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Circadian Rhythm and the Prediction of Relapse in Bipolar Disorder

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Chronobiological disturbances have long been suspected to be associated with bipolar disorder. Several of the clinical features required to establish the diagnosis highlight the central role that these disruptions play in the phenomenology of the illness.[1] Decades of research support the notion that disturbances of rhythm not only are associated with the clinical presentation of the disorder but may represent clues to the possible physiologic mechanisms of the illness.[2] As with other complex trait disorders, the search for etiologic mechanisms of bipolar disorder is hampered by the fact that the illness most likely represents a heterogeneous group of disorders with multiple etiologic factors. The problem presented is how to identify homogenous subgroups in bipolar disorder. Focusing on chronotypic characteristics may provide an avenue toward this aim. The goal of the study by Takaesu and colleagues[3] is to answer the possible role of circadian rhythm sleep-wake disorders (CRSWDs) in the prediction of shorter time to relapse of mood episodes in euthymic patients with bipolar disorder.

This study follows up on previous findings reported by this research group indicating that a significant percentage of patients with bipolar disorder met criteria for a comorbid CRSWD. CRSWDs are a group of conditions that result in the variations of the circadian timing system, disturbances in the entrainment of circadian rhythms, or a misalignment of a person's natural circadian rhythms and their social or physical environment.[4] Takaesu and colleagues[3] have followed up on their initial findings by conducting a 48-week prospective observational study in this same patient population designed to test the hypothesis that CRSWDs were a predictor of relapse in euthymic bipolar disorder subjects. One hundred four bipolar disorder patients (bipolar I or II disorder) were included in the analysis.

The investigators report that approximately half of the sample suffered a relapse over the course of the observational period (30.8% depression, 18.3% mania/hypomania). The investigators also report that, in addition to other clinical (higher baseline Montgomery-Asberg Depression Rating Scale and Pittsburgh Sleep Quality Index scores, higher rates of having 2 or more mood episodes in the past year) and course of illness (younger age at illness onset) characteristics, higher rates of CRSWDs were characteristic of the relapse group. In addition, they found that the presence of a comorbid CRSWD was associated with a shorter time to relapse.

The researchers found that approximately one-third of bipolar patients in the sample met criteria for a comorbid CRSWD when in a euthymic state. These findings are in line with previous reports suggesting a possible relationship between delayed sleep-wake phase disorder and bipolar disorder. This study supports previous research that suggests a relationship between chronobiological disturbances and affective states in bipolar disorder[5–10] in which these disturbances have been associated with an increased symptom severity in the disorder[10] and an increased susceptibility toward the development of mood episodes.[11–13]

These findings, however, also demonstrate a heterogeneity in the forms of chronobiological disturbances associated with the illness. Delayed sleep phase, non–24-hour, and irregular sleep-wake disorders were all identified in this sample. Multiple forms of rhythm disturbances have been reported in association with bipolar disorder. For example, in addition to phase delays,[14,15] phase advances[5,16–19] and an inherently shorter circadian period (< 24 hours)[20,21] have also been reported in association with the disorder. Some quite compelling evidence indicates an inherent instability in the biological rhythms of those suffering from the illness, with a wide degree of variability in biological rhythms having been reported in bipolar disorder.[6–9,22,23] This variability has been observed in the psychomotor activity patterns for which a greater variability[22,23] and a less stable degree of rhythmicity[22,23] have been reported.

Most of the research conducted thus far has sought to answer the questions as to whether chronobiological disruptions are state or trait features of bipolar disorder. While this study highlights the impact that comorbid CRSWDs have on the course of illness and clinical presentation of the illness, we believe that the study offers great promise for establishing viable phenotypes for the disorder. In this sample, bipolar patients with a coexisting CRSWD were also found to have a lower age at onset of their

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illness, higher baseline rates of sleep disturbances as defined by the Pittsburgh Sleep Quality Index, and an increased prevalence of having had 2 or more previous mood episodes in the preceding year.

Interest in exploring the role that chronobiological characteristics can play in defining bipolar disorder phenotypes has expanded in recent years. An example of this has been demonstrated with regards to chronotype, or the diurnal preference for daily activities. Research in this area has noted that an evening chronotype is associated with rapid mood swings,[24] greater recurrence rates of affective episodes,[24] and an earlier age at illness onset.[24] Rhythm-based phenotyping may also prove to be of importance in defining treatment response,[21] associated variations in the functioning of molecular clocks,[25] genetic variations associated with the illness,[26–30] and heritable features of the disorder.[31]

Longitudinal studies are needed to better understand the relationships between chronobiological disturbances and bipolar disorder and to establish potential chronobiologically based phenotypes for the illness. Further research is also required to further explore biological and clinical correlates associated with rhythm disturbances noted in bipolar disorder. A greater understanding of these relationships may have significant diagnostic, illness monitoring, and treatment implications. While there is a lot of work to be done, the study by Takaesu and colleagues[3] is a positive step toward these aims.

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