



## Management of Bipolar Disorder in Liver Transplantation: A Single Center Experience

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### Abstract

Bipolar disorder and end stage liver disease commonly intersect and their management may include evaluation for liver transplantation. Psychiatric illness may impair adherence to medical regimens jeopardizing the allograft, thus, generating divided opinions by liver transplant selection committees whether transplantation is even possible in this scenario. There is very limited data about the optimal management of bipolar disorder before and after liver transplantation. We analyze a case series of 8 liver transplant recipients with bipolar disorder at Mayo Clinic (Rochester, MN) for medical and psychiatric outcomes. Neuropsychiatric pharmacology and alternative immunosuppressive regimens are reviewed to make "best practice" recommendations in this challenging patient population.

### Keywords

Bipolar disorder, Liver transplantation, Pharmacotherapy, Management

confidence interval 95% 6.4-8.8) [4]. The 3 main indications for liver transplantation in the US include hepatitis C, alcoholic liver disease and nonalcoholic steatohepatitis (NASH). BD patients are at a heightened risk of liver disease given behavioral and specific pharmacotherapy for this condition [1].

Hepatitis C (HCV) is the principal cause of death from liver disease and is currently the leading indication for liver transplantation in the US [5]. The primary mode of transmission is through injection drug use [6]. The prevalence of HCV in BD is 15.5%, as comorbid substance abuse disorders are very common in this population [4]. Alcoholic cirrhosis remains the second most common indication for liver transplantation [7]. Mental illnesses are frequently associated with alcoholism. BD co-exists with alcoholic cirrhosis in 1.6% of individuals (odd ratio 3.82, confidence interval 95% 2.3-6.1) [4,8]. Patients with severe mental illness and co-occurring substance use disorders experience worse long term outcomes when compared to those without co-occurring substance abuse [9]. Nonalcoholic fatty liver disease (NAFLD), which includes the spectrum from isolated hepatic steatosis to NASH, is the most common cause of chronic liver disease worldwide. In the US, NASH has become the third most common indication for liver transplantation and is projected to be the leading indication in the next 10-20 years [10]. The main risk factors for NAFLD/NASH include hypertriglyceridemia, diabetes mellitus, and obesity [11]. Patients with BD have a high rate of obesity (approximately 40%) and associated metabolic syndrome (32% to 50%), making this population vulnerable to NAFLD/NASH. Additionally, atypical antipsychotics are associated with metabolic syndrome and weight gain [12].

The management of BD in the context of liver transplantation presents specific challenges. Hepatic encephalopathy, impaired

### Introduction

Orthotopic liver transplantation is the most effective form of treatment for end stage liver disease as it offers extended survival and improved quality of life [1]. There continues to be a disparity between organ supply and demand which mandates a thorough medical, surgical and psychosocial evaluation to identify potential organ recipients. The process can be challenging when significant psychiatric illness is present [2].

Bipolar disorder (BD) lifetime prevalence estimates are 1-2% [3]. Patients with BD have a higher prevalence of liver disease as compared with matched controls (21.5% vs. 3.5%, odds ratio 7.58,

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liver metabolism, and kidney injury are common prior to liver transplant, requiring frequent BD medication adjustments [13-15]. Neuropsychiatric complications are frequent immediately after liver transplant, usually multifactorial in nature [16,17]; surgical intervention, intensive care unit hospitalization, infections, medications, metabolic complications, within others. These factors can complicate the evaluation of a BD patient that is not optimally controlled from the psychiatric stand point. Adherence to the immunosuppressive regimen is critical for the allograft survival, and can potentially be jeopardized if active BD symptoms are present.

It is anticipated that more patients with comorbid BD will present for transplantation. Currently, very little is known about the optimal management of patients with BD in the setting of liver transplantation. The international medical literature is scarce and contains only 2 case reports describing treatment and outcomes [18,19].

In this case series we sought to determine both liver and psychiatric outcomes in patients with BD that underwent liver transplantation at Mayo Clinic in Rochester, MN. We also aimed to identify risk factors and optimal management strategies associated with these outcomes. Through our experience and review of the literature we provide a perspective of the optimal management for this special patient population.

## Patients and Methods

This case series was identified by a retrospective chart review of the Mayo Clinic liver transplant database, where the diagnoses of BD and liver transplantation were cross-matched, from January 2004 to January 2014. We identified 8 liver transplant recipients with co-existing BD of varying severity.

The electronic medical records were reviewed to investigate patient's demographics, etiology of liver disease, comorbid conditions, laboratory data, hospital length of stay and necessity of psychiatric admission. Additionally, immunosuppressive regimens, psychiatric medications and their dose adjustments before and after liver transplantation were recorded. A psychiatrist evaluated and adjusted medications to all patients before the transplant in the office or in the hospital ward depending of their clinical condition. Patients were followed after transplantation while hospitalized and later on in the office. The diagnosis of BD was established according to the DSM-4-TR and DSM-5 prevailing criteria. For patients to be included in this study a minimum of 12 months of follow up after liver transplantation was required to assess outcomes.

The clinical cases with optimal and suboptimal outcomes are described in detail. One patient underwent 2 liver transplants, both with different management approaches to the psychiatric disorder, with different outcomes noted. This study was approved by the Mayo Clinic IRB and was conducted in accordance to the 2000 Declaration of Helsinki and 2008 Declaration of Istanbul.

## Results

### Clinical cases

**Case A:** A 58-year-old female with a prior liver transplant presented with decompensated cirrhosis (Model of end stage liver disease (MELD) 40) secondary to recurrent HCV genotype 4. She had a longstanding history of BD for which she was previously hospitalized and underwent electroconvulsive therapy remotely. For many years she was stable on quetiapine, which was gradually decreased and eventually discontinued one month prior to transplantation due to liver failure and history of hepatic encephalopathy. The patient remained euthymic during this period.

Her liver related complications included hepatorenal syndrome requiring renal replacement therapy and medically controlled hepatic encephalopathy. Other comorbidities included diabetes mellitus, hypothyroidism and hypertension. Under compassionate care, sofosbuvir and ribavirin were started prior to transplant and maintained for one week after liver transplant achieving sustained virological response.

The patient underwent an uneventful deceased donor liver transplant. She received steroids, basiliximab (postoperative day (POD) 0 and 4), mycophenolate mofetil (POD 0) and tacrolimus (TAC) (POD 17 secondary to renal insufficiency) as immunosuppressive regimen. After reoperation on POD 10 for delayed arterial bleeding, the patient became catatonic and remained in this state for two weeks, despite intravenous haloperidol and slowly increasing doses of oral and rectal quetiapine. Cross-sectional imaging of the brain ruled out posterior reversible leukoencephalopathy. She became responsive after the administration of intravenous lorazepam and recovered both physically and mentally. She was discharged on 50 mg of quetiapine three times a day with an additional night dose of 200 mg. Lorazepam was administered at 0.5 mg daily. Two weeks later, psychiatric hospitalization was required for auditory hallucinations. The patient was treated with haloperidol and later with 22 session of bitemporal electroconvulsive therapy in addition to her baseline regimen with eventual resolution of symptoms over two months.

**Case B:** A 58-year-old male with recurrent cryptogenic cirrhosis required a repeat liver transplant with a MELD score of 37. His comorbidities included medically managed hepatic encephalopathy, hypertension, dyslipidemia, and kidney insufficiency. He had a long history of BD which remained untreated owing his euthymic state, prolonged QTc interval and advanced liver disease. However he was started on olanzapine and lamotrigine four days prior to transplantation. His immunosuppression included steroids, basiliximab (POD 0 and 4), mycophenolatemofetil (POD 0) and TAC (POD 5). Olanzapine was resumed on POD 1 and lamotrigine on POD 2. The patient did well from a medical perspective and was discharged from the hospital on POD 5. He required readmission 3 days later and subsequent psychiatric hospitalization secondary due mania and agitation; grandiose affect, ideas of reference and rapid speech. There, he was successfully managed with 5 mg of olanzapine and 50 mg twice daily of lamotrigine and discharged home after one week.

**Cases C and D:** Both patients had a long-standing history of BD and were on much higher doses of medications prior to liver decompensation.

Case C was stable on 200 mg of sertraline daily. This was decreased by about 75% over the course of six months prior to transplantation. He received standard immunosuppression with steroids, mycophenolate mofetil (POD 0), and TAC (POD 19 secondary to renal insufficiency). He was continued on sertraline and olanzapine was initiated on POD 0 (Table 1). Both medications were titrated up slowly. He required psychiatric hospitalization secondary to mania. The patient was stabilized with 200 mg of sertraline daily and 5 mg of olanzapine daily. He required the addition of 500 mg of divalproex on POD 27. He was discharged home after 12 days of inpatient psychiatric stay.

Case D was stable on high doses of 500 mg of quetiapine daily and 200 mg of sertraline about 6 months prior to transplantation. Both medications required multiple dose reductions and just prior to transplantation the patient was taking only 5% of his usual doses given his advanced liver disease. He received immunosuppression with steroids, basiliximab (POD 0 and 4), mycophenolate mofetil (POD 0), and TAC (POD 5). Both quetiapine and sertraline were restarted on POD 1 at low doses and titrated up slowly (Table 1). His hospital course was prolonged due to severe mania. The patient eventually required psychiatric hospitalization for control of mania and aggression while his medications were slowly titrated up. After two months, he was discharged to a chronic care facility and eventually to home a month later on 400 mg of quetiapine daily and 50 mg of sertraline daily.

### Case and control E

**Case E-I and E-II:** 64-year-old female who had NASH cirrhosis underwent deceased donor liver transplantation with a MELD of 29. Her comorbidities included type II diabetes mellitus, remote jejunal bypass for weight loss, coronary artery disease, and acute renal failure.

Her liver disease was manifested by esophageal varices and hepatic encephalopathy. Prior to liver transplant there was no documented history of psychiatric disorder or mood altering medications. Her immunosuppressive regimen consisted of daclizumab (POD 0 and 4), mycophenolate mofetil (POD 0), and TAC (POD 78 – delayed initiation secondary to kidney failure requiring intermittent dialysis). The patient developed acute mania post operatively (POD 12) requiring treatment with haloperidol and lorazepam. On POD 22 her psychotropic regimen was switched to olanzapine and lorazepam, and she was admitted to the psychiatric ward for protracted mania. She was followed closely for 18 months, and her mood disorder remained well controlled.

Within 18 months, the patient experienced ductopenia and progressive liver failure requiring re-transplantation with a MELD of 34. Her immunosuppression regimen consisted of basiliximab (POD 0 and 4), mycophenolate mofetil (POD 0), and TAC (POD 1). Olanzapine, at her stable pre-transplant dose, was restarted on POD 1. She had an uneventful hospitalization from a medical and psychiatric perspective and was dismissed.

**Case F:** 56-year-old male with cryptogenic cirrhosis and a MELD score of 31 had portopulmonary hypertension and a spontaneous splenorenal shunt resulting in hepatic encephalopathy, which was medically managed. He had a longstanding history of BD including psychiatric hospitalization. His condition was controlled with 450 mg of sustained release lithium twice daily and 20 mg of paroxetine daily. Other comorbid conditions included diabetes and chronic kidney disease.

He had a deceased donor liver transplant and received steroids, basiliximab (POD 0 and 4), mycophenolate mofetil (POD 0), and TAC (POD 5). Psychotropic medications were continued throughout surgery at the same doses. The post operative course was uneventful and he was discharged home on POD 7.

**Case G and H:** Patient G was a 43 year-old female with cholangiocarcinoma in the setting of primary sclerosing cholangitis. Her comorbidities included diabetes mellitus and hyperlipidemia. Her BD manifested as mood lability and racing thoughts. Her disease was well controlled for over 2 years prior to liver transplantation on a combination of 300 mg of lamotrigine, 100 mg of topiramate, 150 mg of venlafaxine, and 160 mg of ziprasidone. She underwent deceased donor liver transplantation with a MELD of 24. She received steroids, dacluzimab (POD 0), mycophenolate mofetil (POD 0), and cyclosporine (POD 3). Psychiatric medications were restarted at pre-transplant doses on POD 0.

Patient H was a 58-year-old woman with primary biliary cirrhosis. She was diagnosed with BD many years prior to transplantation after she required hospitalization for severe depression followed by an episode of goal oriented activities, excessive money spending and impulsive behavior. Her disease was well managed with 600 mg of lithium daily. She underwent liver transplantation with a MELD of 26. She received on POD 0 steroids, azathioprine, and mycophenolate mofetil. Tacrolimus was initiated on POD 3 and her psychotropic medications on POD 5 at pre-transplant doses. Both patients had uneventful hospital stays and were discharged home.

All patients were alive and had excellent allograft function at 1 year post-transplant. Additional details on these patients with B Dare described in table 1. One-year outcomes including readmission, acute cellular rejection, allograft and patient survival are summarized in table 2.

## Discussion

To date, there are only 2 cases reports describing the management of BD in liver transplantation. Vieta et al. described a patient who developed rapidly cycling BD after OLT on POD2. This patient received cyclosporine and steroids for immunosuppression. He was managed with imipramine, which was later switched to lithium

**Table 1:** Patient Characteristics and Outcomes.

	Age/ Gender Ethnicity	Clinical Setting and Procedure	MELD	HE	Pre-OLT psychiatric medications	Pre-OLT % Dose Reduction	Post-OLT meds	POD of med restart	IMS	Medical LOS (days)	Outcome And Psych LOS
A	58/F Arabic	Recurrent Allograft HCV OLT	40	Yes	None	100%	Quetiapine 25 mg Ativan 1 mg Haloperidol 2 mg	1 29 50	BAS, ST, MMF, TAC	22	Psych Admit 25 days
B	58/M Caucasian	Recurrent Allograft Cryptogenic OLT	37	Yes	Olanzapine 2.5 mg Lamotrigine 25mg	0%	Olanzapine 2.5 mg Lamotrigine 25 mg	1 3	BAS, ST, MMF, TAC	6	Psych Admit 11 days
C	49/M Caucasian	NASH OLT	40	Yes	Sertraline 50mg	75%	Olanzapine 2.5 mg Sertraline 50 mg	5 5	DAC, ST, MMF	14	Psych Admit 12 days
D	59/M Caucasian	HCV/ETOH sLK	30	Yes	Quetiapine 25 mg Sertraline 50 mg	95%	Quetiapine 25 mg Sertraline 50 mg	0 0	BAS, ST, MMF, TAC	12	Psych Admit 14 days
E - I	64/F Caucasian	NASH OLT	29	Yes	None	0%	Olanzapine 7.5 mg	22	DAC, ST, MMF	29	Psych Admit 5 days
E - II		Allograft Ductopenia sLK	34	No	Olanzapine 10 mg	0%	Olanzapine 10 mg	1	BAS, ST, MMF, TAC	9	Home
F	56/M Caucasian	Cryptogenic OLT	31	Yes	Lithium 900 mg Paroxetine 20 mg	0%	Lithium 900 mg Paroxetine 20 mg	0 0	BAS, ST, MMF, TAC	7	Home
G	43/F Caucasian	PSC/CCA OLT	24	No	Lamotrigine 300 mg Topiramate 100 mg Venlafaxine 150 mg Ziprasidone 160 mg	0%	Lamotrigine 300 mg Topiramate 100 mg Venlafaxine 150 mg Ziprasidone 160 mg	0 0 0 0	DAC, ST, MMF	7	Home
H	58/F Caucasian	PBC OLT	26	No	Lithium 600 mg	0%	Lithium 600 mg	5	AZA, ST, MMF, TAC	7	Home

MELD: Model of End Stage Liver Disease, HE: Hepatic Encephalopathy, OLT: Orthotopic Liver Transplant, Meds Medications, POD: Postoperative Day, IMS: Immunosuppression, LOS: Length of Stay (in days), Psych LOS: psychiatric length of stay (in days), F: Female, M: Male, HCV: Chronic Hepatitis C, NASH: Nonalcoholic Steatohepatitis, ETOH alcohol, sLK: Simultaneous Liver and Kidney Transplant, PSC: Primary Sclerosing Cholangitis, CCA: Cholangiocarcinoma, PBC: Primary Biliary Cirrhosis, BAS: Basiliximab, ST: Steroids, MMF: Mycophenolate, TAC: Tacrolimus, DAC: Daclizumab, AZA: Azathioprine, Psych Admit: Psychiatric Admission

**Table 2: One-Year Outcomes.**

Patient	Readmission*	Episode of Acute Cellular Rejection	Medication Compliance	1 year Allograft Survival	1 Year Patient Survival
A	No	No	Yes	Yes	Yes
B	No	No	Yes	Yes	Yes
C	Yes, 1, Unrelated to BD/OLT	No	Yes	Yes	Yes
D	No	No	No, has not followed-up	Yes	Yes
E and F	Yes, 1, Rejection	Yes, IMS held for kidney dysfunction on 1 <sup>st</sup> OLT	Yes	No/Yes	Yes
G	No	No	Yes	Yes	Yes
H	No	No	No, has not followed-up	Yes	Yes
I	Yes, Unrelated to BD/OLT	No	Yes	Yes	Yes

\*Subsequent readmission after initial psychiatric hospitalization following liver transplantation, BD: Bipolar Disorder, OLT: Orthotopic Liver Transplant, IMS: Immunosuppression

**Table 3: Dosing and relative side effects of medications used for treatment of bipolar disorder.**

Medication	Initial Dosing (mg)	Typical Therapeutic Dose Range (mg)	Weight Gain, Glucose, and Lipid Abnormalities	QTc Prolongation	Hypotension	Sedation	Anticholinergic Effects
<i>Mood Stabilizers:</i>							
Lithium	1800	900 - 1800 Level (mania): 1 - 1.5 mEq/L Level (maintenance): 0.6 - 1.2 mEq/L	+	0	0	0/+	0/+
<i>Anticonvulsants:</i>							
Valproic Acid	750	Up to 60 mg/kg/day Level: 50 - 125 mcg/mL	+	0	+	++	0/+
Lamotrigine	25	100 - 200	+	0	0	+	++
<i>Atypical Antipsychotics:</i>							
Aripiprazole	30	10 - 30	0	0	0	0/+	0
Risperidone	3	2 - 8	++	+	0	+	0
Olanzapine	10 - 15	10 - 30	+++	0	+	++	++
Quetiapine	100	300 - 800	++	+	+	++	++
Ziprasidone	80	120 - 200	0	++	0	+	0

0 = No risk or rarely causes side effects at therapeutic dose. + = Mild or occasionally causes side effects at therapeutic dose. ++ = Sometimes causes side effects at therapeutic dose. +++ = Frequently causes side effects at therapeutic dose.

\*Lower starting doses may be indicated for elderly patients, patients with hepatic or renal impairment, or patients taking other medications with potential drug-drug interactions.

with a better response [18]. Mamah et al. reported a patient that underwent OLT for HCV and alcoholic cirrhosis complicated with hepatocellular carcinoma. Steroids and tacrolimus constituted his immunosuppressive regimen. BD was initially managed with lithium but given sedation, the patient was transitioned to olanzapine, lorazepam and lamotrigine [19].

In our cohort of 8 BD patients that underwent liver transplantation, the majority 7/8 (87.5%) were Caucasian and had varied etiologies of liver disease. Five (62.5%) patients required post-transplant psychiatric hospitalization. The main risk factors for post-liver transplant psychiatric admission were the history of hepatic encephalopathy, the use of medications that are primarily metabolized by the liver, pre-transplant psychiatric dose reduction of > 50% paired with slow post-transplant up-titration (Table 1).

The patients that did not require psychiatric hospitalization after liver transplantation were less likely to have a history of hepatic encephalopathy and had their psychotropic medications continued throughout transplant. The use of a particular immunosuppressive regimen was not associated with improved psychiatric outcomes (Table 1). In those patients who developed BD symptom after liver transplantation, the psychiatrist confirmed the diagnosis after ruling out other etiologies by the medical team. Given the small sample size of this study, individual variables were not sufficiently powered to predict psychiatric hospitalization.

One-year follow up outcomes including, acute cellular rejection, readmission, allograft and patient survival were not different when compared to the general transplant population [20,21]. Acute cellular rejection was seen in 1 patient in which immunosuppressant were held due to kidney dysfunction. This particular patient was the only

one that has required re-transplantation (allograft loss). Patient survival at 1 year was 100%.

To our knowledge this is the first case series to describe outcomes in these 2 conditions and to provide general management guidelines to assist the transplant practitioners with this unique subset of patients.

The presence of comorbid BD adds complexity to the already demanding transplant process. The metabolism of certain medications is impaired in advanced liver disease, but this rapidly reverses back to normal with a functioning allograft. Drug-drug interactions are frequent with BD and transplant related medications. It is then necessary to have detailed knowledge of the BD pharmacology, as continuous monitoring and adjustments are needed. Multiple factors can affect neurocognition before and after liver transplantation. BD pharmacology and specific factors that influence neurocognition in liver transplant will be described.

### A. Bipolar disease pharmacology

The goals of therapy in BD include acute stabilization of mania and depression as well as maintenance of long-term remission. Mood stabilizers and antipsychotics are the mainstay of treatment for BD [22-24]. The medical regimen needs to be individualized balancing efficacy and associated side effects. Table 3 outlines the potential side effects of the most commonly used medications in BD [25]. Pharmacotherapy regimens usually include a combination of mood stabilizers, antipsychotics, and novel antipsychotics to adequately manage BD [26,27].

Antidepressants are commonly utilized in the United States as the initial treatment for bipolar depression despite not having Food

**Table 4:** Dose adjustment for hepatic and renal impairment of medications used for treatment of bipolar disorder.

Medication	Metabolism site	Metabolism pathway	Dose adjustment for Hepatic Impairment	Dose adjustment for Renal Impairment	Drug-drug interactions with immunosuppressants, or prophylactic antimicrobials
<i>Mood Stabilizers:</i>					
Lithium	Kidney		None	GFR > 50 ml/min: None GFR 10 - 50 ml/min: reduce dose by 25 - 50% GFR < 10 ml/min: reduce dose by 50 - 75%	None
<i>Anticonvulsants:</i>					
Valproic Acid	Liver	Conjugation	Do not use with hepatic disease.	None	Decreased valproic acid plasma concentrations and potential increased seizure activity with acyclovir.
Lamotrigine	Liver	Conjugation	Moderate-severe impairment without ascites: reduce dose by 25%. Severe impairment with ascites: reduce dose by 50%.	No formal recommendations; may need to reduce maintenance dose for severe renal impairment	None
<i>Atypical Antipsychotics:</i>					
Aripiprazole	Liver	CYP2D6,CYP3A4	None	None	None
Risperidone	Liver	CYP2D6	Initial dose: 0.5 mg ORALLY twice daily; increase dose in increments of no more than 0.5 mg twice a day, with increases to dosages above 1.5 mg twice a day occurring at intervals of at least 1 week.	Same as hepatic	Major interaction with tacrolimus or fluconazole due to increased risk of QT prolongation.
Olanzapine	Liver	CYP1A2,CYP2D6	None	None	Contraindicated with fluconazole due to increased risk of QT prolongation.
Quetiapine	Liver	CYP3A4, Sulfoxidation, Oxidation	Initial dose: 25 mg/day; increase dose daily in increments of 25 to 50 mg/day to an effective dose based on response and tolerability.	None	Contraindicated with fluconazole and major interaction with tacrolimus due to increased risk of QT prolongation.
Ziprasidone	Liver	CYP3A4,CYP1A2, Oxidation, Reduction, Methylation	None	None	Contraindicated with fluconazole and contraindicated with tacrolimus due to increased risk of QT prolongation.

and Drug Administration approval and its controversial role for in this setting [22-24,26]. It has been reported that antidepressants can worsen BD by promoting mood switches, frequency of cycling and suicidal ideation, but the data has yielded mixed results. At present for BD type I, antidepressants should be used in combination with a mood stabilizing agent. For acute depression in BP type II, antidepressants are well tolerated but their efficacy is questionable [28]. Two of our patients (Case C and D) were treated with high dose antidepressants, but did not experience increase in mood switches, cycling or suicidal ideation.

Chronic liver disease and specifically cirrhosis can cause alterations in medication absorption, distribution, and elimination kinetics, thus affecting many drugs [29]. Impaired hepatic function may lead to prolonged elimination half-lives, requiring slower titrations and dose reductions of many commonly used psychiatric medications. Glucuronidation metabolism pathways are relatively spared as compared to the oxidative pathways. Antipsychotics with minimal hepatic metabolism, and lithium, a mood stabilizer, seem to offer the most predictable pharmacokinetics [30]. Medications with extensive hepatic metabolism may accumulate in the setting of hepatic dysfunction resulting in increased blood levels and subsequent side effects even at standard dosages and require careful titration. Drug-metabolizing enzymes like CYP450 have decreased activity and may cause elevated serum concentrations of medications like quetiapine which undergoes extensive hepatic metabolism primarily by cytochrome P450 3A4 [31]. Cirrhosis is often accompanied by reduced effective renal plasma flow and decreased glomerular filtration rate, causing decreased renal elimination of some drugs such as lithium [32]. Ultimately, hepatic and renal impairment may necessitate dose adjustment of BD medications. Table 4 reviews suggested dose adjustments [33].

Adequate allograft function following liver transplantation

requires dose adjustments that are paired with the new normal hepatic metabolism of medications. Drug-drug interactions between BD medications, immunosuppressants, and antimicrobial agents frequently necessitate dose modification, additional monitoring, or discontinuation. Fluconazole, TAC, and atypical antipsychotics can individually cause QT prolongation/torsades de pointes; their combined use increases this risk Table 4 [34]. Baseline and follow-up electrocardiogram is generally advised.

### B. Specific factors that affect neurocognition before and after liver transplantation

With the progression of liver disease, hepatic encephalopathy and acute kidney injury commonly arise. Overt hepatic encephalopathy occurs in approximately 30-45% of cirrhotic patients and is an expression of advanced liver disease. Medications that act on the central nervous system, including neuropsychiatric drugs, are common culprits of hepatic encephalopathy. The development of hepatic encephalopathy implies a poor prognosis and mandates aggressive investigation and correction of the underlying cause, often requiring dose reduction or discontinuation of psychotropic medications [13,14].

Renal dysfunction is a common complication of cirrhosis which occurs in approximately 20% of all hospitalized patients with cirrhosis and is associated with an increased mortality [15]. Uremic encephalopathy complicates severe renal dysfunction and can manifest as mental changes or motor disturbances. Up to 30% of patients receiving hemodialysis may have a degree of cognitive impairment [35]. As kidney disease (acute or chronic) and hepatic encephalopathy aggravate the course of cirrhosis, some psychiatric medications may require further dose adjustments.

Neuropsychiatric complications such as encephalopathy, headache, seizures, intracranial bleeding, etc can occur in up to 21-26% of liver transplant recipients in the early postoperative period. In the post-transplant period mental status changes can be multifactorial and include: the operative intervention, intensive care unit stay, mechanical ventilation, medications (sedatives, narcotic use, antibiotics, immunosuppressive medications – both steroids and calcineurin inhibitors), infections (central nervous system or sepsis), cerebrovascular events (stroke, bleeding, seizures), metabolic conditions (uremia, adrenal insufficiency, central pontine myelinolysis, electrolyte imbalance), and previous alcohol related neurocognitive changes (Wernicke's or Korsakoff Syndrome; masked or misdiagnosed as hepatic encephalopathy) [16,17,36]. Delayed reinitiation, of psychiatric medications, often times at suboptimal doses, and likely compounds these issues (as in 3 of our cases).

Corticosteroids are associated with multiple neuropsychiatric side effects including: depression, mania, agitation, mood lability, anxiety, insomnia, catatonia, depersonalization, delirium, dementia, and psychosis. These adverse drug effects have a reported incidence of 3-60% [37].

Calcineurin inhibitors, cyclosporine and TAC, have been associated with various neuropsychiatric complications, particularly in the early post-transplant period. Elevated blood levels of TAC or cyclosporine are common but not essential for toxicity to manifest. Hypomagnesemia and hypocholesterolemia may increase the risk of calcineurin inhibitor-associated toxicity. The clinical presentation includes: tremor, headache, and encephalopathy. A particular syndrome of calcineurin inhibitor neurotoxicity, posterior reversible encephalopathy, consists of cortical blindness and altered consciousness with a specific magnetic resonance appearance. It is associated with reversible vasogenic subcortical edema mainly seen in calcineurin inhibitor users, but few cases have been described in patients on mTOR inhibitors. The approach to managing calcineurin inhibitor toxicity is supportive care, dose reduction, or change of the immunosuppressive drug [16].

A recent meta-analysis and systematic review revealed that early steroid withdrawal or steroid avoidance in a TAC based immunosuppressive regimen is safe and effective for the prevention of acute and chronic rejection with comparable patient and graft survival rates. This study suggested that these protocols could be effective in lowering the dose of TAC in order to minimize the potential detrimental effect on renal function and neurological complications [38]. Thus, in patients deemed at high risk for neuropsychiatric complications, immunosuppression alterations may be considered either as a prophylactic or reactionary measure, with relative safety to the allograft.

## Conclusion

Psychiatric illness/symptoms can impair an individual's ability to adhere to medical regimens, jeopardizing rejection and allograft function [39], but this should not be an absolute contraindication for liver transplantation. Psychiatric disease course and severity, patient's insight of their condition, and historic adherence to medical regimens should be included in the assessment. It is therefore mandatory that a patient's psychiatric disease be optimally controlled pre-transplant and adequately managed in the early postoperative period and thereafter.

This cases series provides evidence that in carefully selected individuals with BD, liver transplantation is feasible if the medical, surgical and psychiatric teams coordinate efforts. The severe limitation of data in this specific patient population precludes the issuance of evidence based management guidelines. Based on our experience, we suggest the following principles in the management of the BD patient in the liver transplant setting.

1. Comprehensive psychiatric evaluation to assess liver transplant candidacy.
2. Adjustment or correction of medication regimen based on liver and renal function.

3. Use of medications with proven mood stabilizing properties, including but not limited to antipsychotics that do not require adjustment for worsening liver function.

4. Evaluation and close follow-up with a psychiatric team starting upon the initiation of advanced liver disease care and continuing after liver transplantation.

5. Continuation and/or early reinitiation of psychiatric medications with dose escalation to previous levels before pre-transplant dose reductions.

6. Steroid minimization or possibly steroid free immunosuppressive regimens could be investigated.

7. Use of additional induction agents to reduce calcineurin inhibitor needs could be considered.

## Reference

1. Murray KF, Carithers RL Jr; AASLD (2005) AASLD practice guidelines: Evaluation of the patient for liver transplantation. *Hepatology* 41: 1407-1432.
2. Secunda K, Gordon EJ, Sohn MW, Shinkunas LA, Kaldjian LC, et al. (2013) National survey of provider opinions on controversial characteristics of liver transplant candidates. *Liver Transpl* 19: 395-403.
3. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, et al. (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 64: 543-552.
4. Fuller BE, Rodriguez VL, Linke A, Sikirica M, Dirani R, et al. (2011) Prevalence of liver disease in veterans with bipolar disorder or schizophrenia. *Gen Hosp Psychiatry* 33: 232-237.
5. Kim WR (2002) The burden of hepatitis C in the United States. *Hepatology* 36: 30-34.
6. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases (2009) Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 49: 1335-1374.
7. Singal AK, Chaha KS, Rasheed K, Anand BS (2013) Liver transplantation in alcoholic liver disease current status and controversies. *World J Gastroenterol* 19: 5953-5963.
8. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, et al. (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 264: 2511-2518.
9. Brunette MF, Mueser KT (2006) Psychosocial interventions for the long-term management of patients with severe mental illness and co-occurring substance use disorder. *J Clin Psychiatry* 67 Suppl 7: 10-17.
10. Wang X, Li J, Riaz DR, Shi G, Liu C, et al. (2014) Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 12: 394-402.
11. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, et al. (2012) The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 55: 2005-2023.
12. Green CA, Yarborough BJ, Leo MC, Yarborough MT, Stumbo SP, et al. (2015) The STRIDE weight loss and lifestyle intervention for individuals taking antipsychotic medications: a randomized trial. *Am J Psychiatry* 172: 71-81.
13. Poordad FF (2007) Review article: the burden of hepatic encephalopathy. *Aliment Pharmacol Ther* 25 Suppl 1: 3-9.
14. Prakash R, Mullen KD (2010) Mechanisms, diagnosis and management of hepatic encephalopathy. *Nat Rev Gastroenterol Hepatol* 7: 515-525.
15. Wong F, O'Leary JG, Reddy KR, Patton H, Kamath PS, et al. (2013) New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis and infection. *Gastroenterology* 145: 1280-1288.
16. Lewis MB, Howdle PD (2003) Neurologic complications of liver transplantation in adults. *Neurology* 61: 1174-1178.
17. Kizilisik AT, Shokouh-Amiri MH, Tombazzi CR, Desmukh S, Grewal HP, et al. (2001) Psychiatric complications after liver transplantation. *Transplant Proc* 33: 3697.
18. Vieta E, De Pablo J, Cirera E, Grande L, Rimola A (1993) Rapidly cycling bipolar II disorder following liver transplantation. *Gen Hosp Psychiatry* 15: 129-131.
19. Mamah D, Hong BA, Chapman WC (2004) Liver transplantation in a patient with undiagnosed bipolar disorder. *Transplant Proc* 36: 2717-2719.
20. Adams DH, Sanchez-Fueyo A, Samuel D (2015) From immunosuppression to tolerance. *J Hepatol* 62: S170-185.

21. Song AT, Avelino-Silva VI, Pecora RA, Pugliese V, D'Albuquerque LA, et al. (2014) Liver transplantation: fifty years of experience. *World J Gastroenterol* 20: 5363-5374.
22. Geddes JR, Miklowitz DJ (2013) Treatment of bipolar disorder. *Lancet* 381: 1672-1682.
23. Goodwin GM; Consensus Group of the British Association for Psychopharmacology (2009) Evidence-based guidelines for treating bipolar disorder: revised second edition--recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 23: 346-388.
24. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, et al. (2013) Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord* 15: 1-44.
25. American Psychiatric Association (2002) Practice guideline for the treatment of patients with bipolar disorder (revision). *Am J Psychiatry* 159: 1-50.
26. Amerio A, Odone A, Marchesi C, Ghaemi SN (2014) Long-term treatment of bipolar disorder: the controversial role of antidepressants. *Aust N Z J Psychiatry* 48: 1062.
27. Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin K (1999) Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord* 52: 135-144.
28. Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, Grunze H, et al. (2013) The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. *Am J Psychiatry* 170: 1249-1262.
29. Verbeeck RK (2008) Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol* 64: 1147-1161.
30. Sheehan JJ, Sliwa JK, Amatniek JC, Grinspan A, Canuso CM (2010) Atypical antipsychotic metabolism and excretion. *Curr Drug Metab* 11: 516-525.
31. Thyrum PT, Wong YW, Yeh C (2000) Single-dose pharmacokinetics of quetiapine in subjects with renal or hepatic impairment. *Prog Neuropsychopharmacol Biol Psychiatry* 24: 521-533.
32. Delcò F, Tchambaz L, Schlienger R, Drewe J, Krähenbühl S (2005) Dose adjustment in patients with liver disease. *Drug Saf* 28: 529-545.
33. <http://www.micromedexsolutions.com>
34. Bennett WM, Aronoff GR, Morrison G, Golper TA, Pulliam J, et al. (1983) Drug prescribing in renal failure: dosing guidelines for adults. *Am J Kidney Dis* 3: 155-193.
35. Seifter JL, Samuels MA (2011) Uremic encephalopathy and other brain disorders associated with renal failure. *Semin Neurol* 31: 139-143.
36. Zivković SA (2013) Neurologic complications after liver transplantation. *World J Hepatol* 5: 409-416.
37. Dubovsky AN, Arvikar S, Stern TA, Axelrod L (2012) The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. *Psychosomatics* 53: 103-115.
38. Gu J, Wu X, Lu L, Zhang S, Bai J, Wang J, et al. (2014) Role of steroid minimization in the tacrolimus-based immunosuppressive regimen for liver transplant recipients: a systematic review and meta-analysis of prospective randomized controlled trials. *Hepatol Int* 8: 198-215.
39. Errichiello L, Picozzi D, de Notaris EB (2014) Prevalence of psychiatric disorders and suicidal ideation in liver transplanted patients: a cross-sectional study. *Clin Res Hepatol Gastroenterol* 38: 55-62.