Management of fatigue and sleep disorders in patients with chronic liver disease

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INTRODUCTION

Sleep disorders and fatigue are among the most common, detrimental, and neglected symptoms experienced by people living with chronic liver disease (CLD)[1–5]. Fatigue is a complex patient-reported outcome that encompasses symptoms including lethargy, exhaustion, and malaise.[2] Peripheral fatigue is defined as reduced exercise tolerance related to the decline in muscle function, in contrast to central fatigue, which is failure to either initiate or sustain tasks and physical activity related to brain activity.[6–8] Estimates of the prevalence of fatigue in people with CLD range widely from 26% to 70%.[5,9] Similarly, sleep disorders include a range of disturbed sleep patterns, encompassing phenomena such as insomnia, sleep-wake inversion, and excessive daytime sleepiness. Sleep disorders are present in 50%–85% of people with CLD.[7] Untreated sleep disorders can impair function and quality of life. Thus, a growing body of literature aims to promote evidence-based management of fatigue and sleep for this complex population.[10] This brief review summarizes the pathophysiology, diagnosis, and management of fatigue and sleep disorders in CLD.

Causes of fatigue and sleep disorders in people with CLD

Patients with CLD face a litany of challenges to their sleep and energy, including liver disease etiology/stage and compensatory state, medical treatments, and co-occurring conditions (Figure 1).[6] Liver disease-specific contributors to fatigue include sympathetic over-activity, autonomic dysfunction[6], a chronic pro-inflammatory state mediated by TNFa, IL-1B, IL-6, and CCR2+ monocytes[11,12], and effects of the ineffective portal clearance of gut substrates.[7] Muscle dysfunction or peripheral fatigue can be associated with sarcopenia, malnutrition, and deconditioning in the context of CLD. HE often first manifests as disordered sleep or daytime somnolence and is an independent predictor of sleep quality in people with CLD.[13–15] Finally, medications used for cirrhosis can often contribute to fatigue, particularly beta blockers.

However, sleep disturbance and fatigue can occur in the absence of HE in this population. Obstructive sleep apnea, alcohol misuse, and depression are common comorbidities that are associated with sleep alterations.[16] In obstructive sleep apnea, hypoxic episodes cause overexpression of hypoxia-inducible factor 1-alpha, which negatively impacts sleep quality, daytime sleepiness, cognitive function, and driving.[17–19] Alcohol use, even in the absence of CLD, reduces sleep onset latency and quality and causes insomnia and excessive daytime sleepiness.[16,20,21] Mood disorders, including depression and anxiety, have also been identified in multiple studies as independently associated with worsening sleep quality due to altered dysregulation of serotonin and corticotropin, with effects exacerbated by CLD and HE.[22,23] In the context of specific liver disease etiologies, PBC has the highest association with effect on sleep through increased sleep latency, impaired sleep quality, and increase in...
sustained sleep disruptions.[24–26] Besides co-occurring conditions, liver disease stage can also determine symptomatology with higher prevalence in more advanced stages.[5,27]

Evaluating sleep and fatigue in CLD

In the context of cirrhosis, fatigue, and sleep disorders are often attributed solely to HE, resulting in failure to offer further workup for other potential contributors and attention to non-HE-related sleep disorders in this population. Multiple standardized fatigue scales have been proposed for validation in liver disease in the literature, including the Fisk Fatigue Severity Score, Multidimensional Fatigue Inventory, and PROMIS-fatigue short form (Table 1).[7,25,28–32] Similarly, proposed sleep quality scales include the Sleep Timing and Sleep Quality Screening Questionnaire and the Patient-reported Outcome Measurement Information System measure of Sleep Disturbance.[5,16,27,33–37] For evaluation of the impact of sleep and fatigue, investigators have assessed quality of life and patient-reported outcomes using both generic and liver-specific instruments; however, they have not been fully validated.

In clinical settings, we recommend initial screening for a range of symptoms using a symptom checklist or review of symptoms form. Subsequent evaluation should focus on the symptoms that are most concerning to patients. Workups should be based on the clinical scenario, but we generally evaluate nutritional and metabolic factors (eg, vitamin D, thyroid stimulating hormone), review medications, consider medical and psychological contributors, and evaluate HE by checking for asterixis on physical exam and grading HE using the West Haven Scale. We also review the medication list for potential contributors (eg, opioid medications).

Therapeutic approaches

In general, the approach to treating fatigue and sleep disorders in the context of CLD should focus on addressing the underlying contributing factors (eg, depression, vitamin D deficiency), minimizing sedating medications (eg, opioids), and leveraging behavioral interventions and sleep hygiene as a first-line approach. General behavioral methods, such as adding physical activity, have been associated with improved fatigue in CLD.[38,39] Likewise, targeted behavioral interventions, such as cognitive behavioral therapy for insomnia, work in general populations and are likely to work in people with CLD.

CLD-specific fatigue treatments have been trialed with variable success. Treating underlying inflammatory causes of liver disease (eg, HCV) can improve sleep and reduce fatigue. Primary Biliary Cholangitis (PBC) studies have targeted pruritus-induced insomnia using ursodiol and modafinil, with nonsignificant improvements in fatigue.[25,40,41] However, modafinil has been associated with improved Epworth Sleepiness Scale (ESS) after 2 months of treatment in people with PBC.[24,26] In the setting of decompensated cirrhosis, treating HE is the first step in addressing fatigue and disordered sleep. In the case of overt HE, lactulose, but not rifaximin, has
demonstrated improvement in polysomnographic testing and patient-reported outcomes. Mindfulness-based stress reduction has been tested and demonstrated an improvement in the Pittsburgh Sleep Quality Index regardless of the presence of HE. While melatonin is generally safe and well tolerated, zolpidem and hydroxyzine should be used cautiously in this population despite prior trials showing improvement in fatigue, due to potential side effects. Overall, because of the complex underpinnings of fatigue and sleep disorders in this population, treatment approaches should be holistic, patient-centered, and iterative.

CONCLUSIONS

Fatigue and sleep disturbance are common among people with CLD and profoundly impact quality of life. There is an ongoing need to conduct more targeted studies to identify more effective and safe approaches to manage these symptoms.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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