

A Review of Sleep Disturbance in Hepatitis C

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Abstract: Sleep disturbances occur in up to 60% of patients with chronic hepatitis C (CHC) and is often interrelated with comorbid psychiatric disorders. Moreover, neuropsychiatric complications of interferon- α during CHC treatment can manifest as sleep problems. Newly diagnosed sleep disturbance occurs in up to 60% and 30% of untreated CHC patients and patients undergoing interferon- α therapy, respectively. However, the presentation of insomnia in patients with CHC is influenced by significant psychiatric comorbidity, such as depression, and medical conditions, such as anemia and hypothyroidism. Therefore, prompt recognition using screening tools and exclusion of comorbid conditions contributing sleep pathology can enhance treatment outcomes. Owing to the paucity of studies, treatment recommendations for sleep disorders in CHC patients are derived from recommendations from general sleep disorder treatment guidelines. Further research is needed to elucidate the efficacy of pharmacological and nonpharmacological treatments of sleep disorders in CHC patients.

Key Words: hepatitis C, sleep, liver diseases

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Hepatitis C virus infection is a growing public health concern, with approximately 170 million people chronically infected worldwide.¹ The existing literature on the neuropsychiatric comorbidity in chronic hepatitis C (CHC) infected patients has identified depression, fatigue, and anxiety as common comorbid syndromes. However, a paucity of studies have assessed sleep problems in CHC patients. This is surprising given that sleep problems are commonly reported by CHC patients and there is an established relationship between sleep disorders and quality of life in the medically ill patient populations.²

Sleep problems are often interrelated with other comorbid conditions in CHC patients. For example, insomnia during CHC may exacerbate chronic fatigue, which can occur in up to 75% of CHC patients and reduce health-related quality of life.³ Major depression occurs in approximately 30% to 50% of CHC patients and further complicates the differential

diagnosis of sleep problems.^{4,5} Moreover, approximately 20% of CHC patients will develop cirrhosis over 20 years which may culminate in hepatic encephalopathy, which can manifest as sleep-wake reversal. Furthermore, treatment of CHC with interferon-alpha (IFN α) has been associated with 2 distinct syndromes: (i) a depression-specific syndrome consisting of depressed mood, cognitive symptoms, anxiety, and suicidal ideation; and (ii) a neurovegetative syndrome consisting of reduced energy, fatigue, anorexia, and sleep disturbance (also termed “sickness behavior”).⁶ Therefore, prompt recognition and management of sleep problems during CHC treatment may facilitate improved IFN α treatment adherence and treatment outcomes.

The purpose of this review is to summarize the published information about the prevalence rate and risk factors for sleep disorders in patients with CHC, both pre-IFN α and during IFN α treatment. A summary of potential pathoetiologic factors will be discussed in the context of hepatitis C. Finally, we will provide an approach to the diagnosis and management of sleep disturbance in CHC patients.

MATERIALS AND METHODS

Using PubMed, we searched for all English language articles published between January 1985 and September 2008 to identify studies on sleep disorders in CHC. We used combined the following search terms as follows: “hepatitis C” or “chronic hepatitis” or “liver cirrhosis” or “interferon-alpha” and “sleep” or “insomnia.” We supplemented our literature search with manual reviews of references listed in the identified articles. A total of 17 articles were identified, however, we did not find any sleep disorders treatment studies specific to CHC patients. Given the dearth of literature in this area, this review will provide an overview on sleep disorders in CHC patients, diagnosis and general treatment options based upon guidelines on treatment of sleep disorder in the general population. Identified studies will be cited in the relevant sections and supplemented with data extracted from patients with sleep disorders and other liver pathology where applicable.

Most Common Sleep Disorders

Sleep disorders include largely heterogeneous conditions and syndromes and can be classified as primary sleep disorders and secondary sleep disorders. The most detailed definition of sleep disorders can be found in the International Classification of Sleep Disorders, 2nd edition.⁷ The International Classification of Sleep Disorders, 2nd edition classifies sleep disorders in 8 major categories: insomnias, sleep-related breathing disorders, hypersomnias of central origin, circadian rhythm sleep disorders, parasomnias, sleep-related movement disorders,

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isolated symptoms and normal variants, and other sleep disorders.

Parasomnias are abnormal phenomenon that appear suddenly during sleep or during the transition from wake to sleep and usually occur in stages 3 and 4 of sleep. Examples of parasomnias include sleepwalking and rapid-eye-movement (REM) sleep behavior disorder.

In addition to secondary or comorbid insomnia, primary insomnia has been recognized as an independent condition.⁸ Insomnia can be further defined as sleep onset insomnia, sleep maintenance insomnia (unable to stay asleep), terminal insomnia (early morning awakening with an inability to return to sleep), or nonrestorative sleep. Insomnia may result in fatigue, sleepiness, and impairment in daytime functioning.

Beside insomnias, the most common sleep disorders include sleep apnea syndrome and sleep-related movement disorders, such as restless legs syndrome (RLS).

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive closure of the upper airways during sleep, usually at the pharyngeal level, that produce apneas or hypopneas. The main symptoms of OSAS are intense snoring with breathing pauses and excessive daytime sleepiness. It is characterized by frequent arousals and sleep fragmentation resulting in nonrefreshing sleep, restless sleep, alterations in mood, personality changes, morning headache, and dry mouth upon awakening. Frequent associated symptoms of sleep apnea syndrome include fatigue and cognitive impairment, and also increased risk of accidents. Sleep apnea syndrome is further divided into central sleep apnea, which results from disruption of sleep regulatory centers in the central nervous system; and obstructive sleep apnea, which results from the repeated upper airway closure during sleep. The prevalence of sleep apnea syndrome ranges from 2% to 24% due to the diverse study populations and the variable definitions and disease severity in the prevalence studies.

RLS is characterized by an irresistible urge to move the legs when awake and may also include uncomfortable leg sensations, triggered by rest and resulting in sleep-onset insomnia. Periodic limb movements in sleep are the repetitive movement, cramping or jerking of the legs during sleep. It is frequently associated with RLS, and causes fragmented and nonrefreshing sleep and daytime sleepiness.

Sleep Disorders in Untreated Individuals With CHC

Given the high rates of fatigue in CHC patients, one would expect a portion of sleep complaints to be related to specific sleep disorders. Current estimates of sleep problems in untreated CHC patients are approximately 60%⁹ although it has not been fully resolved what proportion of these problems can be attributed to comorbid neuropsychiatric symptoms. Before considering specific sleep disorders, clinicians should rule out sleep disturbance secondary to comorbid psychiatry disorders, such as mood, anxiety, substance use, and psychotic disorders. Retrospective studies of veterans with CHC report a history of substance use disorders in more than 90% of patients, a figure that is not surprising given that intravenous drug use is the primary mode of HCV transmission.^{5,10} Substance abuse may yield sleep

disruptions in the context of either intoxication or withdrawal states. High rates (up to 20% to 30%) of affective disorders in CHC patients further broaden the differential diagnosis for sleep complaints, which can be a component of a major depressive episode.^{11,12} Moreover, a 5% to 40% increased risk of anxiety disorders, specifically posttraumatic stress disorder, has been reported in patients infected with hepatitis C compared with uninfected patients and may further contribute to sleep disruption.^{5,13} Patients with bipolar, schizophrenia, delusional disorder, or other psychotic disorders may present with sleep disturbance in the context of paranoid content. Therefore, comorbid psychiatric disorders should be included in the differential of sleep disturbance in CHC patients.

Moreover, progression of CHC to advanced liver disease also introduces complications, such as cirrhosis and hepatic encephalopathy, into the differential diagnosis of sleep-wake disruption. Approximately 20% of CHC patients will progress to liver cirrhosis, which can have profound effects on sleep quality. In a Brazilian study comparing polysomnographic findings in 42 cirrhotic patients to 24 healthy controls, cirrhotic patients showed lower sleep efficiency, increased REM sleep latency, and lower REM sleep percentage.¹⁴

Few studies have evaluated prevalence rates of specific sleep disorders in CHC patient populations. In a study of patients with liver cirrhosis mainly from hepatitis C and no evidence clinical hepatic encephalopathy, approximately 50% and 35% of patients experienced sleep disruption as per self-report and sleep actigraphy (a portable device used to monitor motor actigraphy and estimate sleep-wake patterns) measures, respectively, which was higher than rates in healthy controls (4.5%).^{15,16} These sleep findings were not associated with abnormalities on neuropsychological testing and the small sample size precluded examination of risk factors. In a study conducted in an academic-based hepatology clinic, 88 of 141 patients (62%) with chronic liver disease had symptoms of RLS on self-report measures, however, only isolated cases of RLS occurring specifically in CHC patients are reported in the literature.^{17,18} This study used self-report measures and only identified self-report neuropathy as a risk factor for RLS in this sample. No other RLS risk factors were noted in this study. Nonetheless, other RLS risk factors such as uremia, iron deficiency, and comorbid medical conditions (eg end-stage renal disease and diabetes) and a family history should be screened for in the patient's history, although the strength of these risk factors in CHC patients is unknown.

Potential hepatopulmonary syndrome associated with chronic liver disease has generated interest in obstructive sleep apnea in CHC patients. Studies suggest that increased rates of OSA are correlated with greater severity of liver disease in CHC patients, defined as a Child-Pugh score of B and C.^{19–21} Ogata and colleagues¹⁹ observed more than 20 apneic-hypopneic events per hour in 2 and 6 of CHC patients with Child B and C scores, respectively, who therefore met the criteria for obstructive sleep apnea. In a study of 24 cirrhotic patients with ascites, Crespo and colleagues¹⁴ have proposed a relationship between OSA and the development of high-volume ascites, with 2 patients achieving remission of OSA after paracentesis. However, these findings should be interpreted with caution due to methodological limitations, specifically limitations with the polygraph device.

IFN α -induced Sleep Disorders in CHC Patients

HCV treatment with IFN α confers an additional risk of sleep disturbance during immunotherapy, which can be 24 to 48 weeks depending on HCV genotype. Rates of new onset insomnia during conventional IFN α treatment have shown similar data ranging from 22% to 24%.^{22–24} Similarly, an estimated 18% to 33% of patients receiving pegylated IFN α suffer from insomnia.^{22–24} In a study of 96 CHC patients, Malaguarnera and colleagues²⁵ found a higher risk of terminal insomnia and persistent insomnia over the course of HCV immunotherapy with recombinant IFN α -2b in comparison of recombinant IFN α -2a, which could be explained by the rapid absorption and onset of adverse effects with IFN α -2b. However, other research has failed to replicate this finding.²⁶ Anecdotally, RLS can also emerge during pegylated IFN α treatment for CHC, with symptoms resolving upon termination of treatment.^{18,27}

The existing literature on IFN α -induced depression further complicates our understanding of sleep disturbance during HCV treatment. Approximately 25% to 33% of CHC patients treated with IFN α will develop depression, with sleep difficulties emerging as part of the mood episode.^{18,28,29} Therefore, it is unclear if the reported rates of IFN α -induced insomnia can be explained by the rates of IFN α -induced depression alone. However, evidence suggests that early emergence of neurovegetative symptoms, including sleep changes, during IFN α treatment is a risk factor for IFN α -induced depression.³⁰ A prospective study of 71 CHC patients receiving 48 weeks of IFN α treatment found a significant correlation between sleep disorders and IFN α -induced depression and suicidal ideation.³¹ These findings were confirmed in a second study of 46 euthymic CHC patients using the Pittsburgh Sleep Quality Index. In this study, poor sleep at baseline yielded a hazard ratio of 6.0 and 4.4 for IFN α -induced depression and irritability, respectively.³² Thus, poor sleep quality at baseline maybe a harbinger for depression during HCV treatment and stabilization of sleep disturbance before commencing IFN α could reduce the risk of potential IFN α -induced depressive symptoms.

Although depression has been the primary focus of research on IFN α -induced mood disorders, Constant and colleagues³³ purport that manic/hypomanic states, characterized as mood episodes associated with a decreased need for sleep, are underdiagnosed in HCV patients undergoing IFN α treatment and occur in 18% of patients during immunotherapy. Future research is needed to clearly delineate the prevalence rates for IFN α -induced sleep disorders and sleep disorders secondary to mood disorders in patients with CHC.

Possible Etiopathology of IFN α -induced Sleep Disorders in CHC

Although recent evidence suggests that IFN α -induced “sickness behavior” and depression a proinflammatory cytokines, including elevations in interleukin-6 (IL-6) and IL-1, animal studies nearly 20 years ago showed increased time spent in nonrapid eye movement sleep after injection with IL-1.^{34–36} Additional reviews have implicated IL-6, IL-1, and tumor necrosis factor in sleep regulation and modulation.^{37,38} In fact, IL-6 mediates the sleep regulating cytokines IL-1 and tumor necrosis factor. Moreover, IL-6 elevations have been observed in sleep disorders characterized by excessive daytime sleepiness, further suggesting that increased levels of this cytokine are of significance to sleep

pathology.^{39,40} IL-1 has somnogenic properties and preliminary evidence suggests that IFN α induces IL-1 secretion.⁴¹ Despite the promise of cytokine abnormalities explaining IFN α -induced hypersomnia, the above findings require further investigation into the role of cytokines in insomnia, in addition to hypersomnia during CHC immunotherapy.

Sleep dysregulation during IFN α treatment can also be explained by observed IFN α -induced changes in serotonin (5-HT) metabolism. Interferon- α increases the activity of indolamine-2,3-dioxygenase (IDO), a tryptophan catabolizing enzyme, and causes an increase in kynurenine levels and an attenuation of 5-HT and tryptophan levels.⁴² Studies of physically healthy patients with remitted depression after antidepressant treatment suggest that acute tryptophan depletion causes a return to sleep abnormalities observed in the depressed states, specifically reduced sleep and REM latencies, increased REM percentage and increased REM density.^{43,44} The relapse in sleep disturbance occurred independently of mood symptoms, suggesting an increased sensitivity of sleep dysregulation to low tryptophan and 5-HT states, for example, which occurs during IFN α treatment. Wichers and colleagues⁴⁵ have elaborated on the IDO-IFN α hypothesis and suggest that IFN α -induced neuropsychiatric adverse effects are secondary to the neurotoxic effects of increased IDO activity and measured elevations in levels of quinolinic acid, a neurotoxic kynurenine metabolite. In addition, kynurenine and tryptophan levels return to pre-IFN α treatment levels upon completion of IFN α therapy.⁴⁶ Research examining the role of IDO activity in sleep disturbed patients without depression who are treated with IFN α is required to clarify this relationship.

Another potential link between IFN α and sleep is suggested by the preliminary findings in narcolepsy patients suggesting an association between IFN α and suppression of the promoter region of the narcolepsy gene, preprorexin.⁴⁷ Moreover, Wiczorek and colleagues⁴⁸ suggest that IFN α may have a pathogenetic role in HLA-DR2-negative narcoleptics. Further genetic studies are needed to elucidate the pathogenetic role of IFN α on hypersomnolence.

Screening and Diagnosis of Sleep Disorders in CHC Patients

The presentation of sleep problems in patients with CHC should prompt specific screening points. First, the onset, frequency, duration and severity of sleep complaints should be explored in the history. Second, a review of patients' sleep patterns, sleep environment, or psychosocial stressors are important aspects of the sleep assessment. Medical conditions and symptoms, including pain, can exacerbate sleep disorders in this patient population.⁴⁹ Moreover, clinicians should be cognizant of risk factors for specific sleep disorders, such as hypertension and obesity in the case of OSA, especially given that nearly 30% of CHC patients suffer from obesity.⁵⁰ The high comorbidity between substance use disorders and CHC requires a comprehensive review of drug and alcohol use as part of the sleep history. Substance use may involve intoxication or withdrawal states that can precipitate sleep difficulties. Current medications should be evaluated and CHC treatment status should be determined given the risk of IFN α -induced sleep disorders.

TABLE 1. Common Screening Measures for Sleep Disturbance

Scale	Type (Length)	Measured Domain
Pittsburgh Sleep Quality Index ⁵¹	Self-report (19 items)*	Sleep quality
Athens Insomnia Scale ⁵²	Self-report (8 items)	Insomnia
Berlin Questionnaire ⁵³	Self-report (10 items)	Sleep apnea
Epworth Sleepiness Scale ⁵⁴	Self-report (8 items)	Daytime sleepiness
International Restless Legs Syndrome Study Group Rating Scale ⁵⁵	Self-report (10 items)	RLS
Restless Legs Sleep Questionnaire ⁵⁶	Self-report (8 items)	RLS
Sleep Logs or Diaries	Self-report	Subjective sleep experience

*Additional 5 questions rated by bed partner.
RLS indicates restless legs syndrome.

When evaluating sleep complaints in patients with CHC, the clinician should screen for additional symptoms of sleep disorders, such as uncontrollable limb movements, loud snoring, or frequent awakenings at night. If available, history from the patient's partner is valuable and can provide additional information on sleep routine and symptoms, for example, apneic episodes.

Several comorbid psychiatric and hepatic conditions may present with significant sleep problems in CHC patients. Treatment of depression and anxiety may ameliorate insomnia or hypersomnia symptoms. Given the high comorbidity of substance use disorders in CHC and the effect of substances on sleep quality, assessment of drug and alcohol use is an important component to the assessment of sleep disruption in CHC patients. Moreover, pruritus is associated with advanced liver disease and can contribute to sleep quality, specifically frequent awakenings. Metabolic abnormalities, such as hyperammonemia, which may increase the risk of central sleep apnea, can contribute to sleep disruption. In patients with CHC and advanced liver disease, hepatic encephalopathy should be considered as another source of sleep abnormalities.

The use of specific screening questionnaires can also facilitate early identification and diagnosis of sleep disorders (Table 1).^{51,54,55} Sleep diaries usually involve patient recordings of total sleep duration, sleep schedule, time to sleep onset, number of awakenings, daytime nap, and medication use over a 2-week period. Several validated self-report scales may also be useful in the assessment of sleep disorders and are easy to administer. Specific instruments for sleep disorders, such as the Athens Insomnia Scale or the Berlin Questionnaire and Restless Legs Sleep Questionnaire for sleep apnea and RLS, respectively, can be useful during the sleep assessment.^{53,56} Patients with CHC who present with symptoms suggestive of specific sleep disorders or chronic, treatment-refractory sleep difficulties not solely attributable to a comorbid psychiatric disorders should be considered for polysomnographic studies. Polysomnography is indicated in conditions associated with hypersomnolence or excessive daytime sleepiness, in general, in sleep-related movement disorders and breathing disorders, in parasomnias, seizure disorders, certain circadian sleep disorders, in treatment-resistant chronic insomnia, and also in certain other medical conditions or to follow-up treatment effect.^{57,58} Overnight polysomnographic studies can be supplemented next day with objective measures of alertness and sleepiness.⁵⁹

Treatment of Sleep Disorders in CHC Patients

Nonpharmacological Treatment

During the course of the sleep assessment, clinicians may be able to identify areas of sleep hygiene and lifestyle that could be targeted through education and counseling. The essential principles of sleep hygiene are outlined in Table 2 and there is evidence to support its efficacy in daily clinical practice.⁶⁰ Moreover, identification and removal of offending agents, such as caffeine or medications, can result in amelioration of sleep difficulties. Detailed recommendations for nonpharmacological approaches to sleep disorders have been outlined by the American Academy of Sleep Medicine.^{60,61}

Cognitive-behavioral therapy is now a recognized treatment for insomnia and can improve sleep quality and quality of life in patients suffering from insomnia.^{62,63} Moreover, cognitive-behavioral therapy (CBT) is cost-effective and known to have persistent benefits on sleep beyond the termination of therapy, as measured by the Pittsburgh Sleep Quality Index.⁶⁴ In general, CBT for insomnia involves education on sleep hygiene, stimulus control, sleep restriction, muscle relaxation, and sleep education. Although there are no studies examining the efficacy of CBT for CHC insomniacs, findings from general patient populations suggest that CBT may provide added benefit in combination with pharmacotherapy for CHC patients suffering from insomnia.

Similarly, the treatment of OSA should begin with identification and elimination of exacerbating lifestyle

TABLE 2. Principles of Sleep Hygiene

Sleep only when sleepy. If you cannot fall asleep within 20 min, get up and do something boring until you feel sleepy
Take naps as your doctor advises
Maintain a regular sleep-wake schedule even on weekends.
Do regular exercise at least 4 h before bedtime
Develop sleep rituals (listening to music, etc.) as cues to your body to sleep
Only use your bed for sleeping and intimacy
Stay away from caffeine-containing beverages, foods, and medications, nicotine, and alcohol at least 4-6 h before bedtime
Have a light snack before bed with a glass of milk, which contains sleep-promoting tryptophan
Take a hot bath before bedtime, as a drop in the body temperature will promote sleep
Make sure your bed and bedroom are quiet and comfortable. For example, a cooler room is recommended and you can use a humidifier if the air is too dry

factors, such as sleeping in the supine position and the use of alcohol or other sedative in the evening. For mild OSA, changes in sleep position, weight loss, or oral devices, surgery (eg, uvulopalatopharyngoplasty) can improve symptoms. The mainstay of treatment for moderate-to-severe OSA is continuous positive airway pressure, which has been shown to improve daytime sleepiness, hypertension associated with apnea, quality of life and neuropsychiatric symptoms in patients with OSA.^{65,66} No studies have investigated the effectiveness of continuous positive airway pressure in patients with comorbid CHC and OSA.

Nonpharmacological interventions for RLS also include removal, if possible, of potential offending agents such as caffeine, nicotine, alcohol, antidepressants, or antipsychotics. In addition, mild-to-moderate RLS may benefit from distracting activities, using a bicycle or mental alerting activities (reading, cross-word puzzle). A history and physical to identify and treat other secondary causes of RLS, for example, pain due to neuropathy or peripheral vascular disease, is an essential component to the management of RLS.

Pharmacological Treatment

Insomnia

Benzodiazepines are often used for sleep disturbance, however, they are associated with several risks including tolerance, dependence, withdrawal, impaired cognition, respiratory depression, and disrupted sleep architecture, namely reduced slow wave sleep and rapid eye movement.⁶⁷ Benzodiazepines may provide short-term benefit in the acute phase of treatment of comorbid anxiety or mood disorders resulting in sleep disruption. If benzodiazepines are needed for acute stabilization of insomnia in patients with untreated CHC or during IFN α treatment, lorazepam, oxazepam, and temazepam are preferred due to their primary elimination by glucuronidation, which is selectively spared in the presence of liver disease.⁶⁸ Lorazepam and temazepam are preferred for maintenance insomnia due to their intermediate half-life. Anecdotally, triazolam 0.25 mg at bedtime has shown benefit for IFN α -induced sleep disturbance during CHC treatment, however, its short half-life and propensity for rebound insomnia, addiction potential, and association with retrograde and anterograde amnesia limit its utility in CHC patients.⁶⁹

The so-called postbenzodiazepine hypnotics (zaleplon, zolpidem, zopiclone, and eszopiclone) may be more favorable due to their theorized reduced propensity to cause clinical residual effects or dependence.⁷⁰ The short half-lives of these novel hypnotics are less likely to result in residual daytime drowsiness, somnolence. No studies have examined the safety and efficacy of these agents in CHC patients; however, product monographs of the z-hypnotics recommend a dose reduction in patients with severe hepatic impairment due to prolonged half-life.

Antidepressants with sedating properties are preferred for CHC patients with depression and prominent sleep complaints. Mirtazapine, a noradrenergic and specific serotonergic antidepressant, promotes sleep through its 5HT $_{2A}$ and H $_{1}$ blockade. Moreover, mirtazapine has showed efficacy and safety, both as a monotherapy and augmentation agent, for treating IFN α -induced depression in CHC patients.^{71,72} Reports of neutropenia associated with mirtazapine may theoretically increase the risk of

neutropenia related to CHC immunotherapy, however, this adverse effect has not been observed to date in CHC treatment trials involving mirtazapine, although study sample sizes are limited (largest $n = 36$).^{72,73} Trazodone, a serotonin antagonist-reuptake inhibitor, is often used as a hypnotic at lower doses, although the literature has questioned its effectiveness in insomniacs.⁷⁴ In addition to common side effects such as dizziness, sedation, and psychomotor impairment, cases of hepatotoxicity with trazodone have been published in the literature.^{75,76} Therefore, larger studies are needed to establish the overall safety of trazodone in CHC patients.

Given the widespread use of second-generation antipsychotic medications for a variety of psychiatric disorders, it may be tempting to use sedating antipsychotics for managing primary insomnia. However, clinicians should be cognizant of the metabolic risks associated with atypical antipsychotic use, such as weight gain, diabetes and hyperlipidemia, and their potential effects on sustained virological response rates during IFN α and ribavirin combination therapy. Studies have shown that insulin resistance and obesity are poor prognostic factors in the treatment of CHC with immunotherapy.^{77,78} Therefore, atypical antipsychotics should be reserved for sleep disturbance occurring in the context of comorbid major psychiatric disorders, such as bipolar disorder or IFN α -induced psychosis, which are uncommon neuropsychiatric complications of IFN α treatment.^{33,79,80} Dosage adjustment is recommended for quetiapine, olanzapine, and risperidone in patients with hepatic insufficiency.⁸¹

Pharmacological treatment studies for sleep disorders in CHC patients are limited. Spahr and colleagues⁸² examined the off-label use of hydroxyzine, a histamine H $_{1}$ blocker, for the treatment of sleep difficulties in patients with chronic liver disease. In their randomized-placebo controlled trial of 35 patients with minimal hepatic encephalopathy and biopsy-proven cirrhosis, hydroxyzine-treated patients showed significant improvements in sleep efficiency and reduced nighttime activity. Furthermore, antihistamines may provide benefit in reducing pruritus, which can further exacerbate sleep problems. However, antihistamines may precipitate a delirium in some patients or exacerbate underlying hepatic encephalopathy. Therefore, antihistamines should be used cautiously in CHC patients with insomnia.

Other alternative therapies for insomnia include supplements, such as L-tryptophan. In fact, a recent small case series ($n = 3$) showed the utility of tryptophan augmentation for depressed CHC patients undergoing IFN α therapy who showed persistent depressive symptoms despite antidepressant treatment.⁸³ The patients were found to have low serum tryptophan levels and showed an improvement of depressive symptoms, including sleep disturbance, with the addition of tryptophan 1000 mg in the evening in keeping with the IDO hypothesis of sleep dysregulation in CHC.

Delays in peak nocturnal melatonin levels are associated with insomnia in the elderly and may also provide a rationale for managing IFN α -induced insomnia with melatonin.^{84,85} In a small study of noncirrhotic CHC patients ($n = 7$), administration of IFN α resulted in increased melatonin levels in comparison with pre-IFN α treatment levels, and thus could explain altered circadian rhythm during IFN α therapy.⁸⁴ Melatonin and melatonin agonists are purported to have chronotherapeutic effects specifically through regulation of sleep rhythm.⁸⁶ Rat studies have showed that ramelteon, a melatonin agonist, can be used safely in the context of liver dysfunction and has even resulted in improved liver function

after hemorrhagic shock.⁸⁷ Although studies suggest that ramelteon is efficacious in treating chronic insomnia, further studies are needed to elucidate the effectiveness of this agent in CHC patients.⁸⁸

Hypersomnia

Hypersomnia and daytime sleepiness in CHC patients may warrant treatment with a wake-promoting agent, such as modafinil, which appears to exert its effects through either inhibition of presynaptic dopamine reuptake or stimulation of postsynaptic $\alpha 1$ -receptors. It also selectively targets the tuberomammillary nucleus and lateral hypothalamus to stimulate orexin and histamine release. Modafinil has a minimal risk of dependence, which is ideal in CHC patients, as many patients have concurrent substance use disorders. Despite being well tolerated by CHC patients receiving IFN α , modafinil resulted in minimal improvement of IFN α -induced fatigue in an open-label study.⁸⁹ Research involving larger sample sizes and using hypersomnia as an outcome measure are needed to determine the utility of modafinil in CHC patients. Owing to the high rates of substance abuse and dependence in CHC patient populations, methylphenidate and dextroamphetamine should be used cautiously although they may be helpful in CHC patients without a history of substance abuse or dependence.

RLS

Pharmacological management of RLS in CHC patients should follow exclusion of medication-induced RLS. RLS can be exacerbated by tricyclic antidepressants, serotonin reuptake inhibitors, dopamine antagonists, and lithium. Substance use, specifically nicotine, alcohol, and caffeine, can also precipitate or worsen RLS and should be considered in CHC patients presenting with RLS. The treatment of RLS consists of levodopa or dopamine agonists (eg, pramipexole, ropinirole), although dopamine agonists are preferred due to their reduced risk of rebound morning RLS and insomnia in comparison with levodopa.⁹⁰ Cautious titration of ropinirole is recommended in patients with hepatic impairment. Gabapentin has efficacy in treating RLS and should be considered in CHC patients with hepatic impairment and RLS, as it does not undergo hepatic metabolism.⁹¹ Moreover, iron replacement may be indicated in patients with low serum ferritin and RLS symptomatology. It should be noted that many patients with mild or intermittent RLS do not require pharmacotherapy and alternative nonpharmacological methods should be preferred to relieve symptoms.

CONCLUSIONS

Sleep difficulties in the context of CHC is under-recognized and undertreated despite the recognized impact of sleep disturbance on CHC treatment outcomes and purported impairment in quality of life based on other medically ill patient populations. It is paramount that the primary sleep disorders be differentiated from underlying psychiatric disorders and hepatic complications in patients with CHC to facilitate appropriate treatment. Moreover, neuropsychiatric sequelae of IFN α treatment can include sleep disturbance, which may be a harbinger for IFN α -induced mood disorders. Although preliminary findings suggest a link between 5-HT, proinflammatory cytokines, melatonin, and IFN α -related sleep disturbance in CHC patients, studies are needed to determine the specific pathophysiology of such sleep changes. Clinicians should

screen for sleep difficulties during routine visits and consider using self-report screening questionnaires to improve case identification. Current treatment of sleep disorders in CHC patients is primarily guided by general treatment recommendations for sleep disorders and highlights the need for future studies in this area.

REFERENCES

1. WHO. Hepatitis C: global prevalence. *Wkly Epidemiol Rec.* 1997;72:341–344.
2. Mucci I, Molnar MZ, Ambrus C, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. *Nephrol Dial Transplant.* 2005;20:571–577.
3. Kallman J, O'Neil MM, Larive B, et al. Fatigue and health-related quality of life (HQRL) in chronic hepatitis C virus infection. *Dig Dis Sci.* 2007;52:2531–2539.
4. Bini EJ, Brau N, Currie S, et al. Prospective multicenter study of eligibility for antiviral therapy among 4,084 US veterans with chronic hepatitis C virus infection. *Am J Gastroenterol.* 2005;100:1772–1779.
5. El-Sarag HB, Kunik M, Richardson P, et al. Psychiatric disorders among veterans with hepatitis C infection. *Gastroenterology.* 2002;123:476–482.
6. Raison CL, Demetrashvili M, Capuron L, et al. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs.* 2005;19:105–123.
7. American Academy of Sleep Medicine. *International Classification of Sleep Disorders, 2nd ed, Diagnostic and Coding Manual.* Westchester, IL: American Academy of Sleep Medicine. 2005.
8. National Institutes of Health, State-of-the-Science Conference Statement: Manifestations and Management of Chronic Insomnia in Adults. Available at <http://consensus.nih.gov/ta/026/026InsomniaPostConfIntro.htm>. 2005.
9. Lang CA, Conrad S, Garrett L, et al. Symptom prevalence and clustering of symptoms in people living with chronic hepatitis C infection. *J Pain Symptom Manage.* 2006;31:335–344.
10. Yovtcheva SP, Rifai MA, Moles JK, et al. Psychiatric comorbidity among hepatitis C-positive patients. *Psychosomatics.* 2001;42:411–415.
11. Carta MG, Hardoy MC, Garofalo A, et al. Association of chronic hepatitis C with major depressive disorders: irrespective of interferon-alpha therapy. *Clin Pract Epidemiol Ment Health.* 2007;23:22.
12. Lee DH, Jamal H, Regenstein FG, et al. Morbidity of chronic hepatitis C as seen in a tertiary care medical center. *Dig Dis Sci.* 1997;42:186–191.
13. Butt AA, Khan UA, McGinnis KA, et al. Co-morbid medical and psychiatric illness and substance abuse in HCV-infected and uninfected veterans. *J Viral Hepat.* 2007;14:890–896.
14. Crespo J, Cifrian J, Pinto JA, et al. Sleep apnea obstructive syndrome: a new complication previously undescribed in cirrhotic patients with ascites. *Am J Gastroenterol.* 2003;98:2815–2816.
15. Cordoba J, Cabrera J, Lataif L, et al. High prevalence of sleep disturbance in cirrhosis. *Hepatology.* 1998;27:339–345.
16. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep.* 2007;30:519–529.
17. Franco RA, Ashwathnarayan R, Deshpande A, et al. The high prevalence of restless legs syndrome symptoms in liver disease in an academic-based hepatology practice. *J Clin Sleep Med.* 2008;4:45–49.
18. Tembl JJ, Ferrer JM, Sevilla MT, et al. Neurological complications associated with hepatitis C infection. *Neurology.* 1999;53:861–864.
19. Ogata T, Nomura M, Nakaya Y, et al. Evaluation of episodes of sleep apnea in patients with liver cirrhosis. *J Med Invest.* 2006;53:159–166.

20. Nikaina I, Pastaka C, Zachou K, et al. Sleep apnoea syndrome and early stage cirrhosis: a pilot study. *Eur J Gastroenterol Hepatol.* 2006;18:31–35.
21. Teodoro VV, Lucchesi L, Bragagnolo M, et al. Sleep aspects and sleepiness in patients with hepatic cirrhosis. *Sleep.* 2008;31 (Abstract Supplement):A298.
22. Heathcote EJ, Shiffman ML, Cooksley GE, et al. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med.* 2000;343:1673–1680.
23. Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med.* 2000;343:1666–1672.
24. Reddy KR, Wright TL, Pckros PJ, et al. Efficacy and safety of pegylated (40-kd) interferon alpha-2a compared with interferon alpha-2a in noncirrhotic patients with chronic hepatitis C. *Hepatology.* 2001;33:433–438.
25. Malaguarnera M, Laurino A, Di Fazio I, et al. Neuropsychiatric effects and type of IFN-alpha in chronic hepatitis C. *J Interferon Cytokine Res.* 2001;21:273–278.
26. Neri S, Pulvirenti D, Bertino G. Psychiatric symptoms induced by antiviral therapy in chronic hepatitis C: comparison between interferon-alpha-2a and interferon-alpha-2b. *Clin Drug Investig.* 2006;26:655–662.
27. LaRochelle JS, Karp BI. Restless legs syndrome due to interferon-alpha. *Mov Disord.* 2004;19:730–731.
28. Horikawa N, Yamazaki T, Izumi N, et al. Incidence and clinical course of major depression in patients with chronic hepatitis type C undergoing interferon-alpha therapy: a prospective study. *Gen Hosp Psych.* 2003;25:34–38.
29. Bonaccorso S, Marino V, Biondi M, et al. Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *J Affect Disord.* 2002;72:237–241.
30. Wichers KC, Koek GH, Robaey G, et al. Early increase in vegetative symptoms predicts IFN-alpha-induced cognitive-depressive changes. *Psychol Med.* 2005;35:433–441.
31. Gohier B, Goeb JL, Rannou-Dubas K, et al. Hepatitis C, alpha interferon, anxiety and depression disorders: a prospective study of 71 patients. *World J Biol Psychiatry.* 2003;4:115–118.
32. Franzen PL, Buysse DJ, Rabinovitz M, et al. Poor sleep quality increases vulnerability for depression and irritability following interferon treatment (abstract). *Sleep.* 2008;31(Abtract Supplement):A36.
33. Constant A, Castera L, Dantzer R, et al. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry.* 2005;66:1050–1057.
34. Bonaccorso S, Puzella A, Marino V, et al. Immunotherapy with interferon-alpha in patients affected by chronic hepatitis C induces an intercorrelated stimulation of the cytokine network and an increase in depressive and anxiety symptoms. *Psychiatry Res.* 2001;105:45–55.
35. Wichers MC, Kenis G, Leue C, et al. Baseline immune activation as a risk factor for the onset of depression during interferon-alpha treatment. *Biol Psychiatry.* 2006;60:77–79.
36. Wichers MC, Kenis G, Koek GH, et al. Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not cortisol. *J Psychosom Res.* 2007;62:207–214.
37. Kreuger JM, Majhde JA. Humoral links between sleep and the immune system: research issues. *Ann N Y Acad Sci.* 2003;992:9–20.
38. Opp MR. Sleep and psychoneuroimmunology. *Neurol Clin.* 2006;24:493–506.
39. Okun ML, Giese S, Lin L, et al. Exploring the cytokine and endocrine involvement in narcolepsy. *Brain Behav Immun.* 2004;18:326–332.
40. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Circadian interleukin-6 secretion and quantity and depth of sleep. *J Clin Endocrinol Metab.* 1999;84:2603–2607.
41. Gerrard TL, Siegel JP, Dyer DR, et al. Differential effects of interferon-alpha and interferon-gamma on interleukin 1 secretion by monocytes. *J Immunol.* 1987;138:2535–2540.
42. Bonaccorso S, Marino V, Puzella A, et al. Increased depressive ratings in patients with hepatitis C receiving interferon-alpha-based immunotherapy are related to interferon-alpha-induced changes in the serotonergic system. *J Clin Psychopharmacol.* 2002;22:86–90.
43. Landolt HP, Kelsoe JR, Rapaport MH, et al. Rapid tryptophan depletion reverses phenelzine-induced suppression of REM sleep. *J Sleep Res.* 2003;12:13–18.
44. Moore P, Gillin C, Bhatti T, et al. Rapid tryptophan depletion, sleep electroencephalogram, and mood in men with remitted depression on serotonin reuptake inhibitors. *Arch Gen Psychiatry.* 1998;55:534–539.
45. Wichers MC, Koek GH, Robaey G, et al. IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis tryptophan depletion to neurotoxicity. *Mol Psychiatry.* 2005;10:538–544.
46. Zignego AL, Cozzi A, Carpenedo R, et al. HCV patients, psychopathology and tryptophan metabolism: analysis of the effects of pegylated interferon plus ribavirin treatment. *Dig Liver Dis.* 2007;39(Suppl 1):S107–S111.
47. Waleh NS, Apte-Deshpande A, Terao A, et al. Modulation of the promoter region of prepro-hypocretin by alpha-interferon. *Gene.* 2001;262:123–128.
48. Wiecek S, Dahmen N, Kasten M, et al. A rare form of narcolepsy (HLA-DR2-) shows possible association with (functionally relevant) alpha-interferon gene polymorphisms. *Psychiatr Genet.* 2004;14:47–51.
49. Kozanoglu E, Canataroglu A, Abayli B, et al. Fibromyalgia syndrome in patients with hepatitis C infection. *Rheumatol Int.* 2003;23:248–251.
50. Chen W, Wong T, Tomlinson G, et al. Prevalence and predictors of obesity among individuals with positive hepatitis C antibody in a tertiary referral clinic. *J Hepatol.* 2008;49:711–717.
51. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28:193–213.
52. Soldatos CR, Dikeos DG, Paparrigopoulos TJ. The diagnostic validity of the Athens Insomnia Scale. *J Psychosom Res.* 2003;55:263–267.
53. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999;131:485–491.
54. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* 1991;14:540–545.
55. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. *Sleep Med.* 2003;4:121–132.
56. Allen R, Earley C. Validation of a diagnostic questionnaire for the restless legs syndrome (RLS) (abstract). *Neurology.* 2001;58(suppl 3):A4.
57. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep.* 2005;28:499–521.
58. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med.* 2008;4:487–504.
59. Littner MR, Kushida C, Wise M, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep.* 2005;28:113–121.
60. Chesson AL, Anderson WM, Littner M, et al. Practice parameters for the nonpharmacologic treatment of chronic insomnia. *Sleep.* 1999;22:1128–1133.
61. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American academy of sleep medicine report. *Sleep.* 2006;29:1415–1419.

62. Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. *Cochrane Database Syst Rev*. 2003;1:CD003161.
63. Morin CM, Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia: update of recent evidence (1998-2004). *Sleep*. 2006;29:1398-1414.
64. Morgan K, Dixon S, Mathers N, et al. Psychological treatment for insomnia in the regulation of long-term hypnotic drug use. *Health Technol Assess*. 2004;8:iii-iv, 1-64.
65. Dhillon S, Chung SA, Fargher T, et al. Sleep apnea, hypertension, and the effects of continuous positive airway pressure. *Am J Hypertens*. 2005;18:594-600.
66. Kawahara S, Akashiba T, Akahoshi T, et al. Nasal CPAP improves the quality of life and lessens the depressive symptoms in patients with obstructive sleep apnea syndrome. *Intern Med*. 2005;44:422-427.
67. Barbera J, Shapiro C. Benefit-risk assessment of zaleplon in the treatment of insomnia. *Drug Saf*. 2005;28:301-318.
68. Huet PM, Villeneuve JP. Determinants of drug disposition in patients with cirrhosis. *Hepatology*. 1983;3:913-918.
69. Maddock C, Baita A, Orru MG, et al. Psychopharmacological treatment of depression, anxiety, irritability and insomnia in patients receiving interferon-alpha: a prospective case series and a discussion of biological mechanisms. *J Psychopharmacol*. 2004;18:41-46.
70. Montplaisir J, Hawa R, Moller H, et al. Zopiclone and zaleplon versus benzodiazepines in the treatment of insomnia: Canadian consensus statement. *Hum Psychopharmacol*. 2003;18:29-38.
71. Russo S, Boon JC, Korf J, et al. Mirtazapine for the treatment of interferon-induced psychopathology. *Gen Hosp Psych*. 2003;25:497.
72. Schaefer M, Schwaiger M, Garkisch AS, et al. Prevention of interferon-alpha associated depression in psychiatric risk patients with chronic hepatitis C. *J Hepatol*. 2005;42:793-798.
73. Ozcanli T, Unsulver B, Ozdemir S, et al. Sertraline- and mirtazapine-induced severe neutropenia. *Am J Psychiatry*. 2005;162:1386.
74. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry*. 2005;66:469-476.
75. Fernandes NF, Martin RR, Schenker S. Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. *Am J Gastroenterol*. 2000;95:532-535.
76. Rettman KS, McClintock C. Hepatotoxicity after short-term trazodone therapy. *Ann Pharmacother*. 2001;35:1559-1561.
77. Romero-Gomez M, Vilorio MDM, Andrade RJ, et al. Insulin resistance impairs sustained response rate to perinterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology*. 2005;128:636-641.
78. Bressler BL, Guindi M, Tomlinson G, et al. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. *Hepatology*. 2003;38:639-644.
79. Hosoda S, Takimura H, Shibayama M, et al. Psychiatric symptoms related to interferon therapy for chronic hepatitis C: clinical features and prognosis. *Psychiatry Clin Neurosci*. 2000;54:565-572.
80. Onyike CU, Bonner JO, Lyketsos CG, et al. Mania during treatment of chronic hepatitis C with pegylated interferon and ribavirin. *Am J Psychiatry*. 2004;161:429-435.
81. Crone CC, Gabriel GM, DiMartini A. An overview of psychiatric issues in liver disease for the consultation-liaison psychiatrist. *Psychosomatics*. 2006;47:188-205.
82. Spahr L, Coeytaux A, Giostra E, et al. Histamine H1 blocker hydroxyzine improves sleep in patients with cirrhosis and minimal hepatic encephalopathy: a randomized controlled pilot trial. *Am J Gastroenterol*. 2007;102:744-753.
83. Schaefer M, Winterer J, Sarkar R, et al. Three cases of successful tryptophan add-on or monotherapy of hepatitis C and IFN-alpha-associated mood disorders. *Psychosomatics*. 2008;49:442-446.
84. Monti JM, Alvarino F, Cardinali C, et al. Polysomnographic study of the effect of melatonin on sleep in elderly patients with chronic primary insomnia. *Arch Gerontol Geriatr*. 1999;28:85-98.
85. Haimov I. Melatonin rhythm abnormalities and sleep disorders in the elderly. *CNS Spectr*. 2001;6:502-506.
86. Zemlan FP, Mulchahey JJ, Scharf MB, et al. The efficacy and safety of the melatonin agonist beta-methyl-6-chloromelatonin in primary insomnia: a randomized, placebo-controlled, cross-over clinical trial. *J Clin Psychiatry*. 2005;66:384-390.
87. Mathes AM, Kubulus D, Waibel L, et al. Selective activation of melatonin receptors with ramelteon improves liver function and hepatic perfusion after hemorrhagic shock in rat. *Crit Care Med*. 2008;36:2863-2870.
88. Zammit G, Erman M, Wang-Wigand S, et al. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med*. 2007;3:495-504.
89. Martin KA, Krahn LE, Balan V, et al. Modafinil's use in combating interferon-induced fatigue. *Dig Dis Sci*. 2007;52:893-896.
90. Silber MH, Ehrenberg BL, Allen RP, et al. An algorithm for the management of restless legs syndrome. *Mayo Clin Proc*. 2004;79:916-922.
91. Happe S, Sauter C, Klosch G, et al. Gabapentin versus ropinirole in the treatment of idiopathic restless legs syndrome. *Neuropsychobiology*. 2003;48:82-86.