

An Article Review Concerning New Treatments and Prevention Strategies for Schizophrenia Based on Mechanisms also Involved in Sleep and Circadian Dysfunction

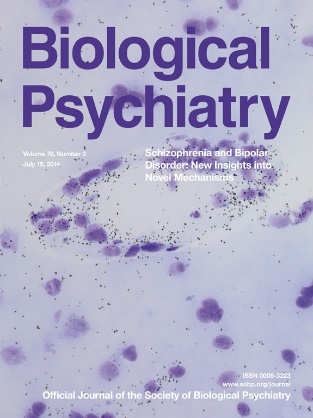
By T. S.

Pritchett, D., Wulff, K., Oliver, P. L., Bannerman, D. M., Davies, K. E., Harrison, P. J., …

Foster, R. G. (2012). Evaluating the links between schizophrenia and sleep and circadian rhythm

disruption. *Journal of Neural Transmission*, *119*(10), 1061–1075.

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oes sleep hold the key to uncovering new schizophrenia treatments? This may not seem like a particularly relevant question, but the fact that schizophrenia and sleep/circadian disruptions are highly comorbid is a little known truth. In their 2012 literature review published in *Biological Psychiatry*, lead author David Pritchett and his colleagues suggest that the comorbidity of these two disorders is due to the involvement of common brain mechanisms, and that this fundamental relationship presents a very significant new direction for research concerning schizophrenia treatments.

Pritchett and colleagues are all associated with the University of Oxford. Pritchett is both a researcher and a student there. He is currently completing his PhD in neuroscience. One of his dissertation advisors, Russell Foster, contributed to this literature review. Foster is one of the world’s leading experts on circadian rhythms. He is currently the Chair of Circadian Neuroscience at the University of Oxford and has published 77 articles. Pritchett notes the relationship between schizophrenia and sleep/circadian disturbances as one of his primary areas of research.

Schizophrenia is a serious neurodegenerative disease characterized by delusions, hallucinations, and abnormalities in affect as well as cognitive deficits. Antipsychotic medication is the most commonly prescribed treatment for schizophrenic patients. However, these drugs have a number of negative side effects that reduce quality of life and increase risks for other serious health problems. In addition, antipsychotic medication often becomes ineffective for patients after long-term use.

Familiarity with terms relating to sleep and circadian functions is also important for understanding the fundamental points of this review. SCRD stands for Sleep and Circadian Rhythm Disruption. Insomnia and shifted sleep/wake cycles are just a few examples of SCRD symptoms. In the context of this article, circadian rhythms refer to endogenous cycles that have a 24-hour period.

The three most intriguing ideas that I will present from this review are the hypothesis that schizophrenia and sleep/circadian control involve common brain mechanisms, that both abnormalities have linked genetic markers that can be identified using animal models, and that the prodromal appearance of SCRD symptoms presents a window for prevention as well as treatment.

First, Pritchett calls attention to the fact that many lines of evidence suggest that common brain mechanisms are responsible for both schizophrenia symptoms as well assleep and circadian rhythm abnormalities. 

One of the key pieces of evidence he cites that allows for the common mechanisms hypothesis is that sleep/circadian rhythms and schizophrenia involve many complex neurotransmitter systems that are involved in regulating numerous additional processes. This means that abnormalities in one system can cause disruptions in systems that may appear completely independent.

Second, treating SCRD symptoms typically results in an improvement in psychiatric symptoms, such as delusions. The observation that treatment of SCRD results in improved psychiatric symptoms provides another line of evidence supporting the common mechanisms hypothesis.

Third, 30-80% of all schizophrenic patients suffer from SCRD symptoms. In other words, at a minimum, just under one third of all schizophrenic patients have sleep or circadian disturbances. The sheer number of comorbid cases alone suggests a fundamental linkage. Indeed, recent research presented in the review indicates schizophrenia and SCRD are linked genetically as well as symptomatically.

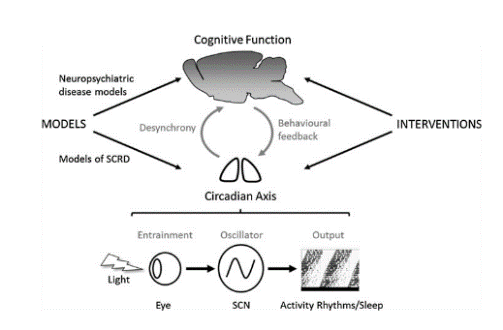
While a number of genes are now associated with the development of schizophrenia, only a few of these genes have also been studied in connection with increased risk for SCRD. Pritchett argues that animal models are necessary to explore the fundamental basis for the linkage of these two disorders. He also asserts that the use of animal models is necessary for the development of future treatments that rely the relationship between SCRD and schizophrenia. Without greater knowledge of the molecular and genetic factors at work, developing effective treatments becomes much more difficult. Further genetic research focusing on the comorbidity of SCRD and schizophrenia is required. However, in the four cases known to Pritchett where SCRD symptoms have been assessed in animals designed to model schizophrenia, sleep/circadian abnormalities have been observed in all four models. These results justify further research and strongly indicate that the use of animal models may be the best way to develop and test new treatments.

Russell Foster, Head of the Nuffield Department of Clinical Neurosciences at University of Oxford.

Finally, perhaps the most intriguing observation noted in this review is that SCRD symptoms often manifest prodromally in schizophrenic patients. In other words, many schizophrenic patients begin to experience sleep/circadian disturbances *before* their first psychotic episode. This observation is extremely significant because the fact that a prodromal stage exists suggests there is a window not only for treatment but perhaps even disease prevention in at risk populations. Pritchett suggests that both environmental and pharmacological treatments could potentially be used. Prodromal manifestation of SCRD symptoms indicates there may be a time in the course of the disease where development may still be reversible if the right treatment is administered. Further research should also focus on identifying factors that could halt or slow further degeneration following the prodromal stage.

This diagram (Pritchett) articledemonstrates the basis for the common mechanisms hypothesis.

Pritchett presents an excellent synthesis of current research about both schizophrenia and SCRD, building the foundation of evidence suggesting a relationship between these two disorders. I appreciate that in this literature review, Pritchett notes -- where appropriate -- the limitations in the studies used to support his analysis. Pritchett also emphasizes the fact that more research is required to determine the precise genetic linkages that exist and treatment regiments that would be most effective. However, Pritchett and colleagues state that the task of isolating the genes to use to create animal models is very difficult, but they do not propose new strategies for identifying genes or creating models. Given that his hypothesis relies on more information from animal model experiments, he could have included more content about new techniques or strategies to improve the research model, focusing in particular on how to apply this research method to most effectively develop new treatments for patients.

Pritchett’s review covers the breadth of evidence that supports the existence of a strong connection between schizophrenia and sleep/circadian based on common mechanisms research and justifies future study.

Future studies should specifically focus on the development of new treatments exploiting this relationship. Exploring prodromal treatment regiments using animal models, as suggested in this review, would also be worthwhile. This avenue of research has the potential to produce new alternatives to antipsychotic drugs that could significantly enhance the quality of life for schizophrenic patients. In addition, the new treatment methods and research strategies have the potential to improve other disorders known to be comorbid with schizophrenia such as depression.