Journal of Cognitive and Behavioral Psychotherapies,
Vol. 13, No. 1a, July 2013, 239-254.

CHRONOBIOLOGY AND CHRONOTHERAPY OF AFFECTIVE DISORDERS

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Abstract
Circadian rhythms are recurring cycles across a range of behavioural, physiological and cognitive domains that display periods of approximately twenty four hours and are generated by an endogenous circadian timing system. In this review we examine the evidence that circadian rhythms are disrupted in affective disorders such as major depression, bipolar disorder and seasonal affective disorder, and examine what the nature of such circadian dysfunction may be. Further, we examine the evidence that chronotherapeutic interventions (both behavioural and pharmacological) that address underlying abnormalities of circadian phase in patients with affective disorders may produce rapid onset and long-lasting symptom relief. We conclude that there is promising data in the literature to support the utility of drawing on a considerable body of neuroscientific knowledge of circadian clock fundamentals to design and implement chronotherapeutic interventions in major affective disorders, but that there is also a need for a more systematic approach involving larger scale studies.

Keywords: Circadian, affective, chronotherapy, depression, bipolar, sleep

Introduction to the circadian system

A most striking finding across a range of common psychiatric conditions is the high rates of co-morbid sleep disturbances. For example, co-morbid insomnia, as defined by the DSM-IV criteria for secondary insomnia, is present in 37% of those with a diagnosis of schizophrenia (Xiang et al, 2008), 41% in major depression (Stewart et al, 2006), 24% in the euthymic phase of bipolar disorder (Brill, Penagaluri, Roberts, Gao, & El-Mallakh, 2011) and 27% in adult attention deficit hyperactivity disorder (Schredl, Alm, & Sobinski, 2011). Indeed, when one examines the rates of sleep disturbances that are sub-threshold for a diagnosis of insomnia, or sleep disturbances such as hypersomnias, these are found to occur

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in the vast majority of such patients. For example, in major depression the rates of sleep dysfunction is 90% (Breslau, Roth, Rosenthal, & Andreski, 1996) leading to the contention that sleep dysfunction should not be considered a co-morbid condition of major depression, and rather should be viewed as a core symptom (Mendlewicz, 2009).

Out of these striking findings arises the fundamental question of why there is this very close link between such conditions and sleep disturbances. Aside from the numerous unanswered questions about the aetiology of common psychiatric conditions, we may look towards what is known about the regulation of sleep for clues. Borbely (1982) proposed the two process model of sleep-wake control, where the drive towards sleep or wakefulness is determined by the interaction of two processes, the homeostatic process (process S) and the circadian process (process C). It is to the circadian regulation of the sleep-wake cycle that we will concern ourselves in this review, as there is considerably greater mechanistic insight into this over homeostatic processes, but we will also consider the important interplay between these two key processes (for example in considering the anti-depressant effects of sleep deprivation).

Circadian rhythms are recurring cycles that display periods of about twenty four hours, and are manifested across a range of behavioural, physiological and cognitive processes (Cagampang and Bruce, 2012; Valdez, Ramirez,& Garcia, 2012). These rhythms are driven by an endogenous circadian timekeeping system, and persist in the absence of environmental time cues (Reppert & Weaver, 2002). At a systems level, the master circadian pacemaker is located to the suprachiasmatic nuclei (SCN) of the ventral anterior hypothalamus (Ralph, Foster, Davis, & Menaker, 1990). There are also a large number of central and peripheral sites that possess autonomous or semi-autonomous circadian clocks as well (Guilding & Piggins, 2007; Dibner, Schibler & Albrecht, 2010), and as such the circadian timing mechanism as a whole functions as a highly complex, distributed and hierarchical system with communication and transmission of phase information between component parts a key factor in the maintenance of appropriate biological time in an organism. As the nature of the circadian system is that it maintains time on a *near* daily basis, in order for internal biological time to match appropriate environmental cycles, the circadian system must be entrainable to appropriate environmental time cues (zeitgebers). In mammals, including humans, the dominant zeitgeber is light. The principal neural pathway through which light information is passed to the circadian system is via the retinohypothalamic tract, a glutamatergic projection arising from specialised photoreceptive retinal ganglion cells that directly innervates the SCN (as well as other brain areas involved in non-visual pathways; Baver, Pickard, Sollars, & Pickard, 2008). Through this pathway photic stimulation can alter circadian phase and ensure appropriate synchronisation between the internal pacemaker and the light/dark cycle of the environment. It appears that appropriate entrainment of the clock may be a key component in ensuring both mental and

physical health and wellbeing. We shall discuss later the evidence that misalignment of circadian phase may be a key component in mood disorders, but it is worth noting here that such influences may also impinge on metabolic processes (Wyse, Selman, page, Coogan, & Hazlerigg, 2011) and even on longevity (Wyse, Coogan, Selman, Hazlerigg, & Speakman, 2010).

Another key component of the circadian system is the pineal hormone melatonin. In mammals the production of melatonin is gated through the SCN, via the paraventricular nucleus of the hypothalamus, the sympathetic ganglion chain (superior cervical ganglion) and the release of noradrenaline onto β-adrenoreceptors expressed on pinealocytes which drives the biosynthesis of melatonin. Melatonin may then act through its G-protein-coupled MT1 and MT2 receptors in various central and peripheral sites. For example, cells of the SCN express MT1 and 2 receptors, are responsive to melatonin and exogenous melatonin can alter circadian phase (Lewy, Emens, Jackman, & Yuhas, 2006). Therefore melatonin signal may serve in part to feedback onto the SCN. Light suppresses melatonin biosynthesis, and therefore melatonin is usually produced during the lights off phase, with production starting in humans normally around 9pm and reaching a peak about 3am. Given that under dim-light conditions that melatonin biosynthesis is gated by the SCN clock, the time of melatonin onset under such circumstances (the dim light melatonin onset, or DLMO) is found to be a reliable indicator of internal circadian phase in human studies (Pandi-Perumal et al, 2007). Melatonin is not the only hormone under substantial circadian regulation, with other factors such as prolactin, vasopressin, and corticosteroids all showing classical circadian rhythms of secretion (Kalsbeek et al, 2006). Corticosteroids seem particular strongly linked with the circadian system, both in terms of the temporal control the SCN clock exerts on their production via the hypothalamic-pituitary-adrenal axis and also in terms of their ability to alter circadian processes in target tissues (Dibner et al, 2010).

With regards to the molecular mechanisms by which circadian rhythms are generated, it is known that the core processes involve a panel of "clock genes", which form a series of interlocking feedback/feedforward loops that regulate their own expression on a near twenty four hour basis (Dibner et al, 2010). Core components of this circadian clock gene cycle include *PER1, PER2, PER3, CLOCK, BMAL1, CRY1, CRY2* and *REV-ERB-α*. The essential nature of this timekeeping mechanism, based on transcriptional feedback loops, seems well conserved, with clock gene cycles demonstrated in lower order organisms such as fungi and yeast (Dibner et al, 2010). In essence, the clock gene cycle works on the basis of CLOCK and BMAL1 forming a heterodimer, which in turn binds to E-box elements on the promoter sequences of *per* and *cry* genes. This drives the transcription of these genes, whose protein products then dimerise themselves and re-enter the nucleus to suppress the transcriptional activation abilities of the CLOCK:BMAL1 complex. Further, there is another feedback loop in which

Rev-erb α and RORa have their expression driven by CLOCK:BMAL1, and in turn regulate the transcription of *bmal1* (Dibner et al, 2010). The cycling of these core clock genes also in turn drives the rhythmic regulation of clock-controlled genes, the identity of which appears to be regulated in a tissue specific manner. The influence of the circadian clock on the transcriptional landscape appears to be extensive and highly complex and result in between 10%-20% of transcripts showing circadian regulation in any given tissue (Panda et al, 2001; Koike et al, 2012). It is thought that it is through such regulation of clock controlled genes that rhythmic changes in behaviour and physiology subsequently arise.

The tracking of daily patterns of clock gene expression has allowed for the identification of a number of central nervous sites outside of the SCN as displaying such daily patterns (Guilding & Piggins, 2007). A number of such sites, for example the hippocampus, the amygdala, the basal forebrain and cerebral cortex, are all also long implicated in the pathophysiology of mood disorders. Although it is not fully appreciated what physiological role that these clock gene cycles may play in each central nervous site it can be shown that disruption of these cycles leads to various behavioural and cognitive impairments in experimental animal studies (Jilg et al, 2010; Loh et al, 2010).

Evidence for the involvement of circadian rhythms in mood disorders

The observation that abnormal circadian rhythms may be manifest in patients with mood disorders were first reported nearly fifty years ago (Elithorn, Bridges, Lobban, & Tredre 1966; Halberg, Vestergaard, & Sakai, 1968). Since then there have been numerous studies that have sought to characterise the nature of circadian disturbances that are associated with different mood disorders. Overall, there is an unfortunate lack of cohesiveness in the literature on this subject. There are many studies that point towards biological rhythm disruption in mood disorders, but many of these are seriously underpowered and there are too frequent methodological differences in the approaches adopted to allow for meaningful meta-analysis. Having said this, the majority of published studies do indicate that there are often phase abnormalities of circadian rhythms associated with mood disorders, perhaps indicating a failure of the normal processes of entrainment of the circadian system to appropriate environmental zeitgebers, leading to a state of internal desynchronisation, for example between the sleep cycle and the circadian cycle. In major depression there are reports that circadian rhythms are either phase-advanced or phase delayed, or neither (van der Hoofdakker, 1994; Robillard et al, 2009; Emens, Lewy, Kinzie, Arntz, & Rough, 2009; Hasler, Buysse, Kupfer, & Germain, 2010). It may be that there are a subset of individuals with affective symptoms that express circadian changes, and then a population with affective disorders who do not display circadian abnormalities. Certainly, it seems that circadian misalignment on its own is not sufficient to cause depression, as evidenced by the lack of association of depression with shift

work, in contrast to many common chronic medical conditions (Vogel, Braungardt, Meyer, & Schneider, 2012). Another important factor may be age: young subjects with depression may display different changes in circadian rhythms compared to older subjects (Tsujimoto, Yamada, Shimoda, Hanada, & Takahashi, 1990), and it is known that normal healthy aging exerts considerable influence on the circadian system (Weinert, 2000). There are a number of studies that have indicated that depression is associated with a shift of chronotype towards evening preference (Chelminski, Ferraro, Petros, & Plaud, 1999; Kitamura et al, 2010) and evening preference is associated with phase delayed circadian rhythms (Mongrain, Carrier, & Dumont, 2006).

Interestingly a couple of small studies have indicated that depressive symptom severity in non-seasonal depression is correlated to the phase misalignment of the circadian rhythm (Emens et al, 2009; Hasler et al, 2010), and correlations between symptom severity and circadian parameters have been reported in other psychiatric conditions, such as attention deficit hyperactivity disorder (Baird, Coogan, Siddiqui, Donev, & Thome 2012). However, there are significant issues concerning study heterogeneity (sex, age, diagnosis, psychopharmacology) and study methodology (which subjective and/or objective measures are used to determine circadian phase, field or laboratory based studies, issues of statistical power) that will need to addressed in future larger studies in order to gain a systematic insight into the nature of circadian changes that occur in major depression.

There is also evidence for circadian rhythm disturbance in bipolar disorder (BPD). Salvatore et al (2008), using wrist actigraphy, describe significant advances of the daily activity rhythm in BPD-I patients both in their euthymic and manic/mixed phases. Jones, Hare, & Evershed (2005) also report findings from actigraphy in BPD patients. These authors describe less robust and more inconsistent rhythms in BPD patients compared to controls, although they did not examine acrophase of these rhythms to test for any underlying phase shift. These circadian changes were present when the patients were not acutely ill. These studies seem to complement findings from earlier studies of rhythms in bipolar patients (eg. Kupfer, Weiss, Foster, Detre, & McPartland, 1974; Wehr, Muscettola, & Goodwin, 1980) and suggest that circadian dysfunction may be a trait characteristic of BPD. Yang, Van Dongen, Wang, Berrettini, & Bucan (2009) examined what might be the underpinning mechanism of such circadian rhythm abnormalities in BPD by examining the rhythmic expression of clock genes in fibroblasts obtained from BPD patients and controls. They report that there were changes in the amplitude of the rhythms for the clock gene *BMAL1* and the clock-controlled output gene *DBP*. Since circadian phase is understood to be determined by the interaction of circadian period and amplitude (Brown et al, 2008) these described changes in clock gene rhythm amplitude may be a contributing factor to altered circadian phase observed in BPD.

Seasonal affective disorder (SAD), also known as winter depression, is a form of depression usually associated with onset of symptoms in the autumn/winter (although symptoms may have their onset at different times of the year), with symptoms then remitting but recurring with a similar temporal pattern in following years (Westrin & Lam, 2007). SAD is also associated with atypical neurovegative symptoms such as increased appetite (particularly for carbohydrates) and resultant weight gain, hypersomnia and fatigue. The picture of symptom onset associated with seasonal change and atypical symptoms in physiological parameters that normally show strong circadian control has lead to the postulation that a deficit in circadian resetting at season change may underpin the aetiology of SAD. This change may be triggered by longer nights and hence a change in the duration of the melatonin signal during winter, by the later onset of dawn as a key zeitgeber, or by a combination of these (Levitan, 2007). A seminal study by Lewy, Lefler, Emens, & Bauer (2006) report that there was a correlation between SAD ratings and desynchronisation between sleep and circadian cycles, and that further 71% of SAD patients in the study had phase delayed rhythms and 29% had phase advanced rhythms. Regression analysis revealed that the DLMO/midsleep relationship used in the study to account for circadian phase shifts accounted for 17% of the variance in SAD ratings. These results indicate that there is a substantial subpopulation of SAD patients that display advanced rhythms, and that it may be the presence of a phase shift, rather than the direction of that phase shift (delayed vs. advanced) that may be prescient in determining the circadian basis of SAD.

Another area in which there are consistent findings is the examination of chronotype in affective disorders, and indeed in other common psychiatric conditions. There are numerous reports that affective disorders are associated with a shift towards greater eveningness, and eveningness is also associated with increased impulsivity and risk taking and novelty seeking, all traits associated with psychoticism (reviewed in Adan et al, 2012). It is not fully understood which factors make up chronotype: there certainly appears to be a biological basis for this phenomenon in circadian clock characteristics in individuals (Brown et al, 2008), but environmental factors, such as increased nocturnal light exposure which may phase-shift the clock, are also likely to be key contributing factors in determining chronotype (Adan et al, 2012). Therefore, an intrinsic phase delay in depression may itself lead to move nocturnal activity and light exposure, which in turn could reinforce the evening orientation associated with affective disorders.

An interesting and important facet that is very relevant for understanding the chronobiology of mood disorders is how affect is regulated on a daily basis. Non clinical populations show daily variation of affect, with positive affect showing a circadian rhythm with a nadir at the time of the trough of body temperature, whilst negative affect did not display a rhythm (Murray, Allen, & Trindler, 2002). Boivin et al (1997) demonstrated under forced desynchrony (allowing for the separation of circadian and sleep/wake components) that affect

displays a circadian regulation, but is also sensitive to prior wakefulness in a circadian time-dependent mechanism. Another study using textual analyses of millions of social media messages have shown peaks of positive affect in the morning across a number of cultures, with negative affect increasing as the day wears on, and these patterns persist at the weekends but are delayed, perhaps reflecting the opportunity to "lie in" (Golder & Macy, 2011). In clinical populations there are studies which have reported a delay of the peak of lowest mood in major depression, so that it occurs during the early morning (Von Zerssen et al, 1985), and under a forced desynchrony protocol in patients with SAD mood in the patient and control groups both showed circadian and sleep/wake control (Koorengevel, Beersma, den Boer, & van den Hoofdakker, 2003). On a molecular basis the monoamine oxidase A gene, intimately implicated in mood, is found to regulated by the core mechanisms of the circadian clock, thus offering one mechanism through which affect may be under circadian control (Hampp et al, 2008). Overall, affect appears to be sensitive to both circadian and sleep/wake cycle control, and the interaction between these is vital. Therefore, any circadian misalignment with the sleep/wake cycle that may accompany mood disorders may impact on this and contribute to the labiality of mood in these conditions.

As we consider circadian changes that appear to occur in mood disorders, we are inevitably left with the "chicken and egg" question of do circadian abnormalities contribute to the aetiology of these conditions, or whether circadian rhythms become disturbed as a secondary effect of the sympatomatology of these conditions, or a combination of the two? Given the fundamental gaps in our understanding of the aetiology of such conditions, this is a question that is not possible to address in any satisfactory way based on current evidence. There have been a number of studies examining the association of polymorphisms in circadian clock genes and mood disorders, and these studies have demonstrated various significant associations (reviewed in Partonen, 2012). Such studies are somewhat hindered by sufficient lack of power (for example there are no published genome wide studies of SAD), as well as the issue of lack of knowledge of the functional consequences on many such polymorphisms on these genes' protein products, but they do indicate that circadian factors may be of significance in the aetiology of mood disorders. To help further address these issues there is a need for meaningful prospective studies. Ritter et al (2012) have recently described that subjects being at high risk of developing BPD show some sleep and activity changes compared to controls. Ankers & Jones (2009) also report circadian rhythm changes in individuals at high risk of developing BPD. Such promising findings should lead to the inclusion of measures of circadian rhythms in large cohort prospective studies. Such approaches have recently shown that altered circadian timing is a significant predictor for subsequent mild cognitive impairment or dementia (Tranah et al, 2011).

Chronotherapy of affective disorders

As outlined above, there is reasonable evidence that circadian dysfunction accompanies major affective disorders, and that such dysfunction may in part contribute to the aetiologies of these conditions. The principal component of these circadian dysfunctions seems to revolve around inappropriate phase shifts leading to internal desynchronisation. This is in contrast to other neurological conditions, such as dementias, in which the principal circadian abnormalities appear to be in the realm of decreased rhythm amplitude (Coogan et al, 2012). In order to address these phase misalignments, and to produce clinical benefit by resynchronising rhythms, we can draw on an extensive literature on phase-shifting of the circadian clock. It is known that presentation of light stimuli will produce phase shifts of the human circadian system, and the nature of these shifts (eg. advances versus delays) will depends on the point in the endogenous circadian cycle in which they are presented (Revell, Molina & Eastman, 2012). Other non photic manipulations can also induce phase shifts of circadian rhythms – for example exogenous melatonin or melatoninergic agonists (Lewy & Sack, 2006). Indeed, compounds such as serotonin/and or noradrenaline reuptake inhibitors that are used as antidepressants can also induce phase shifts in animal models (Gannon & Millan, 2007; O'Keeffe, Thome, & Coogan, 2012). So application of core neuroscientific knowledge regarding mechanism of phase shifting might be applied fruitfully in the clinic (Benedetti, Barbini, Colombo, & Smeraldi, 2007).

To date most attention has focussed on the application of chronotherapeutics in SAD, due to the strong implication of the circadian system in the aetiology of this condition. Most studies have utilised bright light therapy, involving exposure to white light (usually 5,000-10,000 lux) for 30-60 minutes each day, usually aimed at the morning (to produce phase advances) or sometimes in the evening (to produce phase delays). In the SAD literature, there had been descriptions that light therapy was associated with significant remission rates, and in general morning light was associated with better outcomes than evening light, although some studies did report benefit of evening light on SAD ratings (Terman, Schlager, Fairhurst, & Perlman, 1989; Lewy et al, 1998). A plausible explanation for these apparent discrepancies is the finding of Lewy et al (2006) that the majority of SAD patients show a delay of their DLMO in relation to midsleep, whilst a significant minority demonstrated an advance. In terms of chronotherapy of SAD, these authors then demonstrated a pairing of morning light and evening melatonin to induce phase advances in SAD patients with phase delays produced diminution of SAD symptom, as did phase delaying morning melatonin and evening light for those patients with a SAD-related phase advance (decrease in SAD ratings of 34% for the correct-intervention groups versus 13-15% for the control groups). However, when the inappropriate intervention is applied (eg. phase-delaying stimulus to patients with a pre-existing phase delay) there is no resulting significant improvement in SAD scores, indicating that

ascertaining the underlying phase-misalignment in SAD patients is critical in selecting the optimal chronotherapeutic approach. Other more naturalistic approaches to light treatment in SAD, for example dawn simulation, also appear effective in producing phase shifts (Terman & Terman, 2010), whilst the use of blue light (the wavelength of light to which the circadian system is maximally sensitive to; Revell et al, 2012) may allow for lower light intensities and resulting better compliance (Meesters, Dekker, Schlangen, Bos, & Ruiter, 2011).

In the treatment of non seasonal major depression and bipolar disorder chronotherapeutic interventions also show promise. Studies have used combinations of light therapy, changes of scheduled sleep timing, melatonin and sleep deprivation as interventions. Total sleep deprivation has long been described as exerting a rapid anti-depressant action in depressed patients, although the usefulness of such an approach has historically been limited by the short duration of these effects (Bunney & Bunney, 2012). However a number of studies have shown that combining total sleep deprivation with melatonin and/or light therapy produces significant and enduring symptom amelioration. Benedetti et al (2007) demonstrated that in BPD patients suffering depressive episodes application of a six day regime of 3 days of total sleep deprivation combined with morning light therapy produced significant relief of depression in two thirds of patients (a decrease in the Hamilton Depression Rating Scale of ~70% compared to ~30% in non-responders), and this effect was correlated with the phase advance produced by the intervention (eg. responders showed a significant advance and decreases in depression ratings, non-responders did not show significant phase shifts or symptom relief). Wu et al (2009) demonstrate that such approaches can produce enduring symptom relief. These authors applied a regime of sleep deprivation, light therapy and advances of sleep time to BPD patients in addition to their normal medication, and demonstrated that the chronotherapy-augmented group showed significant reductions in depression ratings that persisted over the seven weeks these patients were followed for compared to the control group on their normal medication alone (decrease in the Hamilton Scale scores of ~50% for the chronotherapy group compared to ~25% for the treatment as usual group). These results indicate that chronotherapy can effectively be applied in conjunction with treatment-as-usual to significant clinical benefit. Moscovici & Kotler (2009) trialled a chronotherapeutic approach comprising of light therapy, sleep advances and partial sleep deprivation in a small population of patients with major depression. This intervention produced significant lessening of depression ratings (~70% reductions in clinician scored ratings, no control group) that persisted over the 30 days of the study, again pointing to the potential for wider use of such protocols. A study in drug-resistant depression using a six day protocol of total sleep deprivation, sleep advance and light therapy has demonstrated a rapid onset alleviation of depression (~ 50% reduction in the Hamilton score, again no control group in this study) that persisted for the twenty days of the study (Echizenya, Suda, Takeshima, Inomata, & Shimizu, 2013).

From a mechanistic point of view it is not known how sleep deprivation may exert its antidepressant effects although these may be in part mediated via manipulation of the circadian system (Bunney & Bunney, 2012). For example, Antle & Mistlberger (2000) report that in hamsters sleep deprivation phase advances the circadian clock, raising the possibility that a similar mechanism might be at play in humans.

Another area of considerable interest is in pharmacological chronotherapeutics. To date most attention has been directed towards agents that act on the melatoninergic system. The most significant of these is agomelatine, a drug approved by the European Medicines Agency for the treatment of depression. Agomelatine was initially designed as an agonist for MT1 and MT2 melatonin receptors, but also has antagonist actions at the 5HT-2C receptor (deBodinat et al, 2010). Clinical trials show that agomelatine may have significant benefit for the treatment of depression (Kasper et al, 2013; Laux et al, 2012), is well tolerated and appears to have a favourable side-effect profile, although there may be issues with regards to hepatotoxicity (Carney & Shelton, 2011). For example, the study of Laux et al (2012) report a decrease in the MADRS score of ~60%, and 65% of patients were responders and 55% were remitters. In a pooled analysis of 4 studies over six months Demyttenaere et al (2013) report remission rates of ~ 60% compared to ~50% for SSRIs. Agomelatine appears to confer significant benefit for insomnia comorbid with depression, and it may be that this drug is best suited to the treatment of the (not insubstantial) specific populations of depressed patients with significant insomnia and other sleep disturbances (Srinvassan et al, 2012). It has been shown that, as might be expected for a short acting melatoninergic agonist, that agomelatine alters circadian rhythms. For example, early evening administration of agomelatine appears to phase advance a number of endocrine diurnal rhythms (LeProult et al, 2005). This would suggest that part of agomelatine's mode of action is via resynchronisation of circadian rhythms. However, if this is the case then the timing of the dose of agomelatine and the underlying circadian characteristic of any given patient may well determine whether maximal efficacy is achieved. Therefore, there may be a need for chronodiagnostics before the appropriate chronotherapy might be applied. Other melatoninergic agonists, such a ramelteon, may also have clinical benefits. In a recent study Norris et al (2013) describe that ramelteon significantly decrease relapse rate in BPD patients. It is to be hoped that well constructed (including chronobiological consideration), well powered future trials will further point towards the potential to produce antidepressant effects via manipulation of the circadian/mealtoninergic system.

Considerations and future directions

There is reasonable evidence in the literature that dysregulation of the circadian timing system occurs in affective disorders, that such dysregulation may

contribute to the psychopathology of these conditions directly or indirectly via co-morbid conditions (eg. insomnia), and that addressing these circadian dysregulations appears to produce rapid and significant clinical benefit. However, there are a number of important areas that need to addressed. First is the requirement for multilevel assessment of circadian rhythms in clinical population in large studies in order to systematically define the nature of circadian disturbances in affective disorders. Multilevel assessments are required to understand the nature of whatever internal desynchronisation may take place (eg. between DLMO and midsleep, or DLMO and core body temperature). There are too many examples of small/pilot type studies in the literature that provide interesting sign posts but make it impossible to draw definitive conclusions. On the chronotherapeutics front, there is also a need for larger studies, as well as a need to undertake some type of chronophenotyping of study subjects to allow for the apparently maximally effective strategy to be used. The blanket application of say morning light therapy may only benefit a subset of study subjects who have an underlying phase delay, but not those who may already be phase advanced. There is also the intriguing question as to whether current treatments (either pharmacological or psychotherapeutic) that produce relief of depression also produce changes in circadian rhythms? There is also the question as to if an effective psychotherapeutic approach based on addressing circadian dysfunction might be developed as has been successful in the treatment of insomnia?

Overall, chronobiology provides us with many opportunities to build on our considerable neuroscientific understanding of the circadian system to produce novel and meaningful interventions to relieve the burden of suffering from the millions worldwide who suffer from affective disorders.

Acknowledgements:
Research in the author's laboratory is currently funded by Science Foundation Ireland.
The author has no conflicts of interest to declare.

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