Andrea Truncali, MD, MPH **October 2025**

Dear Colleagues,

I have recently enjoyed working with addiction medicine fellows at Maine Medical Center. A patient was referred to our office with cirrhosis due to alcohol use disorder, to maybe start naltrexone (NTX). The fellow was nonplussed; why wouldn't we start it? And there I was: Crusty. I had seen some folks with cirrhosis prescribed NTX, but the last advice I'd received from a hepatologist, maybe 5 years ago, was a pretty strong message to avoid its use in patients with cirrhosis: compensated or decompensated. I myself had not made that prescribing decision. But as a 2025 paper (Shenoy et al) suggests, practice is changing. More people are receiving meds for AUD, including NTX, in the setting of cirrhosis. I needed to get up to speed to understand if this is something to emulate or something to watch out for. (Spoiler: mostly emulate).

Read on for more about why. You'll find background, a link to a nice (and short) video with clinical recommendations, and a study review to gain insight into the greyest area on this question- decompensated cirrhosis.

I hope that if this is not enlightening, that something else both fresh and liberating comes your way soon!

Andrea

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Naltrexone (NTX) for Alcohol Use Disorder (AUD) in Cirrhosis

Background

Where did the concern about NTX and the liver come from?

Studies in the late 1980s documented reversible transaminase elevations for doses of 300mg NTX daily in subjects over 40 years old and in patients with obesity (Pfohl et al., 1986; Mitchell et al., Biol Psychiatry, 1987). This led to an FDA black box warning cautioning about the use of NTX in the setting of liver disease. Though this warning was removed in 2013, it has impacted practice.

Practice is changing…is that ok?

Nicely, medical management of AUD is increasing. And with that, there has been increased use of NTX in patients with liver disease (Shenoy et al, 2025). Anecdotally, patients are being discharged with decompensated cirrhosis on NTX, including the injectable formulation.

Generally, the supporting argument is that "nothing is worse than drinking". This makes sense but assumes that NTX has a big enough impact to counter the potential and uncertain risk in advanced liver disease. It also implies that this impact is bigger than acamprosate, which is metabolized renally and considered safe in liver disease.

It is worth considering that impaired hepatic metabolism increases the actual exposure to NTX. Ie, Revia's (brand name oral naltrexone) FDA label notes "an increase in naltrexone AUC of approximately 5-and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function". This seems to be due to a slower conversion of NTX to its active metabolite, 6Beta-naltrexol. (Bertoletti et al, 1997).

Backup - what do you mean when you say 'compensated vs. decompensated cirrhosis'?
Liver cirrhosis can be, but usually is not made by biopsy, so it is diagnosed with a combination of clinical history, labs, and imaging. Decompensated cirrhosis means the body cannot compensate for the liver impairment, resulting in jaundice, ascites, variceal bleeding, and/or encephalopathy.
One can use the Childs-Pugh class to help risk-stratify a person diagnosed with cirrhosis. (MedCalc can help). Class A and B generally correspond to compensated cirrhosis and Child's Class C, decompensated.

What data support this practice change?
Data is emerging about the potential benefit and lack of harm in people with alcoholic cirrhosis. Except for an exciting RCT in India whose data have only yet been reported at conferences (and had high loss to follow-up), all of the data are observational. This means they are comparing those treated with medication versus those not treated, and introduces lots of potential confounding that may not be fully adjusted for. However, in this data, there is remarkable consistency across studies for the benefit of NTX, including reduced progression to decompensated disease, reduced mortality, and lack of NTX harm. Further, there are studies from patients with AUD in populations with high rates of hepatitis C and HIV treated with injectable medication that did not show liver toxicity out to six months (Mitchell et al, 2012, and Springer et al, 2018).

A table is worth 1000 words..

Reference	Study design	Population, intervention and follow up time	Findings	Of note
Vannier et al, 2022	Retrospective cohort using large database at mass general	Pts dxd with AUD followed x 9yrs. those treated with med vs those not. Mean duration of MAUD for those treated was 4.1 yrs.	Among those with cirrhosis, **meds reduced incidence of hepatic decompensation**. For NTX aOR, 0.27 (0.10-0.64), p = .005)	Possible unmeasured confounders. Those given medication may have been more adherent/less ill/drank less than those not treated in ways not adjusted for.
Ayyala et al, 2022	Retrospective cohort in safety net hospital	Pts prescribed NTX for AUD with lab data before, during and within a year after dc of medication. Median	In those without liver disease, no difference in lab data.	-Excluded those with hep B or C. - 80% male - Selection bias (for healthier group) as

		fup 10months and median rx duration 57days.	**In those with liver disease AST, ALT, and total bilirubin improved while on naltrexone.** -3 cases of liver enzyme elevation →1.2/1000person-yrs (not necessarily 2/2 ntx) - no hepatic decompensation or death attributed to NTX	only included those adherent to lab testing. This is supported by a relatively low mortality rate for hepatic decompensation.
Alla et al, 2023 CONFERENCE proceedings only	**Double blind RCT**	Patients in India with compensated cirrhosis given naltrexone 50mg or placebo x 12wks, observed 6months	- 12wk abstinence: 64% NTX vs 22% placebo - 6 month abstinence: 22% NTX vs 8% placebo, p=0.09 - No incidence of worsening liver disease	Not yet published in peer review literature
Rabiee et al, 2023	Retrospective cohort using VA database	Among pts with cirrhosis with continued high-risk alcohol use, those who got meds within a year of cirrhosis dx were compared to those who did not (propensity score matching used). Duration of MAUD exposure was ≤3 months in 61%, and >3 months in 39%.	**MAUD** (of which 59% was NTX , and 7% NTX+ campral) was associated with **20% reduced all cause mortality** (HR: 0.80, 95% CI: 0.67–0.97, *p* = 0.024).	- NTX not the only MAUD included here -Potential unmeasured confounders
Varshney et al, 2023. CONFERENCE proceedings only	**Double blind RCT**	Patients in India with cirrhosis and active alcohol use given naltrexone 50mg or placebo, 12 weeks	- **New onset decompensation: 7.1% NTX vs 28.6% placebo** -Abstinence higher and use parameters lower in NTX than plac	- 44% (n=44) lost to fup - Not yet published in peer review literature
Thompson et al, 2024	Retrospective cohort using VA database	Patients with cirrhosis and a new start NTX who had liver enzymes checked within a 3-month time frame.	- 2% had liver enzyme elevations. Of those: - 30 (48%) were "DILI excluded", 32 (52%) "DILI unlikely"	- History of decompensation prior to initiation of naltrexone was present in 915 people (31%) and

		-Defined DILI using standard framework and reviewed charts of those with liver enzyme elevation	- **None were considered possible, probable, or highly probable DILI.** - No deaths or new decompensations were attributed to naltrexone.	433 (15%) had Child-Pugh class B or C cirrhosis at the time of NTX start - Even one dose of NTX would lead to study inclusion (could underestimate risk of DILI) - 4% women

NTX= naltrexone

AUD = alcohol use disorder

MAUD= medication for AUD

DILI = drug induced liver injury

What is the clinical bottom line!?

A nice 12min summary of MAUD in liver disease by hepatologist and addiction med specialist

Dr Lamia Haque is a good place to get your answer.

https://www.youtube.com/watch?v=V1iKTJg-eBI

Dr Haque essentially says that NTX is safe to use in compensated cirrhosis and can be considered in decompensated /Child's Class C.

When you say "consider" NTX in decompensated cirrhosis, what does that mean!?

Be on the lookout for worsening liver disease. It can occur from alcohol use but also from medications. Use shared decision making. Do shorter follow ups until you see stability and if there is no reduction in alcohol use, you might re-evaluate whether it is indeed worth the risk and/or if you can try a different medication or approach.

Also, it is nice to look at the data to have a sense of what we know. See the chart above and below is a look at one of the observational studies that had a subset of people with decompensated disease.

What about injectable long acting NTX (LA NTX)?

RCT data shows that LA NTX given to people actively drinking led to lower GGT compared with placebo but that was in patients without pre-existing liver disease (Lucey et al, 2008). In the observational studies in people with cirrhosis, a handful were on LA NTX and as above, there is data in populations with high risk for hepatic fibrosis and cirrhosis (ie, Hep C and HIV), that suggest safety.

There is some pharmacologic data to add to this. The LA NTX package insert states that "Compared to daily oral dosing with naltrexone 50 mg over 28 days, total naltrexone exposure is 3 to 4-fold higher following administration of a single dose of VIVITROL 380 mg." However, Turncliff et al, 2005 showed no difference in NTX or its active metabolite in people with mild or moderate hepatic impairment when comparing LA and oral NTX. The active metabolite, 6Beta naltrexol, is the longer acting compound and Dunbar et al 2005 show that because of slow release, LA NTX blunts its peak, *maybe making it safer in liver disease than the oral form.*

And **remember the most likely serious adverse event with naltrexone is probably precipitating opioid withdrawal in those not known to be opioid dependent!**

Ok, what about that study?

Here's something to give you an in-depth sense of the kind of data we have to address this question.

Title: Ayyala, D., Bottyan, T., Tien, C., Pimienta, M., Yoo, J., Stager, K., Gonzalez, J. L., Stolz, A., Dodge, J. L., Terrault, N. A., & Han, H. (2022). Naltrexone for alcohol use disorder: Hepatic safety in patients with and without liver disease. *Hepatology communications*, *6*(12), 3433–3442. https://doi.org/10.1002/hep4.2080

Link: https://pubmed.ncbi.nlm.nih.gov/36281979/

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METHODS:
Retrospective cohort of adults at a large safety net hospital, prescribed naltrexone (NTX), (oral or LA injectable) for AUD between 2015-2019 from inpatient or outpatient setttings. **Excluded** were those prescribed NTX for other indications and **those with chronic hepatitis B and C.**

Patients were categorized as liver disease (+LD) or no liver disease (no LD) based on radiographic and lab findings. Outcomes were liver enzymes, hospitalizations, and death. Enzymes were assessed before (1 year prior to start of), during, and after (1-12months after discontinuation of) prescription if available, and elevation was considered >3x baseline, and severe elevation >10x baseline.

RESULTS:
Of the 160 included in the cohort, the mean age was 49, 80% male, and 64% Hispanic. 54% had a "psychiatric history". Mean BMI was 28. About one quarter were unhoused, and 89% received Medicaid (Medi-Cal).

Median follow-up was 10 months (IQR, 4–18) from the first naltrexone prescription, with comparable follow-up among patients with and without LD. The median duration of NTX prescription was 57 days (IQR, 28–115).

There were baseline differences between those with LD and those without LD. In particular absence of liver disease was more likely with a psychiatric history (39% +LD, 80 % no LD), and among women (30% +LD, 14% no LD).

100 had LD (**n=47 cirrhosis, of which 22 were decompensated**) and 60 had no LD. 19% had an alcohol related hospitalization after starting NTX (7% no LD vs 26% for +LD) and 5% died (2 vs 7 no LD vs +LD).

Liver enzymes decreased in the total cohort, driven by reductions in those with liver disease, including cirrhosis. 3 of 160 pts had significant enzyme elevations (one ALT and two Total Bili (TB)). One of these was in Child Class C, started on NTX after two months of abstinence. TB decreased after starting NTX (from 36 to 23 mg/dl) but on day 29 of NTX, developed pneumonia, status epilepticus and died. The other had continued alcohol use, a variceal bleed and developed high TB which peaked four days after dc of NTX. (NTX typically causes ALT/AST elevations). The third patient had an ALT increase from 25 to 124, such that NTX was dcd. ALT didn't normalize suggesting alcohol use as the cause.

Risk of alcohol related hospitalization was assessed in multivariable analysis with the following independently associated with risk:

LD (hazard ratio [HR], 3.70; 95% CI,1.19–11.51)

Cirrhosis (HR, 5.16; 95% CI, 1.69–15.75),

Shorter naltrexone duration (HR, 2.50; 95% CI, 1.20–5.20)

There were 8 deaths occurring a median of 5months after initial NTX prescription. **No deaths were attributed to hepatic decompensation or NTX-related hepatotoxicity. One death was attributed to complications of alcohol**. The 2-year cumulative mortality for decompensated cirrhosis was 28.7%, which is much lower than typical (54% 2-year survival).

COMMENTARY

This study aimed to assess the safety of NTX in liver disease. It looked at a cohort of people with AUD who had been prescribed naltrexone and evaluated liver biomarkers before, during, and after NTX treatment, as well as hospitalization and mortality. Out of this group of 160 people, 47 had cirrhosis, 22 of whom were decompensated. Biomarkers of liver disease improved after NTX was started in all groups, but mostly in those with liver disease. In multivariable analysis, factors associated with the risk of hospitalization were the presence of liver disease, cirrhosis, and **shorter** NTX duration. Over the median of 10months observed, 42% were hospitalized or died. Survival was 90% in those with cirrhosis and 81% in those with decompensated cirrhosis, higher than would be expected.

Internal validity *(how likely are the study results what they appear to be for the study group)*

Liver disease, including cirrhosis, may have been underestimated as not all people had extensive evaluation, ie, imaging that might pick up findings not determined by biomarkers alone. This would tend to make NTX look less safe than it is.

On the other hand, since not everyone had biomarkers at all three time points, hepatotoxicity of NTX among those who are less adherent could have been missed. However, a sensitivity analysis suggested little impact.

Actual medication taking was not evaluated, which could overestimate medication safety.

The observed decreases in liver enzymes are thought due to reduced alcohol use but without confirmatory data about alcohol use, that is a conjecture.

Finally, while there was no clear harm to patients with decompensated liver disease, there were not enough people to fully assess safety outcomes in that group.

External validity *(can these results be applied beyond the study)*

The higher than expected survival rate for decompensated cirrhosis may be due to selection bias (though it could also be due to NTX!). The mere fact of including individuals to whom a provider

prescribed NTX may select for a slightly healthier population. It may apply less to people who are not engaging in medical care, and/or have hepatic encephalopathy or enough competing medical needs that NTX prescribing does not become a priority. The inclusion of data from an inpatient setting mitigates this a bit. The study excluded individuals with hepatitis B or C, which limits its application to groups with those comorbidities.

While there is growing evidence of help over harm for NTX in cirrhosis, more data in those who have decompensated cirrhosis are needed. In the meantime, the data we have, along with insights from pharmacology, support a rationale for considering closely monitored oral or injectable NTX in individuals with this high-mortality condition.

Thanks to academic pharmacist, Nicolette Centanni, Pharm D, for highlighting and sharing seminal articles related to this topic.

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