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Review Article

Dysregulation of circadian rhythms has been reported to be particularly high in bipolar disorder, to evaluate whether this relationship is causal

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ABSTRACT

Bipolar disorder is a mental illness characterized by dramatic alterations in mood and has several features which suggest a relationship to the biological clock. In bipolar disorders, there are extreme swings of mood, behavior, motivation and cognitive abilities in the same person. Also sleep and circadian rhythm disruptions are common observation in these patients, both during acute episodes as well as during disease-free periods. A plethora of evidence from various studies, including chronotype studies, studies of sleep-wake cycles, studies estimating neuroendocrine/biochemical markers, genetic studies, studies involving social zeitgebers and life events, pharmacological and therapeutic evidence all show a strong association of circadian disruption and bipolar disorder. There is a necessity of establishing a definite hypothesis in the pathways altered in bipolar disorder for development of novel and effective pharmacotherapy. Once the specific mechanistic pathways have been delineated, it will definitely aid in the discovery of novel treatment modalities.

Keywords: Bipolar disorder, Circadian rhythm, Chronotypes, Mood

INTRODUCTION

Bipolar disorder is a mental illness characterized by dramatic alterations in mood and has several features which suggest a relationship to the biological clock.[1] Numerous psychiatric disorders are associated with sleep and EEG abnormalities. As per DSM-V (Diagnostic and statistical manual of mental disorders) classification of mental disorders, changes in sleep behavior such as a decreased need for sleep, hypersomnia or insomnia are some of the main criteria for diagnosis of mood disorders.[2] The changes in sleep behavior usually include difficulty in initiating and maintaining sleep. In bipolar disorders, there are extreme swings of mood, behavior, motivation and cognitive abilities in the same person. Also sleep and circadian rhythm disruptions are common observation in these patients, both during acute episodes as well as during disease-free periods.[3] Several studies reveal the origin of bipolar disorder to be the result of a malfunctioning circadian system. Genetic variations involving genes of the circadian input system, the molecular feedback loop itself or the output systems could result in such disorders.[1] Patients with Bipolar disorder exhibit symptoms which relate to circadian rhythmicity such as- disturbances in the sleep-wake cycle, diurnal variations in mood and behavior, and a periodic pattern of symptoms.[4] The endogenous rhythmicity of core body temperature and secretion of hormones are also altered in these patients. There are various studies showing behavioral, neuroendocrinal or genetic associations of circadian dysrhythmicity and bipolar disorder. Before going into the detailed evidence of such associations, core concepts of Circadian rhythm and its dysregulation and bipolar disorder are outlined.

CIRCADIAN RHYTHM AND ITS DYSREGULATION

The suprachiasmatic nucleus (SCN) in the hypothalamus is a ‘master clock’ which regulates rhythmicity of different biological processes in the human body including the

sleep-wake cycle, body temperature and different neuro-endocrine secretions.[5] This endogenous clock is influenced by external zeitgebers, of which light is primary. The physiological markers of circadian rhythm are melatonin, cortisol and CBT (core body temperature). Melatonin is considered to be the most accurate indicator of circadian function.[6]

Dysregulation of the circadian rhythm may occur either due to dysfunction of the SCN or its input or output systems or it may result from failure of the clock to entrain to external 'cues' or 'zeitgebers'.[7] Dysregulation of the circadian rhythm manifests as various CRSDs (Circadian rhythm sleep disorders).

The international classification of sleep disorders-3 (ICSD-3), divides CRSDs into the following types-delayed sleep phase type (DSPS), advanced sleep phase type (ASPS), irregular sleep-wake phase type (ISWP), free-running type, jet-lag type, shift work type and circadian sleep-wake disorder not otherwise specified.

Previous studies have shown association of CRSDs with bipolar disorder-specially the DSPS which are suggestive of the fact that circadian dysregulation could lead to bipolar disorder.[8,9] Again, some studies have documented an advanced circadian phase during mania and a delayed circadian phase during depression and mixed mania.[10]

Thus, circadian rhythm phase shifts could be involved in the pathophysiological mechanism of bipolar disorder.

While delayed sleep phase disorder is characterized by a stable sleep schedule which is several hours later than the conventional sleep time, an advanced sleep phase is characterized by a stable sleep which is several hours ahead of the normal or conventional sleep time. Both of these can be diagnosed by sleep logs, actigraphy, sDLMO (salivary dim light melatonin onset) and CBT minimum (core body temperature minimum).

The endogenous circadian clock is regulated by rhythmic expression of clock genes including CLOCK, BMAL 1, PER, CRY, TIMELESS and many other proteins. The rhythmic expression of these genes controls the rhythmicity of functions such as the sleep-wake cycle, feeding, CBT, metabolism and hormone release. Variation of gene expression can be seen in patients with bipolar disorder.

Apart from the SCN, the pineal gland is another important element of the circadian system which synthesizes melatonin. Melatonin secretion peaks in the dark and is suppressed by light. DLMO is one of the key markers of circadian phase.

Circadian rhythm also affects neurotransmitters of the serotonergic, dopaminergic and noradrenergic pathways. In Bipolar disorder, there is dysregulation of circadian rhythm as well as emotional lability which may occur as a result of complex interactions between the different neurotransmitter pathways and the circadian clock.

BIPOLAR DISORDER

According to the American psychiatric associations' DSM-V, bipolar disorders comprise a group of brain disorders causing extreme fluctuations in a person's mood, energy and ability to function.[2] It encompasses three different conditions-bipolar I, bipolar II, and cyclothymic disorder.

Bipolar I

It is a manic- depressive disorder, which can exist both with or without psychotic episodes.

Bipolar II

Alternating episode of hypomania and depression which are usually less severe and do not inhibit function.

Cyclothymic disorder

Cyclic disorder causing brief episodes of hypomanic and depressive symptoms but does not meet the criteria for hypomania or major depressive disorder.

People with Bipolar disorder experience periods of great excitement, overactivity, delusions and euphoria known as mania, along with periods of extreme sadness and hopelessness which is known as depression. In some cases, a Bipolar episode can be of mixed type where symptoms of both mania and depression are present.

Patients with bipolar disorder have circadian dysregulation characterized by alterations in sleep-wake activity, hormonal secretions, feeding behavior etc.[11] They also exhibit seasonal differences in behavior with manic episodes seen during spring and summer months and depressive episodes during winter. This might be due to seasonal differences in day length.

Bipolar disorder is a chronic disorder rendering lifetime disability. Several studies have shown that there is an association between circadian rhythm disruption and bipolar disorder.[12] Since there is evidence for genetic etiology of bipolar disorder, it is possible that dysfunction of circadian genes may be responsible for the pathogenesis of this disorder.[13] Once established, this will definitely aid in the management of this disabling disorder.

The following main section of the essay will discuss in detail the evidences for circadian dysregulation in bipolar disorder, some of which prove that the association is causal. The various types of studies include-phenotype characteristics studies, neuroendocrine/ biochemical marker studies, genetic studies, pharmacological studies and social zeitgebers and life events studies.

PREVALENCE OF CIRCADIAN DYSREGULATION IN BIPOLAR DISORDER

In a study in 2016 by Takaesu et al the prevalence of CRSDs in patients with bipolar disorder was estimated.[8] 104 patients having euthymic bipolar disorder were included in the study. Patients were assessed using questionnaires for both disorders. Subjective sleep was assessed by Pittsburgh sleep quality index (PSQI) and CRSD was diagnosed with the help of interview, sleep logs of more than 4 weeks by sleep specialists. Current mood status was assessed using MADRS (Montgomery-asberg depression rating scale) and YMRS (Young mania rating scale). Of the 104 subjects, 35 were found to have CRSD (32.4%). This proved that the prevalence of circadian dysregulation in bipolar disorder was much more than in the general population. Therefore, it can be said that they share a common pathophysiology. Also, about one-third of the study subjects reported that onset of sleep disturbance was prior to that of mood disturbance suggesting a definite role of circadian dysregulation in the aetiology of bipolar disorder. The main limitation of this study was a small sample size and a single collection center. Objective measures such as actigraphy or DLMO were not done. Biological rhythm assessment using BRIAN was also not done. However, this study does reveal the close and frequent association of CRSDs with bipolar disease.

PHENOTYPE CHARACTERISTICS STUDIES

Circadian rhythm disruptions are commonly observed in patients who progress to bipolar disorder. Rhythm disruptions precede disease onset, are present during acute attacks of mania, hypomania and even in the euthymic periods.[14]

Chronotype studies

Chronotype refers to the preference of a person to daytime or nighttime for his activities. The Horne-Ostberg questionnaire (HO questionnaire) or Munich chronotype questionnaire (MCTQ) are frequently used to categorize a person as ‘morning type’ or ‘evening type’. In a study by Moon et al it was reported that advanced circadian phase in mania and delayed circadian phase in mixed mania and depression normalized after treatment of bipolar disorder.[10] They studied 26 patients of bipolar disorder along with 18 controls. Circadian rhythms of bipolar disorder patients were evaluated on admission to hospital, every two weeks thereafter, and at discharge using actigraphy, cortisol estimation and circadian gene expression. It was seen that 23 patients of acute mania had a 7-hour advanced circadian phase which returned to normal after treatment. In 3 cases of mixed mania and 5 cases of depression there was a phase delay of 4-7 hours. This too returned to normal after treatment. Their study clearly suggest that acute mood episodes occur during misalignment between a person’s endogenous circadian rhythm and external physical environment. Previous studies have reported a higher prevalence of evening chronotypes with bipolar disorder.[8] The researchers suggest that both depression and mania in bipolar disorder result from a tendency to phase delay, but the delay in mania is very extreme and perhaps more than 12 hours, so that there is a 360-degree delay rotation of phase. It can be concluded from this study that circadian rhythms could pose as a biomarker for diagnosis, monitoring and treatment of bipolar disorder.

Sleep-wake cycle studies

Talbot et al studied the effects of bipolar disorder on sleep.[15] Particular emphasis was laid on relation of mood with sleep onset latency (SOL) and REM. Polysomnography (PSG) data was used for analysis of sleep stages. Happy mood induction caused increase in SOL while sad mood induction decreased it and increased REM density. As compared to controls, REM sleep density was increased in bipolar disorder patients.

Similarly, several actigraphy studies have shown longer SOL, longer total sleep time, increased wake after sleep onset and decreased sleep efficiency.[3] Jones et al used actigraphy for assessment and sleep patterns in bipolar disorder patients.[16] They found a variable activity pattern in these patients. Evidence of circadian rhythm disruption in absence of acute attack was also present. They suggested the use of actigraphy for measuring treatment outcome in bipolar disorder patients. The findings also agreed with the proposition that circadian dysregulation posed a vulnerability factor for Bipolar episodic attacks. Another study by Esaki et al reported the association between circadian activity rhythms measured using accelerometer and subsequent mood episodes in bipolar disorder. They found that robust circadian activity rhythm was significantly associated with decrease in relapses in depressive episodes. Also, a delayed circadian rhythm was found to be significantly associated with relapse of depressive episodes.[17]

Overall sleep-wake studies suggest that individuals with bipolar disorder are more sensitive to environmental factors that can lead to mood or sleep disruptions which constitute the prodromal symptoms of this disorder.

Biochemical marker studies

There is a cyclic pattern of cortisol and melatonin secretion which is altered in bipolar disorder.

Cortisol secretion studies

In a study by Moon et al cortisol estimation was done in patients with bipolar disorder.[10] They found that acute episodes of mania were associated with 7-hour advancement of cortisol acrophase as compared to controls. Mixed mania had 6-hour delay while depression patients had 4-5-hour delay in acrophase. This provides an understanding that bipolar mood episodes have strong relation with circadian dysregulation. Some studies have

shown that 24-hour cortisol secretion is higher in patients with bipolar disorder as compared to controls.[3]

Melatonin secretion studies

Several studies report suppression of nocturnal melatonin secretion in patients of bipolar disorder. In a study in Lam et al nocturnal melatonin suppression to light exposure was compared in bipolar patients with controls.[18] A significant suppression of secretion to 500 lux light exposure in acutely ill bipolar patients was seen. This suggested that light super sensitivity may be specific for bipolar disorder. Baseline melatonin levels were also lower in patients with bipolar disorder as compared to controls. Thus, super sensitivity in the melatonin response to light exposure can be used as a high-risk factor for bipolar disorder.

Genetic studies

Bipolar disorder may arise partly due to dysregulation of the circadian gene system. Study of circadian genes could help to identify genes and their pathways which may predispose to bipolar disorder. Genetic variations may affect input to the circadian clock, the molecular feedback loop or the regulatory output systems, thus resulting in many psychiatric disorders including bipolar disorder where there is maladaptation to daily or seasonal cycling.

In a study by Neevergelt et al linkage and association involving polymorphism in ten circadian clock genes to Bipolar disorder was assessed.[1] The genes studied were ARNTL, CLOCK, CRY2, CSNK1, DBP, GSK3β, NPAS2, PER1, PER2 and PER3. Both linkage analysis and association studies were done. They found evidence of association of circadian genes PER3 and ARNTL with Bipolar disorder.

Another genetic study Virginia et al estimated the differential association of circadian genes with mood disorders.[4] In this study, 209 single-nucleotide polymorphisms (SNP) in 19 circadian genes was assessed in 534 patients of bipolar disorder. They found a significant association of CLOCK and VIP with bipolar disorder. Their findings support the role of circadian genes in susceptibility to bipolar disorder. While some gene alterations caused depression, others led to manic liability. Thus, it is important to consider the circadian system as a therapeutic target in treatment of bipolar disorder. Also, specific genetic markers for susceptibility to depression could be used for diagnosis of bipolar disorder.

Animal studies also support the role of circadian genes in bipolar disorder. In a study by Coyle et al CLOCK gene deletion was done in mice to assess the effect.[19] It was seen that deletion of exon 19 in CLOCK gene resulted in manic-like hyperactivity, which was somewhat similar to that seen in bipolar disorder. This behavior could be reversed by treatment with lithium or reimplantation of a functional CLOCK gene. Thus, these studies highlight the fact that disruption in circadian rhythm as a result of alterations in circadian genes may lead to bipolar disorder. These gene alterations may result in a high sensitivity to rhythm changes that is seen in patients with bipolar disorder, especially with disease onset or when there is a relapse.

Pharmacological studies

Lithium is used as a maintenance treatment for bipolar disorder. Studies have shown that lithium acts by correcting circadian dysregulation.[20,21] Lithium is reported to shorten or lengthen period of the circadian clock in different studies and thereby correct phase-delay or phase-advance rhythms. Lithium is known to inhibit GSK3β and GSK3α and expression of CLOCK genes NR1D1, CRY1, ARNTL and PER2 showing a genetic involvement in its mechanism of action.

Melatonin which regulates circadian rhythm is also effective in treatment of mood symptoms in bipolar disorder.[22] In a randomized controlled trial conducted by Norris et al the efficacy of melatonin agonist Ramelteon as an adjunctive therapy in bipolar disorder was detected. In a six months study period, it was found to prevent relapse.[23]

Similarly, adjunctive light therapy may also help in improving depression in bipolar disorder. In a study by Benedetti et al it was seen that when light therapy was combined with sleep deprivation and lithium, it helped not only in correcting suicidality but also improved depression in drug-resistant bipolar disorder.[24]

Some studies have shown effectiveness of dark therapy in synchronizing the circadian rhythm and thus correcting manic episodes in bipolar patients.[25,26]

Thus, various pharmacological studies point to the fact that therapy aimed to correct circadian dysregulation is effective in treating all states of bipolar disorder and prevent onset and relapse. Therefore, circadian dysregulation, it can be said has a definite role in the pathophysiology of bipolar disorder.

Social zeitgebers and life events studies

Social time cues as meal timings, regular sleep timings, work schedules, exercises etc. all play a role in entraining the circadian rhythm. In Ehlers et al proposed the 'social zeitgeber theory' in the aetiology of mood symptoms of bipolar disorder.[27] Maintaining regularity of social time cues may promote synchronization of the endogenous circadian rhythm thus facilitating stabilization if mood symptoms in bipolar disorder. Several studies have shown that Bipolar patients experience stressful life events and have social rhythm disruption (SRD) which leads to onset of manic and depressive episodes. In a study by Malkoff-Schwartz et al in 1998, it was shown that there is a strong association of SRD with manic symptoms.[28] Life events causing SRD leads to sleep and circadian rhythm disruption which is related to the onset of mania in bipolar

disorder. Longitudinal studies have also demonstrated that patients with bipolar disorder have mostly experienced stressful life events prior to the onset of either mania or depression.[29,30]

Thus, regularity of social time cues plays an important role in synchronizing the biological clock. Disruption of this rhythm could lead to a circadian deregulation and onset of manic and depressive episodes.

PROPOSED THEORIES/ MODELS OF BIPOLAR DISORDER

Bidirectional relationships between sleep and circadian functioning, external time cues and mood regulation in bipolar disorder

As proposed by Yoshikazu et al there is a complex and bidirectional relationship between circadian rhythm, external zeitgebers and onset and relapse of mood episodes in bipolar disorder.[31] Genetic alteration may lead to circadian dysregulation. Stressful life events may usher in social rhythm disruption. In genetically susceptible individuals due to a gene-environment interaction this may possibly play a role in the pathogenesis of mood dysregulation in bipolar disorder. Changes in circadian/ sleep patterns have been documented prior to changes in mood patterns in bipolar disorder patients as regards to onset, clinical course and relapse.

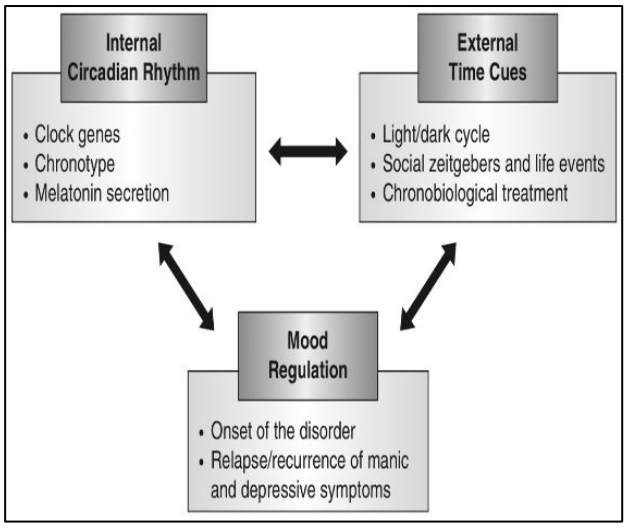

Figure 1: Relation between internal circadian rhythm, external time cues and mood regulation in bipolar disorder.[31]

Triple susceptibility model of bipolar disorder

Another hypothesis of bipolar disorder was proposed by Lee et al.[12] They described a triple-susceptibility model of bipolar disorder. The three factors responsible are: Hypothalamic-pituitary-adrenal axis (HPA axis) hyperactivation, monoamine dysregulation, and circadian rhythm dysregulation.

These three factors interact to induce mania or hypomania via monoamine overactivity.

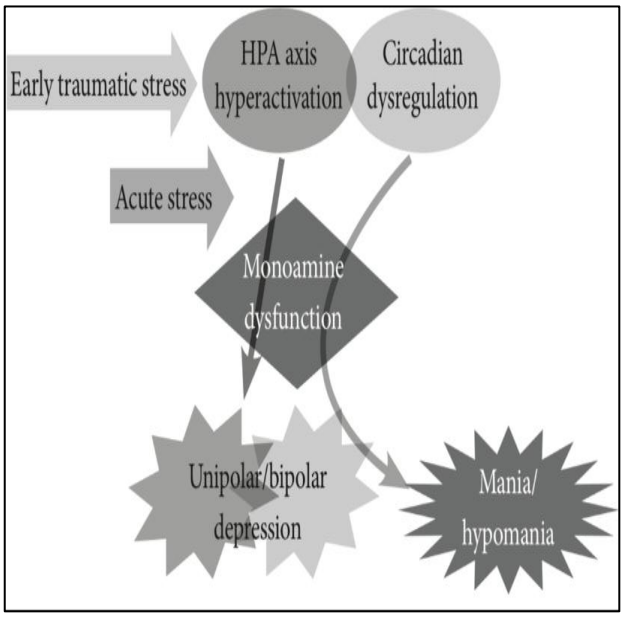

Figure 2: Triple-susceptibility model of bipolar disorder.[12]

According to this model, stress during early life alters HPA axis through impaired function of glucocorticoid receptors. This results in HPA hyperactivity in adulthood which in turn increases susceptibility to bipolar mood disorders.

Monoamine dysregulation either as deficiency of monoaminergic neurotransmitters such as noradrenaline, serotonin, dopamine etc. leads to depression while excess of monoamines leads to mania. They suggested that some individuals with depression may progress to mania/ hypomania due to circadian dysregulation also in addition to the previous two factors.

CONCLUSION

Bipolar disorder is a chronic illness comprising of cyclic episodes of mania and depression. Prevalence of CRSD in Bipolar disease patients was found to be 32.4% by Takaesu et al which is significant. Of the study subjects, 33% reported that sleep disturbance occurred prior to occurrence of mood disorders. In patients of bipolar disorders, circadian rhythms such as sleep, daily activity, social rhythms, meal timings are altered not only during acute episodes but also in the inter-illness period. There are increasing evidences showing complex associations between circadian dysregulation and bipolar disorder. Disruptions in sleep-wake cycle often precede mood episodes in patients with this disease. Indeed, one of the core concepts of psychotherapy in bipolar disorder is maintenance of a stable circadian rhythm. A plethora of evidence from various studies, including chronotype studies, studies of sleep-wake cycles, studies estimating

neuroendocrine/biochemical markers, genetic studies, studies involving social zeitgebers and life events, pharmacological and therapeutic evidence all show a strong association of circadian disruption and bipolar disorder. Circadian rhythm disturbances result in numerous biological effects including that on the oxidative stress systems. Oxidative stress, particularly lipid peroxidation, maybe an important factor leading to bipolar disorder. Lipid peroxidation has been considered as a trait marker of bipolar disorder.

Melatonin, which is the primary circadian signaling molecule, is also abnormal in patients with bipolar disorder. While some studies report irregular melatonin secretion, others observe lower nocturnal melatonin levels. Some studies have also shown that there is impaired inhibition to melatonin synthesis on light exposure in bipolar disease patients. There are also reports of upregulation of melatonin receptors in SCN, in patients with depression. Thus, melatonin super sensitivity can be used as a trait marker for patients with bipolar disorder. Cortisol secretion acrophase advancement or delay is also seen in bipolar disorder patients, indicating a dysregulated circadian system. Chronotype studies have shown that patients of bipolar disorder usually are evening chronotypes. It has been suggested that phase-delay has a definite role in the etiopathology of bipolar disorder. However, some other studies have reported an advanced phase in mania and a delayed phase in depression. Genetic studies have clearly identified the role of polymorphisms of circadian genes in susceptibility to bipolar disorder. Particularly the role of PER3, ARNTL, CLOCK and VIP has been shown. Animal studies have also proved the association of CLOCK gene with manic episodes. Circadian gene alterations may pose a vulnerability to mood changes in bipolar disorder.

Pharmacological studies have also shown that Bipolar patients show good response to lithium which acts by correcting phase advances or delays. Similarly, other measures to correct circadian dysregulation such as melatonin, light or dark therapy are effective in improving bipolar disorder. Disruptions in social cues or stressful life events may lead to altered circadian rhythms and precipitate mood disorders. Thus, susceptibility to several core symptoms of bipolar disease during onset or relapse appear to be related to underlying abnormalities in the circadian rhythm. Such patients characteristically show disturbances in sleep-wake cycles, diurnal or cyclical pattern of mood changes and periodicity in symptom remission and relapse. Clinical, biochemical, genetic, pharmacological studies have all proved beyond doubt that dysregulation in sleep and circadian rhythm occur in bipolar disease. This has provided strong insights into the pathophysiological pathways involved in the onset and progression of bipolar disorder and has also helped in shaping treatment modalities. However, till date, the precise relations between circadian dysregulation and the aetiopathophysiology of bipolar disorder remain unclear. Also, the findings of various studies have been inconsistent in deciding whether to regard circadian rhythm dysregulation as a trait-marker or a mood state dependent. Further studies to clarify the relation between circadian dysregulation and pathogenesis of bipolar disorder is warranted. Newer antipsychotics for treatment of bipolar disorder have also not evolved since the last few decades. There is a necessity of establishing a definite hypothesis in the pathways altered in bipolar disorder for development of novel and effective pharmacotherapy. To conclude, it can be suggested that genetically susceptible individuals when exposed to stressful life events may experience social and circadian rhythm disruptions, which may culminate in onset of Bipolar mood disorder. The exact pathways and mechanisms however remain to be discovered. Once the specific mechanistic pathways have been delineated, it will definitely aid in the discovery of novel treatment modalities.

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