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Safety and efficacy of pharmacologic weight loss in patients with cirrhosis

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Abstract

Background: Obesity poses unique risks in patients with advanced liver fibrosis; however, given surgical risks of bariatric surgery in cirrhosis treatment recommendations are currently limited to lifestyle interventions. This study seeks to inform a potential treatment gap by describing the safety and efficacy of pharmacologic weight loss in patients with advanced liver disease.

Methods: A retrospective chart review of the electronic medical record was conducted for all patients in the Scripps Health system from 2005 to 2017 with established advanced liver fibrosis that were prescribed medications associated with weight loss. The primary outcome was safety as defined by the model for end-stage liver disease (MELD) score. Secondary outcomes included total body weight loss, reasons for medication discontinuation, medication adverse events, and hospitalization before and after medication initiation.

Results: Thirty-eight patients and 63 prescriptions were included in the final analysis. The most frequently prescribed medication associated with weight loss was metformin (63%, $n = 24$) followed by a GLP-1 agonist (39%, $n = 15$). There was no significant effect of weight-loss medication on MELD score ($p > 0.18$) or number of hospitalizations when adjusting for subject ($p > 0.26$). There was a significant adjusted mean weight loss of 2.2 kg ($p < 0.02$) following prescription of a medication associated with weight loss. The Federal Drug Administration-approved anti-obesity medications as a group resulted in a significant adjusted weight loss of 7.22 kg ($p < 0.013$). In a linear mixed-effects model accounting for subjects, weight loss was not independently associated with a change in MELD ($t[51] = -1.972$, $p > 0.05$).

Conclusion: Pharmacologic weight loss in patients with advanced liver fibrosis appears feasible based on preliminary safety and efficacy outcomes in this study. Future prospective studies are warranted to evaluate a potential significant treatment gap in the management of obesity in this vulnerable population.

KEYWORDS
cirrhosis, liver disease, medications, obesity, weight loss

Waiver of informed consent for authorization to use and/or disclose protected health information for publication per institutional protocol was obtained.

1 | INTRODUCTION

Obesity in the general population has been linked to multiple liver-related morbidities including primary liver malignancy and nonalcoholic steatohepatitis with progressive fibrosis leading to cirrhosis.[1,2] The risk of hepatocellular carcinoma is nearly doubled in patients with body mass index (BMI) ≥30 kg/m^2 compared to BMI <25 kg/m^2 independent of other known risk factors.[3,4] It's not surprising then that in patients with underlying chronic liver disease obesity has been shown to be an independent risk factor of fibrosis progression and clinical decompensation.[5,6] In a cohort of patients with cirrhosis of mixed etiology, a one unit increase in BMI independently predicted a 6% increased risk of clinical decompensation over an average 5 year follow-up period.[7]

In patients with decompensated liver cirrhosis, liver transplantation is often the only intervention capable of extending life expectancy and improving quality of life.[8] Unfortunately, elevated BMI, especially 40 kg/m^2 and above, has been shown to result in up to 41% increased risk of death posttransplant due to infectious complications and cancer.[9] For these reasons liver transplantation is a relative contraindication in patients with class 3 obesity.[10]

The benefits of weight loss in patients with obesity are well-established and extend to patients with cirrhosis and liver-related morbidities with additional unique considerations as discussed above.[11-14] Unfortunately, treatment of obesity in this patient population is limited by increased operative risks of bariatric surgery,[15] limited data for endoscopic bariatric procedures, and the complexity of nutritional management and weight loss in patients with concurrent sarcopenia, catabolic chronic disease, and elevated BMI. Current guideline recommendations for weight loss in patients with cirrhosis are limited to lifestyle interventions under the supervision of a dietician.[10] Bariatric surgery is contraindicated in patients with decompensated cirrhosis and not routinely recommended in those with compensated cirrhosis or advanced fibrosis.

To date there have been no recommendations or data published promoting pharmacologic management of obesity in patients with cirrhosis, representing a potential treatment gap. The American Association of Clinical Endocrinologists and American College of Endocrinology 2016 clinical practice guidelines suggest an overall favorable safety profile of weight-loss medications in patients with liver disease and provide guidance for dosing adjustments. Ultimately, however, the guidelines simply advise caution with the use of weight-loss medications in patients with hepatic impairment and avoidance in patients with severe hepatic impairment defined as Child-Pugh score >9.[16] Indeed, the use of weight-loss medications in patients with cirrhosis is likely limited in practice due to the lack of safety data and complexity of the true nutritional status in this patient population. The purpose of this study is to provide preliminary data on the safety of pharmacologic agents typically prescribed for weight loss in patients with advanced liver disease, as well as the potential efficacy.

2 | MATERIALS AND METHODS

2.1 | Design

A retrospective chart review of the electronic medical record (EMR) was conducted for all patients in the Scripps health system over a 12-year period between 2005 and 2017. Scripps Health is a health system in San Diego county consisting of 5 hospitals and over 20 ambulatory care sites caring for over 1 million patients annually with support by various multispecialty groups. This study was approved and waiver of authorization for research granted by the Scripps Health Institutional Review Board.

2.2 | Sample

Potential subjects were identified by an EMR query for adults over the age of 18 years old with a diagnosis of cirrhosis or advanced liver fibrosis based on ICD-10 coding and a documented prescription of a weight-loss medication during the study period. Weight-loss medications as defined in this study consist of medications associated with weight loss and Federal Drug Administration (FDA)-approved anti-obesity medications. Multiple prescriptions were considered for the same patient only for different weight-loss medications. Only the initial prescription event was considered when consecutive prescriptions were encountered for the same medication in a single patient.

Inclusion criteria of the study were confirmation of cirrhosis based on liver biopsy or hepatology subspecialty evaluation in the EMR and confirmation of a weight-loss medication in the EMR that was started following the diagnosis of cirrhosis. From initial screening, $n = 75$ patients met inclusion criteria (Figure 1). Exclusion criteria were patients with neither model for end-stage liver disease (MELD) labs nor weights documented in the EMR and for prescriptions of weight-loss medication that were started after liver transplant. Specifically, weight-loss prescriptions were excluded from the primary safety outcome analysis if there was a concurrent warfarin prescription during the weight-loss medication prescription period. Criteria for exclusion from the secondary outcome analysis of weight loss were concurrent prescriptions of furosemide, spironolactone, bumetanide, or metolazone during the prescription period of the weight-loss medication or a prescription period of less than 30 days (Figure 2). Obesity status was not considered in the inclusion or exclusion criteria since the study's primary outcome was related to medication safety in patients with advanced liver disease. Because pharmacologic management of obesity in patients with advanced liver disease is not common in clinic practice as described above, many of the patients were anticipated to receive the weight-loss medications as defined in this study for indications other than obesity.

A total of $n = 38$ patients and $n = 63$ prescriptions met inclusion and exclusion criteria for the retrospective analysis (Figures 1 and 2).

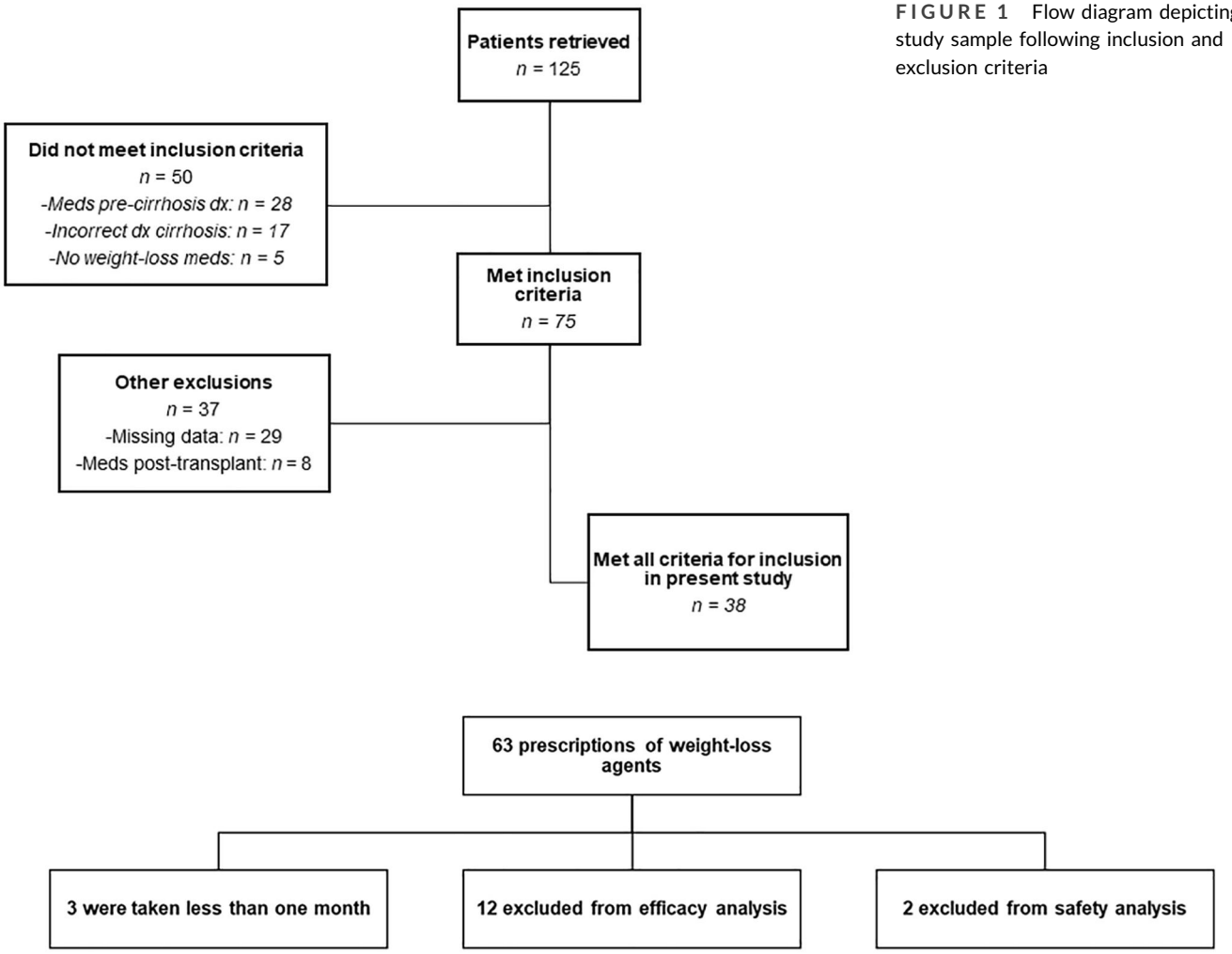

FIGURE 1 Flow diagram depicting study sample following inclusion and exclusion criteria

FIGURE 2 Flow diagram depicting prescription inclusion and exclusion criteria for study analyses

2.3 | Data collection

The primary outcome was safety as defined by change in MELD score before and 1 year after initiation of weight-loss medication. Secondary outcomes included hospitalizations 1 year before and 1 year after medication initiation, reasons for medication discontinuation, medication adverse events, and weight loss at 1 year after initiation of weight-loss medication.

All MELD scores were calculated using the revised 2016 Organ Procurement and Transplantation Network and the United Network for Organ Sharing equation. Premedication measurements of MELD score and weight were retrieved at time of medication start or the closest measurement within the previous year. Post-medication measurements of MELD score and weight were retrieved at time of medication end or closest measurement to 1 year after medication start, whichever came sooner, to mitigate potential changes related to the natural history of cirrhosis. The number of hospitalizations outcome was collected for the year prior to and year following medication start. Child's Pugh Class (CPC) was retrieved when available from hepatology consultation reports within the year preceding start of weight-loss medication. If the documentation reported decompensated cirrhosis but did not specify CPC this was collected as well.

2.4 | Statistical analyses

Patient characteristics, medications prescribed, and reasons for medication discontinuation were descriptively analyzed as percentages of the sample for categorical variables, or as medians and interquartile ranges for continuous variables since the data were not normally distributed. The outcomes of changes in MELD scores, weight, and hospitalizations were compared pre- and post-medication for each prescription on record and adjusted to account for individuals that had multiple weight-loss medication prescriptions through linear mixed-effect models. Therefore, all outcomes described in terms of change (i.e., weight, MELD change) are derived from regression coefficients and are interpreted as expected average weight change to account for the subject effect in the mixed effects model. Time between measurements was tested as a fixed effect for each outcome, and each mixed effects model included subject as a

random effect. Follow-up mixed effects models were run for each outcome to determine whether any weight-loss medication class was predictive of a change in the outcome over time.

Medication classes used in these models included the FDA-approved anti-obesity medications GLP-1 receptor agonists, phentermine, and lorcaserin as well as medications associated with weight loss including metformin, SGLT-2 inhibitors, topiramate, and bupropion. FDA-approved anti-obesity medications were included in the model as a group post-hoc due to low sample sizes of lorcaserin and phentermine. Adjusted means (estimated marginal means) of outcome measures were reported for any significant predictors. Associations of change in weight with MELD score were also tested in a mixed effects model with change in MELD as the dependent and change in weight as the independent variable. Change in MELD scores, changes in weight, and the occurrence of any adverse events were also run as dependent variables in linear mixed-effects models for MELD and weight, and in a generalized logistic mixed effects model for adverse events with CPC using a dummy-coded predictor for CPC A versus all other classes. Exploratory analyses of predictors of change in MELD scores and change in weight were independently conducted through a linear mixed effects model with percent weight change, sex, ethnicity, age at diagnosis, etiology of liver disease, diuretics, bariatric surgery, history of transplant, and known weight-gain medication use. The model was reduced for variables that reached significance in the full model, and only included weight change and alcoholic liver disease etiology in the final model. The statistical software R v 3.5.3 and GraphPad Prism 8 were used to conduct all analyses. A two-tailed *p*-value of 0.05 or less was considered statistically significant.

3 | RESULTS

Thirty-eight patients and 63 prescriptions were included in the final analysis. Patient characteristics are shown in Table 1. The median BMI of 33.11 (IQR = 11.26) was consistent with class I obesity. Over 65% ($n = 41$) of patients had a BMI of 30.0 or above. The majority of cirrhosis cases were secondary to Non-alcoholic steatohepatitis (NASH) (55%, $n = 21$). The most frequently prescribed medication associated with weight loss was metformin (63%, $n = 24$) followed by a GLP-1 agonist (39%, $n = 15$) (see Table 2). Collectively, FDA-approved anti-obesity medications (GLP-1 agonists, lorcaserin, and phentermine) made up 50% of all prescriptions and were presented collectively in efficacy analyses due to sample size limitations. Naltrexone and topiramate were not included in efficacy analyses due to small sample size in the present study. Half of the patients ($n = 19$) were also on a medication known to cause weight gain. The most common weight-gain medication was a beta-blocker which was prescribed in 29% ($n = 11$) of patients (Table 2).

CPC at the time of medication start was identified in 82% ($n = 52$) of prescriptions. Among all prescriptions, the severity of liver disease at time of medication start was identified as CPC A in 59% ($n = 37$), CPC B in 14% ($n = 9$), CPC C in 3% ($n = 2$), and decompensated cirrhosis in 6% ($n = 4$). Supporting the finding of predominantly compensated liver disease in this study cohort was also a median MELD of 7 Interquartile range (IQR = 4) and median number of hospitalizations of zero (IQR = 0) prior to medication start.

TABLE 1 Patient characteristics are described as either mean (SD) for continuous, normally distributed data, median (IQR) for continuous, skewed data, or as a percentage (*n*) of total sample for categorical data

Patient characteristics	
	Mean (SD)
Age	55.05 (2.85)
Baseline weight (kg)	91.96 (22.10)
	Median (IQR)
BMI at medication start	33.11 (11.26)
	% (*n*)
Sex (male)	42% (16)
Ethnicity (Hispanic)	18% (7)
Diabetes	84% (32)
Etiology of cirrhosis	
NASH	55% (21)
HCV	32% (12)
EtOH	16% (6)
Other (HBV, PBC, AIH)	11% (4)
Diuretic use >3 months	24% (9)
Coumadin	3% (1)
Prior bariatric surgery	11% (4)
Received transplant	13% (5)
Cancer diagnosis (HCC)	13% (5)

Abbreviations: AIH, Autoimmune hepatitis; BMI, body mass index; EtOH, Ethanol; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; IQR, Interquartile range; NASH, Non-alcoholic steatohepatitis; PBC, Primary biliary cholangitis.

TABLE 2 Prescription characteristics are shown for all weight-gain medications and broken down into percentage (*n*) of patients with a prescription of each class of weight-gain medication

Weight-gain medications	% (*n*) of patients
Beta-blockers	29% (11)
Insulin	21% (8)
Sulfonylurea/TZD	18% (7)
Anti-psychotics	8% (3)
Prednisone (>3 months)	3% (1)
Gabapentin	3% (1)
Any weight-gain medication	50% (19)

Abbreviation: TZD, thiazolidinedione.

TABLE 3 Prescription characteristics are shown for all weight-negative medications, with each category further broken down into percentage (*n*) of total sample of prescriptions in each class as well as median (and range) of doses, duration of medication prescriptions, and interval follow-up of MELD and weight in days

Weight-loss medication	% (*n*)	Total dose median [range]	Median time on treatment (days) [range]	Median time to MELD follow-Up (days) [range]	Median time to weight follow-Up (days) [range]
Metformin	63% (24)	1000 [500–2000] (mg/day)	1153 [172–2462]	363 [47–622]	335 [140–463]
GLP-1 agonists	39% (15)	-	708 [36–1586]	353 [47–794]	296.5 [64–439]
Liraglutide	-	1.2 [1.2–2.4] (mg/day)	616.5 [36–1586]	353 [91–794]	305 [64–366]
Dulaglutide	-	0.75 [0.25–1.5] (mg/week)	567 [198–929]	327 [47–546]	140 [113–364]
Exenatide	-	15 [10–20] (mcg/day)[a]	875 [249–1166]	332.5 [228–441]	332 [228–439]
SGLT-2 inhibitors	24% (9)	-	357 [12–1314]	363 [47–454]	326 [94–737]
Canagliflozin	-	300 [100–300] (mg/day)	357 [95–1314]	395 [94–454]	326 [94–737]
Dapagliflozin	-	5 (mg/day)	12	[b]	[c]
Empagliflozin	-	10 [10–25] (mg/day)	519 [13–708]	47	252 [140–364]
Bupropion	16% (6)	225 [100–300] (mg/day)	926.5 [346–3509]	256 [244–349]	356.5 [258–618]
Topiramate	8% (3)	50 [25–75] (mg/day)	1011 [750–1011]	431 [391–589]	397 [376–500]
Phentermine	8% (3)	16 [15–30] (mg/day)	135 [29–146]	215 [213–217]	135 [29–151]
Naltrexone	5% (2)	27 [4–50] (mg/day)	734.5 [102–1367]	455 [101–809]	232.5 [101–364]
Lorcaserin	3% (1)	20 (mg/day)	275	317	330

Abbreviation: MELD, Model for End-Stage Liver Disease.

[a]A 2 mg/week dose was considered equivalent to 10 mcg/day.

[b]No MELD labs meeting data collection criteria.

[c]Excluded from weight loss analysis due to prescription period <30 days.

With regards to safety outcomes, there was no significant overall effect of weight-negative medications on MELD score or number of hospitalizations when adjusting for subject ($t[52] = 1.593$, $p > 0.11$; $t[35.9] = -1.121$, $p > 0.26$, respectively). There were additionally no significant effects of any particular medication class tested (all FDA-approved weight-loss medications, metformin, SGLT-2 inhibitors, bupropion; see Table 4). All FDA-approved weight-loss medications were presented collectively since phentermine and lorcaserin were infrequently prescribed in the present study; however, no conclusions were changed when GLP-1 agonists were analyzed as a standalone group, which also had nonsignificant changes in MELD and hospitalizations (p's > 0.4). Of all weight-loss medications, 40% ($n = 25$) were discontinued. Reasons for discontinuation are shown in Figure 3. Adverse effects constituted the reason for discontinuation in 32% ($n = 8$) of prescriptions with one event requiring hospitalization for diabetic ketoacidosis and acute pancreatitis attributed to SGLT-2 initiation in a patient with decompensated alcoholic liver disease (see Table 6). Thirty-two percent ($n = 8$) of patients discontinued medications after undergoing successful liver transplantation. CPC did not significantly predict incidence of adverse events (>0.5, data not shown).

With regards to secondary outcomes, there was a significant adjusted mean weight loss of 2.2 kg ($t[37.3] = -2.46$, $p < 0.02$) following prescription of a weight-loss medications (Table 5, Figure 4), and this was not significantly predicted by the time between weight measurements ($p > 0.2$; data not shown). Each of the weight-loss medications demonstrated a trend toward expected weight loss in the model but none were statistically significant. The FDA-approved anti-obesity medication as a group, however, resulted in a significant adjusted weight loss of 7.22 kg, on average ($p < 0.013$) (Table 5). In a linear mixed-effects model accounting for subjects, weight loss was not significantly associated with a change in MELD ($t[51] = -1.972$, $p > 0.05$). However, when weight change is included in an exploratory mixed-effects linear model with other potential clinical predictors, the reduced model indicates that weight change inversely ($\beta = -0.201 \pm 0.080$, $p < 0.04$) and alcoholic liver disease ($\beta = 4.101 \pm 0.1.737$, $p < 0.03$) positively predict change in MELD score following weight-loss medication use. Child's Pugh scores were not predictive of either change in MELD or change in weight following weight-loss medications ($t[19.85] = -1.398$, $p > 0.17$; $t[41.02] = -0.198$, $p > 0.84$).

4 | DISCUSSION

Treatment of obesity in patients with cirrhosis is a common clinical challenge with significant potential implications on morbidity and mortality. Current guideline recommendations are limited in patients

MELD change			
	Average MELD change[a]	SE	*p*
Approved anti-obesity med.	−0.317	2.212	0.887
Metformin	1.123	2.052	0.587
SGLT-2 inhibitor	−1.119	2.441	0.649
Bupropion	0.530	2.829	0.852
Hospitalizations change			
	Average change in number of hospitalizations[a]	SE	*p*
Approved anti-obesity med.	−0.217	0.486	0.659
Metformin	0.121	0.446	0.788
SGLT-2 inhibitor	−0.264	0.504	0.604
Bupropion	0.182	0.662	0.784

Notes: Regression coefficients (*b*), their SE, and *p*-values presented are derived from linear mixed effects models adjusting for subject as a random effect.

[a]Expected average change based on regression coefficient from a mixed effects model adjusting for subject as a random effect.

TABLE 4 Patient-adjusted mixed effects models show the effects of classes of weight-negative medications on the outcomes of MELD score change and change in hospitalizations before and after prescription

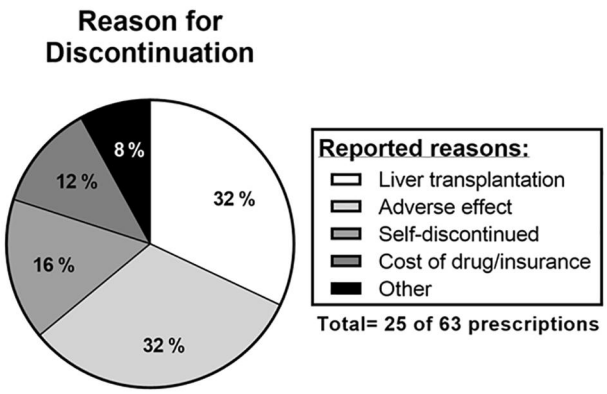

FIGURE 3 Pie chart representing reasons for discontinuation of weight-negative medications

with liver disease due to a lack of data, representing a true unmet need. While pharmacologic treatment can be two to three times more effective at achieving weight loss compared to placebo,[17] there is a scarcity of information regarding use of pharmacologic agents for the treatment of obesity in patients with advanced liver fibrosis and cirrhosis.

This study provided novel retrospective data on the safety and efficacy of medications associated with weight loss, including FDA-approved anti-obesity medications, in a patient population with advanced liver disease. Study results did not show any concerning safety signals such as increased MELD scores or hospitalizations after median follow-up of 1 year after initiation of a medication associated with weight loss. While weight loss significantly predicted increase in MELD in an exploratory mixed-effects linear model, the effect was small and weight loss was otherwise not independently associated with a significant increase in MELD score. Therefore, despite the high frequency of protein-calorie malnutrition in cirrhotic patients, associated risks of increased mortality, and clinical complications of sarcopenic obesity,[18-20] preliminary data on pharmacologic weight loss in patients with mixed compensated and decompensated cirrhosis do not suggest significant exacerbation of this pathophysiology. These findings should be confirmed in a clinical trial setting and certainly cannot be extrapolated to patients with decompensated, high MELD cirrhosis.

As a secondary endpoint, medication discontinuation was common at 40%. Approximately one-third of discontinuations were due to successful liver transplantation. Medication discontinuation due to cost or insurance coverage occurred in 8% of cases, a relatively low occurrence in the setting of weight-loss pharmacology likely driven by inclusion of metformin in the study. While 32% of discontinuations were due to a variety of reported medication adverse effects, only one was severe enough to result in hospitalization. This event occurred in a patient with CPC B alcohol-related cirrhosis and active alcohol use admitted for diabetic ketoacidosis and acute pancreatitis. The patient had a prior episode of alcohol-induced pancreatitis; however, dapagliflozin had been initiated one week prior to presentation and was therefore presumed to be the etiology of his acute pancreatitis. While this adverse effect has been reported for SGLT-2 inhibitors and underwent investigation by the United States Food and Drug Administration in 2016, a recent cohort study and meta-analysis did not show increased risk of acute pancreatitis with this class of medications.[21-23] Furthermore, dapagliflozin has been shown previously to be well-tolerated in hepatic impairment including CPC C cirrhosis.[24] Overall, based on the results of the primary and secondary endpoints of safety and at least 23% of prescriptions occurring in the setting of non-CPC A cirrhosis, commonly prescribed medications associated with weight loss appear well-tolerated in patients with advanced hepatic fibrosis.

Secondary end-points of efficacy demonstrated an overall modest weight loss at a median of approximately 2.4% total body

TABLE 5 Patient-adjusted mixed effects models show the overall change in weight (kg) among all weight-negative medications, and the effects of classes of weight-negative medications on weight loss before and after prescription

Weight change (kg)					
	Median wt pre-med	Median wt post-med	Average wt change[a]	SE	*p*-value
All weight-negative med	92.53	87.09	−2.23	0.91	0.0186
By medication type					
FDA-approved anti-obesity medications	92.31	87.77	−7.22	2.79	0.013
GLP-1 agonists	91.63	87.32	-	-	-
Phentermine	92.99	85.27	-	-	-
Lorcaserin[b]	104.78	100.70	-	-	-
Metformin	91.17	81.19	−4.14	2.58	0.115
SGLT-2 inhibitor	123.83	113.40	−4.15	2.91	0.162
Bupropion	100.24	94.57	−4.96	3.61	0.1751
Topiramate[c]	92.08	88.00	-	-	-
Naltrexone[c]	72.12	78.70	-	-	-

Note: Median weight (kg) pre-and post-prescription are shown. Regression coefficients (*b*), their SE, and *p*-values presented are derived from linear mixed effects models adjusting for subject as a random effect.

Abbreviation: FDA, Federal Drug Administration.

[a]Expected average weight change (kg) based on regression coefficient from a mixed effects model adjusting for subject as a random effect.

[b]Lorcaserin median weights represent a single sample.

[c]Topiramate and Naltrexone not included in mixed effects model for medication types due to low sample size ($n = 3$ and 2, respectively).

TABLE 6 Adverse events that were reported as reason for discontinuation are listed by weight-negative medication class and include overview of adverse events

Medication class (*n*)	Adverse event
GLP-1 agonist (2)	Decreased appetite; nausea
SGLT-2 (3)	Vulvovaginal itching; acute pancreatitis[a]; urinary frequency
Metformin (2)	GI side effects; headache
Lorcaserin (1)	Cognitive dysfunction

[a]Required hospitalization.

weight when all weight-loss medications were analyzed as a group. The prescription numbers in this study were likely too small to make definitive conclusions regarding the efficacy of individual medications. Regardless, the results seem to encourage the use of topiramate, bupropion, SGLT-2 inhibitors, and metformin for their respective indications when weight loss is desired in patients with underlying advanced liver fibrosis.

When only FDA-approved anti-obesity medications were evaluated, a statistically significant median weight loss of 7.8% was observed, which is generally consistent with the published efficacy of these medications in patients without cirrhosis.[17] These results seem to extend established efficacy of the FDA-approved anti-obesity medications to patients with both obesity and cirrhosis. It's worth noting that since the design of this study, lorcaserin was voluntarily withdrawn from the market following an FDA request in February 2020 due to increased incidence of cancer in the CAMELLIA-TIMI 61 study.[25] Phentermine use additionally may be limited given increasing prevalence of NAFLD with associated cardiovascular disease and hypertension which may serve as relative or absolute contraindications. Therefore, GLP-1 agonists continue to have the most appeal in this patient population as they have been shown to have weight-independent improvements in NASH and liver fibrosis.[26]

One of the main limitations of this study was the inability to discriminate between lean mass, fat mass, and fluid losses which is especially relevant in a population at high risk of sarcopenia and development of ascites. Based on patient MELD scores and low rate of hospitalizations; however, it appears likely that a large portion of the patient population did not have significant volume overload. Additionally, the effects of volume overload were mitigated by excluding patients on diuretics from the efficacy analysis. The study also lacked a control group or confirmation of patient adherence to

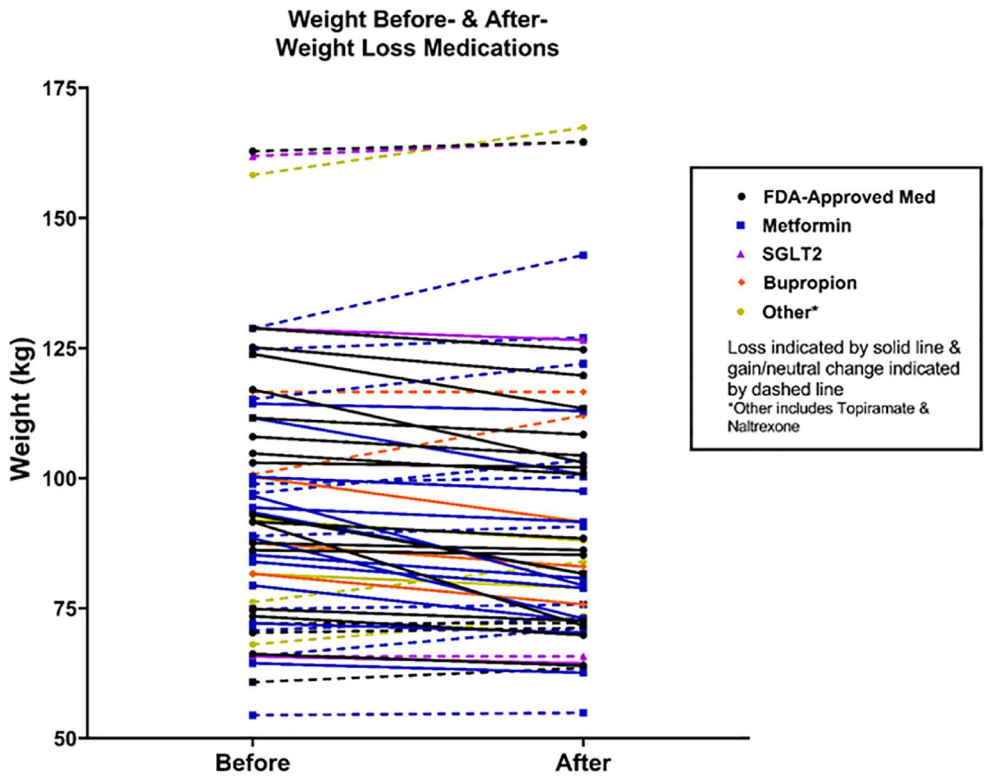

FIGURE 4 Spider plot of unadjusted pre- and post-medication weights per prescription

prescribed medications. Finally, there was no prescription data on three FDA-approved anti-obesity medications: orlistat, phentermine-topiramate, and bupropion-naltrexone. Based on the prescription pattern in this study and given that 84% of patients had comorbid diabetes, the primary indication for the majority of prescriptions was likely diabetes management. Bupropion and naltrexone constituted the only prescriptions seen in patients without diabetes. The strengths include a complete medical record with frequent patient care management by hepatology and obesity medicine specialists.

In summary, this study did not demonstrate any clear contraindications to the use of medications associated with weight loss in patients with obesity and cirrhosis. The weight loss effect of these medications appears to be maintained without apparent worsening of MELD, increased decompensation events, or serious medication intolerance even in the setting of decompensated cirrhosis. Based on the findings above, GLP-1 agonists should be further investigated as strong candidates for the treatment of obesity or diabetes in patients with excess weight and underlying liver disease. Phentermine similarly appears safe and efficacious as an anti-obesity medication in this population when no contraindications are present. Finally, medications that might contribute to weight loss, specifically bupropion, topiramate, SGLT-2 inhibitors, and metformin do not appear detrimental in patients with advanced liver disease and when indicated may deserve preferential use in the setting of excess weight. Given limited treatment options in patients with advanced liver disease and the various liver-related and nonliver-related obesity-driven morbidities, further research is warranted to confirm these findings and help elucidate a potential treatment gap in this vulnerable population.

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AUTHOR CONTRIBUTIONS

All authors: study concept and design; Ali Y. Fakhreddine acquisition of data; all authors: analysis and interpretation of data; Ali Y. Fakhreddine and Samantha Bagsic drafting of the manuscript; all authors: critical revision of the manuscript for important intellectual content; Catherine T. Frenette and Ken Fujioka study supervision).

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