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The Overlooked Symptoms of Cirrhosis

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Cirrhosis is increasingly common and morbid. While contemporary care often focuses on the classic complications of cirrhosis, the overlooked symptoms of cirrhosis pose a great toll on patient well-being. These symptoms include muscle cramps, itching, sleep disorder, falls, sexual dysfunction, itching, and chronic pain. This review aims to provide a practical way of addressing the symptoms of cirrhosis with the aim of enriching quality of life for those living with cirrhosis.

INTRODUCTION

Cirrhosis is common and morbid. Its prevalence exceeds >1 million persons in the United States (US) alone,[5] rising by 50% in the past 20 years.[6] There has been substantial progress in the early detection and supportive care for cirrhosis. While contemporary care often focuses on screening for and managing the complications of cirrhosis such as hepatocellular carcinoma, varices, ascites, and hepatic encephalopathy (HE), the overlooked symptoms of cirrhosis take a great toll on patient well-being.[7] These symptoms include muscle cramps, sleep disorder, falls, sexual dysfunction, itching, and chronic pain. It is recognized that the identification and management of these symptoms is part of high-quality care.[1-4] This review aims to provide a practical way of addressing the symptoms of cirrhosis with the aim of enriching quality of life for those living with cirrhosis. Recommendations are summarized in Figure 1.

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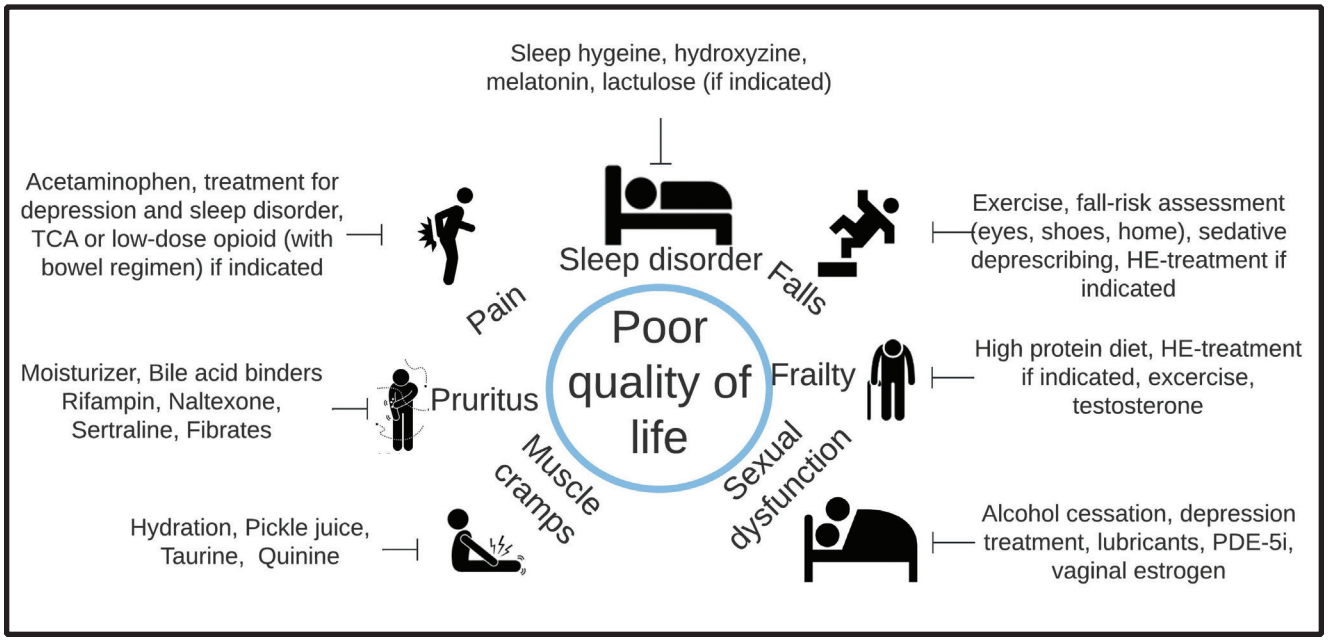
Pruritus

Patients with cholestatic liver disease can experience profound itching.[8] Patients with non-cholestatic liver disease also experience bothersome itching, however the evidence supporting specific interventions is often lacking for these patients. Pruritus can be screened with the question "How much of the time have you been troubled by itching during the last two weeks?", after which its severity can be assessed using a visual analog scale. The mechanisms of itch in cirrhosis are varied and involve dry skin, increased pruritogens (known, like bile salts, or unknown), and increased itch perception or catastrophizing. For this reason,

Figure 1. Etiology Directed Therapies to Prevent Decompensations of Cirrhosis



HE = hepatic encephalopathy, PDE = phosphodiesterase, TCA = tricyclic antidepressant

treatments address each step in this conceptual model of pruritis.[8] Pharmacotherapeutic options for cholestatic pruritus that have been tested in clinical trials include bile acid binders cholestyramine (4-8g BID-QID),[9] colesevelam (2-8g BID),[10] rifampin (150-300mg BID),[11,12] naltrexone (50mg daily),[13-15] sertraline (25-100mg daily),[16] and bezafibrate (can be replaced with fenofibrate, 100-145mg daily).[17,18] These therapies are often ineffective in non-cholestatic cirrhosis. A prudent clinical strategy is to identify bothersome itch, counsel on the importance of frequent whole-body moisturizing, and cautiously utilize therapies for patients with persistent unmet needs.

Muscle Cramps

Muscle cramps are common in cirrhosis, impacting 1 in 3 patients and causing poor health-related quality of life.[19-21] Muscle cramps can be identified by asking "During the past month, how many painful muscle spasms, cramps, or charley horses have you had? Do they bother you?" Thereafter, the severity of muscle cramps should be assessed using a visual analog scale. Pharmacological treatments for muscle cramps in patients with cirrhosis include taurine (1g TID),[22] quinidine,[23,24] and sips of pickle juice at cramp onset.[25] The largest trial enrolling patients with cirrhosis in the US is the PICCLes trial. Upon contact with the oropharynx, the ascetic acid triggers a nerve reflex that aborts the muscle cramp. Though pickle brine has sodium, only 1 tablespoon (~25mg sodium) is required. Compared to a tap water control, sips of kosher or dill pickle brine at cramp onset were more likely to abort the muscle cramp and reduce cramp severity. This intervention did not reduce the frequency of muscle cramps. For this reason, if short-duration, high frequency cramps are the patient's problem, a trial of taurine may be reasonable.

Sexual Dysfunction

Sexual dysfunction impacts 53%-93% of patients with cirrhosis.[19] Sexual satisfaction can be assessed with the questions: Have you had any sexual activity in the past few weeks? How satisfied were you with your sexual function during the past few weeks? Patients who report dissatisfaction who are smoking should be counselled that smoking interferes with sexual function and cessation therapy should be considered. Comorbid depression should be assessed, and care initiated if present. Finally, if the patient is consuming alcohol, abstinence should be recommended with assistance from psychotherapy or pharmacotherapy. Sexual function improves

with freedom from alcohol and this expectation can be used when counseling patients.[26] A randomized controlled trial of tadalafil safely enhanced erectile function along with improved depression, anxiety, and quality of life compared to placebo.[27] Similar results may be seen from sildenafil but this has not been trialed. Testosterone has been trialed and is a promising therapy for men with low testosterone without HCC or prostate cancer who have been counselled regarding cardiovascular risks.[28] It may also improve frailty and sarcopenia. There have been no clinical studies of pharmacological treatments for female sexual dysfunction in patients with cirrhosis.[29] Vaginal dryness can be queried and addressed with personal lubricants. For post-menopausal women, a trial of topical vaginal estrogen can be helpful. In patients who experience recurrent urinary tract infection, vaginal estrogen can significantly reduce recurrence rates.[30]

Sleep Disturbances

Sleep disturbances, which include sleep-wake inversion, excessive daytime sleepiness, and insomnia, affect 50-80% of patients with cirrhosis.[19,31-33] Sleep quality can be assessed with the following question "During the past month, how would you rate your sleep quality overall?" (graded with a 5-point Likert scale from Very Good to Very Bad). Sleep quality can be poor if sleep hygiene is poor, or the patient has sleep apnea. These things can be addressed in parallel with considering the influence of cirrhosis with factors including muscle cramps and HE. Treatment of HE may help to improve sleep disturbances in patients with cirrhosis.[34,35] Minimal HE can be identified with using the EncephalApp.com or the animal naming test. Short courses of melatonin (1-3mg), zolpidem, and hydroxyzine (25-50mg) have also been shown to improve sleep quality in randomized trials of patients with Child Pugh A and B cirrhosis.[36-38] However, zolpidem should be avoided as it increases the risk of falls and fractures.[39,40]

Falls

Falls are common. The probability of falls among patients without prior HE was 28.8% and 50.2% at 1 and 3 years.[4] HE is likely an even stronger risk factor. The CDC recommends screening for falls among those older than 65 by asking about falls within the past 6 months. However, cirrhosis is a risk factor for falls and falls occur at younger ages in cirrhosis. As such, screening may be beneficial. Interventions should be focused on eliminating as many risk factors as possible in each individual patient. Evidence-interventions include HE-directed therapy for those with cognitive dysfunction, tai chi, exercise programs, and reduction of polypharmacy, particularly hypnotics like zolpidem.[41]

Pain

Chronic pain is a challenging comorbidity in the management of cirrhosis. Pain is common – cramps, symptomatic ascites, injurious falls with fractures – and its management is complicated by a narrow therapeutic index related to cirrhosis physiology. For example, nonsteroidal anti-inflammatory medications can cause renal injury and worsened ascites and opioids can cause constipation, precipitating HE. The management of chronic pain benefits first from an accurate classification of pain: nociceptive (bodily injury), neuropathic, and nociplastic. Nociplastic pain is typically widespread and features no evidence of tissue or nerve damage such as fibromyalgia or irritable bowel syndrome. Nociceptive pain should be managed with low dose (maximum 2000mg daily) acetaminophen, topical therapy (e.g., topical diclofenac), or low dose opioids for acute pain such as fractures, provided that constipation is proactively avoided. Neuropathic pain can be treated with topical therapy (e.g., capsaicin, lidocaine), local injections if amenable, or tricyclic antidepressants. Nociplastic pain benefits from a holistic approach including addressing sleep disorder and mood disorder and promoting physical and mindfulness activities prior or in addition to any pharmacologic interventions.[42]

CONCLUSION

The overlooked symptoms of cirrhosis are common, morbid, and matter to patients. There are simple, quick ways to screen for these symptoms. Each symptom, furthermore, can be improved with evidence-based therapies and approaches. In many cases, first-line therapies may not prove effective. However, patients will appreciate the attention to a distressing problem after which stepwise, multidisciplinary care can deliberately trial supportive therapies. The expectation is not that these recommendations will solve all symptoms – though in some cases they will – but rather that patient's well-being becomes of focus of their clinical care. ■

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