Mental Health in Chronic and End-Stage Liver Disease

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Introduction

Mental health care professionals caring for patients with liver disease require both an understanding of the inherent liver disease process and an awareness of mental health disorders that commonly co-occur with liver diseases. The main causes of cirrhosis worldwide, alcoholic liver disease (ALD) and some cases of viral hepatitis, develop due to substance use behaviors, and clinicians need to be aware of the evaluation and treatment of addiction disorders. In other liver diseases, the presenting symptoms can be psychiatric in nature, and patients may seek psychiatric care before the correct liver disease diagnosis is known. For all patients with liver disease, as sequelae of end-stage disease develop, associated physiological changes may affect cognition, physical functioning, and medication pharmacokinetics. In this chapter we review the symptoms, sequelae, and psychiatric conditions common to liver diseases. Although we will briefly review the basics of drug metabolism in end-stage liver disease, Chap. 42 Psychopharmacology in Transplant Patients provides a comprehensive overview of psychotropic medications following transplant. Additionally, while Chap. 3 covers the evaluation of transplant candidates in general, here we will briefly address psychotherapeutic issues more commonly encountered by mental health professionals evaluating end-stage liver disease patients undergoing transplant evaluation. The medical/surgical indications for liver transplantation (LT) are further reviewed in Chap. 11. Finally, we review the issues relevant to terminal care management, with consideration for palliative care consultation.

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Specific Common Liver Diseases with Mental Health Disorder Implications

ALD, chronic hepatitis C, and nonalcoholic steatohepatitis are the most common causes of chronic liver disease (CLD) worldwide and the most common indications for LT in the USA [1–6].

Alcoholic Liver Disease

In addition to being a common liver disease and indication for LT, ALD accounts for 48% of all deaths from cirrhosis [7]. ALD represents a continuum of liver pathology caused by excessive alcohol consumption [8] that includes alcoholic steatosis, alcoholic hepatitis, and cirrhosis. Interestingly, a study examining the effects of alcohol on liver disease found that the total lifetime alcohol intake is similar in alcoholic patients who develop liver disease and those who do not develop liver disease [9]. However, among adult females who drink alcohol, an increased number of drinking days was associated with an increased risk of ALD. In addition, females with ALD had a lower overall lifetime alcohol intake than males with ALD, suggesting that females require lower overall alcohol exposure to progress to ALD than do males [9]. Nevertheless, while there is no specified amount of consumed alcohol that predictably results in ALD and while the diagnosis of ALD is not synonymous with a history of alcohol use disorder (AUD) [8, 10], heavy prolonged alcohol use (80 g/day in males or 20 g/d in females) is associated with

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Table 12.1 National Institute on Alcohol Abuse and Alcoholism definition of at-risk drinking levels for developing an AUD

	Men	Women
On any single day	>4 standard drinks[a] or >3–4 units[b]	>3 standard drinks or >2–3 units
Total drinks per week	>14 standard drinks or >21 units	>7 standard drinks or >14 units

Source: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking.
According to NIAAA, only 2 in 100 who drink below these limits have an AUD. However, low risk does not mean "no" risk especially for those with health problems.
[a]A US standard drink equals 0.6 fluid ounces or 14 g of pure alcohol (e.g., a 12 oz. 5% beer or 1.5 oz. of 80 proof liquor)
[b]In the UK, one unit of alcohol is defined as 10 mL (7.9 g of pure alcohol). In other European countries, units differ in size, ranging from 8 to 14 g of pure alcohol

ALD [8, 10, 11]. Indeed, 10–35% of heavy drinkers will develop alcoholic hepatitis, and 10% will go on to develop cirrhosis [12]. Of all patients diagnosed with ALD, 70–95% likely meet criteria for AUD [13–15] (see Table 12.1 for levels of at-risk drinking).

Clearly important to the diagnosis of ALD is the collection of an accurate, detailed alcohol consumption history. Mental health providers may be better suited to the task of asking such detailed questions in a nonjudgmental fashion, avoiding the constraints of patient denial, underreporting, or underestimation of alcohol-related problems by the clinician. Indirect phrasing using simple declarative sentences that invite the patient to agree or disagree can create a less confrontational interview and provide a context for more accurate disclosure [16]. While primary interventions for at-risk drinkers could prevent ALD, once developed, the definitive treatment is complete sustained abstinence, not reduced drinking. Clinicians should work diligently to get patients into addiction treatment (see section on AUDs below). Clinicians should additionally evaluate for and recommend treatment of other common comorbid psychiatric disorders. In a recent study, patients hospitalized for ALD had an increased prevalence of psychiatric diagnoses compared to patients hospitalized for non-ALD, with significantly higher rates of depression, anxiety disorders, adjustment disorders, post-traumatic stress disorder, and personality disorders [7].

Chronic Viral Hepatitis

Hepatitis C (HCV) is responsible for the vast majority of chronic viral hepatitis cases in the USA. The primary route of HCV transmission is intravenous (IV) drug use; once infected, 75–85% of individuals will develop a chronic HCV infection, and 60–70% will progress to CLD [17]. Early detection is key to preventing liver disease as newer extremely effective oral HCV treatments are resulting in high cure rates with shorter treatment times. Ultimately treatment of the underlying drug addiction is needed as cured individuals can become reinfected. Hepatitis B (HBV) is implicated in a small percentage of CLD cases; its incidence decreased significantly following the introduction of the HBV vaccine [18, 19].

Chronic viral hepatitis B and C are associated with a lower health-related quality of life (QOL) as compared to the general population, including in domains of mental health and role limitation due to emotional problems [20, 21]. HCV is able to invade neuronal tissue, and HCV-positive patients have been shown to suffer from neurocognitive deficits, such as impaired concentration, working memory, and visuomotor processing [22, 23]. HCV is associated with an increased risk of psychiatric disorders [22–28], although there is significant variability in prevalence estimates between studies [21–29]. In addition, although many psychiatric diagnoses are associated with increased risk of HCV infection, it is often difficult to determine whether an individual's psychiatric disorder(s) antedated or developed after their HCV infection [27]. In contrast, rates of depression in patients with HBV (4–6.4%) [21, 26, 28] are similar to those of the general population but do tend to increase with disease severity [30, 31]. Individuals with HCV are also more likely to have a history of substance abuse, as compared to the general population and those with HBV. Studies have demonstrated that 51–88% of patients with HCV have a substance abuse history, compared with 10–20% of general population, and an estimated 16% of patients with HBV [11, 23, 32–34]. Similarly, 28–83% of patients with HCV have a history of IV drug use [11, 32, 34, 35], compared to 2.6% of the general population [36].

Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is a growing cause of CLD and hepatocellular carcinoma [3, 4, 6, 37–39]. It encompasses a range of liver pathology, from incidental hepatic steatosis (also called nonalcoholic fatty liver, NAFL) to nonalcoholic steatohepatitis (NASH) [38, 39]. It is estimated that 27–55% of patients with NAFLD also hold a diagnosis of depression [28, 40], and a correlation between generalized anxiety disorder and major depressive disorder and severity of liver histological findings has been demonstrated [40]. Since obesity increases the risk for NAFLD, binge eating disorder and other overeating disorders are also overrepresented in the NAFLD population [41]. The connection between NAFLD and psychiatric disorders is multifactorial and bidirectional in nature. Common mediators of both include alterations in behavioral patterns (decreased activity), eating patterns, level of neuroinflammation and oxidative stress, and lack of access to health care [40, 41]. Many

psychiatric disorders, including depression and psychotic disorders, are associated with poor adherence to medical interventions, and many psychotropic medications carry a risk of weight gain [40, 41]. Whether switching psychotropic medications could help weight reduction without destabilizing the underlying psychiatric disorder would need to be decided by the psychiatric provider.

Treatment guidelines for NAFLD recommend lifestyle changes prior to medication trials [42]. Behavioral therapies including cognitive behavioral therapy (CBT) can be effective in weight loss and improving markers of liver disease [41, 42]. Psychotherapeutic approaches combined with weight loss programs have also been studied, although patients often regain a portion of the weight lost during the intervention [41]. As obesity is a chronic health problem, some level of ongoing support is likely necessary to maintain long-term treatment effects [41]. However, such treatments are unlikely to be provided in the gastroenterologist's clinic. Mental health clinicians may be best suited to evaluating and arranging for such therapies. Collaborative care models are best suited to addressing the comorbid liver and mental health disorders in these complex cases [41]. If psychotropic medications are indicated, the potential risk of psychotropics that promote weight gain should be carefully considered.

Neurocognitive and Neuropsychiatric Manifestations of CLD

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome arising out of declining liver function and/or portosystemic shunting [43]. Patients can present with alteration of consciousness (including stupor or coma), cognitive impairment, confusion/disorientation, affective/emotional dysregulation, psychosis, behavioral disturbances, and physical signs such as asterixis. HE can be episodic or persistent [44]. While overt HE is typically evident on clinical examination, subtle or subclinical HE may require neurocognitive testing to identify it [44] (see Vilstrup et al. [43] for review). While less obvious, subclinical HE can be deleterious to daily self-management tasks such as medication taking or complex tasks such as driving [45]. Mental health clinicians are more likely than other clinicians to use and be able to interpret basic neurocognitive testing. Commonly used HE screening instruments, such as the trail making tests, examine processing speed, concentration, and attention. To overcome time and provider barriers, a recent study piloted the use of neurocognitive testing through a self-scoring smart phone app using the Stroop test [46]. Eventually such apps may allow clinicians and patients to monitor minimal HE symptoms in real time, perhaps even remotely [46].

While high blood ammonia levels alone do not add any diagnostic, staging, or prognostic value in HE patients [43], they can aid in a questionable diagnosis, and if ammonia-lowering drugs are being used, repeated measurements of ammonia may be helpful to follow treatment efficacy [43]. Malnutrition is implicated in the development of HE, and the amelioration of nutritional status is an effective goal to decrease the prevalence of cognitive impairment in these patients [47]. As with other types of delirium, the use of antipsychotic medications may aid in severe symptom relief but not in treating the underlying disorder. Also see Chap. 11 for additional discussion of HE.

Alcohol Related Cognitive Impairment in CLD

Cognitive impairment in individuals with AUD and CLD is often multifactorial, reflecting a combination of alcohol neurotoxicity, nutritional derangements, and HE. In general, malnutrition is a common feature of CLD resulting from inadequate intake, impaired absorption, and altered metabolism that is often associated with neuropsychiatric complications as well as outcomes following LT [47]. Alcohol-related dementia encompasses clinical entities such as Wernicke-Korsakoff syndrome. Heavy alcohol use is associated with nutritional deficiencies including thiamine deficiency [48, 49]. Thiamine deficiency can result in Wernicke's encephalopathy, classically described as a triad of symptoms including oculomotor findings, cerebellar dysfunction, and altered mental status, but in reality presenting more subtly [50]. If untreated, Wernicke's encephalopathy can progress to Korsakoff's dementia, a syndrome of permanent cognitive impairment characterized by the inability to create new memories [49].

Wilson's Disease

Wilson's disease (WD) is an autosomal recessive disorder of copper transport resulting in the inappropriate deposition of copper in multiple organs, including the liver, eyes, and brain. Copper deposition in the liver parenchyma leads to an increased risk of HE. Copper deposition in the brain leads to direct damage to neuronal tissue and a broad variety of psychiatric and neurological symptoms. Neurological and psychiatric symptoms in WD typically begin in the second or third decade. Psychiatric symptoms include affective disorders, changes in personality/behavior, cognitive dysfunction, and psychotic symptoms [51–53]. Psychiatric or cognitive symptoms can antedate the diagnosis of WD, and almost half of patients will first present with neurological or psychiatric symptoms: 30–60% will have depressive symptoms, 18–30% will have bipolar illness, 46–71% will have personality

changes, approximately 25% will have cognitive impairment, and 4–16% will engage in suicidal behaviors during the course of the disease [54, 55]. Patients can also present with extrapyramidal symptoms, as the caudate and putamen are the most common areas of the brain to be affected [52, 54]. Typically, the presence of the ocular findings of Kayser-Fleischer rings and serum ceruloplasmin <10 mg/dl are sufficient to establish the diagnosis [56]. In general, treatment options include the copper chelators, which must be taken lifelong. LT is a rare consideration in WD since the condition usually responds to medical therapy.

Porphyrias

Porphyrias are inherited or acquired disorders of heme production. Five of the eight classes of porphyrias result in the accumulation of heme precursors in the liver. Four of these five have prominent neuropsychiatric symptoms. Porphyrias present as discrete, acute "attacks" of psychiatric and physical symptoms. Common psychiatric symptoms include anxiety, depression, psychosis, delirium, and catatonia, and common physical symptoms include abdominal pain, constipation, vomiting, peripheral neuropathy, and bullous or erythematous rash. Of note, psychiatric symptoms can persist after the resolution of other symptoms associated with the acute episode [52, 57–59]. Porphyrias can be easily misdiagnosed as conversion disorders, primary psychotic disorders, personality disorders, primary mood disorders, and a chronic fatigue disorder [57]. Triggers for episodes can include stress, dieting/eating disorders, sun (if cutaneous), cocaine, certain alcoholic drinks (whisky and red wine), and a host of medications, many of which are psychotropics (http://www.drugs-porphyria.org/) [52, 57, 58]. Acute attacks of porphyria can be confirmed by demonstration of a markedly increased urinary porphobilinogen and aminolevulinic acid levels. If severe, LT can be pursued although this does not necessarily correct the underlying etiology [58].

Common Mental Health Disorders in Liver Disease

Depression

Depressive disorders are among the most prevalent mental health disorders in the general population, and depression can influence a patient's course and symptomatology in the presence of liver disease. While the WHO estimates 19% of US adults will experience depression in their lifetime [60], lifetime rates of depression were 35% in one study of patients with advanced liver disease, using a diagnostic structured lifetime interview [61]. The mechanisms underlying the association between liver disease and depression are not fully understood. A study found that after adjusting for confounding variables including age, sex, ethnicity, marital status, smoking status, and amount of alcohol consumed, patients with liver disease have a risk of developing depression that is 2.2 times that of individuals without liver disease [62]. There is some evidence to suggest that the etiology of the liver disease may explain the development of depressive symptoms. For example, in patients with HCV, the virus impacts dopaminergic and serotonergic neurotransmission [63]. There is also a psychological component to the etiology of depressive symptoms in HCV patients due to stigma associated with the diagnosis of a chronic infectious disease [25]. In addition to higher rates of depression diagnoses, liver disease is associated with a threefold increase in risk of a suicide attempt compared to those without liver disease [62]. As is seen in other chronic disease states, liver disease is associated with decreased overall health-related QOL [62]. HE is a relatively common finding in liver disease patients and can manifest as changes in mood, personality, cognition, and alertness as well as psychomotor changes. While there is overlap in the symptomatology of HE and major depressive disorder, these represent two distinct syndromes [63]. It is important to screen patients for depressive symptoms, as untreated depressive symptoms contribute to worse treatment outcomes throughout the course of CLD.

Alcohol and Substance Use Disorders in Liver Disease Patients

Alcohol As noted above, substance use disorders (SUDs) are commonly associated with alcoholic and viral liver disease. Perhaps due to the prevalence of ALD, the bulk of the literature addresses the co-occurrence of ALD and AUD. The definitive treatment for AUD and ALD is sustained abstinence—not reduced drinking—and this information should be made very clear so that patients do not "tailor" advice to suit their beliefs or denial [64]. Nevertheless, simply educating on the dangers of continued alcohol use, while necessary, is insufficient to produce sustained abstinence. Additionally, brief interventions in this population would likely not be effective. A meta-analysis of behavioral interventions in primary care settings found no evidence for the use of brief interventions for patients with AUD [65]. While ALD patients may seek treatment for their ALD symptoms, they often do not consider that they have any need for addiction counseling. In fact, study of ALD patients being evaluated for LT found these patients did not perceive themselves to have an addiction disorder, were more preoccupied with their medical treatments, and were reluctant or resistant to consider addiction counseling [66]. Motivational interviewing (MI) can be a helpful strategy to overcome ambivalence

and resistance to seeking treatment [66, 67] and is described in more detail in Chap. 43. Clinicians should additionally evaluate carefully for comorbid psychiatric disorders as an estimated 36% of patients with AUD will also have a depressive disorder, 12% will have an anxiety disorder, and 25% will abuse substances other than alcohol [14].

Clinicians should work diligently to get patients into addiction treatment or dual diagnosis addiction treatment if indicated. Follow-up to ensure patients are participating in treatment may be necessary. Unfortunately, patients diagnosed with ALD often continue to consume alcohol and, even after a period of pre-transplant sobriety, can relapse following LT [12, 68–73]. The intensity of treatment will depend on the severity of the AUD, likelihood of requiring detoxification, and type and intensity of prior rehabilitation attempts. For patients with ALD, motivational enhancement therapy (MET), CBT, MI, supportive therapy, and psychoeducation, either alone or in combination, have been used to reduce alcohol consumption [74, 75]. Weinrieb et al. [75] demonstrated a reduction in number of drinking days and total number of drinks for patients receiving MET, relative to a treatment as usual group who were referred to local resources. Other groups have achieved increased rates of abstinence and reduced rates of recidivism but have done so only when combining psychotherapy with medical treatment [74]. A multidisciplinary team approach in the gastroenterologist's office where ALD patients may initially seek care could be the most effective means to provide for the comprehensive care needs of ALD-AUD patients. In one center, embedding psychiatry and social work in a gastroenterology service resulted in a marked improvement in the accuracy of drinking histories obtained, ability to provide medical and psychiatric care at one appointment, and referral for addiction treatment and communication between patients, their families, and their clinicians [76]. Importantly, monitoring of alcohol abstinence by regular interviewing and random biological marker testing are necessary as both methods independently contribute to the identification of ongoing use [77].

Medications to reduce the positive effects of and cravings for alcohol and thereby reduce alcohol consumption can be used to augment psychotherapeutic treatments. Acamprosate may be a potential pharmacological treatment but is renally excreted, and the dose may require reduction if hepatorenal syndrome exists. While naltrexone could also be considered in stable cirrhosis, it is contraindicated in acute hepatitis or liver failure. In particular, naltrexone is not advised for patients with serum aminotransferase levels greater than 3–5 times the normal limit [78].

Tobacco Patients with AUD or ALD also have an increased prevalence of co-occurring tobacco use compared to others [7, 79]. Like alcohol use, tobacco use is also harmful to liver health. There is increasing evidence that cigarette smoking may negatively affect the incidence, severity, and clinical course of many types of CLDs, perhaps due in part to its promotion of fibrogenesis [80]. Cigarette smoking predicts reduced survival time in patients with hepatocellular carcinoma with concurrent HCV and HBV [81]. Thus, in addition to other potential health benefits, promoting and assisting patients in smoking cessation for liver health are strongly recommended. In addition to pharmacological therapies such as nicotine replacement therapy, varenicline or bupropion, there are a number of online self-help programs for smoking cessation (e.g., American Lung Association's Freedom From Smoking program, www.freedomfromsmoking.org).

Opioid Maintenance Therapy Opioid use disorders are common in patients with viral hepatitis/cirrhosis. Opioid maintenance therapy (OMT) (e.g., methadone or buprenorphine) can be an effective and long-term strategy for achieving stability for those with an opioid addiction. However, when stably abstinent methadone-maintained patients are tapered and discontinued from their methadone, relapse rates typically exceed 80% [67], and similar relapse rates exceeding 50% are seen in those who involuntarily discontinue buprenorphine [82]. Therefore, while dose adjustments may be required to accommodate deteriorating hepatic functioning and/or development of HE, the standard of care would be to continue OMT until the patient and treating addiction clinician determine the proper time to taper and discontinue treatment. A mandate to taper off OMT as prerequisite for LT or other medical treatments (e.g., HCV treatment) is not recommended and puts the patient at risk of relapse during a highly stressful time of medical illness. A 2000 survey of LT programs' approaches to OMT showed 56% of programs accepted patients on methadone maintenance, but 32% of programs required that patients discontinue methadone use [83]. Although attitudes may have since changed toward OMT LT candidates, mental health clinicians may need to educate the LT team about the appropriateness of continuing OMT.

Marijuana Aside from the health risks of smoked marijuana (e.g., respiratory inflammation and infection), there is equivocal evidence that cannabinoids directly affect the progression of liver disease. This is likely related to the fact that cannabinoid receptors produce complimentary effects on the liver, some exerting profibrogenic and pro-inflammatory effects, while others inhibit or even reverse liver fibrogenesis [84, 85]. Thus, while some studies of HCV and NAFLD patients demonstrate worsening of liver disease in those who used cannabis [86–88], others do not find such an association

[89, 90]. However, in healthy individuals, the use of exogenous cannabinoids is well known to impair cognition. In addition to these known effects, for those with liver disease, one subset of cannabinoid receptors may worsen symptoms of HE [91].

Although patients may assert a need to use cannabis for medicinal reasons, there is no medical indication for smoked marijuana, and no other medicine is smoked [92, 93]. Additionally, studies demonstrating the beneficial effects of cannabinoids for various medical illnesses and symptoms were conducted using pharmaceutical agents approved by the FDA (e.g., dronabinol and nabilone), not smoked or eaten cannabis [92, 93]. If use of marijuana is medically indicated, then rather than relying on medicinal marijuana which has no regulatory oversight for quality and purity [92, 93], using a prescribed pharmaceutical would be safer, especially in medically ill individuals. However, until the exact effects of cannabinoids on the progression of liver disease are fully understood, the use or prescription of any cannabinoid in patients with liver disease should be done with significant caution.

Pain in Cirrhosis

Pain is commonly reported in patients with cirrhosis, with recent studies suggesting upward of 80% of patients experiencing pain [94–96] and a similarly high percentage, 75% in one study, experiencing chronic pain-related disability [94]. Chronic pain in cirrhosis is associated with the disease stage and increases in prevalence as cirrhosis progresses [97, 98]. Disability related to pain is additionally associated with the severity of pain, psychiatric symptoms, prescription opioid use, and elevated inflammatory markers [94]. While patients with cirrhosis may experience non-liver-related pain, the high prevalence of abdominal pain is likely associated with liver disease-related factors including ascites, hepatic capsular distension, and splenomegaly [94, 99, 100]. Patients with ascites and abdominal pain require evaluation to rule out spontaneous bacterial peritonitis. HCV has been associated with irritable bowel symptoms and visceral hyperalgesia, which may further contribute to the prevalence of abdominal pain complaints in this population [101]. Furthermore, one of the key elements of cirrhosis pathophysiology is systemic inflammation with associated increased production of pro-inflammatory cytokines [102], the same cytokines associated with pain.

Despite the awareness of the opioid epidemic and increasingly strict regulations for the prescription of opioid analgesics, the use of prescribed opioids in this population is high. Prescription prevalence estimates of opioids are 24–54% for patients with cirrhosis [100]. Although the use of opioid analgesics is likely partly due to poor alternatives for the treatment of moderate to severe pain, cirrhosis is a risk factor for opioid-related complications (e.g., respiratory and central nervous system depression). Additionally, opioids can contribute to symptoms of HE and further slow intestinal motility, diminishing the efficacy of ammonia-reducing medications. Opioid use predicts hospital readmissions in cirrhosis [103] and, in a study of cirrhotic patients who underwent LT, the use of opioids before and after LT was associated with poor patient and graft survival [104]. Whether opioid use itself or comorbidities associated with opioid use are driving mortality requires further investigation. Additionally, only a minority of LT recipients who use opioids have been found able to taper and discontinue opioid analgesics following transplant, suggesting that perhaps a large proportion of patients had pain unrelated to liver disease [104].

While any cirrhotic patient must be carefully managed to assure they do not become addicted to opioids or develop complications, patients with prior opioid and other SUDs present an especially complicated pain treatment dilemma to clinicians. These patients can have legitimate pain but may find it difficult to obtain treatment in a pain clinic. Those in opioid agonist therapy programs may not be eligible for or may find it difficult to obtain additional pain medication. Patients with such complex needs may be best managed by pain specialists in chronic pain clinics where oversight and monitoring for abuse behaviors are provided. Liver disease specialists should be involved in collaborative care to provide advice on the severity of liver disease and potential issues with associated liver disease complications. The potentially negative effects of opioid use and the high prevalence of psychiatric symptoms and possible inflammation in cirrhosis suggest other pharmacological treatment targets for pain management in these patients. Pain clinics may be able to provide a range of therapies in addition to pharmacological management.

Pharmacotherapy in the Context of Liver Disease

As the liver plays a critical role in the metabolism and clearance of most medications, liver disease will impact most aspects of drug pharmacokinetics. Depending on the severity of liver disease and its associated sequela, pharmacokinetic processes from absorption to metabolism, protein binding, and volume of distribution can be altered. The loss of functional liver tissue with subsequent loss of hepatic enzymes (cytochrome P450 and conjugation/glucuronidation enzymes) will cause a reduction in intrinsic hepatic clearance and loss of biliary excretion. Loss of functional tissue can also reduce the production of binding proteins resulting in less drug binding and higher levels of free drug. Portal

hypertension with portosystemic shunting of blood flow will reduce first pass metabolism, while vascular congestion can slow drug absorption. Development of ascites and peripheral edema can alter volume of drug distribution and, depending on whether a drug is less protein-bound or is water-soluble, can lower drug levels by increasing the volume of distribution. Finally, liver disease can be associated with renal insufficiency (e.g., hepatorenal syndrome), with associated reduced glomerular filtration and alteration in fluid status. However, while disease-related changes in metabolism and elimination can alter drug pharmacokinetics in complex and significant ways, compensatory mechanisms can offset clinically significant effects on free drug levels. For example, while the loss of hepatic enzymes reduces metabolism leading to higher drug levels, a reduction in binding proteins results in greater amount of free drug available for metabolism, thus lowering drug levels [105, 106].

Unlike the kidneys where a measure of elimination (creatinine clearance) can guide drug dosing, in liver disease, perhaps due to the multiplicity of the liver's contribution to overall pharmacokinetics, there is no precise measure of reduced intrinsic liver metabolism. Clinicians should consider the severity of the liver disease, the therapeutic drug level range, and potential for toxicity, as well as the presence of HE. A strategy of beginning with lower initial doses and possibly longer dosing intervals and then gradually titrating the dose may be the safest. As liver functioning deteriorates over time, drug doses and dosing schedules should be reevaluated. If HE is present, avoiding drugs that can worsen encephalopathy (i.e. sedatives, tranquilizers, anticholinergic medications) is recommended. Drugs metabolized into active metabolites (e.g., amitriptyline, venlafaxine), extended or slow release drug formulations, or those with long half-lives (e.g., fluoxetine) may be difficult to adjust or predict clinical response/toxicity and should be used with caution. Drugs distributed in total body water (e.g., lithium) can be difficult to manage with concurrent use of diuretics or therapeutic paracentesis that can dramatically alter the volume of distribution, potentially making previously therapeutic drug levels toxic. Serotonin reuptake inhibitors are the most commonly prescribed class of antidepressants for patients with liver disease [63]. However, concerns over increased risk for bleeding make them less desirable, especially if other antiplatelet medications or nonsteroidal anti-inflammatory drugs are concurrently prescribed [63]. Few psychotropic drugs are potentially toxic to the liver. While most of these reactions are idiosyncratic, there is some evidence that patients with existing liver disease are at heightened risk of developing toxicity (e.g., duloxetine) [107, 108]. Additionally, for patients with existing loss of hepatic function, additional tissue loss may not be well tolerated, and existing alterations in liver enzymes may mask a developing drug problem, making monitoring for toxicity difficult. Nevertheless, severe drug-induced liver injury is usually reversible and rarely results in fatality if the drug is discontinued.

Psychotherapeutic Issues in CLD

Patients with CLD face a slow decline in both physical and cognitive function, as their liver function slowly declines and ammonia levels rise [52, 109, 110]. For patients awaiting LT, this gradual decline is overlaid by the daily uncertainty of whether or not a matching organ is going to be found; this uncertainty is further compounded by the fear that the patient may become ineligible for an organ due to some unforeseen future illness or catastrophe [52, 109, 111, 112]. Patients are also not guaranteed resolution of symptoms following transplant and face an arduous postoperative course of immunosuppressive regimens and surveillance of transplant function [111]. These stressors are often magnified by comorbid psychiatric disorders including depression, anxiety, and substance use [109, 112–115].

Several groups have developed psychotherapeutic approaches to help patients with CLD improve their ability to effectively manage these challenges [109, 116–120]. As in the general population, therapies involving both pharmacological and psychotherapeutic approaches are likely most effective [115, 121]. However, for patients who are medically fragile, on an extensive number of medications, and who will hopefully be undergoing LT with immunosuppressive regimens, special care must be taken to avoid drug-drug interactions and drug-induced side effects that could further worsen the patient's liver function or symptoms [122]. As a result, psychotherapeutic approaches can be acceptable and safer alternatives to drug-based therapies [115, 123]. Approaches that have been tested specifically in CLD patients include CBT [118], bibliotherapy, scheduled telephone-based contacts with patients [109], mindfulness-based stress reduction (MBSR) [116], and multidisciplinary team approaches [119].

For example, Sharif et al. [120] demonstrated improvement in physical and psychological measures in patients with CLD after a series of four 90-minute sessions that combined education, relaxation training, and coping strategies, relative to care as usual. Evon et al. [117] described an integrated care approach for patients with chronic hepatitis C that combined counseling and case management and increased the patients' eligibility for interferon-based treatment relative to standard of care. Neri et al. [119] used multidisciplinary teams with psychotherapy to reduce the incidence of depression and the number of antidepressant and benzodiazepine prescriptions required for patients receiving interferon and ribavirin therapy, when compared to care as usual.

While many interventions resulted in improved patient outcomes over time or relative to care as usual, these gains

were at times reduced when compared to an active comparator control group. For example, Bailey et al. [109] compared patients with CLD awaiting LT who either received a telephone-based psychotherapeutic intervention (CBT-based coping skills training and uncertainty in illness theory-based symptom management) or participated in an active control condition (telephone-based education regarding liver disease and symptoms management). Although neither group showed appreciable change in depression, anxiety, QOL, or illness uncertainty, both groups appeared to improve in perceived self-efficacy for managing liver disease symptoms, with no significance difference in degree of improvement.

Specific Coping Challenges During the Pre-transplant Period

Waiting Period

After acceptance onto the LT wait list, patients typically experience improved hopefulness and even elation. However, the realities of the wait for a scarce organ, the deteriorating health, and the need to be at the top of the list based on medical urgency in order to get the next available organ mean many LT candidates wait for years, and 10–15% each year do not survive to transplant. Many patients and families feel that the waiting period is the most psychologically stressful period of transplantation, and mental health providers should be aware of the stresses unique to this phase of the transplant process. In addition to the use of traditional psychotherapies to alleviate distress, therapeutic interventions based on transplant specific themes have been developed to help patients and families weather the uncertainty of the waiting period. In one example, a study of patients wait-listed for LT and their caregivers tested an intervention focused on uncertainty management, improvement in QOL, and caregiver support [109]. In this and other studies, the use of telephone-delivered therapy sessions aided in overcoming logistical issues for chronically ill patients and their caregivers (e.g., debility, transportation, time off work, traveling regularly to a clinic for therapy).

Maintaining Hope While Preparing for Eventualities

Patients and families often focus on the goal of obtaining a liver transplant, yet should consider preparation for the possibility that a donor organ will not come in time. As the patient's health deteriorates, they will become increasingly dependent on caregivers and may experience medical setbacks or hospitalizations. Patients may also develop complications making them ineligible for transplantation (e.g., stroke or metastasizing hepatocellular carcinoma), and both patient and family should be made aware that their eligibility might change over time for many reasons. Discussions about end-of-life directives or palliative care consultation are not commonly undertaken for LT candidates [124, 125], yet the overlap in the intensity of the patient's medical care, the nature of the day-to-day clinical problems, and the intensity of the commitment to patients and their families makes consideration of engaging palliative care services a natural collaboration. Patients, families, and even the transplant team may be reluctant to consider such input, believing it is a sign of giving up hope or abandoning the goal of transplantation. However, palliative care input can assist in providing improvement in QOL in parallel with the intent to go forward with transplantation. Early engagement of palliative care services allows patients an opportunity to participate in treatment planning while they are still able. Two intervention studies using palliative care services for LT candidates demonstrated improved continuity of care and treatment planning, increased goals-of-care discussions, increased do-not-resuscitate status, reduced symptom burden, and improved depressive symptoms [126, 127]. Neither study found an increase in mortality rate compared to patients not in the interventions. Please see Chap. 47 for further discussion of palliative care in transplant patients.

Conclusions

Mental health-care professionals caring for patients with liver disease should be aware of the high prevalence of psychiatric disorders in this population, especially SUDs. For SUDs in particular, the complete abstinence from alcohol or drugs is the definitive strategy for the stabilization and ultimate treatment of the underlying liver disease. Mental health professionals serve a key role in identifying these disorders and arranging adequate addiction treatment.

For some types of liver diseases, the presenting symptoms may appear as primary psychiatric disorders, and patients may initially seek psychiatric help for their problems. Careful consideration of the differential diagnosis, with possible input from additional medical specialists, may be needed to identify the underlying liver disease.

Beyond traditional psychotherapies and addiction counseling, the psychiatric treatment of patients with liver disease may necessitate attention to disease-specific issues. Patients with CLD often need to adjust to being chronically ill, experiencing decrements in QOL, and enduring limitations in their daily functioning. For those facing LT, special challenges exist during the pre-transplant wait period, as health is typically deteriorating and the wait may be long. Strategies to address patients' and caregivers' particular needs during this period are required.

Pharmacotherapy is also complex in patients with liver disease. As the liver is responsible for the metabolism of most drugs, medication prescription requires careful

consideration as liver disease progresses, with consideration of specific drug metabolism, severity of liver disease and potential for drug side effects. Additionally complex is the high prevalence of chronic pain disorders in this population. For patients with cirrhosis, strategies to minimize opioid analgesics would be best. The combination of potential ill effects of opioids coupled with the contributions to pain of psychiatric symptoms and possible systemic inflammation in cirrhosis suggest alternative treatment strategies targeting these issues may be beneficial. HE should also be considered with the use of drug therapies. Subclinical HE may not always be identifiable on clinical exam, and mental health clinicians may need to consider whether formal neurocognitive testing is required.

The traditional sub-specialization model of medicine lends to providers focusing on a patient's specific issues relative to their clinical expertise. In this model, each clinician may fashion a treatment plan in isolation of the patient's other comorbid yet interrelated disorders. However, many of these complex and comorbid disorders cannot be fully addressed in isolation. An interdisciplinary team approach for overall coordination of care would be the best strategy. As outlined above, depending on the specific needs of the individual patient, coordination of care may require simultaneous input from mental health providers, gastroenterologist/hepatologists, addiction and pain management specialists, and palliative care. In other comorbid chronic medical and mental health diseases, the use of a collaborative care team approach compared to usual care demonstrated overall better medical and mental health outcomes as well as greater patient satisfaction [128]. Additionally, as comorbid liver and psychiatric diseases are often chronic conditions, longitudinal care management will likely be required. By virtue of their comprehensive assessment of patient histories, mental health providers may be best suited to recognize the totality of the CLD patients' needs and recommend—if not facilitate—a more comprehensive approach to care.

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