Long-Term Opioid Use Among Veterans with Cirrhosis: High-Dose Prescriptions in an Exceedingly High-Risk Population

J Gen Intern Med 37(12):3205–7
DOI: 10.1007/s11606-021-07282-7

INTRODUCTION

Cirrhosis patients have high rates of chronic pain, yet providers often struggle to manage pain in this population due to risks associated with multiple classes of analgesics.[1] Opioids, in particular, are thought to exacerbate hepatic encephalopathy, and experts typically recommend dose reduction or complete avoidance in this population.[2] Despite these recommendations, we found that cirrhosis inpatients were more likely to receive opioids than inpatients without cirrhosis.[3] In the present study, we analyzed detailed clinical data from a large contemporary cohort of Veterans on long-term opioid therapy (LTOT), with and without cirrhosis, in an effort to better understand patient characteristics and analgesic prescribing patterns among cirrhosis patients on LTOT.

METHODS

Our cohort includes all Veterans on long-term opioid therapy (LTOT) in 2014–2018, excluding those at the end of life (e.g., hospice). We identified patients with a urine drug screen (UDS) positive for opioids, and then limited our cohort to those with a VA prescription for opioids for ≥ 84 of 90 days before the UDS. Validated International Classification of Diseases (ICD) codes in the 2 years prior to UDS were used to define cirrhosis, decompensation, and comorbidities.[4, 5] Pharmacy records identified concurrent medication use and average morphine equivalent daily dose (MEDD), with high-dose opioids defined as MEDD ≥ 50 mg. Multivariable logistic regression models determined predictors of high-dose opioid use.

Received September 20, 2021
Accepted November 16, 2021
Published online January 17, 2022

RESULTS

Among Veterans on LTOT (n=112,843), 3% had cirrhosis. Compared to patients without cirrhosis, cirrhosis patients were older (p<0.001) and had more medical and psychiatric comorbidities (Table 1). Cirrhosis patients were twice as likely to have common types of chronic pain (p<0.001 for all), >3 times more likely to use alcohol (p<0.001), and more likely to have had falls or functional impairment (p<0.001). Mean MEDD was 53 mg in patients with cirrhosis compared to 45 mg in those without cirrhosis (p<0.001). Concurrent cannabis and gabapentinoid use was more common in patients with cirrhosis ($p \leq 0.001$). On multivariable logistic regression, patients with cirrhosis prescribed LTOT were 40% more likely to receive high-dose opioids (OR 1.37, 95% CI 1.26–1.48, p<0.001), after adjustment for demographics, comorbidities, and other substance/medication use (Table 2).

Similar patterns were observed in the 25% (n=787) of cirrhosis patients with decompensated disease: these patients were older and had more functional impairment and substance use than compensated patients (all p<0.001; Table 1). Mean MEDD was similar (p=0.52), though decompensated patients were less likely to use other psychoactive medications, such as muscle relaxants (p<0.001).

DISCUSSION

Although there are limited data on real-world harms of prescribed opioids in cirrhosis patients, the primary metabolic pathways for most opioids are impaired in cirrhosis, with malnutrition and renal failure further impacting susceptibility to toxicity. As a result, lower opioid doses are recommended in this population. In the present study of Veterans on LTOT, however, we found the opposite to be true: cirrhosis patients were *more* likely to receive high-dose opioids than patients without cirrhosis.

What explains these findings? We found that cirrhosis patients were more likely to have most types of pain, suggesting that they may have higher rates of pain and/or opioid dependence than patients without cirrhosis, perhaps related to concurrent psychiatric comorbidities and substance use disorders. Additionally, providers may feel handcuffed regarding analgesic use in this population due to concerns and about medication-related risks of nonopioid agents, resulting in

Table 1 Demographic, Clinical, and Pain-Related Characteristics by Cirrhosis and Decompensation Status Among Veterans on LTOT, 2014–2018

Data presented as mean (SD) or percent		No cirrhosis, *n*=109,718; 97%	Cirrhosis, *n*=3,125; 3%	*p* value	Compensated, *n*=2,338; 75%	Decompensated, *n*=787; 25%	*p* value
Demographics							
Age, years		61 (12)	62 (9)	<0.001	62 (9)	64 (9)	<0.001
Male		93	96	<0.001	95	97	0.024
Non-White race		20	18	0.007	18	18	0.93
Hispanic ethnicity		3	5	<0.001	5	4	0.50
Comorbidities							
Medical comorbidities	Hypertension	66	77	<0.001	78	82	0.015
	Diabetes	33	50	<0.001	49	52	0.11
	Heart disease[1]	26	39	<0.001	35	51	<0.001
	COPD	21	33	<0.001	30	42	<0.001
	Obstructive sleep apnea	12	22	<0.001	22	21	0.76
	Severe CKD (eGFR <30)	1	3	<0.001	2	4	<0.001
Mental health comorbidities	Any psychiatric diagnosis	52	61	<0.001	61	61	0.87
	Depression	38	48	<0.001	47	49	0.27
	Anxiety	20	26	<0.001	26	26	0.89
	PTSD	21	21	0.70	22	18	0.02
Frailty/fall risk diagnoses	History of falls	3	8	<0.001	7	10	0.002
	Functional impairment	13	17	<0.001	16	20	0.003
	Dementia	6	13	<0.001	10	22	<0.001
Substance use	Tobacco use	38	37	0.55	36	40	0.099
	Alcohol use	6	20	<0.001	15	36	<0.001
	Cannabis use	25	31	<0.001	30	33	0.12
	Other drug use[2]	2	2	0.49	2	2	0.4
Pain and medication characteristics							
Type of pain	Back pain	69	73	<0.001	72	73	0.74
	Neck pain	24	28	<0.001	28	28	0.95
	Osteoarthritis	34	40	<0.001	41	39	0.50
	Neuropathy	18	31	<0.001	39	35	0.002
Daily morphine equivalents (mg)		45 (49)	53 (60)	<0.001	53 (56)	54 (71)	0.52
High-dose opioid use (>50 mg MEDD)		27	35	<0.001	35	34	0.76
Other psychoactive medications	Benzodiazepines	22	23	0.70	24	19.7	0.02
	Gabapentinoids	27	30	0.001	30	30	0.90
	Muscle relaxants	22	19	<0.001	21	15	<0.001
	Antidepressants	34	34	0.97	35	30	0.01

[1]*Ischemic heart disease, congestive heart failure, or atrial fibrillation;* [2]*Amphetamine or cocaine use*
LTOT long-term opioid therapy; SD standard deviation; eGFR estimated glomerular filtration rate; COPD chronic obstructive pulmonary disease; PTSD post-traumatic stress disorder; MEDD morphine equivalent daily dose

Table 2 Risk Factors for High-Dose Opioid Use (≥ 50 MEDD) Among Veterans on LTOT, 2014–2018 (*N* = 112,843)

		Unadjusted			Adjusted		
		OR	95% CI	*p* value	aOR	95% CI	*p* value
Cirrhosis		***1.42***	***1.32–1.53***	***<0.001***	***1.37***	***1.26–1.48***	***<0.001***
Age (per year)		0.99	0.99–0.99	<0.001	0.99	0.99–0.99	<0.001
Male gender		1.19	1.13–1.26	<0.001	1.35	1.27–1.43	<0.001
White race		1.25	1.21–1.29	<0.001	1.23	1.19–1.28	<0.001
Hispanic ethnicity		0.93	0.86–1.00	0.05	-	-	-
Mean eGFR (per 1 mL/min/1.73 m^2)		1.01	1.01–1.01	<0.001	1.00	1.00–1.01	<0.001
Psychiatric disease		1.46	1.42–1.50	<0.001	1.20	1.16–1.24	<0.001
Type of pain	Back pain	1.60	1.55–1.65	<0.001	1.48	1.43–1.52	<0.001
	Neck pain	1.32	1.28–1.36	<0.001	1.15	1.11–1.19	<0.001
	Osteoarthritis	0.98	0.96–1.01	0.2	-	-	-
	Neuropathy	1.23	1.19–1.27	<0.001	1.20	1.15–1.24	<0.001
Substance use	Tobacco use	1.24	1.22–1.28	<0.001	1.20	1.16–1.23	<0.001
	Alcohol use	0.83	0.79–0.88	<0.001	0.70	0.66–0.74	<0.001
	Cannabis use	1.06	1.03–1.09	<0.001	-	-	-
Frailty/fall risk diagnoses	History of falls	1.27	1.19–1.37	<0.001	-	-	-
	Dementia	1.16	1.10–1.23	<0.001	-	-	-
Other psychoactive medications	Benzodiazepines	1.52	1.47–1.57	<0.001	1.35	1.30–1.40	<0.001
	Gabapentinoids	1.27	1.23–1.31	<0.001	1.13	1.09–1.17	<0.001
	Muscle relaxants	1.11	1.07–1.14	<0.001	0.96	0.93–0.99	0.01
	Antidepressants	1.38	1.34–1.42	<0.001	1.17	1.13–1.21	<0.001

MEDD average morphine equivalent daily dose; LTOTlong-term opioid therapy; OR odds ratio; CI confidence interval; eGFR estimated glomerular filtration rate

higher rates of prescription opioid use. For example, we found that muscle relaxants and benzodiazepines were less commonly used in patients with decompensated cirrhosis, possibly reflecting concerns regarding fall risk or deliriogenic effects of such medications.

Unfortunately, the same comorbidities that likely lead to increased rates of pain and opioid dependence in cirrhosis patients (e.g., psychiatric disease, substance use, functional impairment) may further increase the risk of opioid-related adverse events in this population, on top of risk related to hepatic impairment and demographic characteristics (e.g., older age). Interestingly, patients with these high-risk characteristics were the precise target for the VA's 2013 opioid safety initiative,[6] so these patterns may be even more pronounced in non-VA healthcare settings. It remains unknown, however, whether high-dose LTOT in this population truly leads to feared adverse events, such as hepatic encephalopathy, falls, or hospital admission. Future pharmacoepidemiologic studies answering these questions will be essential to developing evidence-based recommendations for providers treating the large proportion of cirrhosis patients living with chronic pain.

Acknowledgements: *This project was supported by VA HSR&D IIR 18-231-2 (Keyhani), AASLD Anna S. Lok Advanced/Transplant Hepatology Award (Rubin), NIH National Center for Advancing Translational Sciences KL2TR001870 (Rubin), and NIA Research Project Grant R01AG059183 (Lai).*

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