Sleep disturbances in patients with liver cirrhosis: prevalence, impact, and management challenges

Marie Bruyneel1
Thomas Sersté2,3

1Sleep Unit, Department of Pneumology, Centre Hospitalier Universitaire Saint Pierre, Université Libre de Bruxelles, Brussels, Belgium; 2Department of Hepatogastroenterology, Centre Hospitalier Universitaire Saint Pierre, Université Libre de Bruxelles, Brussels, Belgium; 3Liver Transplantation Unit, Department of Hepatogastroenterology, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium

Abstract: Sleep–wake disturbances are common in liver cirrhosis and associated with impaired quality of life. The most common abnormalities are insomnia (difficulties falling asleep and maintaining sleep, or unrefreshing sleep), excessive daytime sleepiness, and sleep–wake inversion (disturbances of circadian rhythmicity). The underlying pathophysiological mechanisms for sleep disturbances in cirrhosis are complex and may include disturbed metabolism of melatonin and glucose, alterations in thermoregulation, and altered ghrelin secretion profiles. Sleep–wake abnormalities are related to the presence of hepatic encephalopathy (HE) and improvement in sleep parameters can be observed when HE is properly managed. A few non-specific treatments for sleep–wake abnormalities have been tried with encouraging results for hydroxyzine and modafinil. However, due to the potential for medication toxicity in these disabled patients, further studies are needed to address the potential role of non-drug therapies in this population (eg, cognitive behavioral therapy, mindfulness, yoga) that have demonstrated usefulness in insomnia disorders.

Keywords: sleep disorders, hepatic encephalopathy, liver cirrhosis, excessive daytime sleepiness, circadian rhythm, insomnia

Introduction

Liver cirrhosis is a common life-threatening hepatic disorder. The main causes of cirrhosis are related to harmful alcohol consumption, viral hepatitis B and C, metabolic disorders, and non-alcoholic fatty liver disease. These causal factors explain the growing prevalence of the disorder which has reached 0.27% of the population in the United States.1 Clinical manifestations of chronic cirrhosis are highly variable and include ascites, jaundice, gastrointestinal hemorrhage, and hepatic encephalopathy (HE). Fatigue and sleep disturbances have also been observed and this can lead to impairments in quality of life (QoL).2,3 Several sleep disturbances have been described in cirrhosis. However, the underlying pathophysiological mechanisms are complex and not yet fully understood.4 The purpose of this review was to describe these different disorders, their impact, and current treatment options.

Clinical manifestations of sleep disturbances in liver cirrhosis

Sleep disturbances in liver cirrhosis are closely related to the presence of HE. HE has a broad spectrum of clinical severity, ranging from subclinical disorders (covert) to overt HE with coma.5 Diagnosis of HE still remains difficult and is primarily based on clinical
findings. In recent American and European guidelines, altered sleep rhythm is an essential factor in the diagnosis of HE. In a recent study by Singh et al, 32% of patients with liver cirrhosis exhibited HE. In these patients, sleep disorders have serious implications for daytime functioning and are best described as a panel of sleep–wake abnormalities. This was first described in 1954, by Sherlock et al, as a phenomenon of “sleep–wake inversion.” The most common abnormalities include insomnia (difficulty falling asleep or maintaining sleep), excessive daytime sleepiness (EDS), and sleep–wake inversion (disturbances of circadian rhythmicity).

If most sleep disturbances in cirrhotic patients are attributed to HE, sleep disturbances seem to be already present in compensated cirrhosis. Indeed, Bajaj et al have observed EDS attributed to HE, sleep disturbances seem to be already present in compensated cirrhosis. In these patients, sleep disorders have serious implications for daytime functioning and are best described as a panel of sleep–wake abnormalities. This was first described in 1954, by Sherlock et al, as a phenomenon of “sleep–wake inversion.” The most common abnormalities include insomnia (difficulty falling asleep or maintaining sleep, or unrefreshing sleep), excessive daytime sleepiness (EDS), and sleep–wake inversion (disturbances of circadian rhythmicity).

Characteristics and prevalence of sleep disturbances in liver cirrhosis

The reported prevalence of sleep–wake abnormalities in cirrhosis depends upon the diagnostic tools used to assess them. Subjective tools, such as questionnaires and sleep logs, can be used to collect sleep quality and daytime complaints. Objective methods classically applied in the sleep lab, such as polysomnography (PSG) and actigraphy, allow more precise assessment.

It should also be emphasized that correlations between subjective and objective sleep disturbances are not strong. This is due to the fact that patients, especially insomniacs, tend to underestimate their sleep quality. Therefore, it seems essential to rely on both subjective and objective methods to obtain a global picture of sleep in patients.

Prevalence estimates of sleep disturbances in liver cirrhosis based on questionnaires such as the Pittsburgh Sleep Quality Index (PSQI), the Basic Nordic Sleep Questionnaire, and the Sleep Timing and Sleep Quality Screening questionnaire range from 48% to 81%. This is much higher than the prevalence observed in the general population. Patient complaints include increased sleep latency (SL), reduced total sleep time (TST), and frequent awakenings. When compared to healthy subjects, the sleep of cirrhotic patients was worse in three out of four studies.

Objective measurements, by actigraphy, have confirmed the altered sleep quality in cirrhotic patients: reduced SL, and frequent awakenings. PSG has also been performed, confirming the presence of short TST, decreased sleep efficiency (SE), frequent awakenings, and lower amounts of slow wave sleep (SWS) and rapid eye movement (REM) sleep in cirrhotic patients. Animal studies in cirrhotic rat models have corroborated these findings. Interestingly, when we performed 24h-PSG, we were able to show that the amount of objective sleep over 24 hours is much more important than nighttime sleep (575 vs 471 minutes), since a number of naps are recorded in this population (Figure 1).

When compared to healthy subjects, deteriorated sleep quality was confirmed by actigraphy in cirrhotic patients in all studies.

EDS, which is present in 21%–50% of cirrhotic patients, has also been well documented using the Epworth Sleepiness Score (ESS). Compared to healthy subjects, cirrhotic patients show a higher degree of EDS.

Objective and subjective sleep–wake measurements are summarized in Tables 1 and 2.

Chronotopy also seems to be disturbed in cirrhotic patients. Córdoba et al showed a marked eveningness chronotype in these patients. In contrast, in comparison with healthy subjects, Montagnese et al observed no significant differences in sleep patterns.
difference. However, this team stressed that sleep quality was deteriorated in evening-type patients.

**Impact of sleep disturbances in liver cirrhosis**

Sleep disturbances have been shown to negatively impact QoL in cirrhotic patients and have been measured in the majority of studies by the SF-36,13,21,28 or the Chronic Liver Disease Questionnaire.3,22 For example, QoL in patients with liver cirrhosis is worse than QoL in healthy controls2,13 for both the Physical Component Summary and the Mental Component Summary. Samanta et al, in a study comparing 100 cirrhotic patients with minimal HE or no HE, showed that minimal HE was associated with poor sleep and EDS, but also that sleep disturbances aggravate neuropsychiatric impairment.21 Sleep disturbances have also been shown to negatively impact psychological distress and depression.35

**Pathophysiological mechanisms of sleep disturbances in liver cirrhosis**

Sleep disturbances have been associated with the presence of HE and also with disruptions of melatonin metabolism in cirrhotic patients. Some of the features of sleep–wake regulation disturbances may be attributable to melatonin metabolism.
associated with poor sleep, measured by PSQI. Based on these levels of interleukin-6, and not the presence of HE, were associated between sleep disturbances and HE. In another study, high values of ghrelin in cirrhotic men with minimal HE compared to matched controls, that low values of ghrelin in cirrhotic patients were associated with SWS loss on PSG.

Many lines of research remain to be explored in order to understand these complex pathophysiological mechanisms. A summary of current research in this area is shown in Table 3.

**Treatment for sleep disturbances in liver cirrhosis**

As sleep disturbances and EDS are mainly related to HE, it has been hypothesized that HE treatment could positively influence these disorders. Other non-specific treatments for sleep disturbances have also been tried. They are detailed here.

**Effectiveness of HE treatment on sleep disturbances**

Non-absorbable disaccharides

Lactulose and lactitol aim to decrease ammonia absorption from the gut and are effective for improving HE. Treatment improves neurocognition and QoL. A recent work from Singh et al., comparison of cirrhotic patients without HE and those with minimal HE who were given lactulose for 3 months, showed that HE treatment led to improvements in EDS (measured by ESS), sleep quality (increases in TST, SE, SL, amount of REM sleep on PSG), and QoL (measured by the SF-36).

**Rifaximin**

Rifaximin is a non-absorbable oral antibiotic currently recommended for the treatment of refractory HE and to maintain remission of these episodes. Its mechanism of action includes the reduction of gut microbial ammonia production and the improvement of gut barrier function.

**Table 3** Possible pathophysiological mechanisms explaining sleep–wake abnormalities in cirrhotic patients

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Pathophysiological mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed sleep onset</td>
<td>Decreased melatonin clearance</td>
</tr>
<tr>
<td></td>
<td>Delayed melatonin peak</td>
</tr>
<tr>
<td></td>
<td>Altered circadian variation of core body temperature</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>Hepatic encephalopathy (HE)</td>
</tr>
<tr>
<td>Short total sleep time, low sleep efficiency, frequent awakenings</td>
<td>HE</td>
</tr>
<tr>
<td></td>
<td>Increased interleukin-6</td>
</tr>
<tr>
<td></td>
<td>Glucose level fluctuations</td>
</tr>
<tr>
<td></td>
<td>Low values of ghrelin</td>
</tr>
</tbody>
</table>

70% of cirrhotic patients suffer from glucose intolerance or diabetes, this could also partly explain the disturbed sleep patterns in these patients.

Finally, Bajaj et al have also observed, in five cirrhotic men with minimal HE compared to matched controls, that low values of ghrelin in cirrhotic patients were associated with SWS loss on PSG.

**Possible pathophysiological mechanisms**

- **Glucose level fluctuations**
  - Increased interleukin-6
  - Glucose level fluctuations
  - Low values of ghrelin

**Treatment for sleep disturbances in liver cirrhosis**

As sleep disturbances and EDS are mainly related to HE, it has been hypothesized that HE treatment could positively influence these disorders. Other non-specific treatments for sleep disturbances have also been tried. They are detailed here.

**Effectiveness of HE treatment on sleep disturbances**

Non-absorbable disaccharides

Lactulose and lactitol aim to decrease ammonia absorption from the gut and are effective for improving HE. Treatment improves neurocognition and QoL. A recent work from Singh et al., comparison of cirrhotic patients without HE and those with minimal HE who were given lactulose for 3 months, showed that HE treatment led to improvements in EDS (measured by ESS), sleep quality (increases in TST, SE, SL, amount of REM sleep on PSG), and QoL (measured by the SF-36).

**Rifaximin**

Rifaximin is a non-absorbable oral antibiotic currently recommended for the treatment of refractory HE and to maintain remission of these episodes. Its mechanism of action includes the reduction of gut microbial ammonia production and the improvement of gut barrier function.

**Table 3** Possible pathophysiological mechanisms explaining sleep–wake abnormalities in cirrhotic patients

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Pathophysiological mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed sleep onset</td>
<td>Decreased melatonin clearance</td>
</tr>
<tr>
<td></td>
<td>Delayed melatonin peak</td>
</tr>
<tr>
<td></td>
<td>Altered circadian variation of core body temperature</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>Hepatic encephalopathy (HE)</td>
</tr>
<tr>
<td>Short total sleep time, low sleep efficiency, frequent awakenings</td>
<td>HE</td>
</tr>
<tr>
<td></td>
<td>Increased interleukin-6</td>
</tr>
<tr>
<td></td>
<td>Glucose level fluctuations</td>
</tr>
<tr>
<td></td>
<td>Low values of ghrelin</td>
</tr>
</tbody>
</table>

- **Glucose level fluctuations**
  - Increased interleukin-6
  - Glucose level fluctuations
  - Low values of ghrelin

Finally, Bajaj et al have also observed, in five cirrhotic men with minimal HE compared to matched controls, that low values of ghrelin in cirrhotic patients were associated with SWS loss on PSG.

Many lines of research remain to be explored in order to understand these complex pathophysiological mechanisms. A summary of current research in this area is shown in Table 3.

**Treatment for sleep disturbances in liver cirrhosis**

As sleep disturbances and EDS are mainly related to HE, it has been hypothesized that HE treatment could positively influence these disorders. Other non-specific treatments for sleep disturbances have also been tried. They are detailed here.

**Effectiveness of HE treatment on sleep disturbances**

Non-absorbable disaccharides

Lactulose and lactitol aim to decrease ammonia absorption from the gut and are effective for improving HE. Treatment improves neurocognition and QoL. A recent work from Singh et al., comparison of cirrhotic patients without HE and those with minimal HE who were given lactulose for 3 months, showed that HE treatment led to improvements in EDS (measured by ESS), sleep quality (increases in TST, SE, SL, amount of REM sleep on PSG), and QoL (measured by the SF-36).

**Rifaximin**

Rifaximin is a non-absorbable oral antibiotic currently recommended for the treatment of refractory HE and to maintain remission of these episodes. Its mechanism of action includes the reduction of gut microbial ammonia production and the improvement of gut barrier function.

**Table 3** Possible pathophysiological mechanisms explaining sleep–wake abnormalities in cirrhotic patients

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Pathophysiological mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed sleep onset</td>
<td>Decreased melatonin clearance</td>
</tr>
<tr>
<td></td>
<td>Delayed melatonin peak</td>
</tr>
<tr>
<td></td>
<td>Altered circadian variation of core body temperature</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>Hepatic encephalopathy (HE)</td>
</tr>
<tr>
<td>Short total sleep time, low sleep efficiency, frequent awakenings</td>
<td>HE</td>
</tr>
<tr>
<td></td>
<td>Increased interleukin-6</td>
</tr>
<tr>
<td></td>
<td>Glucose level fluctuations</td>
</tr>
<tr>
<td></td>
<td>Low values of ghrelin</td>
</tr>
</tbody>
</table>
action is complex and is thought to involve a decrease in the load of pathogenic microbial flora. Rifaximin improves neurocognitive function and QoL in HE. With regard to sleep, we have compared 15 recurrent HE patients before and after a rifaximin course. No changes in subjective nighttime sleep quality and daytime sleepiness were observed. REM sleep amounts were increased on PSG, but no changes were observed for EDS or the need for naps, despite improvements in HE scores.

**Probiotics and L-ornithine l-aspartate**

These medications have been proved to improve HE and QoL. However, no specific studies are currently focused on sleep disturbances.

**Liver transplant**

One retrospective study has assessed sleep changes before and after liver transplant in 83 patients using questionnaires. Curiously, sleep quality improvement was excellent in patients with alcoholic liver disease but almost nonexistent in hepatitis C patients. It could be interesting to assess sleep disturbances and treatment effects according to the causal factors of cirrhosis.

### Effectiveness of specific treatments on sleep disturbances

**Light therapy**

A single study on 12 decompensated cirrhotic patients assessed the effect of morning bright light therapy on sleep quality. Compared to controls, no effect was observed on sleep quality, EDS, or QoL.

**Sedatives**

One randomized controlled study using the antihistamine hydroxyzine has shown, after a 10-day course, an improvement in SE.

**Stimulants**

Modafinil, which is a usual treatment used to fight EDS in narcolepsy, has been tested in primary biliary cirrhosis in two studies. The medication was effective in 76% of 42 patients in terms of EDS, fatigue, and QoL. In the second study, on 21 patients, the effects were excellent on EDS and fatigue after 2 months of treatment, with a good toxicity profile.

### Conclusion

Sleep–wake abnormalities are common in liver cirrhosis and associated with impaired QoL. They should be properly addressed with objective measurements to rule out covert HE and to trigger specific adequate management.

Underlying pathophysiological mechanisms are complex and include disturbed metabolism of melatonin and glucose, alterations of thermoregulation, and altered ghrelin secretion. As sleep–wake abnormalities occur when HE is present, the cornerstone of treatment is based on HE treatment. A few non-specific treatments for sleep–wake abnormalities have been tried, with encouraging results for hydroxyzine and modafinil. However, due to the increased potential for medication toxicity in these disabled patients, further studies are needed to address the potential role of non-drug therapies in this population (eg, cognitive behavioral therapy, mindfulness, yoga) that have demonstrated usefulness in insomnia disorders.

### Acknowledgment

The authors acknowledge the contribution of a medical writer, Sandy Field, PhD, to the preparation of this manuscript.

### Disclosure

The authors report no conflicts of interest in this work.

### References


