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Circadian rhythms and depression

Background
Depression is a common disorder in primary care. Disruptions to the circadian rhythms associated with depression have received little attention yet offer new and exciting approaches to treatment.

Objective
This article discusses circadian rhythms and the disruption to them associated with depression, and reviews nonpharmaceutical and pharmaceutical interventions to shift circadian rhythms.

Discussion
Features of depression suggestive of a disturbance to circadian rhythms include early morning waking, diurnal mood changes, changes in sleep architecture, changes in timing of the temperature nadir, and peak cortisol levels. Interpersonal social rhythm therapy involves learning to manage interpersonal relationships more effectively and stabilisation of social cues, such as including sleep and wake times, meal times, and timing of social contact. Bright light therapy is used to treat seasonal affective disorders. Agomelatine is an antidepressant that works in a novel way by targeting melatonergic receptors.

Keywords: circadian rhythm, depression

Over the past 5–10 years, there has been growing community awareness about depression, with an increased emphasis on its treatment in primary care. Evidence based pharmacological and psychological treatments for depression have been outlined in clinical practice guidelines.[1,2] These treatments are recommended on the basis of severity rather than depression type. While such an approach makes treatment decisions relatively straightforward, it does not take into account the different causal explanations for depression; particularly whether the depression is predominantly biological, such as that seen in melancholia[3,4] and bipolar depression, or the result of psychosocial factors.

However, current treatments have been developed on the basis of a causal model for depression. Focused psychological treatments target those depressions that arise from psychosocial difficulties. Examples include:

- cognitive behavioural therapy (CBT), which corrects maladaptive thinking patterns
- behavioural treatments that aim to overcome 'depressogenic' behaviours such as avoiding pleasurable activities, and
- lifestyle modifications, particularly work-life balance, diet and exercise and sleep-wake cycle management.[5]

Antidepressant medications target the neurotransmitter disturbances (serotonin or noradrenaline) considered to underlie biological depression. While the focus of biological aspects of depression has centred on changes in neurotransmitters, there has been relatively little attention paid to the changes in circadian rhythms associated with depression that offer new and rational treatment options for depression.

Circadian rhythms

The regular rhythm of night (dark) and day (light) regulates our life, as it does for most living organisms. Associated with this are regular changes in core body temperature, hormonal secretions, heart rate, renal output and gut motility. Our mental ability and energy levels are highest during daylight hours, when we engage in exercise and social interactions, with our metabolism and physiology adapted to this. During the night, when activity levels drop, core body temperature falls and reaches its nadir, while cortisol levels rise before awakening. There are cyclic changes in the level of sleep (as shown by changes on an electroencephalogram [EEG]) with hormonal release, such as the release of growth hormone linked to specific phases of the regular sleep cycle.[6–8] When our

sleep-wake cycle is out of phase with the day-night cycle (eg. due to jetlag or shift work), we can experience dysphoria, poor functioning and increased health risk.[7,9]

Regulating circadian rhythms

These rhythmic changes in metabolism and psychological activity are under the control of a circadian clock; this ensures that our body is attuned to the level of mental and physical activity associated with a particular time of day or night.

When free of external environmental clues, the amplitude of our daily rhythm is longer than the 24 hour day-night cycle (hence the name *circa diem* – about a day) as demonstrated in experiments when individuals were placed in temporal isolation[10] or in conditions of permanent darkness such as subjects wintering in the Antarctic.[11]

The human circadian pacemaker or 'clock' is located in the suprachiasmatic nucleus of the anterior hypothalamus. This regulates the key circadian rhythmic changes such as cortisol, thyroid hormone and core body temperature. The mechanism for this is governed by a set of genes that operate through a series of feedback mechanisms with a regular cycle of about (but not exactly) 24 hours.[12–14]

The circadian pacemaker has to be resynchronised regularly to compensate for the slightly longer than 24 hour cycle of the 'endogenous' circadian rhythm. This synchronisation to the external environment is mediated through the retinohypothalamic tract.

Light zeitgebers

Light acts a 'zeitgeber' or timekeeper, falling on the retina which then sends impulses to the suprachiasmatic nucleus; a process that is mediated through the protein melanopsin (rather than rods or cones).[15] Bright light also has an effect by suppressing melatonin production. For this to occur, a light intensity of at least 1500 lux (brighter than standard artificial lighting) is required to switch off melatonin production. Suppressing melatonin can have an effect in changing circadian rhythms: bright light administered in the early morning will suppress melatonin and therefore advance circadian rhythms. In this example, the nadir of the temperature rhythm will be moved earlier in the day, while bright light applied in the evening will have an opposite effect by delaying circadian rhythms.[16–18]

Social zeitgebers

Regular patterns of social behaviour can also affect circadian rhythms and aid in regulating them. These cues are known as 'social zeitgebers' and include time of going to bed and waking, social interactions, and meal times.

Disruption to circadian rhythms in depression

Disruptions to circadian rhythms have been found among patients with major depression.[19] While these changes are thought to be a contributing factor to the depression (such as suggested by the dysphoria triggered by jetlag) it is also possible that they may arise as a consequence of the depression.

Sleep

There are a number of features of depression suggestive of a disturbance to circadian rhythms; perhaps the most obvious are the changes in sleep, in particular waking early in the morning which is usually linked to a diurnal mood change. Sleep and polysomnographic studies demonstrate other changes in circadian rhythms, particular to the sleep architecture that indicate a 'phase advance' of such rhythms; specifically of the temperature nadir and cortisol levels, which occur earlier in the night.[19] Sleep architecture also reflects this with a shortened rapid eye movement (REM) latency and REM sleep shifted to the first third, rather than the latter third of the sleep cycle. These observations, along with clinical features, all support the notion of circadian rhythm disturbance in depression.[19]

Seasonal change

The most compelling evidence for a rhythm disturbance hypothesis of depression is the link between mood disorders and seasonal change.[20] In addition to the 24 hour daily rhythm, there are also regular rhythms over a year. These are known as circannual rhythms and reflect the changing day length (photo period) during the year. Circannual rhythms of depression are seen most clearly in seasonal affective disorder (characterised by episodes of depression in winter with remission in spring and summer). Some patients with bipolar disorder also experience episodes of depression or (hypo)mania at the same time each year. These seasonal changes are considered to be the result of a failure to adapt the shift in day length that accompanies seasonal change.[20,21] This adaptive failure leads to circadian rhythms becoming uncoupled, resulting in the onset of mood disorder. For patients with bipolar disorder, this has shown very clearly with disruptions to the sleep-wake cycle triggering off episodes of hypomania or mania.[22] A phase delay in circadian rhythms are proposed as a mechanism for seasonal affective disorder as demonstrated by the temperature nadir and timing of melatonin secretion occurring later in the night.[16]

Manipulating circadian rhythms

The circadian rhythms disturbances of depression can be corrected by novel nonpharmacological and pharmacological methods.

Social zeitgebers

The timing of social zeitgebers, for example sleep or meal times, play a role in regulation and disruption of circadian rhythms. Individuals who suffer from mood disorders show fewer routine activities than controls, and social rhythm regularity predicts time to prospective onset of a bipolar episode.[23] In addition, it is thought these individuals are more sensitive to circadian rhythm disruptions.[24]

The symptoms presented by patients with unipolar and bipolar depression tend to display circadian rhythmicity. For example, sleep, hunger and concentration all have a propensity to follow a 24 hour clock, and will be affected by disruption to biological rhythms. The implementation of frequent and stable social rhythms has been shown to be an important prophylactic treatment in affective disorders.[24] These activities, when performed regularly, have the ability to entrain biological rhythms such as cortisol and body temperature.[25]

As a result, interpersonal social rhythm therapy (IPSRT) was created.[24] Interpersonal social rhythm therapy involves learning to manage interpersonal relationships more effectively and stabilisation of social cues, such that the patient performs routine daily activities at the same time

each day[26] in particular maintaining a stable sleep-wake cycle. The therapy allows for no more than a 45 minute variation each day for any given activity, and aims to prevent relapse by providing the patient with a stable environment. The social rhythm metric (SRM) is a tool designed to aid in social rhythm stabilisation.[27] In its entirety, the SRM contains 17 items, including sleep and wake times, meal times, and timing of social contact.

Light therapy

Bright artificial light of at least 1500 lux, has been used to treat some forms of depression, particularly seasonal affective disorder.[28] This treatment was originally utilised on the premise that seasonal affective disorder was a consequence of the short day length of winter and bright light would mimic the day length of summer. While this proved to be effective it is now clear that the mechanism for light therapy is in its effect on shifting circadian rhythms. Thirty minutes of bright light therapy (10 000 lux) in the morning advances circadian rhythms and overcomes the phase delay associated with seasonal affective disorder, exhibiting its effect in 2–3 days.[18]

Role of melatonin

Melatonin can be used to shift circadian rhythms and melatonin is marketed as a hypnotic in Europe. Its ability to promote sleep can results in improved mood.[28,29] While there may be some improvement in depression symptoms arising from improving sleep with persons with depression, melatonin administration during the day leads to dysphoria and worsening of depressive symptoms, indicating melatonin does not have an inherent antidepressant action.[30]

Melatonin is used to correct dysphoric symptoms induced by circadian rhythm disruption following transmeridian travel (jetlag). Taken the night before departure, (0.5–5.0 mg) it has been shown to be effective in reducing symptoms of jetlag.[31]

Agomelatine

Theoretically, medications that target melatonergic receptors in the brain will have an affect on circadian rhythms. Agomelatine is an agonist of melatonergic (MT1 and MT2) receptors and a 5-HT_{2C} antagonist. When taken at bed time, it appears to have an effect by resynchronising the circadian rhythms. It has been demonstrated to be an effective antidepressant in placebo controlled trials[32,33] and equivalent efficacy compared to selective serotonin reuptake inhibitors (SSRIs)[33] and venlafaxine.[34] It has a very short term action (half life 2 hours) and must be taken at night before going to sleep. While agomelatine does improve sleep itself, its primary effect is in synchronising circadian rhythms. At present, the main studies on agomelatine have been carried out on patients with major depression, but this medication may prove to be useful where circadian rhythm disturbances underpin the patient's clinical problem.

Agomelatine is indicated for use for the treatment of major depression. It needs to be taken at bed time with an initial dose of 25 mg (which is the generally effective dose) that can be increased to 50 mg if there is no response within 2 weeks.

The side effect profile is favourable, with no associated sexual side effects, day time somnolence or weight gain.[35] The most common side effects associated with agomelatine are: headache, nausea, diarrhoea, dry mouth, constipation and nasopharyngitis.[35] Agomelatine has been found to increase serum transaminases in some patients treated with 50 mg/day; it is recommended that liver function tests are conducted every 6 weeks while the patient is taking it.[36] It is metabolised by the cytochrome P450 isoforms 1A1, 1A2 and 2C9[35] and co-administration of potent CYP1A2 inhibitors (such as fluvoxamine) is contraindicated. Combination of agomelatine with oestrogens (moderate CYP1A2 inhibitors) can increase agomelatine levels.[37]

Agomelatine is currently undergoing further evaluation, has recently been licensed for use in Europe, and will offer a new therapeutic tool for the treatment of depression when it is released in Australia, especially for those who have been unable to tolerate the side effects of current antidepressants.

Conclusion

Depression is one of the most common reasons for people to visit their general practitioner. While diagnostically it is treated as a unitary disorder, the varying aetiologies and treatments for depression suggest it is not. Circadian rhythm disruption as a proposed cause of mood disorders presents an opportunity for unique and efficacious treatment that includes pharmacological, behavioural and novel interventions such as bright light therapy.

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