Opioid Use Is More Common in Nonalcoholic Fatty Liver Disease Patients with Cirrhosis, Higher BMI, and Psychiatric Disease

Andrew M. Moon^a Stephanie E. Watkins^b Anna S. Lok^c
Roberto J. Firpi-Morell^d Huy Ngoc Trinh^e Justin T. Kupec^f Cheryl Schoen^b
Brent A. Neuschwander-Tetri^g A. Sidney Barritt^a

^aDivision of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill, UNC Liver Center, Chapel Hill, NC, USA; ^bTARGET PharmaSolutions, Inc., Durham, NC, USA; ^cDivision of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI, USA; ^dSection of Hepatobiliary Diseases and Transplantation, University of Florida, Gainesville, FL, USA; ^eSan Jose Gastroenterology, San Jose, CA, USA; ^fDepartment of Medicine, Section of Digestive Diseases, West Virginia University, Morgantown, WV, USA; ^gDivision of Gastroenterology and Hepatology, Saint Louis University, St. Louis, MO, USA

Keywords

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Abstract

Background: Opioid use is a topic of growing concern among patients with nonalcoholic fatty liver disease (NAFLD). Given safety concerns of opioids, proactively identifying subgroups of patients with an increased probability of opioid use may encourage practitioners to recommend alternative therapies for pain, thus reducing the likelihood of opioid misuse. This work assessed the prevalence and patient characteristics associated with opioid use in a real-world cohort of patients with NAFLD. **Methods:** TARGET-NASH, an observational study of participants at 55 academic and community sites in the United States, includes patients with NAFLD defined by pragmatic case definitions. Opioid use was defined as any documented opioid prescriptions in the year prior to enrollment. The association between patient characteristics and the odds of opioid use were modeled with stepwise multivariable logistic regression and tree ensemble methods (Classification and regression tree/Boosted Tree). **Results:** The cohort included 3,474 adult patients with NAFLD including 18.0% with documented opioid use. Vari-

ables associated with opioid use included presence of cirrhosis (OR 1.51, 95% CI 1.16–1.98), BMI ≥ 32 kg/m² (OR 1.29, 95% CI 1.05–1.59), depression (OR 1.87, 95% CI 1.50–2.33), and anxiety (OR 1.59, 95% CI 1.27–1.98). In the boosted tree analysis, history of back pain, depression, and fibromyalgia had the greatest relative importance in predicting opioid use. **Conclusion:** Prescription opioids were used in nearly 1 of 5 patients with NAFLD. Given the safety concerns of opioids in patients with NAFLD, alternative therapies including low-dose acetaminophen and nonpharmacologic treatments should be considered for these patients.

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Introduction

More than 50 million adults in the United States had painful chronic health conditions in 2016 [1]. Prescribing rates of opioids, commonly used in the management of patients with chronic pain, have increased in the United States since 2006 with >70,000 opioid-related overdose deaths in recent years [2]. In 2016, to improve patient safety with pain management, the Centers for Disease Control and Prevention published guidelines

providing recommendations for alternative treatment options [3].

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide [4], yet little is known regarding the prevalence of pain and associated opioid use in this population. NAFLD is commonly associated with both obesity and metabolic syndrome due to biomechanical changes which increase the mechanical load on the joints and spine, inflammatory mediators which may alter pain modulation, and poor sleep habits [5–7]. In a single center cohort of patients with NAFLD, 30% experienced pain [8]. Furthermore, model for end-stage liver disease (MELD) and Child-Pugh score (CPS) have been positively associated with pain and pain-related disability [8–11].

Currently, there is a paucity of safety data, societal misconceptions, and fear of litigation associated with the treatment of chronic pain in patients with liver disease [12]. Many patients with severe liver disease receive opioid prescriptions for pain due to the increased risk of hepatic and renal toxicities associated with acetaminophen and non-steroidal anti-inflammatory drug (NSAID) use [8, 9, 13]. Yet, use of opioids among patients with severe liver disease is associated with an increased risk of complications including prolonged hospitalization, hospital readmission, and decreased health-related quality of life [14–16].

Exercise is an alternative nonpharmacologic therapy for pain, which decreases hepatic steatosis among patients with NAFLD and improves mobility, potentially reducing the need for opioids [17–21]. In light of the safety guidelines for opioid use from the Centers for Disease Control and Prevention, there is promising evidence demonstrating that early physical therapy is associated with a reduction in future opioid use [22]. Therefore, it is possible that proactive identification of characteristics of patients at risk for opioid use may encourage health practitioners to consider alternative non-opioid therapies that may improve long-term health outcomes in these patients. This study estimated the real-world prevalence of prescription opioid use among patients with NAFLD enrolled in the TARGET-NASH cohort. Additionally, this study utilized traditional modeling analyses as well as machine learning techniques to develop a patient phenotype at risk for opioid use.

Methods

Cohort

TARGET-NASH is an ongoing longitudinal cohort of adult and pediatric patients with NAFL, nonalcoholic steatohepatitis (NASH), or NAFLD-related cirrhosis managed according to lo-

cal practice guidelines across academic and community gastroenterology, hepatology, and endocrinology clinics in the United States. A description of the study design has been previously published [23]. Briefly, enrolled patients consent to review of their medical records for 3 years prior to enrollment and are followed prospectively for 5 years. Clinical information from the electronic medical records, including patient narratives, laboratory results, pathology reports, and imaging data are extracted and uploaded into a secured database at 6 month intervals from the date of enrollment. Approvals from central and/or local institutional review boards are obtained prior to subject recruitment and at enrollment.

This analysis included all adult patients (≥ 18 years old) enrolled in TARGET-NASH between August 1, 2016, and March 4, 2019.

Case Definitions

All patients were diagnosed by their treating physician with NAFLD based on liver biopsy and/or pragmatic case definitions. After enrollment, patients were classified as having NAFL, NASH, or NAFLD-related cirrhosis. NAFL was defined as the presence of hepatic steatosis not attributable to other causes (e.g., heavy alcohol consumption) and without evidence of biochemical and/or histological inflammation. NASH was defined as the presence of steatohepatitis on biopsy or both steatosis and elevated alanine aminotransferase levels in a patient with obesity, type 2 diabetes, dyslipidemia, or metabolic syndrome. Cirrhosis was based on clinical determination (i.e., clinical decompensation events, labs, imaging) or liver biopsy (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000511074) [23].

Medication Use

Patients with documentation in the medical record of any use of the following medications codeine, buprenorphine, butorphanol, hydrocodone, dihydrocodeine, oxycodone, fentanyl, hydromorphone, methadone, morphine, oxymorphone, tramadol, pethidine, and tapentadol, within 1 year up to or at the time of enrollment were considered “opioid users.” We classified these opioids into abuse potential based on scheduling categories set by the United States Drug Enforcement Administration [24]. Information on the duration of prescription opioid use was not available.

Clinical Characteristics

Medication use, medical history, and procedure and laboratory values were ascertained prior to or at enrollment. Psychiatric and medical comorbidities were determined by review of medical records for keywords within clinical notes or relevant medications. For patients with cirrhosis, CPS and MELD were calculated based on labs and clinical assessment at the time of enrollment [25, 26].

Statistical Analysis

The proportion of patients with documented opioid and/or non-opioid analgesic use was calculated and stratified by severity of liver disease. The distribution of opioid use by demographic characteristics, patient comorbidities, reported symptoms (abdominal pain, back pain, headache), severity of liver disease, and decompensation events was also calculated.

A χ^2 test was used to compare the distribution of categorical variables and an ANOVA was used to compare the distribution of continuous variables among opioid users versus nonusers.

Stepwise logistic regression was used to estimate the association between patient characteristics and the odds of receipt of opioids among all patients with NAFLD and within the strata of NAFLD cirrhosis using variables determined a priori as well as those identified via univariate analyses (significance level for entry = 0.25; significance level to remain in the model = 0.1). Collinear variables were removed, and a forward, stepwise regression model was fit. These analyses were performed using SAS version 9.4 (Cary, NC, USA).

Classification and Regression Tree Analysis

The predicted probability of opioid use at enrollment was estimated using a classification and regression tree analysis (CART) among all patients with NAFLD. A CART analysis is a data driven, nonparametric method of estimating the association between independent variables (clinical characteristics) and the predicted probability of a given outcome (opioid use). In a CART analysis, a decision tree is created using a series of dichotomous splits of patient variables that have a similar probability of opioid use [27]. At each terminal split, the algorithm predicts the outcome by classifying the response that creates the greatest difference in the prevalence of the outcome across the splitting category [28].

CART analysis has several advantages over traditional modeling techniques. First, it allows for multiple comparisons and thus can be used to assess outcomes with many possible predictor variables. Second, it does not make assumptions about the distribution or normality of the modeled outcome and it avoids the need to inform the model with transformations of predictor variables. Third, it provides modeling of the complex interactions between predictor variables, resulting in an estimated probability of use among subgroups of patients with similar characteristics, which may be more clinically applicable.

Cross validation was performed to assess the stability of the estimate. The validation data set was created using 75% of the data as the training set and 25% as the validation set with equal balance of opioid users in each group. The misclassification rate and area under the receiver operating curve were calculated for the final model.

In addition to the CART analysis, boosted trees, which applied the classification algorithm over multiple iterations of classification trees, were used to estimate the variable importance of predictors of opioid use while decreasing the prediction error of the algorithm. The following variables were included in the tree-based analysis: age, sex, race, ethnicity, BMI, recent alcohol use, Alcohol Use Disorders Identification Test (AUDIT) score, history of diabetes mellitus, depression, anxiety, osteoarthritis, rheumatologic diagnosis, dyslipidemia, gastroesophageal reflux disease, fibromyalgia, nephrolithiasis, headache, back pain, abdominal pain, ESRD, bariatric surgery, and any use of anxiolytics, antipsychotics, and antidepressants. All tree-based analyses were performed in JMP SAS (Cary, NC, USA).

Results

Cohort Characteristics

The cohort included 3,474 adult patients with NAFLD including 1,054 (30.3%) with NAFL, 1,303 (37.5%) with

NASH, and 1,117 (32.2%) with NAFLD cirrhosis. At the time of enrollment, patients' mean age ($\pm$ SD) was 56.9 $\pm$ 13.0 years, 58.9% were female, 74.5% white, 5.3% black, 12.3% Hispanic, and 83.9% non-Hispanic. The mean BMI was 33.3 $\pm$ 7.6 kg/m², 50.5% of patients had diabetes, and 61.7% had dyslipidemia (Table 1).

Characteristics of Patients by Opioid Use

Among all patients with NAFLD, 56.1% of patients were users of analgesics and 18.0% had documentation of opioid use within a year prior to or at enrollment. Of all opioid prescriptions, 12.2% were DEA schedule II, 1.4% were schedule III, and 7.7% were schedule IV. Opioid use was more common in patients with more advanced liver disease (12.0% NAFL, 17.7% NASH, 23.9% NAFLD cirrhosis, $p < 0.001$). Opioid use was more often documented among females (20.0%) compared to males (15.1%) ($p < 0.001$), and opioid users had higher mean BMI (35.4 vs. 33.8 kg/m², $p < 0.001$) compared to users of non-opioid analgesics. The prevalence of opioid use was highest among black race (23.5%) compared to white (19.9%) and other races (6.5%) ($p < 0.001$) (Table 1).

Non-opioid analgesic use was documented in 38.1% of patients with NAFLD. Ninety percent of non-opioid analgesic users were users of NSAIDs and 12.1% were users of acetaminophen. The proportion of non-opioid analgesic use was highest among patients with NASH (42.4%) followed by NAFLD cirrhosis (37.5%) ($p < 0.001$) (Table 2). Patients who were users of non-opioid analgesics were 27.5 and 47.1% less likely to have a history of a mental health diagnosis or back pain, respectively, compared to opioid users (Table 1).

Multivariable Model of Opioid Use in NAFLD

In the multivariable-adjusted logistic regression model, variables associated with opioid use included NAFLD cirrhosis versus NAFL (OR 1.51, 95% CI 1.16–1.98), BMI ≥ 32 kg/m² (OR 1.29, 95% CI 1.05–1.59), depression (OR 1.87, 95% CI 1.50–2.33), anxiety (OR 1.59, 95% CI 1.27–1.98), osteoarthritis (OR 1.42, 95% CI 1.07–1.89), rheumatologic disease (OR 1.95, 95% CI 1.40–2.70), gastroesophageal reflux disease (OR 1.28, 95% CI 1.03–1.60), fibromyalgia (OR 2.17, 95% CI 1.55–3.04), nephrolithiasis (OR 1.69, 95% CI 1.25–2.29), back pain (OR 2.25, 95% CI 1.76–2.87), and abdominal pain (OR 1.58, 95% CI 1.28–1.95) (Table 3).

Characteristics of Opioid Use in NAFLD Cirrhosis

The prevalence of splenomegaly (17.2 vs. 10.1%, $p = 0.003$), hepatic encephalopathy (34.8 vs. 23.4%, $p < 0.001$),

Table 1. Descriptive characteristics of patients with NAFLD by opioid status

Summary	Opioid use (N = 624)	Other Analgesic use (N = 1,324)	No Analgesic use (N = 1,526)	All participants (N = 3,474)	p value
Disease severity, <i>n</i> (%)					
NAFLD cirrhosis	267 (42.8)	419 (31.6)	431 (28.2)	1,117 (32.2)	<0.0001
NASH	231 (37.0)	553 (41.8)	519 (34.0)	1,303 (37.5)	
NAFL	126 (20.2)	352 (26.6)	576 (37.7)	1,054 (30.3)	
Age at study entry, years ¹					
Median (<i>n</i>)	58.0 (624)	61.0 (1,324)	56.0 (1,525)	59.0 (3,473)	<0.0001
Mean (SD)	57.2 (11.04)	59.4 (12.21)	54.7 (13.89)	56.9 (12.96)	
Min-max	19.0–83.0	18.0–91.0	18.0–87.0	18.0–91.0	
Age at study entry by category, <i>n</i> (%)					
<50	139 (22.3)	233 (17.6)	507 (33.2)	879 (25.3)	<0.0001
≥50	485 (77.7)	1,091 (82.4)	1,018 (66.7)	2,594 (74.7)	
Not available	0	0	1 (0.07)	1 (0.03)	
Gender, <i>n</i> (%)					
Female	409 (65.5)	786 (59.4)	852 (55.8)	2,047 (58.9)	<0.0001
Male	215 (34.5)	538 (40.6)	674 (44.2)	1,427 (41.1)	
Not available	0	0	0	0	
Race, <i>n</i> (%)					
White	515 (82.5)	1,057 (79.8)	1,016 (66.6)	2,588 (74.5)	<0.0001 ²⁰
Black or African American	43 (6.9)	81 (6.1)	59 (3.9)	183 (5.3)	
American Indian or Alaska native	1 (0.2)	6 (0.5)	8 (0.5)	15 (0.4)	
Asian	14 (2.2)	77 (5.8)	335 (22.0)	426 (12.3)	
Native Hawaiian or other Pacific islander	0 (0.0)	2 (0.2)	3 (0.2)	5 (0.1)	
Other	22 (3.5)	44 (3.3)	53 (3.5)	119 (3.4)	
Not reported	29 (4.6)	57 (4.3)	52 (3.4)	138 (4.0)	
Not available	0	0	0	0	
Ethnicity, <i>n</i> (%)					
Hispanic or latino	71 (11.4)	148 (11.2)	207 (13.6)	426 (12.3)	0.1749
Not hispanic or latino	531 (85.1)	1,124 (84.9)	1,260 (82.6)	2,915 (83.9)	
Not reported	14 (2.2)	38 (2.9)	45 (2.9)	97 (2.8)	
Other	8 (1.3)	13 (1.0)	13 (0.9)	34 (1.0)	
Not available	0	1 (0.08)	1 (0.07)	2 (0.06)	
BMI, kg/m ² at enrollment					
Median (<i>n</i>)	34.0 (616)	33.0 (1,305)	31.0 (1,473)	32.0 (3,394)	<0.0001
Mean (SD)	35.4 (7.9)	33.8 (7.3)	31.9 (7.5)	33.3 (7.6)	
Min-max	17–76	16–80	17–103	16–103	
BMI, kg/m ² category, <i>n</i> (%)					
<32	202 (32.3)	538 (40.6)	789 (51.7)	1,529 (44.0)	<0.0001
≥32	414 (66.3)	767 (57.9)	684 (44.8)	1,865 (53.7)	
Not available	8 (1.3)	19 (14.4)	53 (3.5)	80 (23.0)	
Alcohol usage					
Never	242 (38.8)	431 (32.6)	479 (31.4)	1,152 (33.2)	0.2298
Current	111 (17.8)	326 (24.6)	320 (21.0)	757 (21.8)	
Former	43 (6.9)	68 (5.1)	86 (5.6)	197 (5.7)	
Unknown	48 (7.7)	98 (7.4)	126 (8.3)	272 (7.8)	
Not available	180 (28.8)	401 (30.3)	515 (33.7)	1,096 (31.5)	
Smoking status					
Never	303 (48.6)	712 (53.8)	883 (57.9)	1,898 (54.6)	<0.0001
Current	68 (10.9)	92 (6.9)	100 (6.6)	260 (7.5)	
Former	196 (31.4)	388 (29.3)	294 (22.2)	878 (25.3)	
Not available	57 (9.1)	132 (99.7)	249 (18.8)	438 (12.6)	
Bariatric surgery, <i>n</i> (%) ²					
No	595 (95.4)	1,287 (97.2)	1,502 (98.4)	3,384 (97.4)	<0.0001
Yes	29 (4.6)	37 (2.8)	24 (1.6)	90 (2.6)	
Renal failure, <i>n</i> (%) ³					
No	611 (97.9)	1,311 (99.0)	1,514 (99.2)	3,436 (98.9)	0.0219
Yes	13 (2.1)	13 (1.0)	12 (0.8)	38 (1.1)	
GERD, <i>n</i> (%) ⁴					
No	180 (28.8)	519 (39.2)	884 (57.9)	1,583 (45.6)	<0.0001
Yes	444 (71.2)	805 (60.8)	642 (42.1)	1,891 (54.4)	
Dyslipidemia, <i>n</i> (%) ⁵					
No	202 (32.4)	348 (26.3)	780 (51.1)	1,330 (38.3)	<0.0001
Yes	422 (67.6)	976 (73.7)	746 (48.9)	2,144 (61.7)	
Diabetes, <i>n</i> (%) ⁶					
No	237 (38.0)	542 (40.9)	941 (61.7)	1,720 (49.5)	<0.0001
Yes	387 (62.0)	782 (59.1)	585 (38.3)	1,754 (50.5)	

Table 1 (continued)

Summary	Opioid use (N = 624)	Other Analgesic use (N = 1,324)	No Analgesic use (N = 1,526)	All participants (N = 3,474)	p value
Autoimmune/rheumatologic, n (%) ⁷					
No	542 (86.9)	1,231 (93.0)	1,464 (95.9)	3,237 (93.2)	<0.0001
Yes	82 (13.1)	93 (7.0)	62 (4.1)	237 (6.8)	
Fibromyalgia, n (%) ⁸					
No	530 (84.9)	1,246 (94.1)	1,497 (98.1)	3,273 (94.2)	<0.0001
Yes	94 (15.1)	78 (5.9)	29 (1.9)	201 (5.8)	
Chronic fatigue, n (%) ⁹					
No	621 (99.5)	1,320 (99.7)	1,523 (99.8)	3,464 (99.7)	0.2791
Yes	3 (0.5)	4 (0.3)	3 (0.2)	10 (0.3)	
Chronic fatigue/fibromyalgia, n (%) ¹⁰					
n	624	1,324	1,526	3,474	<0.0001
No	528 (84.6)	1,243 (93.9)	1,495 (98.0)	3,266 (94.0)	
Yes	96 (15.4)	81 (6.1)	31 (2.0)	208 (6.0)	
Osteoarthritis, n (%) ¹¹					
No	509 (81.6)	1,148 (86.7)	1,462 (95.8)	3,119 (89.8)	<0.0001
Yes	115 (18.4)	176 (13.3)	64 (4.2)	355 (10.2)	
Nephrolithiasis, n (%) ¹²					
No	537 (86.1)	1,219 (92.1)	1,428 (93.6)	3,184 (91.7)	<0.0001
Yes	87 (13.9)	105 (7.9)	98 (6.4)	290 (8.3)	
Any mental health diagnosis, n (%) ¹³					
No	157 (25.2)	607 (45.8)	1,012 (66.3)	1,776 (51.1)	<0.0001
Yes	467 (74.8)	717 (54.2)	514 (33.7)	1,698 (48.9)	
Any depression diagnosis, n (%) ¹⁴					
No	233 (37.3)	762 (57.6)	1,146 (75.1)	2,141 (61.6)	<0.0001
Yes	391 (62.7)	562 (42.4)	380 (24.9)	1,333 (38.4)	
Any anxiety diagnosis, n (%) ¹⁵					
No	341 (54.6)	946 (71.)	1,262 (82.7)	2,549 (73.4)	<0.0001
Yes	283 (45.4)	378 (28.5)	264 (17.3)	925 (26.6)	
Any other mental health diagnosis, n (%) ¹⁶					
No	423 (67.8)	1,036 (78.2)	1,347 (88.3)	2,806 (80.8)	<0.0001
Yes	201 (32.2)	288 (21.8)	179 (11.7)	668 (19.2)	
Headache, n (%) ¹⁷					
No	556 (89.1)	1,246 (94.1)	1,481 (97.1)	3,283 (94.5)	<0.0001
Yes	68 (10.9)	78 (5.9)	45 (2.9)	191 (5.5)	
Back pain, n (%) ¹⁸					
No	453 (72.6)	1,132 (85.5)	1,443 (94.6)	3,028 (87.2)	<0.0001
Yes	171 (27.4)	192 (14.5)	83 (5.4)	446 (12.8)	
Abdominal pain, n (%) ¹⁹					
No	391 (62.7)	995 (75.2)	1,258 (82.4)	2,644 (76.1)	<0.0001
Yes	233 (37.3)	329 (24.8)	268 (17.6)	830 (23.9)	
Acetaminophen use, n (%)					
No	362 (58.0)	1,164 (87.9)	1,526 (100.0)	3,052 (87.9)	
Yes	262 (42.0)	160 (12.1)	0 (0.0)	422 (12.1)	
NSAID use, n (%)					
No	263 (42.1)	229 (17.3)	1,526 (100.0)	2,018 (58.1)	
Yes	361 (57.9)	1,095 (82.7)	0 (0.0)	1,456 (41.9)	

Opioid use reported within 1 year prior to or at enrollment. Other medication use, medical history, procedures and laboratory values reported on or prior to enrollment. NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; NSAID, nonsteroidal anti-inflammatory drug; GERD, gastroesophageal reflux disease. ¹ Age calculated based on year of consent minus birth year. ² From procedures coded as “Gastric banding” or “Gastric bypass.” ³ Medical history coded as “Renal failure.” ⁴ Medical history coded as “Gastroesophageal reflux disease” or any use of a proton pump inhibitor. ⁵ Medical history coded terms indicative of dyslipidemia or any use of medications indicative of dyslipidemia. ⁶ Medical history coded to diabetes (excluding prediabetes or insulin-resistant diabetes), medications used to treat diabetes or HbA1c > 6.5. ⁷ Medical history coded to terms indicative of autoimmune/rheumatologic conditions. ⁸ Medical history coded to “Fibromyalgia.” ⁹ Medical history coded to “Chronic fatigue syndrome.” ¹⁰ Medical history coded to “Chronic fatigue syndrome” or “Fibromyalgia.” ¹¹ Medical history coded to “Osteoarthritis.” ¹² Medical history coded to “Nephrolithiasis.” ¹³ Medical history coded to “Psychiatric disorders” or medications used to treat mental health disorders. ¹⁴ Medical history indicative of depression or medications used to treat depression. ¹⁵ Medical history indicative of anxiety or medications used to treat anxiety. ¹⁶ Medical history coded to “Psychiatric disorders” that are not indicative of depression or anxiety, or medications used to treat schizophrenia. ¹⁷ Medical history coded terms indicative of headache. ¹⁸ Medical history coded terms indicative of back pain. ¹⁹ Medical history coded terms indicative of abdominal pain. ²⁰ Race grouped as white, black or African American, or other.

Table 2. Frequency of analgesic use overall and by NAFLD category

	Overall (N = 3,474) N (%)	NAFLD cirrhosis (N = 1,117) N (%)	NASH (N = 1,303) N (%)	NAFL (N = 1,054) N (%)	p values
Opioid use ¹	624 (18.0)	267 (23.9)	231 (17.7)	126 (12.0)	<0.001
Non-opioid analgesic use ²	1,324 (38.1)	419 (37.5)	553 (42.4)	352 (33.4)	<0.001
No analgesic use	1,526 (43.9)	431 (38.6)	519 (39.8)	576 (54.6)	<0.001

NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; GERD, gastroesophageal reflux disease. ¹ Opioid use within 1 year prior to enrollment or at the time of enrollment. ² Excludes patients with prior opioid use.

Table 3. Odds of opioid use among patient with NAFLD by patient characteristics*

	OR	95% CI
NAFLD severity		
NAFL	Reference	Reference
NASH	1.15	0.89–1.50
NAFLD cirrhosis	1.51	1.16–1.98
Age ≥59 years (vs. <59)	0.86	0.70–1.06
BMI ≥32 kg/m ² (vs. <32)	1.29	1.05–1.59
Diabetes mellitus	1.21	0.98–1.49
Depression	1.87	1.50–2.33
Anxiety	1.59	1.27–1.98
Osteoarthritis	1.42	1.07–1.89
Rheumatologic diagnosis	1.95	1.40–2.70
Fibromyalgia	2.17	1.55–3.04
GERD	1.28	1.03–1.60
Nephrolithiasis	1.69	1.25–2.29
Back pain	2.25	1.76–2.87
Abdominal pain	1.58	1.28–1.95

Variables included in the stepwise model: disease severity, age(years), sex, race (white vs. non-white), BMI, type 2 diabetes, osteoarthritis, depression, autoimmune/rheumatologic disease, hyperlipidemia, GERD, fibromyalgia, nephrolithiasis, anxiety, headache, back pain and abdominal pain: significance level to remain in the model = 0.1. * Patient characteristics were ascertained from the medical record at or prior to enrollment. NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; GERD

and ascites (43.1 vs. 34.4%, $p = 0.010$) was significantly higher among opioid users compared to patients without documentation of opioid use. The prevalence of hepatocellular carcinoma was not significantly different among patients with cirrhosis who had documentation of opioid use compared to nonusers (3.4 vs. 2.0%, $p = 0.214$).

Among opioid users and nonusers with NAFLD cirrhosis, there was no significant difference in mean MELD score (10.3 vs. 10.1, $p = 0.501$) or CPS (8.0 vs. 7.7, $p = 0.195$) (Table 4).

Multivariable Model of Opioid Use in NAFLD Cirrhosis

In the multivariate analysis of opioid use among patients with NAFLD cirrhosis, age, sex, BMI, osteoarthritis, rheumatologic diagnosis, depression, MELD, ascites, HCC, and hepatic encephalopathy were considered in our initial model (Table 5). In our final model, age >62 years (OR 0.70, 95% CI 0.51–0.96), depression (OR 2.29, 95% CI 1.66–3.18), rheumatologic disease (OR 2.53, 95% CI 1.48–4.30), and osteoarthritis (OR 2.30, 95% CI 1.53–3.46) were associated with opioid use (Table 5).

Classification and Boosted Tree Analysis

In the boosted tree analysis, a history of fibromyalgia, depression, or back pain in the medical record had the greatest variable importance for predicting opioid use over 100 trees at a sampling rate of 0.75. The area under the receiver operating curve was 0.76 for the learning sample and 0.73 for the validation sample. The misclassification rate was 0.18 for both the training and the validation sample (Fig. 1).

Forty six percent of patients with NAFLD who had a history of depression and back pain were opioid users. The probability of opioid use among patients with a combined history of depression and fibromyalgia without back pain was 44%. Among patients without depression, the probability of opioid use was approximately 20% for patients with anxiety, abdominal pain, or back pain. The misclassification rate in the training sample and validation sample was 0.18 (Table 6).

Table 4. Characteristics of opioid users versus nonusers with NAFLD cirrhosis*

	Opioid use (<i>n</i> = 267) <i>N</i> (%)	No opioid use (<i>n</i> = 850) <i>N</i> (%)	<i>p</i> value <i>N</i> (%)
MELD (mean) (SD)	10.3 (4.5)	10.1 (4.0)	0.5008
CPS (mean) (SD)	8.0 (2.0)	7.7 (1.9)	0.1950
Hepatic encephalopathy (%)	93 (34.8)	199 (23.4)	0.0003
Ascites	115 (43.1)	292 (34.4)	0.0104
Variceal bleeding	19 (7.1)	50 (5.9)	0.4718
Hepatocellular carcinoma	9 (3.4)	17 (2.0)	0.2138
Splenomegaly	46 (17.2)	86 (10.1)	0.0025

MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; CPS, Child-Pugh Score. * Patient characteristics were ascertained from the medical record at or prior to enrollment.

Table 5. Odds of opioid use among patient with NAFLD cirrhosis by patient characteristics*

	OR	95% CI
Age ≥62 years (vs. <62)	0.70	0.51–0.96
BMI ≥34 kg/m ² (vs. <34)	1.24	0.90–1.71
Depression	2.29	1.66–3.18
Osteoarthritis	2.30	1.53–3.46
Rheumatologic diagnosis	2.53	1.48–4.30
Ascites	1.26	0.89–1.78
Hepatic encephalopathy	1.39	0.97–2.00

Variables included in the stepwise model: age (years), sex, BMI, osteoarthritis, rheumatologic diagnosis, depression; MELD, ascites; HCC, and hepatic encephalopathy; significance level to remain in the model = 0.1. * Patient characteristics were ascertained from the medical record at or prior to enrollment. NAFLD, nonalcoholic fatty liver disease; MELD, model for end-stage liver disease.

Fig. 1. Variable importance predictive of opioid use among patients with NAFLD using boosted trees. Gini improvement measure of relative importance estimates the difference in the prevalence of the outcome in the child nodes after the classification split [27]. AROC_{learning}: 0.7602; AROC_{validation}: 0.7321. Misclassification rate_{learning}: 0.1796; misclassification rate_{validation}: 0.1797. Any opioid use at enrollment or 1 year prior: 100 layers. Multiple splits per tree: 3. Sampling rate: 0.60 for rows and 0.40 columns. AUDIT, Alcohol Use Disorders Identification Test; GERD, gastroesophageal reflux disease. * Medical history on or prior to enrollment; ** medical history of or drug use on or prior to enrollment.

Table 6. CART estimating the predicted probability of opioid use among patients with NAFL*

Patient phenotypes	Probability of opioid use
<i>Patients with depression</i>	
Depression, back pain	0.4578
Depression, no back pain, fibromyalgia	0.4368
Depression, no back pain, no fibromyalgia	0.2348
<i>Patients without depression</i>	
No depression, abdominal pain	0.2142
No depression, no abdominal pain, back pain	0.2518
No depression, no abdominal pain, no back pain, anxiety	0.2067
No depression, no abdominal pain, no back pain, no anxiety, white or African American race	0.0710
No depression, no abdominal pain, no back pain, no anxiety, other race	0.0210

CART, Classification and Regression Tree; AUDIT, Alcohol Use Disorders Identification Test; GERD, gastroesophageal reflux disease. * Variable included in the model: age, sex, race, ethnicity, BMI, severity of liver disease, recent alcohol use, AUDIT score, history of diabetes mellitus, depression, anxiety, osteoarthritis, rheumatologic diagnosis, dyslipidemia, GERD, fibromyalgia, nephrolithiasis, headache, back pain, abdominal pain, ESRD, bariatric surgery, and any use of anxiolytics, antipsychotics, and antidepressants. AUROC, test: 0.7257, AUROC, validation: 0.7172, Misclassification Rate test: 0.1796, Misclassification Rate test: 0.1797. Depression: medical history or medication use for depression. Anxiety: medical history or medication use for anxiety.

Discussion

This cross-sectional study estimates real-world opioid use among patients with NAFLD. Nearly one-fifth of those with NAFLD and one-quarter of patients with NAFLD cirrhosis reported recent or ongoing opioid use. Opioid use was twice as common among those with NAFLD cirrhosis compared with NAFL and was associated with higher BMI, painful comorbidities, and psychiatric disease.

In the CART analysis, which allows for the identification of distinct subgroups of patients with NAFLD who are likely to use opioids, both depression and back pain were associated with opioid use across patient subgroups. Approximately half of patients who had both a history of depression as well as a history of fibromyalgia were opioid users. The probability of opioid use among patients with back pain and depression was twice that of patients with back pain who were not depressed.

The results of both analyses, CART and logistic regression, suggested that depression and back pain were significantly associated with opioid use in patients with NAFLD. A logistic regression analysis estimated the average effect for the association between independent variables and the odds of an outcome, while a CART analysis can define clinical subgroups of patient's that are associ-

ated with an increased probability of opioid use. The results of this classification analysis suggest that patients with NAFLD who also suffer from back pain, fibromyalgia, and/or depression might be at particularly high risk of future opioid use and may benefit from proactive alternative therapies to address pain, such as scheduled low-dose acetaminophen or referral to physical therapy and/or a psychologist where appropriate.

Among patients with cirrhosis, the proportion of patients who were users of opioids in our cohort is slightly lower than prior studies reporting a 25–47% prevalence of opioid use among patients with cirrhosis [8, 9, 13, 29]. This may be due to differences in how opioid use was ascertained or a reflection of our “real world” population of patients with NAFLD who were receiving care from both academic and community practices. These clinical practices may have less severe liver disease and fewer comorbidities than cohorts drawn exclusively from tertiary referral centers. In addition, given that our cohort was enrolled recently, this may be a reflection of the national trend toward reduced opioid prescribing [30].

This work supports previously findings in the literature which have suggested that opioid use was more common as liver disease progressed, with the highest reported prevalence of use in patients with NAFLD cirrhosis [8]. This could reflect an appropriate avoidance of NSAIDs

given their risk of precipitating acute kidney injury and gastrointestinal bleeding or misinformation about the harms of acetaminophen use in the setting of cirrhosis. However, the higher reported use of non-opioid analgesics, including acetaminophen and NSAIDs, among patients with NASH and cirrhosis compared to NAFL suggests that this observation may be due to an increased prevalence of pain in those with higher BMI or lower levels of physical activity, both of which promote liver disease progression.

Another potential explanation for opioid use among patients with NAFLD is the association between metabolic syndrome and painful complications such as osteoarthritis due to increased mechanical load or diabetic neuropathy. Even after adjusting for BMI, osteoarthritis was significantly associated with opioid use. A lower pain threshold may also be attributable to higher levels of inflammatory cytokines seen in NAFLD [9, 31]. It is possible that mood disturbances, seen more frequently in cirrhosis, and sleep disturbances, a common manifestation of hepatic encephalopathy, could contribute to opioid use even in the absence of pain [32]. In our cohort, fibromyalgia, anxiety, and depression were all associated with opioid use and hepatic encephalopathy was more commonly reported in opioid users.

Opioid use in patients with NAFLD is concerning given the potential role of opioids in sedentary behavior. Large prospective studies have demonstrated that the development of obesity is associated with a higher risk of chronic low back, neck, and shoulder pain and that this effect may be attenuated by exercise [33]. In our cohort, opioids were associated with obesity, suggesting that opioid use may predispose to the development or worsening of NAFLD.

While there are situations in which opioid prescription may be appropriate, particularly for acute pain, there are many reasons why opioids should be used cautiously in patients with NAFLD and cirrhosis [15, 34]. First, opioids have limited efficacy data for the treatment of chronic noncancer pain (>3 months) [34, 35]. Additionally, the use of long-acting opioids for noncancer pain is associated with increased risk for opioid abuse, opioid dependence, opioid overdose, and all-cause mortality compared to no opioid treatments or non-opioid analgesics [34, 36]. Last, opioids have specifically been associated with poor outcomes in patients with cirrhosis including an increase in hepatic encephalopathy, length of stay, and hospital readmission [14, 37, 38].

Given opioids' limited long-term efficacy data and substantial risks, alternative options for patients with

NAFLD and pain should be fully explored [35]. Nonpharmacologic options should be considered first-line options in patients with NAFLD [3]. Exercise, which remains a cornerstone of treatment for NAFLD, has the dual benefits of improving hepatic steatosis in patients with NAFLD and decreasing back pain, joint pain, and symptoms of fibromyalgia [17–19, 39–42]. This may be facilitated through early referral to physical therapy which is associated with reduced future opioid use [22]. Other nonpharmacologic treatment options that deserve additional study in patients with NAFLD and cirrhosis include multidisciplinary rehabilitation, mindfulness-based stress reduction, and cognitive behavioral therapy [34]. Last, treatment for coexisting depression, anxiety, substance use disorders, and sleep disturbances may improve pain and reduce inappropriate opioid use. Acetaminophen (≤ 2 g/day) should be considered a first-line non-opioid analgesic option in cirrhosis given its safety and efficacy data [43]. Further study is needed to determine alternative analgesics or analgesic combinations that optimize physical function and limit adverse effects in patients with NAFLD and cirrhosis.

Our study has several strengths. It includes a large, real-world cohort of patients with NAFLD and, to our knowledge, represents the largest study to date examining use of opioids in this population. Many prior observational studies of patients with NAFLD have been limited to tertiary centers or large administrative databases, which may be more prone to referral bias, misclassification bias, and limited generalizability [44, 45]. In contrast, our cohort encompasses patients with NAFLD diagnosed by histology and clinical data, rather than billing codes, and includes patients from both community and academic settings. Therefore, our estimates of opioid use are likely to more accurately reflect patients with NAFLD receiving care in usual clinical practice.

There are a few limitations of this work. The cross-sectional design of this study does not allow one to determine the temporal relationship between patient characteristics and current opioid use. Prospective studies, including the TARGET-NASH cohort, will help to shed light on the use of opioids in patients with NAFLD and the potential for associated complications. Moreover, the definition of opioid use is based on reports of a prescription for opioids at or within a year of enrollment and not on pharmacy fills. It is possible that patients who were prescribed but never took opioids were misclassified as opioid users and those who took nonmedical prescription opioids were misclassified as nonusers. Our cohort included primarily White and non-Hispanic patients who

were actively receiving care in largely gastroenterology and hepatology practices across the United States. Patterns of opioid use may differ among other racial/ethnic groups or patients receiving care in other specialty or primary care clinics. Last, we were unable to differentiate between short-term and chronic opioid use.

Opioid use occurred in 1 of 5 patients with NAFLD and was more common among those who have more severe liver disease, anxiety, or depression. Given the safety concerns associated with opioid treatment, use of non-pharmacologic options and non-opioid analgesics should be considered for the treatment of pain in patients with NAFLD.

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Statement of Ethics

This study was approved by WCG (WIRB Copernicus Group); reference number: 20161381. Clinical information from the electronic medical records, including patient narratives, laboratory results, pathology reports, and imaging data are extracted and uploaded into a secured database at 6-month intervals from the date of enrollment. Approvals from central and/or local institutional review boards are obtained prior to subject recruitment and at enrollment.

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Conflict of Interest Statement

A.M. has no conflicts related to this work. S.W. is an employee of TARGET PharmaSolutions. A.S.L. has received research grants from BMS, Gilead, and TARGET PharmaSolutions (to University of Michigan) and is an advisor for TARGET PharmaSolutions. R.F.M. has no conflicts related to this work. H.N.T. has no conflicts related to this work. J.K. has no conflicts related to this work. C.S. is an employee of TARGET PharmaSolutions. B.A.N.-T. has no conflicts related to this work. A.S.B. is a consultant for TARGET PharmaSolutions.

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Author Contributions

All authors approved the final version of this manuscript. A. Sidney Barritt is the guarantor of this paper. Andrew M. Moon: Study concept and design, interpretation of data, drafting and critical revision of manuscript. Stephanie E. Watkins: Study concept, analysis, interpretation of data, drafting and critical revision of manuscript. Anna S. Lok: Study concept and design, interpretation of data, and critical revision of manuscript. Roberto Firpi-Morell: Study concept and design, interpretation of data, and critical revision of manuscript. Huy Ngoc Trinh: Study concept and design, interpretation of data, and critical revision of manuscript. Justin T. Kupec: Study concept and design, interpretation of data, and critical revision of manuscript. Cheryl Schoen: Data extraction, data analysis, interpretation of the data, and critical revision of the manuscript. Brent A. Neuschwander-Tetri: Study concept and design, interpretation of data, and critical revision of manuscript. A. Sidney Barritt: Study concept and design, interpretation of data, and critical revision of manuscript.

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