Sleep disorder in patients with chronic liver disease: a narrative review

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Abstract: Sleep disturbance is a common feature of chronic liver disease (CLD) with impact on health-related quality of life; 60–80% of patients with CLD report subjective poor sleep; frequent presentations of sleep disturbance include insomnia, reduced sleep efficiency, increased sleep latency, reduced time in rapid eye movement (REM) sleep, restless leg syndrome and excessive daytime sleepiness (EDS). Key contributors to sleep disturbance include hepatic encephalopathy (HE) and circadian rhythm imbalance due to altered melatonin metabolism. Specific conditions causing CLD, such as non-alcoholic fatty liver disease (NAFLD), chronic viral hepatitis and primary biliary cholangitis (PBC) result in different types of sleep disturbance, and the treatment of these conditions can often also lead to sleep disturbance. There are currently limited management options for sleep disturbance in CLD. Obstructive sleep apnoea (OSA) is a common condition that causes chronic intermittent hypoxia due to airway collapse during sleep. This chronic intermittent hypoxia appears to contribute to the development of NAFLD. The presence of reactive oxygen species and the overexpression of hypoxia inducible factor 1-alpha secondary to hypoxia may be responsible for the second ‘hit’ of the ‘two-hit’ hypothesis of NAFLD. Treatment of the intermittent hypoxia with continuous positive airway pressure therapy has limited efficacy against liver dysfunction. There remain many outstanding areas of investigation in the management of sleep disturbance in CLD, and of liver dysfunction in OSA.

Keywords: Chronic liver disease; cirrhosis; non-alcoholic fatty liver disease; sleep disturbance; obstructive sleep apnoea

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Introduction

The association between sleep disturbance and chronic liver disease (CLD) is increasingly recognized as an important part of the disease course of patients with CLD. Sleep disturbance in patients with cirrhosis is independently associated with reduced health-related quality of life (1,2). In addition, patients with sleep disorders may be at increased risk of developing liver malignancy (3); it is therefore an important area to review. This review will discuss the prevalence and character of sleep disturbance in CLD and then describe possible pathophysiological mechanisms causing sleep disturbance within this population. The limited management options currently available for sleep disturbance in CLD will then be described. Finally, liver dysfunction in obstructive sleep apnoea (OSA), and particularly the association with non-alcoholic fatty liver disease (NAFLD), will be explored. This review will focus...
on the respiratory contribution to the development of sleep disturbance in CLD. While it is recognised that neurology has an important contribution, it is beyond the scope of this review to discuss this. Many clinical and research questions remain unanswered in this field and this review highlights potential future avenues for investigation.

We present the following article in accordance with the Narrative Review Checklist (available at http://dx.doi.org/10.21037/jtd-cus-2020-012).

Methods

Literature for this narrative review was identified using the following terms in Medline and Embase: liver, chronic, sleep, excessive daytime sleepiness, non-alcoholic fatty liver disease, cirrhosis, obstructive sleep apnoea, respiratory and pulmonary. There were no restrictions on dates or study design. English language articles were included.

Sleep disturbance in CLD

Sleep disturbance is relatively common in patients with CLD and cirrhosis; 60–80% of patients with cirrhosis rated themselves as poor sleepers, according to the Pittsburgh Sleep Quality Index (PSQI). PSQI was higher in those patients with evidence of hepatic encephalopathy (HE) and those with increased PSQI suffered from worse health-related quality of life (1,4). Almost 50% of patients with cirrhosis without HE reported unsatisfactory sleep. Nocturnal actigraphy and polysomnography studies have demonstrated short sleeping time (<6 hours per night), reduced sleep efficiency, increased sleep latency, increased rapid eye movement (REM) latency and reduced REM sleep, frequent nocturnal awakening, and excessive daytime sleepiness (EDS) (5,6). Excessive periodic limb movements during sleep have also been reported (7); 25–40% of cirrhotic patients reported insomnia, with increased prevalence of insomnia with worsening severity of cirrhosis. In addition, patients reporting insomnia also reported higher EDS (8,9). It is therefore important to screen for sleep disturbance in any patient known to have or presenting with CLD, including cirrhosis. There are currently no specific tools to assess sleep quality in CLD. The PSQI remains the gold-standard self-reported tool and the Epworth Sleepiness Scale can be used to assess EDS. Objective assessment of sleep quality involves polysomnography or nocturnal actigraphy, and their feasibility in liver disease patients has been demonstrated (10).

Pathophysiology of sleep disturbance in CLD

The cause of sleep disturbance in CLD is likely to be multifactorial and has not been fully elicited. Several mechanisms have been observed that can be associated with poor sleep and are proposed here as possible causes of sleep disturbance.

A common feature of sleep disturbance in CLD is delayed sleep onset. Disruption of the melatonin metabolism pathway is a potential cause for this. The liver plays a central role in the metabolism of melatonin, as it is predominantly metabolized by cytochrome P450 (11). Normal melatonin rhythm is disturbed in patients with CLD, likely due to impaired melatonin clearance in liver dysfunction (12,13). The cause of this impaired melatonin clearance is unclear but may be related to decreased hepatic blood flow and competition with bilirubin in the intrahepatic transport system (14). Patients with cirrhosis have elevated daytime melatonin levels and a delayed onset of melatonin peak at night (12,13,15). Elevated daytime melatonin causes a biological clock phase-shift and this disruption to the circadian rhythm may be related to sleep disturbance in CLD (13,16). Indeed, disrupted melatonin rhythm has been associated with delayed sleep onset in cirrhosis (17). Importantly, these melatonin abnormalities have been observed in patients without significant HE, demonstrating that this derangement is independent of HE (14). A case report has demonstrated that melatonin rhythm can be corrected back to normal values following a liver transplant, providing further evidence for the role of liver dysfunction in melatonin disruption (18). Another possible cause of delayed sleep onset is disturbed regulation of core body temperature. Sleep onset relies on core body temperature cooling through thermoregulatory mechanisms (19). Distal/proximal skin temperature and their gradient (DPG) are reliable predictors of sleep latency; the greater the peripheral vasodilatation, the shorter the time taken to fall asleep (20). A cohort of cirrhotic patients demonstrated higher proximal temperature and significantly lower DPG than healthy controls, and these changes were correlated with an altered sleep-wake profile (21). A potential cause for this impaired cooling is splanchnic and systemic vasodilatation, due to a hyperdynamic circulation (22), causing peripheral vasoconstriction and cooler peripheries.

Another common feature of sleep disturbance in CLD is EDS. EDS is widely recognized as a feature of HE (2,5,8,23,24). EDS, assessed by the Epworth Sleepiness Scale, is well correlated with the
The pathophysiology of sleep disturbance in CLD remains unclear with several different mechanisms proposed. It is particularly difficult to elicit the exact mechanism as the mechanisms proposed can often contribute to sleep disturbance in all patients, not only those with CLD, and the literature does not delineate this well. It is likely that sleep disturbance in CLD is a multifactorial phenomenon and may be disease-specific (Table 1) and so requires tailored means to manage it.

**NAFLD**

NAFLD is a common condition, prevalent in 25% of the global population and increasing as the prevalence of obesity increases (42). NAFLD is characterized by fatty deposition in the liver in the absence of any secondary causes of fatty deposition (43). Increased fat deposition in the liver causes inflammation and fibrosis, eventually leading to cirrhosis. Sleep disruption is increased in patients with NAFLD compared to healthy controls, with NAFLD patients reporting higher PSQI than control (44). Although a meta-analysis reported no relationship between sleep duration and NAFLD (45), subsequent cohort studies have continued to suggest that short sleep duration increases the risk of NAFLD (46-48). Conversely, optimal sleep duration (7–9 hours) has been negatively correlated with liver stiffness in NAFLD patients (49). The most common forms of sleep disturbance in NAFLD include OSA, insomnia and restless leg syndrome (50,51).

**Chronic viral hepatitis**

Sleep disturbance affects up to 60% of untreated patients with chronic hepatitis C (HCV) (52,53) and is one of the most commonly reported symptoms (54). When compared to healthy controls, HCV patients reported significantly worse sleep quality, assessed by PSQI and actigraphy (55). HCV patients suffered from more awakenings, and worse sleep efficiency and latency. Unlike other causes of cirrhosis, sleep disturbance in HCV is independent of the extent of fibrosis (56). Treatment with direct antiviral agents appears to improve subjective sleep quality (57), while
Table 1 Specific forms of chronic liver disease and the features of sleep disturbance that patients most frequently suffer from. Potential specific treatments for sleep disturbance under investigation are also provided, although the evidence base supporting these is of mixed quality.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features of sleep disturbance</th>
<th>Potential specific treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>Insomnia</td>
<td>Lactulose</td>
</tr>
<tr>
<td></td>
<td>Short sleep duration</td>
<td>Rifaximin</td>
</tr>
<tr>
<td></td>
<td>Decreased sleep efficiency</td>
<td>Hydroxyzine</td>
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<td></td>
<td>Increased sleep latency</td>
<td>Zolpidem</td>
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<td></td>
<td>Reduced time spent in REM sleep</td>
<td></td>
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<tr>
<td></td>
<td>Frequent nocturnal awakening</td>
<td></td>
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<tr>
<td></td>
<td>Excessive periodic limb movements</td>
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<tr>
<td></td>
<td>Excessive daytime sleepiness</td>
<td></td>
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<tr>
<td>Non-alcoholic fatty liver disease</td>
<td>Obstructive sleep apnoea</td>
<td>Continuous positive airway pressure therapy</td>
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<tr>
<td></td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Restless leg syndrome</td>
<td></td>
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<tr>
<td>Chronic hepatitis C infection</td>
<td>Decreased sleep efficiency</td>
<td>Antiviral agents</td>
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<tr>
<td></td>
<td>Increased sleep latency</td>
<td></td>
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<tr>
<td></td>
<td>Disturbance due to immunotherapy</td>
<td></td>
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<tr>
<td>Primary biliary cholangitis</td>
<td>Excessive daytime sleepiness</td>
<td>Modafinil</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Wilson's disease</td>
<td>Insomnia</td>
<td>None available</td>
</tr>
<tr>
<td></td>
<td>Frequent nocturnal awakening</td>
<td></td>
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<td></td>
<td>Reduced time spent in REM sleep</td>
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<td>Excessive daytime sleepiness</td>
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<tr>
<td></td>
<td>Fatigue</td>
<td></td>
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<tr>
<td>Liver transplantation</td>
<td>Restless leg syndrome</td>
<td>None available</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

immunotherapy with interferon therapy appears to increase the risk of sleep disturbance. Patients receiving interferon therapy suffered from worse subjective sleep quality when compared to those not receiving any treatment (58). They also suffered from worse actigraphy markers of sleep quality than patients receiving direct antiviral treatment without interferon therapy (59). The addition of resveratrol (a natural phenol) to interferon therapy appears to improve subjective sleep quality (60).

The impact of chronic hepatitis B infection (HBV) on sleep quality is less clear. A cohort study has reported that 60% of HBV patients reported poor sleep quality (PSQI >5) (61), while a case-control study reported that 64% of HBV patients reported symptoms of insomnia compared to 35% in healthy controls (62). No literature has been identified reporting the impact of interventions on sleep quality in HBV.

**Primary biliary cholangitis (PBC)**

PBC, formerly known as primary biliary cirrhosis, is an autoimmune condition resulting in progressive destruction...
of the biliary system, ultimately leading to cirrhosis. Prevalence of PBC is 35 per 100,000 population (63). Patients are likely to suffer from fatigue, pruritus and EDS; these symptoms have a profound effect of quality of life (64). When compared to healthy controls, PBC patients suffer from greater EDS (measured by Epworth Sleepiness Scale) and worse sleep quality (measured as PSQI) (65). Self-reported sleep timing and quality are worse in PBC compared to healthy controls and pruritus appears to coincide with feeling of sleepiness (66). Modafinil has been investigated as a treatment for EDS in PBC. Although an open-label study demonstrated improvement in subjective and objective sleep quality, although whether this directly acts on pruritus, or provides benefit through sedation is not clear (71). Morning bright light therapy appears to have beneficial effect on subjective sleep quality as well as actigraphy markers of sleep quality, as well as quality of life (72). Despite these potential treatments, a recent meta-analysis investigating treatments for fatigue in PBC were unable to identify any beneficial intervention aside from liver transplantation (73).

Wilson’s disease (WD)

WD is an autosomal recessive disorder of copper metabolism, characterized by excessive accumulation of copper in the liver, brain (basal ganglia) and cornea. This manifests as hepatic failure, and neuropsychiatric and parkinsonian symptoms. Sleep disturbance in WD has been well described. The most common symptoms of sleep disturbance include EDS, frequent nocturnal awakening, difficulty falling asleep and fatigue (74-77). Polysomnographic assessment reveals that these patients suffer from reduced total sleep time, sleep efficiency, time spent in REM sleep, and prolonged sleep onset latency (74). Subjective assessments of sleep quality have also demonstrated poorer sleep quality when compared to age-matched controls (77), and these correlate well with polysomnographic studies (76). Cheating therapy with D-penicillamine is the mainstay of treatment for WD. Patients receiving D-penicillamine suffered from prolonged REM sleep-onset latency (74) and reported a higher incidence of REM behaviour disorders, such as vivid dreams and cataplexy-like episodes than age-matched controls (76).

Liver transplantation

As liver transplantation reverses many of the effects of CLD, it may be assumed that following transplantation, there will be an improvement in sleep quality. Prior to transplantation, 60–70% of candidates for transplantation reported poor sleep quality (78,79). Following transplantation, 50–80% of transplant recipients reported poor sleep quality (79-81). One study reported that poor sleep quality was reported by only 40% of patients (82), however this study reported poor sleep quality as PSQI >7, whereas other studies report poor sleep quality as PSQI >5, so they are likely to have underreported their proportion patients reporting poor sleep. It therefore appears that liver transplantation does not have a positive impact on the prevalence of sleep disturbance. Sleep disturbance after liver transplantation has been correlated with anxiety and depression (82,83), the presence of minimal HE and restless leg syndrome (81) and increased fatigue levels (79). Importantly, sleep disturbance was significantly correlated with reduce health-related quality of life in these patients (81). The underlying cause of CLD may also have relevance to the presence of sleep disturbance; patients with alcohol-related liver disease were significantly more likely to report an improvement in sleep disturbance following transplantation, whereas patients with HCV did not report any difference in sleep disturbance (84).

Management of sleep disturbance in CLD

Limited interventions have been investigated specifically targeting sleep disturbance in CLD. Lactulose is widely used to treat HE. A randomized study demonstrated a significant improvement in subjective sleep quality after three months of lactulose in cirrhotic patients with minimal HE (85). An observational study investigating three-month lactulose therapy in minimal HE patients revealed improvements in PSQI, Epworth Sleepiness Scale and polysomnographic measures of sleep quality (total sleep time, sleep efficiency, sleep latency and amount of REM sleep) (86). Rifaximin, an antibiotic used for refractory HE has been demonstrated to improve the amount of time spent in REM sleep, without changes to EDS or subjective
sleep quality (87). A randomized trial investigating the
effect of short-term hydroxyzine in patients with cirrhosis
demonstrated an improvement in sleep efficiency and a
subjective improvement in sleep quality (71). A randomized
study investigating a month’s treatment of zolpidem in
patients with cirrhosis revealed improvements in total
sleep time, sleep efficiency, sleep latency and the number
of arousals and subjective sleep quality (PSQI), without
any changes to sleep architecture (88). Interestingly, given
the close association between melatonin rhythm and sleep
disturbance in CLD, the administration of melatonin has
not been specifically investigated. Light therapy has been
investigated as a means to correct circadian rhythm, but
despite positive case report evidence (89), a randomized
trial failed to demonstrate any benefit (90).

OSA and NAFLD

Having reviewed the presence of sleep disturbance in CLD,
we now consider the presence of liver dysfunction in OSA.
OSA is a relatively common respiratory disorder, with an
estimated global prevalence of clinically relevant OSA
of 6% (91). It is closely related to obesity and has close
association with other metabolic conditions such as type II
diabetes mellitus. It is therefore unsurprising that it is also
closely associated with NAFLD (92). Secondary to this,
liver dysfunction is often present in patients with OSA (93).
Studies investigating the prevalence of liver dysfunction in
OSA have reported that OSA is independently associated
with elevated transaminases (94-96), and progression to
non-alcoholic steatohepatitis (NASH) and liver fibrosis
(94,97-99). In addition, in obese patients, the absence
of OSA was significantly associated with normal liver
histology (100), further demonstrating the close association
between OSA and NAFLD. There are limited data
reporting liver function in obesity hypoventilation
syndrome; a single study has reported that when compared
with OSA, patients with obesity hypoventilation syndrome
have a significantly higher serum alkaline phosphatase
level (101). However, when compared with OSA patients
with a body mass index >30, there was no difference, and so
this effect on liver function may have been related to obesity
rather than sleep-disordered breathing per se.

The pathophysiology of NAFLD, and its progression
to NASH and fibrosis, is widely explained by the ‘two-
hit hypothesis’. The first ‘hit’ is the build-up of lipids in
hepatocytes. The second ‘hit’ then causes hepatocyte injury,
inflammation and eventual fibrosis, and can be initiated by
oxidative stress, proinflammatory cytokines or mitochondrial
dysfunction (102). Clear understanding of the second ‘hit’
and its antecedents remains to be discovered. The literature
is suggestive that the chronic intermittent hypoxia of OSA
is an important contributor to this second ‘hit’ (Figure 1).
In patients with OSA, the overnight desaturation index
and mean nocturnal oxygen saturation are independent
risk factors for the development of liver injury, indicated

Figure 1 The contribution of obstructive sleep apnoea to the pathophysiology of non-alcoholic fatty liver disease (NAFLD). Following
the first ‘hit’ of fatty liver deposition, the chronic intermittent hypoxia of obstructive sleep apnoea contributes to endothelial damage that
contributes to the fibrotic change seen in NAFLD. ROS, reactive oxygen species; HIF 1-alpha, hypoxia inducible factor 1-alpha; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1.
by rising transaminases (103,104), NAFLD (105), and hepatic fibrosis (106,107). Similarly, patients with NAFLD have a higher apnoea-hypopnoea index and lower mean nocturnal oxygen saturation than controls (108,109), and these are independent risk factors for progression to hepatic fibrosis (110,111). In addition, increasing severity of OSA appears to be in a dose-relationshipt with the prevalence of NAFLD (112) and severity of liver dysfunction, both in terms of transaminases (113,114) and liver morphology (115-117).

Human studies have not clearly demonstrated the pathophysiological impact of chronic intermittent hypoxia on liver function, so our current understanding comes from animal models. In a mouse model, intermittent hypoxia resulted in a cyclic reduction in oxygen tension in the liver (118), suggesting that it causes cycles of hypoxia and reoxygenation, which may result in oxidative stress from reactive oxygen species, similar to hypoxia-reperfusion injury. Contiguous to this, many human studies have demonstrated that OSA can cause high levels of oxidative stress (119,120). Despite this, two studies investigating the utility of the antioxidants, vitamin C (121) and carbocisteine (122), were not able to provide strong evidence for their use in improving OSA outcomes. Hypoxia-inducible factor 1-alpha (HIF 1-alpha) is a transcription factor that regulates the cellular response to hypoxia. In a mouse model of NAFLD, deletion of the HIF 1-alpha gene protected hepatocytes from progression to liver fibrosis (123,124).

Pathological angiogenesis in the liver is closely associated with the fibrogenic progression of CLDs to fibrosis. Both hypoxia and HIF 1-alpha act as proangiogenic stimuli so appear to be a key contributor to the fibrotic changes observed with progressive NAFLD (125). Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a cell surface protein that facilitates the endocytosis of oxidized lipoproteins in endothelial cells. The deletion of HIF 1-alpha downregulates the expression of LOX-1 (126) and so it can be surmised that overexpression of HIF 1-alpha, such as in OSA will result in overexpression of LOX-1. Indeed, a cohort of treatment-naive OSA patients demonstrated that LOX-1 levels were higher in patients with OSA than control and that the proportion of sleep spent with oxygen saturations below 90% was positively correlated with LOX-1 levels (127).

Importantly, in vitro data have revealed that LOX-1 expression is associated with endothelial injury and the defenestration of human liver sinusoidal endothelial cells, which is a pathological feature of NAFLD (128). Based on this mechanistic data, the progression of NAFLD to NASH and cirrhosis appears to be mediated by HIF 1-alpha and its effect on LOX-1 expression, which is released in response to the chronic intermittent hypoxia caused by OSA.

We could therefore posit that treating the intermittent hypoxia of OSA, by continuous positive airway therapy (CPAP), would be protective against liver dysfunction in OSA patients. A meta-analysis that identified limited data concluded that CPAP is effective at improving serum liver enzyme levels in patients with NAFLD (129). Subsequently published data support this finding (130,131). In addition, CPAP therapy appears to delay progression from NAFLD to liver fibrosis (132). Despite this, and although hepatic steatosis is a reversible condition, CPAP does not appear to improve morphological changes in the liver in OSA patients (133,134). A meta-analysis of five randomised studies has also concluded that CPAP does not appear to have any effect on liver fibrosis and that the existing evidence for this is of low quality (135).

The relationship between NAFLD and OSA is clearly complex and causality remains uncertain; the hypoxia of OSA does appear to contribute to the development of NAFLD and to the progression of NAFLD to liver fibrosis. However, eliminating this hypoxia does not result in a complete reversal of the morphological liver changes and so there are likely to be contributions from other mechanisms that remain to be discovered. There are also outstanding clinical questions that need to be answered through further work. The clinical benefit of screening all NAFLD patients for OSA and vice versa remains unclear, but we would recommend the inclusion of simple screening tools such as questionnaires (OSA) and liver function tests (NAFLD) in the baseline work-up of these patients, as suggested by the authors of a meta-analysis investigating abnormal liver enzymes in OSA (136). There is increasing interest in biomarkers of liver fibrosis in OSA (137,138); if a simple non-invasive biomarker can be identified, this would further support the rationale to screen all OSA patients for liver dysfunction. If evidence of liver dysfunction is present, should an OSA patient be treated more aggressively with earlier initiation of CPAP than in patients without liver dysfunction? Clinical trials are needed to address the correct timing of CPAP initiation in the context of liver dysfunction. Other treatment of OSA, such as the mandibular device, also aim to eliminate the intermittent hypoxia. The role that treatments for OSA, other than CPAP, have in improving liver dysfunction is yet to be investigated.
Summary

Sleep disturbance in CLD is common and associated with reduced health-related quality of life. It can manifest in various forms, including delayed sleep onset, EDS and poor subjective sleep quality. The causes are complex, multifactorial and remain to be elucidated clearly. Specific conditions leading to CLD manifest sleep disturbance in different ways, and surprisingly, liver transplantation does not result in an improvement in sleep quality. There are currently minimal management options specifically for sleep disturbance in patients with CLD, with the most convincing evidence available for established treatments of HE, such as lactulose and rifaximin. There is a need to conduct more randomised trials to identify useful pharmacological agents specifically aimed at improving sleep quality. NAFLD is closely associated with OSA; mechanistic studies and animal models provide a potential pathophysiological explanation for the contribution of OSA to the progression of NAFLD to liver fibrosis and cirrhosis, through chronic intermittent hypoxia. Despite this, treatment of intermittent hypoxia with CPAP does not result in a significant reversal of progressive liver disease in NAFLD. There is therefore a need to further identify the exact contribution of OSA to progressive NAFLD, the optimal tool and time point to screen for OSA in NAFLD and for NAFLD in OSA, and whether the timing of CPAP initiation has any impact on the progression of NAFLD.

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