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Advances in Drug Therapy and Medication Safety in Liver Cirrhosis: A Pharmacological Review

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A B S T R A C T :

Aim: This review looks at recent progress in drug therapy and medication safety in liver cirrhosis. It covers treatment of the underlying cause, portal pressure control, drug therapy for specific complications, and high-risk medicines needing dose adjustment or deprescribing. **Methods:** A narrative review of 30 key sources published between 2006 and 2024 (AASLD and EASL guidelines, consensus statements, randomized trials, a meta-analysis and observational studies) was carried out and summarised descriptively. **Results:** Chronic liver disease and cirrhosis cause more than 1.3 million deaths each year, and after decompensation estimated 5-year survival drops from over 80–90% to under 50% [1,3]. Pangenotypic direct-acting antivirals cure over 95% of hepatitis C patients [2], and carvedilol has largely replaced older non-selective beta-blockers for portal hypertension [6,9]. Ascites, hepatic encephalopathy and hepatorenal syndrome are treated with spironolactone plus furosemide, lactulose plus rifaximin, and terlipressin plus albumin, respectively. Because the diseased liver handles drugs differently, NSAIDs, opioids, sedatives and unneeded proton pump inhibitors are the main high-risk drugs [25–29]. **Conclusion:** Good care combines disease-directed pharmacotherapy with dose adjustment, deliberate deprescribing and regular medication-safety monitoring, with clinical pharmacists playing a key part.

Keywords: Liver cirrhosis, portal hypertension, carvedilol, direct-acting antivirals, hepatic encephalopathy, medication safety, deprescribing, clinical pharmacist

1. INTRODUCTION

Cirrhosis is where many chronic liver diseases end up, driven by continuing hepatocellular injury, chronic inflammatory signalling and progressive scarring. Chronic liver disease and cirrhosis are responsible for more than 1.3 million deaths worldwide every year [1]. The causes have changed over time. Hepatitis B (HBV) is increasingly prevented through infant vaccination, and hepatitis C (HCV) can now be cured with direct-acting antivirals (DAAs) [1,2], while obesity, metabolic syndrome and type 2 diabetes have made metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) a leading cause. Alcohol-associated liver disease is still another major cause [1].

Cirrhosis is staged as either compensated or decompensated. Around 5–7% of compensated patients decompensate each year [3,4], showing up as ascites, variceal bleeding, hepatic encephalopathy (HE), jaundice or kidney failure. Once decompensation occurs, estimated 5-year survival falls from over 80–90% to under 50% [3,5]. These patients often end up on several drugs, and a damaged liver changes how each of them behaves. This review pulls together etiology-directed therapy, the management of portal hypertension and its complications, and medication safety into one practical framework for pharmacy students, clinicians and clinical pharmacists.

Objectives. (i) To outline the cellular and vascular mechanisms behind portal hypertension, fluid retention and encephalopathy; (ii) to evaluate etiology-directed therapy (DAAs for HCV, nucleos(t)ide analogues for HBV); (iii) to analyse haemodynamic control with NSBBs and carvedilol; (iv) to describe the multi-drug management of ascites, HE, variceal bleeding, SBP and HRS; (v) to examine how impaired liver function, low albumin and shunting change drug disposition; (vi) to identify high-risk drug classes that need dose reduction or withdrawal; (vii) to outline emerging targets; and (viii) to show what clinical pharmacists and team-based care contribute [6,7].

2. METHODOLOGY

This is a narrative review of the published literature. Thirty key sources published between 2006 and 2024 were included: AASLD and EASL practice guidelines, international consensus statements (Baveno VII, International Club of Ascites), randomized controlled trials, a meta-analysis and observational studies. Information on pathophysiology, etiology-directed therapy, portal hypertension, ascites, HE, hepatorenal syndrome (HRS) and drug safety was drawn from each source and summarised descriptively, and no statistical pooling was attempted.

3. PHARMACOLOGICAL BACKGROUND AND THERAPY

3.1 Pathophysiology relevant to pharmacotherapy

Activated hepatic stellate cells lay down type I and III collagen and block the sinusoidal pores (capillarization), limiting the exchange of nutrients, toxins and drugs between blood and hepatocytes [4,8]. Portal hypertension (HVPG >5 mmHg; clinically significant at ≥10 mmHg) arises from fixed structural resistance plus dynamic resistance, in which contractile stellate cells respond to excess endothelin-1 and thromboxane A_2 and too little nitric oxide [8,9]. The resulting splanchnic vasodilation lowers effective arterial volume and activates the sympathetic, renin–angiotensin–aldosterone and vasopressin systems, causing sodium and water retention, ascites and hyponatraemia [7,10]. Most drug targets and hazards discussed below trace back to this circulatory dysfunction.

3.2 Etiology-directed pharmacotherapy

Taking away the cause of injury can stop further damage, lower portal pressure and even let fibrosis regress [4,9] (Fig. 1). **HCV:** all-oral DAAs achieve sustained virologic response (SVR12) in over 95% of patients [2,11,12]. NS5B inhibitors (sofosbuvir) and NS5A inhibitors (velpatasvir, ledipasvir, pibrentasvir) make up the backbone of safe regimens, whereas NS3/4A protease inhibitors (glecaprevir, voxilaprevir) are contraindicated in Child-Pugh B/C disease because of raised drug levels and the risk of hepatotoxicity [2,12] (Table 1). **HBV:** treatment aims for lifelong viral suppression with tenofovir alafenamide, tenofovir disoproxil fumarate (with renal and bone monitoring) or entecavir (dose-adjusted when creatinine clearance is <50 mL/min) [13,14]. **MASLD, autoimmune and cholestatic disease:** pioglitazone, GLP-1 receptor agonists (semaglutide, tirzepatide) and resmetirom help correct metabolic risk [15,16]; autoimmune hepatitis is treated with steroids plus azathioprine, and primary biliary cholangitis with ursodeoxycholic acid 13–15 mg/kg/day, whereas obeticholic acid is best avoided in decompensated cirrhosis [17].

Table 1. DAA regimens for chronic HCV by disease stage [2,11,12]

Regimen	Target	Compensated	Decompensated
Sofosbuvir / Velpatasvir	NS5B + NS5A	12 weeks	+ Ribavirin 12 wk (24 wk if RBV-intolerant)
Glecaprevir / Pibrentasvir	NS3/4A + NS5A	8 weeks	Contraindicated (Child-Pugh B/C)
Sofosbuvir / Ledipasvir	NS5B + NS5A	Genotypes 1, 4, 5, 6	With ribavirin

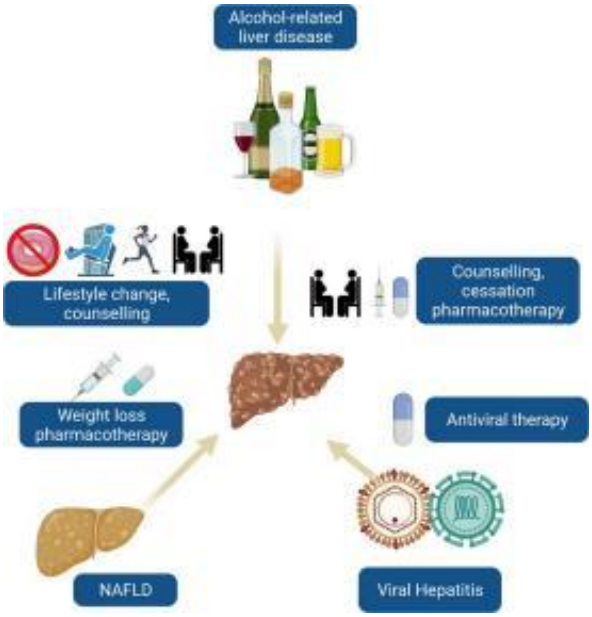


Fig. 1. Etiology-directed management of chronic liver disease (alcohol-related, NAFLD, viral hepatitis) [2,13–15,17]

3.3 Portal hypertension and variceal bleeding

The treatment goal is an HVPG <12 mmHg or a reduction of ≥20% from baseline [6,9]. Non-selective beta-blockers (NSBBs) lower portal pressure through β1-blockade (reduced cardiac output) and β2-blockade (unopposed splanchnic vasoconstriction) [6,18]. Carvedilol adds α1-blockade, which reduces intrahepatic resistance, and is preferred in compensated cirrhosis (Baveno VII); it is started at 6.25 mg daily and titrated to 12.5 mg daily while blood pressure and heart rate are monitored [6,9]. The safety margin narrows in advanced disease, so the dose should be reduced or interrupted in refractory ascites, infection, systolic BP <90 mmHg or serum sodium <130 mEq/L [9]. Acute variceal bleeding calls for volume restoration, early vasoactive therapy (terlipressin, or octreotide/somatostatin), ceftriaxone 1 g/day for up to 7 days and endoscopic band ligation [9,18].

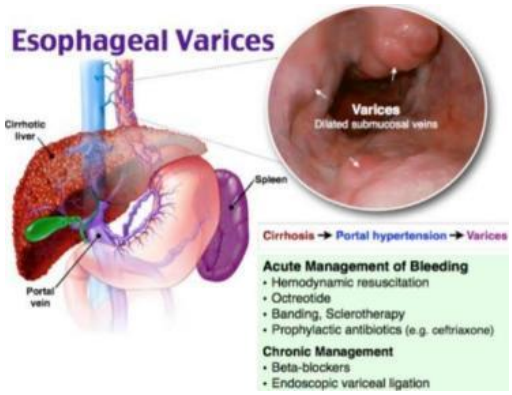


Fig. 2. Oesophageal varices: cirrhosis, portal hypertension and acute/chronic management of variceal bleeding [6.9.18]

3.4 Ascites and fluid overload

About 60% of patients develop ascites within 10 years of diagnosis. Management combines 2 g/day sodium restriction with spironolactone (100 mg, up to 400 mg/day) and furosemide (40 mg, up to 160 mg/day) in the standard 100:40 ratio, limiting weight loss to 0.5 kg/day (1 kg/day with oedema) [7,19,20] (Table 2). After large-volume paracentesis (>5 L), albumin 6–8 g per litre removed prevents circulatory dysfunction; in spontaneous bacterial peritonitis (SBP), albumin 1.5 g/kg at diagnosis and 1 g/kg on day 3 reduces renal failure and mortality [20].

Table 2. Diuretics used in cirrhotic ascites [7,20]

Drug	Action	Key risks	Monitoring
Spironolactone	Aldosterone-receptor blocker	Hyperkalaemia, gynaecomastia, acidosis	K^+, Na^+, creatinine, BP
Furosemide	Loop diuretic (Na–K–2Cl)	Hypokalaemia, hyponatraemia, volume loss	Electrolytes, weight, renal function
Torsemide / Bumetanide	High-potency loop diuresis	Electrolyte disturbance, ototoxicity (high IV dose)	Urine output, renal function

3.5 Hepatic encephalopathy

Ammonia from the gut bypasses the failing liver, crosses the blood–brain barrier and is converted to glutamine in astrocytes, which causes osmotic swelling and raises GABA tone [21]. Treatment aims to lower ammonia and remove precipitants such as bleeding, constipation and infection. **Lactulose** (first line; 15–30 mL two to four times daily, titrated to 2–3 soft stools/day) acidifies the colon and traps ammonia as NH_4^+ [21]. **Rifaximin** 550 mg twice daily, added to lactulose, reduces ammonia-producing bacteria and prevents recurrent overt HE [22]. L-ornithine L-aspartate and branched-chain amino acids serve as adjuncts [21].

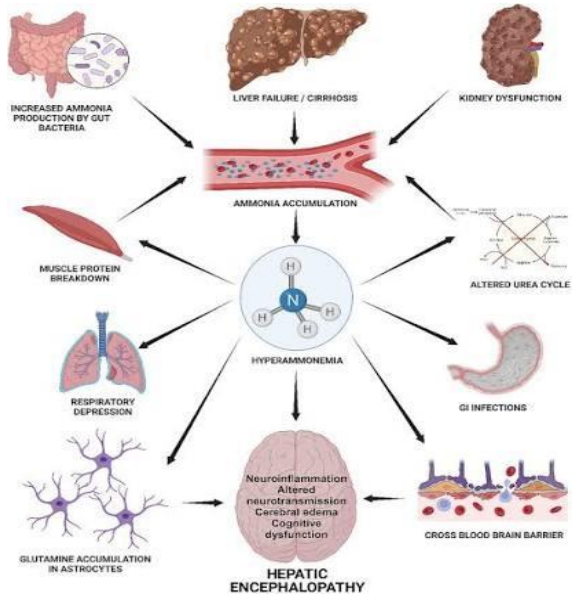


Fig. 4. Hepatic encephalopathy: hyperammonaemia and contributing mechanisms [21,22]

3.6 Hepatorenal syndrome

HRS-AKI is a functional kidney failure caused by intense renal vasoconstriction after splanchnic vasodilation. By International Club of Ascites criteria, it is diagnosed when AKI persists after diuretics are withdrawn and after 48 h of albumin (1 g/kg/day), with no shock, nephrotoxins or structural kidney disease [20,23]. Treatment combines a vasoconstrictor with albumin [20,24] (Table 3).

Table 3. Vasoactive regimens for HRS-AKI [24]

Regimen	Dosing	Considerations
Terlipressin + albumin	0.85–2 mg IV every 6 h; albumin 20–40 g/day	FDA-approved (2022); monitor oxygenation, ischaemic events, pulmonary oedema
Norepinephrine + albumin	0.5–3 mg/h IV infusion, MAP rise ≥10 mmHg	Needs central line/ICU; efficacy similar to terlipressin
Midodrine + octreotide + albumin	Midodrine 7.5–12.5 mg TID; octreotide 100–200 mcg SC TID	Outpatient option where IV agents unavailable; lower response

3.7 Medication safety, pharmacokinetics and deprescribing

Since the liver is the main site of drug clearance, cirrhosis alters pharmacokinetics in four ways [25,26]: (i) reduced first-pass clearance through shunting raises the levels of morphine, propranolol and labetalol [25,27]; (ii) Phase I CYP activity (CYP1A2, 2C19, 3A4/5) falls and half-lives lengthen, while Phase II activity is preserved until late disease [25]; (iii) hypoalbuminaemia increases the free fraction of highly bound drugs such as phenytoin, warfarin and furosemide [25,26]; and (iv) the expanded volume of distribution caused by ascites and oedema means hydrophilic drugs (aminoglycosides, beta-lactams) may need higher loading doses [25].

High-risk drugs. NSAIDs block renal prostaglandins and can cause AKI, fluid retention and ulcer bleeding, and are contraindicated in ascites [10,26]. Acetaminophen is the safest analgesic but is limited to 2 g/day; opioids need lower doses and longer intervals; and benzodiazepines can precipitate overt HE (if one is essential, lorazepam or oxazepam at reduced doses) [26,27]. Proton pump inhibitors (PPIs) are often prescribed without a clear indication and are associated with SBP, *C. difficile* infection, HE and mortality, so unneeded PPIs should be deprescribed [28,29].

The stepwise pharmacological strategy outlined above is summarised in Table 4 [6,7,9,26].

Table 4. Stepwise pharmacological management strategy [6,7,9,26]

Step	Key actions
1. Diagnosis	Baseline clinical assessment, staging and etiology identification
2. Etiology-directed therapy	HCV: sofosbuvir/velpatasvir; HBV: entecavir/TAF; MASLD: metabolic optimisation, GLP-1 RA, resmetirom; AIH/PBC: immunosuppression/UDCA
3. Portal hypertension	Assess for CSPH (HVPG ≥10 mmHg or varices); start carvedilol 6.25–12.5 mg/day or standard NSBB
4. Complication therapy	Ascites: spironolactone + furosemide (100:40) + salt restriction; HE: lactulose + rifaximin 550 mg BID; variceal bleed: terlipressin/octreotide + ceftriaxone + EBL; HRS-AKI: terlipressin + albumin; SBP: ceftriaxone + albumin
5. Safety check	Stop NSAIDs, nephrotoxins and unnecessary sedatives; review PPI indication; acetaminophen ≤2 g/day; review renal/hepatic dosing

3.8 Emerging approaches, team care and challenges

Newer agents aim to slow progression rather than just treat complications: anti-fibrotic drugs (TGF-β, galectin-3, pan-PPAR and LOXL2 targets), gut–liver–brain axis modulators (synbiotics, faecal microbiota transplantation) and incretin-based agonists for MASH [4,16]. Clinical pharmacists reconcile medications at each transition of care, adjust doses to Child-Pugh/MELD score and renal function, screen for interactions, lead deprescribing of NSAIDs, sedatives and unneeded PPIs, and counsel patients on regimens and sodium goals [25–27,29,30]. Key challenges remain: unpredictable drug clearance with no practical bedside tool, polypharmacy and comorbidity, the exclusion of Child-Pugh C patients from phase III trials, and the burden of self-managing lactulose and diuretic titration in patients with subtle cognitive impairment [21,25,26,30].

4. REVIEW OF KEY EVIDENCE

The evidence base is layered. Epidemiological and natural-history data [1,3] establish the burden and staging; secondary reviews [4,5] support a three-part strategy of treating the cause, lowering portal pressure and managing complications; and guidelines and consensus documents [2,6,7,9] supply graded drug recommendations. Randomized trials back sofosbuvir/velpatasvir in decompensated HCV [11], rifaximin for preventing recurrent HE [22] and terlipressin plus albumin for HRS [24]. The evidence on PPI harm [28,29] is observational and shows association rather than causation, although it is consistent across 28 pooled studies (260,854 patients) [29]. An outpatient study found that many of the medication-related problems in decompensated cirrhosis were high-risk, which supports pharmacist-led review [30].

Table 5. Summary of key sources underpinning this review

Source	Type	Key contribution
Devarbhavi 2023 [1]	Global epidemiology update	>1.3 million deaths/year; shift toward metabolic and alcohol-related disease and older, polymedicated patients
EASL 2020 [2]	HCV guideline	Pangenotypic DAAs with cure rates above 95% (SVR12)

Source	Type	Key contribution
D'Amico 2006 [3]	Systematic review (118 studies)	Complication-based staging; 5–7% yearly decompensation; survival falls below 50% at 5 years
Kaplan 2024 [6]	AASLD guidance	Non-invasive risk stratification; early NSBB/carvedilol in CSPH
Angeli 2018 [7]	EASL guideline	Graded recommendations for all decompensation complications
Bass 2010 [22]	Clinical trial	Rifaximin added to lactulose prevents recurrent overt HE
Wong 2021 [24]	Clinical trial	Terlipressin plus albumin for HRS-AKI
Dam 2016 [28]	Observational study	PPI use linked to HE and SBP in cirrhosis with ascites
Wong 2024 [29]	Meta-analysis (28 studies)	PPI use associated with mortality, decompensation and infection (n = 260,854)
Hayward 2019 [30]	Outpatient study	Medication-related problems common; almost half rated high-risk

5. RESULTS

Disease burden: more than 1.3 million deaths per year, 5–7% annual decompensation, and 5-year survival under 50% after decompensation [1,3,5]. Etiology: DAAs cure over 95% of HCV, and long-term nucleos(t)ide analogues control HBV [2,11,13,14]. Portal hypertension: NSBBs, led by carvedilol, lower portal pressure and the long-term risk of decompensation [6,9,18]. Ascites: spironolactone plus furosemide, with albumin for large-volume paracentesis [19,20]. HE: lactulose plus rifaximin [21,22]. HRS-AKI: terlipressin plus albumin [23,24]. Medication safety: altered clearance, shunting, hypoalbuminaemia and distribution volume mean NSAIDs should be avoided, opioids and sedatives used cautiously, unneeded PPIs deprescribed and doses adjusted [25–30].

6. DISCUSSION

Drug treatment of cirrhosis has moved from reacting to late complications towards modifying the disease itself: spotting portal hypertension early, preventing the first decompensation and removing underlying causes [4,5]. Carvedilol is now foundational therapy rather than just prophylaxis against variceal bleeding, and DAAs can stabilise liver function and allow selected patients to return to a compensated state [6,11]. Lactulose with rifaximin strengthens secondary prevention of HE, and terlipressin offers a targeted vasoactive option in HRS-AKI [22,24]. These gains make medication safety even more important: altered drug handling, reduced functional liver mass, altered protein binding and a high pill burden leave patients vulnerable to toxicity, and inappropriate NSAIDs, PPIs or sedatives can precipitate kidney failure, severe infection or encephalopathy [10,26,28]. Modern care therefore needs advanced disease-targeted therapy paired with deliberate deprescribing and careful safety monitoring.

7. CONCLUSION

Recent advances in drug therapy have made liver cirrhosis easier to manage by treating its causes and controlling its complications. Medicines such as antivirals, carvedilol, diuretics, lactulose, rifaximin, and terlipressin with albumin have improved patient care [2,6,9,11,20–24]. At the same time, these medicines have to be used carefully, since liver damage raises the risk of side effects. Avoiding harmful drugs, adjusting doses and reviewing prescriptions regularly can help prevent complications [25–29]. Clinical pharmacists also play an important part in counselling patients and making medication use safer [26,27,30]. Overall, pairing effective treatment with proper medication monitoring can improve patient care and lessen the risks linked to liver cirrhosis.

ABBREVIATIONS

AASLD, American Association for the Study of Liver Diseases; AKI, acute kidney injury; CSPH, clinically significant portal hypertension; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; EBL, endoscopic band ligation; HBV/HCV, hepatitis B/C virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; MASLD/MASH, metabolic dysfunction-associated steatotic liver disease/steatohepatitis; NSAID, non-steroidal anti-inflammatory drug; NSBB, non-selective beta-blocker; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; SVR12, sustained virologic response at 12 weeks.

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