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PSYCHIATRIC DISORDERS AND SLEEP

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SYNOPSIS

Psychiatric disorders and sleep are related in important ways. In contrast to the longstanding view of this relationship which viewed sleep problems as symptoms of psychiatric disorders, there is growing experimental evidence that the relationship between psychiatric disorders and sleep is complex and includes bi-directional causation. In this article we provide the evidence that supports this point of view, reviewing the data on the sleep disturbances seen in patients with psychiatric disorders but also reviewing the data on the impact of sleep disturbances on psychiatric conditions. Although much has been learned about the psychiatric disorders-sleep relationship, additional research is needed to better understand these relationships. This work promises to improve our ability to understand both of these phenomena and to allow us to better treat the many patients with sleep disorders and with psychiatric disorders.

Keywords

Psychiatric Disorders; Sleep; Insomnia; Depression; Anxiety; Substance Use Disorders

I. INTRODUCTION

It has long been appreciated that sleep problems are common among those with psychiatric disorders. The prevailing view has been that sleep problems are generally symptoms of the associated psychiatric conditions. Consistent with this point of view is that sleep problems are defining features of a number of psychiatric disorders and included among the diagnostic criteria for these conditions.[1] However, there are a number of additional ways that psychiatric disorders and sleep are inter-related. The emerging view is that the relationships of psychiatric disorders with sleep are complex and marked by bi-directional causality. For example, the longstanding view that treating some psychiatric conditions improves sleep is complemented by recent evidence suggesting that treating sleep disturbances can have important effects on the outcome of treatment of psychiatric conditions. Further, contrary to the prevailing view, some sleep disorders increase the risks of developing episodes of psychiatric disorders. It is also the case that some treatments are used to treat both psychiatric disorders and sleep disorders.[2–5] Also, some treatments for psychiatric disorders may trigger disturbances of sleep and some treatments for sleep disorders may increase the risks for psychiatric disorders.[6–7] A further complexity in the sleep-psychiatric disorders

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relationship is that sleep deprivation may have therapeutic effects for some psychiatric disorders but may aggravate others.[8] In this article we provide the evidence that supports this point of view, reviewing the data on the sleep disturbances seen in patients with psychiatric disorders but also reviewing the data on the impact of sleep disturbances on psychiatric conditions. It is organized into 6 sections: 1) The sleep of patients with psychiatric disorders; 2) The risks of psychiatric disorders in those with sleep disturbances; 3) The impact of sleep disturbances on the course and treatment of psychiatric conditions; 4) The sleep effects of psychiatric treatments; and 5) The impact of sleep deprivation on psychiatric disorders. This article is focused on the subset of psychiatric disorders which have the most important relationships with sleep including: Major Depressive Disorder (MDD- Diagnostic Criteria appear in Table 1); Bipolar Disorder (Diagnostic Criteria appear in Table 2); Generalized Anxiety Disorder (Diagnostic Criteria appear in Table 3); Post-Traumatic Stress Disorder (PTSD) (Diagnostic Criteria appear in Table 4); Schizophrenia (Diagnostic Criteria appear in Table 5) and Alcoholism.[1]

II THE SLEEP OF PATIENTS WITH PSYCHIATRIC DISORDERS

A. Major Depressive Disorder (MDD)

Problems with sleep, which could include insomnia or hypersomnia, is one of the diagnostic criteria for MDD (See Table 1).[1] As such, it is not surprising that some type of sleep difficulty occurs in as many of 90% of MDD patients.[9] The type of sleep difficulty experienced by those with MDD can include difficulty falling asleep, difficulty staying asleep, insufficient sleep quality, nightmares and daytime sleepiness. Troubles falling asleep and staying asleep have been documented polysomnographically, however, there are no studies finding objective evidence of daytime sleepiness with the multiple sleep latency test, the standard for clinical and research assessment of sleepiness.[10–13] Patients with MDD also appear to have alterations in their sleep stages that are evident with polysomnography. These include: shortened latency to the onset of REM sleep (REM latency);[14–22] increased number of eye movements per minute of REM sleep (REM density)[10,15,23–24]; increased percentage of the night that meets scoring criteria for REM sleep;[10,13,22] a longer duration of the first REM period;[13,25–26] and decreased amount of slow-wave sleep.[10,11,13,16,25,27]

The prolonged sleep onset and difficulties with sleep maintenance found in patients with MDD are established indicators of disturbance of sleep. However, the significance of the alterations in sleep stages seen in those with MDD is unknown. There is some evidence suggested that shortened REM latency and diminished slow-wave sleep may be trait markers of MDD,[28–32] whereas the increased REM density and sleep disturbance appear to be state markers as they are most evident during episodes of depression.[29,33–34] However, these sleep-stage changes appear to be of limited clinical utility as they are not specific to those with MDD but are seen in those with other types of psychiatric disorders.[20]

B. Bipolar Disorder

For the manic phase of bipolar disorder, the diagnostic criteria include decreased need for sleep.[1] So, as with MDD, it is not surprising that changes in sleep are nearly universal among those with bipolar mania.[35] However, the nature of the sleep problem in this condition, decreased need for sleep, is an alteration in sleep that is only seen in mania. Decreased sleep need is not synonymous with insomnia. It is a condition where an individual can, and do, decrease their sleep time, at least to some degree, without experiencing any impairment in function or quality of life. In contrast, insomnia is a condition where individuals experience impairments in function and/or quality of life due to failing to be able to sleep despite having the adequate opportunity to do so.[1] Diagnostic confusion might arise because those with mania may experience difficulties falling and

staying asleep much like insomnia patients. However, in the case of manic patients this problem arises because they are attempting to sleep more than the amount they need to be restored. Whereas insomnia patients are unable to sleep enough to feel restored despite their efforts to do so.

During the depressed phase of bipolar disorder, the most common sleep complaint is hypersomnia, which reportedly occurs more frequently in those with bipolar depression than unipolar depression.[36] The little research carried out to determine if there is objective evidence of daytime sleepiness in patients with bipolar depression using the multiple sleep latency test (MSLT) has not found evidence of clinically significant sleepiness.[36]

Interestingly, the alterations in sleep seen with polysomnography in patients with bipolar mania are comparable to what has been observed in those with MDD.[37–38] This may indicate that there is a common pathophysiology in MDD and bipolar mania. However, it is important to keep in mind that these polysomnographic findings are also seen in those with other psychiatric conditions and, therefore, may not be reflective of specific pathophysiologic mechanisms.[20]

C. Generalized Anxiety Disorder

As with MDD and bipolar disorder, a change in sleep is among the core features of GAD. In this case this alteration is disturbance of sleep (difficulty falling or staying asleep) which affects over half of those with GAD.[1,39–41]

Few data exist on the polysomnographic features that characterize the sleep of patients with GAD. However, those that exist suggest that GAD patients have: longer sleep onset latency, a greater number of arousals, and greater wake time during the night.[42–43] In contrast to bipolar disorder and MDD, GAD does not appear to be marked by any alterations in REM latency or percentage of the night comprised of REM sleep, however, one study reported that GAD patients had a decreased percentage of the night spent in slow-wave sleep and a relative increase in the percentage of the night meeting criteria for stage 1 sleep compared with controls.[42–43]

D. Post-Traumatic Stress Disorder

Sleep problems are also among the diagnostic criteria for PTSD, though in this case the sleep difficulties include distressing dreams along with difficulties falling or staying asleep.[1] Accordingly, complaints of sleep difficulties are ubiquitous among those who have PTSD.[44]

A number of studies including polysomnography have examined the sleep of patients with PTSD in an effort to explore the associated neurophysiologic changes.[45–49] The most consistent findings suggest disruption of sleep. This includes diminished total sleep time, which has been reported in 5 studies, while an elevation in the time spent awake after initially falling asleep (WASO) has been noted in 3 reports.[45–49] In one additional study, there was an association between an increase in WASO and nightmares.[50] However, it should be noted that there are several studies that have not found evidence for sleep difficulties in the PSG in PTSD patients.[51] This inconsistency may not be specific to PTSD, however. There is evidence that among patients with insomnia complaints occurring in other settings there is often a weak relationship between PSG and self-report measures of sleep.[52–53]

Another frequent PSG finding in PTSD patients is an alteration in REM sleep such as is seen in those with MDD and bipolar disorder. The most frequently reported REM sleep aberration has been an increase in REM density (eye movements per minute of REM sleep).[45–46,48] As discussed above, this measure of the “intensity” of REM sleep does not

reflect a physiologic alteration specific to PTSD because it has also been reported to be elevated in those with MDD that has a high-rate of co-morbidity with PTSD.[54]

E. Schizophrenia

Unlike the psychiatric disorders discussed above, sleep is not a core feature of schizophrenia. However, sleep problems, including difficulty falling and staying asleep and diminished sleep quality, are common in those suffering from schizophrenia, though systematic epidemiologic data on the prevalence of sleep disturbances in this population do not exist.[55–59] An additional type of sleep problem that has been reported to affect people with schizophrenia are shifts in circadian rhythm which are reflected in a tendency to be awake at night and sleep during the day.[56,60] The reason for this is unknown, however, some have speculated that alcohol and illicit drug use or antipsychotic medications used to treat this condition might play a role.

Several studies employing polysomnography have attempted to characterize the neurophysiologic changes in sleep in those with schizophrenia and have identified the following differences form healthy controls: increased latency to sleep onset, increased wake time during the night, decreased total sleep time, decreased latency to the onset of REM sleep, a decreased amount of slow-wave sleep, and a decrease in the amplitude of EEG slow-waves during non-REM sleep.[59,61–71]

In addition, those with schizophrenia have been identified to experience other sleep disorders at a relatively higher rate than the general population. This includes an increase in the prevalence of sleep disordered breathing (15%) and periodic limb movements of sleep (PLMS).[72]

F. Alcoholism

Two types of alcohol-use related problems can occur: dependence and abuse. Dependence is characterized by an adaptation occurring with repeated alcohol use that results in tolerance to the effects of alcohol and withdrawal symptoms occurring on discontinuation.[1] Abuse, on the other hand, is defined by problems arising in an individual's life due to the adverse consequences deriving from the direct effects of alcohol.[1] Insomnia is extremely common among those who suffer from alcohol dependence and/or abuse where its prevalence is estimated to be 36–72% .[73–75] It is believed that the sleep disturbance stems from a rebound of wakefulness occuring as the effects of alcohol, which has sleep promoting effects, wear off. In this regard, it has been reported that alcohol hastens sleep onset, suppresses REM sleep and relatively increases the amount of non-REM sleep.[76] However, the effects are relatively short-lived and as the sleep-enhancing effects dissipate over the night a predisposition to sleep disruption and increased REM activity occur.[77] This problem is exacerbated as tolerance develops to the sleep enhancing effects with repeated use.[1,20,78]

Like those with schizophrenia, those suffering from alcoholism may experience disruption of the usual circadian sleep-wake rhythm. This is also believed to derive from the sleep-enhancing effects of alcohol. It is hypothesized that regular daytime drinking may predispose to regular daytime sleeping which tends to erode the usual circadian sleep rhythm.[77]

The sleep problems of those with alcohol-related problems are not restricted to periods when alcohol ingestion is occurring. The available evidence suggests that following periods of regular alcohol use sleep disturbance may persist during up to several years of abstinence during which a relative increase in REM sleep has been documented.[79]

III. THE RISKS OF PSYCHIATRIC DISORDERS IN THOSE WITH SLEEP DISTURBANCES;

The risks of psychiatric disorders in those with sleep disturbances are less well appreciated than the sleep disturbances associated with psychiatric disorders. Yet, the evidence that sleep disturbances are associated with an increased risk of developing psychiatric disorders has existed since the 1980s.

A. MDD

In terms of MDD, this evidence includes that those with insomnia and those with hypersomnia are roughly ten times as likely to have MDD as healthy controls without sleep disorders.[80–82] Also, a series of longitudinal studies indicate that having insomnia at one point in time significantly increases the risk for the subsequent development of new onset MDD.[82–84]

B. GAD

There is also longitudinal data indicating that insomnia increases the risk for the subsequent development of anxiety disorders. Those with insomnia appear to have approximately double the risk of healthy controls.[80]

C: PTSD

To date there is no evidence suggesting that pre-existing insomnia is a predisposing factor for the development of the PTSD syndrome following an extreme event, though we are aware of no studies which have specifically investigated this question. There is, however, one study suggesting that sleep complaints occurring at 1 month or longer after trauma were significant predictors of the presence of a diagnosis of PTSD at 1 year post-trauma.[85] While this report is intriguing it is of uncertain significance.

D. Schizophrenia

Severe disturbance of sleep has been noted to occur prior to the development of episodes of acute psychotic decompensation in patients with schizophrenia.[58,86–87] However, it remains unknown if this sleep disturbance is a harbinger of impending difficulties, or if it has any causal relationship.

Alcoholism

There is a body of evidence suggesting that sleep difficulties may increase the risks for alcoholism and may contribute to continued alcohol consumption among drinkers. Several longitudinal studies suggest that those with insomnia are at increased risk for the development of subsequent alcohol use problems compared to those without disturbed sleep.[80,92,88] Several studies suggest that those with alcoholism often use alcohol as a means to treat sleep difficulties. This includes that such individuals are more likely than those without alcoholism to choose alcohol as a way to improve sleep and to report difficulty falling asleep if they don't drink alcohol prior to going to bed.[74,89–90]

IV. THE IMPACT OF SLEEP DISTURBANCES ON THE COURSE AND TREATMENT OF PSYCHIATRIC CONDITIONS;

There is a growing body of literature indicating that sleep disturbances impact the course and treatment of psychiatric conditions. This literature includes reports of studies on the relationship of sleep disturbance to psychiatric symptoms as well as their relationship with

treatment outcome, and risk of relapse in psychiatric conditions. Studies also document the impact of treating sleep disorders on the outcome of psychiatric conditions.

A. MDD

Though long thought of as a symptom of depression, insomnia appears to have an impact on the course and treatment response of MDD.[91] According to the symptom model, sleep disturbance would be expected to resolve with appropriate antidepressant therapy along with the other MDD symptoms. Although this certainly occurs to a degree, the available evidence suggests that in 20–44% of those with MDD, sleep difficulties fail to resolve despite the administration of standard antidepressant treatments.[92–93] This residual insomnia also appears to be associated with an increased risk of MDD relapse as well as a number of impairments including decreased concentration, sleepiness, and diminished performance capacity.[94–95]

Among those with MDD, there are several other ways that poor sleep appears to have an adverse impact on the course of MDD. Perhaps the most important and most concerning of these is that sleep disturbance appears to increase the risks of suicidal ideation, suicide attempts, and completed suicide. To date, at least 32 studies have identified that sleep disturbance is linked to suicidal ideation or completed suicide. This includes: 10 studies in children and adolescents; 22 studies in younger and older adults; and studies spanning multiple countries (U.S., England, France, Canada, Turkey, Finland, Sweden, Brazil, China, and Japan).[96–111] Notably, these studies include five prospective studies and in many the associations between sleep disturbance and suicidality remained after adjusting for depression severity. However, despite all of the evidence linking insomnia and suicidality, insomnia is generally overlooked as a suicide risk factor and as a means of preventing suicide in those with MDD.[112]

Sleep disturbance also has other adverse effects on the course of MDD. Those MDD patients with poor sleep have slower treatment response and lower remission rates than those without sleep disturbance.[113–116] Greater sleep disturbance is also independently correlated (independent of depression severity) with poorer quality of life in those with MDD.[117]

There is additional evidence to support the independent importance of disturbed sleep in MDD and these data speak to the need to target treatment specifically to the sleep problems in those with MDD. Several studies indicate that targeting treatment to insomnia in addition to providing standard antidepressant therapy may improve not sleep but also enhance the improvement in depression. In one such study, the hypnotics lormetazepam and flurazepam were compared with placebo as adjunctive insomnia therapies to antidepressant treatment with nortriptyline or maprotiline.[118] Those subjects randomized to lormetazepam had greater depression improvement than subjects receiving placebo. In another study, co-administration of eszopiclone 3 mg and fluoxetine led to greater improvement in sleep and a more rapid and greater improvement in depression (greater improvement in the Hamilton Depression Rating Scale with sleep items removed and greater percentage of responders and remitters) than fluoxetine plus placebo.[119–120] However, it should be noted that a study of identical design employing zolpidem extended release preparation 12.5 mg instead of eszopiclone found that insomnia therapy improved sleep and sleep related daytime function but not depression outcome compared with placebo.[121] Lastly, a study was carried out where cognitive behavioral insomnia was compared to a behavioral control intervention in depressed patients treated with escitalopram.[122] In this study, those receiving the active insomnia therapy experienced a 62% remission rate compared with 33% for the control intervention.

Thus, three of four studies indicate that targeting treatment to insomnia improves not only sleep outcome but also depression treatment response. In the one study where this was not the case, sleep and function were improved, however, it remains unclear why depression outcome did not improve.[121] Further studies will be needed to better understand the impact of insomnia therapy on MDD treatment outcome. Nonetheless, multiple lines of research suggest that sleep disturbance has a substantial impact on MDD and the antidepressant response, and, generally speak to the need to treat insomnia in those with MDD.

B. Bipolar Disorder

Relatively less research has been carried out on the impact of sleep on the course of bipolar disorder. However, several studies indicate that preventing patients with bipolar disorder from sleeping predisposes them to the development of mania.[123–125] On this basis it has been hypothesized that sleep loss plays an etiologic role in the development of mania such that loss of sleep predisposes towards mania which, in turn, leads to further loss of sleep in a positive feedback cycle.[123]

Whether this is the case remains unclear as are the mechanisms by which sleep loss might predispose patients with bipolar to develop mania. However, the clinical implications of this hypothesis is that management of bipolar patients should include interventions to prevent sleep loss and lengthen sleep time as a means of preventing and/or treating mania. Although this approach has yet to be systematically studied, it is probably no accident that all anti-manic therapies have significant sleep-enhancing effects.

C. GAD

Relatively few data exist on the impact of sleep on the course of GAD. However, two placebo-controlled trials of adding insomnia co-therapy to the treatment of GAD with escitalopram have been carried out.[126–127] These studies include a trial of eszopiclone 3 mg plus escitalopram vs placebo plus escitalopram and a trial of zolpidem Extended Release 12.5 mg plus escitalopram vs placebo plus escitalopram. Much like the results seen in nearly identical studies carried out with MDD patients, eszopiclone significantly improved sleep and GAD response/remission compared with placebo, whereas zolpidem Extended-Release only improved sleep and sleep-associated daytime function compared with placebo. As with MDD, these studies support the utility and importance of targeted insomnia therapy in GAD patients, however, it remains unclear whether the treatment of insomnia might impact GAD outcome or whether there are specific characteristics of eszopiclone or zolpidem Extended-Release that affected their impact on GAD outcome.

D. PTSD

There are several placebo-controlled studies demonstrating that treatments aimed at improving sleep in patients with PTSD can improve daytime PTSD symptoms. This includes one study of eszopiclone 3 mg administered at bedtime, four studies of prazosin administered at bedtime, and one study of a behavioral sleep intervention targeting insomnia and nightmares.[128–132] However, whether these sleep-targeted therapies have direct effects on daytime PTSD symptoms or whether daytime PTSD symptoms are improved due to improvements in sleep has not been definitively established. At least for prazosin, there is evidence that this agent improves daytime PTSD symptoms when administered during the day, so it is at least plausible that nighttime administration could directly improve daytime PTSD symptoms and while the half-life of this drug seems to preclude this possibility (half-life is 2–4 hours) it must be borne in mind that this medication has several active metabolites which could contribute to its therapeutic effect.[133] There are no data that indicate whether eszopiclone or behavioral sleep therapy might have direct effects on daytime PTSD symptoms.

Schizophrenia

A number of studies suggest that disturbed sleep can adversely affect the symptoms and course of schizophrenia. In one study self-ratings of sleep quality were significantly correlated with quality of life ratings.[56] As described earlier, sleep problems often occur before episodes with acute psychotic symptoms, though it is unclear whether the sleep disturbance plays an etiologic role in these episodes or is simply the first symptom of decompensation.[58,71,87] A series of studies have also identified associations between polysomnographic sleep indices and the presence of subsets of schizophrenia symptoms classified as either "positive" (delusions, hallucinations, and disorganized thought) or "negative" (affective flattening, avolition, alogia, attention problems). Greater positive symptom severity has been found to be correlated with shorter REM latency, longer sleep onset latency and diminished sleep efficiency (total sleep time divided by time in bed).[64,70,86,134–136] At the same time greater negative symptom severity has been found to be correlated with lower non-REM sleep EEG slow-wave amplitude and shorter REM onset latency.[59,67–68,70,137] Further, greater likelihood of suicidal ideation has been found to be correlated with a greater percentage of the night spent in REM sleep and greater REM density (rapid eye movements per minute of REM).[138–139] The clinical significance and pathophysiologic implications of these findings remains uncertain as the polysomnographic alterations described are not specific to schizophrenia and the findings have not been consistently found across studies.

Alcoholism

A number of studies suggest that sleep problems and polysomnographic alterations in sleep occurring post-abstinence may play an important role in hastening relapse. The link between disturbed sleep during abstinence and relapse to drinking has been identified in several studies.[74,78,140] Polysomnographic sleep variables that have been found to be predictors of relapse include: longer sleep onset latency, decreased sleep efficiency, decreased percentage of the night spent in slow-wave sleep, shorter REM onset latency, greater percentage of the night spent in REM sleep, and greater REM density.[141–142] The variable which best predicts relapse seems to vary with the duration of time since the abstinence period began, though this may not in fact be the case but may reflect that the findings are varying across studies which happened to focus on different time periods. Increased REM density immediately after stopping drinking has been reported to be the best predictor of relapse 3–4 months later, however, at 1 month after the onset of abstinence, sleep onset latency was found to be the best predictor of relapse, whereas at 5 months after the beginning of the abstinence period sleep onset latency and sleep efficiency best predicted relapse at 1 year.[77,79,143]

Although these studies speak to the need to evaluate whether the treatment of sleep disturbances during abstinence might decrease the likelihood of relapse, only two placebo-controlled studies have been carried out addressing this question and both were small trials. One was a study of trazodone 200 mg which included only 16 subjects and found that this medication improved sleep compared with placebo but had no impact on relapse rate, though it could be reasonably argued that the study was under-powered to assess this outcome.[144] The other study evaluated gabapentin 1500 mg in only 21 subjects and, although there was a decrease in relapse rate, there was no difference between drug and placebo groups on sleep parameters.[145] Based on the limited amount of work carried out, it remains unclear whether treating sleep problems during abstinence decreases the rate of subsequent relapse to drinking and studies addressing this issue are clearly needed.

V. THE SLEEP EFFECTS OF PSYCHIATRIC TREATMENTS;

A. MDD

Many antidepressant medications have been documented to have effects on polysomnograhic sleep variables, some are used to treat sleep disturbance, some have a tendency to disturb sleep, and some have a tendency to cause or exacerbate periodic leg movements of sleep (PLMs) and/or restless legs syndrome. In terms of the effects of antidepressant on polysomnographic sleep indices, a number of studies have documented that antidepressant treatments including monoamine oxidase inhibitors, tricyclic antidepressants electroconvulsive therapy, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors, suppress REM sleep.[20,146–152] These findings have served as the basis for the hypothesis that suppression of REM sleep is an important part of the mechanism of action of antidepressant therapies. However, evidence to the contrary is provided by a number of effective antidepressant agents, bupropion, nefazodone, mirtazapine, and trazodone which do not suppress REM sleep,[153] though these medications appear to have other polysomnographic effects including increasing the amount of slow-wave sleep and increasing the amplitude of EEG slow-waves in non-REM sleep.[154–159]

A number of antidepressants are also used to treat problems falling and/or staying asleep and are used for the treatment of insomnia, though few have been demonstrated to have therapeutic effects in placebo-controlled studies. The antidepressants most commonly used for this purpose are trazodone, mirtazapine, amitriptyline, and doxepin, which, other than mirtazapine are prescribed in lower dosages than typically used to treat depression when administered to treat insomnia.[2] Data from placebo-controlled trials supporting a sleep onset and/or maintenance exist only for doxepin and trimipramine, though studies carried out in depressed patients or healthy controls suggest that amitriptyline and mirtazapine might have therapeutic effects in this setting.[156,160–170]

Another sleep-related effect of antidepressant medications is that some can disturb sleep. This includes the norepinephrine and dopamine reuptake inhibitor bupropion, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors all of which have an adverse effect rate of insomnia/sleep disturbance that is in the range of 1.5–3 times that of placebo.[153]

Many antidepressants also have the potential to cause or exacerbate PLMs and restless legs syndrome.[171] Agents most often associated with this are: selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and mirtazapine.[171–172]

B. Bipolar Disorder

Few studies document the sleep effects of agents used to treat bipolar disorder. Most of the available relevant data relate to antipsychotic medications that are often used to treat mania. The sleep effects of these agents are discussed in the section which follows. Otherwise, data exist only for lithium, long a mainstay of the treatment of patients with bipolar disorder. This agent has been found to increase slow-wave sleep, suppress REM sleep and increase REM latency.[173] Like many of the antidepressant medications, lithium has also been reported to cause or exacerbate restless legs syndrome.[174]

C. Schizophrenia

A number of publications document the sleep effects of antipsychotic medications which are the most common pharmacologic therapies administered to patients with schizophrenia. The sleep-related effect of these medications that is of most clinical importance is their tendency to enhance sleep. This effect may be responsible for daytime sedation which may further

impair the already limited daytime functional capacity of many patients with schizophrenia, though for patients with disturbed sleep, this type of effect may be beneficial.[175] Systematic studies of the effects of antipsychotic medications have been carried out in patients with mood disorders, those with schizophrenia, and healthy controls. Both quetiapine (25 and 100 mg) and ziprasidone 40 mg were evaluated in trials in healthy controls where sleep on a night with noise disturbance was compared with a night where no disturbance took place.[176–177] Quetiapine was found to shorten sleep onset latency, improve total sleep time, sleep efficiency, and sleep quality and also suppressed REM sleep.[176] Ziprasidone increased total sleep time, sleep efficiency, and sleep quality, and decreased number of awakenings but also decreased the percentage of REM and increased REM density and the percentage of slow-wave sleep.[177] Several relatively small studies document the sleep effects of olanzapine. These were carried out in those with schizophrenia and those with mood disorders and indicate that this medication decreases sleep onset latency and wake time after sleep onset and increases sleep efficiency, sleep quality ratings and the amount and percentage of slow-wave sleep.[178–185] Small studies also document that cloazapine decreases awakenings, and wake time after sleep onset and increases total sleep time and amount of slow-wave sleep[186–187] and that risperidone 0.5–1 mg decreases wake time after sleep onset as well as the amount of REM sleep.[188]

Because so few data exist on the sleep effects of these agents that derive from placebo-controlled trials, it is helpful to consider the rates of reported daytime sedation adverse effects in placebo-controlled trials with these medications, though in some cases daytime sedation may not be accompanied by nighttime sleep enhancement due to slow absorption and in the case of agents with short half-lives, daytime somnolence rates will substantially underestimate their nighttime sleep enhancement. Based on these data the agents with the highest rates of sedation are clozapine, chlorpromazine, and thioridazine (33–60%), followed by risperidone and olanzapine (approximately 30%) and haloperidol (23%), whereas the agents with the least associated sedation are quetiapine and ziprasidone (16%) and aripiprazole (12%).[175]

Antipsychotic medications, due to their dopamine antagonism may also cause or exacerebate PLMs and restless legs syndrome and, due to the potential for weight gain, these agents may increase the risks of developing sleep disordered breathing.[175]

D. Alcoholism

Only one study has been carried out of the sleep effects of a treatment for alcoholism. This study evaluated acamprosate in 24 subjects prior to and 2 weeks after discontinuation of alcohol consumption and found that it decreased wake time after sleep onset and shortened REM latency.[189]

VI. THE IMPACT OF SLEEP DEPRIVATION ON PSYCHIATRIC DISORDERS

A notable and, perhaps surprising, aspect of the relationship of sleep and psychiatric disorders is that sleep deprivation can have a profound effect on individuals with mood disorders.

A. MDD

A night of sleep deprivation has been reported to have robust antidepressant effects. Studies evaluating this phenomenon suggest that at least 50% of those with MDD meet response criteria following a single night of sleep deprivation.[190–192] However, the clinical utility of sleep deprivation as an antidepressant treatment is limited by the fact that the benefits generally disappear when the treated patient sleeps, even if the period of sleep is short.[192–193] Attempts to prolong the benefits of sleep deprivation with medications and

other interventions have met with limited success[194–195] such that sleep deprivation is not implemented as a treatment for depression in clinical practice to any significant extent, however, it continues to attract attention as a window into the pathophysiology of MDD and the mechanisms of action of antidepressant treatments. There is also a small literature related to attempts to treat MDD with chronic (3 week), in-laboratory, REM sleep deprivation which is based on the evidence that many effective antidepressant therapies suppress REM sleep.[196] Unlike a night of total sleep deprivation, one study found that chronic REM deprivation leads to gradual and persistent improvement in depression,[196] though attempts to replicate this finding have not succeeded in doing so.

B. Bipolar Disorder

In contrast to MDD, sleep deprivation tends to exacerbate symptoms in those with bipolar disorder, predisposing individuals with this condition to develop of mania. A series of studies where patients with bipolar disorder underwent experimental sleep deprivation provide the basis for this conclusion.[35,123–125] The mechanism by which sleep deprivation predisposes bipolar disorder patients remain unknown. Further, sleep deprivation has never been demonstrated to trigger or exacerbate mania in naturalistic studies in patients with bipolar disorder. However, it is generally assumed that this occurs, and, as a result, prudent clinical care should include taking steps to prevent sleep loss in those with bipolar disorder when depressed and/or euthymic and to increase sleep in bipolar patients when manic.

VII. SUMMARY AND CONCLUSIONS

Psychiatric disorders and sleep are related in important ways. In contrast to the longstanding view of this relationship which viewed sleep problems as symptoms of psychiatric disorders,[91] there is growing experimental evidence that the relationship between psychiatric disorders and sleep is complex and includes bi-directional causation. Although much has been learned about the psychiatric disorders-sleep relationship, much remains unknown. For example, further studies are needed to determine if improvement of sleep improves MDD outcome and why some treatments for sleep problems appear to differentially affect the antidepressant response. In some cases correlations have been identified between alterations in sleep and the course and/or outcome of psychiatric conditions and further work will be needed to determine if these are causal links.

From a clinical point of view, the available research on the psychiatric disorder-sleep relationship speaks to the need to direct treatment to sleep disorders and not simply treat what is assumed to be an underlying psychiatric condition. There is some reason to believe that this has the potential to improve the course and treatment response of some psychiatric conditions. This work also speaks to the need to be aware of the sleep effects of psychiatric interventions which may, in turn, affect the course and treatment response of the psychiatric condition being treated.

There are also research implications of the body of literature elucidating the psychiatric disorder-sleep relationship. This literature suggests that the boundaries between sleep disorders and some psychiatric disorders may be indistinct and in many cases the causal relationships between them are unclear. Nonetheless, the work in this field has increased over time and our understanding of these causal relationships have significantly evolved from the long-held symptom model of sleep disturbance.[91] Although much additional research is needed to address the limitations of the current body of literature and to help us better understand the relationships among psychiatric disorders and sleep, the advances made to date suggest that this work promises to improve our understanding of both sleep and psychiatric conditions and to provide better clinical care to patients with psychiatric disorders and with sleep disorders.

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Key Points

1. Psychiatric disorders can have a major impact on sleep.
2. Sleep and sleep disorders can influence psychiatric conditions.
3. Treatment of sleep disorders can improve psychiatric disorders.
4. Sleep deprivation has a complex relationship with psychiatric disorders.

Table 1

DSM-IV TR Diagnostic Criteria for Major Depressive Disorder (MDD)[1]

The presence of 5 of the following 9 criteria symptoms over a period of at least 2 weeks where one of the five symptoms has to be either depressed mood or loss of interest or pleasure:

1	depressed mood;
2	loss of interest or pleasure in activities;
3	change in appetite;
4	insomnia or hypersomnia;
5	psychomotor agitation or retardation;
6	fatigue;
7	feelings of worthlessness or guild;
8	poor concentration and difficulty making decisions;
9	suicidal ideation.

Table 2

DSM-IV TR Diagnostic Criteria for Bipolar Disorder[1]

At least one manic episode which is defined by elevated or irritable mood accompanied by at least 3 associated symptoms which could include:

1. grandiosity;
2. decreased sleep need;
3. pressured speech;
4. flight of ideas;
5. easy distractability;
6. increased goal-directed activity;
7. impulsivity.

Table 3

DSM-IV TR Diagnostic Criteria for Generalized Anxiety Disorder (GAD)[1]

Frequent excessive anxiety for at least 6 months that is accompanied by symptoms which may include:
Restlessness
Easy fatigability
Problems concentrating
Irritability
Muscle tension
Disturbed sleep.

Table 4

DSM-IV TR Diagnostic Criteria for Post-Traumatic Stress Disorder (PTSD)[1]

A history of exposure to a traumatic event where the person has experienced, witnessed, or been confronted with an event or events that involve actual or threatened death or serious injury, or a threat to the physical integrity of oneself or others and the person's response involved intense fear, helplessness, or horror.
Duration is more than 1 month.
Is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.
Symptoms from each of three symptom clusters below:

A. Intrusive recollection: The traumatic event is persistently re-experienced in at least one of the following ways:

1. Recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions. Note: in young children, repetitive play may occur in which themes or aspects of the trauma are expressed.
2. Recurrent distressing dreams of the event.
3. Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur upon awakening or when intoxicated). Note: in children, trauma-specific reenactment may occur.
4. Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event.
5. Physiologic reactivity upon exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

B. Avoidant/numbing: Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by at least three of the following:

1. Efforts to avoid thoughts, feelings, or conversations associated with the trauma
2. Efforts to avoid activities, places, or people that arouse recollections of the trauma
3. Inability to recall an important aspect of the trauma
4. Markedly diminished interest or participation in significant activities
5. Feeling of detachment or estrangement from others
6. Restricted range of affect (e.g., unable to have loving feelings)
7. Sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

C. Hyper-arousal: Persistent symptoms of increasing arousal (not present before the trauma), indicated by at least two of the following:

1. Difficulty falling or staying asleep
2. Irritability or outbursts of anger
3. Difficulty concentrating
4. Hyper-vigilance
5. Exaggerated startle response

Table 5

DSM-IV TR Diagnostic Criteria for Schizophrenia[1]

Social and/or occupational dysfunction occurring in the setting of at least one month where ≥ 2 of the following occur:
1 delusions;
2 hallucinations;
3 disorganized speech;
4 disorganized behavior;
5 loss of motivation, flat affect, or alogia.