PCSS-MAUD: Medications for alcohol use disorder in individuals with liver disease

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ASAM Conference 2024

Learning Objectives

- Recognize PCSS-MAUD and opportunities for engagement by ASAM members
- List FDA approved medications for alcohol use disorder (MAUD) and their number needed to treat
- Describe clinical reasoning to determine safety for use of MAUD in individuals with liver disease

- No disclosures

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Past PCSS Iterations

Current PCSS Programs

Providers Clinical Support System – Universities (PCSS-Universities)

What is PCSS-MAUD?

Funding Organization:

Substance Abuse and Mental Health Services Administration (SAMHSA)

Purpose:

Nationwide education and training network for multidisciplinary healthcare and counseling professionals to improve access to and quality of AUD treatment services

Project Goal

Train 7,000 healthcare professionals in MAUD

Project Period:

09/30/2023 – 09/29/2026

PCSS MAUD Audience

Professional Type

- Doctors (MDs/DOs)
- Nurses (APRNs, RNs, LPNs)
- Physician associates/physician assistants
- Counselors/therapists
- Social workers
- Pharmacists
- Healthcare professionals in specialty settings

Settings

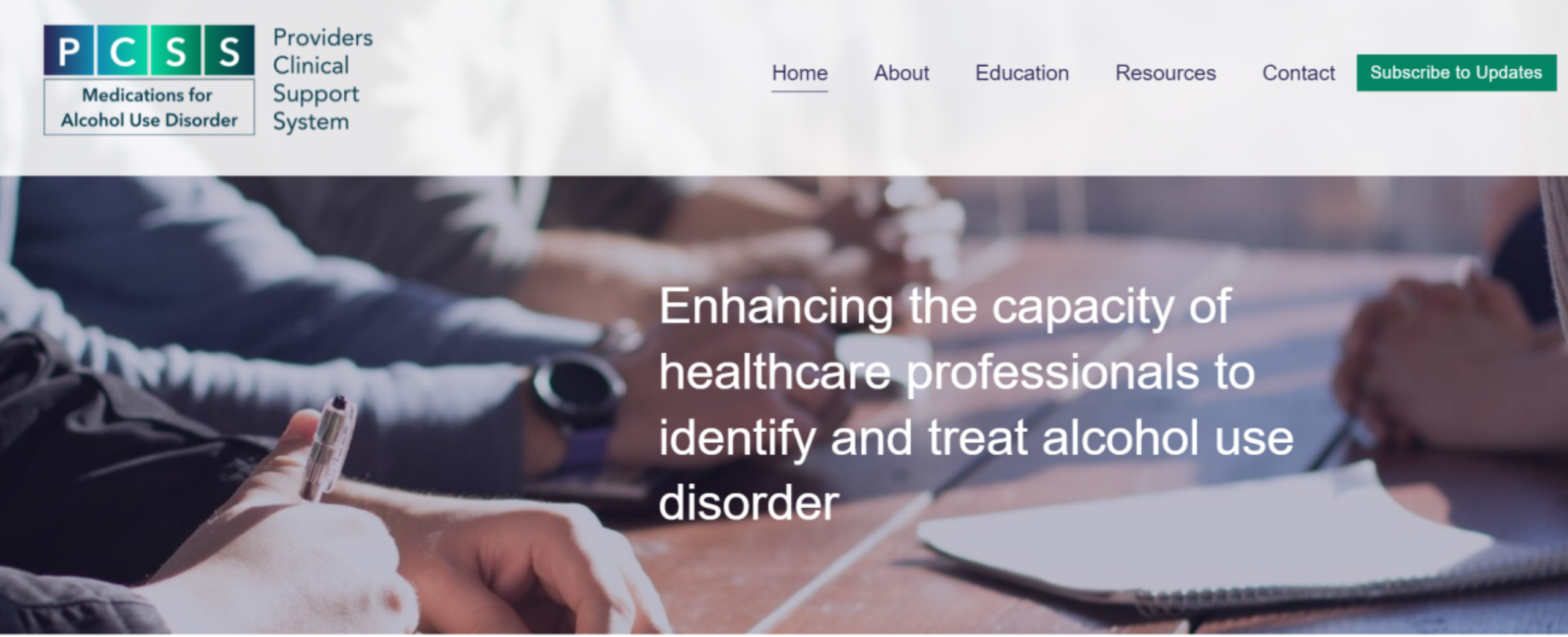
- Obstetrics/gynecology
- Family medicine/primary care
- Federally Qualified Health Centers
- Hospitals/large health systems
- Urgent care/emergency departments
- Pediatrics
- Certified Community Behavioral Health Centers
- Pharmacies
- Indian health centers/tribal healthcare systems
- Rural health clinics

PCSS-MAUD Topics

Medications for Alcohol Use Disorder (MAUD)	Co-occurring Conditions
Models of Care that Integrate MAUD	Screening, Brief Intervention, & Treatment
Withdrawal Management	Advocacy
Special Populations	Prevention
Social Determinants of Health	Non-Medication Treatments for AUD

Year 1 Program Activities

Technical Support and Consultative Services	Mentoring	ECHO Sessions
Online Modules	Webinars	Mini Videos
Skill Based Trainings	Digital Resources (e.g., Toolkits, Factsheets, Infographics, Job Aids)	Live Meetings



About PCSS-MAUD

https://www.pcss-maud.org/

FDA Approved Medications for alcohol use disorder (MAUD)

Acamprosate
Disulfiram
Naltrexone

Medication treatment effects	Naltrexone	Acamprosate	Disulfiram
Reduces heavy drinking	✓	✓	
Manages cravings	✓	✓	
Supports abstinence	✓	✓	
Blocks breakdown of alcohol, causes unpleasant symptoms			✓

Patel, A, Balasanova, A. Treatment of Alcohol Use Disorder. 2021. JAMA Patient Page.

Medications for Alcohol Use Disorder

Medication	Outcome	No. of studies	No. of Participants	NNT (95% CI)#	Strength of Evidence
Acamprosate	Return to any drinking	20	6380	**11 (1-32)**	Moderate
	Return to heavy drinking	7	2496	NA	Moderate (no effect)
Disulfiram*	Return to any drinking	3	622	NA	Low
	Return to heavy drinking	0	0	NA	Insufficient
Naltrexone (50mg/day)	Return to any drinking	16	2347	**18 (4-32)**	Moderate
	Return to heavy drinking	23	3170	**11 (5-41)**	Moderate
Naltrexone ER*	Return to any drinking	2	939	NA	Low
	Return to heavy drinking	2	615	NA	Low

#NNT to prevent 1 person from returning to any or heavy drinking
*Caveats to be explained later in the presentation

McPheeters M, et al. JAMA 2023

Medications for Alcohol Use Disorder

Medication	Outcome	NNT (95% CI)
Acamprosate	Return to any drinking	**11 (1-32)**
	Return to heavy drinking	NA
Naltrexone (50mg/day)	Return to any drinking	**18 (4-32)**
	Return to heavy drinking	**11 (5-41)**

Medication	Outcome	NNT
SSRI	Depression improvement	**7-9**
Statin	Prevention of fatal MI	**104**
DVT prophylaxis	Prevention of fatal PE	**345**

Jonas, D. et al. *JAMA* 2014

Medications for Alcohol Use Disorder

Medication	Outcome	No. of studies	No. of Pts	WMD	Strength of Evidence
Acamprosate	% of drinking days	14	4916	**-8.3 (-12.2 to -4.4)**	Moderate
	% of heavy drinking days	2	123	-3.4 (-6.45 to 5.86)	Insufficient
Disulfiram*	% of drinking days	2	290	NA	Insufficient
	% of heavy drinking days	0	0	NA	Insufficient
Naltrexone (50mg/day)	% of drinking days	15	1992	**-5.1 (-7.16 to -3.04)**	Moderate
	% of heavy drinking days	7	624	**-4.3 (-7.6 to -0.91)**	Moderate
Naltrexone ER*	% of drinking days	2	467	-4.99 (-9.49 to 0.49)	Low
	% of heavy drinking days	3	956	**-4.68 (-8.63 to -0.73)**	Low

Mel Heeters M, et al. *JAMA* 2023

WMD = Weighted Mean Difference

*Caveats to be explained later in the presentation

PCSS Medications for Alcohol Use Disorder — Providers Clinical Support System

All-Cause Mortality Benefit of MAUD

- In individuals with alcohol-associated cirrhosis (n=9131), MAUD use is associated with a 68% reduced hazard for all-cause mortality (HR 0.32, 95% CI 0.18-0.59, p <0.001)

Rabiee, et al. Hepatology Communications, 2023.

Non-FDA Approved Medications for Alcohol Use Disorder

Medication	Outcome	No. studies	No. of Pts	WMD	Strength of Evidence
Baclofen	% of drinking days	5	714	-5.55 (-18.8 to 7.69)	Low (no effect)
	% of heavy drinking days	9	1112	-2.16 (-7.3 to 3.0)	Low (no effect)
Gabapentin	% of drinking days	1	112	No difference	Insufficient
	% of heavy drinking days	3	600	No difference	Low (no effect)
Topiramate	% of drinking days	8	1080	**-7.2 (-14.3 to -0.1)**	Moderate
	% of heavy drinking days	9	1210	**-6.2 (-10.9 to -1.4)**	Moderate

McPheeters M, et al. *JAMA* 2023

WMD = Weighted Mean Difference

Case 1

- 46 yo man with history of severe alcohol use disorder, anxiety, alcohol related liver disease, and hypertension.
- He has never had encephalopathy, varices, or ascites. He has an enlarged, echogenic liver on ultrasound.
- He is prescribed lisinopril and sertraline.
- Current labs

Total Bilirubin	2.0
Albumin	3.8
AST	250
ALT	180
INR	1.8

His Treatment Goals

- Cut back on his alcohol use, but not ready to stop
- Engage in mutual support through AA
- Continue medication management in primary care

Which MAUD is best for him?

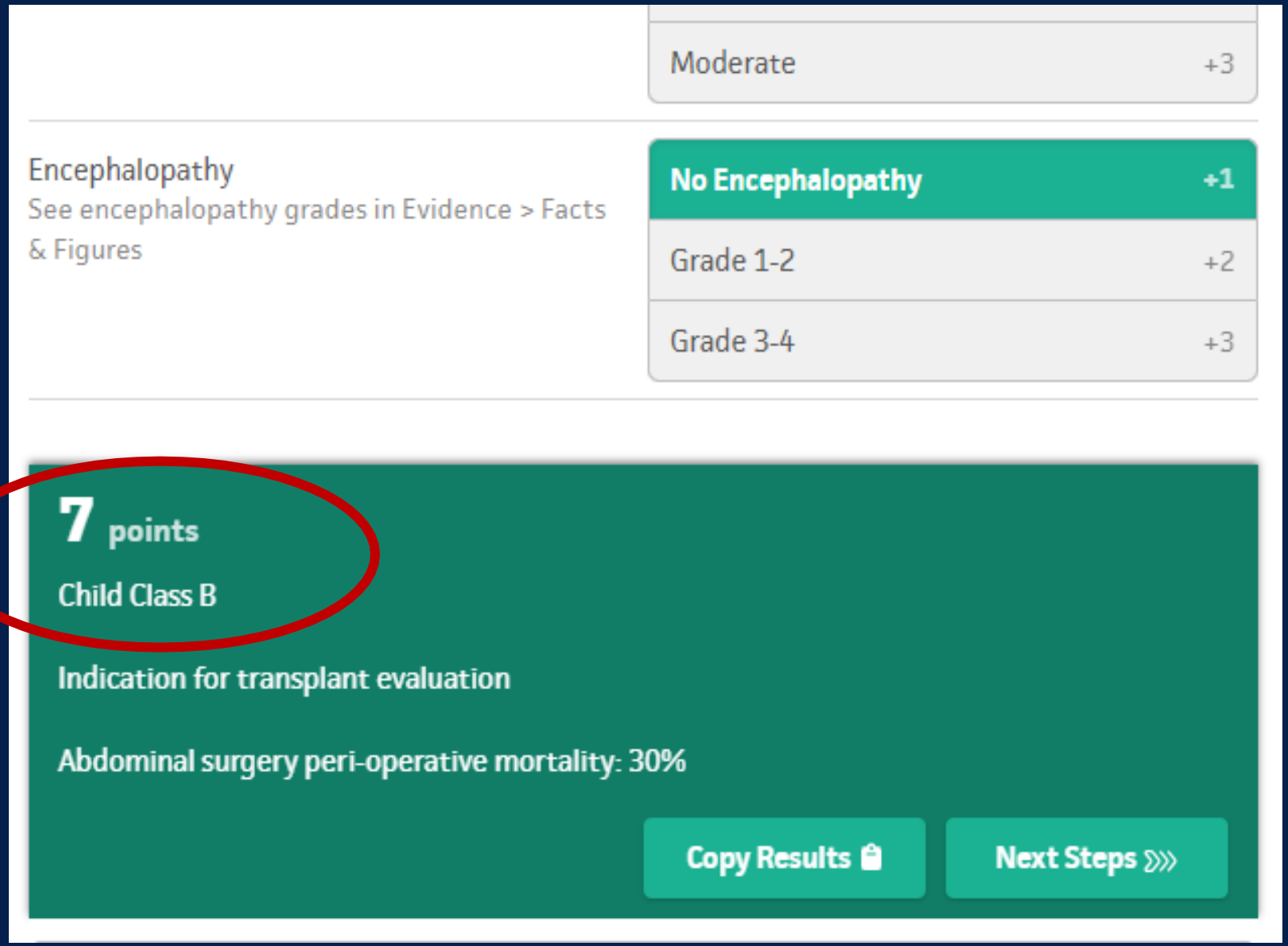
- How do you determine best MAUD recommendation?
- How do you counsel him about risks of MAUD use in liver disease?
- What is your “first line” recommendation to him?

Child-Pugh Score for Cirrhosis Mortality ☆

Estimates cirrhosis severity.

Pearls/Pitfalls

Bilirubin (Total)	<2 mg/dL (<34.2 µmol/L)	+1
	2-3 mg/dL (34.2-51.3 µmol/L)	+2
	>3 mg/dL (>51.3 µmol/L)	+3
Albumin	>3.5 g/dL (>35 g/L)	+1
	2.8-3.5 g/dL (28-35 g/L)	+2
	<2.8 g/dL (<28 g/L)	+3
INR	<1.7	+1
	1.7-2.3	+2
	>2.3	+3
Ascites	Absent	+1
	Slight	+2
	Moderate	+3
Encephalopathy See encephalopathy grades in Evidence > Facts	No Encephalopathy	+1

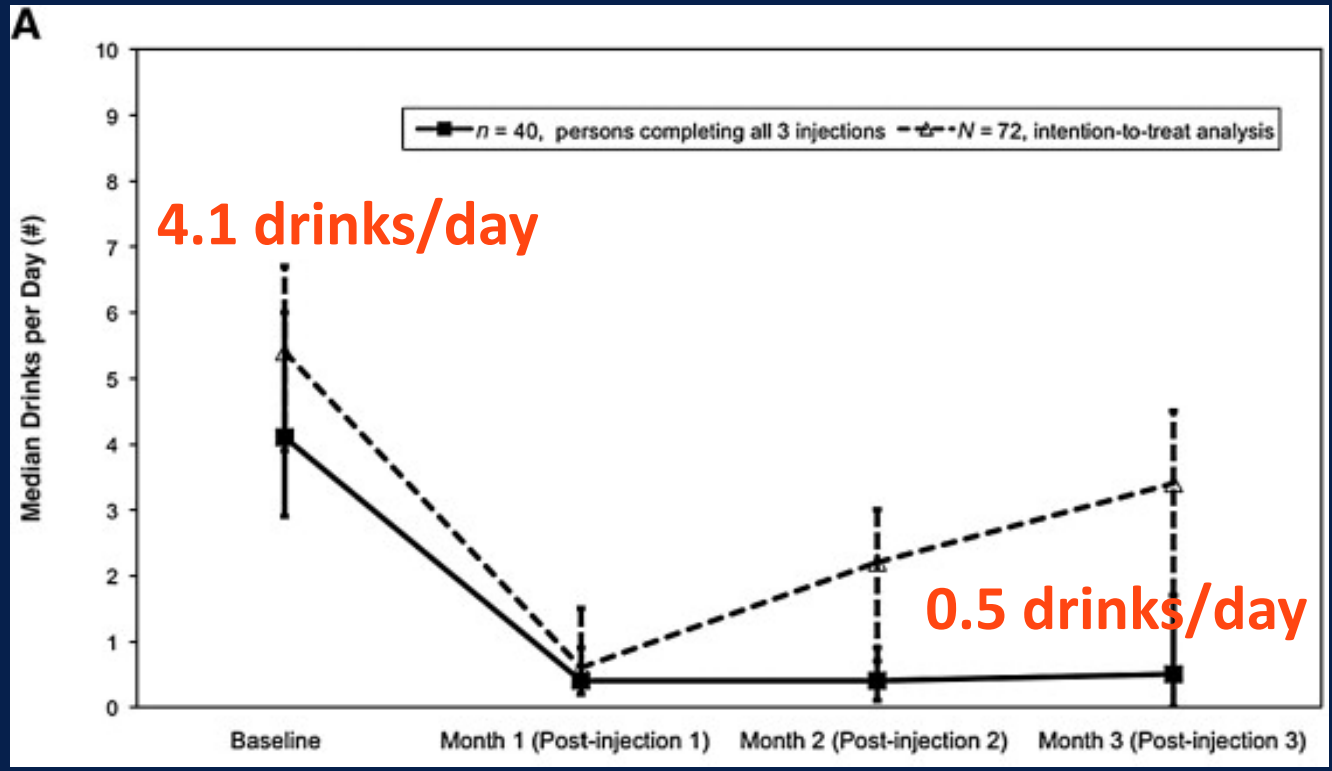


Which MAUD is safe in Child Pugh Class B Liver disease?

XR-NTX for Alcohol Use Disorder

- XR-NTX in 72 patients with AUD + *medication management*
- 56% (n=40) received 3 injections
- Reduction of drinks per day from 4.1 to 0.5 after 3 months
- 2 (3%) patients reported LFT >5x UNL

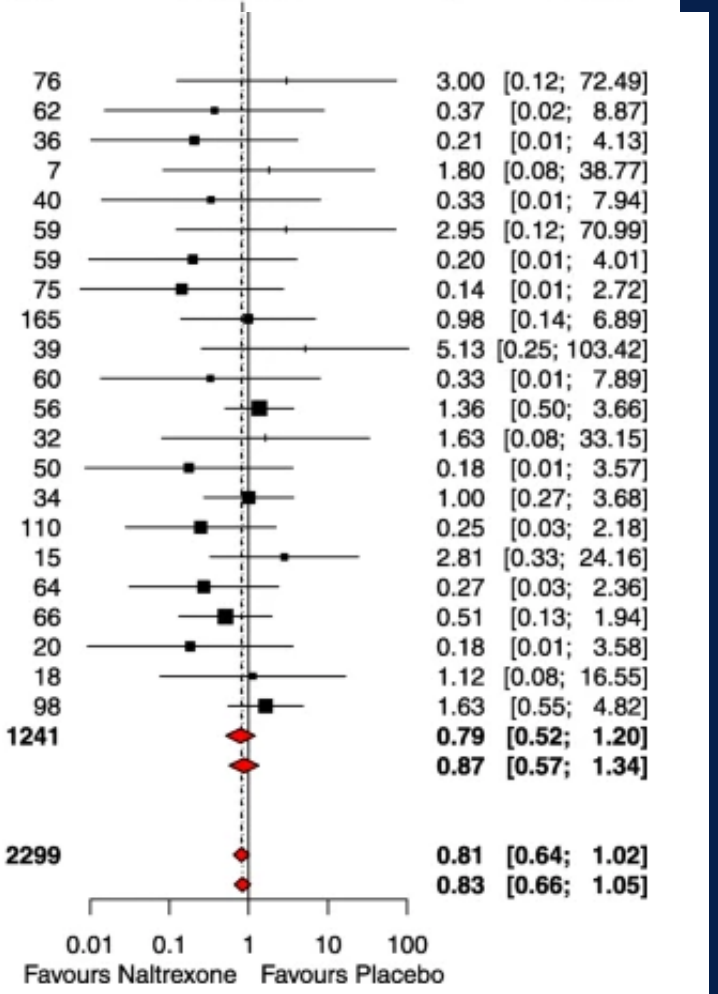
- Extension study, n=19,
- Abstinent 82% vs 38% days, 11% vs 61% heavy drinking days

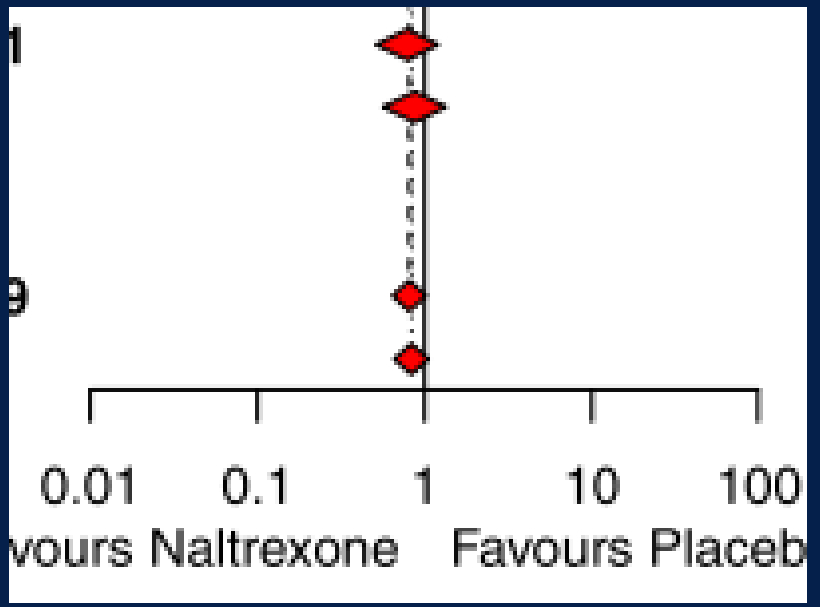


Lee, et al. JSAT 2010
Lee, et al. JSAT 2012

Meta-analysis of 89 RCTs (11,194 patients) of oral naltrexone, no increased AEs

Study	Naltrexone Events	Naltrexone Total	Placebo Events	Placebo Total	RR	95%–CI
50 mg						
Anton 2018 (49 yrs; 69%M)	1	76	0	76	3.00	[0.12; 72.49]
Balldin 2003 (50 yrs; 85%M)	0	56	1	62	0.37	[0.02; 8.87]
Castro 2004 (46 yrs; 82%M)	0	35	2	36	0.21	[0.01; 4.13]
Cook 2017 (49 yrs; 100%F)	1	12	0	7	1.80	[0.08; 38.77]
Garbutt 2016 (47 yrs; 71%M)	0	40	1	40	0.33	[0.01; 7.94]
Greenway 2009a (42 yrs; 11%M)	1	60	0	59	2.95	[0.12; 70.99]
Greenway 2009a bupropion (42 yrs; 11%M)	0	60	2	59	0.20	[0.01; 4.01]
Kahler 2017 (42 yrs; 59%M)	0	75	3	75	0.14	[0.01; 2.72]
King 2012 (42 yrs; 47%M)	2	168	2	165	0.98	[0.14; 6.89]
Kranzler 2009 targeted (49 yrs; 58%M)	2	38	0	39	5.13	[0.25; 103.42]
Mooney 2016 (40 yrs; 50%M)	0	61	1	60	0.33	[0.01; 7.89]
Morris 2001 (48 yrs; 100%M)	8	55	6	56	1.36	[0.50; 3.66]
O'Malley 2006 NTX 50mg (46 yrs; 52%M)	2	99	0	32	1.63	[0.08; 33.15]
O'Malley 2007 (40 yrs; 100%F)	0	57	2	50	0.18	[0.01; 3.57]
O'Malley 2008 (40 yrs; 66%M)	4	34	4	34	1.00	[0.27; 3.68]
Oslin 2015 (49 yrs; 86%M)	1	111	4	110	0.25	[0.03; 2.18]
Petrakis 2004 (46 yrs; 100%M)	3	16	1	15	2.81	[0.33; 24.16]
Petrakis 2005 NTX (47 yrs; 97%M)	1	59	4	64	0.27	[0.03; 2.36]
Petrakis 2005 NTX/disulfiram (47 yrs; 97%M)	3	65	6	66	0.51	[0.13; 1.94]
Petrakis 2012 NTX/paroxetine (47 yrs; 90%M)	0	22	2	20	0.18	[0.01; 3.58]
Schmitz 2014 (42 yrs; 82%M)	1	16	1	18	1.12	[0.08; 16.55]
Wang 2018 (48 yrs; 100%F)	8	96	5	98	1.63	[0.55; 4.82]
Fixed effect model		**1311**		**1241**	**0.79**	**[0.52; 1.20]**
Random effects model					**0.87**	**[0.57; 1.34]**
Heterogeneity: I^2 = 0%, p = 0.78						
Fixed effect model		**2527**		**2299**	**0.81**	**[0.64; 1.02]**
Random effects model					**0.83**	**[0.66; 1.05]**
Heterogeneity: I^2 = 0%, p = 0.84						





Bolton, et al. BMC Med, 2019.

PCSS Medications for Alcohol Use Disorder — Providers Clinical Support System

ASAM

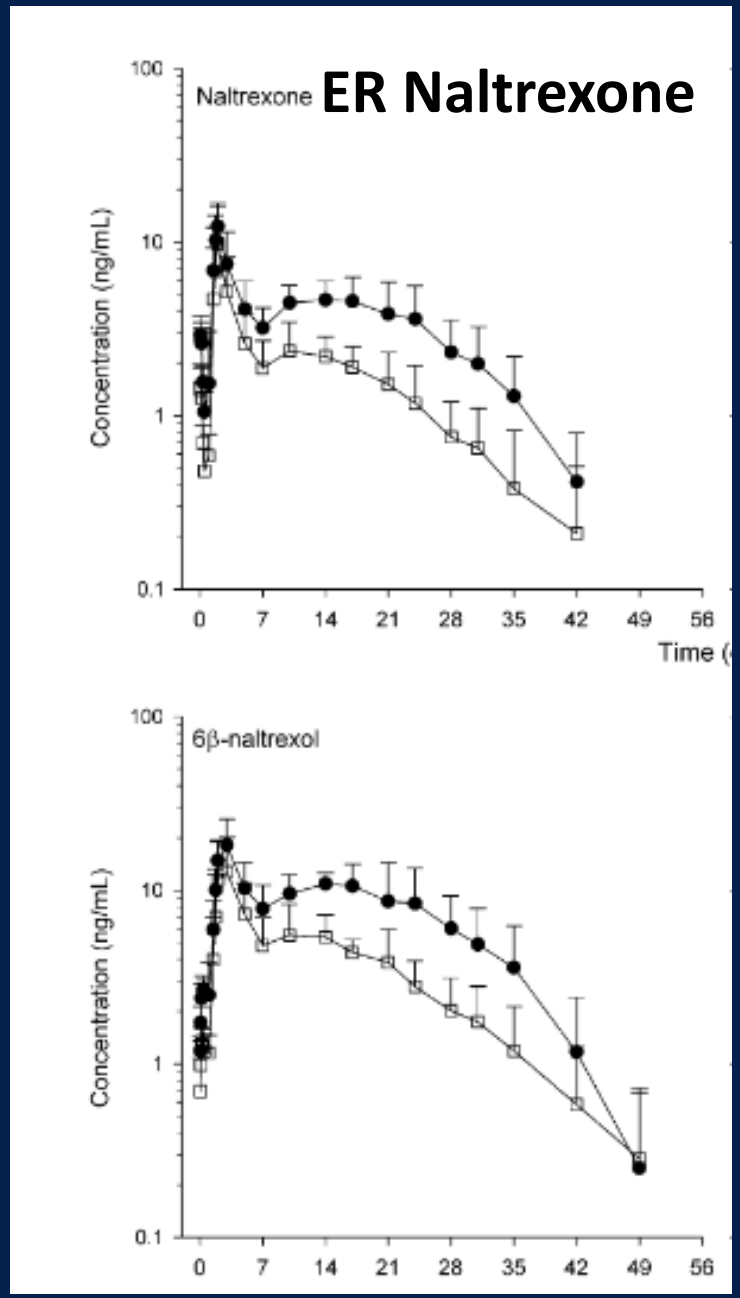
Terg, et al. Efficacy and Safety of oral naltrexone (50mg) for pruritis of cholestasis, crossover DB-RCT

Table 2. Biochemical and clinical data before and after 2 weeks of naltrexone treatment[a]

	Before	After[b]
Serum bilirubin (*N*: <1.2mg/dl)	2.09±2.32	2.29±2.86
Serum albumin (*N*: >3.5 g/dl)	3.73±0.41	3.70±0.59
Prothrombin time (*N*: >70%)	96±8	94±12
AST (*N*: <47 UI/ml)	109±69	88±53
ALT (*N*: <47 UI/ml)	130±88	108±82
Alkaline phosphatase(*N*: <300 UI/ml)	1255±753	1266±932
GGT (*N*: <36 UI/ml)	308±221	296±231
Creatinine (<1.6 mg/dl)	0.70±0.14	0.71±0.10

Terg, et al. Journal of Hepatology, 2002

5mg/kg/month



ER Naltrexone

~20mg/kg /month

Oral Naltrexone

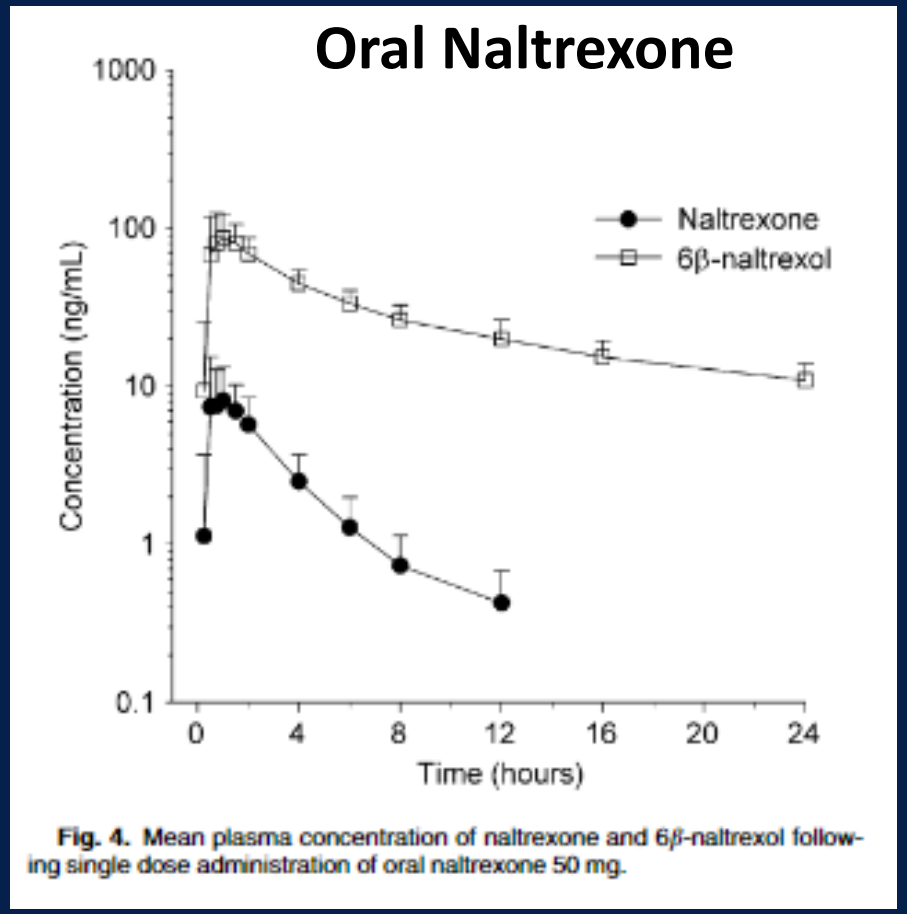


Fig. 4. Mean plasma concentration of naltrexone and 6β-naltrexol following single dose administration of oral naltrexone 50 mg.

Dunbar, et al. Alcoholism, 2006

Emerging Evidence for use of naltrexone in Liver Disease

- 100 patients in India with compensated cirrhosis
- Double blind, RCT, oral naltrexone 50mg/day
- 3 months, 64% abstinent with naltrexone vs 22% placebo
- 6 months, 22% abstinent with naltrexone vs 8% placebo
- No incidence of worsening liver disease

Alla M, et al. Abstract GS-008-YI: Naltrexone is safe and effective in achieving abstinence and reducing alcohol craving in cirrhotic patients: A double blind randomized placebo-controlled trial. Presented at: EASL Congress; June 21-23, 2023; Vienna (hybrid meeting).

Emerging Evidence for use of naltrexone in Liver Disease

- 100 patients with cirrhosis and active alcohol use
- Double blind, RCT
- 96 pts randomized to oral naltrexone (50mg) or placebo x 12 weeks
- 7.1% naltrexone group had new-onset decompensation
  - Experienced “significant reductions” in Child Pugh and MELD scores
- 28.6% placebo group had new-onset decompensation

Varshney MK, et al. Analyzing new onset hepatic decompensation and long-term abstinence/craving in patients with alcohol associated liver diseases (AALD): A double bling randomized control trial (RCT) for effectiveness of self-administered 12 weeks 50 mg oral naltrexone vs. placebo, along with standard counselling. Presented at: The Liver Meeting; Nov. 10-14, 2023; Boston (hybrid meeting).

In sum, safety of naltrexone in LD

- Liver toxicity occurred in 1 study in 6 male obese patients at high doses of naltrexone (300mg), *Mitchell, Biol Psychiatry,1987*
- FDA Black Box warning *lifted* in 2013

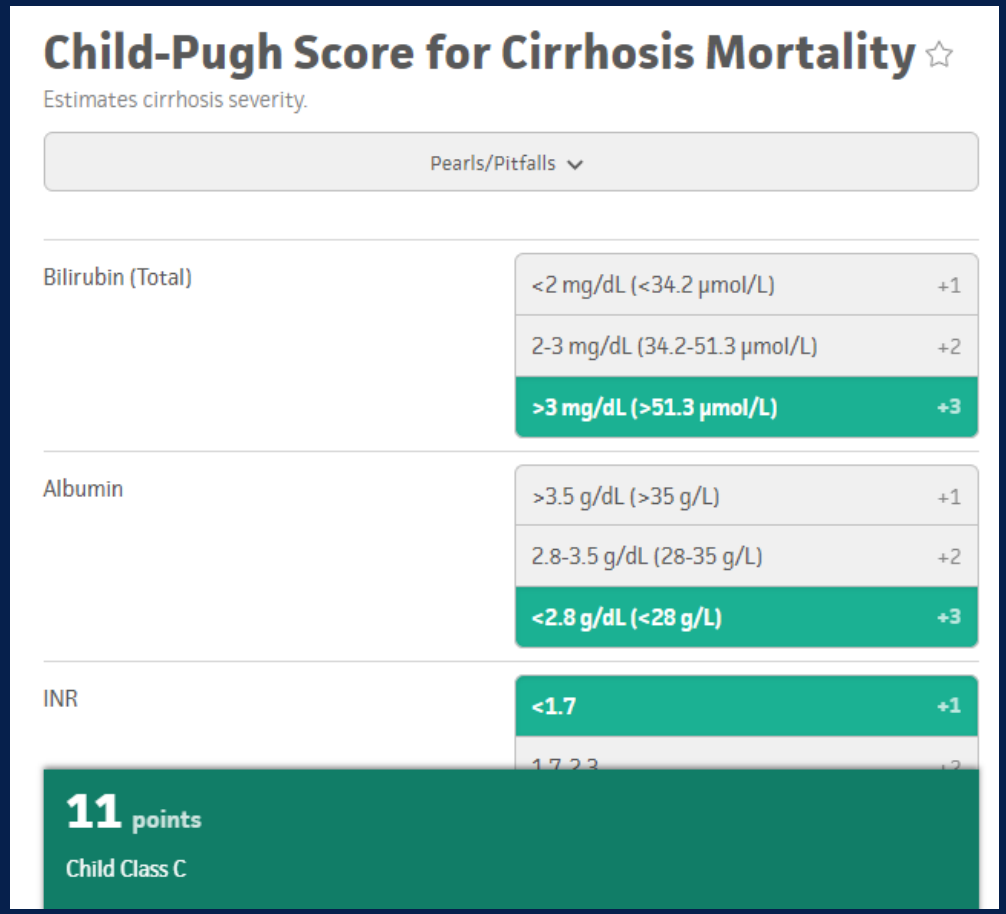
- Use and monitor LFTs periodically in patients with compensated liver disease and those with functional compromise (Child-Pugh Class B)
- Consider and use with caution in patients with Child-Pugh class C (decompensated disease)
- Weigh the risks and benefits of treatment
- If tolerating oral naltrexone, safe to use IM naltrexone due to lower dose exposure over time

Would you recommend naltrexone for this patient? If not, what can you recommend?

Goal: abstinence, liver transplant

Total Bilirubin	4.0
Albumin	2.7
AST	250
ALT	180
INR	1.5

Moderate ascites
No Encephalopathy
No varices



Case 2

- 47 yo male stockbroker with severe alcohol use disorder complicated by two prior hospitalizations for acute pancreatitis, now presenting with same. After safely managing alcohol withdrawal symptoms and providing supportive care for his pancreatitis, you begin a discussion about MAUD. He has previously tried both oral and XR-naltrexone.
- He lives with his wife, who, while supportive, is exasperated by his numerous relapses.
- As he is worried he will lose his job “permanently” if he slips up again, his goal is abstinence.

- Labs
- AST 238 → 102
- ALT 65 → 47
- Total bili 2.3 → 1.6
- INR 1.3
- Albumin 3.7
- Platelets 165
- RUQ US: fatty liver
- Child-Pugh Class A

Which MAUD is best for him?

Medications for Alcohol Use Disorder

Medication	Outcome	No. of studies	No. of Participants	NNT (95% CI)#	Strength of Evidence
Acamprosate	Return to any drinking	20	6380	**11 (1-32)**	Moderate
	Return to heavy drinking	7	2496	NA	Moderate (no effect)
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#NNT to prevent 1 person from returning to any or heavy drinking
*Caveats to be explained later in the presentation

McPheeters M, et al. JAMA 2023

Mixed Messages

Disulfiram?

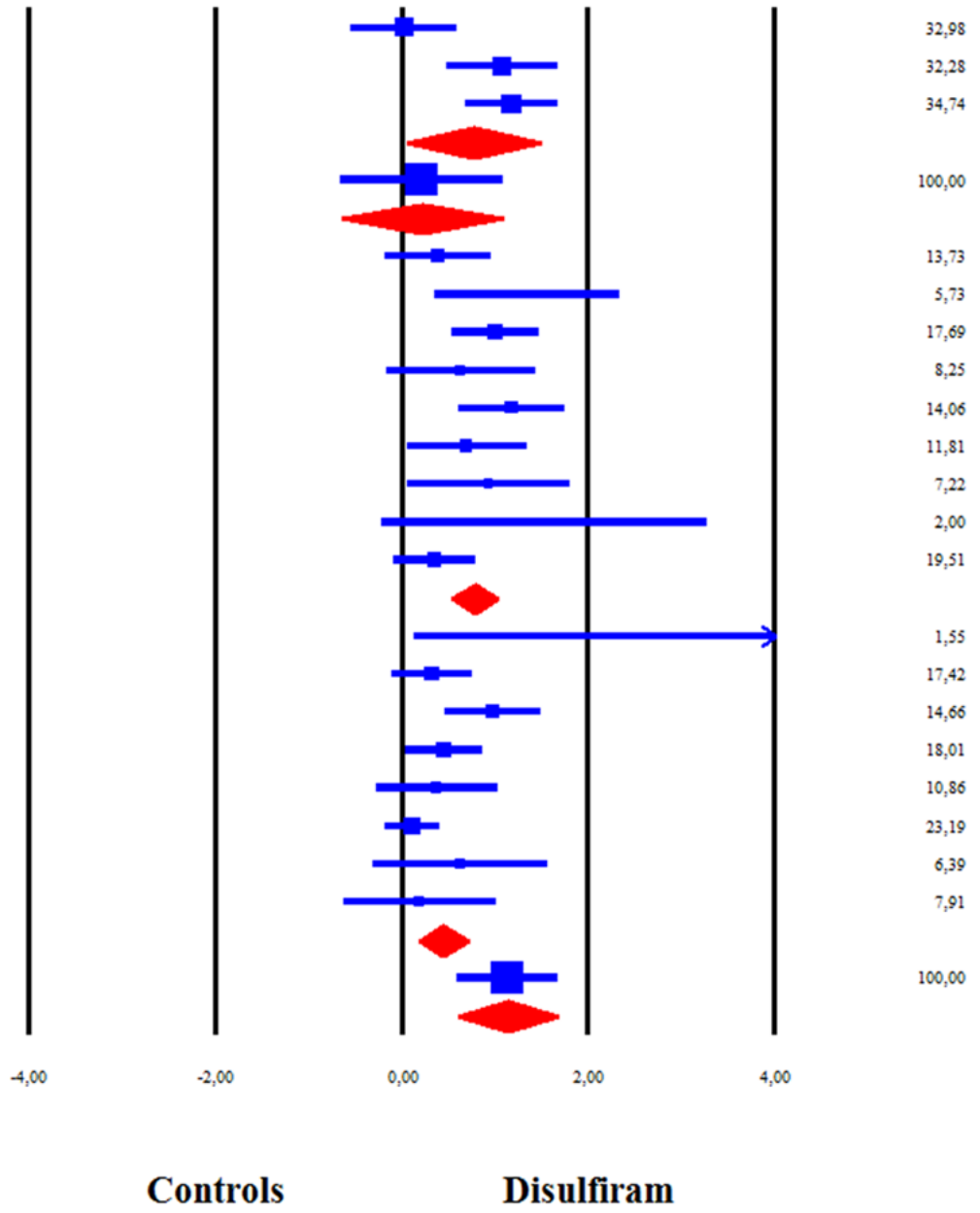
- Efficacy?
- Safety?

Disulfiram

Figure 3. Meta-analysis for blinded versus open-label RCTs. Meta-analysis of Hedges' g effect-size comparing the efficacy of disulfiram and controls in blinded versus open-label RCTs.
doi:10.1371/journal.pone.0087366.g003

Skinner, 2014, PLoS ONE 9(2)

Group by Subgroup within study	Study name	Controls	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Acamprosate	Bardeleben et al 1999	Acamprosate	0,018	0,286	0,082	-0,543	0,579	0,063	0,950	32,98
Acamprosate	De Sousa & De Sousa 2005	Acamprosate	1,070	0,301	0,091	0,480	1,660	3,555	0,000	32,28
Acamprosate	Laaksonen et al 2008	Acamprosate	1,172	0,247	0,061	0,688	1,656	4,745	0,000	34,74
Acamprosate			0,759	0,368	0,135	0,038	1,479	2,063	0,039	
GHB	Nava et al 2006	GHB	0,208	0,440	0,194	-0,654	1,070	0,473	0,636	100,00
GHB			0,208	0,440	0,194	-0,654	1,070	0,473	0,636	
Naltrexone	Bardeleben et al 1999	Naltrexone	0,385	0,289	0,084	-0,181	0,951	1,332	0,183	13,73
Naltrexone	Carroll et al 1993	Naltrexone	1,341	0,501	0,251	0,359	2,323	2,677	0,007	5,73
Naltrexone	Laaksonen et al 2008	Naltrexone	0,998	0,238	0,057	0,532	1,464	4,193	0,000	17,69
Naltrexone	Nava et al 2006	Naltrexone	0,626	0,404	0,163	-0,166	1,418	1,550	0,121	8,25
Naltrexone	De Sousa & De Sousa 2004	Naltrexone	1,178	0,284	0,081	0,621	1,735	4,148	0,000	14,06
Naltrexone	De Sousa & De Sousa 2008	Naltrexone	0,693	0,321	0,103	0,064	1,322	2,159	0,031	11,81
Naltrexone	De Sousa & Jagtap 2009	Naltrexone	0,923	0,438	0,192	0,065	1,781	2,107	0,035	7,22
Naltrexone	Grassi et al 2007	Naltrexone	1,516	0,887	0,787	-0,222	3,254	1,709	0,087	2,00
Naltrexone	Petrakis et al 2005	Naltrexone	0,347	0,219	0,048	-0,082	0,776	1,584	0,113	19,51
Naltrexone			0,770	0,128	0,016	0,518	1,022	5,999	0,000	
no disulfiram	Grassi et al 2007	no disulfiram	2,188	1,050	1,103	0,130	4,246	2,084	0,037	1,55
no disulfiram	Petrakis et al 2005	no disulfiram	0,318	0,216	0,047	-0,105	0,741	1,472	0,141	17,42
no disulfiram	Carroll et al 1998	no disulfiram	0,974	0,257	0,066	0,470	1,478	3,790	0,000	14,66
no disulfiram	Chick et al 1992	no disulfiram	0,452	0,208	0,043	0,044	0,860	2,173	0,030	18,01
no disulfiram	Fuller & Roth 1979	no disulfiram	0,365	0,330	0,109	-0,282	1,012	1,106	0,269	10,86
no disulfiram	Fuller et al 1986	no disulfiram	0,103	0,145	0,021	-0,181	0,387	0,710	0,477	23,19
no disulfiram	Gerrein et al 1973	no disulfiram	0,622	0,474	0,225	-0,307	1,551	1,312	0,189	6,39
no disulfiram	Ulrichsen et al 2010	no disulfiram	0,184	0,413	0,171	-0,625	0,993	0,446	0,656	7,91
no disulfiram			0,431	0,134	0,018	0,169	0,694	3,219	0,001	
Topiramate	De Sousa et al 2008	Topiramate	1,125	0,272	0,074	0,592	1,658	4,136	0,000	100,00
Topiramate			1,125	0,272	0,074	0,592	1,658	4,136	0,000	



Alcohol & Alcoholism Vol. 43, No. 1, pp. 53–61, 2008
Advance Access publication 27 October 2007
doi:10.1093/alcalc/agm136

A RANDOMIZED, MULTICENTRE, OPEN-LABEL, COMPARATIVE TRIAL OF DISULFIRAM, NALTREXONE AND ACAMPROSATE IN THE TREATMENT OF ALCOHOL DEPENDENCE

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Laaksonen, et al. Alc Alc, 2008

Table 2. Drinking outcomes during continuous medication period (up to 12 weeks)

	ACA	DIS	NTX
Time (days) to first HDD, mean ± SD (n)	17.6 ± 22.0 (44)	46.6 ± 27.5 (33)**	22.0 ± 22.0 (47)
Time (days) to first drinking, mean ± SD (*N*)	11.4 ± 17.0 (50)	30.4 ± 27.8 (39)*	16.2 ± 20.2 (50)
Abstinence days/week, mean ± SD (*N*)	4.5 ± 2.1 (52)	6.3 ± 0.9 (54 ***)	4.6 ± 2.0 (53)

* Significance DIS > NTX and ACA; $P = 0.0002$.
** Significance DIS > NTX and ACA ($P < 0.0001$).
*** Significance DIS > NTX and ACA ($P < 0.0001$); difference between weeks ($P = 0.001$).

Laaksonen, et al. Alc Alc, 2008

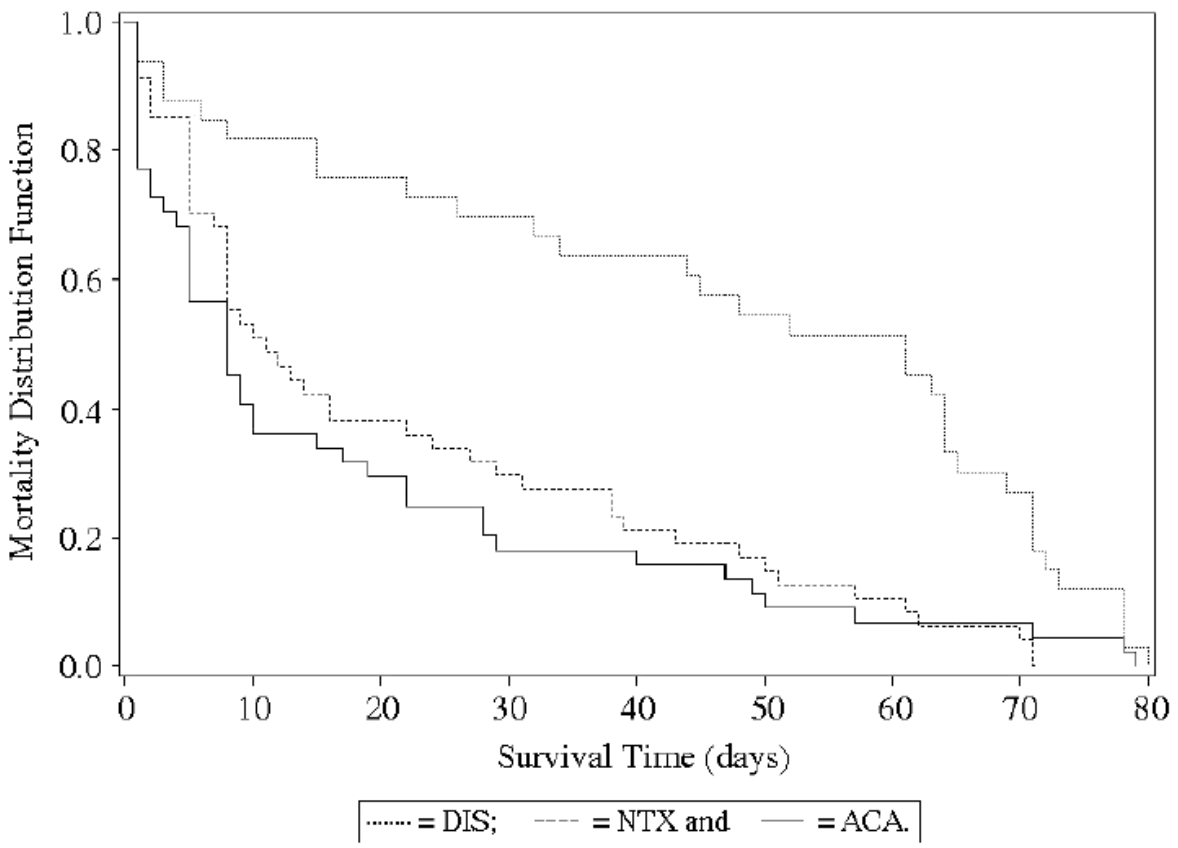

Fig. 2. Time to first heavy drink (days) during the continuous medication period (1–12 weeks). Kaplan–Meier survival analysis on the start of heavy drinking. Significant difference between DIS ($P = 0.001$) and others.

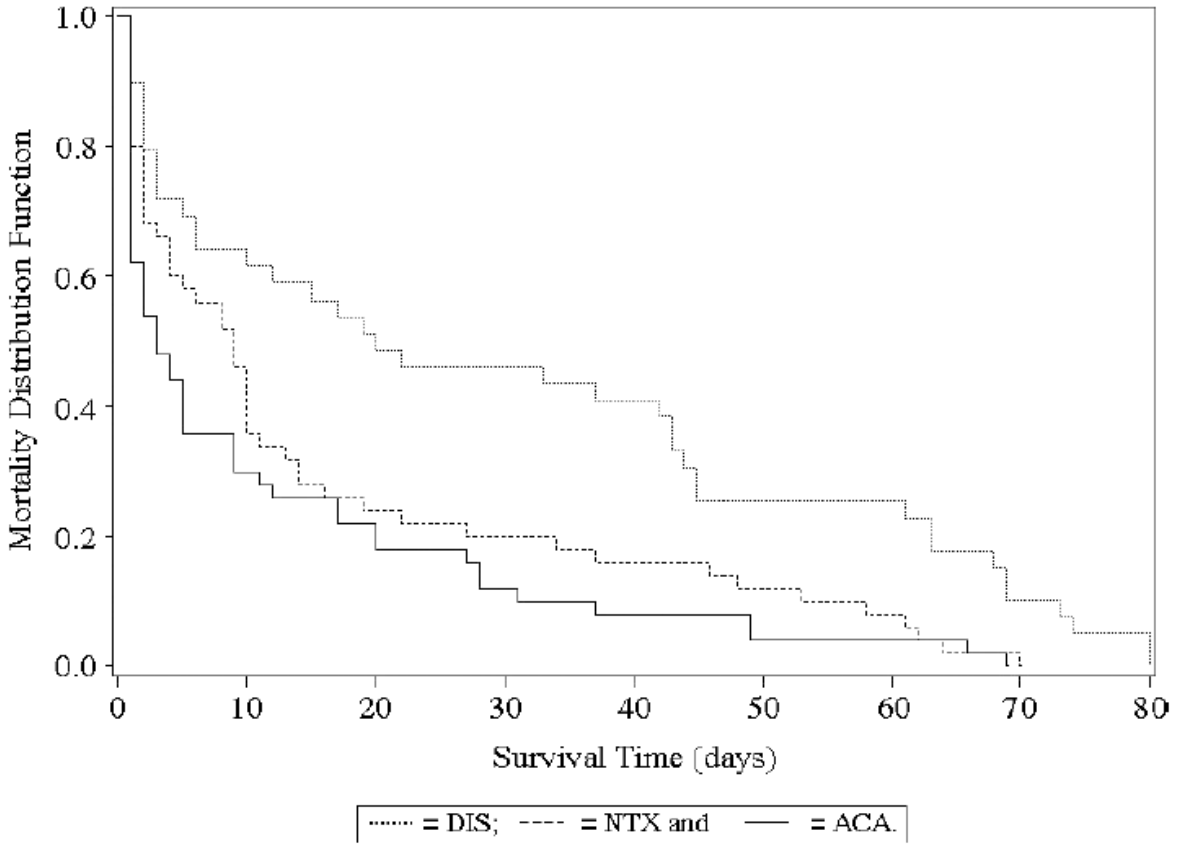

Fig. 3. Time to first drink (days) during the continuous medication period (1–12 weeks). Kaplan–Meier survival analysis when the first drinking started. Significant difference between DIS ($P = 0.0002$) and others.

Laaksonen, et al. Alc Alc, 2008

Safety of disulfiram

Brewer, *Addiction Biology,* 1999; Brewer, *Alcohol and Alcoholism*, 2017; Skinner, *PLOS ONE*, 2014; Alharbi, *Addict Disord*, 2013

Summary

- Offer medications for AUD to individuals with liver disease
- MAUD overall reduces mortality and progression of liver disease
- Offer naltrexone and XR naltrexone to individuals with Child Pugh A and B LD, consider in Child Pugh C
- Offer disulfiram as a first line treatment to individuals with Child Pugh A and B liver disease
- Consider combination therapy of MAUD

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