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Sleep Disturbance in Psychiatric Disorders: Effects on Function and Quality of Life in Mood Disorders, Alcoholism, and Schizophrenia

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Introduction. *While the precise role of sleep in maintaining optimal health and function remains unknown, it is clear that disturbances of sleep have a profound impact on the lives of affected individuals. In psychiatric disorders, not only is there a relationship between sleep disturbances and impaired function, problems with sleep also appear to affect the course of the disorder.*

Methods. *We carried out a literature review of sleep studies in mood disorders, alcoholism and schizophrenia to determine how associated alterations in sleep architecture and disturbances of sleep are related to patient function and quality of life, and the course of these disorders.*

Results. *The literature speaks to the need to address sleep problems in the overall management of mood disorders, alcoholism and schizophrenia. The support for this viewpoint is best established for mood disorders. There is also relatively strong support for treatment in alcoholism. Schizophrenia, however, has received scant attention and the literature suggests a need for more studies in this area.*

Conclusions. *Further research is needed into the treatment of co-morbid insomnia and psychiatric disorders. Successful therapy is more likely to be achieved if the sleep difficulty and co-morbid disorder are simultaneously targeted for treatment.*

Keywords Sleep disturbance, Psychiatric disorders, Schizophrenia

INTRODUCTION

While the precise role(s) of sleep in maintaining optimal health and function remains unknown, it is clear that disturbances of sleep have a profound impact on the course of psychiatric disorders. Depriving healthy individuals of sleep, even as little as 1–2 hours per night, has been shown to lead to impaired attention, alertness, reaction time, cognitive processing capacity, memory, mood, ability to stay awake and heightened pain sensitivity (1–4). Anyone who has traveled across multiple time zones has experienced the deficits in alertness, concentration and motivation that can occur as a result of perturbing the circadian system (the endogenous 24 hour day/night cycle), and the resultant shift in the usual sleep and wake times (5). Furthermore, the impairments in function experienced by those with sleep disorders, such as sleep apnea and chronic insomnia, are well established (6–13).

Disturbances of sleep–wake pattern are common among psychiatric patients. In fact, psychiatric patients represent the largest subgroup of individuals with insomnia (14). Sleep problems can occur co-morbidly with psychiatric disorders for a number of reasons: 1. Sleep disruption is a core symptom of many psychiatric illnesses, including major depression, bipolar

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disorder, post-traumatic stress disorder and generalized anxiety disorder (15); 2. Psychiatric symptoms have been found to have an association with several sleep disorders, such as sleep apnea, narcolepsy and insomnia (7); 3. Episodes of sleep disorders, such as insomnia, appear to increase the risk for incidence and recurrence of a number of psychiatric disorders, including major depression, generalized anxiety and alcoholism (14,16–18); and 4. The co-occurrence of sleep and psychiatric disorders can be a result of treatments for sleep disorders that cause symptoms of psychiatric disorders (e.g., dopamine agonists for restless legs syndrome can cause psychosis; long-acting hypnotic agents can be associated with fatigue that may be mistaken for depression). Conversely, treatments for psychiatric disorders can lead to sleep disturbances (antidepressants can induce restless legs syndrome or insomnia).

There is evidence that sleep disturbances that occur co-morbidly with psychiatric disorders have an adverse impact on quality of life and function, just as disrupted sleep patterns in healthy individuals and in those with sleep disorders can deleteriously affect these aspects of an individual's life. However, when such sleep disturbances occur with psychiatric disorders they also appear to affect the course of the disorder. In this paper, we discuss three psychiatric disorders; mood disorders, alcoholism and schizophrenia, where the links between disturbances in sleep and sleep architecture, and the course of the disorder and ability to function, are best established in the available literature. The practical need to limit the scope and length of this review prevented us from being able to address several other conditions which are commonly associated with sleep disturbances. The most notable of these are chronic pain conditions and anxiety disorders, such as post-traumatic stress disorder, generalized anxiety disorder and panic disorder (19, 20). While it seems likely that sleep disturbances occurring with these disorders affect function and might affect the course of these disorders, the published literature on these effects is relatively limited compared with the relevant literature on mood disorders, alcoholism and schizophrenia.

MOOD DISORDERS

Major Depression

Major depression affects an estimated 10–25% of women and 5–12% of men at some point in their life (15). Sleep difficulties, among the diagnostic criteria for depression, are found in up to 90% of patients (21). Depressed patients complain of difficulty falling asleep, staying asleep, early morning awakening with an inability to return to sleep, disturbing dreams, non-restorative sleep, daytime fatigue and daytime sedation. Corresponding polysomnographic (PSG) evidence of alterations in sleep physiology is often observed. The PSG of depressed patients is often marked by increased sleep latency, wake time after sleep onset and awakenings (22–25). Changes in the duration and timing of sleep stages during the night have also been observed. These include a reduction in the latency to the onset of rapid eye movement (REM) sleep, in density of eye movements in REM sleep, longer duration first REM sleep period and diminished amount of slow wave sleep (22,24–42). These PSG alterations reliably distinguish depressed individuals from healthy controls; however, they appear not to be specific markers of depression as they may occur with other psychiatric disorders (33).

These findings have been associated with impairments in a number of functional aspects in depressed patients, including diminished quality of life and suicidality, and have also been associated with deterioration in the course of the depression. In a study of 88 patients with major depression, the insomnia item of the Beck Depression Inventory was associated with lower ratings of the ability to function and poorer quality of life after controlling for all of the other symptoms of depression (43).

Several studies suggest an independent association of sleep disturbance and suicidality in depressed patients. A study of elderly depressed patients reported a correlation between complaints about sleep quality and an increased incidence of suicide (44). In a study of 113 depressed patients, complaints of both hypersomnia and insomnia were associated with higher suicide scores on the Schedule for Affective Disorders and Schizophrenia scale compared with those without a sleep complaint (45). In a study of 954 patients with depression followed for 10 years, insomnia was a significant predictor of suicide (46).

Contrary to the prevailing view and long-standing clinical guidelines, there is evidence that insomnia often persists, following otherwise effective antidepressant therapy. In fact, among depressed patients treated with fluoxetine, the most common residual symptom in treatment responders was reported to be insomnia (47). There are a number of possible explanations for this, including incomplete antidepressant response, the presence of a chronic independent insomnia, or that the sleep disturbance is a side-effect of the antidepressant medication (48,49).

An association between continued insomnia and impaired function was suggested by a study of 190 depressed patients who had responded to treatment with fluoxetine, paroxetine, or sertraline (50). The addition of zolpidem 10 mg led not only to significant improvement in sleep latency and sleep time compared with placebo, but also significantly better self-ratings of concentration, feeling refreshed, daytime sleepiness and the ability to perform daily activities, as well as a greater Short Form-36 vitality subscale score. There are also data suggesting that this residual insomnia is associated with impaired function and predicts a higher rate of relapse (51). Finally, there is evidence from a study which included PSG data that a shorter REM latency is a predictor of increased risk of recurrence (52).

Further connection between insomnia and the course of depression is suggested by several studies of initial co-administration of insomnia treatment and antidepressant medication. Preliminary evidence that treatment of insomnia may enhance the response to depression was found in a study of 53

treatment-resistant depressed patients given lormetazepam (not available in the United States), flunitrazepam or placebo as an adjunct to antidepressant therapy (nortriptyline or maprotiline) (53). Those treated with lormetazepam experienced greater reductions in Hamilton Depression Rating Scale (HAM-D) scores than those receiving placebo along with an antidepressant agent.

In another study, 545 patients with depression and insomnia were randomized to initial treatment with fluoxetine along with adjunctive treatment with either eszopiclone 3 mg or placebo (54,55). Compared with placebo, eszopiclone co-therapy resulted in significantly greater improvement in sleep latency, wake time after sleep onset, total sleep time and sleep quality. In addition, eszopiclone led to more rapid and greater improvement in HAM-D scores (both total and excluding sleep items), and a greater percentage of antidepressant responders and remitters.

These data provide evidence that insomnia/alterations in sleep in patients with depression appears to have importance with respect to function and the course of depression, and attest to the importance of treating the insomnia in conjunction with treating the co-morbid psychiatric disorder. Further studies are still needed to determine whether treatment of insomnia decreases the risks of suicide and/or decreases relapse risk.

Bipolar Disorder

Reduction in sleep time is a cardinal feature of mania (15). This observation, and evidence that sleep deprivation can precipitate mania in patients with bipolar disorder, has led to the hypothesis that sleep reduction is central to the evolution of mania (56–59). According to this model, individuals with bipolar disorder respond to sleep loss with elevation in mood, energy and goal-directed behavior, along with a further decrease in sleep. It has been suggested that breaking this cycle by pharmacologically preserving sleep is a key to successful treatment of mania, although there are no studies demonstrating that this is the case. One complication is that all of the primary treatments for this condition are sedating, leaving uncertainty as to the degree to which their anti-manic efficacy is due to sleep enhancement versus other physiologic effects. It is also the case that depressive episodes in individuals with bipolar disorder tend to be associated with complaints of hypersomnia more frequently than insomnia, though accompanying physiologic evidence of daytime sleepiness has not been found (60).

PSG data recorded in manic patients demonstrates the same types of disrupted sleep observed in those with major depression (61–64). Furthermore, the same changes in REM latency, density and distribution, and decrease in slow-wave sleep observed with major depression have been observed in some, but not all, of the few investigations in manic patients (61–64).

ALCOHOLISM

Alcoholism, marked by chronic use of alcohol despite adverse consequences and the desire to discontinue use, is estimated to have a lifetime prevalence of 14% in the United States. (15). Among affected individuals, the rate of insomnia is reported to be 36–72% (65–67). A relationship between insomnia and quality of life was observed in a group of individuals with alcoholism, where Nottingham Health Profile sleep subscale scores indicative of decreased quality of sleep were found to be correlated with greater self-rated depression, higher physical/psychological symptoms rating, lower energy, greater social isolation and greater pain (68).

Insomnia has been hypothesized to play an important role in the course of alcoholism. There is evidence that insomnia is a predisposing and/or perpetuating factor in that some individuals drink alcohol in order to attempt to treat their sleep problems (67). Alcohol is a sedative with dose-dependent effects on shortening sleep onset latency (69) and increasing the amount of slow-wave sleep (70). However, there are several factors that tend to disturb sleep and undermine the utility of alcohol as a sleep aid. There is a rebound effect later in the night that is associated with sleep disruption, including REM rebound and increased dreaming, and sympathetic arousal (71). There also appears to be a tendency for tolerance to develop to the sedative effect over time: abstinent alcoholics with insomnia who returned to drinking reported improvement in their sleep only in the first week of alcohol use (72). Also, daytime drinking, which commonly occurs with persistent alcohol use, tends to promote sleeping during the day, thereby undermining the capacity to sleep at night (73).

The hypothesis that insomnia may be a predisposing or perpetuating factor for alcohol use is consistent with a number of published studies. A predisposing role is suggested by evidence that insomnia is a predictor of future alcoholism (14,16,73). There is evidence that those with alcoholism are more likely than non-alcoholics to choose alcohol as a sleep aid when given the choice, and are more likely to report using alcohol as a sleep aid (66,70). In addition, it is frequently the case that persistent alcohol use is associated with reported inability to fall asleep without alcohol (15,72). Accordingly, insomnia is typically experienced with alcohol discontinuation (74). There are a series of studies which suggest that insomnia is a risk factor for relapse in abstinent alcoholics (66,74,75). That sleep disturbance could be a persistent factor predisposing to relapse is suggested by the observation that PSG and self-reported evidence of disrupted sleep has been noted for as long as 2 years following alcohol discontinuation (74).

PSG data recorded during abstinence is notable for a number of features that are also observed in individuals with mood disorders, including short sleep duration, prolonged sleep latency, greater wake time during the night, short latency to REM sleep, increased REM sleep density and a greater percentage of REM sleep during the night (76,77). While depression is common among individuals with alcoholism, these PSG

features were found to be predictive of alcohol relapse even in non-depressed alcoholics (77).

Even though the literature strongly suggests a link between insomnia and the course of alcoholism, there are surprisingly few studies investigating the treatment of insomnia in patients with alcoholism. A study randomizing 16 newly abstinent patients to placebo or trazodone 200 mg reported that trazodone significantly improved PSG sleep efficiency, wake time and awakenings compared with placebo (78). Trazodone was also evaluated in comparison with gabapentin (dosing determined clinically for both) in a non-randomized study of 55 abstinent patients (79). While both agents improved self-reported sleep compared with baseline, greater improvement was observed with gabapentin. A study employing a wait-list control found that cognitive behavioral therapy for insomnia and "self-help" therapy with phone support both led to improvements in sleep that persisted over time. However, no relationship for treatment and relapse was observed (80). Lastly, acamprosate (666 mg) (N = 12) administered from 8 days prior to alcohol discontinuation until 15 days after discontinuation was found to decrease PSG wake time after sleep onset and REM latency compared with placebo (N = 12) both in acute withdrawal and at the end of the study (81). Clearly more controlled treatment studies are needed, particularly those assessing the effects of treatment on relapse.

SCHIZOPHRENIA

Schizophrenia has a lifetime prevalence of 0.5–1% in the global population. This chronic condition is characterized by features including psychotic symptoms comprised of delusions and/or hallucinations, disorganization of speech and/or behavior, and deficits in functional capacity. Impairment in cognitive and executive function often occurs (82,83).

Patients with schizophrenia frequently report difficulties falling asleep, problems staying asleep and impaired sleep quality (84,85). Disturbances of sleep are a consistent finding of PSG studies in this population. A recent meta-analysis of PSG studies, involving 321 untreated patients with schizophrenia and 331 controls, identified prolonged sleep latency, decreased total sleep time and total wake time during the night in the schizophrenia group (86). There are also a number of studies suggesting alterations in sleep architecture. The most common findings are a shortening of REM latency and a decrease in non-REM sleep slow-wave amplitude and slow-wave sleep (85,87–96). Like individuals with alcoholism, those with schizophrenia are predisposed to a reversal in the phase of the circadian rhythm. While co-morbid substance abuse is common in this population, there appears to be an independent tendency to stay awake at night and sleep during the day (97). In a study of 28 older patients with schizophrenia and age-matched controls, monitoring of sleep–wake function with actigraphy suggested greater wake time at night, greater sleep time during the day and less robust circadian rhythmicity in schizophrenia (98).

These alterations of sleep have been found to relate to function, quality of life and the course of the disorder (99–101). One study of 29 patients with schizophrenia on stable medication regimens found that poor sleep quality (Pittsburgh Sleep Quality Index) was associated with lower quality of life ratings on the Heinrichs Quality of Life Scale (99).

Sleep alterations are also related to severity of symptoms and associated functional deficits. The so-called "positive symptoms" of schizophrenia (delusions, hallucinations, disorganized thinking and behavior) have been reported to be correlated with short REM latency, increased REM density, reduced sleep efficiency (time asleep divided by time in bed) and increased sleep latency (87,88,96,102–106). The negative symptoms of this disorder, such as impairment in work and relationships and cognitive impairment, have been associated with slow-wave sleep deficits (85,94,95,106,107) and short REM latency (96,108,109). One study links the slow-wave sleep deficit to the enlarged cerebral ventricular size that is a frequent structural MRI finding suggestive of loss of brain tissue in schizophrenia (85). There has also been a report of a significant correlation between a non-linear measure of the complexity of the electroencephalogram in REM sleep and score on the Wisconsin Card Sort Test in a study of 10 patients with schizophrenia and 10 controls (110).

Several other studies suggest that severe insomnia can be a prodromal symptom of acute psychotic decompensation (104,111,112). In addition, an independent increase in risk of suicidality has been associated with greater REM density and more REM sleep time (113,114).

While these studies suggest associations between sleep disturbances and changes in sleep architecture with impaired quality of life, functional problems and the course of schizophrenia, causal links have yet to be determined. The possibility remains that these associations with sleep are directly linked to disorder severity rather than factors that could have an independent impact. Perhaps greater changes in sleep are a manifestation of more severe brain dysfunction that leads to greater associated functional impairment, poorer quality of life and a more malignant course. Unfortunately, the key question of whether treatment of sleep disturbances in schizophrenia could affect quality of life, function, or course of the disorder, has yet to be systematically tested. The existing data related to sleep deprivation, sleep disorders, and insomnia associated with depression suggest that treatment is likely to have a positive impact on patients with schizophrenia. These data attest to the need to carry out studies to determine whether targeting treatment specifically to the sleep difficulties of schizophrenic patients is likely to be of clinical utility.

CONCLUSIONS

Sleep aberrations in normal subjects and in those with sleep disorders are characteristically associated with impairments in function and quality of life. Sleep problems are very common

in those with psychiatric disorders, although limited data are available on the relationship of sleep difficulties with function and quality of life in these individuals. The data that do exist, which primarily relate to mood disorders, alcoholism, and schizophrenia, suggest that these sleep difficulties have a significant effect on the ability to function, quality of life and the course of these psychiatric disorders. Several findings stand out as common to all three of these disorders: 1. They are all associated with disrupted sleep (difficulty falling asleep, staying asleep, or with diminished sleep quality), and this has been reported to be a prodromal or predisposing factor in each disorder; 2. Disturbance of sleep is associated with greater impairment of function and poorer quality of life; and 3. Greater sleep disruption predicts a greater likelihood of relapse or a more indolent course of the condition. This is also predicted by shorter REM latency, greater REM density and greater percentage of REM sleep in each of these psychiatric disorders.

These observations suggest a number of possibilities. Disturbed sleep and greater REM density may be general manifestations of psychiatric dysfunction. Disturbed sleep and a shift toward more REM sleep intensity may also signal a neurobiological vulnerability to dysfunction. Furthermore, they may signal compensatory mechanics for a variety of neural dysfunctions that fail to address the problem, thereby heralding disorder onset or relapse. It would be of interest to determine whether these findings extend to psychiatric disorders beyond those reviewed in this paper.

Preliminary evidence exists that suggests the clinical relevance of these associations. Several studies targeting adjunctive treatment to insomnia, along with antidepressant medication in those with insomnia and depression, have shown a clinically meaningful positive effect on function, quality of life and the course of illness (53–55). These data suggest the need for future studies that include treatment of insomnia in addition to the treatment of alcoholism and schizophrenia. While it is well established that administering treatments that address elevated REM intensity (such as selective serotonin reuptake inhibitors) have profound impacts on the response, quality of life and risk of relapse in major depression, they do not have comparable utility in the treatment of alcoholism and schizophrenia (49). Furthermore, in terms of effects on REM sleep, some effective antidepressants do not suppress REM, such as bupropion, nefaxodone and mirtazapine.

The possibility of bidirectional causality exists with mutual reinforcement of sleep problems and psychiatric problems. Evidence for mutual reinforcement is that mood disorders tend to be accompanied by disturbed sleep, which appears to increase the likelihood of mania or decrease the likelihood of amelioration of depression, thereby promoting continued sleep difficulties. Poor sleep may lead abstinent alcoholics to consume alcohol, which in turn leads to disrupted sleep and, possibly, to relapse. Schizophrenia appears to lead to shifts in circadian rhythm and/or sleep disruption, which impair cognition and other functional capacities, diminish quality of life and decrease the likelihood of resolution of symptomatology. This contributes to further disturbances of sleep through greater overall disorder severity or diminished ability to implement behaviors that are conducive to sleeping well. All these observations suggest the need for research into the treatment of co-morbid insomnia and psychiatric disorders. They also suggest the need to change clinical practice in order to address sleep problems that occur with these three disorders. There appears to be a greater likelihood of successful therapy if the sleep difficulty and co-morbid disorder (i.e., mood disorder, alcoholism or schizophrenia) are simultaneously targeted for treatment.

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