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Deprescribing zolpidem reduces falls and fractures in patients with cirrhosis

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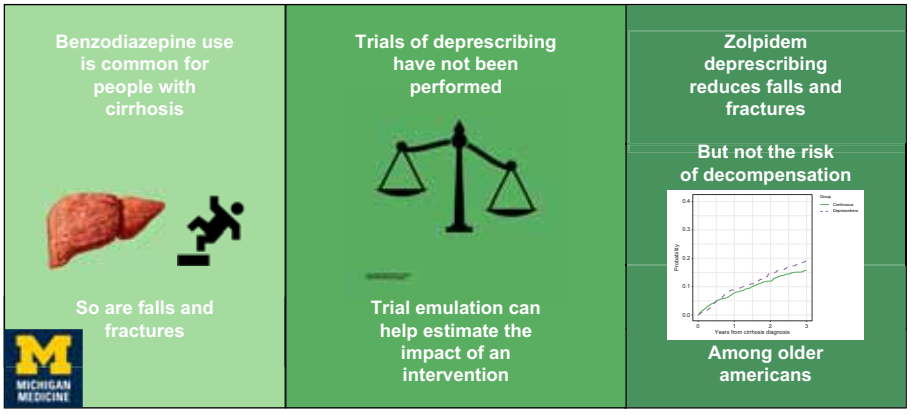
Graphical abstract



Highlights

- Benzodiazepines are frequently and increasingly prescribed to patients with cirrhosis.
- Benzodiazepines may increase the risk of falls and fractures and hepatic encephalopathy.
- Trials of benzodiazepine deprescribing have not been undertaken.
- In this emulated clinical trial, benzodiazepine deprescribing did not decrease the risk of cirrhosis decompensation.
- Zolpidem deprescribing was strongly associated with reduced falls and fractures.

Lay summary

Many people with cirrhosis have anxiety, depression, and sleep disorders. Increasingly, patients with cirrhosis are treated with sedating medications called benzodiazepines, including valium, alprazolam ('Xanax'), clonopin, and the sleep-aid zolpidem ('Ambien'), which can cause falls, broken bones, and maybe other brain disorders. For this reason, many researchers are interested in trials of 'deprescribing' (stopping) benzodiazepines. However, no trials have been performed. We used health record data to simulate a trial of deprescribing. We found that stopping benzodiazepines may reduce the chance of falls or broken bones, but it does not improve survival or liver health.

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Deprescribing zolpidem reduces falls and fractures in patients with cirrhosis

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Background & Aims: Benzodiazepines are associated with an increased risk of harm in patients with cirrhosis. However, stopping benzodiazepines must be done with care to avoid withdrawal or other unintended consequences. The impact of deprescribing on patients with cirrhosis is unknown.

Methods: We emulated a hypothetical 3-year trial of benzodiazepine deprescription among Medicare enrollees with compensated cirrhosis who lacked other life-limiting diagnoses. All received continuous benzodiazepine prescriptions for the 6-months prior to their diagnosis of cirrhosis. During a 90-day landmark period following their diagnosis of cirrhosis, patients were classified as complete deprescribers (no benzodiazepines dispensed), continuous users, or partial deprescribers. We used inverse probability treatment weighting to compare complete deprescribers to continuous users of traditional benzodiazepines and zolpidem. Outcomes accounted for competing risk of mortality and included incident decompensation (hepatic encephalopathy, ascites, or variceal bleeding), fractures, falls, and alcohol-related hospitalizations.

Results: There were 1,651 and 1,463 continuous users of traditional benzodiazepines and zolpidem, respectively, and 728 complete deprescribers. Patients were aged a median of 68 years, 24% had alcohol-related cirrhosis. There was no difference in the risk of death or decompensation for continuous users and deprescribers. Among deprescribers of traditional benzodiazepines, there was no improvement in the risk of falls or fractures. However, compared to continuous zolpidem users, deprescribers had a lower risk of falls (23.2% *vs.* 31%, $p = 0.04$) and fractures (21% *vs.* 29%, $p = 0.02$).

Conclusions: Deprescribing zolpidem reduces the risk of falls and fractures. However, deprescribing benzodiazepines does not improve the risk of decompensation. Efforts to safely address the indications for benzodiazepines such as insomnia and anxiety are urgently needed.

Lay summary: Many people with cirrhosis have anxiety, depression, and sleep disorders. Increasingly, patients with cirrhosis are treated with sedating medications called benzodiazepines, including valium, alprazolam ('Xanax'), clonopin, and the sleep-aid zolpidem ('Ambien'), which can cause falls, broken bones, and maybe other brain disorders. For this reason, many researchers are interested in trials of 'deprescribing' (stopping) benzodiazepines. However, no trials have been performed. We used health record data to simulate a trial of deprescribing. We found that stopping benzodiazepines may reduce the chance of falls or broken bones, but it does not improve survival or liver health.

Introduction

Benzodiazepines are associated with serious adverse events in older patients and especially those with cirrhosis.[1,2] They are associated with increased rates of pneumonia,[2] hepatic encephalopathy (HE),[3] and an increased risk of falls.[4] Benzodiazepines are also frequently prescribed. Roughly 1 in 5 patients with cirrhosis are prescribed benzodiazepines.[5,6] Prescriptions for benzodiazepines among patients with cirrhosis have also risen by 342% over time.[1] Despite this, it is increasingly clear that benzodiazepines may be counterproductive for the management of chronic anxiety and insomnia.[7,8] Accordingly, trials of deprescription have been proposed.[9]

Deprescribing, however, must be conducted in a controlled setting. Multiple trials of deprescription have been conducted in patients without cirrhosis.[10,11] Failure to stop therapy in these trials was related to withdrawal symptoms or the fear of recurrent anxiety or insomnia.[10,11] Furthermore, long-term clinical outcomes after a deprescribing intervention are unknown. Given the potential for benefit, we conducted focus groups with patients with cirrhosis as well as their clinicians and found them interested in stopping benzodiazepines.[9] We found that patients were worried about worsening symptoms and clinicians worried about withdrawal.[9]

Before embarking on a clinical trial, we sought to estimate the risks and benefits of deprescribing with a clinical trial emulation. The data regarding adverse associations are compelling but it is unclear if the associations are causal or whether they reflect unmeasured confounding by indication. While trials to determine the causality of adverse events are unethical, trial emulation using observational data can provide

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estimates of both benefits and harms and inform safe and effective clinical trial design. Herein, emulate a hypothetical trial of benzodiazepine deprescription in a cohort of patients with compensated cirrhosis.

Patients and methods

Target trial

Target trial emulation is a novel analytic approach.[12–14] The core limitations of observational data in the evaluation of therapeutic effects are the lack of data regarding the indications for the therapies and misalignment of the start of follow-up between treated/untreated patients within the trajectory of disease. Emulation overcomes these challenges by enrolling patients when they first meet trial eligibility criteria and produces robust estimates of the intention-to-treat effect by assigning eligible individuals to treatment strategy based on their exposure at the time of eligibility. As no trials of benzodiazepine depresecription have been performed, we used a modification of the PREDESCI trial of non-selective beta-blockers as the target trial design.[15] We used the inclusion and exclusion criteria to isolate a group of well characterized patients with compensated cirrhosis lacking other life-limiting diseases (*e.g.* dementia, metastatic cancer, end-stage renal disease) and we used the analytic framework to detect important clinical outcomes (Fig. S1: inclusion/exclusion flow chart). We also examined other outcomes of specific linkage to benzodiazepine use such as falls, fractures, and alcohol-related hospitalizations.

Study population: Medicare

We examined a random sample of outpatient US Medicare enrollees with cirrhosis (ICD9 571.2, 571.5, 571.6) and continuous Part D (prescription) coverage from 2008-2019. Medicare is government subsidized healthcare for all persons ≥65 years old and those receiving disability benefit, or hemodialysis. Part D is the part of the program that was developed to provide outpatient prescription coverage starting in 2008. A summary of diagnostic codes used is provided in Table S1. We included all patients who met criteria for cirrhosis using a coding algorithm validated for Medicare data (≥2 *outpatient* diagnostic codes for cirrhosis).[16] We subsequently applied the PREDESCI exclusion criteria to finalize the cohort.[15] As this was an emulated trial of deprescribing, we required that all patients in the sample were continuous users of benzodiazepines during their pre-cirrhosis follow-up (Fig. 1, Fig. S1). We limited our analyses to beneficiaries that had both 180 days of continuous enrollment prior to their first cirrhosis code.

Outcomes

All outcomes were analyzed at 3 years following patients until death, liver transplantation, or loss-to-follow-up (censoring patients at last follow-up). We examined mortality and a composite of all-cause decompensation (variceal bleeding, ascites requiring paracentesis and/or spontaneous bacterial peritonitis, and grade 3-4 HE). To operationalize this definition of HE as overt (≥grade 2), we required that the patient required an inpatient HE diagnosis. Each decompensation was also examined separately. We also evaluated the incidence of fractures (skull, spine, arm, rib, pelvis, hip, leg), falls, and intracranial hemorrhage to determine if deprescribing was associated with a lower risk of bodily injuries. Finally, we assessed the risk alcohol-related hospitalizations defined by the primary diagnosis code for the hospitalization.

Treatment comparisons

An overview of the study design is provided in Fig. 1. Allocation to treatment arm was defined by prescription fills within the 90-days following the cirrhosis diagnosis. Patients were categorized as continuous users or complete deprescribers (0 days). Patients with intermediate usage were not analyzed. Then, to construct a 'per-protocol' cohort to test the impact of successful deprescribing, we focused our primary analysis on those with at least 90-days of event-free follow-up after the first cirrhosis diagnosis. The PREDESCI exclusion criteria and the lengthy pre-morbid observational period result in a very selected cohort. Accordingly, in a sensitivity analysis, we constructed an "intent-to-deprescribe" cohort of

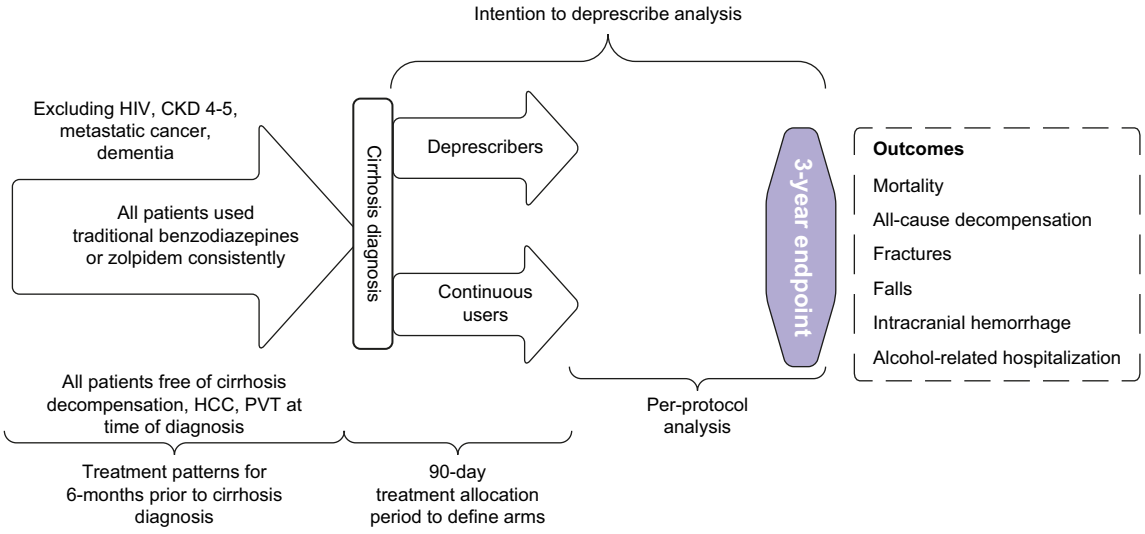

Fig. 1. Overview of the study design. All patients are included based on being consistently prescribed benzodiazepines for the 6-months prior to their diagnosis of cirrhosis. The 'treatment arms' are determined within the 90-days following their cirrhosis diagnosis and those who were complete benzodiazepine deprescribers were compared to continuous users. CKD, chronic kidney disease; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis.

patients who could develop trial outcomes immediately after their diagnosis of cirrhosis at any point in their Part D coverage. We also reduced the pre-cirrhosis requirement for continuous benzodiazepine use to 45 days (Table S2).

Covariates

For complete description of the cohort and to facilitate close matching/risk-adjustment we also included age, sex, race, comorbidities, liver disease etiology, and evaluation by a gastroenterologist/hepatologist. In addition, as there are medications which may modify the risk of outcomes and also reflect severity of disease, we also included statins, insulin, and opioids. As performed by multiple investigators, we classified a group of patients with likely non-alcoholic fatty liver disease (NAFLD)-related cirrhosis who had cirrhosis (ICD-9 571.5) but lacked any diagnostic codes for viral hepatitis, alcohol-related use disorder or alcohol-related organ injury, or auto-immune liver disease.[17,18] Owing to the lack of specific codes for NAFLD, we refer to this as non-alcohol, non-viral related cirrhosis. For the purposes of the matching procedures, we examined cardiovascular comorbidities and risk factors separately.

Weighting

We could not employ randomization. To control for confounders (described above and in Table 1), we therefore used the inverse propensity treatment weighted (IPTW) method with the overlap weights, where each case is weighted proportionally to the probability of receiving the opposite treatment arm.[19] These weights were then included in a cause-specific hazard model to estimate the average treatment effect. Balance of the covariates was checked using standardized mean differences (Fig. S2A-2B). Overlap weights focus on the causal effects of 2 treatments on the population with the most overlap in covariates, effectively recapitulating a homogenous trial population with limited variability in baseline clinical covariates. We then created weighted cumulative incidence curves to visualize the difference in incidence across different treatment groups. Table 1 represents the integrated matched comparisons.

Data analyses

In summary, this is a landmark analysis (time-zero for cohort entry was 90 days following the diagnosis of cirrhosis) with an intention-to-treat design that assumed treatment allocation based on the prescriptions during the 90-days after enrollment. Subdistribution hazard ratios (sHR) and 95% CIs were estimated using a competing-risk analysis.[20] The competing-risk framework was also used to estimate outcome probabilities from cumulative incidence functions. The assessment of each outcome – *i.e.* decompensation, fractures – accounts for the competing risk of death or transplantation. These data are analyzed under a data use agreement with the Center for Medicare and Medicaid services and cannot be shared publicly.

Results

Cohort characteristics

Table 1 summarizes the cohort. There were 1,651 and 1,463 continuous users of traditional benzodiazepines and zolpidem, respectively. Among traditional benzodiazepines, the most common were alprazolam, clonazepam, and lorazepam. Given the even split between classes of benzodiazepine, IPTW matching with deprescribers was performed separately. There was no statistical difference in any cohort characteristic. Most patients received disability benefit, were chronic opioid users, and had multiple extrahepatic comorbidities. Less than half of patients had received a gastroenterology consultation. After the 90-day landmark period, the categories of continuous users and deprescribers were stable, both remained >95% within category.

Table 1. Study population.

	Continuous traditional benzodiazepine	Continuous zolpidem	Deprescribed benzodiazepines
N	1,651	1,463	728
Demographics			
Age (standard deviation)	68.0 (14.2)	68.6 (14.5)	68.4 (13.8)
White race	87.7% (1,448)	83.7% (1,224)	83.2% (606)
Male	40.2% (664)	41.3% (604)	43.0% (313)
Urban	64.1% (1,059)	64.8% (948)	63.6% (463)
Disability	64.1% (1,058)	61.0% (892)	57.4% (418)
Gastroenterology consult	39.7% (656)	46.7% (683)	39.1% (285)
Cirrhosis etiology			
Alcohol-related	33.1% (546)	27.9% (408)	27.9% (408)
Viral	23.2% (383)	26.8% (392)	21.0% (153)
NAFLD	43.7% (722)	45.3% (663)	45.7% (333)
Comorbidities			
Varices	5.1% (84)	5.6% (82)	5.6% (41)
Alcohol use disorder	28.8% (476)	25.4% (372)	29.3% (213)
Diabetes	30.7% (507)	26.6% (389)	35.0% (255)
Hypertension	79.6% (1,315)	82.3% (1,204)	82.0% (597)
Hyperlipidemia	52.2% (862)	53.7% (785)	54.9% (400)
Myocardial infarction	7.6% (126)	8.5% (124)	10.9% (79)
Congestive heart failure	18.8% (311)	20.8% (305)	26.2% (191)
COPD	51.8% (855)	46.6% (682)	51.9% (378)
Chronic kidney disease 1-3	6.1% (101)	7.4% (108)	7.1% (52)
Opioid user	72.7% (1,200)	65.6% (959)	65.2% (475)
Statin user	34.5% (570)	35.1% (513)	35.9% (261)
Insulin user	15.6% (257)	17.6% (257)	17.3% (126)

There were no statistically significant differences between either traditional benzodiazepine or zolpidem users and deprescribers. As described in the methods, an inverse probability treatment weighting was used to balance the cohorts. Medication usage was assessed within the year prior to cirrhosis diagnosis and up to 90 days after cirrhosis diagnosis.
COPD, chronic obstructive pulmonary disease; NAFLD, non-alcoholic fatty liver disease.

Table 2. Outcomes associated with continuous use of or deprescribed traditional benzodiazepines.

Outcome	Continuous use	Deprescribed	Impact of deprescribing sHR (95%CI)	*p* value
Death, %	22.9	23.3	-	1.0
Time to event, years (IQR)	1.6 (0.7-3.1)	1.6 (0.6-3.1)		
Decompensation				
Any decompensation, %	16.4	17.5	1.08	0.5
Time to event, years (IQR)	1.3 (0.5-2.4)	1.1 (0.5-2.1)	(0.87-1.34)	
Hepatic encephalopathy, %	7.6	7.3	0.96	0.8
Time to event, years (IQR)	1.5 (0.6-2.4)	1.1 (0.5-2.5)	(0.69-1.35)	
Ascites, %	13.9	14.0	1.02	0.9
Time to event, years (IQR)	1.5 (0.4-2.7)	1.2 (0.5-2.2)	(0.80-1.30)	
Injuries				
Fractures, %	20.6	20.5	0.98	0.8
Time to event, years (IQR)	1.2 (0.4-2.5)	1.3 (0.4-2.5)	(0.80-1.20)	
Falls, %	21.6	21.3	0.96	0.7
Time to event, years (IQR)	1.3 (0.6-2.5)	1.6 (0.6-2.9)	(0.79-1.16)	
Intracranial hemorrhage	2.1	2.0	0.90	0.7
Time to event, years (IQR)	1.5 (0.8-3.4)	2.9 (0.7-3.8)	(0.47-1.14)	
Other				
Alcohol-hospitalizations, %	21.9	22.1	0.98	0.8
Time to event, years (IQR)	0.9 (0.4-1.9)	0.9 (0.4-1.9)		

The raw proportions for each outcome are listed as percentages and the times to event are listed as median days. All outcomes are then assessed using Fine-Gray competing-risk regression to yield sHRs. The competing-risk analysis demonstrates the risk of death as a competing risk with each outcome. Variceal bleeding is not evaluated for insufficient events.
sHR, subdistribution hazard ratio.

In the 'intent-to-deprescribe' sensitivity analysis, we identify 4,976 continuous users (2,707 using traditional benzodiazepines, 2,975 using zolpidem) and 1,976 deprescribers (Table S2).

Outcomes: Traditional benzodiazepines

The clinical events are displayed for both arms in Table 2. There were no differences in any of the outcomes between continuous users and deprescribers. The most common outcome was mortality (23%), followed by falls, fractures, alcohol-related hospitalization, and ascites. Fig. 2A-B presents the cumulative risk of all-cause decompensation and fractures. In our 'intent-to-deprescribe' sensitivity analysis (Table S3A) we observe similar results. However, deprescribers were more likely to develop ascites (sHR 1.22, 95% CI 1.06-1.40) and possibly less likely to incur a fall (sHR 0.87, 95% CI 0.75-1.00).

Outcomes: Zolpidem

The clinical events are displayed for both arms in Table 3. The most common outcome was mortality (29% for deprescribers, 33.2% for continuous users, $p = 0.2$), followed by falls (23.2% *vs.* 31%, $p = 0.04$), fractures (21% *vs.* 29%, $p = 0.02$), alcohol-related hospitalization (21% *vs.* 24%, $p = 0.8$), and ascites (17% *vs.* 22%, $p = 0.2$). Fig. 3A-B presents the cumulative risk of all-cause decompensation and fractures. The risk of decompensation was not significantly different but after 6 months, there may be a trend towards higher risk for deprescribers. Conversely, there is a clear, consistent increase in the risk of fractures among continuous benzodiazepine users. In our 'intent-to-deprescribe' sensitivity analysis (Table S3B) we observe similar results. Deprescribers were more likely to die (23.1% *vs.* 21.2%, $p = 0.03$), or develop ascites (18.4% *vs.* 16.5%, $p = 0.04$), but possibly less

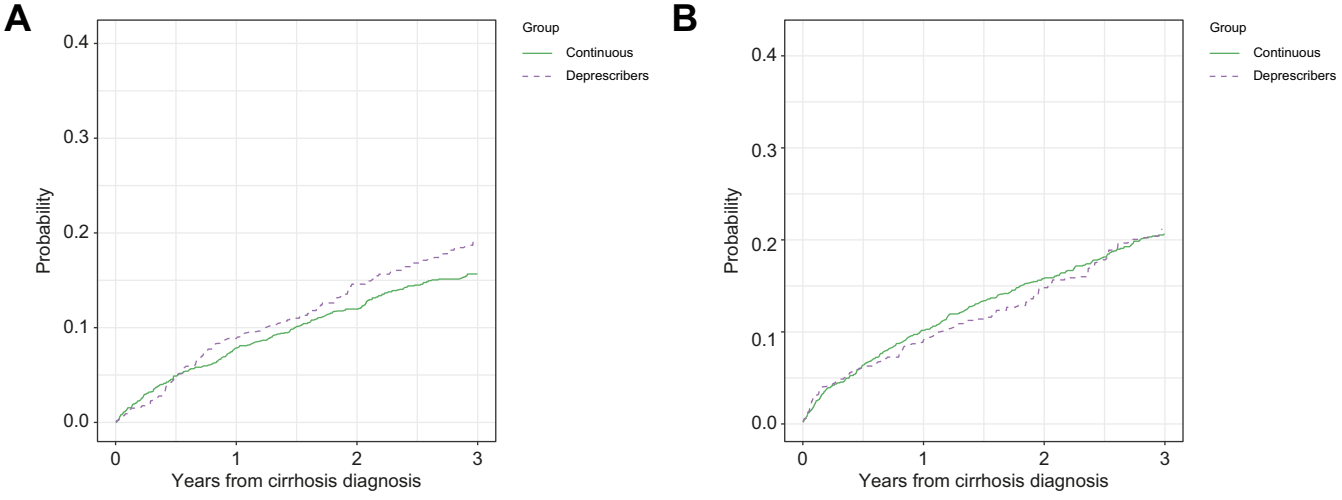

Fig. 2. Cumulative incidence of decompensation and fractures for traditional benzodiazepine users and deprescribers. Both panels display the cumulative incidence of outcomes accounting for the competing risk of death. The dotted line describes outcomes for patients who stopped or were deprescribed traditional benzodiazepines while the solid line shows those who continued without interruption. (A) There no difference in the risk of decompensation after deprescribing, sub-distribution hazard ratio by Fine-Gray test (sHR) of 1.08 ($p = 0.5$). (B) There is no difference in fractures between arms, sHR 0.98 ($p = 0.8$).

Table 3. Outcomes associated with continuous use of or deprescribed zolpidem.

Outcome	Continuous use	Deprescribed	Impact of deprescribing sHR (95%CI)	*p* value
Death, %	33.2	29.1	-	0.2
Time to event, years (IQR)	2.7 (1.2-4.8)	2.0 (0.7-3.7)		
Decompensation				
Any decompensation, %	24.7	20.2	0.94	0.5
Time to event, years (IQR)	1.9 (0.6-3.8)	1.3 (0.5-2.4)	(0.77-1.15)	
Hepatic encephalopathy %	10.1	8.7	1.03	0.9
Time to event, years (IQR)	2.2 (1.2-4.0)	1.6 (0.5-2.8)	(0.75-1.41)	
Ascites, %	21.8	16.7	0.87	0.2
Time to event, years (IQR)	1.9 (0.5-3.6)	1.4 (0.6-2.6)	(0.69-1.08)	
Falls/fractures				
Fractures, %	28.9	21.1	0.80	**0.02**
Time to event, years (IQR)	1.7 (0.6-3.1)	1.4 (0.4-3.1)	(0.66-0.97)	
Falls, %	30.9	23.2	0.84	**0.04**
Time to event, years (IQR)	1.8 (0.8-3.9)	1.7 (0.8-3.8)	(0.70-0.99)	
Intracranial hemorrhage, %	3.5	1.9	0.65	0.2
Time to event, years (IQR)	2.8 (1.3-5.2)	3.2 (0.6-4.5)	(0.35-1.23)	
Other				
Alcohol-hospitalizations, %	24.1	20.6	0.97	0.8
Time to event, years (IQR)	1.6 (0.5-3.5)	1.0 (0.4-2.1)	(0.80-1.18)	

The raw proportions for each outcome are listed as percentages and the times to event are listed as median days. All outcomes are then assessed using Fine-Gray competing-risk regression to yield sHRs. The competing-risk analysis demonstrates the risk of death as a competing risk with each outcome. Variceal bleeding is not evaluated for insufficient events.
sHR, subdistribution hazard ratio.

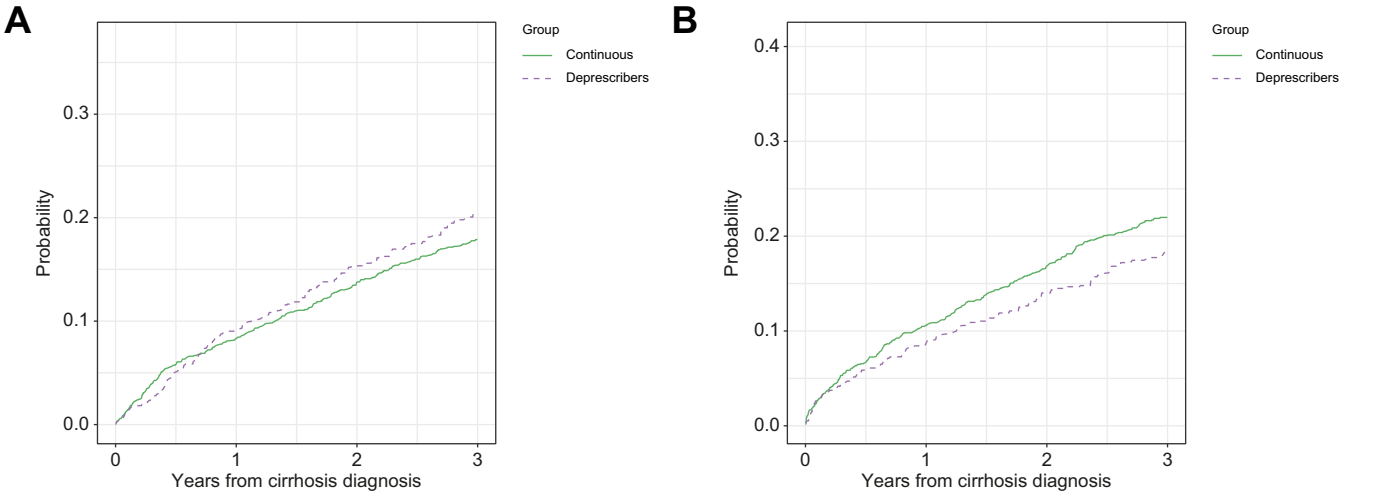

Fig. 3. Cumulative incidence of decompensation and fractures for zolpidem users and deprescribers. Both panels display the cumulative incidence of outcomes accounting for the competing risk of death. The dotted line describes outcomes for patients who stopped or were deprescribed zolpidem benzodiazepines while the solid line shows those who continued without interruption. (A) There is no difference in the risk of decompensation after deprescribing, subdistribution hazard ratio by Fine-Gray test (sHR) of 0.94 (p = 0.5). (B) There is a significant reduction in the risk of fractures among those whose zolpidem was deprescribed, sHR 0.80 (p = 0.03).

likely to incur a fall (17.2% *vs.* 20.4%, p = 0.01) or fracture (16.0% *vs.* 20.2%, p = 0.0006).

Discussion

Although it is widely recognized that benzodiazepines are over-prescribed and risky, particularly for patients with cirrhosis, the safety and efficacy of deprescribing is unknown. The hypothesized risks of benzodiazepine use in patients with cirrhosis include HE and falls/fractures.[1,4,21] These risks have been extrapolated from limited studies from which causality cannot be inferred. It cannot be assumed that deprescribing will reverse these associations – or be free of unintended consequences. Missing from prior studies are the *indications* for the benzodiazepines, which may, themselves, be more associated with the adverse outcomes we intend to prevent through deprescription than the medication itself. In this clinical trial emulation, we find that zolpidem deprescription but not traditional benzodiazepine deprescription is associated with a lower risk of falls and fractures. We also find that regardless of whether patients are continuous users or stop using benzodiazepines, particularly traditional benzodiazepines, they remain at high risk of decompensation and trauma. In sum, these data underscore the potential benefits of deprescribing benzodiazepines, particularly zolpidem, but also the need for close monitoring and adjunctive therapy for patients with cirrhosis and sleep disorder and those at high fall risk.

Falls and fractures are common in patients with cirrhosis.[6,22] We find that those who stopped zolpidem experienced a lower risk of fractures and falls. Although benzodiazepine use (including zolpidem) has been associated with an increased risk of injurious falls,[4] it will be important to understand why zolpidem is clearly associated with fractures and falls while traditional benzodiazepines are not. Lacking in our data are the indication for prescriptions of traditional benzodiazepines. Conversely, all zolpidem is prescribed to address sleep disorder. This distinction is crucial. Sleep-directed sedatives and hypnotics are associated with an increased risk of harm for older persons, with a number need to harm of 6.[8] These risks include daytime sleepiness and psychomotor disturbances. Additionally, the Food and Drug Administration issued a black box warning for zolpidem in 2019 to suggest an increased risk of engaging in activities while not fully awake such as sleepwalking. Indeed, fall risk is highest at night.[23] As such, there may be risk-reduction benefits in deprescribing for persons with cirrhosis taking zolpidem. Regardless, patients with cirrhosis have a very high risk of sleep disorders and it is imperative to address these while considering deprescription.[24]

In this study we examined cirrhosis decompensations, mortality, and alcohol-related hospitalization. No differences in mortality were observed for traditional benzodiazepines deprescribing, though there was a small increase in the risk of ascites in our 'intent-to-deprescribe' sensitivity analysis. Small increases in mortality and ascites were observed for zolpidem deprescribing. These data do not prove causality; however, they do underscore a couple of conclusions. First, patients with cirrhosis on continuous use of benzodiazepines represent a high-risk group for adverse outcomes. Second, deprescribing does not guarantee improved outcomes.

These data do not suggest that deprescribing is without benefits. Instead, our findings only highlight the complexity of the trade-offs inherent to the management of benzodiazepine use and its indications. While prospective studies have not found an independent association between benzodiazepines and incident HE when accounting for disease severity,[25] the effects of the benzodiazepine toxidrome may manifest like HE, potentially increasing the risk of over-diagnosis of HE. Patients with HE are at high risk of falls and fractures and polypharmacy may worsen this risk.[26] Discontinuation of benzodiazepines without deliberate care can be risky. Withdrawal symptoms are not uncommon in deprescription trials.[10,11] Further, the indication for the benzodiazepines persists despite discontinuation. Without this close attention to the withdrawal procedures and effects, patients may be vulnerable to maladaptive compensating measures, like drinking alcohol. Psychological interventions increase the effectiveness of dose-reductions or deprescribing.[27] High quality deprescribing in cirrhosis is therefore complex. Prior trials of deprescribing among persons without cirrhosis have been administered at the level of local pharmacies.[10,11] Such a design likely provides inadequate monitoring for those with cirrhosis.

Randomized clinical trials are the best way to determine causal effects. It is unethical, however, to perform clinical trials to determine causality of adverse events. Given the potential harms of benzodiazepines, a deprescription trial was therefore warranted. Given no such trial has been performed, we chose to emulate PREDESCI because it was a trial that enrolled fit patients with compensated cirrhosis and had clinical outcomes that were universally meaningful and a simple, implementable analytic strategy. In so doing, we excluded patients with life-limiting extrahepatic diseases. Conventional end-of-life or palliative indications for benzodiazepine therapy are lacking in our dataset. We emulated randomization with IPTW to rigorously match patients and homogenize the study sample. Therefore, these data can clearly inform any future trial on deprescription.

We modified the 'new-user' design by requiring that all patients were all prior users – a 'new deprescriber' design. As all patients were consistent benzodiazepine users who were diagnosed with cirrhosis after at least 180 days of follow-up, we created a clear landmark on which to emulate trial enrollment without a hazard of immortal time bias. The use of stringent inclusion/exclusion criteria and the robust matching procedure constrained the risk of confounding by indication. Some unmeasured confounding may persist. Given the high risk of decompensation and fractures/falls, these data show that all patients were high risk.

Our findings must be interpreted in the context of the study design. First, laboratory results were not available to calculate model for end-stage liver disease scores. However, we have previously shown that treatment effect estimates from our Medicare data are validated in other cohorts when adjusting for laboratory data.[28] Second, we lacked data on the degree of portal hypertension as determined invasively. Though this is the truest limitation of the fidelity of our emulation framework to the PREDESCI template, portal pressures are not routinely measured in clinical practice. In fact, we have found among Medicare enrollees with cirrhosis, only 1.7% underwent hepatic venous pressure gradient determination. Third, we could not determine which patients with alcohol-related disease were actively drinking at the time of simulated enrollment. Fourth, our data from Medicare enrollees may not generalize to younger, commercially insured patients. Fifth, although we used multiple novel strategies to address confounding – adjusting for medication use, gastroenterology consultation, stringent exclusion criteria, 'new deprescriber' design, and the common landmark of cirrhosis diagnosis – residual unmeasured confounding may remain. Finally, our landmark analysis creates a common starting point for all individuals but does not fully emulate randomization.

Our emulation of benzodiazepine deprescription suggests that there is substantial value in pursuing a trial. Given the need to closely monitor patients and their high risk of decompensation, our data suggests the previously published trials of benzodiazepine prescription which were directed at the level of clinical pharmacies may not provide the level of monitoring required to safely deprescribe benzodiazepines for patients with cirrhosis. Deprescribing for those with cirrhosis will require close monitoring, adjunctive therapies for alcohol use disorder, and fall risk prevention. Initial trials should begin by focusing on zolpidem. Beyond trials of zolpidem deprescription, there is an urgent unmet need in the management of sleep disorders for those with cirrhosis.

Abbreviations

HE, hepatic encephalopathy; IPTW, inverse propensity treatment weighted; NAFLD, non-alcoholic fatty liver disease; sHR, subdistribution hazard ratio.

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Conflicts of interest

Elliot Tapper has served as a consultant to Norvartis, Axcella, and Allergan, has served on advisory boards for Mallinckrodt, Bausch Health, Kaleido, Novo Nordisk, and has received unrestricted research grants from Gilead and Valeant. No other author has a conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Tapper is the guarantor of this article. Concept: Tapper. Analysis: Zhe, Tapper, Parikh, Winder. Data acquisition: Zhe, Tapper. Writing: Tapper. Revision: Zhe, Parikh, Winder.

Data availability statement

Due to the confidentiality of data, the data which support the findings of this study are only available in a redacted form upon request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2022.100478.

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