NCSCG
8TH ANNUAL LIVER SYMPOSIUM

JANUARY 21, 2023
HOTEL NIA | MENLO PARK, CA

Pain management in liver disease

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NCSCG LIVER SYMPOSIUM

JANUARY 21, 2023

Mr. S

- 62-year-old man
- DM, HTN, chronic low-back pain, peripheral neuropathy, decompensated NASH cirrhosis
- Admitted with acute cholecystitis, surgeons recommend medical management
- 7/10 pain
- "The doctors said I can't get any pain medication because of my liver. Please can I have something? I'm so uncomfortable."

Outline

- Challenges of pain management in liver disease
- Existing data on analgesic safety
- Published guidance
- Future directions

Pain in chronic liver disease patients

- 67-80% of cirrhosis patients have pain
  - Higher rates than in general population
  - More advanced liver disease = ↑ rates of pain
  - Varies by type of liver disease
- Why?
  - Overlapping risk factors (e.g. substance use disorders, metabolic syndrome)
  - Complications of cirrhosis (e.g. ascites, leg cramps)
- Pain associated with disability, poor quality-of-life, and increased health care utilization → impaired transplant candidacy

Table 2 Pain-on-average ratings from the Brief Pain Inventory by cause of liver disease[a]

Statistic	HCV	ALC	HCV+ALC	NASH
Mean	5.15[b]	1.90[c]	4.00[b]	4.71[b]
SD	2.56	1.91	2.86	3.55
n	34	10	40	7

Abbreviations: ALC, alcoholic cirrhosis; HCV, hepatitis C; NASH, nonalcoholic steatohepatitis.

[a] There was a main effect for cause of disease on pain ratings ($F_{3,87} = 3.90$, $P = .01$). Different superscript letters indicate significant differences ($P < .05$) between groups from post-hoc (least significant difference) testing.

References: Madan A, et al. Prog Transplant. 2012;22(4):379-384; Peng J-K, et al. Palliat Med. 2019;33(1):24-36; Whitehead AJ, et al. J Pain Symptom Manage. 2008;36(1):39-45.

Pain in UCSF cirrhosis patients

- Retrospective analysis of all patients seen for initial visits in our HEP/LT clinics between 2013-2020 (N=6440)
- **Defining pain:**
  - Nonzero pain score at time of visit **OR** pain diagnosis
  - **56%** of patients had pain; half of those reported **any** pain at time of visit:
    - 21% mild
    - 42% moderate
    - 27% severe
  - **Opioid use:**
    - 16% on opioids at time of initial visit

Primary pain location	% of patients
Abdomen	43%
Back/Neck	21%
Generalized	9%
Leg	6%
Knee	5%
Hip	3%
Foot	2%
Shoulder	2%
Head	2%
Other	7%

Unpublished data

Challenges of pain management in cirrhosis

PATIENT

- Metabolic comorbidities
- Substance use
- Psychiatric disease
- Low socioeconomic status / health literacy

DISEASE

- Variable presentations
- Minimal research on cirrhosis-related pain

PHARMACOLOGIC

- Impaired hepatic metabolism
- No biomarkers to measure hepatic function
- Impaired renal excretion
- Risk for adverse effects
  - Renal failure
  - GI bleeding
  - Hepatic encephalopathy
- Potential for abuse

CLINICIAN

- No guidelines
- Discomfort with analgesic options
- Stigma/bias

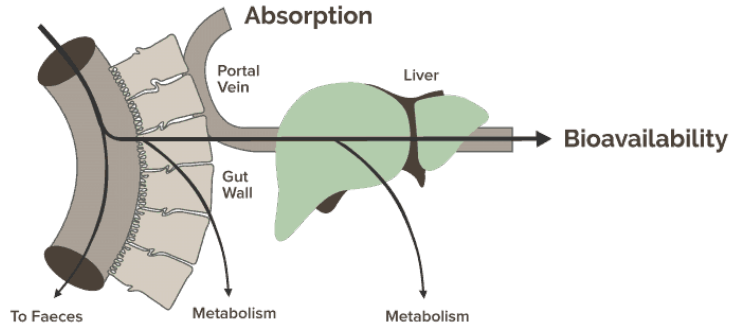
SYSTEM

- Regulatory issues
- Transplant center requirements
- Fragmentation of care

Adapted from Rakoski M, et al. Clinical Liver Disease. 2018;11(6):135-140.

Cirrhosis and impaired drug metabolism

First-Pass Effect: many oral drugs undergo substantial metabolism in liver before reaching systemic circulation



- **How is drug metabolism impaired in cirrhosis?**
  - Portosystemic shunts → Increased oral bioavailability
  - ↓ metabolic enzyme activity (e.g. CYP) → Decreased hepatic clearance
  - ↓ production of drug-binding proteins → Increased drug distribution volume
  - Fluid overload and decreased muscle mass → Changes in drug distribution volume
  - Impaired renal function (e.g. HRS) → Reduced renal drug clearance
  - Overestimation of GFR (low muscle mass) → Reduced renal drug clearance

Reference: Bosilkovska et al. Drugs. 2012;72:1645-1669.

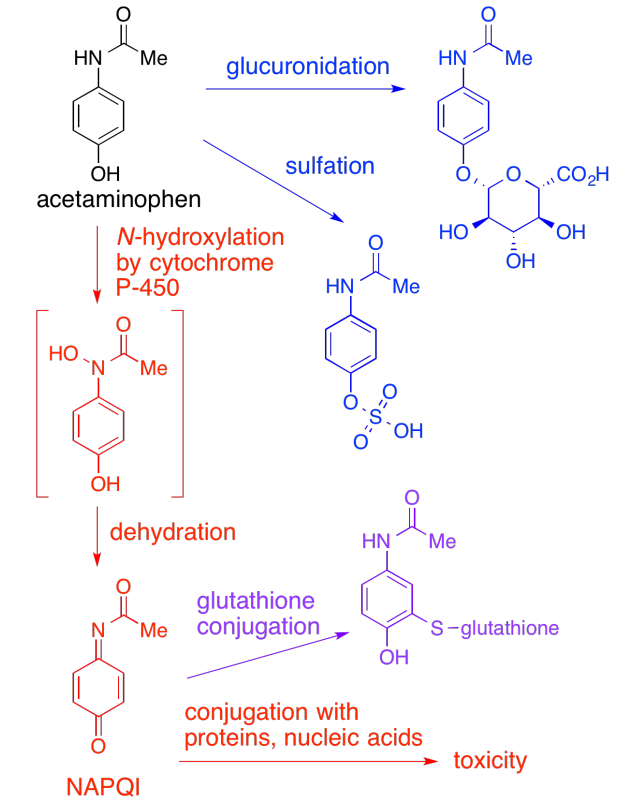
Acetaminophen (APAP)

- Well-known association between APAP and acute liver failure
  - Perception that it is dangerous in patients with chronic liver disease
- No prospective, long-term studies have assessed the safety of APAP in cirrhosis
- Existing data:
  - 1983: Small pharmacokinetic study (n=26), clearance of APAP in cirrhotics decreased by 50%, but pattern of toxic urinary metabolites unchanged
  - 1983: Small study (n=20) chronic liver disease patients (8 with cirrhosis) tolerated APAP 4g/day without adverse effects or significant changes in lab tests
  - 2000: Small RCT in patients with chronic HCV, APAP 3g/day x 7 days did not affect ALT
  - 2009: Small case-control study looking at over-the-counter analgesics and acute decompensation found no association between 2-3g/day of APAP and decompensation

References: Bosilkovska et al. Drugs. 2012;72:1645-1669; Villeneuve et al. Gastroenterol Clin Biol. 1983;7(11)898-902); Benson. Clin Pharmacol Ther 1983;33(1):95-101; Dargere S, et al. Gastroenterol. 2000;118(4):A947. Khalid, et al. Clin Gastroenterol Hepatol. 2009;7(9):994-9.

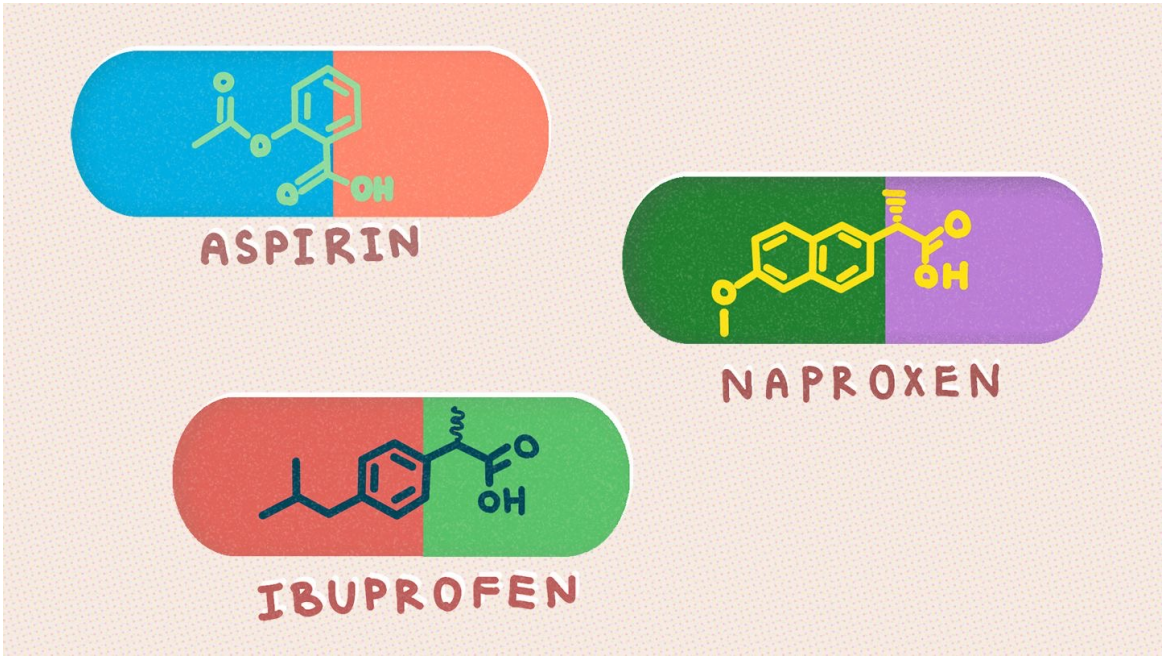
Acetaminophen (APAP): a few caveats

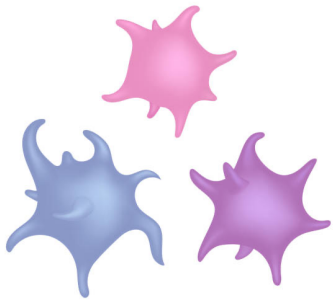
- Patients with chronic liver disease have lower levels of glutathione, but no evidence for adverse effects from APAP in these patients
- Except in patients with chronic alcohol use:
  - ↓ glutathione and ↑ CYP activity
  - Increased toxic urinary metabolites
- Increased risk of acute liver injury from APAP overdose in patients with preexisting liver disease, but NOT at therapeutic doses



References: Bosilkovska et al. Drugs. 2012;72:1645-1669; Villeneuve et al. Gastroenterol Clin Biol. 1983;7(11)898-902); Lauterburg BH. Am J Ther. 2002;9(3):225-33; Myers and Shaheen. Hepatology. 2009;49(4)1399-400.

Nonsteroidal anti-inflammatories (NSAIDs)





Nonsteroidal anti-inflammatories (NSAIDs)

1. Altered metabolism and increased bioavailability in patients with impaired hepatic function
2. Inhibition of prostaglandins → decreased renal perfusion → ↓ GFR and ↑ Na retention
   - Several small studies have shown these effects in decompensated patients who receive multiple different types of NSAIDs
   - 1983: NSAIDs reduce natriuresis in patients receiving diuretics, reversible if short-term administration stopped, but long-term effects unknown
   - Small studies of selective COX-2 inhibitors inconclusive regarding renal effects
3. Increased risk of bleeding
   - Inhibition of platelet production of proaggregatory thromboxane A2 → ↑ bleeding risk
   - Induction of gastric mucosal damage
   - 1999: Case-control study showed that cirrhotic patients using NSAIDs are 3x more likely to present with variceal bleed than cirrhotics who do not use NSAIDs

References: Bosilkovska et al. Drugs. 2012;72:1645-1669; Ackerman Z, et al. Am J Gastroenterol 2002; 97(8):2033-9; Laffi G, et al. Gastroenterology 1986;90(1):182-7; Claria, et al. Hepatology 2005;41(3):579-87 94; Brater, et al. Am J Med Sci 1987; 294(3):168-74 95; Mirouze, et al. Hepatology 1983;3(1): 50-5 96; De Ledinghen, et al. Gut 1999;44(2):270-3

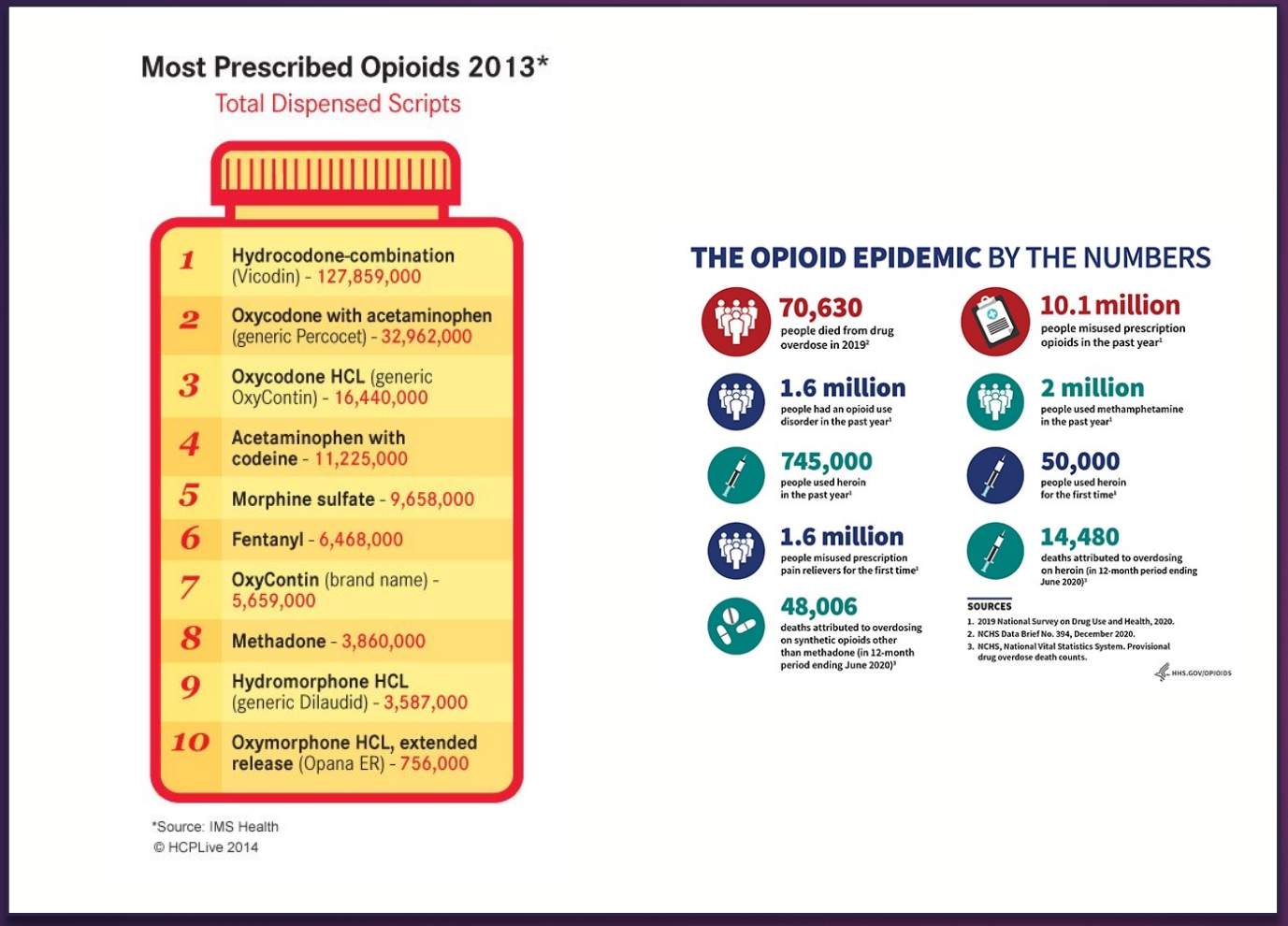
NSAIDs: Outstanding questions

What are risks of NSAIDs in mild chronic liver disease?

Should NSAIDs be avoided in all patients with compensated cirrhosis (i.e. do they increase risk of first decompensation)?

Are COX-2 inhibitors safe in this population?

Opioids


Most Prescribed Opioids 2013*
Total Dispensed Scripts
1 Hydrocodone-combination (Vicodin) - 127,859,000
2 Oxycodone with acetaminophen (generic Percocet) - 32,962,000
3 Oxycodone HCL (generic OxyContin) - 16,440,000
4 Acetaminophen with codeine - 11,225,000
5 Morphine sulfate - 9,658,000
6 Fentanyl - 6,468,000
7 OxyContin (brand name) - 5,659,000
8 Methadone - 3,860,000
9 Hydromorphone HCL (generic Dilaudid) - 3,587,000
10 Oxymorphone HCL, extended release (Opana ER) - 756,000
*Source: IMS Health
© HCPLive 2014

THE OPIOID EPIDEMIC BY THE NUMBERS
70,630
people died from drug overdose in 2019[2]
10.1 million
people misused prescription opioids in the past year[1]
1.6 million
people had an opioid use disorder in the past year[1]
2 million
people used methamphetamine in the past year[1]
745,000
people used heroin in the past year[1]
50,000
people used heroin for the first time[1]
1.6 million
people misused prescription pain relievers for the first time[1]
14,480
deaths attributed to overdosing on heroin (in 12-month period ending June 2020)[3]
48,006
deaths attributed to overdosing on synthetic opioids other than methadone (in 12-month period ending June 2020)[3]
SOURCES
1. 2019 National Survey on Drug Use and Health, 2020.
2. NCHS Data Brief No. 394, December 2020.
3. NCHS, National Vital Statistics System. Provisional drug overdose death counts.
HHS.GOV/OPIOIDS

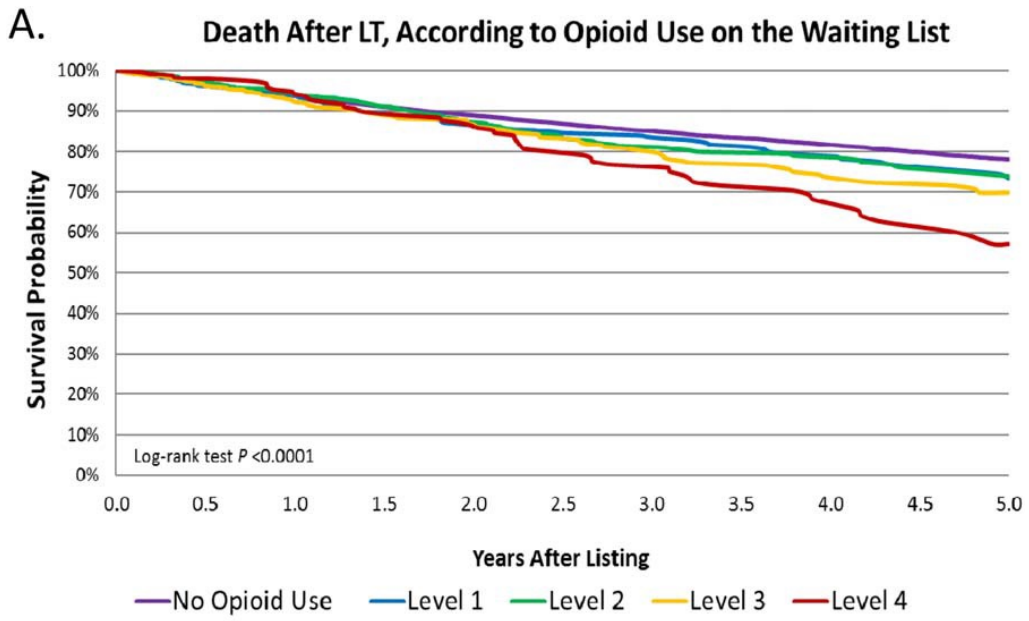
Opioids: cirrhosis-related concerns

- Liver is primary metabolic site for most opioids → decreased clearance, increased bioavailability
  - Significant variability by type of opioid
  - Need to be aware of renal dysfunction and opioid toxicity as well
- Concern for precipitation of hepatic encephalopathy in cirrhosis patients
  - HE → ↑ GABAergic inhibitory neurotransmission → decrease in endogenous opioid levels → upregulation of μ-opioid receptors in the brain and increased sensitivity to exogenous opioids
  - May also be changes in blood-brain barrier in patients with severe liver disease
  - Opioids can cause intestinal mucosal injury and microbial changes
  - Opioid-induced constipation
- Data on clinical outcomes:
  - 2017: Longitudinal study of cirrhotic patients on chronic opioids compared to those not on opioids
    - Opioid users had higher all-cause readmissions (not HE-related)
    - Opioid users had alterations in gut microbiome, increased endotoxemia and IL-6 (systemic inflammatory markers)

References: Bosilkovska et al. Drugs. 2012;72:1645-1669; Acharya, et al. Aliment Pharmacol Ther. 2017;45:319-331; Chandok and Watt. Mayo Clin Proc. 2010;85(5):451-458.

Opioids: transplant-related outcomes

- 2016: Pre-transplant opioid use associated with 30-day all-cause post-transplant readmissions, and 30-day and 1-year pain-related readmissions
- 2016: National transplant registry data integrated with pharmaceutical claims data:
  - High-dose opioid use pre-transplant was associated with high rates of opioid use post transplant
  - Pre- and post-transplant opioid use associated with 5-year post-transplant mortality and graft failure
- 2021: Single-center (UCSF) study
  - Opioid use at the time of liver transplant is associated with increased risk of post-LT mortality



References: Rogal, et al. Clin Transplant. 2016;30(10):1222-1229; Randall et al. Liver Transplant. 2017;23(3):305-314; Braun et al. Am J Surg. 2021;222:234-40.

Opioids: summary of concerns

Liver-related

- Impaired metabolism and increased bioavailability
- Association with hepatic encephalopathy

Transplant-related

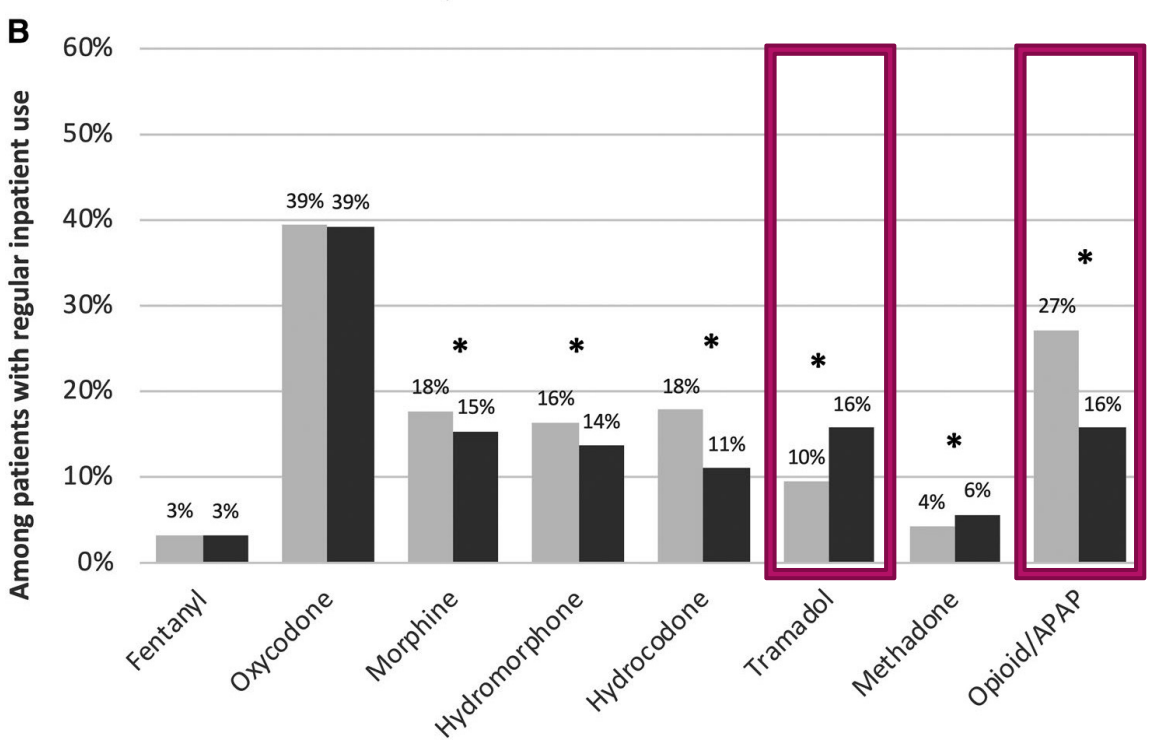
- Increased opioid use post-transplant
- Worse post-transplant outcomes
- Transplant center policies

General concerns

- Potential for addiction and abuse
- Increased regulation / scrutiny
- Ineffective in management of many types of pain

Opioids are still commonly used in cirrhosis

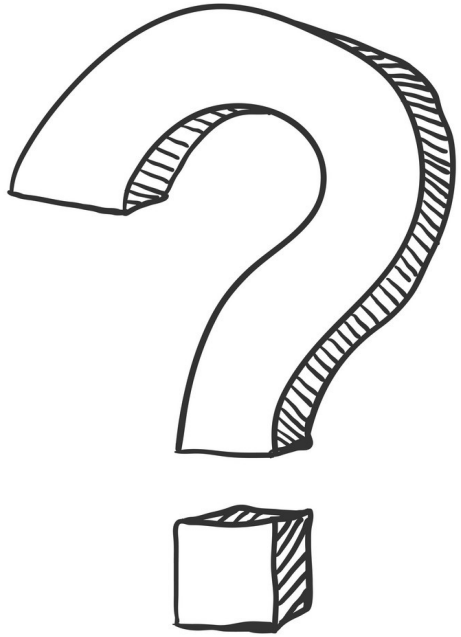
- Estimates of prevalence of opioid use in cirrhosis patients:
  - Outpatients: 15-25%
  - Veterans: 77% any prescription, 54% long-term, 20% high-dose
  - Listed for transplant: 45%
  - 10-12 months post-transplant: 21%
  - Inpatients: 62% at least one dose, 34% regular use (higher than in patients without cirrhosis)
- Types of opioids differ between patients with and without cirrhosis



References: Rogal, et al. *Dig Dis Sci*. 2013;58(10):2976-2985; Rogal, et al. *Clin Gastroenterol Hepatol*. 2019;17(6):1165-1174; Cron, et al. Transplantation. 2021;105(1):100-107; Rubin et al. Hepatol Commun. 2021;5(6):1081-1094.

And they may be used in higher doses

- Cohort of all Veterans (n=113,000) on long-term opioid therapy, 2014-2018
  - ~3000 (3%) with cirrhosis
- Cirrhosis patients also more likely to have other risk factc of opioid-related adverse events (e.g. comorbidities, substance use, functional impairment)
- Despite this, cirrhosis patients ***more*** likely to receive high dose opioids than patients without cirrhosis
- Other analgesics less likely to be used concurrently in cirrhosis patients



Reference: Rubin, et al. J Gen Int Med. 2022.

A quick note on buprenorphine

- Most commonly prescribed as an alternative to methadone for treatment of opioid dependence, but increasingly being used for chronic pain
- Safety in liver disease:
  - 2000: Retrospective study found significant increases in transaminases in patients with HBV or HCV
  - 2007: Case series of patients starting opioid substitution therapy – 4 patients with acute HCV with abnormal liver enzymes, tolerated buprenorphine
  - 2013: Large RCT (methadone vs buprenorphine) – no differences in liver enzymes (chronic liver disease excluded)
  - Multiple studies suggesting safety of buprenorphine in renal disease
- More data is needed on safety, efficacy, and dosing of buprenorphine in cirrhosis patients for treatment of both opioid dependence and chronic pain

References: Bosilkovska et al. Drugs. 2012;72:1645-1669; Petry, et al. Am J Addict. 2000;9(3):265-9; Bruce and Altice. Am J Drug Alcohol Abuse. 2007;33(6):869-74; Saxon et al. Drug and Alcohol Depend. 2013;128(1-2):71-76; Boger RH. Palliative Med. 2006;20 Supp. 1:S17-23.

Opioids: Outstanding questions

- Which types opioids are safest in patients with cirrhosis (i.e. what are real-world clinical outcomes)?
- Are opioids effective in types of pain most common in cirrhosis patients?
- Are there subpopulations of chronic liver disease patients in which benefits of opioids outweigh risks?
- How do we safely prescribe opioids in these subpopulations?

Adjuvant analgesics

- Typically used for neuropathic pain, but now increasingly being used earlier for many types of acute and chronic pain as alternate to opioid therapy
  - Neuropathic pain is common in cirrhosis patients due to concurrent diabetes, alcoholism, etc.
- No specific studies on safety and efficacy in cirrhosis

Gabapentanoids

Gabapentin, pregabalin

- No hepatic excretion, not bound to plasma proteins (though caution in those with renal dysfunction)
- Dose-dependent dizziness and sedation can exacerbate HE, increase risk of falls

Tricyclic antidepressants

Nortriptyline, desipramine, amitriptyline, imipramine

- Metabolized by CYP2D6, can accumulate in patients with liver disease
- Start at low doses and titrate slowly, look out for anticholinergic effects, constipation can precipitate HE

SNRIs

Venlafaxine, duloxetine

- Clearance decreased significantly in patients with hepatic dysfunction
- Should probably be avoided in patients with chronic liver disease

References: Bosilkovska et al. Drugs. 2012;72:1645-1669; Chandok and Watt. Mayo Clin Proc. 2010;85(5):451-458.

Cannabis

- Increasing in popularity as treatment for chronic pain
- In large observational studies, marijuana use may be associated with **better** outcomes:
  - Reduced incidence of alcohol-related liver disease in patients with alcohol abuse
  - Reduced prevalence of NAFLD
  - Improved liver disease outcomes in patients with HCV
  - Decreased rates of hospital admissions for most decompensating events, though higher risk of admission for HE
- Transplant outcomes:
  - Marijuana use not associated with waitlist or post-transplant outcomes
- More data needed on safety and efficacy in cirrhosis patients with pain

References: Adejumo et al. Liver Int. 2018;38(8):1475-1486. Adejumo et al. PLoS One. 2017;12(4):e0176416; Adjumo et al. Can J Gastroenterol Hepatol. 2018;23:9430953; Sobotka et al. Ann of Hepatol. 2021;23:100280; Kotwani, et al. Transplantation. 2018;102(5);794-802; Rodriguez, et al. Liver Transpl. 2019;25(5):734-740.

Summary of data on analgesics in cirrhosis

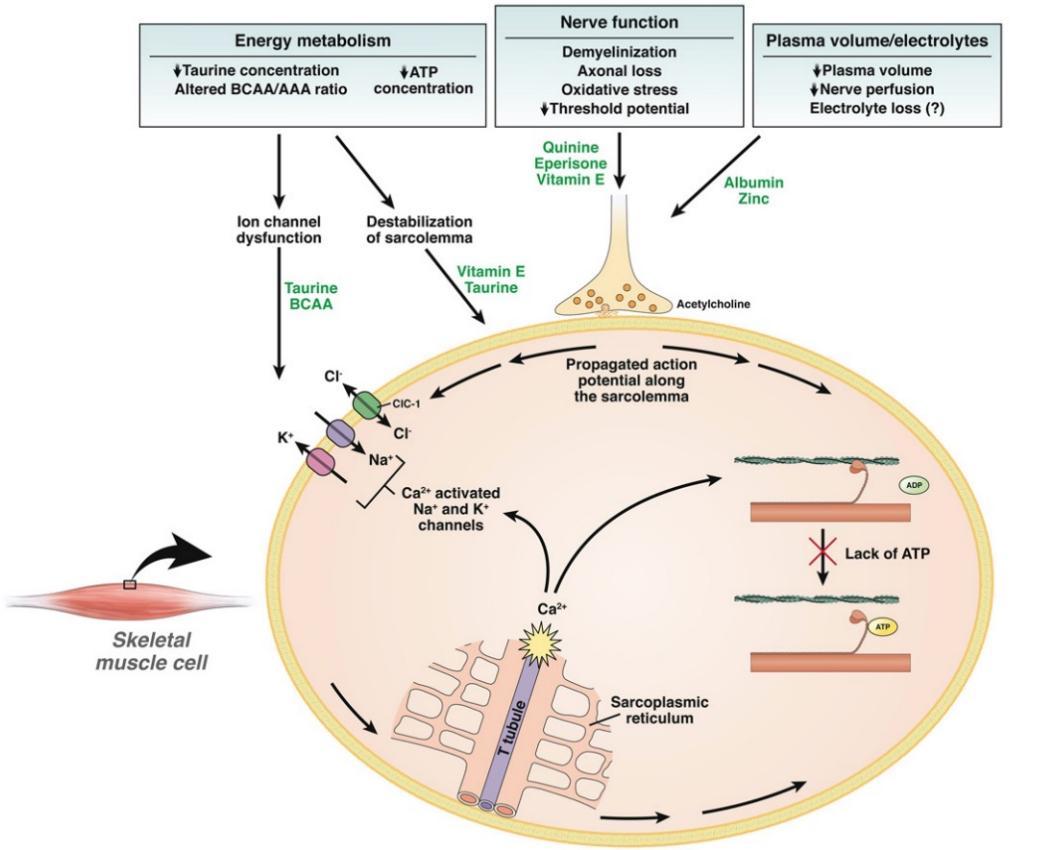
APAP 	• Small studies suggest safety at therapeutic doses in cirrhosis patients • Depleted glutathione stores in alcohol patients • Increased risk of liver injury from overdose in patients with chronic liver disease
NSAIDS 	• Good data that they ↓ renal blood flow, ↓ GFR, and ↑ Na retention in patients with cirrhosis and ascites • May increase risk of variceal bleeding in cirrhosis patients
Opioids 	• ↓ metabolism, ↑ bioavailability suggest need for dose reductions • May precipitate/worsen HE, not much real-world evidence of this • Associated with worse transplant outcomes • They are very commonly used in cirrhosis patients
Adjuvant 	• Essentially no data on clinical safety or efficacy in this population • Pharmacokinetic studies suggest gabapentin/pregabalin are probably safe, SNRIs should be avoided, TCAs may be safe in low doses (but watch for anticholinergic effects)

Muscle cramps in liver disease

- Muscle cramps present in up to 88% of patients with cirrhosis; 5-6x higher than in general population / other chronic diseases
- Significant impairment in quality of life in cirrhosis patients
- Possible mechanisms:
  - Nerve dysfunction, possibly due to oxidative injury and structural alterations
  - Energy metabolism
    - Altered regulation of amino acid and protein metabolism results in decreased concentrations of taurine in muscles, altering skeletal muscle electrical properties
    - Reduction in ATP production causing prolonged muscle contraction
  - Plasma volume, electrolytes, and zinc
    - Shifts in plasma volume → decreased perfusion to nerves
    - Electrolyte concentrations and diuretic use are not thought to contribute, though intracellular electrolyte concentrations may contribute

Reference: Mehta and Fallon. Clin Gastroenterol and Hepatol. 2013;11:1385-1391.

Treatment of muscle cramps in liver disease



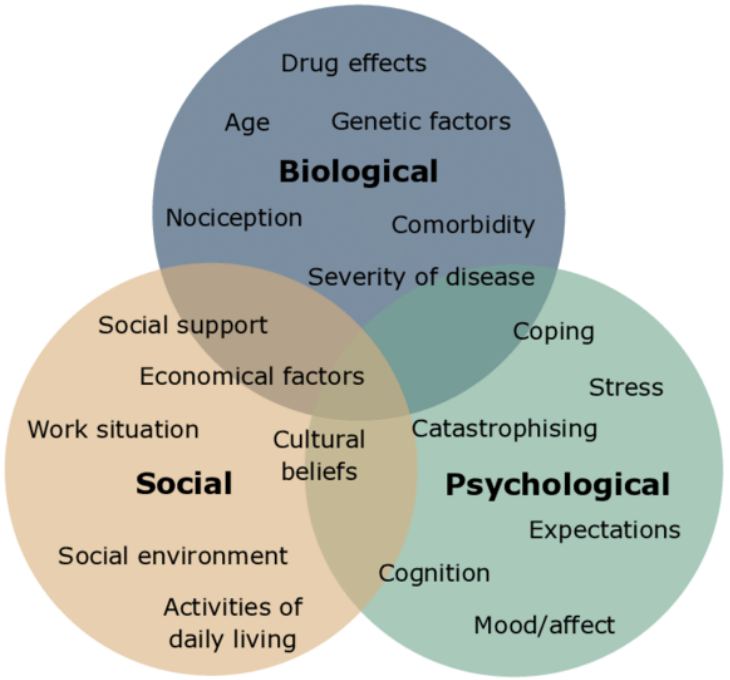
- **Quinine** sulfate: increases muscle refractory period, rare significa is not recomm
- **Vitamin** s have mixed re
- **Eperison** le relaxant
- **Taurine:** ut significa
- **Branche** urine producti AEs
- **Albumin** ctive but costly
- **Electroly** els are low

NO PUBLISHED GUIDELINES

Reference: Mehta and Fallon. Clin Gastroenterol and Hepatol. 2013;11:1385-1391.

Nonpharmacologic pain management

- Biopsychosocial approach to pain management
  - Nonpharmacologic options
  - Treatment of underlying psychiatric comorbidities
  - Individualized approach
- No data for these modalities in cirrhosis, but would be ideal target population given analgesic risks:
  - Physical therapy
  - Weight loss
  - Cognitive behavioral therapy (CBT)
  - Mindfulness
  - Analgesic injections (consider bleeding risk)



Reference: Klinge et al. Curr Hepatol Rep. 2018;17(1):42-51.

Published guidance

- No official guidelines or comprehensive systematic reviews – likely due to to limited real-world data on risks and efficacy specific to the cirrhosis population
- Several helpful reviews:

REVIEW

Pain Management in the Cirrhotic Patient: The Clinical Challenge

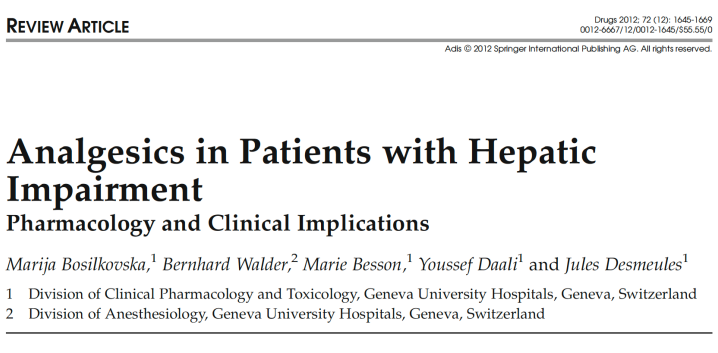
NATASHA CHANDOK, MD, AND KYMBERLY D. S. WATT, MD

Pain management in patients with cirrhosis is a difficult clinical challenge for health care professionals, and few prospective studies have offered an evidence-based approach. In patients with end-stage liver disease, adverse events from analgesics are frequent, potentially fatal, and often avoidable. Severe complications from analgesia in these patients include hepatic encephalopathy, hepatorenal syndrome, and gastrointestinal bleeding, which can result in substantial morbidity and even death. In general, acetaminophen at reduced dosing is a safe option. In patients with cirrhosis, nonsteroidal anti-inflammatory drugs should be avoided to avert renal failure, and opiates should be avoided or used sparingly, with low and infrequent dosing, to prevent encephalopathy. For this review, we searched the available literature using PubMed and MEDLINE with no limits.

Mayo Clin Proc. 2010;85(5):451-458

drug metabolism may be altered, and thus concerns and dose reductions, as discussed in this article, may be warranted.[2-4] A patient with well-compensated cirrhosis and near-normal synthetic function will have impaired drug metabolism, but to a lesser extent than will patients with abnormal synthetic function or decompensated cirrhosis. Decompensated cirrhosis can be a result of progressive liver dysfunction, worsened portal hypertension, or both. Such patients may have even greater restrictions on analgesic choice. This article pertains to all patients with cirrhosis (compensated or decompensated) and to patients with liver dysfunction (with elevated bilirubin levels and prothrom-

Chandok N, Watt KDS. *Mayo Clin Proc*. 2010;85(5):451-458. https://pubmed.ncbi.nlm.nih.gov/20357277/



REVIEW ARTICLE

Drugs 2012; 72 (12): 1645-1669
0012-6667/12/0012-1645/$55.55/0

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Analgesics in Patients with Hepatic Impairment

Pharmacology and Clinical Implications

Marija Bosilkovska,[1] *Bernhard Walder,*[2] *Marie Besson,*[1] *Youssef Daali*[1] and *Jules Desmeules*[1]

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2 Division of Anesthesiology, Geneva University Hospitals, Geneva, Switzerland

Bosilkovska M, et al. Drugs. 2012;72(12):1645-1669. https://pubmed.ncbi.nlm.nih.gov/22867045/

REVIEW

Pain Management in Patients With Cirrhosis

Mina Rakoski, M.D., M.Sc., Preeya Goyal, M.D., Michelle Spencer-Safier, Pharm.D., Jill Weissman, Pharm.D., Gina Mohr, M.D., and Michael Volk, M.D., M.Sc.

Pain is a common, undertreated symptom in patients with cirrhosis and is associated with increased health care utilization (hospitalizations, clinic visits, and phone calls).[1]

(Fig. 2), which can lead to an increased risk for hepatotoxicity and accumulation of toxic metabolites.[2] Table 1 summarizes the unique management considerations in this population.

Rakoski M, et al. *Clinical Liver Disease*. 2018;11(6):135-140. https://pubmed.ncbi.nlm.nih.gov/30992804/

Published guidance

HEPATOLOGY AASLD

PRACTICE GUIDANCE | Free Access

AASLD Practice Guidance: Palliative care and symptom-based management in decompensated cirrhosis

Shari Rogal, Lissi Hansen, Arpan Patel, Nneka N. Ufere, Manisha Verma, Christopher Woodrell
... See all authors

First published: 01 February 2022 | https://doi.org/10.1002/hep.32378

https://aasldpubs.onlinelibrary.wiley.com/doi/abs/10.1002/hep.32378

Table 5. Palliative management of chronic pain for patients with decompensated cirrhosis

The management of pain is complex and requires treatment of other contributing symptoms (e.g., sleep disorders, depression). Multidisciplinary approaches are often beneficial.

Nonpharmacological options
- Hot/cold
- Physical therapy
- Mindfulness/meditation
- Other behavioral pain self-management strategies (e.g., cognitive behavioral therapy)
- Acupuncture (caution if platelets < 50 k)
- Other complementary options based on preferences (e.g., transcutaneous nerve stimulation)

Pharmacological options
Topical/injection treatments
- Lidocaine patches
- Capsaicin cream or patch
- Topical nonsteroidal anti-inflammatory medications (e.g., diclofenac sodium 1% gel)
- Injections by pain specialists (e.g., osteoarthritis of knee)

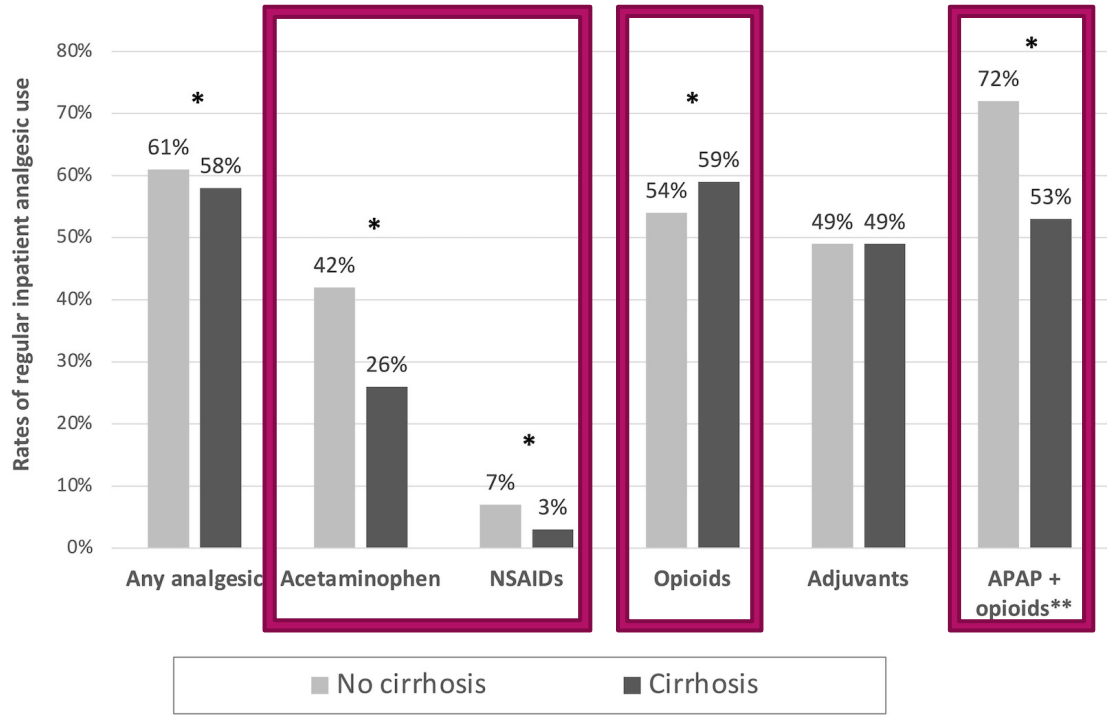
Systemic therapies
- Acetaminophen 500 mg q6h for a maximum of 2 gm/day is safe in most patients with liver disease
- Gabapentin 300 mg daily (starting dose) or pregabalin 50 mg bid (starting dose)* (for neuropathic pain)
- Fentanyl patch 12 μg starting dose (typically not recommended as the initial agent; avoid in patients with sarcopenia/cachexia or fever)
- Hydromorphone 1 mg q6h prn starting dose
- Oxycodone 2.5 mg PO q6–8h prn starting dose

NOTE: Once the goals of care are focused on comfort, opioid medications should be titrated up to meet the patient's needs without concerns for long-term impacts.

*Renal dosing adjustments needed; cannot be stopped without tapering; can cause nausea, sedation, ataxia

How are we managing pain in inpatients?

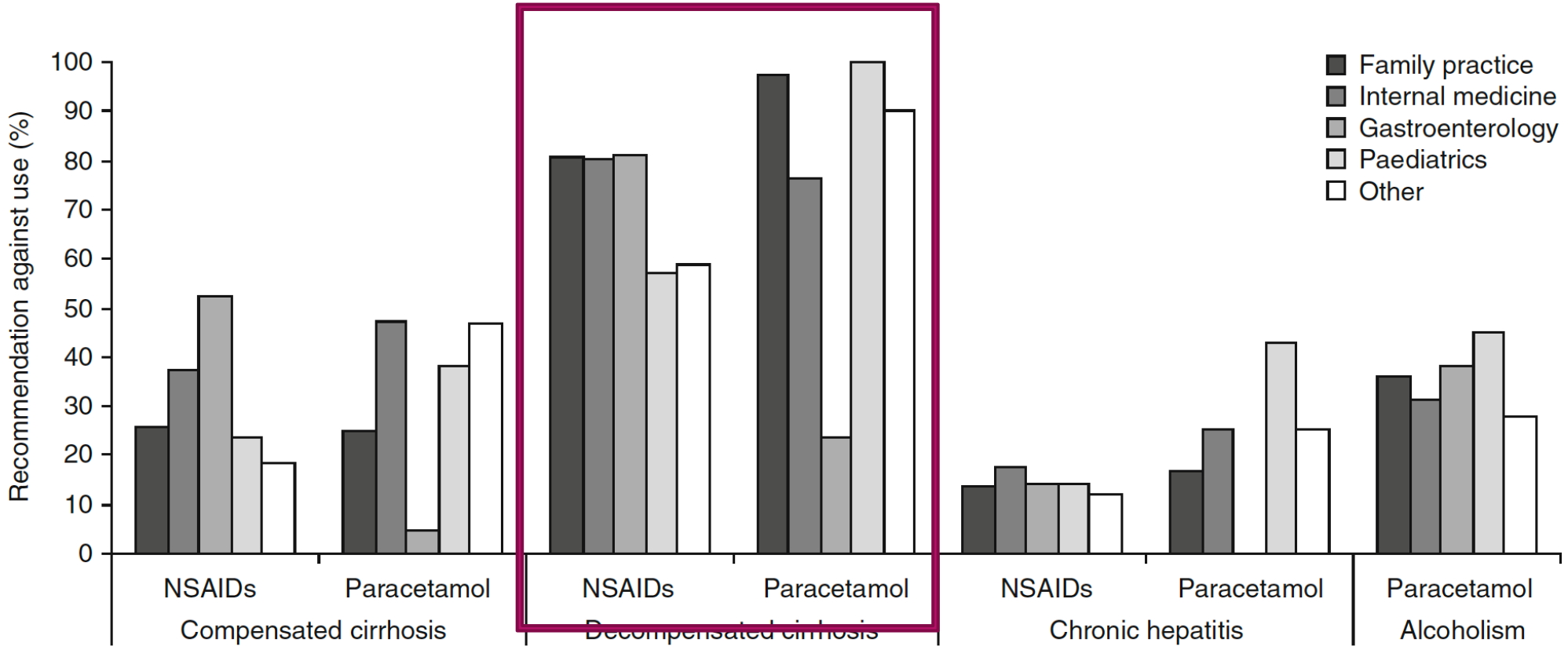
- 116,363 inpatients with cirrhosis, and matched controls without cirrhosis
- **83%** of patients received at least 1 dose of an analgesic during hospitalization
- **58%** had regular inpatient use
- Cirrhosis patients were **half** as likely to receive acetaminophen, **more likely** to receive opioids
  - Particularly true in decompensated patients
- Cirrhosis patients who are getting opioids regularly are often not given a trial of acetaminophen



* p<0.001 on conditional logistic regression
** Any APAP use among patients with regular opioid use

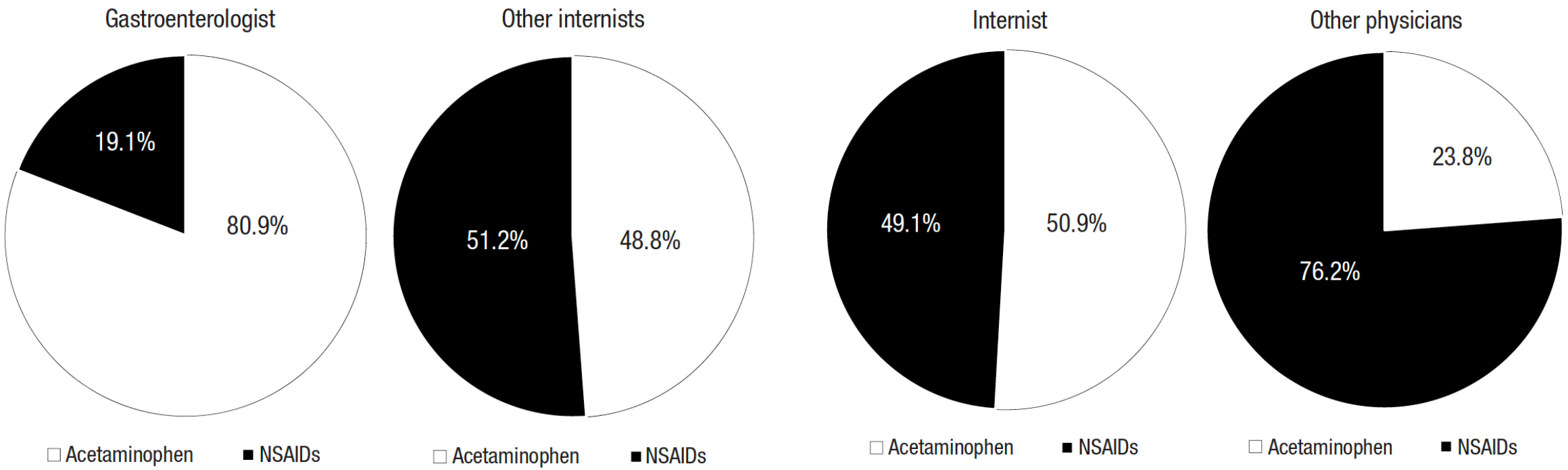
Reference: Rubin, et al. *Journal of Clinical Gastroenterology*. 2021.

Effects of lack of guidelines: variability



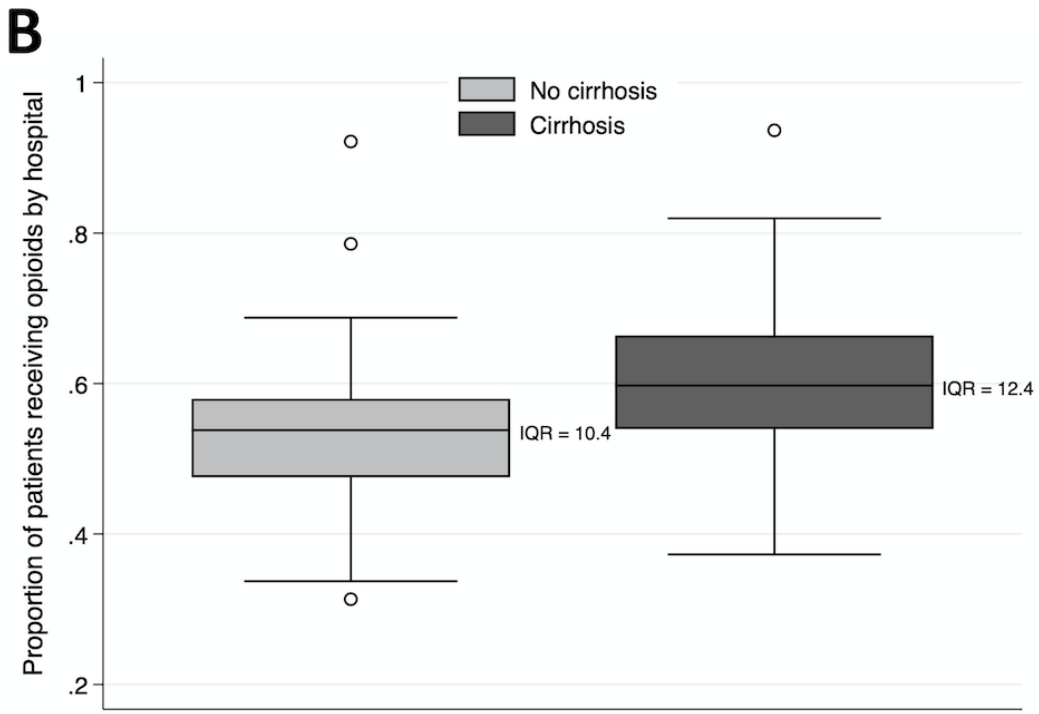
Reference: Rossi S, et al. Drug Safety. 2008;31(3):261-270.

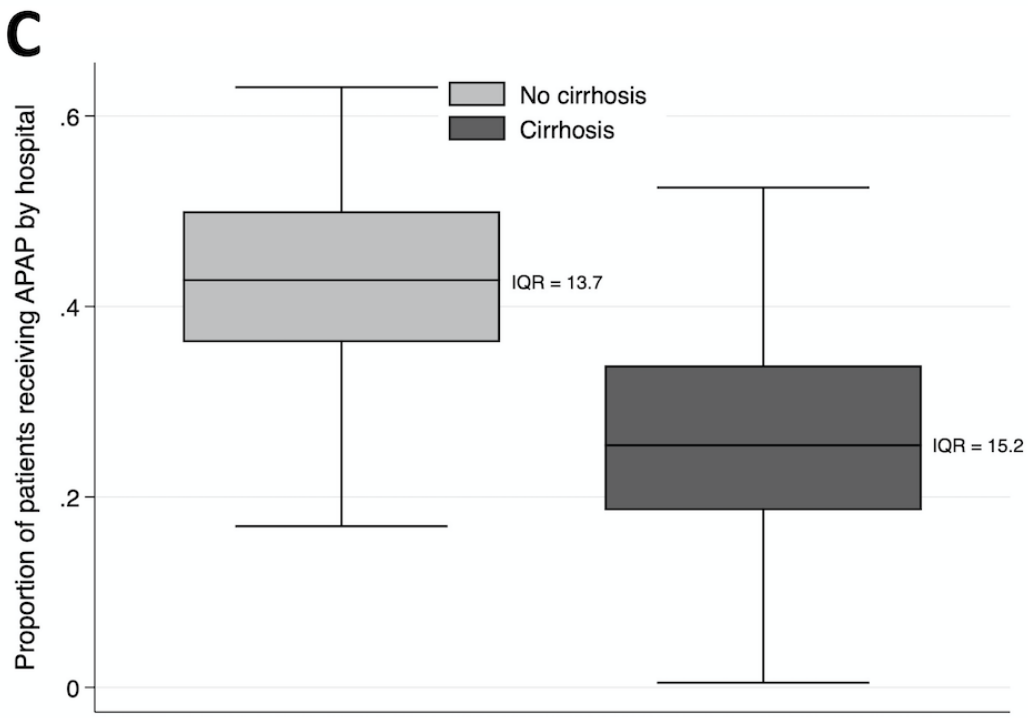
Effects of lack of guidelines: variability



Reference: Hong YM, et al.. *J Korean Med Sci*. 2016;31(10):1604-1610.

Effects of lack of guidelines: variability





Reference: Rubin, et al. *Journal of Clinical Gastroenterology*. 2021.

Managing pain is complex

Managing pain in cirrhosis is *even more* complex

PATIENT

- Metabolic comorbidities
- Substance use
- Psychiatric disease
- Low socioeconomic status / health literacy

DISEASE

- Variable presentations
- Minimal research on cirrhosis-related pain

PHARMACOLOGIC

- Impaired hepatic metabolism
- No biomarkers to measure hepatic function
- Impaired renal excretion
- Risk for adverse effects
  - Renal failure
  - GI bleeding
  - Hepatic encephalopathy
- Potential for abuse

CLINICIAN

- No guidelines
- Discomfort with analgesic options
- Stigma/bias

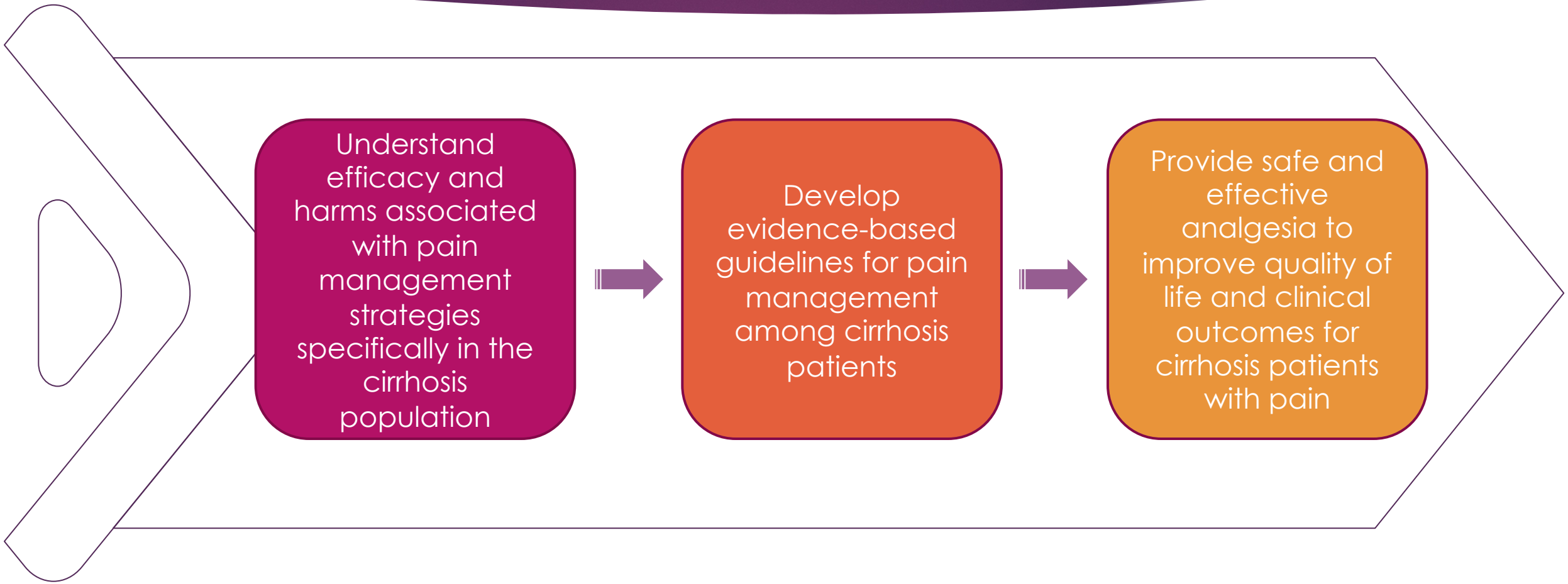
SYSTEM

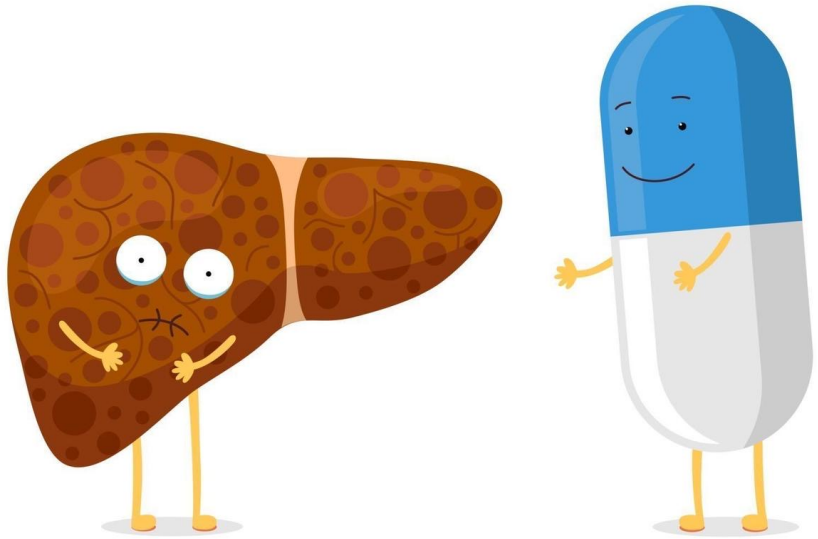
- Regulatory issues
- Transplant center requirements
- Fragmentation of care

UNDERTREATMENT

Adapted from Rakoski M, et al. Clinical Liver Disease. 2018;11(6):135-140.

Next steps


Understand efficacy and harms associated with pain management strategies specifically in the cirrhosis population
Develop evidence-based guidelines for pain management among cirrhosis patients
Provide safe and effective analgesia to improve quality of life and clinical outcomes for cirrhosis patients with pain



Thank you!

Additional slides

What do we know about pain in cirrhosis?

- Madan et al. 2012: retrospective chart review of 108 transplant candidates at single center
  - Psychosocial evaluation includes Brief Pain Inventory-Short Form
    - 77% moderate bodily pain within past 24 hours
    - Abdomen > Back > Lower Extremities
    - Alcohol < HCV or NASH
    - 90% prescribed analgesics; only associated with average of 33% pain control
- Poonja et al. 2014: retrospective chart review of 102 patients removed or declined for LT – looking at access to palliative care, relief of symptoms, goals of care
    - 65% had pain (based on Edmonton Symptom Assessment System)
- Rogal et al. 2015: prospective study of 193 patients with cirrhosis → McGill Pain Questionnaire, Pain Disability Index, lab markers of inflammation
    - 79% of patients reported pain, 75% pain-related disability
    - Abdomen > lower back > large joints (similar between those with and without ascites)
    - Associated with cirrhosis etiology (NASH, HCV > alcohol)
    - 40% believed liver was etiology of abdominal pain