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Circadian Dysregulation: A Mainstream Mess of the Present World

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The physiological systems of humans and other organisms are periodic in nature. One such system is a circadian rhythm, a biological internal clock that is endogenous and entrainable. The circadian rhythm regulates essential functions such as the sleep/wake cycle, hormones, feeding behaviour, metabolism and cell division as well. Due to shift work or jet lag or even irregular sleep, diet, etc., circadian rhythm disorders are one of the most common problems in this century. It is a major factor that can trigger various diseases like depression, lung tumorigenesis, cancer, anxiety, depression and many more. The purpose of this review is to discuss circadian dysregulation and its potential long-term effects in cancer including lung tumor and mental illness including depression, anxiety. Loss of autonomous cells containing Bmal1 and Per2 (the core components of circadian rhythm) will increase growth and metabolism imbalance and increase in c-Myc levels. To treat circadian rhythm disorders, zeitgebers (external cues) should be used to entrain or synchronize the circadian rhythm and sleep phase chronotherapy can also be used.

Keywords: Circadian rhythm; circadian dysregulation or desynchronization; autonomous cells; shift work; zeitgeber; cancer; depression; anxiety; chronotherapy.

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1. INTRODUCTION

A biological clock is a natural system that controls the physiological exercises of an organic entity which change on an everyday, occasional, yearly, or other ordinary cycle. Motions are found all through the physical and natural universes. Their collaborations can bring about a precise course of synchronization called entrainment, which is particular from a basic improvement pattern. The periods of biological oscillations, based on biochemical and neuronal processes or even predator–prey interactions, range from milliseconds to years. A subset of these oscillators is synchronized (entrained) to cycles that themselves can be endogenous or ecological. The main ecological cycles that synchronize endogenous oscillators are the tides, the revolution of the earth, the lunar cycle, and the seasons. Without data about the climate's fleeting construction (in consistent conditions), the comparing natural oscillators can run "free" with their endogenous period, approximating however not really indistinguishable from that of the ecological cycle. These four around rhythms (circatidal, circadian, circalunar, and circannual) fill in as endogenous clocks to put together the inside worldly program as per and fully expecting exogenous changes. Two fundamental components of a natural oscillator are 1) an inhibitory criticism circle, which incorporates at least one wavering factors, and 2) a wellspring of postponement in this input circle, which permits a swaying variable to overshoot a consistent state esteem before the criticism hindrance is completely successful. The circadian rhythm is approximately one day long. Franz instituted the term circadian, subsequent to archiving those biologic rhythms steer the result among wellbeing and infection and even among life and demise. His outcomes were generally distributed, including a 1969 reference exemplary. This is a 24-hour biological rhythm that is influenced by pacemaker which is present in the hypothalamus area of the brain called the Suprachiasmatic nucleus (SCN) (also known as master clock) which receives information directly from the eyes and sends it to other slave clocks in other systems in the body. The brain's master clock coordinates all biological clocks in living things and keeps them in sync. The structure formed by a master clock is called the suprachiasmatic nucleus (SCN) (Fig. 1).

SCN regulates melatonin secretion. The information is received by SCN from the optic nerve about incoming light, which transfers information to the brain from the eyes. When there is not enough light (for example, at night), SCN increases melatonin in the brain, causing you to fall asleep. It affects the sleep-wake cycle, the regulation of body temperature, eating, drinking, the secretion of hormones and neurotransmitters, and other patterns of activity. The rhythm is endogenous (self-sustaining), lasting about 24 hours and can be adjusted or modified depending on the environment. The circadian rhythm can be adjusted by external cues called zeitgeber. These zeitgebers can generate the body's biological rhythm for 24-hours and synchronize with earth's light and dark cycles. Examples: light, temperature, exercise, eating, drinking pattern, pharmacological manipulation. The study of circadian rhythm is called chronobiology. The molecular transcription and translation feedback loop (TTFL) is the mechanism that brings rhythm in mammals, which is made up of factors that help in transcriptionsuch as CLOCK and BMAL1, which influences the illustration of clock genes that includes Period and Cryptochrome, and generate response to regulate their expression (Fig. 2) [2].

The disorder occurs when an individual tries to sleep at different times that do not coincide with their basic biological clock. There are two types of these disorders– intrinsic and extrinsic. Intrinsic disorders are caused by internal reasons, such as weak circadian rhythms, while extrinsic disorders are caused by external causes such as different shift hours. Intrinsic disorders are of four types – delayed sleep syndrome (DSPS), advanced sleep syndrome (ASPS), irregular sleep and wake rhythm, and 24-hour insomnia syndrome. On the other hand, Extrinsic disorders are of two types such as shift work and time zone change disorders such as jet lag. Jet lag here includes the external environment that can affect circadian rhythm. Frequent jet lag can lead to persistent symptoms. For example, airline employees or businessmen frequently travel in different time zones and become excessively sleepy. The effects of circadian dysregulation include excessive or poor drowsiness, sleeplessness, depression, reduced work performance, disturbed social interactions, which can also lead to lung tumorigenesis [4].

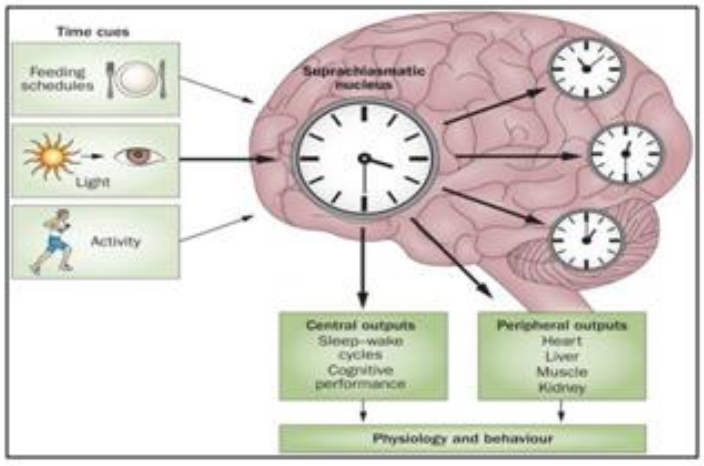

Fig. 1. Suprachiasmatic nucleus (The clocks that time us)
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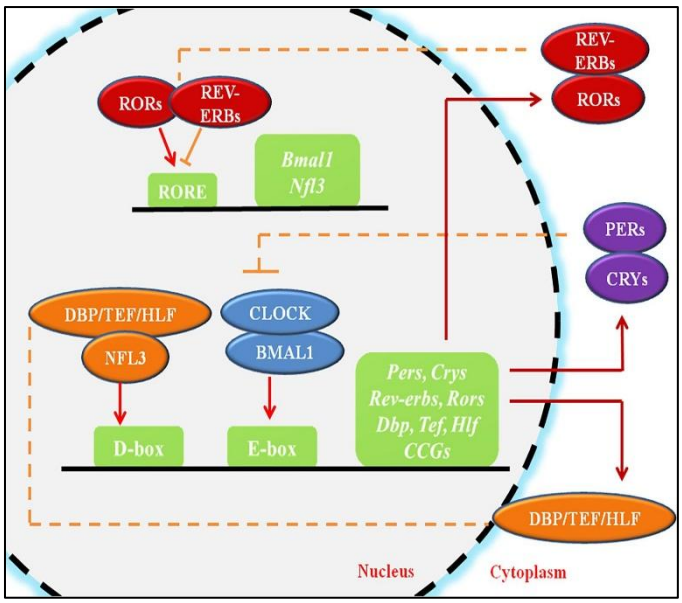

Fig. 2. Molecular mechanism of Circadian rhythm
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Treatments include behaviour therapy, avoid stimulants such as caffeine, bright light therapy, blue-blocking glass therapy, medications (such as melatonin and modafinil), tasimelteon is also effective and sleep phase chronotherapy. [5] The effects of dark shifts and work in different shifts on health, except for the degradation of performance throughout accidents and work insideor outside the office, are widely known and can cause long-term health problems. In acute and long-term studies, fat digestion [6], simple carbohydrate digestion [7], insulin resistance, development hormone [8] and adrenal cortical steroid production patterns [9] have been changed negatively and/or blood concentration as well.

1.1 Circadian Disruption Endorses Lung Tumor

The alteration or disturbance of the circadian rhythm favours lung tumors. Dysregulation of circadian rhythms leads to elevated levels of c-Myc and metabolic reprogramming. The central components of the circadian rhythm mechanism that is the Per2 and Bmal1 genes play a role in the transformation and growth of autonomous tumor suppressive cell. Once these genes are

lost, they will genetically accelerate lung cancer [10]. Interference with the circadian rhythm of night shift workers is more likely to cause cancer and a poor cancer prognosis [11]. Changes in specific system and tissue in the diurnal rhythm mechanism led to changes incell division, metabolism and other functions in cells and are closely linked to tumor [12].

The circadian dysregulation caused by jet lag accelerates the growth of tumors in the lungs [10]. Preclinical GEMM was used with human lung adenoma and adenocarcinoma. In this experiment, the 8-hour-ahead time difference plan simulates the circadian rhythm interference that occurs during shift work [13]. This phenomenon indicates that jet lag interferes with circadian behaviour. It is important to note that most studies cited are experimental in animals.

The total loss of the genes of Per2 and Bmal1 in tumor bearing animals accelerated the appearance of lung tumors. In this experiment, the genetic destruction of the circadian rhythm mechanism was accomplished by destroying the entire animal clock in the normal condition of LD12: 12 was performed.[14] Animals lacking systemic Per2 function showed increased tumor problem and grade [10].

In the K and KP models, the Bmal1 conditional allele (Bmal1flox/flox) is used to kill Bmal1 in cancer cells. [15] Loss of this gene in the tumor results in acceleration of lung tumors in the K model, while it does not affect the case of the KP model. The possibility arises that Bmal1 depends on p53 to function. [16] Knockout of Per2 in cells using CRISPR / Cas9 showed tumor formation [10].

1.2 Interpretation of above Experiments

Dysregulation of 24-hour patterns during shift work is linked with an amplified risk of cancer [17]. Previous experiments show that circadian rhythm disorders promote or support lung tumors, and also suggest a tumor suppressive effect on circadian rhythm homeostasis. These experiments demonstrate that Per2 and Bmal1, which are the core components of circadian rhythms, work together with Kras and p53 to increase lung tumorigenesis. Tumor cell-specific removal of core components has also been shown to lead to proliferation, increase in c-Myc levels, and increased metabolic activity. It also shows the cell's autonomous circadian control important for cellular processes, which is a hallmark of cancer and tumor progression [10].

1.3 Mental Illness and Circadian Dysregulation- A Connecting Link

Disturbance in sleep is a prominent continuing symptom that can lead to mental illness. Most of the patients that are suffering from schizophrenia, bipolar disorder and depression shows sleep disruption, even if the relationship between these disorders and sleep is uncertain [18]. The circadian rhythm controls the sleep and wake cycle and studies revealed that, in terms of the aetiology of these diseases, the disruption of the circadian rhythm involves the clock gene itself and the clock output. This shows that dysregulation in circadian rhythm can affect the mental abilities and functionality. One of the most common characteristics of neuropsychiatric diseases is sleep and circadian rhythm disorders (SCRD) [19]. Maximum 80% of patients that are suffering from depression or serious psychological illness including schizophrenia shows abnormal sleep. The link between SCRD and mental illness is not a linear relationship of SCRD due to the axis of tension, social inaccessibility and medicine, but current proof shows that there is a more cyclical relationship (Fig. 3) between mental illness and SCRD, and they promote each other and share common and overlapping mechanisms. Neurotransmission or neurodevelopmental defects and cognitive health problems can affect the circadian (sleep) and psychiatric axis at the same time and stress caused by psychiatric illness, social isolation, and medication can cause circadian rhythm disruption (sleep disorders). These results shows that circadian disruption can lead to mental disorders such as bipolar, schizophrenia, depression and many more which have devastating impact on health. One small disruption in cells that can result in various major diseases if not treated well on time.

Recent studies provide evidence in relation to SCRD linked with schizophrenia, clearly illustrating the irregular phase and uncertainty of the diurnal pattern, sleep disruption and fragile patterns of motion at rest. Researcher evaluated the resting action patterns of a group of people that are suffering from schizophrenia with a control group of healthy and fit unemployed

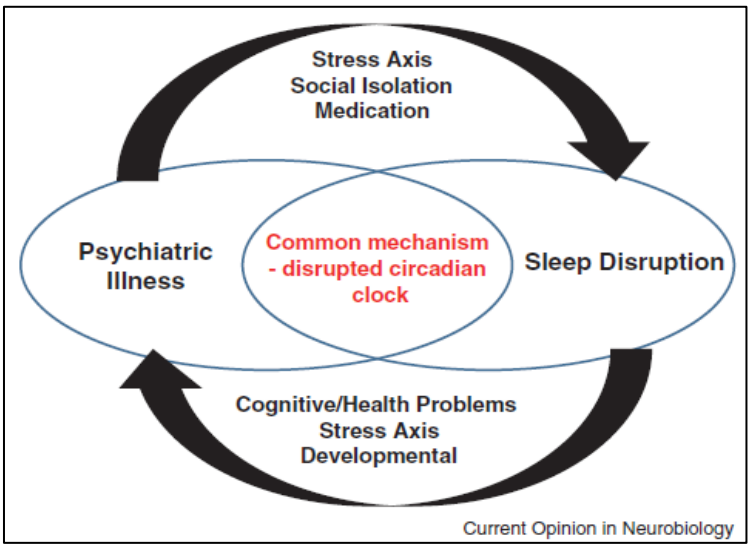

Fig. 3. Links between SCRD and psychiatric disorders.
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and showed obvious circadian rhythm disturbances in all 20 patients in all studies. Half of them have severe circadian rhythm disturbances during the sleep/wake cycle and the melatonin cycle, indicating that the irregular entrainment of the 24-hour rhythmic system is common in schizophrenic patients [20].

Most obvious link between SCRD and mental illness may be major depression, in which sleep disturbances occur in 90% patients. [18] Studies have found that cortisol secretion in depressed patients loses 24-hour rhythm. [21] Sleep management in depression has shown therapeutic effects [22], indicating that there is a strong mechanical link between sleep and depression. Although SCRD is not a potential factor that can alone cause mental illness [23]. SCRD can trigger or exacerbate symptoms in people at peakthreat for psychological illness by cause ofenvironmental or hereditary factors. Sleep interruption and recurrentjourney of different time regions can induce hectic events in susceptible individuals. [24] SCRD can become an important indicative marker in case of beginning of psychiatric symptoms before when SCRD is uncertain.

1.4 Circadian Disruption and Cancer Biology

Compared to normal breast tissue, reduction in expression of genes such as Per1 and Per2 were discovered in sporadic and familial breast cancers. As compared to the sporadic form, low expression of the Per1 genein the familial form of breast tumor, suggesting that possible relaxation of the circadian rhythm may be a genetic type of illness [25]. Addition of methyl in the promoter site of genes such as Per1 and Cry1 can give rise to the persistence of breast tumor cells by inactivating the gene expression and altering the 24-hour rhythm [26]. Furthermore, a noteworthy increase in the threat of breast tumoris related with the clock gene polymorphism has been observed in the Chinese population [27].

The function of the strictly controlled rhythm of pacemaker in human is described. Here time represents highest endocrine function, peak sleep time, metabolic regulator, immune response, attentiveness and cardiac constraints in 24 hours. The relationship between cancer, metabolism and circadian rhythm (Fig. 4) [28,29].

Epigenetic inactivation of Bmal1 leads to the growth of hematologic malignancies, non-Hodgkin lymphoma, and acute lymphoblastic leukaemia by hypermethylation of the cytosine guanine island (CpG) promoter and alters the circadian rhythm of cells, leading to the disruption of pattern of marked genes including c-myc, catalase, and p300 [31].

The hereditary variation of functional genes for instance Cry2 and Ala394Thr polymorphisms

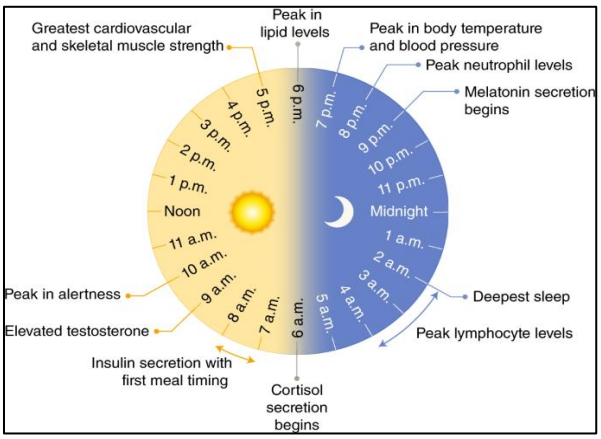

Fig. 4. The emerging link between Cancer, Metabolism and Circadian rhythm Image Web Location - https://europepmc.org/article/med/30523327#R96 [30]

within the neuron of circadian gene increases genetic susceptibility to non-Hodgkin lymphoma [32]. The alteration of the circadian rhythm can be a new threatreason for prostate cancer. A study from population showed indication that genetic alterations in genes of 24-hour rhythm are connected with the growth of prostate tumor [33].

The clock regulates the ability of the cell's response to DNA impairment. Repair pathways in DNA sustain genomic constancy and protect integration of DNA from external or internal stimuli [34]. In mouse, nucleotide excision repair in brain appears to display a 24-hour rhythm, primarily facilitated by xeroderma pigmentosum A, a recognition protein in DNA damage [35].

The proliferation rate of tumor cells follows a different periodic law than that of normal tissues [36]. The destruction of the cellular circadian rhythm is related to the change in the proliferation of cancer cells. Genes downregulation for instance Per1 or Per2 only rises tumor cell development in vitro or outside at precise times of the day and increases time-dependent growth of tumor in vivo [37]. Per1 geneis a tumor suppressor gene [38] and hinders breast cancer cell production and growth of tumor in a 24-hour mode of impression. [39] While Per2 downregulation increases breast cancer cell production and growth of tumor in a circadian time-dependent in vivo [40].

The International Agency in 2007 for Research on Cancer characterized “Shift work involves disruption of the circadian rhythm may be carcinogenic to humans” [41]. The night light can inhibit melatonin and alter the circadian rhythm [42]. Melatonin or 5-methoxy-N acetyl tryptamine is present as a hormone of the 24-hour rhythm, produced in the pineal gland and retina [43]. In untreated people along with non-small cell lung cancer (NSCLC), the mean nocturnal melatonin/cortisol ratio and the night-time melatonin level are reduced [44]. The outcomes can show that the endocrinal neuroimmune system is dysfunctional. People having NSCLC after standard chemotherapy, the concentration of melatonin gradually decreases [45].

The mixture of cetuximabs, an antibody for epidermal growth factor receptors, can effectively use in the initial non-resection of residual metastatic colorectal cancer [46]. In the 2nd study, the anti-tumor activity made-up of 5-fluorouracil and leucovorin with local hyperthermia with preoperative radiotherapy for low rectal adenocarcinoma ought to increase anticancer amount and the occurrence of severe reactions is low [47]. Patients with ovarian cancer show changes in the rhythm of day and night cortisol, compared to peoplethrough benign diseases, high in the after lunch and night levels of cortisol and reduced cortisol changeability. The disruption of the function of pattern of the hypothalamus-pituitary and adrenal axis is defined in the breast tumor survivors, in lumbar disc surgery, metastatic colorectal cancer patients and patients with cancer-related depression [48].

1.5 Circadian Dysregulation and Depression

Major depressive disorder is categorized by temper swings, usually increasing in grief and

irritation go together with the following physiological psychology symptoms: sleepiness, changes within sensual wish or hunger, incapability to enjoy desire, low mood, expression or action, tearful and hopeless thoughts [49]. It should be noted that the incidence of MDD is closely related to social modernization [50]; This may reflect an increase in circadian rhythm disorders (i.e., night lighting, jet lag and shift work) or collaboration between 24-hour dysregulation besides other ecological parameters in modern countries. Studies in human have specifically inspected the connection among 24-hour rhythm disorders besides MDD, because maximum record of human mingle all kinds of depression. However, researches have yielded different consequences inspecting the relationship amid shift work and MDD. Among approximately 4,000 Koreans, the frequency of MDD amid shift employees is meaningfully advanced as compared to day workers [51]. Among the approximately 36,000 employees in Brazil, shift dark work was suggestivelyrelatedthrough MDD alonein the case of women, while it found no associationof night work with MDD in a study in France [52]. If all types of depression are considered together, there will be a clear link among shift work and melancholy [53]. An investigation of 11 researches resulted night shift workers are 40% further probably toward suffer than day employees. [54].

Human clinical information encourages the powerful interlinking among MDD and 24-hourmethods [55]. Depressive signs show circadian changes; affected people show worse indications in the morning or at night. People affected with MDD often show additionalextremesigns in the morning, which is supposed to be related to furtherdrastic depression [56]. The alteration of circadian rhythms is a hallmark in case of MDD; precisely, changes in sleep and wake state (reducing frequent eye motion, sleep dormancy, increasing frequent eye motion, rest and reducing deep sleep), social patterns, hormonal patterns and a rhythm of temperature of body in patients with MDD [57].

1.6 Circadian Dysregulation along with Anxiety

Some researchers have shown that anxiety can be caused by night work and constant jet lag, a currentinvestigation suggests temper swings can result in sleep disturbances comparatively than 24-hour rhythm disturbances [55]. A study in case of day shift workers with no previous sleep disorders showed that after switching to shift work schedules, both anxiety and sleep disturbances increased [58]. Similarly, nurses with dysregulation in changes in shift work showed increase in level of anxiety on depression scale [59]. Rodents studies revealed the relationship between the 24-hour rhythm and nervousnesslike diseases. Aimed destruction of the normative molecular timer component warns of nervousness like performance. Compared to wild-type mice, a Δ19 alteration in the Clock gene in mice showed reduction in nervousness like behavior and fear less of unresponsive stimuli [60]. It is worth noting that Clock regulates the expression of cholecystokinin in the ventral tegmental area (VTA), in addition Δ19 alteration in the Clock gene is enough to bring overexcited behavior [61]. In comparison, lacking of both Per1 and Per2 in mice showed increased nervousnesslike behavior, while lack of Per1 or else Per2 did not change nervousness like behaviour in mice [62]. Hinderance of Per1 or Per2 expression in the NAc of mice, the wildtype also formed nervousness like response, indicating that these central clock components play an underlying role in the NAc that regulates anxiety.

2. CONCLUSION

The foremost implication of the modern lifestyle is the alteration of the circadian rhythm. Circadian rhythm disorder caused by night light, genetic or epigenetic variation of the circadian rhythm gene, and the interaction occurring amongst genes and environment make a data that indicates cancers can be explained by these mechanisms. Elucidating the relationamong formation of circadian rhythm and cancer besides determining molecular mechanism on how the peripheral circadian clock contributes to tumor transformation is critical to provide important clues for the development of new cancer prevention, control and treatment strategies based on the circadian rhythm in the future. The phase shifting in circadian rhythm in case of human time structure experienced through working in shifts and trans meridiantrip, event that has a profound impact on the levels of cells and moleculesin the human. Time changes can lead to transitory metabolic disorders, in which fat and sugardigestion, resistance in insulin and various purposes change, while pituitary and adrenal axis changes and development hormone and production of melatonin also change. The

metabolic changes caused by phase changes are complex and may be mediated in part by lack of sleep, that is characteristic in many works in shifts plans and turnson sameterminations. Future studies will be required to better describe the types of shift work and deliver a nearerevaluation of exposure of shift work. Purpose of shift work'splans that can be longer and are fewer disruptive. So to complete such operation in a meaningful time, a surrogate endpoint for carcinogenesis must be established. The temporary effects of jet lag dysfunction will heal in a few days, and long-term interference can lead to various diseases such as cancer (colon cancer, lung cancer, breast cancer, prostate cancer), anxiety, depression, etc. Circadian rhythm function can help with various perspectives, such as productivity, health and proper cell function (including metabolism and division). Several studies have shown that if we adopt the circadian rhythm in case of drugs or therapies, such as the timing of the appropriate medication, it will be effective, or in the case of cancer chemotherapy (if the treatment is performed according to the timing of the rhythm), it will have a more positive impact and lesser side effects.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Videnovic, Aleksandar, et al. The Clocks That Time Us'—circadian Rhythms in Neurodegenerative Disorders. Nature Reviews Neurology; 2014.
2. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature. 2010;418:935-941.
3. Xie Yanling, et al. New insights into the circadian rhythm and its related diseases. Frontiers; 2019
4. Circadian rhythm sleep disorders: Types, symptoms and management. (n.d.). Cleveland Clinic; 2015. Available:https://my.clevelandclinic.org/health/diseases/12115-circadian-rhythm-disorders
5. Circadian Rhythm Disorders. NHLBI, NIH; 2019. Available:https://www.nhlbi.nih.gov/health-topics/circadian-rhythm-disorders#:~:text=circadian%20rhythm%20disorders.,Treatment,bright%20light%20therapy%2C%20and%20melatonin.
6. Al-Naimi S, Hampton SM, Richard P, Tzung C, Morgan LM. Postprandial metabolic profiles following meals and snacks eaten during simulated night and day shift work. Chronobiol Int. 2004;21:937–947.
7. Morgan L, Hampton S, Gibbs M, Arendt J. Circadian aspects of postprandial metabolism. Chronobiol Int. 2003;20:795–808.
8. Van Cauter E, Plat L, Copinschi G. Interrelations between sleep and the somatotropic axis. Sleep. 1998;21:553–566.
9. Lac G, Chamoux A. Biological and physiological responses to two rapid shift work schedules. Ergonomics. 2004;47:1339–1349.
10. Papagiannakopoulos, et al. Cell Metabolism. 2016;24:324–331.
11. Kloog I, Haim A, Stevens RG, Portnov BA. Global co-distribution of light at night (LAN) and cancers of prostate, colon, lung in men. Chronobiol. Int. 2009;26:108–125.
12. Bass J, Takahashi JS. Circadian integration of metabolism and energetics. Science. 2010;330:1349–1354.
13. Lee S, Donehower LA, Herron AJ, Moore DD, Fu L. Disrupting circadian homeostasis of sympathetic signaling promotes tumor development in mice. PLoS ONE. 2010;5:e10995.
14. Zheng B, Larkin DW, Albrecht U, Sun ZS, Sage M, Eichele G, Lee C.C, Bradley A. The mPer2 gene encodes a functional component of the mammalian circadian clock. Nature. 1999;400:169–173.
15. Storch KF, Paz C, Signorovitch J, Raviola E, Pawlyk B, Li T, Weitz C.J. Intrinsic circadian clock of the mammalian retina: Importance for retinal processing of visual information. Cel. 2007;130:730–741.
16. Mullenders J, Fabius AW, Madiredjo M, Bernards R, Beijersbergen RL. A large scale shRNA barcode screen identifies the circadian clock component ARNTL as putative regulator of the p53 tumor

suppressor pathway. PLoS ONE. 2009;4:e4798.
17. Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. Night work and risk of breast cancer. Epidemiology. 2006;17:108–111.
18. Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. Nat Rev Neurosci. 2010;11:589-599.
19. Jagannath A, et al. Sleep and circadian rhythm disruption in neuropsychiatric illness. Curr Opin Neurobiol; 2013.
20. Wulff K, Dijk DJ, Middleton B, Foster RG, Joyce EM. Sleep and circadian rhythm disruption in schizophrenia. Br J Psychiatry. 2012;200:308-316.
21. Sachar EJ, Hellman L, Roffwarg HP, Halpern FS, Fukushima DK, Gallagher TF. Disrupted 24-hour patterns of cortisol secretion in psychotic depression. Arch Gen Psychiatry. 1973;28:19-24.
22. Fava M, Thase ME, DeBattista C, Doghramji K, Arora S, Hughes RJ. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann Clin Psychiatry. 2007;19:153-159.
23. Menet JS, Rosbash M. When brain clocks lose track of time: Cause or consequence of neuropsychiatric disorders. Curr Opin Neurobiol. 2011;21:849-857.
24. Plante DT, Winkelman JW. Sleep disturbance in bipolar disorder: Therapeutic implications. Am J Psychiatry. 2008;165:830-843.
25. Winter SL, Bosnoyan-Collins L, Pinnaduwage D, Andrulis I.L. Expression of the circadian clock genes Per1 and Per2 in sporadic and familial breast tumors. Neoplasia. 2007;9:797–800.
26. Kuo SJ, et al. Disturbance of circadian gene expression in breast cancer. Virchows Arch. 2009;454:467–74.
27. Dai H, et al. The role of polymorphisms in circadian pathway genes in breast tumorigenesis. Breast Cancer Res. Treatment. 2011;127:531–540.
28. Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. Nat Rev Immunol. 2013;13:190–198.
29. Partch CL, Green CB, Takahashi JS. Molecular architecture of the mammalian circadian clock. Trends Cell Biol. 2014;24:90–99.
30. Masri S, Sassone-Corsi P. The emerging link between cancer, metabolism and circadian rhythms. Nature Medicine. 2018;24(12):1795-1803.
DOI: 10.1038/s41591-018-0271-8.
31. Taniguchi H, et al. Epigenetic inactivation of the circadian clock gene BMAL1 in hematologic malignancies. Cancer Res. 2009;69:8447–54.
32. Zhu Y, et al. Ala394Thr polymorphism in the clock gene NPAS2: A circadian modifier for the risk of non-Hodgkin's lymphoma. Int. J. Cancer. 2007;120:432–5.
33. Zhu Y, et al. Testing the circadian gene hypothesis in prostate cancer: A population-based case-control study. Cancer Res. 2009;69:9315–22.
34. Pardo B, Gómez-González B, Aguilera A. DNA repair in mammalian cells. Cell. Mol. Life Sci. 2009;66:1039–56.
35. Kang TH, Reardon JT, Kemp M, Sancar A. Circadian oscillation of nucleotide excision repair in mammalian brain. Proc. Natl. Acad. Sci. USA. 2009;106:2864–7.
36. You S, et al. Daily coordination of cancer growth and circadian clock gene expression. Breast Cancer Res. Treat. 2005;91:47–60.
37. Xiaoming Y, Wood P.A, Ansell C, Hrushesky WJM. Circadian time-dependent tumor suppressor function of period genes. Integr. Cancer Ther. 2009;8:309–16.
38. Gery S, et al. The circadian gene Per1 plays an important role in cell growth and DNA damage control in human cancer cells. Mol. Cell. 2006;22:375–82.
39. Yang X, et al. The circadian clock gene Per1 suppresses cancer cell proliferation and tumor growth at specific times of day. Chronobiol. Int. 2009;26:1323–39.
40. Yang X, et al. Down regulation of circadian clock gene period 2 accelerates breast cancer growth by altering its daily growth rhythm. Breast Cancer Res. Treat. 2009;117:423–31.
41. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Painting, firefighting, and shiftwork. Lyon (France). IARC. IARC monographs on the evaluation of carcinogenic risks to humans. 2007;98.
42. Davis S, Mirick D. Circadian disruption, shift work and the risk of cancer: A summary of the evidence and studies in Seattle. Cancer Causes Control. 2006;17:539–45.

43. Dubocovich ML, et al. International union of basic and clinical pharmacology. LXXV. Nomenclature, classification and pharmacology of G protein-coupled melatonin receptors. Pharmacol. Rev. 2010;62:343–80.
44. Mazzoccoli G, Vendemiale G, De Cata A, Carughi S, Tarquini R. Altered time structure of neuro-endocrine-immune system function in lung cancer patients. BMC Cancer. 2010;10:314.
45. Hu S, Shen G, Yin S, Xu W, Hu B. Melatonin and tryptophan circadian profiles in patients with advanced non-small cell lung cancer. Adv. Ther. 2009;26:886–92.
46. Lévi F, et al. Cetuximab and circadian chronomodulated chemotherapy as salvage treatment for metastatic colorectal cancer (mCRC): Safety, efficacy and improved secondary surgical resectability. Cancer Chemother. Pharmacol. 2011;67:339–48.
47. Asao T, et al. The synchronization of chemotherapy to circadian rhythms and irradiation in pre-operative chemoradiation therapy with hyperthermia for local advanced rectal cancer. Int. J. Hyperthermia. 2006;22:399–406.
48. Weinrib AZ, et al. Diurnal cortisol dysregulation, functional disability and depression in women with ovarian cancer. Cancer. 2010;116:4410–9.
49. Belmaker RH, Agam G. Major depressive disorder. N. Engl. J. Med. 2008;358:55–68.
50. Hidaka BH. Depression as a disease of modernity: Explanations for increasing prevalence. J. Affect Disord. 2012;140:205–214.
51. Ohayon MM, Hong SC. Prevalence of major depressive disorder in the general population of South Korea. J. Psychiatr. Res. 2006;40:30–36.
52. Murcia M, Chastang JF, Niedhammer I. Psychosocial work factors, major depressive and generalised anxiety disorders: Results from the French national SIP study. J. Affect. Dis. 2013;146:319–327.
53. Booker LA, et al. Exploring the associations between shift work disorder, depression, anxiety and sick leave taken amongst nurses. J. Sleep Res. 2019;e12872.
54. Lee A, et al. Night shift work and risk of depression: Meta-analysis of observational studies. J. Korean Med. Sci. 2017;32:1091–1096.
55. Walker II, et al. Circadian rhythm disruption and mental health. Translational Psychiatry. 2020;10:28.
56. Rusting CL, Larsen RJ. Diurnal patterns of unpleasant mood: Associations with neuroticism, depression, and anxiety J. Pers. 1998;66:85–103.
57. Vadnie CA, McClung CA. Circadian rhythm disturbances in mood disorders: Insights into the role of the suprachiasmatic nucleus. Neural Plast. 2017;1504507.
58. Kalmbach DA, Pillai V, Cheng P, Arnedt JT, Drake CL. Shift work disorder, depression and anxiety in the transition to rotating shifts: The role of sleep reactivity. Sleep Med. 2015;16:1532–1538.
59. Flo E, et al. Shift work disorder in nurses – assessment, prevalence and related health problems. PLoS ONE. 2012;7: e33981.
60. Roybal K, et al. Mania-like behavior induced by disruption of CLOCK. Proc. Natl Acad. Sci. USA. 2007;104:6406–6411.
61. Arey RN, et al. An important role for cholecystokinin, a CLOCK target gene in the development and treatment of manic-like behaviors. Mol. Psychiatry. 2014;19:342–350.
62. Spencer S, et al. Circadian genes Period 1 and Period 2 in the nucleus accumbens regulate anxiety-related behavior. Eur. J. Neurosci. 2013;37:242–250.

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