Management of pain in patients with advanced chronic liver disease or cirrhosis

AUTHORS: James P Hamilton, MD, Eric Goldberg, MD, Sanjiv Chopra, MD, MACP
SECTION EDITOR: Bruce A Runyon, MD, FAASLD
DEPUTY EDITOR: Kristen M Robson, MD, MBA, FACG

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Literature review current through: **Sep 2023.**
This topic last updated: **Jul 18, 2023.**

INTRODUCTION

Patients with liver disease may develop acute or chronic pain from a variety of causes. In addition to causes that are common in an otherwise healthy population, patients with advanced liver disease may have ascites (leading to abdominal and lower back pain) and gynecomastia (leading to mastalgia).

Pain is a common symptom among patients with chronic liver disease or cirrhosis, and prescriptions for analgesic medications are often provided [1,2]. In a systematic review of five studies, the prevalence of pain in patients with end-stage liver disease ranged from 30 to 79 percent [1]. In a database study from the Veterans Health Administration including over 100,000 patients with cirrhosis, the annual percentage of patients receiving an opioid prescription increased over time from 36 percent in 2005 to 47 percent in 2014 [2].

This topic will summarize safety considerations of nonselective nonsteroidal antiinflammatory drugs (NSAIDs), selective NSAIDs (COX-2 inhibitors), opioids, acetaminophen, and agents for neuropathic pain in patients with advanced chronic liver disease or cirrhosis. The recommendations regarding analgesic use in patients with advanced chronic liver disease are also summarized in the accompanying table (table 1).

A general approach to patients with cirrhosis is presented separately. (See "Cirrhosis in adults: Overview of complications, general management, and prognosis".)

GENERAL PRINCIPLES

Management of pain in patients with liver disease raises special concerns. The choice of appropriate analgesic agents requires a thorough understanding of their pharmacokinetic and side effect profiles [3] (table 1).

As a general rule, patients with mild liver disease can be treated with a similar choice of drugs as those who are otherwise healthy. Susceptibility to adverse effects increases with worsening liver function due to altered pharmacokinetics and hemodynamic changes. (See "Tests of the liver's capacity to transport organic anions and metabolize drugs".)

The exact cutoff at which drug doses and the selection of drugs should be altered is uncertain. Modifications of drug-prescribing should generally be considered in patients who have developed advanced chronic liver disease (eg, bridging fibrosis on biopsy) or cirrhosis, particularly when accompanied by portal hypertension (such as those with esophageal varices, ascites, or portal gastropathy/colopathy) or renal insufficiency. Important exceptions are patients who are actively drinking alcohol and those on multiple medications, who can develop severe hepatotoxicity from concomitant use of acetaminophen regardless of the severity of liver disease.

NONSELECTIVE NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of variceal hemorrhage, impaired renal function, and the development of diuretic-resistant ascites [4]. Thus, NSAIDs (including aspirin) should generally be avoided in patients with advanced chronic liver disease or cirrhosis (table 1).

The primary effect of NSAIDs is to inhibit cyclooxygenase (prostaglandin synthase), thereby impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes. Two related isoforms of the cyclooxygenase (COX) enzyme have been described: COX-1 and COX-2. (See "NSAIDs: Pharmacology and mechanism of action".)

Gastrointestinal toxicity — NSAIDs inhibit the production of prostaglandins involved in the protection of the gastrointestinal mucosa from noxious agents such as gastric acid. They also inhibit the production of thromboxane leading to decreased platelet aggregation and impaired hemostasis. Multiple studies have demonstrated that patients who take aspirin or other NSAIDs are at least three times as likely to have severe gastrointestinal bleeding from peptic ulcers

compared with patients who do not take NSAIDs. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity".)

This risk may be further increased in patients who have an underlying coagulopathy, such as occurs in those with advanced cirrhosis. Aspirin alone or in conjunction with other NSAIDs has been associated with variceal bleeding. In one case-control study, patients with variceal bleeding were 2.8 times as likely to have used NSAIDs in the week prior to the bleed compared with patients with cirrhosis with esophageal varices who had not bled [5].

Renal toxicity — NSAIDs can induce two different forms of acute renal failure: hemodynamically-mediated and acute interstitial nephritis (which is often accompanied by the nephrotic syndrome). The former and perhaps the latter are directly related to the reduction in prostaglandin synthesis induced by the NSAID. (See "NSAIDs: Acute kidney injury".)

Although renal prostaglandins are primarily vasodilators, they do not have a major role in the regulation of renal hemodynamics in healthy subjects since the basal rate of prostaglandin synthesis is relatively low. By contrast, the release of these hormones (particularly prostacyclin and prostaglandin E2) is increased by underlying glomerular disease, renal insufficiency, hypercalcemia, and the vasoconstrictors angiotensin II and norepinephrine. The secretion of the last hormones is increased in states of effective volume depletion such as cirrhosis, heart failure, and true volume depletion due to gastrointestinal or renal salt and water losses. (See "NSAIDs: Acute kidney injury".)

The adverse effect of NSAIDs on renal function in patients with cirrhosis has been demonstrated in multiple studies (figure 1) [6-8]. In one study, patients given 50 mg of indomethacin every six hours for one day had a 19 percent reduction in glomerular filtration rate (GFR) and 23 percent reduction in renal plasma flow [7]. Furthermore, there was a 29 percent increase in serum creatinine. Another study examined the effect of indomethacin on renal function in patients with Child-Pugh class A cirrhosis [8]. Significant reductions in GFR, urinary sodium, urinary output, and renal plasma flow were observed.

Effect on ascites management — Another concern related to use of NSAIDs in patients with cirrhosis is that they diminish the natriuretic effects of diuretics in patients with ascites, leading to impaired free water clearance and worsening of ascites and edema. Use of NSAIDs should be considered when evaluating patients with apparent diuretic-resistant ascites. (See "Ascites in adults with cirrhosis: Diuretic-resistant ascites".)

COX-2 INHIBITORS

Selective COX-2 inhibitors are effective analgesics that are associated with a decreased incidence of gastrointestinal and renal toxicity. However, they have been associated with an increased incidence of adverse cardiovascular events. At present, we advise against using these agents in patients with advanced liver disease or cirrhosis because data are limited on their use in such patients (table 1). (See "NSAIDs: Adverse cardiovascular effects".)

In rat models of cirrhosis and ascites, selective COX-2 inhibitors caused significantly less decline in glomerular filtration rate (GFR), urine volume, and free water clearance than a nonselective COX inhibitor [9]. However, rats given the COX-2 inhibitor still had nearly a 25 percent decrease in urine volume and a 20 percent decline in GFR from baseline.

Experience with COX-2 inhibitors in patients with advanced chronic liver disease or cirrhosis is limited. The largest study in humans included 28 patients with cirrhosis and ascites who were randomly assigned to celecoxib (200 mg every 12 hours for a total of five doses), naproxen (500 mg every 12 hours for a total of five doses), or placebo [10]. A significant reduction in GFR, renal plasma flow, urinary prostaglandin E2 excretion, and suppression of the diuretic and natriuretic response to furosemide was observed in the group receiving naproxen but not celecoxib or placebo. Furthermore, naproxen, but not celecoxib or placebo, significantly inhibited platelet aggregation. The authors concluded that celecoxib may be a reasonable option for anti-inflammatory treatment of patients with cirrhosis.

However, the study evaluated only short-term treatment, involved only a small number of patients, and, as noted above, celecoxib has the potential to decrease GFR compared with baseline. Further studies are needed to address the use of COX-2 inhibitors in patients with advanced liver disease or cirrhosis.

OPIOIDS

Opioids should be used cautiously in patients with advanced liver disease or cirrhosis (table 1) [11]. Fentanyl appears to be safe in patients with modest hepatic dysfunction. Morphine, oxycodone, and hydromorphone should be used at reduced doses and prolonged intervals of administration. Tramadol may be safe but experience is limited, and thus it should not be used in those with decompensated cirrhosis. The effects of codeine are difficult to predict, and therefore alternatives should be considered. Chronic administration of any opioid may lead to tolerance requiring escalating doses and therefore an increasing risk of hepatic encephalopathy.

A variety of opioids are used for pain control. Opioids exert their analgesic effect through at least four groups of receptors and probably other subpopulations as well. The distribution of these receptors throughout the body, along with their tissue densities within numerous organ systems, account for the global and varied effects of these drugs. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Opioids'.)

As a general rule, these medications are metabolized through hepatic oxidation and glucuronidation. The clearance of opioids depends upon plasma protein binding, hepatic blood flow, and hepatic enzyme capacity. Oxidative enzyme pathways and opioids clearance are impaired in cirrhosis, which may lead to the accumulation of toxic metabolites [12,13].

- Morphine undergoes rapid glucuronidation in the liver with subsequent systemic metabolism. Although glucuronidation is usually preserved despite diminished liver function, multiple studies have demonstrated that the clearance of morphine is delayed in patients with cirrhosis by 35 to 60 percent [12,14-16]. In addition, morphine has increased oral bioavailability in patients with advanced chronic liver disease or cirrhosis secondary to reduced first pass hepatic metabolism [12,16].

  As a result, morphine must be used with caution in patients with advanced chronic liver disease or cirrhosis to avoid accumulation. A twofold increase in the interval of administration has been recommended [14]. Furthermore, if oral forms of morphine are used, the dose must be decreased to account for the increased bioavailability. In a patient with cirrhosis with concomitant renal failure, morphine should be avoided as an accumulation of hydrophilic metabolites can lead to seizure activity, respiratory depression, and hepatic encephalopathy [17].

- Meperidine is metabolized extensively in the liver, and its clearance is significantly affected by hepatic dysfunction. In patients with cirrhosis, the plasma clearance is diminished by 50 percent and the half-life doubles after a single intravenous dose of 0.8 mg/kg [18,19]. In addition, it is highly bound to serum protein and has unpredictable analgesic effects and an increased risk of toxicity in patients with cirrhosis [13]. As a result, we suggest that meperidine be avoided in patients with advanced chronic liver disease or cirrhosis.

- Other opioids that are metabolized by oxidative systems also have decreased clearance. This has been demonstrated with meperidine, propoxyphene, alfentanil, and tramadol. Similar to morphine, these drugs have increased bioavailability in patients with advanced chronic liver disease or cirrhosis [17]. Thus, repeated administration of these drugs can lead to unwanted accumulation of the drugs and their metabolites.

- Codeine requires the oxidative enzyme capacity of the liver to convert it to its active metabolites, potentially decreasing its effectiveness in patients with advanced chronic liver disease or cirrhosis.

- Similarly, tramadol requires conversion to O-desmethyltramadol by hepatic oxidation, so the analgesic effects of this drug may be unpredictable [12]. However, some hepatologists have had favorable experiences with tramadol in patients with cirrhosis in whom acetaminophen was not effective.

- Fentanyl is a lipid-soluble synthetic opioid that is approximately 80 to 100 times as potent as morphine. It is converted by hydroxylation and dealkylation in the liver into inactive and nontoxic metabolites. In a study of patients with histologically confirmed cirrhosis, the pharmacokinetics of fentanyl were unchanged when compared with healthy subjects [20]. However, the patients with cirrhosis in this study had normal serum albumin, and the prothrombin times were only slightly abnormal. It is not known if the metabolism of fentanyl is affected in patients with severe hepatic dysfunction.

- Oxycodone is a derivative of opium that has similar opioid effects to morphine. Oxycodone is metabolized in the liver and excreted by the kidneys. A study of 24 patients with mild to moderate hepatic dysfunction showed that peak plasma concentrations of oxycodone were 50 percent greater compared with those in healthy controls [21]. In addition the t1/2 elimination for oxycodone was increased by 2.3 hours. Oxycodone should be used with caution in patients with advanced chronic liver disease or cirrhosis, and if used, it should be administered at reduced doses and prolonged dosing intervals.

- Hydromorphone is a hydrogenated ketone of morphine that is metabolized by the liver. This opiate lacks toxic metabolites, but it is approximately five times stronger than morphine. In patients with advanced chronic liver disease or cirrhosis, the elimination of hydromorphone is impaired and the half-life is prolonged. Hydromorphone, like oxycodone, should be used with caution in patients with advanced chronic liver disease or cirrhosis, and if used, it should be administered at reduced doses and prolonged dosing intervals [21].

- Methadone is a long-acting opioid that is frequently used to treat heroin addiction. In a study of patients with mild to moderate cirrhosis, the pharmacokinetic profiles of methadone were unchanged compared with healthy individuals [22]. Although the half-life of methadone in patients with severe cirrhosis can be mildly prolonged, drug disposition is not significantly altered [22]. Thus, methadone appears to be safe in patients with advanced chronic liver disease or cirrhosis, at least for short-term administration.

ACETAMINOPHEN (PARACETAMOL)

It is crucial to dismiss the misconception that acetaminophen should be strictly avoided in patients with liver disease. Acetaminophen is an effective and safe analgesic for patients with chronic liver disease, provided that they do not actively drink alcohol (table 1). For patients with cirrhosis or advanced chronic liver disease, the acetaminophen dose is often limited to 2 grams per day because of concern over altered metabolism of acetaminophen in the setting of chronic liver disease [23]. We typically limit acetaminophen intake to 2 grams per day for most patients, while avoiding it entirely in patients with alcoholic hepatitis or acute liver injury.

Acetaminophen is a widely available over-the-counter medication used for analgesic and antipyretic purposes. Based on the drug label provided by the manufacturer, the maximum recommended daily dose for acetaminophen is 3 grams, while a maximum daily dose of 4 grams may be prescribed at the discretion of the clinician [24]. It is well established that acetaminophen is hepatotoxic in larger doses. When ingested at doses greater than 10 grams, it causes severe hepatic necrosis and acute liver failure. The pharmacokinetics and toxicity of acetaminophen are discussed in more detail separately. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and evaluation".)

Acetaminophen appears to be safe in patients with advanced chronic liver disease or cirrhosis when used at the recommended doses. In one study, six patients with chronic liver disease were given 4 grams per day for five days [25]. There was no evidence of drug accumulation or hepatotoxicity in these subjects. In another trial by the same author, 20 patients with cirrhosis were given 4 grams per day for 13 days [26]. Only one patient developed abnormal liver enzymes. After the labs returned to normal, the same patient was subsequently challenged with 10- and 14-day courses of 4 grams per day of acetaminophen without incident. It was thought that the earlier biochemical deterioration in this patient was not related to acetaminophen use.

Patients with alcohol use disorder (even those without cirrhosis) should use acetaminophen with extreme caution. We suggest that patients who actively drink alcohol consume no more than 2 grams per day. In healthy subjects, only a fraction of acetaminophen is metabolized by the cytochrome P450 enzyme system to NAPQI. In patients with alcohol use disorder, the P450 system is induced and therefore more of the toxic metabolite NAPQI is generated. The hepatotoxicity of NAPQI is diminished by glutathione conjugation. However, patients with alcohol use disorder have reduced stores of glutathione secondary to impaired production and poor nutritional status. (See "Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment".)

These factors lead to an increased likelihood of developing hepatotoxicity with acetaminophen use among patients with alcohol use disorder. A retrospective analysis of 67 patients, described as regular users of alcohol who developed hepatic injury after acetaminophen ingestion, showed that 60 percent of the patients took less than 6 grams per day; 40 percent of those patients took less than 4 grams per day [26]. The majority of patients (90 percent) had aspartate aminotransferase levels ranging from 3000 to 48,000 units/L, indicating severe hepatic necrosis, and 20 percent overall died [27].

However, conflicting data have also been published suggesting that acetaminophen use is safe for patients with alcohol use disorder when used according to the drug label information. In a randomized trial, 102 patients with alcohol use disorder were given 4 grams per day for two days [27]. There was no elevation in aminotransferases compared with the placebo group. Unfortunately, there are limitations when interpreting these data. First, patients were in an inpatient alcohol detoxification program and were therefore not actively drinking when using acetaminophen. Second, it was not clear whether patients had advanced liver disease (which may have made them more predisposed to liver injury); that patients were excluded who had an international normalized ratio of >1.5 suggested that hepatic synthetic function was relatively preserved. Thus, these data may not be applicable to patients with advanced chronic liver disease or cirrhosis who are actively drinking alcohol.

COMBINATION FORMULATIONS

Many prescription and over-the-counter remedies are offered as combination preparations. As an example, Percocet is a combination of oxycodone-acetaminophen. Acetaminophen can also be found in cold and flu remedies such as Nyquil, Alka-Seltzer Plus, and Theraflu. Clinicians need to use caution when prescribing combination formulations because of the potential for toxicity. Two Percocet tablets taken every four hours, for example, contain 3.9 grams of acetaminophen. This represents the upper limit for dosing acetaminophen. Patients may not be aware that Percocet contains acetaminophen and may take acetaminophen in addition to Percocet. Patients with advanced chronic liver disease or cirrhosis need to be warned to read medication labels carefully before starting any new medicine.

AGENTS FOR NEUROPATHIC PAIN

Several medications are used for the treatment of patients with neuropathic pain, including topical lidocaine patches, gabapentin, pregabalin, nortriptyline, and carbamazepine.

Gabapentin, pregabalin, and nortriptyline can be used in patients with cirrhosis at lower than normal doses, though carbamazepine should be avoided (table 1).

Gabapentin and pregabalin are anticonvulsants that are not hepatically metabolized and are dependent on renal function for clearance [13,23]. They can cause sedation, ataxia, dizziness, and nausea, which may limit their usefulness in patients with advanced chronic liver disease or cirrhosis. Gabapentin can be started at a dose of 300 mg orally per day and pregabalin at 50 mg orally twice per day. The doses can be gradually titrated (this should be done over weeks because the drugs have a delayed onsets of action). Both drugs require dose adjustments in patients with renal dysfunction. Neither drug should be stopped abruptly due to risk of discontinuation syndrome and/or rebound seizures. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Antiseizure medications'.)

Nortriptyline is a tricyclic antidepressant that is also used in the treatment of neuropathic pain. It has extensive first-pass hepatic metabolism and has dose-related anticholinergic and cardiovascular side effects [13,23]. In patients with advanced chronic liver disease or cirrhosis, it should be started at a dose of 10 mg orally each night. The dose can be gradually titrated (as with gabapentin and pregabalin, this should be done over weeks because the drug has a delayed onset of action). Low maintenance doses (eg, 25 to 50 mg) should be used to decrease the risk of drug and metabolite accumulation. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Pharmacologic therapy for neuropathic pain, or nociplastic or centralized pain'.)

Carbamazepine should be avoided in patients with advanced chronic liver disease or cirrhosis because it has been associated with hepatotoxicity and may precipitate rapid decompensation in patients with cirrhosis [13,23].

CANNABIS

Cannabis has many beneficial effects, such as pain and nausea control, anxiolysis, and appetite stimulation [28]. Cannabinoid-type drugs are commercially available in the United States. They are approved for chemo-induced nausea and vomiting and appetite stimulation. However, the use of cannabis and cannabinoids for symptom control in patients with advanced liver disease and cirrhosis is not routinely recommended.

The active component of cannabis is delta-9-tetrahydrocannabinol (THC) and there are two known cannabinoid receptors (CB1 and CB2). THC is metabolized by CYP2C9 and 3A4 in the liver.

In cell culture, CB1 receptor activation is associated with hepatic stellate cell activation, inflammation and fibrosis. Conversely, CB2 receptor activation inhibits liver fibrosis [29].

The clinical data on the safety of cannabis use is limited and conflicting and long-term risks of cannabis use are unclear. Cross-sectional studies in patients with hepatitis C virus infection suggest that daily cannabis use is associated with hepatic steatosis and fibrosis [30-32]. However, longitudinal studies in patients with HIV-hepatitis C virus coinfection have not found an association between cannabis use and progression of liver fibrosis [33,34]. Cannabis intoxication may worsen or mimic hepatic encephalopathy. Positive urine toxicology for THC may negatively impact candidacy for liver transplantation.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cirrhosis".)

SUMMARY AND RECOMMENDATIONS

- **General principles** – As a general rule, patients with mild liver disease can be treated with a similar choice of drugs as those who are otherwise healthy. Susceptibility to adverse effects increases with worsening liver function due to altered pharmacokinetics and hemodynamic changes. While the exact cutoff at which drug doses and the selection of drugs should be altered is uncertain, modifications of drug-prescribing should generally be considered in patients who have advanced chronic liver disease (eg, bridging fibrosis on biopsy) or cirrhosis, particularly when accompanied by portal hypertension (such as those with esophageal varices, ascites, or portal gastropathy/colopathy) or renal insufficiency. Important exceptions are patients who are actively drinking alcohol, who can develop severe hepatotoxicity from concomitant use of acetaminophen regardless of the severity of liver disease. (See 'General principles' above.)

- **Specific analgesic agents** – The choice of appropriate analgesic agents in patients with advanced chronic liver disease or cirrhosis requires a thorough knowledge of their pharmacokinetics and side effect profiles (table 1).

  - Acetaminophen is an effective and safe analgesic for most patients with chronic liver disease. It is frequently recommended that patients with cirrhosis or advanced chronic liver disease limit acetaminophen intake to 2 grams per day. We typically limit acetaminophen intake to 2 grams per day for most patients, while avoiding it entirely in

patients with severe alcoholic hepatitis or acute liver injury. (See 'Acetaminophen (paracetamol)' above.)

- Many prescription and over-the-counter remedies are offered as combination preparations. Patients with advanced chronic liver disease or cirrhosis need to be warned to read medication labels carefully before starting any new medicine to avoid accidental overdose. (See 'Combination formulations' above.)

- Nonsteroidal antiinflammatory drugs (NSAIDs) are associated with an increased risk of variceal hemorrhage, impaired renal function, and the development of diuretic-resistant ascites. Thus, NSAIDs (including aspirin) should generally be avoided in patients with advanced chronic liver disease or cirrhosis. (See 'Nonselective NSAIDs' above.)

- Selective COX-2 inhibitors are effective analgesics that are associated with a decreased incidence of gastrointestinal and renal toxicity and an increased incidence of cardiovascular events. Experience in patients with advanced chronic liver disease or cirrhosis is limited. At present, we advise against using these agents in such patients. (See 'COX-2 inhibitors' above.)

- Opioids should be used cautiously in patients with advanced chronic liver disease or cirrhosis. Fentanyl appears to be safe in patients with modest hepatic dysfunction. Morphine, oxycodone, and hydromorphone should be used at reduced doses and prolonged intervals of administration. Tramadol may be safe, but experience is limited. The effects of codeine are difficult to predict, and therefore alternatives should be considered. (See 'Opioids' above.)

- Gabapentin, pregabalin, and nortriptyline can be used to treat neuropathic pain in patients with advanced chronic liver disease or cirrhosis, but the doses are lower than those used in patients who do not have cirrhosis. Carbamazepine should be avoided. (See 'Agents for neuropathic pain' above.)

- **When to refer** – Strong consideration should be given to referring patients with advanced chronic liver disease or cirrhosis who require long-term analgesics to a pain management program. This is especially true for patients with continuous, severe pain.

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Topic 1236 Version 23.0

GRAPHICS

Analgesic use in adult patients with advanced chronic liver disease or cirrhosis

	Altered response and pharmacokinetics	Management suggestions
Non-opioid analgesics		
Acetaminophen (paracetamol)	▪ Glutathione tissue stores needed to block formation of acetaminophen's toxic metabolite (NAPQI) are reduced in individuals with cirrhosis or malnutrition, thereby lowering the dose threshold of acetaminophen that can be safely administered each day. ▪ Active alcohol consumption further reduces available glutathione stores. ▪ Half-life of acetaminophen may be prolonged by up to 2-fold compared with healthy patients.	▪ Acetaminophen is generally well tolerated in patients with CLD or cirrhosis who do not consume alcohol, provided the total daily dose is limited to no more than 2 g/day. ▪ For short-term or one-time use, a maximum total acetaminophen dose of up to 4 g/day may be considered in lower risk patients who do not consume alcohol and have CLD or early stage compensated cirrhosis. ▪ Warn patients concerning acetaminophen content in combination prescription analgesics (eg, oxycodone-acetaminophen) and non-prescription (OTC) preparations. ▪ Avoid use in patients with advanced CLD or cirrhosis who are actively consuming alcohol, malnourished, not eating, receiving multiple medications that undergo hepatic biotransformations, or any co-administered medication that is a potent inducer of hepatic enzymes. ▪ A list of medications that induce hepatic enzymes is provided in a separate table.
Nonselective nonsteroidal	▪ An increased risk of GI mucosal bleeding, variceal hemorrhage,	▪ NSAIDs and aspirin should be avoided in patients with advanced

antiinflammatory drugs (NSAIDs) including aspirin	impaired renal function, and development of diuretic-resistant ascites is seen with use of NSAIDs in patients with cirrhosis with portal hypertension. ▪ NSAIDs can decrease GFR and impair renal function in patients with advanced CLD or cirrhosis. ▪ Most NSAIDs are metabolized by CYP and highly bound to serum albumin, increasing drug bioavailability and potential for toxicity in patients with advanced CLD or cirrhosis. ▪ Individual NSAIDs (eg, diclofenac) have been associated with hepatotoxicity in general population.	CLD or cirrhosis. ▪ Low-dose acetaminophen should be used instead of NSAIDs.
Selective COX-2 inhibitors	▪ Available data are inadequate to establish the safety of selective COX-2 inhibitors in patients with advanced CLD or cirrhosis. Refer to UpToDate content for detail. ▪ Excess cardiovascular events have been observed with this class of medications when used by patients without cirrhosis.	▪ We advise against use of selective COX-2 inhibitors in patients with advanced CLD or cirrhosis, pending availability of additional safety data. ▪ If used, celecoxib product information suggests a 50% dose reduction for Child-Pugh class B cirrhosis.
Opioid analgesics (refer to important note)*		
Fentanyl	▪ Metabolized by CYP3A4 to inactive (nontoxic) metabolites. ▪ Parent drug can accumulate after repeated dosing or when administered as a continuous infusion due to tissue and protein binding. ▪ Less histamine release than other opiates. ▪ Less hemodynamic disturbance than other opiates.	▪ Generally a good choice for patients with CLD or cirrhosis when opiate treatment is indicated. ▪ Useful option in patients with renal failure in setting of cirrhosis. ▪ No dose adjustment needed for single dose. ▪ With repeated dosing, reduce dose and frequency by approximately 25 to 50%. ▪ Initiate transdermal patch at half usual dose.
Hydrocodone, oxycodone	▪ Metabolized to active metabolite by CYP2D6 and CYP3A4, which	▪ Due to variability of onset and analgesic efficacy in hepatic

	may result in a prolonged time to onset, variable analgesic efficacy, and risk of accumulation in patients with advanced CLD or cirrhosis.	insufficiency, fentanyl or hydromorphone may be better tolerated and more safely and predictably adjusted than hydrocodone and oxycodone in patients with advanced CLD or cirrhosis. ▪ If used, reduce dose and frequency.
Hydromorphone	▪ Hepatically metabolized by non-CYP transformations (glucuronidation) to apparently inactive metabolites. ▪ Oral bioavailability in advanced CLD or cirrhosis seems to be increased relative to healthy individuals due to diminished first-pass extraction, but specific data are lacking, and wide inter-individual variability is observed.	▪ Generally a good choice for patients with advanced CLD or cirrhosis. ▪ Reduce dose and frequency by approximately 50%. ▪ Titrate dose gradually to avoid accumulation of active drug. ▪ Useful option in patients with renal failure in setting of cirrhosis. ▪ Small volume for IV preparation and non-CYP3A4 metabolism may be advantageous given clinical setting.
Meperidine (pethidine), codeine	▪ Altered oral bioavailability and elevated risk of accumulation of intermediates (codeine) or toxic metabolite (normeperidine). ▪ Meperidine is highly bound to serum protein. ▪ Unpredictable analgesic efficacy and increased risk of toxicity in patients with advanced CLD or cirrhosis.	▪ Meperidine and codeine should be avoided in patients with advanced CLD or cirrhosis.
Morphine	▪ Oral bioavailability in advanced CLD or cirrhosis increased up to 100% relative to healthy individuals due to diminished first-pass extraction. Wide inter-individual variability may be seen. ▪ Hepatically metabolized by non-CYP transformations (glucuronidation). ▪ Half-life can be increased by up to 2-fold.	▪ Reduce dose and frequency by approximately 50% in advanced CLD or cirrhosis. ▪ Titrate dose gradually to avoid accumulation of active drug. ▪ Avoid in patients with cirrhosis and renal failure.

	▪ Accumulation of metabolites with complex effects (eg, respiratory depression, analgesic tolerance, neurotoxicity) can occur in patients with cirrhosis and renal failure.	
Naloxone-containing opioid combinations	▪ Orally administered naloxone, which is included in these combinations to deter abuse (ie, crushing, snorting) and counteract constipation by a local effect, is systemically absorbed in patients with moderate to severe hepatic impairment. ▪ Systemic absorption of naloxone will reverse analgesic efficacy and can precipitate opioid withdrawal.	▪ Oxycodone-naloxone: • Reduce starting dose by one-half to two-thirds in mild hepatic impairment. • Use in advanced CLD or cirrhosis is contraindicated. ▪ Pentazocine-naloxone: Avoid use.
Remifentanil	▪ Cleared by nonspecific plasma esterases to inactive metabolites. ▪ Does not accumulate in hepatic or renal insufficiency. ▪ Prompt reversal of analgesia and sedation upon discontinuation.	▪ No adjustment needed.
Tramadol	▪ Hepatically metabolized to active metabolite by CYP3A4, CYP2D6, and glucuronidation. ▪ Unpredictable onset, variable analgesic efficacy, and risk of accumulation in patients with cirrhosis. ▪ Can interact with serotoninergic medications, including antidepressants.	▪ Avoid use in patients with decompensated cirrhosis. ▪ Avoid use in patients at risk for seizures. ▪ Based on limited experience, a reduced dose of 25 mg every 8 hours may be considered for treatment of pain in patients with advanced CLD or well-compensated cirrhosis.
Adjunctive agents for neuropathic pain		
Carbamazepine	▪ Carbamazepine is a potent inducer of hepatic enzymes and has been associated with hepatotoxicity and serious allergic reactions in genetically predisposed individuals. ▪ May precipitate rapid decompensation in patients with	▪ Carbamazepine should be avoided as there are safer options for treatment of neuropathic pain in patients with advanced CLD or cirrhosis.

	cirrhosis.	
Gabapentin	▪ Not hepatically metabolized or bound to plasma proteins. ▪ Highly dependent on renal function for clearance of unchanged drug. ▪ Sedation, ataxia, dizziness, and nausea may limit usefulness in patients with advanced CLD or cirrhosis.	▪ Initiate treatment at 300 mg orally per day and gradually titrate dose if needed over weeks due to delayed onset of action and to improve tolerability. ▪ Maintenance dose is dependent on renal function. For specific adjustment, refer to Lexicomp monograph included with UpToDate. ▪ According to the product information, should not be abruptly stopped due to risk of discontinuation symptoms (eg, nausea, insomnia, anxiety) and/or rebound seizures in at-risk patients.
Lidocaine topical patch	▪ Low (3 to 5%) systemic absorption through intact skin.	▪ A good choice for local relief of pain in limited areas of intact skin in patients with advanced CLD or cirrhosis. ▪ No adjustment needed in hepatic impairment.
Nortriptyline	▪ Subject to extensive first-pass metabolism and CYP2D6 transformations, which include active and inactive metabolites. ▪ Accumulation of metabolites in hepatic impairment is less likely with nortriptyline than amitriptyline. ▪ Dose-related anticholinergic and cardiovascular side effects may be poorly tolerated in medically ill patients with advanced CLD or cirrhosis.	▪ Initiate treatment at 10 mg orally each night and gradually titrate dose if needed over weeks due to delayed onset of action and to improve tolerability. ▪ Use "low" maintenance dose for neuropathic pain (eg, 25 mg to no more than 50 mg daily) to decrease risk of accumulation.
Pregabalin	▪ Not hepatically metabolized or bound to plasma proteins. ▪ Highly dependent on renal function for clearance of unchanged drug.	▪ Initiate treatment at 50 mg orally twice per day and gradually titrate dose if needed over weeks due to delayed onset of action. ▪ Maintenance dose is dependent on renal function. For specific

	▪ Sedation and dizziness may limit usefulness in patients with advanced CLD or cirrhosis.	adjustment, refer to Lexicomp monograph included with UpToDate. ▪ According to the product information, should not be abruptly stopped due to risk of discontinuation symptoms (eg, nausea, insomnia, anxiety) and/or rebound seizures in at-risk patients.

For information on medications other than analgesics, refer to UpToDate content on non-analgesic medication adjustments for adult patients with cirrhosis.

NAPQI: n-acetyl-p-benzoquinone imine; CLD: chronic liver disease; OTC: over the counter; GI: gastrointestinal; GFR: glomerular filtration rate; CYP: cytochrome P-450; COX-2: cyclooxygenase 2; IV: intravenous; HE: hepatic encephalopathy.

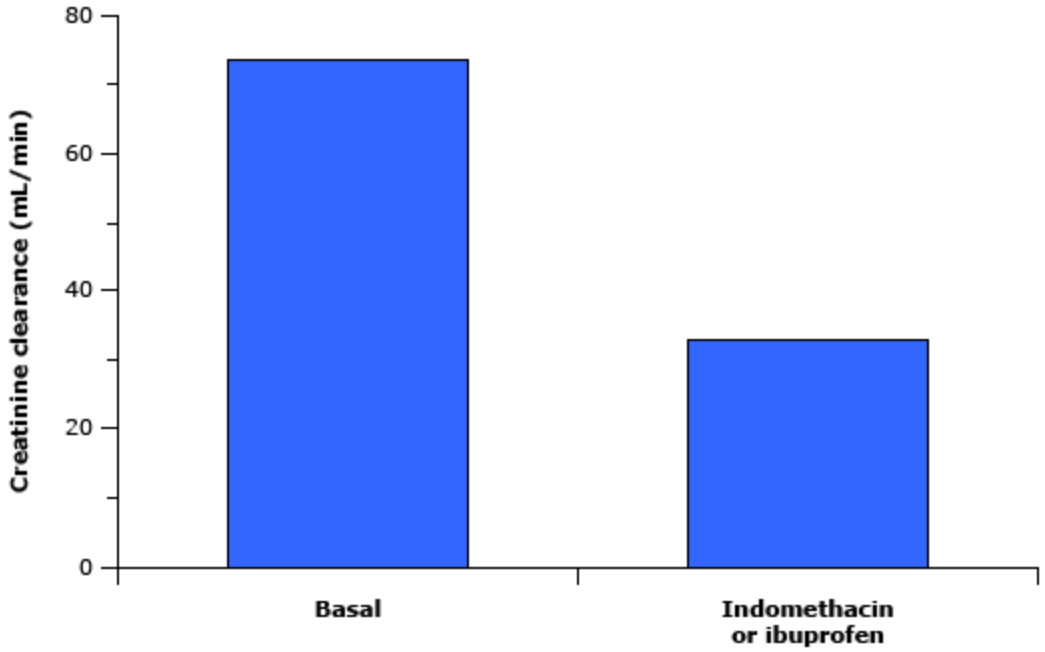
* **NOTE:** All opioids can worsen or precipitate HE and should be used cautiously or avoided in patients with portal hypertension and preexisting HE.

Prepared with data from:

1. *Lewis JH, Stine JG. Review article: Prescribing medications in patients with cirrhosis – a practical guide. Aliment Pharmacol Ther 2013; 37:1132.*
2. *Chandok N, Watt KD. Pain management in the cirrhotic patient: The clinical challenge. Mayo Clin Proc 2010; 85(5):451.*

Graphic 90196 Version 16.0

Graph showing reduction in creatinine clearance after NSAIDs in patients with hepatic cirrhosis



Reduction in glomerular filtration rate, as estimated from the creatinine clearance, from a mean of 73 mL/min down to 32 mL/min, after the administration of an NSAID (indomethacin or ibuprofen) to 12 patients with stable hepatic cirrhosis and ascites. Urinary prostaglandin E_2 excretion was initially elevated and then fell markedly following therapy.

NSAID: nonsteroidal anti-inflammatory drug.

Graphic 89932 Version 5.0

Contributor Disclosures

James P Hamilton, MD No relevant financial relationship(s) with ineligible companies to disclose. **Eric Goldberg, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Sanjiv Chopra, MD, MACP** No relevant financial relationship(s) with ineligible companies to disclose. **Bruce A Runyon, MD, FAASLD** No relevant financial relationship(s) with ineligible companies to disclose. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

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