinase-3 β (GSK-3 β). This is a striking finding as GSK-3 β is a known substrate for the mood stabiliser lithium. Further, lithium is known to alter the master circadian clock, and its molecular mechanism has recently been described as involving GSK-3 β and *rev-erb- α* (Yin et al. 2006). Thus there appears to be a molecular pathway for the action of lithium on the core circadian clock with apparent therapeutic implications.

If circadian rhythms are altered in bipolar disorder, then might interventions that alter the circadian clock be efficacious in symptomatic relief? It has long been a clinical observation that sleep deprivation is associated with anti-depressant effects, although the mechanism underpinning such effects have been obscure. One such putative mechanism is a phase-resetting effect of sleep deprivation on circadian rhythms, which in turn may counter circadian desynchrony that contributes to depression. Benedetti et al. (2007) examined the effects of total sleep deprivation coupled to light therapy in type I bipolar patients. Anti-depressant effects of the sleep deprivation/light therapy intervention was correlated with increases in daytime activity and phase advances in the actigraphically determined diurnal rhythm, whilst non-responders did not show changes in these parameters. Therefore these authors posit that phase advances of the circadian rhythm is a correlate of the antidepressant action of sleep deprivation/light therapy in a situation that can be seen as being similar to that described above in SAD. The role of circadian factors in symptom cycling in bipolar

disorder has also been examined, with findings that imposition of strict light/dark cycles and bed times as strong Zeitgebers stabilise rapid cyclers (Wehr et al. 1998).

Another common psychiatric condition in which circadian rhythms are being increasingly implicated is attention deficit/hyperactivity disorder (ADHD). Sleep problems are very common in ADHD, in children, adolescents and adults (~50% of children reporting sleep problems and ~80% of adults; Konofal et al. 2010). Again, delayed sleep onset appears to be a common feature, implicating circadian dysfunction in ADHD. This sleep onset insomnia in ADHD has been associated with a phase delay in the DLMO in children (van der Heijden et al. 2005). Such a phase delay in the DLMO has also been reported in adult ADHD patients with chronic sleep onset insomnia (van Veen et al. 2010). These findings are in agreement with previous data that shows a shift towards eveningness in ADHD (Rybak et al. 2007), suggesting again that ADHD may be associated with a circadian desynchrony that may contribute to the psychopathology of the condition. Light therapy in adults with ADHD has been reported to elicit decreased scores on measures of the core pathologies for ADHD, with the strongest predictor for such symptomatic relief being phase advances of the circadian rhythm (Rybak et al. 2006). Melatonin treatment of children with ADHD has also been shown to be effective in treating sleep onset insomnia (Bendz and Scates 2010), raising the possibility that these positive effects may also be mediated through melatonin's circadian actions.

Finally, we come to the issue of agomelatine and depression, a touchstone topic in contemporary chronotherapeutics. Agomelatine is a mixed melatonergic/serotonergic agent which is an agonist at the MT₁, MT₂ receptors and an antagonist at the 5-HT_{2B} and 5-HT_{2C} receptors which is approved by the European Medicines Agency for the treatment of major depression (de Bodinat et al. 2010). Similar to other conditions addressed above, major depression is associated with alterations in circadian rhythms, with patients displaying both phase advances and delays of circadian rhythms (Lam 2008), and a small pilot study has indicated a positive correlation between the severity of depression and the magnitude of the circadian misalignment (Emens et al. 2009). Clinical use of agomelatine is associated with phase advances of circadian rhythms as well as with amelioration of depressive symptoms, particularly in those with severe depression (Gorwood, 2010). A key issue that remains to be resolved is the extent to which the anti-depressant effects of agomelatine are mediated by its chronobiotic effects, by its non-chronobiological effects

through the serotonergic system, and through the interplay of circadian and non-circadian effects. Resolution of these issues will cast much new light on the circadian involvement in mood disorders and lay the ground for the development of novel behavioural and pharmacological treatment.

Conclusion

There are consistent indications in the literature for the perturbation of circadian rhythms in numerous psychiatric disorders. Congruent with this, treatments that alter circadian phase and possibly ameliorate illness-related circadian dysfunction appear to be effective in symptom relief. Further study is needed to understand the causality of the circadian-psychiatric disorder relationship and to better understand how behavioural and pharmaceutical interventions can be best applied in the clinic.

Acknowledgement

None.

Statement of Interest

None.

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