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Prevalence and characteristics of patients prescribed opioids and central nervous system depression agents on discharge to hospice care

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Background: Hospice patients with end-stage liver disease (ESLD) have an increased risk of adverse drug events due to physiological changes and changes in pharmacokinetic and pharmacodynamic properties of medications; however, the use of opioid and central nervous system (CNS) depressant prescribing among patients with ESLD is prevalent. This study quantified the frequency and distribution of opioid and concomitant respiratory and CNS depressant prescribing among hospice patients with ESLD compared to other common hospice diagnoses of cancer, chronic obstructive pulmonary disorder (COPD), heart failure, and end-stage renal disease.

Methods: This was a cross-sectional study of adult (age 18 years or older) decedents of a large hospice chain. Patients included had a primary diagnosis of liver, cancer, cardiovascular, or respiratory disease.

Results: Among 119,424 hospice decedents, mean age of 77.9 years (standard deviation =13.5 years), 54.6% were female, and 58.9% were of a non-Hispanic white race. There was a similar frequency of prescribing a "scheduled" and "as needed [pro re nata (PRN)]" opioid or benzodiazepine in patients with ESLD compared to other common hospice diagnoses. In addition, there was a high prevalence of concurrent opioid and benzodiazepine prescriptions among patients with ESLD compared to cardiovascular and respiratory disease at admission (65.4% *vs.* 63.9% and 64.9%). Opioid requirements, oral morphine equivalent (OME) median [interquartile range (IQR)] at discharge were similar between cancer, liver, and respiratory disease, 120 OME [60–300], 120 OME [50–240], and 120 OME [50–240], respectively.

Conclusions: We observed a high frequency of opioid and CNS depressant prescribing in a hospice patient population with ESLD which was similar to other common admitting hospice diagnoses.

Keywords: Hospice care; liver disease; opioids; central nervous system depressants (CNS depressants)

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Introduction

Chronic liver disease is increasingly prevalent in the United States and with than 4.5 million adults have been diagnosed with liver disease, it is the fourth leading cause of death for persons between the ages of 45 and 64 years (1-3). Patients with end-stage liver disease (ESLD) suffer from an array of symptoms including pain, insomnia, delirium, dyspnea, and anxiety requiring a multimodal medication regimen for

symptom management. However, with the pharmacokinetic and pharmacodynamic challenges associated with liver dysfunction, there are risks and potentially harmful medication-related events and toxicity, particularly with opioids and concurrent central nervous system (CNS) depressants (4,5). In addition to the complexity of pain and symptoms of advanced illness in hospice patients, patients with ESLD experience liver-specific symptoms such as hepatic encephalopathy, which may be attributable to medication toxicity or worsening of hepatic function.

Drug metabolism is altered in ESLD, requiring drug dose reduction or discontinuation. An analysis of Veterans' Health Administration data of 1,877,841 patients with an opioid prescription found multiple variables, including liver disease and impaired drug metabolism or excretion, highly associated with opioid-induced respiratory or CNS depression (6). Further analysis of this study revealed that comorbid conditions such as liver disease were significantly associated with opioid-related toxicity and overdoses (7,8). Unfortunately, little is known about the frequency of opioid and CNS depressant prescribing in patients with ESLD in the hospice setting.

In this study, we aimed to investigate the frequency of opioid and concomitant CNS depressant prescribing in patients with ESLD and compare it to other common hospice diagnoses such as cancer, chronic obstructive pulmonary disorder (COPD), heart failure, and end-stage renal disease. We present this article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-537/rc).

Highlight box

Key findings

- Hospice patients with end-stage liver disease (ESLD) were frequently prescribed opioids at high dosages (120 oral morphine equivalent), similar to other common hospice diagnoses such as cancer, cardiovascular, and respiratory disease.
- The high prevalence of pain and symptoms, as evidenced by opioid and central nervous system depressant prescribing, is a clinical challenge in the face of ESLD and impaired hepatic metabolism and elimination of medications.

What is known and what is new?

- Previous studies have identified chronic ESLD as one of the highest risk factors for opioid-related adverse events, including respiratory depression and overdose.
- These results highlight the high prevalence of opioid and benzodiazepine prescribing among those with ESLD in the hospice setting, which may not be highly recognized and studied as in cancer, cardiovascular, and respiratory disease.

What is the implication, and what should change now?

- At the end of life, patients with ESLD have a high symptom burden. This study highlights the prevalence of common medications for pain and anxiety prescribed similar to other common hospice diagnoses such as cancer, cardiovascular, and respiratory disease.
- The high prevalence and frequency of opioid, benzodiazepine, and gabapentinoid prescribing among hospice patients with ESLD should be further studied and monitored for adverse effects that may occur. It is essential to consult clinical pharmacists to individualize pharmacotherapy treatment plans to minimize symptom burden and medication-related adverse events.

Methods

This retrospective cross-sectional study utilized data from a national for-profit hospice chain across the United States, including 19 states, between January 1, 2010, and December 31, 2019. Before data acquisition, the University of Maryland, Baltimore, and Oregon Health & Science University institutional review boards deemed this study was not a human research subject because all patients were deceased at the time of data collection. Hospice decedents who died while receiving hospice care were included in the analysis if they were 18 years of age and had a primary diagnosis of ESLD, cancer, cardiovascular, or respiratory disease. We identified the primary hospice diagnoses at the time of hospice admission using International Classification of Diseases (ICD) versions 9 and 10 codes. Patients were excluded if they did not meet the inclusion criteria. Patient demographics collected included demographics (e.g., age, sex, race/ethnicity), hospice service site (e.g., assisted living facility, home, hospital, inpatient hospice, nursing home), hospice length of stay, and primary hospice admitting diagnosis.

We used medication utilization data to estimate the prevalence of scheduled and pro re nata (PRN) opioids, benzodiazepines, and adjuvant analgesics, including gabapentinoids prescribed at admission, at any time during hospice care, and at discharge or death for each admitting diagnosis. These data were extracted from the hospice electronic medical record data which contained the patient's clinical and pharmacy records, including primary diagnosis and medication name, dosage, formulation, strength, and frequency. Medications were grouped by their pharmacological class. The medications included were within the hospice organization formulary or preferred drug list in their respective pharmacological class (*Table 1*).

Table 1 Medication utilization data grouped by pharmacological class

Opioids	Benzodiazepines	Adjuvant analgesics
Morphine	Alprazolam	Antiepileptic (carbamazepine, lamotrigine, pregabalin, gabapentin)
Fentanyl	Clonazepam	Steroids (dexamethasone)
Methadone	Lorazepam	Acetaminophen
Hydrocodone	Diazepam	Non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, diclofenac, celecoxib)
Hydromorphone	Temazepam	Serotonin-norepinephrine reuptake inhibition (duloxetine, venlafaxine)
Oxymorphone	Oxazepam	
Codeine		

Table 2 Opioid equianalgesic conversion ratios

Opioid	Conversion factor
Morphine oral	1
Codeine	0.125
Fentanyl transdermal (mcg/h)	2
Hydrocodone oral	1
Hydromorphone oral	5
Methadone	4
1–20 mg/day	4
21–40 mg/day	4
41–60 mg/day	4
61–80 mg/day	4
Oxycodone oral	1.25
Oxymorphone	2.5
Tapentadol	0.25
Tramadol	0.2
Morphine parenteral	2.5
Fentanyl parenteral (mg)	165
Hydromorphone parenteral	12.5

Adjuvant analgesic, opioid, benzodiazepine, and gabapentinoid prescribing were collected for each study group. We excluded intravenous infusions that did not have information on medication administration and titrations throughout hospice admission. CNS depressants included in this study were benzodiazepines, gabapentinoids, and opioids. The frequency of patients prescribed an opioid with a gabapentinoid, opioid with a benzodiazepine, and opioid with a benzodiazepine and gabapentin medication order was evaluated and compared between each disease group. Opioid utilization was evaluated as total daily oral morphine equivalent (OME), which includes scheduled and all possible PRN dosages patients are able to receive, at admission and discharge. Total daily OME calculations were determined using the most recently published opioid equianalgesic conversion table (8) (*Table 2*).

Statistical analysis

We used descriptive statistics, including means and standard deviations, 95% confidence intervals (CIs), medians, interquartile ranges (IQRs), and percentages. In addition, we stratified patients by primary diagnoses of the liver, cardiovascular, respiratory, and cancer disease to compare the differences in opioid, adjuvant analgesics, benzodiazepine, and gabapentinoid utilization between subgroups. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

This study included 119,424 hospice decedents in the analysis, with the most prevalent hospice diagnoses being cancer (46.2%) and about 2.2% of the patients with ESLD. Overall, the mean age was 77.9 years, and 54.6% were female. More than half of the patients were non-Hispanic white (58.9%). The median hospice length of stay measured by days of overall hospice decedents was 9 (IQR, 3–33). The majority of patients referred to hospice care resided at home (36.1%) or at an inpatient hospice facility (24.4%) (*Table 3*).

The prevalence of prescribing a scheduled regimen and scheduled and PRN regimen consisting of adjuvant analgesics, benzodiazepine, and opioid prescriptions at admission, during hospice stay, and discharge are shown

Table 3 Demographics

Characteristics	Overall (n=119,426)	Liver disease (n=2,584)	Cancer (n=55,150)	Cardiovascular disease (n=45,768)	Respiratory disease (n=15,924)
Age (years)	77.9±13.5	65.5±12.4	72.1±13.4	84.7±10.5	80.3±11.4
Sex (female)	65,191 (54.6)	1,083 (41.9)	28,132 (51.0)	27,059 (59.1)	8,917 (56.0)
Race					
Non-Hispanic White	70,399 (58.9)	1,413 (54.7)	30,430 (55.2)	28,430 (62.1)	10,126 (63.6)
Non-Hispanic Black	20,437 (17.1)	329 (12.7)	11,018 (20.0)	7,182 (15.7)	1,897 (11.9)
Hispanic/Latino	8,167 (6.8)	313 (12.1)	3,914 (7.1)	2,903 (6.3)	1,039 (6.5)
Other	20,423 (17.1)	529 (20.5)	9,788 (17.7)	7,253 (15.8)	2,862 (18.0)
LOS (days)	9 [3–33]	5 [2–15]	10 [3–31]	10 [3–46]	4 [1–16]
Admission location					
Assisted living facility	9,091 (7.6)	59 (2.3)	2,023 (3.7)	6,157 (13.5)	852 (5.4)
Home	43,083 (36.1)	811 (31.4)	26,481 (48.0)	12,191 (26.6)	3,600 (22.6)
Hospital	15,684 (13.1)	445 (17.2)	6,174 (11.2)	5,391 (11.8)	3,674 (23.1)
Inpatient hospice	29,100 (24.4)	865 (33.5)	13,180 (23.9)	9,714 (21.2)	5,341 (33.5)
Nursing home	19,679 (16.5)	349 (13.5)	6,158 (11.2)	11,197 (24.5)	197 (1.2)
Other	2,787 (2.3)	53 (2.1)	1,134 (2.1)	1,118 (2.4)	482 (3.0)

Data are presented as mean ± SD, n (%), or median [IQR]. LOS, length of stay; SD, standard deviation; IQR, interquartile range.

in *Table 4*. Although patients with ESLD were less frequently prescribed a scheduled benzodiazepine and adjuvant analgesic, they were more frequently prescribed a scheduled opioid compared to patients with cardiovascular and respiratory disease at any time (39.4% *vs.* 36.4%, 95% CI for difference: 0.01 to 0.05; and 41.8%, 95% CI for difference: 0.25 to 0.29).

The prevalence of patients with ESLD prescribed a scheduled and PRN benzodiazepine was less than patients with cancer, cardiovascular, and respiratory disease at admission (67.3% *vs.* 71.7%, 95% CI for difference: –0.07 to –0.03; 68.1%, 95% CI for difference: –0.03 to 0.01; and 68.0%, 95% CI for difference: –0.03 to 0.01). However, patients with ESLD were prescribed a scheduled and PRN benzodiazepine more frequently than those with respiratory disease at any point during hospice stay (75.0% *vs.* 74.9%, 95% CI for difference: –0.02 to 0.02). Patients with ESLD were more frequently prescribed a scheduled and PRN opioid than patients with cardiovascular and respiratory diseases at admission (78.3% *vs.* 76.0%, 95% CI for difference: 0.01 to 0.04; and 75.9%, 95% CI for difference: 0.01 to 0.04) and patients with respiratory disease at any time (84.2% *vs.* 82.6%, 95% CI for difference: 0.002 to 0.03) and discharge (80.5% *vs.* 77.8%, 95% CI for difference: 0.01 to 0.04).

The prevalence of patients with concurrent CNS depressant prescriptions, including an opioid, gabapentinoid, and benzodiazepine, were collected at admission and discharge. It was found that patients with ESLD received concurrent opioid and benzodiazepine prescriptions similarly to those with cardiovascular and respiratory disease at admission (65.4% *vs.* 63.9%, 95% CI for difference: –0.003 to 0.03; and 64.9%, 95% CI for difference: –0.01 to 0.03) and those with respiratory disease at discharge (68.4% *vs.* 67.6%, 95% CI for difference: –0.01 to 0.03). Patients prescribed all three CNS depressants, an opioid, benzodiazepine, and gabapentinoid prescription at admission (4.4%) and discharge (4.2%) were compared between disease groups. Patients admitted with a diagnosis of ESLD receiving all three pharmacologic categories had a similar frequency as those admitted with respiratory disease on admission (3.6%, 95% CI for difference: –0.002 to 0.014) (*Table 5*).

Opioid utilization was collected at admission and discharge and presented in *Table 6* with median OME (IQR). From hospice admission to hospice discharge, overall OME

Table 4 Analgesics and benzodiazepine prescribing

Analgesic medication class	Overall (n=119,426)	Liver disease (n=2,584)	Cancer (n=55,150)	Cardiovascular disease (n=45,768)	Respiratory disease (n=15,924)
Prevalence of medication prescription with a scheduled regimen (adjuvant, BZD, or opioid) at admission					
Adjuvants	2,1670 (18.1)	213 (8.2)	12,457 (22.6)	7,119 (15.6)	1,881 (11.8)
BZD	12,617 (10.6)	211 (8.2)	5,700 (10.3)	4,559 (10.0)	2,147 (13.5)
Opioids	30,234 (25.3)	497 (19.2)	18,520 (33.6)	7,225 (15.8)	3,992 (25.1)
Prevalence of medication prescription with a scheduled and PRN regimen (adjuvant, BZD, or opioid) at admission					
Adjuvants	81,274 (68.1)	1,443 (55.8)	38,312 (69.5)	31,946 (69.8)	9,593 (60.2)
BZD	83,545 (70.0)	1,738 (67.3)	39,515 (71.7)	31,167 (68.1)	10,828 (68.0)
Opioids	95,107 (79.6)	2,024 (78.3)	46,214 (83.8)	34,786 (76.0)	12,083 (75.9)
Prevalence of medication prescription with a scheduled regimen (adjuvant, BZD, or opioid) at any time during hospice stay					
Adjuvants	30,415 (25.5)	285 (11.0)	17,637 (32.0)	9,830 (21.5)	2,633 (16.5)
BZD	25,738 (21.6)	487 (18.8)	11,841 (21.5)	9,727 (21.3)	3,683 (23.1)
Opioids	53,650 (44.9)	1,017 (39.4)	29,297 (53.1)	16,680 (36.4)	6,656 (41.8)
Prevalence of medication prescription with a scheduled and PRN regimen (adjuvant, BZD, or opioid) at any time during hospice stay					
Adjuvants	10,463 (8.8)	1,584 (61.3)	42,024 (76.2)	34,750 (75.9)	10,463 (65.7)
BZD	94,488 (79.1)	1,938 (75.0)	44,694 (81.0)	35,924 (78.5)	11,932 (74.9)
Opioids	104,548 (87.5)	2,177 (84.2)	49,483 (89.7)	39,742 (86.8)	13,146 (82.6)
Prevalence of medication prescription with a scheduled regimen (adjuvant, BZD, or opioid) at discharge					
Adjuvants	21,598 (18.1)	202 (7.8)	12,828 (23.3)	6,619 (14.5)	1,949 (12.2)
BZD	20,725 (17.4)	399 (15.4)	9,377 (17.0)	7,911 (17.3)	3,038 (19.1)
Opioids	47,221 (39.5)	917 (35.5)	25,595 (46.4)	14,786 (32.3)	5,923 (37.2)
Prevalence of medication prescription with a scheduled and PRN regimen (adjuvant, BZD, or opioid) at discharge					
Adjuvants	82,919 (69.4)	1,467 (56.8)	38,936 (70.6)	32,686 (71.4)	9,830 (61.7)
BZD	88,172 (73.8)	1,809 (70.0)	41,468 (75.2)	33,730 (73.7)	11,165 (70.1)
Opioids	99,208 (83.1)	2,081 (80.5)	46,863 (85.0)	37,869 (82.7)	12,395 (77.8)

Data are presented as n (%). BZD, benzodiazepine; PRN, pro re nata.

increased across all disease groups. The median OME (IQR) was the same between ESLD, cancer, and respiratory disease, but the OME utilization was higher in ESLD than in cardiovascular disease (120 OME *vs.* 75 OME).

Discussion

Liver disease has been identified as one of the highest risk factors for opioid-related toxicity and overdoses (6,7,9-12). High opioid and benzodiazepine utilization in patients with ESLD is problematic due to impaired hepatic metabolism and elimination. While multiple studies have demonstrated high utilization of opioid and concurrent benzodiazepine prescriptions in liver disease, this is the first study to assess the prevalence of opioid and CNS depressant prescribing in the hospice setting and patients with ESLD. This is important because patients in the hospice setting are often prescribed multiple medications to treat suffering pain, anxiety, and insomnia, and changes in pharmacokinetics and pharmacodynamics must be considered.

A previous study has demonstrated patients with ESLD to have a high burden of mortality and morbidity and

Table 5 CNS depressant prescriptions among patients with primary diagnoses of liver, cancer, cardiovascular, or respiratory disease

CNS depressant prescribing	Overall (n=119,426)	Liver disease (n=2,584)	Cancer disease (n=55,150)	Cardiovascular disease (n=45,768)	Respiratory disease (n=15,924)
Opioid & gabapentinoid at admission	6,333 (5.3)	114 (4.4)	3,506 (6.4)	2,057 (4.5)	656 (4.1)
Opioid & gabapentinoid at discharge	5,715 (4.8)	102 (3.9)	3,024 (5.5)	1,932 (4.2)	657 (4.1)
Opioid & benzodiazepine at admission	80,071 (67.0)	1,691 (65.4)	38,816 (70.4)	29,227 (63.9)	10,337 (64.9)
Opioid & benzodiazepine at discharge	85,213 (71.4)	1,768 (68.4)	40,301 (73.1)	32,381 (70.8)	10,763 (67.6)
Opioid, benzodiazepine, & gabapentinoid at admission	5,290 (4.4)	93 (3.6)	2,933 (5.3)	1,697 (3.7)	567 (3.6)
Opioid, benzodiazepine, & gabapentinoid at discharge	5,040 (4.2)	87 (3.4)	2,688 (4.9)	1,681 (3.7)	584 (3.7)

Data are presented as n (%). CNS, central nervous system.

Table 6 Opioid utilization at admission and discharge: OME

OME utilization	Overall (n=91,117)	Cancer (n=79,966)	Cardiovascular disease (n=44,516)	Liver disease (n=2,764)	Respiratory disease (n=16,363)
OME at admission (dose per day)	60 [40–142]	80 [40–180]	40 [40–118]	64 [40–125]	64 [40–150]
OME at discharge (dose per day)	120 [40–240]	120 [60–300]	75 [40–160]	120 [50–240]	120 [50–240]

Data are presented as median [IQR]. OME is a value calculated to represent opioid dosage equivalency to morphine. Each specific opioid has an equianalgesic potency factor compared to morphine. Using the conversion factors shown in *Table 2*, the OME dose per day the sum of the OMEs of all opioids a patient is prescribed in a 24-hour period. This is a metric to determine the total amount of opioids utilized at a point in time. OME, oral morphine equivalent; IQR, interquartile range.

approximately 72% of patients report an overall poor quality of life. Pain, dyspnea, insomnia, and daytime sedation were reported in more than 75% of patients (13). Therefore, symptomatic management of patients with ESLD will require multiple interventions including non-pharmacological and pharmacological agents. This study found a high prevalence of opioid and CNS depressant utilization, as evidenced by a prescription in patients with ESLD compared to other common hospice diagnoses. As evidenced by previous studies, these results were not surprising given the high prevalence of pain and anxiety that patients with ESLD experience at the end of life (14-17). Our findings reveal that hospice patients with ESLD were frequently prescribed a scheduled and PRN opioid regimen at any time during their hospice length of stay (39.4%) at very high doses, typically defined as 90 or more OME, similar to other common hospice diagnoses (18). Commonly utilized opioids at the end of life, include morphine, hydromorphone, methadone, and oxycodone. These opioids are significantly metabolized by the liver, therefore hepatic impairment may result in greater plasma concentrations and prolonged half-lives (19-26). Given the high prevalence of pain, patients with ESLD are started on multiple analgesics, including opioids, non-steroidal anti-inflammatory agents, gabapentinoids, and antipyretic agents. A large nationwide database of insured US patients demonstrated higher rates of prescription opioids and benzodiazepines for patients with cirrhosis than other chronic diseases, which is concerning in the face of impaired drug metabolism in hepatic dysfunction (14). This study adds to the existing literature by presenting a large, national hospice patient population database and the high prevalence of CNS depressing agents and adjuvant analgesics prescribed to patients with ESLD and compared to other common admitting diagnoses with significant symptom burden. Considering the safety of opioids in patients with ESLD and impaired hepatic metabolism, opioid prescribing should be considered carefully. It is advisable to consult a pharmacist or clinician with extensive training in pharmacology to adjust medications to lower dosages, extended dosing frequencies, and continual monitoring.

Patients with ESLD often experience anxiety and

agitation throughout their disease trajectory and especially at the end-of-life (16). Benzodiazepine prescribing was prevalent among all disease groups (74.9%), including ESLD (75.0%), with a scheduled and PRN benzodiazepine regimen at any time of hospice stay. Providing appropriate symptom management with minimal side effects with pharmacological agents at the end of life is challenging. Our results demonstrate the comparable prevalence of concomitant CNS depressant prescribing (e.g., opioid, gabapentinoid, and benzodiazepine) between diseases. However, in the face of hepatic dysfunction and ESLD, given the extensive hepatic biotransformation of benzodiazepines, clinicians must consider the implications of these pharmacokinetic changes (27,28).

This study had some limitations. The study population included hospice decedents from a single hospice provider in the United States, which may not be generalizable to all hospice and end-of-life patients. The study did not include data before hospice admission; therefore, the investigators were unaware of acute or chronic medications starting before hospice admission. When calculating the assumed total daily OME, all possible PRN dosages were included which may not account for all actual doses patients were taking. Lastly, study investigators were unable to identify medications that were part of the emergency kit (or comfort pack), so we could not specifically exclude the medications but included those medications as other PRN medications. This study's strengths are the large sample size, including hospice admissions across all admission locations over 10 years, and the extensive medication database.

Conclusions

In conclusion, this study demonstrated the significant opioid, benzodiazepine, and gabapentinoid prescribing among hospice patients with ESLD compared to other common admitting diagnoses. These findings should be further studied in other patient populations and monitored for adverse effects that may occur. It is essential to take additional precautions in prescribing medications for patients with ESLD and impaired hepatic metabolism. Furthermore, clinicians should consult pharmacists to individualize pharmacological treatment plans and minimize symptom burden.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-23-537/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-23-537/coif). J.P.F. serves as an unpaid editorial board member of *Annals of Palliative Medicine* from June 2023 to May 2025. He also serves as an unpaid board member of Oregon Hospice and Palliative Care Association, unpaid member of Diversity, Equity, and Inclusion Committee and editor of Diversity, Equity, and Inclusion LAB of the American Academy of Hospice and Palliative Medicine, and unpaid member of eLearning Continuing Education subcommittee and paid Statistical of the Society of Healthcare Epidemiology of America. J.P.F. received research funding from federal sponsors for other activities: First, AHRQ R01HS027820. This is a multi-site project using a mixed methods approach to develop, implement, and evaluate novel antibiograms to improve antibiotic prescribing in nursing homes, developing a novel antibiogram tool to improve empiric antibiotic prescribing in nursing homes. Second, Agency for Healthcare Research and Quality R01HS026747. This project utilizes a mixed methods approach to develop interventions to improve antibiotic prescribing among hospitalized inpatients on discharge to nursing homes, optimizing antibiotic prescribing on discharge to long-term care facilities. Third, Centers for Disease Control and Prevention Contract 75D30122F00001. This is a multisite study to develop knowledge and infrastructure to respond to public health emergencies in the nursing home setting, and nursing home public health response network. Last, National Institutes of Health R01AG079555. This is for Decision trajectories of patients at the end of life: An epidemiological exploration of MAID and the impact on caregivers and clinicians. This is a multisite longitudinal cohort study to understand quantitative and qualitative outcomes of seriously ill persons pursuing MAID as well as their caregivers, and health care providers. None represent

any conflicts of interest related to this article. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Asrani SK, Larson JJ, Yawn B, et al. Underestimation of liver-related mortality in the United States. Gastroenterology 2013;145:375-82.e1-2.
2. CDC/National Center for Health Statistics. FastStats. 2023. Accessed August 14, 2023. Available online: https://www.cdc.gov/nchs/fastats/liver-disease.htm
3. Peery AF, Crockett SD, Barritt AS, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology 2015;149:1731-1741.e3.
4. Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc 2010;85:451-8.
5. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008;64:1147-61.
6. Zedler B, Xie L, Wang L, et al. Development of a Risk Index for Serious Prescription Opioid-Induced Respiratory Depression or Overdose in Veterans' Health Administration Patients. Pain Med 2015;16:1566-79.
7. Zedler B, Xie L, Wang L, et al. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. Pain Med 2014;15:1911-29.
8. McPherson ML. Demystifying Opioid Conversion Calculations: A Guide for Effective Dosin: A Guide for Effective Dosing. 2nd ed. Bethesda: ASHP; 2018.
9. Rogal SS, Bielefeldt K, Wasan AD, et al. Inflammation, psychiatric symptoms, and opioid use are associated with pain and disability in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:1009-16.
10. Rogal SS, Beste LA, Youk A, et al. Characteristics of Opioid Prescriptions to Veterans With Cirrhosis. Clin Gastroenterol Hepatol 2019;17:1165-1174.e3.
11. Moon AM, Jiang Y, Rogal SS, et al. Opioid prescriptions are associated with hepatic encephalopathy in a national cohort of patients with compensated cirrhosis. Aliment Pharmacol Ther 2020;51:652-60.
12. Moon AM, Watkins SE, Lok AS, et al. Opioid Use Is More Common in Nonalcoholic Fatty Liver Disease Patients with Cirrhosis, Higher BMI, and Psychiatric Disease. Dig Dis 2021;39:247-57.
13. Philips CA, Kedarisetty CK. Palliative Care for Patients with End-Stage Liver Disease. J Clin Exp Hepatol 2023;13:319-28.
14. Konerman MA, Rogers M, Kenney B, et al. Opioid and benzodiazepine prescription among patients with cirrhosis compared to other forms of chronic disease. BMJ Open Gastroenterol 2019;6:e000271.
15. Potosek J, Curry M, Buss M, et al. Integration of palliative care in end-stage liver disease and liver transplantation. J Palliat Med 2014;17:1271-7.
16. Peng JK, Hepgul N, Higginson IJ, et al. Symptom prevalence and quality of life of patients with end-stage liver disease: A systematic review and meta-analysis. Palliat Med 2019;33:24-36.
17. Rogal SS, Winger D, Bielefeldt K, et al. Pain and opioid use in chronic liver disease. Dig Dis Sci 2013;58:2976-85.
18. Mazoit JX, Sandouk P, Zetlaoui P, et al. Pharmacokinetics of unchanged morphine in normal and cirrhotic subjects. Anesth Analg 1987;66:293-8.
19. Crotty B, Watson KJ, Desmond PV, et al. Hepatic extraction of morphine is impaired in cirrhosis. Eur J Clin Pharmacol 1989;36:501-6.
20. Hasselström J, Eriksson S, Persson A, et al. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. Br J Clin Pharmacol 1990;29:289-97.
21. Kotb HI, el-Kabsh MY, Emara SE, et al. Pharmacokinetics of controlled release morphine (MST) in patients with liver cirrhosis. Br J Anaesth 1997;79:804-6.
22. Bosilkovska M, Walder B, Besson M, et al. Analgesics in patients with hepatic impairment: pharmacology and clinical implications. Drugs 2012;72:1645-69.
23. Durnin C, Hind ID, Ghani SP, et al. Pharmacokinetics of oral immediate-release hydromorphone (Dilaudid IR) in subjects with moderate hepatic impairment. Proc West

Pharmacol Soc 2001;44:83-4.
24. Novick DM, Kreek MJ, Fanizza AM, et al. Methadone disposition in patients with chronic liver disease. Clin Pharmacol Ther 1981;30:353-62.
25. Kaiko RF. Pharmacokinetics and pharmacodynamics of controlled-release opioids. Acta Anaesthesiol Scand 1997;41:166-74.
26. Rogal SS, Winger D, Bielefeldt K, et al. Healthcare utilization in chronic liver disease: the importance of pain and prescription opioid use. Liver Int 2013;33:1497-503.
27. Brecher DB, West TL. Pain management in a patient with renal and hepatic dysfunction. J Palliat Med 2014;17:249-52.
28. Diep U, Chudow M, Sunjic KM. Pharmacokinetic Changes in Liver Failure and Impact on Drug Therapy. AACN Adv Crit Care 2017;28:93-101.

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