Sleep Disturbance as a Universal Risk Factor for Relapse in Addictions to Psychoactive Substances

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Abstract

Relapse to uncontrolled use of a psychoactive substance is arguably the single most defining characteristic of an addiction. Relapse following addiction treatment is very common with serious consequences to individuals, families, and the public system of care, making predictors of relapse a highly significant area of study. Before the turn of the century, most of the addiction treatment outcome literature focused on psychosocial predictors of relapse. More recently, investigating biological predictors of relapse specifically and treatment outcome broadly has gained momentum. This line of research has linked sleep disturbances to the risk of relapse among persons who are recovering from an alcohol addiction. Given common neurobiological and psychosocial processes in sleep and addictive behaviors, we hypothesize that the link between sleep disturbance and relapse risk observed among alcohol addiction generalizes to all other types of psychoactive substances. This hypothesis has the potential for helping develop more effective and targeted treatment approaches for persons with addiction. As initial support for the hypothesis, this paper reviews evidence on common neurobiological processes among various types of psychoactive substances that suggests sleep is a universal risk factor for relapse. A conceptual framework is also presented to articulate causal mechanisms. The paper concludes with implications for research and practice.

Introduction

Relapse to uncontrolled use of a psychoactive substance is arguably the single most defining characteristic of an addiction, a source of immense frustration that is accompanied by tragic consequences for patients and society, and a primary target for addiction treatment research. Unfortunately, relapse following addiction treatment is very common and, therefore, predictors of relapse are a highly significant area of study. Before the turn of the century, most of the addiction treatment outcome literature focused on psychosocial predictors of relapse, which includes the long list of variables in Table 1. The underlying premise for studying these variables is that some might be modifiable, such as increasing self-efficacy, while other variables might respond optimally to specifically targeted treatment programs (e.g., gender, age).

More recently, investigating biological predictors of treatment outcome has gained momentum. Human studies in this area have shown relationships between relapse and (a) genetic variants, [1-5] (b) size of specific brain structures,[6] (c) functioning of various neurotransmitters and

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neuroendocrine systems,[7-17] (d) activation of specific neuroanatomical regions as measured with functional brain imaging,[18-20] and (e) patterns of electrophysiological brain patterns, [21-26] including neurophysiological correlates of sleep.[27-29] The investigation of biological predictors—which for the most part are *neuro*biological predictors—is consistent with the currently dominant paradigm in addiction research, namely that addiction is a brain disease. According to this paradigm, if we can delineate how the brain is altered in affected individuals, then we can improve upon treatment strategies by targeting these specific neurobiological alterations, for example, with pharmacotherapy agents. Not surprisingly for a dominant paradigm, a proliferation of scholarly reviews of the neurobiology of addiction has recently been published.[30-33]

Of course, most experts would agree that addiction is not simply a brain disease, but rather a disorder that is strongly influenced by psychological, social, and cultural factors in addition to genetic, epigenetic, and neurobiological ones. While agreeing to the importance of non-biological factors in the etiology and course of substance use disorders, we will focus on a biological one, specifically sleep, which is also influenced strongly by psychosocial and cultural factors. Sleep disturbance offers a number of advantages when investigating predictors of addiction treatment outcome. For example, it is a common symptom across all substance-related withdrawal disorders recognized in the DSM-IV.[34] Psychological and pharmacological treatments are available to address sleep disturbances among persons with substance-related disorders.[35, 36] Thus, with proper assessment and targeted sleep-related interventions, treatment providers can increase the likelihood of successful outcomes for this at-risk population. Finally, systematic investigation of the relationship between sleep disturbance and relapse can advance our knowledge on the basic science of addiction and treatments.

Hypothesis

Current research suggests that sleep disturbances among persons who are recovering from an alcohol addiction and have a sleep disturbance are at an elevated risk of relapse compared to those without a sleep disturbance. Given common neurobiological and psychosocial processes in sleep and addictive behaviors, we believe this sleep-related relapse risk for alcohol generalizes to all other types of psychoactive substances. In formalized terms, we hypothesize that *persons who are recovering from an addiction to any psychoactive substance and have a sleep disturbance are at an increased risk of relapse compared to those without a sleep disturbance*. In other words, sleep disturbance is a universal risk factor for relapse in addiction to all psychoactive substance. For this hypothesis, a *sleep disturbance* refers to any problems involved with falling asleep, staying at sleep, distressing dreams, or inability to progress through normal stages of sleep.

We describe this hypothesis by first presenting research that shows an association between sleep disturbance and relapse among persons with an alcohol addiction. This is followed by a review of other research highlighting common neurobiological factors that provides a foundation for generalizing this association to other psychoactive substances. We then present sleep disturbance as a universal risk factor for relapse within a conceptual framework to describe the underlying causal mechanisms for this universal risk factor in relapse. We conclude with research and treatment implications based on the hypothesis.

Evidence that Sleep Predicts Relapse across Psychoactive Substances

Alcohol

The largest body of evidence relating sleep disturbance to relapse involves studies of alcohol dependence, for which both subjective and objective measures of sleep at baseline have predicted subsequent relapse.[27, 37] A 2003 review of the literature cited 12 publications from

1975 to 2001 by six different research groups demonstrating a relationship between sleep disturbance and relapse.38 Since that time, at least three other reports have appeared which extend the evidence.39-41 In general, the literature indicates that increased sleep latency and its subjective correlate (trouble falling asleep) as well as significantly more rapid eye movement (REM) sleep or "REM pressure" are replicated predictors of alcoholic relapse. Not included in this review is a 1973 publication citing dreams of alcohol-dependent patients as a prognostic factor.42 Since then, another data-based publication describing polydrug users, including alcohol abusers, was consistent with this early observation.43 Finally, a more recent report describing a series of cases stressed the importance of paying treatment attention to so-called "using" dreams in order to prevent relapse.44

Cocaine and Amphetamines

Although the literature on addiction-related dreaming and relapse is less substantial than for other sleep parameters, there are three reasons to take the phenomenon seriously. First is the inclusion of unpleasant, vivid dreams as a criterion symptom for both amphetamine and cocaine withdrawal.34 Second, Sofuoglu and colleagues45 reported from a cross-sectional survey that vivid, unpleasant dreams during cocaine withdrawal were associated with a history of addiction treatment, severe depression, and trading sex for cocaine or cocaine for sex; i.e., a more severe course of the disorder. Third is the association of rapid eye movement (REM) sleep pressure —a correlate of dream sleep—and relapse to alcohol dependence that has been independently documented by two different research groups.29, 46

Nicotine

At least three recent studies are suggestive that events during the sleep period predicted relapse to smoking tobacco.47-49 One of these reported that awakening during the night as measured by a nicotine withdrawal scale was negatively associated with abstinence for 6 months after starting treatment.47 Another found that participants who had a history of smoking during their sleep period (after going to bed but before their final awakening in the morning) had an earlier time to their first smoking episode within four weeks of their quit date.49 None of these studies employed polysomnography.

Opioids

We were unable to find evidence that poor sleep predicted relapse in patients dependent on opioids. Paradoxically, one recent study reported that poor sleep during opioid detoxification was associated with abstinence during a 4-week follow-up period.50 The authors speculated that treatment staff may have given more attention to poor sleepers, resulting in better outcomes, but they could not support that explanation with data. Again, polysomnography was not performed.

Sedative-Hypnotics

Regarding sedative-hypnotic dependence, there is general consensus that sleep disturbances perpetuate the disorder,51-54 but this relationship has not been formally tested.

Conceptual Framework for the Sleep Disturbance-Relapse Hypothesis

The evidence that sleep disturbance is linked to relapse is strongest for alcohol dependence. Two sets of arguments for generalizing the link between sleep disturbance and relapse to other psychoactive substances are provided below. The first of these arguments is based on the commonality of sleep disturbances across psychoactive substances, while the second of these sections is based on the unique advantages of sleep disturbances as a predictor of treatment outcome.

Commonality of Sleep Disturbance

The phenomenology and course of acute withdrawal following a reduction in or discontinuation of dependent substance use is well-described diagnostically for six classes of substances, namely alcohol, amphetamine, cocaine, nicotine, opioids, and sedative-hypnotics.[34] An examination of the diagnostic criteria across this list of substances reveals that sleep disturbance is the only group of symptoms that all withdrawal disorders share in common (refer to DSM-IV). Insomnia *per se* is listed across all substance withdrawal disorders, although sleep disturbance for some substances (cocaine and amphetamines) also includes hypersomnia or unpleasant, vivid dreams. Accordingly, we define insomnia as a *universal withdrawal symptom*, meaning that it occurs across all DSM-IV diagnoses of substance withdrawal. Likewise, if anxiety and depressed mood are combined to represent *negative affect*, then they form another group of universal withdrawal symptoms.[55]

Depending on the class of substance and its elimination pharmacokinetics, acute withdrawal generally lasts one week or less, and sometimes for 3-4 weeks with longer-acting drugs. Other symptoms and their neurophysiological correlates have been shown to persist after acute withdrawal has abated in both humans and animal models.[56] These persistent symptoms, which include insomnia and negative affect, have been variously labeled as *protracted* withdrawal[56, 57] or *subacute* withdrawal symptoms.[58] Protracted or subacute withdrawal can be defined as a constellation of symptoms and neurobiological alterations that (a) persist beyond the time-course of acute substance withdrawal and (b) increase the risk for relapse. The notion of protracted or subacute withdrawal implies that its symptoms begin during acute withdrawal and persist. Some symptoms, however, including insomnia and negative affect may begin prior to the development of substance dependence[59] and continue to persist during protracted abstinence. Therefore, we prefer the term *protracted abstinence symptoms*,[60] because it is descriptive of symptoms that are evident after the period of acute withdrawal without making any assumptions about chronology. (Nevertheless, the clinical implications of such chronological differences in symptom onset are worthy of further study.) A third class of symptoms, although not included in DSM-IV criteria for any substance withdrawal disorders, consists of craving or urges to use, which may also be a candidate for universal symptoms of protracted abstinence.

The conceptual framework of universal protracted abstinence symptoms proposes that clinical symptoms (such as sleep disturbances, negative affect, and craving) are manifestations of underlying neurobiological abnormalities, which are common to addictions across drugs of abuse.

Sleep Disturbance as a Predictor of Treatment Outcome

Several properties of sleep disturbance suggest that investigating their role in addiction may be particularly advantageous in furthering our knowledge about predicting treatment outcome. While there are numerous advantages to be considered, we focus on four that are particularly salient to the hypothesis presented.

First, as discussed above, sleep disturbances occur commonly with use and withdrawal across a number of addictive substances. This literature has recently been reviewed for dependent users of alcohol,[61] cannabis,[62, 63] cocaine,[62, 64, 65] nicotine,[66] opioids,[67] and hallucinogens such as MDMA.[62, 68] In addition, sedative-hypnotics drugs, which are a mainstay of insomnia treatment worldwide, are associated with abuse and dependence, and ongoing sleep disturbance is common among individuals that either abuse or become dependent on sedative-hypnotics.[51-54]

Second, unlike the other proposed universal protracted abstinence symptoms (craving and negative affect), sleep is the only one that can directly be studied objectively, whereas craving and negative affect cannot be studied without relying on subjective self-report of the experience. While neurophysiological correlates of self-reported craving[69-71] and negative affect[72] in addicted individuals can be studied, one really only knows that people are having these experiences if they say they are. By contrast, sleep is *defined* neurophysiologically as measured by polysomnography. Thus, it is known and measurable when people are asleep without them having to say so. Nevertheless, sleep can also be studied by correlating neurophysiological measures with subjective reports. When this is done, important discrepancies between self-reported and objectively measured sleep become apparent to sleep researchers and clinicians.[73] Individuals commonly underestimate or overestimate how much time they spent sleeping and awake during the night, as well as how long it took them to fall asleep. Moreover, such discrepancies have recently been reported in alcohol-dependent individuals.[39, 74] By inference, therefore, correlations between neurophysiological measures and either self-reported craving or negative affect are likely subject to similar discrepancies. With sleep, however, polysomnography represents the gold standard of measurement, whereas no such gold standard exists for craving or negative affect.

Third, sleep is an unconscious activity. With the possible exception of lucid dreaming,[75] what happens during sleep is not under our conscious control. Likewise, much of what happens during addiction is not under the conscious control of its sufferers. From a diagnostic perspective, loss of control or impaired control over use of a substance has long been recognized as the *sine qua non* of addiction. Puzzling to both addicted individuals and those who observe them, they ingest substances recurrently despite every conscious reason and desire not to. From a neurobiological perspective, such puzzling behavior has been attributed to alterations in subcortical and limbic system activity that operate outside a conscious level. Therefore, sleep offers a window into the activity of the brain in its unconscious state, which may potentially provide clues about the unconscious brain activity that underlies and drives addiction.[30-33]

Finally, addiction researchers have prolific allies in the study of sleep. Sleep medicine is a recognized specialty that is informed by an extensive base of scientific evidence, much of which is published in at least 11 English-language sleep-specific journals.[76] In addition, both basic and clinical research are generating new knowledge about the neurobiology[77-79] and genetics[80] of sleep, some of which has particular relevance for the study of addictions.[81, 82] Therefore, ongoing research activity regarding the effects of several different drugs of abuse on sleep is of interest to both sleep and addiction researchers.[59, 83-92]

Implications

Research

Despite over 30 years of evidence that addiction-related sleep disturbances are predictors of relapse, this area of research is still in its infancy. While details of a comprehensive research agenda are beyond the scope of this article, a few next steps for studying sleep as a predictor of relapse are offered. As discussed above, the current evidence for linking sleep and relapse is strongest for alcohol dependence, because it is the best studied. Additional studies on the potential relationship between sleep disturbances and relapse are needed for dependence on amphetamines, cannabis, cocaine, nicotine, and opioids.

Sleep measures should be considered for inclusion in all randomized clinical trials and naturalistic studies of treatment outcome. Although polysomnography is the gold standard, much information could be gained by simpler measures such as actigraphy, sleep logs, and self-report instruments. Unfortunately, these measures have not been validated specifically for sleep disturbances that occur among patients with addiction. Validating sleep measures in

addicted populations can lead to consensus about which ones are most useful in clinical research. Furthermore, validation studies will decrease the number of instruments currently employed and allow for better comparability between studies.

The mechanisms for a relationship between sleep disturbance and relapse is unknown and an area for further study. One possibility is that insomnia is linked to co-occurring psychiatric disorders that worsen the course of substance dependence, particularly mood disorders, anxiety disorders, and attention deficit disorder, which all have well-described sleep disturbances. Another possibility is that insomnia is an indicator of severity of dependence, which would be expected to increase relapse rates. Third, insomnia may be linked to impulsivity,[93] which in turn is linked to relapse.[94] Fourth, it is possible that chronic sleep deprivation from insomnia adversely affects cerebral executive functions such as judgment during high relapse-risk situations. Fifth, it is possible that patients relapse to substances as an attempt to self-medicate their sleep disturbance, which worsens during and persists after acute withdrawal.

Even after accounting for all of these factors, which are not mutually exclusive, we believe that addiction to substances is associated with dysfunction in regions of the brain that regulate sleep. In this regard, animal studies are particularly conducive for research on dysfunctional brain systems, which overlap in the pathogenesis of both addiction and sleep disturbance.

Treatment

The conventional wisdom among addiction treatment professionals is that both the pharmacological effects of drugs and the psychosocial stressors associated with addiction disrupt sleep. This is reasonable, except when patients are subsequently told that their natural sleep rhythms will return to normal with abstinence from substances and recovery from addiction. While this may be true for some patients, it is not true for everyone. Indeed, sleep disturbances can persist for months to years following initiation of abstinence,[37] if they do not result in relapse before then. Therefore, other approaches may be indicated and have been reviewed elsewhere.[35, 36] It deserves emphasis, however, that although insomnia may predict relapse, it is unproven that treatment of insomnia prevents relapse. For example, one recent randomized controlled trial of trazodone (a sedating antidepressant) vs. placebo found that alcohol-dependent participants receiving active medication had improved sleep but drank more frequently and heavily during the study.[95] Although the explanation for this finding is unclear at this time, clinicians should use medication judiciously, employ behavioral techniques whenever possible, and monitor dependent patients with sleep disturbances closely.

Summary

Measures of sleep disturbance in substance-dependent patients are common across different drugs of abuse and persist following the course of acute withdrawal into the period of protracted abstinence. Sleep disturbances are theorized to reflect neurobiological dysfunction, increase relapse risk, and be amenable to pharmacotherapy when the mechanisms underlying addiction and sleep disturbance are better understood. Although the current evidence is strongest for alcohol addiction, we have specifically examined the hypothesis that *persons who are recovering from an addiction to any psychoactive substance and have a sleep disturbance are at an increased risk of relapse compared to those without a sleep disturbance*. Sleep disturbance can include both objectively measured and subjectively reported problems involved with falling asleep, staying at sleep, distressing dreams, or inability to progress through normal stages of sleep. Sleep disturbance was further described as belonging to a group of *universal withdrawal symptoms* or *universal symptoms of protracted abstinence*. Negative affect and craving (or urges to use substances) are the other two members of the group. What makes these symptoms universal is their occurrence during withdrawal and prolonged abstinence from each of the most frequently used addictive substances (alcohol, amphetamines,

cannabis, cocaine, nicotine, opioids, and sedative-hypnotics). What makes sleep most unique when compared to negative affect and craving is that objective measurement (via polysomnography) is possible, whereas the other two require subjective self-report to define their presence. Objective measurement will allow more direct correlations with other neurobiological mediators of addiction. Future research will determine if hallucinogens other than MDMA, inhalants, and phencyclidine/ketamine are also characterized by sleep disturbance.

Acknowledgments

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Table 1

Psychosocial Predictors of Relapse to Substance Dependence

Demographics
Severity of dependence
Age at onset of problem use
Family history of substance use disorders
Co-occurring mental and other substance use disorders
Psychiatric severity
Character traits and disorders
Social support
Motivation for abstinence
Treatment adherence
Length of treatment stay
Participation in Alcoholics Anonymous or similar mutual-help groups
Therapeutic alliance
Self-efficacy