Psychiatric Disorders and Their Treatment: Impact of Outcomes in Patients With Chronic Liver Disease

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Psychological and substance use disorders are highly prevalent in persons living with chronic liver disease (CLD). This review will summarize the mechanisms through which comorbid psychiatric and substance use disorders impact CLD-related outcomes. Furthermore, this review will summarize evidence supporting the treatment of comorbid psychiatric and substance use disorders to improve CLD-related outcomes.

PSYCHOLOGICAL DISORDERS/DISTRESS AND CLD

It has been established that psychological disorders and distress are related to a range of poor outcomes, including more severe liver symptoms, more advanced liver histological abnormalities, higher liver disease-related mortality, and poor compliance with medical treatment. Even in the modern era of hepatitis C (HCV) treatment, psychological disorders and distress reduce the odds of treatment success. Depression and anxiety are the most prevalent psychological disorders that impact patients with liver disease, with anxiety impacting 25% to 45% of CLD patient populations and depression impacting 29% to 72%. The rates of depression vary across liver diagnosis; patients with nonalcoholic fatty liver disease (NAFLD) and HCV diagnosis demonstrate increased rates of depression, and patients with hepatitis B report a similar rate of depression to the general population. Most of these studies were single center or cross-sectional. We should also note a lack of consensus on the definitions of “depression” and “anxiety” used in studies. For example, scales such as the hospital anxiety and depression scale and patient health questionnaire-9 measure anxiety and depressive symptoms, while instruments such as the structured...
clinical interview for DSM are able to differentiate clinical diagnoses, such as major depressive disorder (MDD) or generalized anxiety disorder (GAD).

Multiple causal pathways exist between psychological disorders/distress and CLD. There is a large body of evidence that highlights the key roles of inflammation and gut microbiota in psychological distress and CLD, such as NAFLD (Fig. 1). Several studies have suggested that probiotic administration improves levels of liver-associated enzymes, demonstrating beneficial psychotropic effects on anxiety and depression. Sickness behavior theory, a theory used to describe changes in behavior and subjective experience of ill patients, supports peripheral inflammation causing sickness behaviors, such as fatigue, lethargy, impaired concentration, and withdrawal from social interactions. When illness and these associated behaviors persist, psychological distress (such as depression) may develop.

Likewise, it is common for patients to experience a psychological reaction that develops from the burden of chronic illness. Patients with comorbid psychological disorders are more likely to have thought distortions about their medical situations. Patients experiencing depression and anxiety have a lower sense of personal control, are less likely to believe that treatment will help, and have lower confidence
in their ability to manage their medical situation. Patients are also more likely to have diminished or poor coping (such as substance use/abuse, emotional eating, and avoidance behaviors), increased sickness behaviors, such as lack of motivation for exercise and attending to activities of daily living, and sleep dysregulation.

**SUBSTANCE USE/ABUSE AND CLD**

Substance abuse and CLD are inherently linked and negatively impact patient-centered and medical outcomes. The highest rate of substance abuse related to CLD is due to alcohol abuse. The prevalence of adjustment disorders, anxiety, depression, and posttraumatic stress disorder (PTSD) are higher in those with alcoholic liver disease (ALD) compared with those patients with nonalcoholic CLD. ALD is also the main cause of alcohol-related morbidity, which accounts for 48% of all deaths from cirrhosis. Patients are less likely to receive care for both psychiatric and addiction disorders but may receive care for only one or the other. This leads to negative medical outcomes because the underlying risk factors that contribute to both psychiatric and substance abuse disorders are not addressed. Alcohol is a depressant; it impacts mental health by altering mood, affect, cognitive impairments, as well as the risk/reward circuit. Biologically, alcohol affects gut microbes and can lead to deficiencies in thiamine, malnutrition because of absorption concerns, and other comorbid medical disorders.

Opioid use can contribute to CLD, particularly in those with NAFLD. Prescription opioids are used in nearly one of five patients with NAFLD. Opioid use is associated with increased complications, prolonged hospitalizations, hospital readmission, and decreased health-related quality of life (HRQOL). Opioid use is also more common as CLD progresses. Opioids act as a depressant and can promote sedentary behavior. Opioid use has been linked to an increased risk for hepatic encephalopathy, length of hospital stays, and hospital readmissions.

The intersection of behavioral health and addiction in CLD is multifaceted and interlocking, because behavioral and biological pathways weave together to increase risk factors in patients. Both psychological disorders/distress and substance use/abuse share common underlying mechanisms, such as impaired cognitive capacity, maladaptive thought patterns, and impaired coping, and both affect patient-reported and medical outcomes (Fig. 2). An important note is that relapse is a normal part of substance abuse and recovery, which can further put a patient at risk for decompensation, recurrent alcoholic hepatitis, poor compliance, and in cases of transplant, graft loss. Studies demonstrate that integrated behavioral health models that also address addiction actually improve the quality of life for patients and can reduce the aforementioned risk factors.

**IMPACT OF BEHAVIORAL HEALTH CARE ON CLD OUTCOMES**

Several lines of evidence suggest that treatment of psychological and substance use disorders can improve patient-reported and medical outcomes in CLD. These will be reviewed by disease state with a focus on HCV, ALD, and NAFLD.

The large majority of studies in those with comorbid HCV and psychological disorders focus on integrated care models to improve HCV treatment uptake. Collectively, these studies indicate that integrated care models have a significant and positive impact on HCV-related outcomes. Rates of antiviral therapy were significantly higher with earlier initiation of treatment, higher adherence rates, and higher SVR rates in those enrolled into integrated care compared with those receiving standard of care. Importantly, subgroups with a prior psychiatric disorder and/or active drug or alcohol use also achieved improved HCV outcomes. It is also likely that treatment of comorbid psychological disorders in addition to HCV is needed to significantly improve patient-reported outcomes, such as HRQOL. For example, prior diagnosis of depression was the only predictor of lack of improvement in patient-reported mental health after HCV treatment. Finally, risk for reinfection is highest in persons who inject drugs, followed by HIV coinfected individuals and those with a history of psychiatric disorders and problematic alcohol use. Preventing reinfection through reduction of high-risk behaviors can best be achieved by active management of substance use disorders, such as opioid agonist therapy.

In ALD, currently, there are no curative therapies; cessation of alcohol use and management of relapse remain the foundation of ALD treatment. To this end, both behavioral and pharmacotherapy have been studied. Psychological interventions have been proved to improve rates of abstinence and prevent relapse even at lower-intensity brief formats. In those with CLD, psychological interventions integrated with medical care were most impactful. For example, integration of alcohol addiction units into a liver
transplant center resulted in lower recidivism rates and improved post–liver transplant mortality. Furthermore, there is growing evidence of the benefits of combining behavioral interventions with medications targeted to reduce cravings, although studies in those with comorbid ALD are limited. In noncirrhotic ALD, several medications have been proved to reduce cravings: acamprosate, baclofen, disulfiram, gabapentin, naltrexone, and topiramate. However, studies focusing specifically on liver disease outcomes are lacking, and they require monitoring of liver function. For example, there are reports of drug-induced liver injury with naltrexone, albeit rare. In advanced ALD, studies are more limited. Baclofen is the only drug to be studied in randomized controlled trials and resulted in longer abstinence duration, reduced cravings, and improved liver function.

In NAFLD, weight loss remains a key pillar of disease management. A study evaluating adherence to lifestyle modification recommendations for weight loss showed that depressive symptoms strongly impacted adherence to physical activity and diet recommendations. Depressive symptoms also mediated the relationship between physical quality of life, social support, and diet/exercise adherence. Furthermore, those with NAFLD and stable MDD had improvement in liver enzymes after 48 weeks of standard of care compared with those with unstable MDD who had no improvement. In another study, readiness to change after receiving nutritional education and guidance did not predict weight change, psychiatric symptoms did. It is also likely that treatment of metabolic disorders that underlie NAFLD may also improve outcomes in psychiatric disorders through reduction of inflammation, oxidative stress, and insulin sensitization, further highlighting the complex interplay between NAFLD and psychological symptoms. Finally, in those with comorbid psychiatric disorders and NAFLD, the metabolic side effects of psychiatric medications need to be considered prior to treatment.

In less prevalent liver diseases, including immune-related, cholestatic, and genetic CLDs, studies assessing the impact of behavioral health treatment on CLD outcomes are lacking. In primary sclerosing cholangitis, however, it has been shown that improved self-management through a structured intervention improved HRQOL, coping, and care navigation. In Wilson's disease, it is known that decoppering does not reduce the burden of psychiatric disease; thus, lifelong management of comorbid psychiatric disorders is likely needed as part of comprehensive care.
CONCLUSIONS

CLD, psychiatric disorders such as MDD and GAD, and addiction disorders are inherently linked because of shared psychosocial and metabolic risk factors. Review of existing studies shows that treatment of psychiatric disorders and distress improves liver disease-related clinical and patient-centered outcomes, although the lines of evidence need to be strengthened. Specifically, future research in comorbid psychiatric disorders and CLD needs to be collaborative, focusing on teasing out the impact of a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnosed disorder versus psychological symptom burden on CLD, because this will allow for more specific interventions in those with CLD. Finally, integrated models of care that structure the health delivery system to deliver comprehensive behavioral health and medical care are supported by studies in other chronic disease states.23 Within hepatology, these models are efficacious but underused.9 More universal use of such models will require careful patient-centered health care redesign at the institutional level, as well as policy change for reimbursement for colocalized multidisciplinary care, patient navigation, and care coordination.

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