The Liver-Impaired Patient

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H. Leigh and J. Streltzer (eds.), *Handbook of Consultation-Liaison Psychiatry*,
DOI 10.1007/978-3-319-11005-9_30, © Hoyle Leigh & Jon Streltzer 2015

30.1 Introduction

Among all organs in the human body, the liver is the largest and carries out the greatest number of functions. The liver's important and multiple activities impact all body systems, including the nervous system. The relationship between the liver and the brain has been known for centuries (Frerichs 1860; Lewis and Howdle 2003; Tarter et al. 1989; Wilson 1912). Patients with hepatic dysfunction frequently experience neuropsychiatric syndromes, of which the most well known is hepatic encephalopathy (Ferenci et al 2002).

Chronic liver disease in the USA is a significant cause of morbidity and mortality for adults. In 2010, cirrhosis and chronic liver disease accounted for the 12th leading cause of all deaths in the USA (Murphy et al. 2013). With the increase in incidence of diagnosed nonalcoholic fatty liver disease and the epidemic of chronic hepatitis C (CHCV) infection, the number of chronic liver diseased adults in the USA is expected to escalate in the next decades. There are approximately 3.9 million cases (2 % of the US population) of HCV infection in the USA, of whom 85 % are expected to develop CHCV. Alcoholic liver disease (ALD) may occur independently, though ALD is often comorbid with CHCV, resulting in a more rapid progression to cirrhosis. Nonalcoholic fatty liver disease, which may be the most common liver disease in the USA (accounting for 5 % of the US population), has a high prevalence in the obese, type 2 diabetic population, and can lead to nonalcoholic steatohepatitis (NASH) (Farrell 2003). There are also a number of less common diseases which affect the liver including Wilson's disease, mitochondrial hepatopathies, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), porphyria, hemochromatosis, and chronic hepatitis B liver disease.

Individuals with psychiatric and substance-use disorders have a much greater risk of developing chronic liver disease, including CHCV and fatty liver disease, than the rest of the population. Hepatitis C has been termed the "psychiatric epidemic." It is estimated that 20 % of severely mentally ill patients have HCV, which is more than ten times the prevalence in the general US population. Substance-use disordered individuals are at even higher risk (40 % and higher) for CHCV from intravenous or intranasal drug abuse, and they often have comorbid alcoholic liver disease. Further, psychiatric patients, due to factors of lifestyle and medication exposure, often develop metabolic syndrome in adulthood, which can lead to nonalcoholic fatty liver disease. Because liver disease is prevalent among psychiatric patients, and since hepatic dysfunction itself creates neuropsychiatric symptoms, psychiatrists in the twenty-first century must be equipped to diagnose and treat the liver-impaired patient.

30.1.1 Neuropsychiatric Symptoms in Chronic (Mild, Noncirrhotic) Liver Disease

30.1.1.1 Neuropsychiatric Symptoms of Mild (Noncirrhotic) Chronic Liver Disease, All Etiologies

In patients with hepatic dysfunction which has progressed to cirrhosis and end-stage liver disease, neuropsychological impairment has been well studied (Lewis and Howdle 2003). However, in patients with mild chronic liver disease who may have two decades or more before developing complications of cirrhosis, neuropsychiatric symptoms including cognitive impairment have only recently been evaluated. Now neuropsychological abnormalities have been described from mild liver disease to end-stage liver disease and the spectrum of symptoms has expanded so that the full range is from subtle changes in concentration and attention to the severe impairment of coma and death due to cerebral edema. The level of neurocognitive impairment seems to correlate directly with the degree of liver pathology (Hilsabeck 2003). The neuropsychiatric abnormalities in chronic liver disease include (1) cognitive impairment, (2) fatigue, and (3) depression and anxiety.

30.2 Cognitive Impairment

Cognitive impairment in liver disease ranges from mild cognitive changes to overt hepatic encephalopathy (Collie 2005; Lewis and Howdle

2003). Although extensive serial studies of cognitive decline in liver dysfunction of all types have not been done, evidence to date suggests that concentration abilities and complex attention are affected earlier in the liver disease process, while problems with psychomotor speed, learning, and mental flexibility occur later, in more diseased patients, and verbal skills are less impaired (Hilsabeck 2003).

The varieties of liver disease in which cognitive dysfunction has been documented have expanded to include other liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic liver disease, and Wilson's disease (Collie 2005). Impaired performances have been reported in up to 50 % of noncirrhotic patients (Hilsabeck 2003). Most of the studies to date have compared liver pathology with neuropsychiatric dysfunction without specifying the etiology of the liver disorder, and there are few comparative studies on neuropsychiatric differences among these distinct diseases (Collie 2005). Individuals who are affected cannot perform driving, household, and job duties as accurately as before their liver disease, and often make disability claims (Hilsabeck et al 2003).

There is growing evidence of neuroinvasion of the HCV virus which either directly or indirectly causes the cognitive deficits in this group of patients. In a recent study of 201 CHCV patients with advanced fibrosis, one-third showed evidence on neuropsychological testing of a mild, nonfocal processing deficit (Fontana et al. 2005). Using proton magnetic resonance spectroscopy (MRS), Forton et al. (2002) detected cerebral metabolite abnormalities in the white matter and basal ganglia of HCV patients with mild liver disease. These abnormalities were not evidenced in chronic hepatitis B patients or healthy controls. The same researchers later found that the HCV patients were more impaired on cognitive tasks than those who had cleared HCV and healthy controls, with the most notable differences being in measures of concentration and information processing speed. The most impaired patients had the greatest neuroimaging abnormalities, which supports a cerebral effect of the HCV virus associated with neurocognitive deficits. Depression, fatigue, and intravenous drug use history could not account for the differences in cognitive functioning (Forton et al 2005).

30.2.1 Assessment and Treatment

Cognitive dysfunction in noncirrhotic liver disease has been measured by neuropsychological tests which can assess attention, motor ability, learning, and memory, and assist in the evaluation of an individual's functional capacity. Objective testing is helpful for clinical assessments because the patient's self-assessment often does not correlate with the measured abilities or deficits. Such a battery might include the Repeatable Battery for the Assessment of Neuropsychological Status, the Rey Complex Figure Test, Digit Cancellation, Trail Making Test, Symbol Digit Modalities Test and the Number Connection Test. Providing education about neuropsychiatric test results to the patient and family is recommended. The natural history of cognitive dysfunction in liver disease is unknown and there are no well-controlled studies of specific treatments for this dysfunction, apart from treatment of the underlying liver disease, including hepatitis C.

30.3 Fatigue

Fatigue, which may or may not correlate with neurocognitive dysfunction, has also been well documented in chronic liver disease patients (Wessely and Pariante 2002). From a review of the literature, Wessely and Pariante (2002) concluded that there is no compelling epidemiological evidence that fatigue and depression are specific to HCV liver disease per se, but instead may be simply a correlation of chronic liver disease of any type. These reviewers argued that fatigue (and depression) are associated with HCV simply because the HCV patients have the same risk for metabolic and mood disorders, demographics, and lack of exercise, as for patients with other physical illnesses.

In two studies, fatigue was not related to neurocognitive dysfunction, as measured by cognitive tests or by electrophysiologic measurement of P300 event related potentials (Hilsabeck 2003; Kramer et al. 2002). In 2005, Kramer et al. emphasized that fatigue severity and age correlated with the measured health-related quality of life, whereas neurocognitive dysfunction or hepatic function did not, and reported the need for effective therapy to reduce the burden of fatigue in HCV patients.

30.3.1 Assessment and Treatment

Fatigue in chronic disease patients, including hepatitis C, has been measured by the Fatigue Severity Scale, the Fatigue Impact Scale and the Brief Fatigue Inventory. The serotonin antagonist, odansetron, at 4 mg twice a day for a month, significantly relieved fatigue symptoms in chronic hepatitis C patients in a randomized, placebo-controlled, double-blind trial. Another medication, modafinil, which has been approved for narcolepsy, has shown reduction in symptoms of fatigue and depression for HIV-positive patients in an open label study and has been used clinically for chronic liver disease patients. Finally, escitalopram, a serotonin reuptake inhibitor, was reported to improve measures of both fatigue and pain in hepatitis C patients.

30.4 Depression and Anxiety

Patients with chronic liver disease experience mild levels of depression and anxiety regardless of hepatic disease etiology, although hepatitis C patients are the most studied. In one study of affective disorders in chronic liver disease, the present of a history of intravenous drug abuse did not affect levels of anxiety or depression. However, depression and anxiety were more prevalent in those with a history of both psychiatric disorders and drug abuse (Hilsabeck and Malek-Ahmadi 2004).

30.4.1 Pathogenesis

The pathogenesis of affective symptoms in chronic liver disease is unclear. Apparently there is no association between the severity of liver disease and depression or anxiety levels (Forton et al 2005). Certainly many patients with hepatitis C have comorbid psychiatric disorders and substance use disorders which may be the sole etiology of the affective symptoms.

30.4.2 Assessment and Treatment

A variety of antidepressants have been used to treat depression in HCV patients. Based on a recent review, caution should be used in prescribing selective serotonin reuptake inhibitors for patients with severe liver disease (cirrhosis, portal hypertension, or liver failure), in combination with aspirin or nonsteroidal anti-inflammatory drugs because of the increased risk of hemorrhage.

30.5 Chronic Diseases of the Liver

30.5.1 Hepatitis C

Hepatitis C virus (HCV) is a single-stranded, positive-sense, enveloped ribonucleic (RNA) virus of the Flaviviridae family, which includes the West Nile virus and the Japanese encephalitis virus. HCV has six major genotypes; genotype 1 accounts for about 75 % of US cases. The hypervariable mutations in the viral envelope protein produce vast quasispecies rapidly, allowing the virus to avoid the host immune response (Crone 2006).

The virus is transmitted primarily by parenteral exposure to infected blood, such as blood transfusions, hemodialysis, or injections with infected needles. In the USA, the major risk of contracting the virus is through intravenous drug use; also intranasal cocaine users, tattoo recipients, individuals who received dental care in a third world, and health care workers who suffer

accidental needle sticks are at risk. In the past, hemodialysis and blood transfusion recipients prior to 1992 were at risk (Crone et al 2006; Bonkovsky and Mehta 2001).

About four million Americans are infected with hepatitis C virus. Although the incidence of acute cases has dropped, there are more chronic cases being detected each year. There are high rates of chronic HCV infection among individuals in the correctional system, as well as for those with psychiatric and substance use disorders (Hensley and Withers 2003). For example, 40 % of 360 male patients seeking substance abuse treatment were HCV antibody positive (Withers 2003). Of 134 patients referred for HCV therapy in an outpatient medical setting, 71 % had a psychiatric disorder and 96 % a substance-use disorder; 70 % were dually diagnosed. In this study, point prevalences for psychiatric disorders were affective, 42 %; anxiety, 37 %; and psychotic, 7 % (Hensley and Withers 2003).

Of infected patients, 85 % develop a chronic disease. This high rate of chronic viral persistence results from both weak host T cell responsiveness and specific viral mechanisms of immune escape. Spontaneous HCV viral clearance is negatively associated with human immunodeficiency virus (HIV) coinfection and alcohol use disorders, and positively associated with hepatitis B (HBV) coinfection and not associated with race. Both acute and chronic hepatitis C are asymptomatic in most patients. However, the disease is slowly, chronically progressive and in about 20 % of HCV patients cirrhosis evolves in 20 years; and of these 20 % develop hepatocellular carcinoma. The considerable variability of end organ damage (fibrosis to cirrhosis) in individuals may be due to host genetic polymorphisms in genes governing the immune response and fibrosis pathways in addition to viral pathogenicity factors. The virus is hepatotropic but can also replicate in leucocytes, including monocytes and macrophages. There are also a number of extrahepatic manifestations, including mixed cryoglobulinemia with leukoclastic vasculitis and porphyria cutanea tarda (Bonkovsky and Mehta 2001). Factors which worsen the progression of HCV liver disease include coinfection with HIV or HBV, alcohol abuse, fatty liver, and iron overload (Crone et al 2006).

Fatigue, depression, anxiety, and cognitive dysfunction are the most commonly reported symptom in CHCV patients (Hilsabeck and Malek-Ahmadi 2004). In fact, fatigue is considered a hallmark symptom in hepatitis C virus infection. Anxiety and mood symptoms are also prevalent. Of 134 male patients with CHCV being evaluated for interferon and ribavirin therapy, more than half the patients experienced significant anxiety (54 %), and almost half (45 %) had depression and aggression symptoms, and 41 % reported a low or very low quality of life. Anxiety was more commonly reported by African-Americans or Hispanics. Depression scores were significantly influenced by a diagnosis of PTSD or being without a partner; and aggression scores were higher in those diagnosed with either PTSD or an alcohol or substance use disorder (Hensley et al. 2003). The cognitive deficits noted on neuropsychological testing in HCV patients include impaired attention, psychomotor and working memory, with intact verbal skills and visuoconstructional abilities. They are commonly experienced by patients as “brain fog” or “mental clouding” (Forton et al 2005; Hilsabeck et al. 2002).

As discussed previously, since HCV patients often have substance use or psychiatric disorders, it is difficult to determine whether or not the virus itself contributes to the preexisting anxiety, aggression, depression, or “brain fog.” However, there is a growing body of recent literature which postulates HCV neuroinvasion.

30.5.2 Hepatitis B

30.5.2.1 The Hepatitis B virus (HBV) Deoxyribonucleic Acid (DNA) is a double-stranded Virus from the Family Hepadnaviridae

The HBV is transmitted through sexual contact and intravenous transmission, including intravenous drug use. For adult-acquired infection, less than 5 % develop a chronic infection. In contrast to HCV which regularly develops into a chronic

infection, hepatitis B infection in most adults (95 %) is an acute infection only. After the acute attacks, most adults recover completely and remain immune to future hepatitis B infection.

About 1.2 million persons in the USA have chronic hepatitis B infection. Among severe mentally ill patients, HBC (based on antibodies to core HBV) is estimated to be five times more prevalent than in the general US population, or 23.4 %.

Of the 5 % of adults who develop a chronic hepatitis infection, about 12–20 % develop cirrhosis. Symptoms vary from the inactive carrier state to the development of cirrhosis, end stage liver disease, hepatic carcinoma, and death. The course varies with the clinical setting. In one study of 296 HbSag-positive blood donors, in a 30-year follow-up period, the incidence of any clinically significant liver-related morbidity was not significantly different from the HBV-negative blood donors. It seems that in low-risk areas, the majority remain asymptomatic with very little risk of cirrhosis or hepatocellular carcinoma.

Many patients with chronic hepatitis B are asymptomatic, while others have nonspecific symptoms like fatigue. Depression and anxiety have also been reported. Chronic hepatitis B liver patients also have similar cognitive deficits, as CHCV patients, with poorer functioning in tasks requiring attention and psychomotor speed, though all these neuropsychiatric symptoms are not as prominent as in the CHCV patients (Hilsabeck, Perry, and Hassanein 2002).

30.5.3 Alcoholic Liver Disease (ALD)

ALD develops when humans chronically ingest too much alcohol. Some adverse liver changes can be seen with as little as 20 g per day in women (one drink = 14 g) and 40 g in men; however liver cirrhosis develops in less than 20 % of humans ingesting this amount of alcohol. Whether or not there is a dose–response relationship between alcohol and liver damage is arguable, but it is generally agreed that between 50 and 80 g, or 4–6 drinks daily or more for 10–20 years substantially increase the risk of cirrhosis, which is 2–3 times greater in women than men (Reuben 2006). Factors which accelerate alcoholic damage to liver tissue are certain drugs, high-fat diet, HCV infection, and genetic factors (female sex, enzymatic polymorphic forms of ADH and ALDH, hemochromatosis) (Lieber 2005).

The epidemiology of alcohol dependence is estimated to be 10–15 % of the adult population in the USA. The incidence of alcohol liver disease is less than this, but estimates vary widely depending upon the population surveyed. Often chronic liver disease is undetected until late stages (cirrhosis) when symptoms become apparent. Also, it is difficult to separate the impact of alcohol from other factors and diseases affecting the liver.

Chronic and excessive ethanol consumption is associated with cellular proliferation, fibrosis, cirrhosis and cancer of the liver. In the past half century it has become apparent that alcohol's toxicity to liver is not primarily due nutritional deficiency (Lieber 2005). Instead, alcoholic hepatoxicity is linked to the metabolic disturbances associated with the oxidation of ethanol by liver alcohol dehydrogenase (ALD) pathway and the redox changes produced by the generated NADH, which in turn affects the metabolism of carbohydrates, lipids, proteins, and purines. The clinical result is hyperuricemia, hypoglycemia, and hepatic steatosis by inhibiting lipid oxidation and promoting lipogenesis. There is also an alternative pathway of ethanol metabolism, the microsomal ethanol-oxidizing system. Alcohol increases both the activity of the main enzyme [ethanol-inducible cytochrome p450E1 (CYP2E1)] and its gene, resulting in ethanol metabolism and tolerance to alcohol. Activation of this enzyme, CYP2E1, explains the susceptibility of heavy drinkers to liver damage by solvents and other compounds. Induction of the microsomal pathway contributes to increased acetaldehyde generation which promotes glutathione depletion, free radical-mediated toxicity, and lipid peroxidation. Acetaldehyde increases hepatic collagen synthesis and thus development of fibrosis and cirrhosis (Lieber 2005).

Alcoholic hepatitis may complicate preexisting alcoholic fatty liver or cirrhosis. The exact pathogenesis of alcoholic hepatitis is uncertain,

but it is known to involve metabolism of alcohol to toxic products, oxidant stress, acetaldehyde adducts, the action of endotoxin on Kupffer cells, and impaired hepatic regeneration. Cytokines and immunity are actively involved in its pathogenesis. In alcoholic hepatitis, inflammation contributes to portal hypertension. Mild alcoholic hepatitis reverses with abstinence and the long-term prognosis is determined by the underlying alcohol-use disorder. Severe alcoholic hepatitis is associated with an almost 50 % mortality rate. Meta-analysis of well-designed clinical trials revealed that, contrary to popular opinion, milk thistle did not significantly improve the course of patients with alcoholic and/or hepatitis B or C liver disease (Rambaldi et al 2005).

Cognitive impairment in alcoholics without liver disease is reported to include impairment in executive functioning, as well as visuospatial, verbal, and nonverbal working memory. Neuroimaging shows alcohol-related damage to the frontal lobes and cerebellum. It is well established that individuals with alcohol dependence are at risk of developing Wernick–Korsakoff's syndrome, which is related to a depletion of thiamine in alcoholism. The neurocognitive deficits are typically impairments in the formation and retrieval of new memory (Collie 2005).

Few studies have investigated the contribution of liver disease to cognitive dysfunction in alcoholics. Although it would be expected that alcoholic liver patients would have greater cognitive dysfunction than alcoholics without liver disease, studies to date on the two groups showed equal level of dysfunction in tests of learning, memory, simple and complex attention, psychomotor function and general intellectual ability (Collie 2005). Walton and Bowden (1997) correlated liver disease status (measured by serum GGT and albumin) with mental ability, and did not find an influence. They concluded that in alcoholics without cirrhosis, liver disease does not appear to be involved in chronic alcohol-related cognitive impairment. However, in cirrhotic patients with Wernicke's encephalopathy, quantitative morphology suggests that alcoholic liver patients lose a disproportionate amount of subcortical white matter compared with cortical gray matter. Further studies are needed to assess the contribution of liver disease to cognitive deficits and morphological changes in the brains of alcoholics.

30.5.4 Nonalcoholic Steatohepatitis (NASH)

NASH is the hepatic manifestation of the metabolic (or insulin resistance) syndrome. It is a result of necroinflammatory changes in the liver. A certain proportion of individuals with nonalcoholic fatty liver disease (NAFLD) can develop NASH (Farrell 2003).

The pathophysiology for NASH involves insulin resistance, which causes steatosis. The second factor is oxidative stress, which produces lipid peroxidation and activates inflammatory cytokines resulting in NASH. Risk factors include type 2 diabetes and obesity. Cases occur most commonly in obese, middle-aged women with diabetes (McCullough 2002).

About 2–4 % of all adults have NASH. The NAFLD affects 5 % of the US population or about 20 % of all adults; about one-fifth of these develop NASH. Cirrhosis from NASH is now the second most common age-related cause of death in type 2 diabetes. It is estimated that by the year 2025 more than 25 million Americans may have NASH-related liver disease (McCullough 2002). Psychiatric patients who develop metabolic syndrome are at risk of developing NASH.

In this disorder, the diagnosis is often delayed. The syndrome of NAFLD and NASH may be clinically silent and undetected by aminotransferase levels or diagnostic imaging. Diagnosis is based on biopsy. The course of the disease is affected by the comorbidities: obesity, diabetes, and hyperlipidemia. Weight reduction and increased exercise, and avoidance of hepatotoxins such as alcohol, can slow the liver damage. Ursodeoxycholic acid has shown benefit and is being investigated as a treatment option. About 25 % of those with NASH develop cirrhosis. Fatigue and cognitive dysfunction, including reduced attention and psychomotor speed, have been reported in patients with NASH (Hilsabeck et al 2002).

30.5.5 Porphyria

The porphyrias are genetic or acquired deficiencies of enzymes in the heme biosynthetic pathway. It is thought that the periodic madness of King George III was a manifestation of hepatic porphyria.

The hepatic porphyrias result from specific enzymatic defects in the synthesis of heme. Interruption of the biosynthetic pathways results in an accumulation of heme precursors in the tissues, serum, urine, and feces. The classification is based on the specific enzyme deficiencies and tissues involved. The symptoms have been divided into "neurovisceral" and "photocutaneous." The neurovisceral symptoms include abdominal pain, psychiatric and neurological symptoms. The porphyrias associated with increased production of delta aminolevulinic acid and/or porphobilinogen are associated with central and nervous system damage and symptoms. The etiology of these symptoms is not clear, but hypotheses include neurotoxicity caused by the precursors, decreased gamma amino butyric acid (GABA) concentration, loss of heme in the CNS, increased levels of brain tryptophan, and decreased plasma melatonin. Photocutaneous symptoms develop because porphyrins cause photosensitization and skin damage through exposure to ultraviolet light, with production of tissue-damaging free radicals.

There is considerable interaction between environmental factors and genetics, so that not all gene carriers develop clinical symptoms. Underlying hepatic disease may be a factor in attacks of porphyria cutanea tarda. These liver diseases may be from HCV, HIV, alcoholic liver disease, hepatocellular carcinoma, and drugs which induce cytochrome 450 activity iron overload states. In many patients, porphyria cutanea tarda was found to be associated with a hemochromatosis gene.

Porphyrias are uncommon. The prevalence of acute intermittent porphyria, the most common form, is estimated to be about 1–8 per million in the USA. Among hospitalized psychiatric patients, acute intermittent porphyria may occur as often as 1 per 500.

The illness consists of a serious of "attacks" which are brought on by a number of triggers including drugs, fasting, surgery, infection, and psychological stress. Symptoms begin after puberty. Variegated porphyria and coproporphyria may cause a photosensitive rash. The symptoms may include acute onset of abdominal pain accompanied by vomiting and constipation. Delirium occurs perhaps with visual hallucinations. A psychosis may appear instead of the delirium. A peripheral sensorimotor polyneuropathy may develop, and the dominant manifestation is a motor neuropathy which may progress to quadriplegia and respiratory failure. The recovery from this may occur within weeks to a year, and symptoms may not remit completely. There is an association between cigarette smoking and repeated attacks of porphyria. Treatment involves avoiding precipitating factors and UV light (for photocutaneous porphyria), oral carotenoids, stress reduction, prompt treatment of infections, and smoking cessation. Individuals can suffer greatly and may die during an attack if not diagnosed and treated appropriately. Liver transplantation for severe hepatic porphyria has had favorable outcomes.

Neuropsychiatric symptoms are associated with the "neurovisceral" presentation of porphyria, and may include episodic presentation of psychoses and/or delirium. Psychiatric medications which are unsafe in porphyria include barbiturates, carbamazepine, clonazepam, and valproic acid; gabapentin is considered safe.

30.5.6 Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive disorder in which mutations cause increased intestinal iron absorption, perhaps through an interaction with the transferrin receptor. The result is iron overload with excessive deposition in tissues, including liver, heart, pancreas and pituitary. The prevalence is 0.5 % in the USA for homozygotes; heterozygotes have a frequency of about 10 % in the Caucasian population.

Many patients are asymptomatic when diagnosed on a routine screening panel showing elevated serum iron levels. Symptoms include liver disease, skin pigmentation, diabetes mellitus, arthropathy, impotence in males, and cardiac enlargement. Liver disease is caused by progressive iron deposition, which leads to hepatomegaly and eventual cirrhosis. The changes are initially reversible with iron removal. Iron overload in hemochromatosis potentiates the development of alcoholic liver disease as well as the deleterious effects of the hepatitis C virus infection on the liver (McDonnell et al. 1999).

One large study, which surveyed 2,851 hemochromatosis patients who reported symptoms for an average of 10 years before diagnosis, determined that the most common symptom was extreme fatigue (46 %), followed by arthralgia (44 %) and loss of libido (26 %) (McDonnell et al. 1999).

30.6 Psychiatric Issues in Treatment of Hepatitis C

30.6.1 Psychiatric Pretreatment Assessment for Hepatitis C Therapy with Interferon Alpha and Ribavirin

Treatment options for chronic hepatitis C infection include subcutaneous interferon alfa-based therapies. Since 1995, interferon alfa has been combined with oral ribavirin for enhanced treatment. Recently, protease inhibitors have been added, promising to improve greatly treatment efficacy (Bakulin et al. 2014). Ribavirin does not affect HCV directly but may enhance immunomodulation. Interferon alfa has been primarily administered in the pegylated form which allows weekly dosing and has yielded, with oral ribavirin, an improvement in viral eradication, with reduction in liver tests and HCV-RNA level and decrease in hepatic inflammation. The treatment course depends on genotype, and may last for 6 or 12 months. The sustained virological response (SVR) has been reported as 63 % for patients who received more than 80 % of their interferon and ribavirin for 80 % of the treatment course, and the SVR is durable for years (Desmond et al. 2006). Factors which influence the SVR include these viral factors: HCV genotype and viral load, and host factors: age, sex, race, body weight, amount of liver fibrosis, alcohol use, and compliance. The dose of interferon/ribavirin can also influence the outcome. The treatment is lengthy and has significant side effects. The major side effects are neuropsychiatric (Crone and Gabriel 2003). Current guidelines consider the natural history of the virus, the cost of treatment, and lack of uniform benefit, and have recommended that therapy should be provided to those at the greatest risk of progressive liver disease and to those in whom quality of life is reduced from chronic HCV infection. Addiction psychiatrists have an important role in assisting the hepatitis C clinic with the selection of patients who are considered capable of withstanding the difficult course of treatment. An important objective is to determine which patients, especially among the psychiatric and substance-use disordered, can be safely treated and to determine how to optimize their treatment outcomes. Positive treatment outcomes include not only viral eradication but also acceptance and completion of antiviral therapy as well as a delay in the progression of hepatic fibrosis to cirrhosis, complications of cirrhosis, and hepatocellular carcinoma.

Appropriate guidelines have been recommended to assist the psychiatrist in the selection process. In general, a 6-month period of abstinence and/or sobriety is recommended, urine toxicology and the AUDIT C can be used to screen for individuals who may require more intensive addiction treatment before and during CHCV therapy. Similarly, screening for psychiatric symptoms using the Beck Depression Inventory II, the Beck Anxiety Disorder Index, and the Aggression Questionnaire are simple methods to define which individuals require more psychiatric stabilization before initiation of therapy. In one study of 134 pretreatment HCV individuals, 12 % had severe symptoms of aggression, depression, or anxiety, and would require further stabilization and reevaluation before initiation of therapy (Hensley and Withers 2003).

30.6.2 Psychiatric Side Effects Induced by Interferon Alfa and Ribavirin

The major neuropsychiatric side effects of interferon and ribavirin therapy which have been reported include cognitive dysfunction, fatigue, depression, anxiety, and irritability (Crone et al. 2006; Kraus et al. 2003). A clinical observation was made that some patients undergoing interferon therapy have experienced anger, reported as episodes of domestic violence, "road rage," and other interpersonal conflicts (Withers 2003). In two separate studies, 16–25 % of patients reported interferon-induced aggression during long-term therapy for CHCV (Withers 2003; Kraus et al. 2003). In patients treated for melanoma, interferon alfa (at higher doses than is used for hepatitis C) led to mood instability with manic symptoms. Studies have shown that the depressive side effects from interferon alfa are dose related. Reported rates of depressive symptoms range from 0 to 80 % across studies; serious episodes have resulted in interrupted treatment, suicidal behavior and completed suicides (Crone and Gabriel 2003; Kraus et al 2003). Symptomatic autoimmune thyroid disorders occurred in 4 % of 439 patients during HCV treatment (Doi et al 2005). Fatigue and cognitive deficits are also exacerbated during interferon and ribavirin therapy for CHCV (Kraus et al 2005). Agranulocytosis has been induced by concomitant use of clozapine with ribavirin and interferon for CHCV in a case report. In a retrospective study, more than half of CHCV patients on interferon described moderate to severe physical, mental and social difficulties and a third quit work or reduced their work hours.

The pathophysiology of psychiatric symptoms from interferon alfa and ribavirin is hypothesized to be multifactorial, involving neurotransmitters, including serotonin and dopamine; proinflammatory cytokine production, nitric oxide, and endocrine regulation including the hypothalamic-pituitary-adrenocortical axis (Crone et al 2006; Crone and Gabriel 2003). Ribavirin can also cause psychiatric symptoms, though there have been no studies on ribavirin (only) induced side effects in HCV treatment, only in conjunction with interferon. Patients who develop severe psychiatric side effects may require dosage reduction or discontinuation of interferon and ribavirin therapy. Substance use disordered patients who are in recovery from alcohol or drug dependence are at risk for relapse on substances during HCV therapy (Hensley and Withers 2003).

In several large clinical studies involving treatment with interferon alfa and ribavirin, depression was the most common severe adverse side effect and the most common reason for dose modification or discontinuation (Raison et al. 2005). Despite the significance of the interferon and ribavirin induced psychiatric side effects in treatment of chronic HCV, only a few studies have investigated the predictors of psychiatric side effects, and the role of pharmacologic options in managing them (Reichenberg et al. 2005). Depression and mood disorders before initiation of interferon and ribavirin are associated with higher levels of treatment-induced depressive symptoms (Reichenberg et al 2005).

30.6.3 Treatment of Neuropsychiatric Side Effects Induced by Interferon Alfa and Ribavirin During Long-Term Therapy for Chronic HCV

While antidepressant treatment may have an important role in supporting interferon therapy, its indication and timing is uncertain (Reimer et al. 2005). Clinical reports suggest that the depressive and anxiety symptoms can be reduced with serotonergic agents, whereas the nausea, anorexia, pain, and psychomotor slowing may respond to more activating medications such as bupropion, modafinil, psychostimulants, or mirtazapine (Crone et al. 2006). Treatment of mania may be managed safely with gabapentin.

30.7 Cirrhosis and End-Stage Liver Disease, Without Hepatic Encephalopathy

Subclinical hepatic encephalopathy (SHE) is a syndrome of cirrhotic individuals who have normal mental status examination but show

abnormalities on formal neuropsychiatric testing. Over two decades ago, quantifiable neuropsychological abnormalities were found to be present in the majority of the ambulant, non-encephalopathic cirrhotic patients. Because of the noted impaired short-term visual memory and delayed reaction times to stimuli, it was cautioned that those patients would be at risk when driving or operating heavy machinery. More recently, 300 patients presenting for liver transplantation were neuropsychiatrically evaluated. The cognitive impairment was highest among those with alcoholic liver disease, and those patients with a history of alcohol abuse or dependence performed more poorly on neuropsychological testing. The patients with cholestatic liver disease, after correcting for liver pathology, had the least cognitive impairment when compared to other groups (Sorrell et al. 2006). In contrast, Pantiaga et al. (2003) found no significant differences in neuropsychological testing between patients with cirrhosis of alcoholic origin and those with cirrhosis from all other etiologies. The patients with cirrhosis had cognitive impairment which was greater with increasing liver damage. The Child C cirrhosis group showed moderate dementia with auditory attention deficit and reduced short-term retention. The liver transplant recipients showed some degree of dysfunction in comparison with the control group, but overall had better results than the cirrhotic patients. These authors confirmed prior findings that neuropsychological testing is valid in liver disease and found the Trails Making Tests A and B to be more sensitive for determining cognitive deficits, but commented that magnetic resonance imaging can detect a large proportion of patients with SHE than neuropsychological testing. A study correlating structural brain abnormalities with cognitive deficits in ten cirrhotic patients showed that the degree of cognitive impairment was directly correlated with functional abnormalities in the basal ganglia and limbic cortex. Another group, (Klos et al. 2005), found evidence of brain manganese accumulation in the basal ganglia associated with neurological syndromes, one of which was cognitive impairment with psychiatric features. The authors found that brain manganese toxicity may result in symptoms other than parkinsonism (Klos et al. 2005). Recent studies showed that reduced blood flow in the anterior cingulate gyrus measured by SPECT or impairment of P3000 may be a good indicator of cerebral functional changes in patients with cirrhosis (Kramer et al. 2002).

In summary, patients with cirrhosis without hepatic encephalopathy suffer neuropsychiatric symptoms with cognitive deficits which seem to be similar but slightly more severe than those noted in chronic liver disease with fibrosis and no cirrhosis and distinct from hepatic encephalopathy. Although cognitive deficits clearly increase with worsening of liver pathology, there are no consistent findings to date to indicate that one etiology (e.g., alcoholic liver disease or hepatitis C pathology) leads to greater worsening of cognitive impairment.

30.8 Hepatic Encephalopathy in Cirrhosis

Hepatic encephalopathy, which occurs in the setting of cirrhosis, end-stage liver disease, or acute liver failure, is a reversible decline in neuropsychiatric function associated with a worsening of hepatic function. It is estimated that 60–80 % of cirrhotics suffer hepatic encephalopathy. Hepatic encephalopathy is characterized by disturbances of consciousness, mood, behavior, and cognition, and can include symptoms of gross disorientation, confusion, agitation and coma (Crone et al 2006; Ferenci et al. 2002; Lewis and Howdle 2003). The stages of hepatic encephalopathy are rated as follows:

Stage 0: sleep disturbances, mild attention deficits

Stage 1: psychomotor slowing, lack of attention, asterixis

Stage 2: personality changes, disorientation, bizarre behavior, lethargy

Stage 3: rigor, pyramidal signs, major speech disturbances, severe ataxia, somnolence, stupor

Stage 4: coma

The earliest signs of hepatic encephalopathy, stage 0, are often sleep disturbances and subtle behavioral changes, which may be reported by

the patient's family. As hepatic encephalopathy progresses to stage 1, problems with attention, mild confusion, asterixis and psychomotor slowing are noted. In stage II there is lethargy and disorientation, which progresses to stage III of somnolence or stupor. In stage IV the patient is in a coma with or without response to painful stimuli (Crone et al. 2006).

The pathophysiology of hepatic encephalopathy is not fully understood. It has been known for decades that elevated ammonia from hepatic dysfunction is implicated and there may be a role for inhibitory neurotransmission through gamma-aminobutyric acid (GABA) receptors in the central nervous system and changes in central neurotransmitters and circulating amino acids. The precipitating cause may often include factors such as gastrointestinal bleeding, increased protein intake, hypokalemic alkalosis, infection, constipation, and use of sedatives and tranquilizers. Treatment involves correction of the underlying disorder. Benzodiazepines should be avoided in hepatic encephalopathy. One new therapy being evaluated involves the hypothesis that the GABA receptor complex, which includes a benzodiazepine receptor site, is a contributor to neuronal inhibition in hepatic encephalopathy. Several studies which have investigated a new drug, flumazenil, a benzodiazepine receptor agonist, reported only some short-term improvement in the symptoms of hepatic encephalopathy.

30.9 Liver Transplantation

To determine priority for deceased liver allocation in the USA, the model for end stage liver disease (MELD) was adopted in February 2002. This new policy gives priority to donate the deceased livers within designated geographic regions to chronic liver disease patients with the highest MELD score, and therefore the greatest waiting list mortality. The MELD score can be calculated based on a formula incorporating the serum bilirubin and serum creatinine levels and an international normalized ratio.

Psychiatrists are consulted to assist with addiction psychiatric assessment before the transplant. Contraindications to liver transplantation are evolving; for example, HIV patients are now considered for transplantation because of improvements in antiretroviral therapy. The current contraindications involving addiction psychiatry are active substance abuse and noncompliance with medical care. There are concerns about the risk of recidivism as well as noncompliance after transplantation. Psychiatrists are asked to review history of suicide attempts and dangerousness, as well as current psychiatric and psychosocial stability. An addiction history, including participation in alcohol and drug treatment programs, and random urine toxicology is important for assessment. Typically a minimum of 6-month sobriety and abstinence is required before liver transplantation can be considered.

Once the transplant evaluations are completed, the patient is placed on the United Network for Organ Sharing (UNOS) waiting list with a MELD score. Typically a median MELD score at transplantation might be 27. Another option for liver transplant is living donor liver transplantation (LDLT). The advantages for living donor transplantation include avoidance of the waiting time for the UNOS listing based on MELD score; transplantation can take place earlier. The disadvantages include the risk to the donor.

Transplantation for patients with either alcoholic liver disease or with heroin dependence on methadone maintenance therapy has been controversial. The reluctance to transplant such individuals is the poor prognosis for treatment of addictions in general, with high rates of relapse and poorer medical compliance, the presence of comorbid medical and psychiatric conditions, and moral evaluations about drug and alcohol use. More recently, a consensus has evolved that patients with alcoholic cirrhosis should be considered for liver transplantation, though the length of the period of abstinence remains uncertain. The relapse rate to return to alcohol use post-transplantation in alcoholic liver disease has been reported as an average of 20 %. There are no nationally accepted selection criteria for

predicting long-term sobriety and compliance. A recent study found that previous alcohol consumption, including length of abstinence before transplant, dependence, number of withdrawals, and family history of alcohol dependence predicted severe relapse to alcohol after transplantation. Another concern is nicotine dependence and impact on development of cancer due to relapse to smoking post-transplant. In one study, more than 40 % of patients who had quit smoking relapsed. Despite the lack of reliable predictors, 6 months of abstinence and sobriety from drugs, including nicotine and alcohol, is required in most programs.

Extension of life after liver transplantation is well documented; research has shown significant improvements in physical health, sexual functioning, ability to perform daily activities, social functioning, and general health-related quality of life. However, improvements in neuropsychiatric functioning post-transplant have been less well established. Pre-transplant candidates typically demonstrated impaired neurocognition, including problems with complex attention, and visuomotor, visuospatial, and memory deficits as well as affective symptoms of depression and anxiety, whereas post-liver transplant patients showed improvements in all areas of neurocognitive abilities, but not to the premorbid level of functioning. The affective psychiatric symptoms of anxiety and depression do not necessarily improve upon transplantation and may increase due to post-transplant stressors, including managing multiple antirejection medications and concerns about returning to the workplace (Hilsabeck et al. 2003).

A prospective study of 164 patients who were assessed for liver transplantation revealed that they had memory impairment, psychomotor slowing, anxiety, and depression, which are consistent with other studies on patients with cirrhosis and end stage liver disease. One year post-liver transplantation, these patients showed significant improvement in most domains compared with a control group and patients who did not undergo transplantation. Immunosuppressive medications did not affect quality of life, fatigue, or affective status. Higher levels of anxiety at pretransplant assessment predicted worse psychosocial outcome at 1 year post-transplantation. The individuals with good psychological outcome at 1 year maintained this at the 3-year follow-up (O'Carroll et al 2003).

30.9.1 Safety of Psychiatric and Pain Medications in Liver Disease

30.9.1.1 Psychiatric Medications

The impact of liver disease on medication pharmacokinetics is complex. Generally, in the setting of mild liver disease, the same dosage and type of medications as would be used in healthy individuals can be administered safely. Susceptibility to adverse effects increases with worsening liver function, due to altered pharmacokinetics and hemodynamic changes. Usually changes in drug dosing begin at the development of cirrhosis and/or renal insufficiency. In cirrhosis, portal hypertension develops which delays drug absorption through the small intestine vasculature. Further, fluid retention (ascites, edema) and the reduced hepatic production of albumin alter the distribution of drugs. Most psychiatric drugs are protein bound in the serum, and the albumin reduction results in higher levels of free active drug. In addition, the slowed hepatic metabolism which is typical in liver disease can lead to even higher serum drug levels for certain psychotropics (Crone et al 2006).

Some useful, general clinical guidelines to assist with psychiatric medication dosing in the setting of liver disease have been provided recently (Crone et al 2006). The clinician is cautioned to review the therapeutic and toxic plasma concentrations of each drug as well as make an assessment of the patient's liver disease, based on the Child-Pugh Score calculations (Childs A, B and C). Three-quarters to full amount of the standard initial dose is recommended for psychiatric patients with Childs A liver disease. More caution should be applied for patients with Childs B liver disease; the initial dose should be half of the normal dose with more gradual dose increases to accommodate the prolonged elimination half-life. The CPS Class C liver disease patients

commonly have hepatic encephalopathy. If hepatic encephalopathy is present, any psychiatric medications must be monitored very closely to avoid worsening of the encephalopathy (Crone et al 2006).

In general, drugs which are lipid soluble are primarily metabolized in the liver, whereas those which are more polar (hydrophilic or water soluble) are excreted largely through renal clearance. Most of the psychiatric medications belong to the hepatically metabolized, hydrophobic group. These are oral medications which are absorbed from the gastrointestinal tract and then are modified by hepatic metabolism which changes by hydroxylation, oxidation, reduction, or conjugation of the lipophilic forms to water-soluble compounds ready for renal excretion. Hepatic metabolism has two phases: I and II. Phase I hepatic metabolism (CYP; CP 1-10) involves oxidation, hydrolysis, or reduction, and utilizes the cytochrome 450 enzymes which are found on endoplasmic reticulum. Of the cytochrome 450 enzymes, most drugs and toxins are metabolized by the CYP3a subfamily. In phase II hepatic metabolism, drugs are conjugated (acetylation, glucuronidation, or sulfation) in the hepatocyte cytoplasm. Phase II glucuronidation is largely preserved in cirrhosis. Chlorpromazine and valproate can reduce phase II reactions.

Diet and alcohol intake can affect drug metabolism. For example, cruciferous vegetables induce CYP enzymes whereas grapefruit juice inhibits CYP3a activity; low-protein diets and malnutrition also reduce CYP activity. Alcohol reduces the availability of glutathione and thus leads to greater hepatotoxicity from acetaminophen or cocaine. Low-protein diets and malnutrition reduce CYP activity.

It is safer in liver disease to avoid drugs which require phase I metabolism, as they may have higher serum levels and reduced metabolism, and to use instead medications which pass through phase II glucuronidation. Drugs which use phase II glucuronidation include olanzapine, lorazepam, and oxazepam and would not require dose reduction in liver disease. For phase I metabolized drugs, including alprazolam, midazolam, diazepam, fluoxetine, paroxetine, nefazodone, bupropion, sertraline, and risperidone, a dose reduction by half is recommended for patients with hepatic impairment. Phenothiazines should be avoided because they can cause cholestasis. The renally excreted psychiatric drugs, including lithium, gabapentin, and topiramate, should only be used with caution and careful monitoring (Crone et al 2006).

Acute liver failure has been reported in case studies, particularly in children, with valproic acid. Recently, in India, there were two cases of children with valproate-induced hyperammonemic encephalopathy enhanced by topiramate. Mitochondrial disease represents a risk factor for valproate-induced liver failure. However, valproic acid may be used safely in most hepatitis C patients, with enzyme monitoring. The transaminase, alanine transferase (ALT), was not elevated during use of valproic acid in hepatitis C patients; the ALT increases were instead correlated with hepatitis C status. In a recent case report, the mood stabilizer, lamotrigine, caused acute hepatitis which led to liver failure, and the patient was managed with the Molecular Adsorbents Recirculating Systems (MARS).

Nefazodone has been associated with liver failure (1 %) and should be discontinued for any signs or symptoms of hepatic failure. In 2005, the Food and Drug Administration (FDA) removed pemoline from the market after receiving 13 reports since 1975, of liver failure from this medication resulting in transplantation or death. An antidepressant, duloxetine, which is a selective serotonin and norepinephrine reuptake inhibitor, has had a revision in its FDA labeling in 2005 to include new precautions that duloxetine has caused liver injury and can aggravate liver damage. In a recent case report, duloxetine caused fulminant hepatic failure and death in an individual with no prior liver disease. Most episodes of drug-induced liver injury are idiosyncratic. Typically the drug-induced heptotoxicity presents as acute hepatitis and/or cholestasis, but may take any pattern of liver disease. Monitoring serum ALT is of unproven effectiveness but should be considered if there is a risk of delayed serious hepatitis reaction. Drug-induced hepatotoxicity has also been reported for

chlorpromazine (cholestatic injury), trazodone and venlafaxine. Hepatic injury has been reported from ingestion of kava root. This traditional herb, kavakava, is used in New Caledonia, for anxiety and insomnia. Apparently kava inhibits all CYP 450 enzymes which leads to significant drug interactions. Patients should be advised to avoid kava due to risk of hepatotoxicity and drug interactions. Psychiatrists should routinely screen for the use of herbs and provide education about the risk of liver damage and/or drug interactions with herbal supplements.

30.10 Pain Medications

The recommendations for safe use of acetaminophen in cirrhosis is to use the limit of 2 g per day if there is a risk of any alcohol abuse, and possibly 4 g per day with alcohol abstinence. All patients should be warned of the risk of severe hepatotoxicity from active alcohol intake and concomitant use of acetaminophen, which can occur regardless of the severity of liver disease. Nonsteroidal anti-inflammatory drugs (including aspirin) should be avoided in patients with cirrhosis, because of the increased risk of variceal hemorrhage, impaired renal function, and diuretic resistant ascites. Opioids should be used with caution; morphine, oxycodone, and hydromorphine should be used at reduced doses and prolonged intervals.

30.11 Addiction and Liver Disease

In patients with cirrhosis, alcohol withdrawal is best managed with a fixed dose of benzodiazepines, with reassessment for daily tapering. The Clinical Institute Withdrawal Assessment for Alcohol (CIWA-AR) is a protocol commonly used, but its use may be impractical and not useful for a population of alcoholics who are at risk of alcohol withdrawal delirium. One reason is that if the protocol is ordered, the patient may not get necessary benzodiazepines, because of the complicated nursing ratings necessary to determine each dose. If medical detoxification is necessary, a simpler technique for cirrhotics is to use a fixed ratio of oxazepam (15–45 mg) every 4 h for the first 24 h, and to hold a dose if patient is asleep. Lorazepam is not recommended because of risk of possible exacerbation of symptoms due to the short half-life leading to repeated withdrawal. Doses can be decreased on a daily basis as symptoms resolve (see also Chaps. 12 and 20 for detoxification techniques).

The diagnosis of liver disease, including HCV, can become a strong motivating factor for a patient to engage in comprehensive alcohol and drug treatment. The use of brief intervention together with motivational interviewing can reinforce and enhance the patient's commitment to abstinence and sobriety. Brief intervention has consistently been measured to be the most effective in terms of evidence-based treatment methods for alcohol-use disorders. In the HCV clinic setting, the AUDIT C is a useful screening test. The identification of lab markers for HCV or HIV in a psychiatric patient is a trigger to inquire about past intravenous drug-use and current drug- or alcohol-abuse disorders (Withers 2001).

The cornerstone for therapy for alcoholic liver disease is drinking cessation; even reduction in alcohol intake improves the rate of liver tissue degeneration from fibrosis to cirrhosis and finally hepatocellular carcinoma. In fact, the ability to maintain sobriety has a major impact on the outcome of patients with alcoholic cirrhosis because maintaining abstinence can lead to significant regression of fibrosis and possibly early cirrhosis. In studies, alcohol intake is often measured as drinks; 1 drink is approximately equal to 14 g of ethanol. In a large prospective clinical trial, veterans who had been drinking 16 drinks per day were assessed by repeated liver biopsy at baseline and 24 months. It was found that with even 2.5 drinks a day, the liver pathology still progressed one stage. The hepatitis C virus patients showed accelerated progression of liver disease. In total, one of five patients showed progressive liver damage even at moderate levels of drinking.

30.12 Summary

It is critical for psychiatrists to appreciate that hepatic dysfunction, even in mild forms, can cause neuropsychiatric symptoms. Some liver diseases, including acute intermittent porphyria, have been misdiagnosed as psychiatric syndromes such as schizoaffective disorder or major depression with psychotic features.

The mechanisms by which hepatic dysfunction can cause cognitive deficits, fatigue, affective symptoms and psychoses are not well understood, although there is growing information from various neuropsychological, neurophysiological, biochemical, and imaging studies which compare liver diseased patients with each other or controls. There appear to be some symptoms and mechanisms common to all liver disease, and others which differ based on type of liver pathology or severity of liver disease. It has been postulated that the neuropsychiatric symptoms of hepatitis C may be the result of direct or indirect neuroinvasion of the virus. Fatigue and cognitive deficits compatible with subcortical dysfunction have been reported in almost all forms of chronic liver disease, and hepatic encephalopathy can evolve regardless of the etiology of the underlying liver disease. Medications which are hepatically metabolized can exacerbate or precipitate liver disease, and should be used with caution in patients with cirrhosis or hepatic encephalopathy. The treatment of chronic hepatitis C, which involves administration of interferon alpha and ribavirin for months, induces neuropsychiatric side effects and requires addiction psychiatric management before and during treatment. Similarly, addiction mental health clinicians provide pretreatment evaluation and management for pre- and post-liver transplant patients. Finally, psychiatric patients have a higher prevalence of liver disease (including hepatitis C, alcoholic liver disease, porphyria, nonalcoholic steatohepatitis) than the general population, and these comorbidities significantly impact the course of psychiatric illness and its treatment.

Case Vignettes

(a) A 59-year-old married white male is referred to psychiatry for mental health evaluation before initiation of interferon and ribavirin for chronic hepatitis C. He has been diagnosed with post-traumatic stress disorder, chronic, major depression, recurrent, amphetamine dependence in sustained full remission, and alcohol dependence in early full remission. Although he has entertained thoughts of suicide in the past, he has never acted on them. He reports chronic insomnia with only about 4 h of sleep at night, and intermittent nightmares, with chronic guilt feelings and social isolation. His employers retired him from work as a truck driver at age 54 when his driver's license was revoked for reasons which are not apparent to the patient. He quit smoking 20 years ago. His medical problems include lumbosacral degenerative joint disease which causes chronic back pain, for which he takes four tablets a day of hydrocodone (5 mg) with acetaminophen (500 mg). Source of HCV is thought to be intravenous drug abuse (which he stopped at age 30); HCV is genotype 1 with a viral load of 700,000. Liver biopsy shows grade 3 with moderately active hepatitis C, with stage 2, periportal fibrosis. He is HCV treatment naïve; he declined treatment in the past.

On pretreatment assessment, his psychiatric medications included bupropion 75 mg twice a day; gabapentin 300 mg HS, trazodone 100 mg HS. His last drink was 6 months ago. His AUDIT C score was 8 (high), pain reported as 4 of 10, BDI II 28 (moderate depression), BAI 21 (moderate anxiety), quality of life measured as very low, and overall aggression measured as average. He was started on pegylated interferon alfa 2a weekly injections with ribavirin

at 600 mg twice a day. By week 2, his depressive symptoms worsened to severe (31 on BDI II). He saw the same psychiatrist at monthly intervals for support, assessment and medication management. Medications which were tried and discontinued due to side effects or inefficacy included mirtazapine, hydroxyzine, doxepin, clonidine, quetiapine, and citalopram. Although his mood remained severely depressed throughout, he had some slight improvement with an increase in bupropion to 150 mg bid, and in gabapentin to 1,200 mg HS, which helped with his sleep disturbance. He reported a headache for 1 day following interferon injection; loss of appetite with weight loss up to 20 lb during treatment. His sleep did not improve beyond 4 h/night. He experienced low motivation and fatigue. At week 4 he complained of worsening back pain, by week 8 he was distraught and "on edge," he reported to his psychiatrist thoughts about grabbing a knife and stabbing himself, though he did not act on this. Citalopram was initiated but discontinued by patient due to sensation of "an electric shock" in his body. Mirtazapine was initiated but discontinued because he felt it was ineffective and did not help him fall asleep, and just made him more sedated. By week 12, his depression was better, but he reported feeling so fatigued that it was an effort just to get out and cut the grass. At this point he was given filgrastim by the HCV clinic for neutropenia. His HCV viral load was undetectable at week 12. By week 18, he reported feeling better; he thought that the increased bupropion was helping with depression and fatigue. He did report "mind fog," or mild difficulty remembering tasks or staying on task. By week 32 he reported worsening nightmares; gabapentin was increased to 1,200 mg HS, which improved his sleep pattern and by week 36, he said the nightmares were less frequent and occurred about three times a month. By week 44, he reported increased irritability and feeling "like a bomb ready to explode." The slightest incident annoys him and he felt like yelling and lashing out; however, he did not act on these feelings. By week 48, he was pleased and surprised that he was able to complete interferon and ribavirin treatment. His HCV viral load was undetectable at week 48. One week after the end of treatment he already reported feeling less irritable.

Discussion: This vignette demonstrates that even very depressed patients, such as this patient with chronic PTSD and depression, can tolerate interferon and ribavirin therapy for CHCV with close mental health treatment and support. The symptoms he reported during his 48 weeks of therapy which include headache, fatigue, irritability, exacerbation of depression, pain and insomnia, and anergia are typical for HCV therapy. In this case, the most effective psychotropic medications were bupropion and gabapentin.

(b) Mr. J. is a 50-year-old married white male referred for mental health evaluation for liver transplantation. His comorbid medical diagnoses include end stage liver disease with hepatosplenomegaly and pancytopenia, rheumatoid arthritis with chronic pain, and hepatitis C. His psychiatric diagnoses include heroin, marijuana, and alcohol dependence in sustained full remission; he admits to a history of intravenous drug abuse which is most likely the source of hepatitis C. He completed four treatment programs for drug and alcohol treatment; three of these were court ordered. He attends regular alcoholics anonymous and narcotic anonymous meetings and has a sponsor. His current medications include levofloxacin, amiloride, potassium, furosemide

and hydrocodone (5 mg) with acetaminophen (500 mg) TID. Spironolactone was discontinued due to gynecomastia. He agrees to discontinue opioids in preparation for transplant. He quit smoking at age 38. He worked as a plumber but became disabled this year due to inability to concentrate.

He reports chronic pain, especially in his legs and knees, insomnia, and low energy but reports "I still show up." His concentration is poor and he cites daily problems with forgetfulness. For example, he would forget where he parked the car, which items he was supposed to buy at the store, or even to turn off the shower when he was interrupted by the telephone. These symptoms were unimproved by a trial of psychotropic medications including fluoxetine, modafinil, and bupropion.

On pretreatment assessment, his urine toxicology was negative, Quality of Life was measured as average, and he had symptoms of mild depression (BDI II—10), moderate anxiety (BAI—29), and average aggression. The Repeatable Battery for Assessment of Neuropsychological Function (RBANS) was well below normal, with a total score at the 0.3 percentile. None of the scores were normal; he was most impaired on attention and delayed memory (0.4 percentile), severely impaired also on immediate memory and visuospatial constructional abilities (both at 1st percentile), and language was measured at the 19th percentile.

Mr. J's adult son agreed to be the donor for living donor liver transplantation (LDLT), and the right lobe of his son's liver was successfully transplanted into Mr. J. His son recovered rapidly; Mr. J's recovery was complicated by postoperative infections and he still complained of significant chronic pain. Two months post-transplant, he was retested. This time he again reported average aggression, but depression had increased to moderate and his anxiety was rated as severe. However, he showed marked improvement on the RBANS with total score improved to a normal range (44 %). Attention improved the most; to 35 %; visuospatial to 30 %, delayed memory to 8 %; immediate memory to 16 %; and language to 35 %. Mr. J. was pleased to learn of his improved performance on neurocognitive testing.

Discussion: This case history demonstrates that end stage liver disease patients suffer from impaired neurocognition, including attention, visuospatial, and memory deficits which improve post-transplant. Most patients, like Mr. J, show significant improvements in all areas of neurocognitive functioning, albeit not to premorbid levels of functioning. Mr. J. was not tested before the onset of his liver disease, so premorbid test results are not available. In contrast, psychiatric symptoms do not necessarily improve and may become increased by post transplant stressors, such as managing and paying for multiple antirejection medications, pressure to return to work, loss of social support, and concern about the health of the donor, who is often a family member. In Mr. J's case, both his depression and anxiety worsened. It is important to educate liver transplant patients about potential neuropsychiatric symptoms pre- and post-transplant, and to provide mental health support throughout the process.

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