AUD Treatment Considerations in Liver Disease: Pharmacotherapy, Polysubstance Use, & Comorbid Conditions

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Faculty/Presenter Disclosure

- **Faculty:** Dr Gerald Scott Winder

- **Relationships with financial sponsors:**
  - **Any direct financial relationships including receipt of honoraria:** One-time honoraria for Columbia University, University of Pennsylvania, AASLD The Liver Meeting 2020-22. Development of online curricula for AASLD. Consultation for Alexion.
  - **Memberships on advisory boards or speakers' bureau:** Professional Advisory Board for the Epilepsy Foundation of Michigan.
  - **Patents for drugs or devices**: N/A
  - **Other: financial relationships/investments** – N/A

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- This program has not received any financial support

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Mitigating Potential Bias

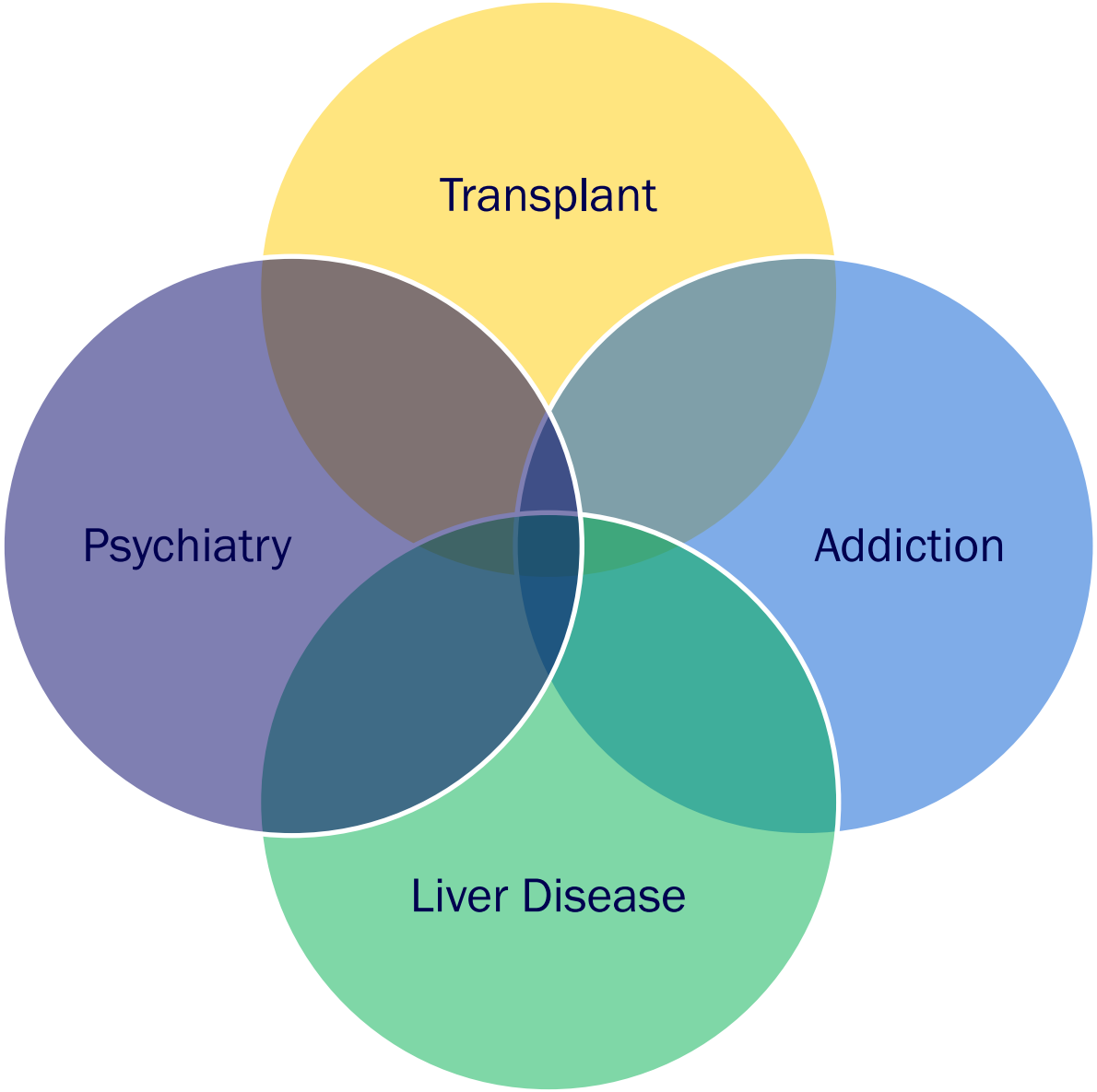
- Material/Learning Objectives and the session description were developed and reviewed by a Planning Committee responsible for overseeing the program's needs assessment and subsequent content development to ensure accuracy and fair balance.
- Information/recommendations in the program are evidence- and/or guidelines-based, and opinions of the independent speakers will be identified as such. Generic names, followed by trade names will be used for any products mentioned in the presentation.

Outline

- Introduction, risks and benefits of AUD pharmacotherapies
- Advantages of concurrent psychotherapies and pharmacotherapies
- First-line therapies for comorbid anxiety, depression, insomnia, and polysubstance use in ALD patients
- Nuances of AUD treatment geriatric and homeless populations

Introduction

AUD in liver disease is a busy intersection!



A pertinent epidemiological backdrop

- 40% liver patients depressed on GDS[1]
- 33% of OLT recipients have depression ± anxiety[2]
- Increasing or persisting depression doubled post-OLT mortality[3]

AUD patients at lifetime risk for[6]:

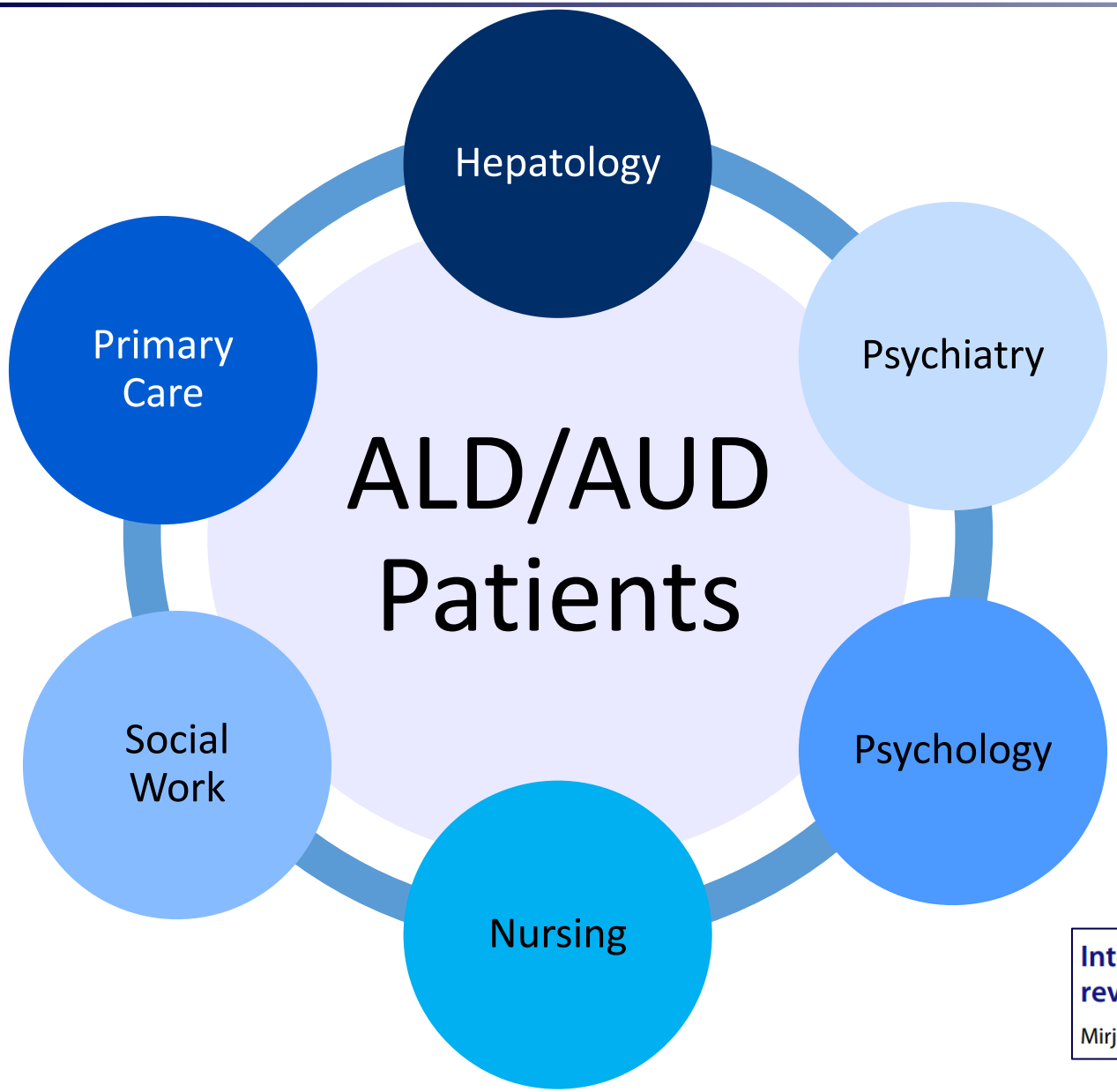
- Mood disorders (**OR 2.4** [2.20-2.71])
- Anxiety disorders (**OR 2.3** [2.11-2.61])
- Drug use disorders (**OR 10.4** [9.03-11.96])

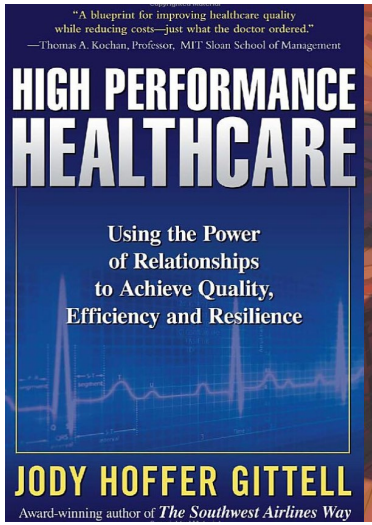
- Cirrhosis patients have ↑ rates of opioid, benzo, high-dose opioid, & opioid + benzo Rx[4]
- Insomnia prevalence in cirrhosis between 26%-77%[5]

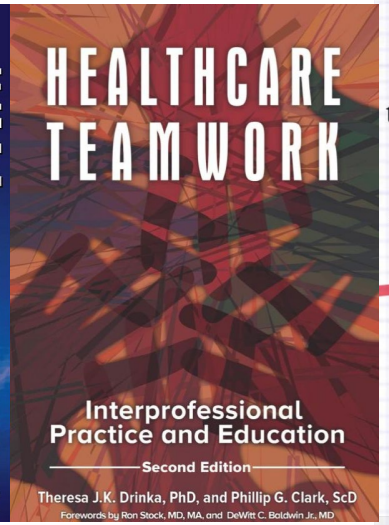
- Marijuana and tobacco use are both increasing in the liver population[7,8]
- Polysubstance use is very common in ALD and HCV populations[9]
- Psych treatment access in ALD is low (10% get a visit, 0.8% Rx)[10]

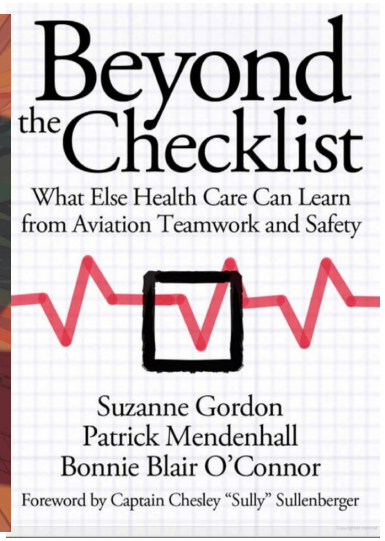
1. Cron DC et al. American journal of transplantation. 2016 Jun;16(6):1805-11
2. Corruble E et al. Journal of psychosomatic research. 2011 Jul 1;71(1):32-7
3. DiMartini A et al. American Journal of Transplantation. 2011 Jun;11(6):1287-95
4. Konerman MA, et al. BMJ Open Gastro. 2019 Apr 1;6(1):e000271
5. Peng JK et al. Palliative medicine. 2019 Jan;33(1):24-36
6. Hasin DS et al. Archives of general psychiatry. 2007 Jul 1;64(7):830-42
7. Likhitsup A et al. Clinical Transplantation. 2021 Apr 7:e14312
8. Likhitsup A et al. Liver Transplantation. 2019 Aug;25(8):1165-76
9. Dimartini A et al. Psychosomatics. 2004 Nov 1;45(6):517-23
10. Mellinger JL et al. Alcoholism: Clinical and Experimental Research. 2019 Feb;43(2):334-41.

Care integration is ideal for ALD comorbidity treatment









Operating Room Teamwork among Physicians and Nurses: Teamwork in the Eye of the Beholder

Martin A Makary, MD, MPH, J Bryan Sexton, PhD, Julie A Freischlag, MD, FACS, Christine G Holzmueller, BLA, E Anne Millman, MS, Lisa Rowen, RN, DNSc, Peter J Pronovost, MD, PhD

The role of teamwork and communication in the emergency department: A systematic review

Emily Kilner (Physiotherapy student) [a],
Lorraine A. Sheppard PhD, MBA, BAppSc (Physio) (Professor) [a,b,*]

Interprofessional teamwork and team interventions in chronic care: A systematic review

Mirjam Körner[a], Sarah Bütof[b], Christian Müller[a,c], Linda Zimmermann[d], Sonja Becker[a], and Jürgen Bengel[e]

Ascending tiers of integration, coordination

- Psychiatry and liver clinicians treat the same ALD patients in the same clinic at the same time
- **Example**: An embedded psychologist sees all new and established ALD patients alongside a hepatologist and hepatology nurse practitioner

- Collaborative ALD education and workflows developed within an institution
- **Example**: University departments of psychiatry and hepatology jointly update addiction clinic programming to include liver health and referrals

- Regular virtual, in-person meetings of liver and psychiatric clinicians which include ALD case presentations, education, relationship building
- **Example**: An academic medical center hosts quarterly online hour-long ALD seminars inviting regional liver and psychiatric colleagues

- Liver and addiction clinicians are aware of each other's services
- **Example**: A hepatologist regularly refers patients to an addiction clinic in town and periodically contacts its clinicians about patient progress

- Psychiatry and hepatology have no formal affiliation or collaboration
- Less understanding of and appreciation for other specialties' expertise
- **Example**: Liver and psychiatry clinics exist in the same city

Winder et al JCEH 2022

AUD Medications

AUD Rx Treatment – US FDA-approved

Rx	Metabolism & Excretion	ALD Considerations
Disulfiram	**M**: hepatic **E**: 70% renal	• Severe (sometimes fatal) hepatitis and/or hepatic failure requiring transplant • Reports of neuropathy, psychosis • Not recommended for use in ALD
Naltrexone	**M**: hepatic **E**: mostly renal, 2% fecal	• US/Canadian warnings re: use in liver disease • We are using PO formulation in select compensated Child-Pugh A; ⃠ IM form • Potential drug and metabolite accumulation in cirrhosis • Interaction w/ opioids • Meta-analysis showing moderate efficacy
Acamprosate	**M**: none **E**: renal	• No evidence of hepatotoxicity • Safer than baclofen in ALD? (Tyson 2022) • Meta-analysis showing moderate efficacy • ↓333mg TID when CrCl 30-50 mL/min, ⃠ CrCl <30mL/min

"Unexplored are the combinations of pharmacotherapies and behavioral treatments and of different medications in patients with AUD and ALD." (Leggio & Lee 2017)

Leggio L, Lee MR. The American Journal of Medicine. 2017;130:124-134
Addolorato G et al. Journal of Hepatology. 2016 Sep 1;65(3):618-30
Roesner S et al. Acamprosate for alcohol dependence. Cochrane Database of Systematic Reviews. 2010(9)
Kranzler HR, Van Kirk J. Alcohol Clin Exp Res. 2001 Sep;25(9):1335-41
Streeton C, Whelan G. Alcohol Alcohol. 2001 Nov-Dec;36(6):544-52
Bertolotti M et al. Journal of hepatology. 1997 Sep 1;27(3):505-11
Tyson LD, et al. European Journal of Gastroenterology & Hepatology. 2022 Mar 31;34(5):567-75.

AUD Rx Treatment – off-label

Rx	Metabolism & Excretion	ALD Considerations
Gabapentin	**M:** none **E:** 75% renal, 25% fecal	• No evidence of hepatotoxicity • Theoretical abuse potential • Dose reductions in renal impairment
Topiramate	**M:** limited hepatic **E:** renal	• No evidence of hepatotoxicity though could affect liver function • Could worsen or confound hepatic encephalopathy • Dosing reductions may be required in hepatic impairment • Dosing reductions in renal impairment
Baclofen	**M:** limited hepatic **E:** renal	• No evidence of hepatotoxicity • Supported use in ALD by randomized, controlled trials (Addolorato, *Lancet* 2007) & observational studies • Dose reductions in renal impairment
Varenicline	**M:** minimal **E:** renal	• No evidence of hepatotoxicity • Dosing reductions in renal impairment
Ondansetron	**M:** extensive hepatic **E:** mostly renal, ~25% fecal	• Possible link with hepatotoxicity (indeterminate) • Dosing reductions in severe hepatic impairment

Leggio L, Lee MR. The American Journal of Medicine. 2017;130:124-134
Addolorato G et al. Journal of Hepatology. 2016 Sep 1;65(3):618-30.

Disulfiram

- Blocks alcohol oxidation at acetaldehyde
- US Boxed Warning regarding administration:
  - Never during alcohol intoxication (within 12 hours)
  - Without full patient knowledge and social support awareness
- Severe (sometimes fatal) hepatitis and/or liver failure resulting in transplantation; (rare; 1/25,000)
- Reversible hepatotoxicity if drug stopped, monitor LFTs
  - before treatment
  - 2-week intervals x 2 months
  - 3 to 6-month intervals afterward
- Avoid ("use with extreme caution") in patients with abnormal LFTs
- Also used for cocaine use disorder

Disulfiram Reaction:
(30 min → hours)

Flushing
Head, neck, chest pain
Nausea & vomiting
Diaphoresis
Palpitations
Dyspnea
Hyperventilation
Tachycardia
Hypotension & syncope
Weakness
Blurred vision
Confusion
Vertigo

Mohanty SR et al. Journal of clinical gastroenterology. 2004 Mar 1;38(3):292-5.
Fuller RK et al. Addiction. 2004 Jan;99(1):21-4.
Suh JJ et al. Journal of clinical psychopharmacology. 2006 Jun 1;26(3):290-302.

Naltrexone

- Best studied AUD medication; also treats OUD
- Mu-opioid receptor antagonist; contraindicated with opioids
  - Wait 7-14 days after last opioid use
  - Pre-operatively, stop oral ≥3 days prior, IM naltrexone ≥30 days prior
  - Avoid during acute hepatitis, acute liver failure
- Oral dosing: 50mg daily and monitor for side effects
- IM dosing: 380mg every 4 weeks (some start with PO to gauge tolerability)
- Meta-analysis of 53 RCTs (n=9140) found naltrexone significantly reduces relapse to any drinking and binge drinking

Jonas DE, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014 May 14;311(18):1889-900

Acamprosate

- Mechanism of action in AUD unclear; NMDA receptor co-agonist
  - Reduce neuronal hyperexcitability?
- 666mg three times daily
- Recommended for the achievement and maintenance of complete abstinence
- Meta-analysis of 27 RCTs (n=7519) found acamprosate reduced risk of **abstinent** patients returning to any drinking
  - did not reduce rates of binge drinking
  - Another meta-analysis (24 RCTs, n=6915) found acamprosate increased total abstinence duration
- Several other studies show acamprosate no different than placebo

Jonas DE, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014 May 14;311(18):1889-900
Rösner S, et al. Acamprosate for alcohol dependence. Cochrane Database Syst Rev. 2010;(9):CD004332
Burnette EM, et al. Novel agents for the pharmacological treatment of alcohol use disorder. Drugs. 2022 Feb;82(3):251-74.

Gabapentin

- Precise therapeutic mechanisms unknown
  - Inhibits selectively voltage-gated Ca++ channels
  - Enhances voltage-gated K+ channels
  - Modulates gamma-aminobutyric acid (GABA) activity
- Meta-analysis of 7 RCTs found good evidence supporting ↓heavy drinking days
  - (but not any of the other 5 outcome measures: complete abstinence, relapse to heavy drinking, % days abstinent, drinks per day, GGT concentration)
  - dosage varied from 300 to 3600 mg/day; trial duration varied from 3 to 26 weeks
- May be particularly useful for AUD comorbidities
  - Anxiety, mild alcohol withdrawal, neuropathy, insomnia

Kranzler HR, et al. A meta-analysis of the efficacy of gabapentin for treating alcohol use disorder. Addiction. 2019 Sep;114(9):1547-55

Baclofen

- Acts on the γ-amino butyric acid (GABA) system as a $GABA_B$ agonist
- Approved for AUD in France in 2018 (off-label use elsewhere)
- Dose around 10mg TID
- Meta-analysis of 12 RCTs (n=703) showed that baclofen associated with higher abstinence rates
  - Did not increase abstinent days or decrease craving, heavy drinking, depression, or anxiety
- Meta-analysis of 13 RCTs (n=1492) indicated that baclofen associated with longer time to relapse and a larger percentage of abstinent patients
  - Higher the patient's drinking rate, the more effective the drug in reducing it
- Meta-analysis of 12 RCTs (n=1128) showed no difference from placebo

Rose AK, Jones A. Baclofen: its effectiveness in reducing harmful drinking, craving, and negative mood. A meta-analysis. Addiction. 2018;113(8):1396–406
Pierce M, et al. Efficacy, tolerability, and safety of low-dose and high-dose baclofen in the treatment of alcohol dependence: a systematic review and meta-analysis. Eur Neuropsychopharmacol. 2018;28(7):795–806
Minozzi S, et al. Baclofen for alcohol use disorder. Cochrane Database Syst Rev. 2018;11:CD012557

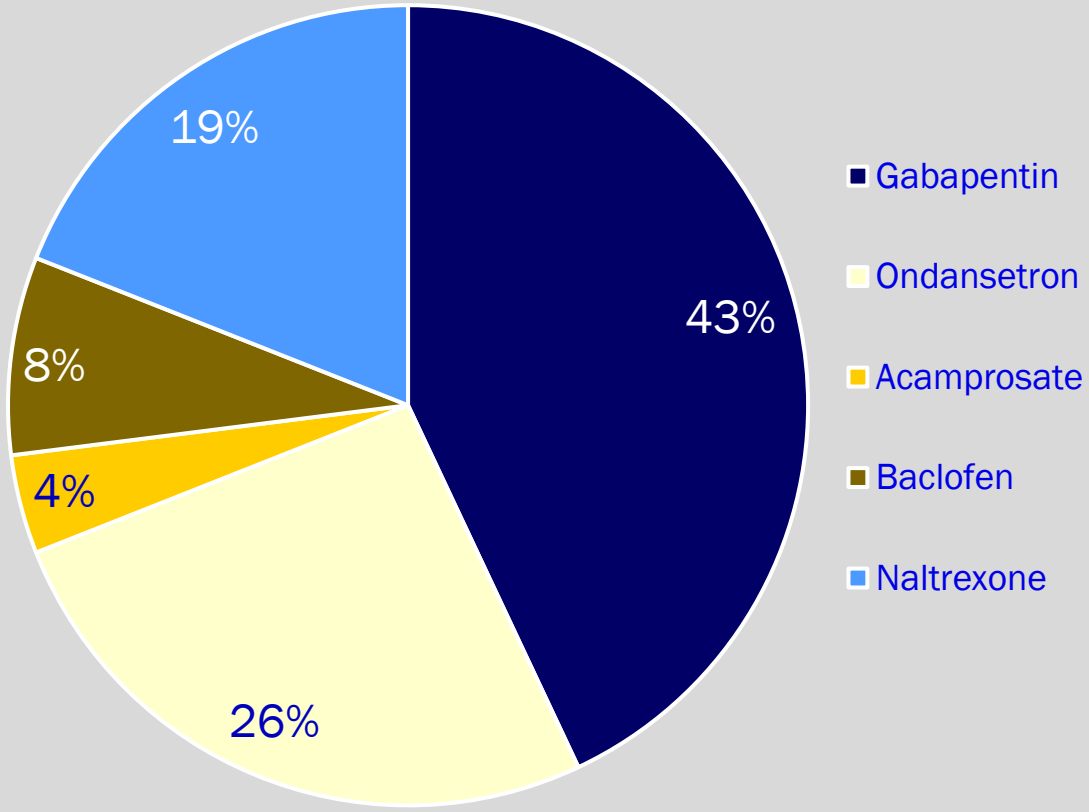
Topiramate

- Mechanism unclear
  - inhibits glutamate α-amino 3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) and kainate receptors and L-type calcium channels; enhances the inhibitory activity of GABA
  - attenuates dopaminergic activity mesolimbic reward circuits, thereby reducing both alcohol craving and withdrawal symptoms
- AUD dose around 300mg total daily dose
- 14-week RCT (n=371) found reductions in heavy-drinking days and improvements in various self-reported drinking-related outcomes
- Meta-analysis including 7 RCTs (n=1125) found topiramate increased number of days abstinence and decreased heavy-drinking days

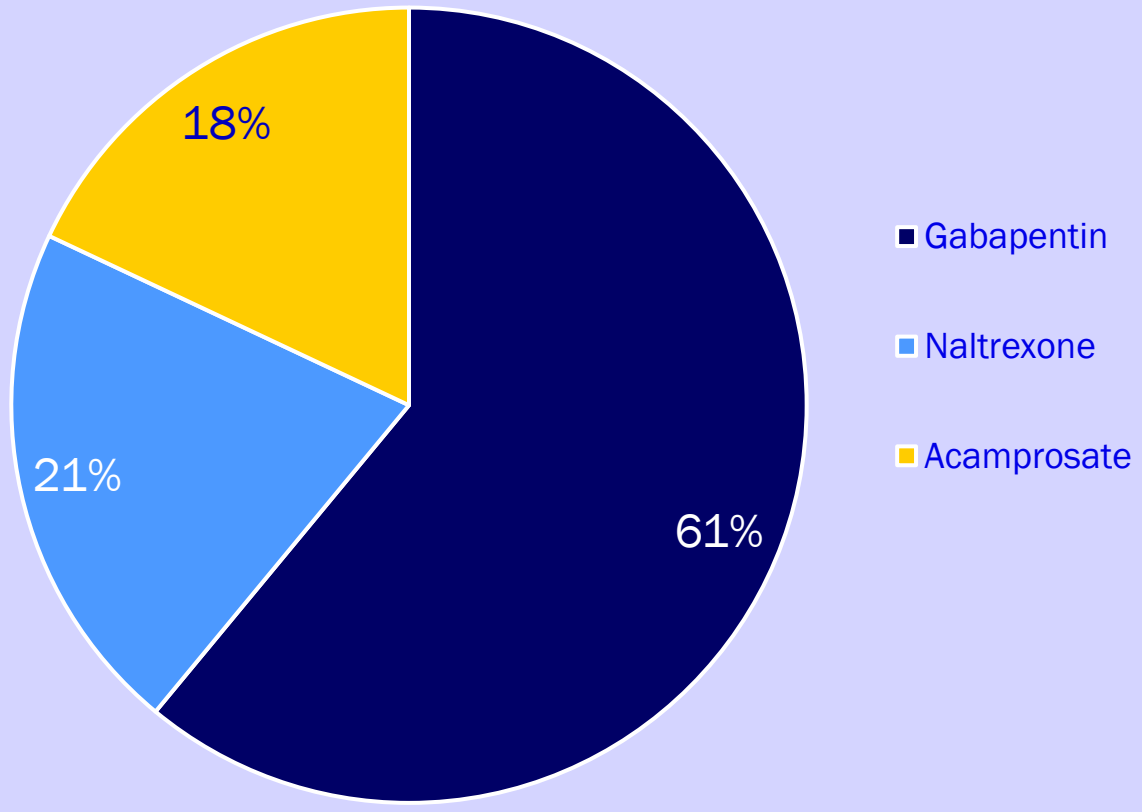
Johnson BA, Rosenthal N, Capece JA, Wiegand F, Mao L, Beyers K, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA. 2007;298(14):1641–51
Blodgett JC, et al. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. Alcohol Clin Exp Res. 2014;38(6):1481–8.

AUD medications used before & after ALD Clinic eval

AUD Rx Used Before Evaluation (n=29)



AUD Rx Prescribed in MAIN Clinic (n=29)

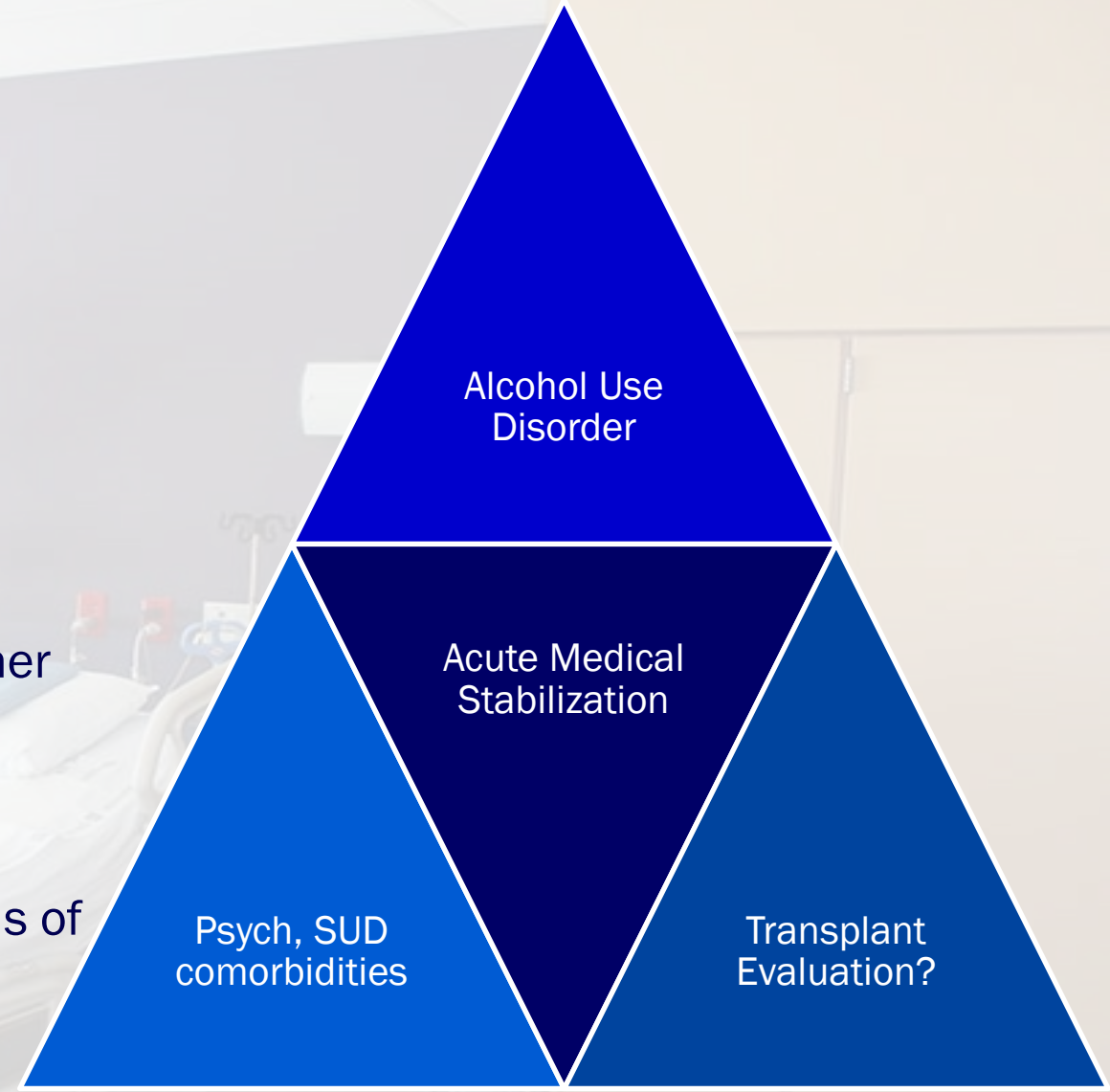


Mellinger JL et L. Feasibility and early experience of a novel multidisciplinary alcohol-associated liver disease clinic. Journal of Substance Abuse Treatment. 2021 Nov 1;130:108396.

Pharmacotherapy Cases

Inpatient AUD/ALD

- **Acute medical stabilization**
  - Alcohol withdrawal, altered mental status, agitation, other toxidromes
- **Alcohol use disorder**
  - Medications, insight & motivation, treatment preferences, tier of recommended treatment
- **Psych, SUD comorbidities**
  - Mood, anxiety, psychosis, suicide, polysubstance, other compulsive behaviors
- **Transplant evaluation?**
  - Urgent psych evaluation ahead of AMS, extra domains of evaluation, abstinence rather than harm reduction



Inpatient AUD/ALD

43yo female admitted with acute alcohol-associated hepatitis (Lille score 0.02) and BAL of 0.244.

Some new mild renal insufficiency and evening confusion and agitation.

Factor V trending upward; LFTs trending downward.

Reporting persistent, significant anxiety to nursing.

CIWA-Ar scores between 8-12

Inpatient AUD/ALD

Alcohol Withdrawal

- Track symptoms using a scale (e.g., CIWA-Ar); proactive tx for ↑risk withdrawal, reactive for ↓risk; weigh sedation risks from Rx against sx severity
- Severe agitation, autonomic sx⟶ *short-acting* benzos (e.g., lorazepam, oxazepam)
- Mild sx (i.e., CIWA-Ar <10): gabapentin (300mg q6 hours)

AUD Care

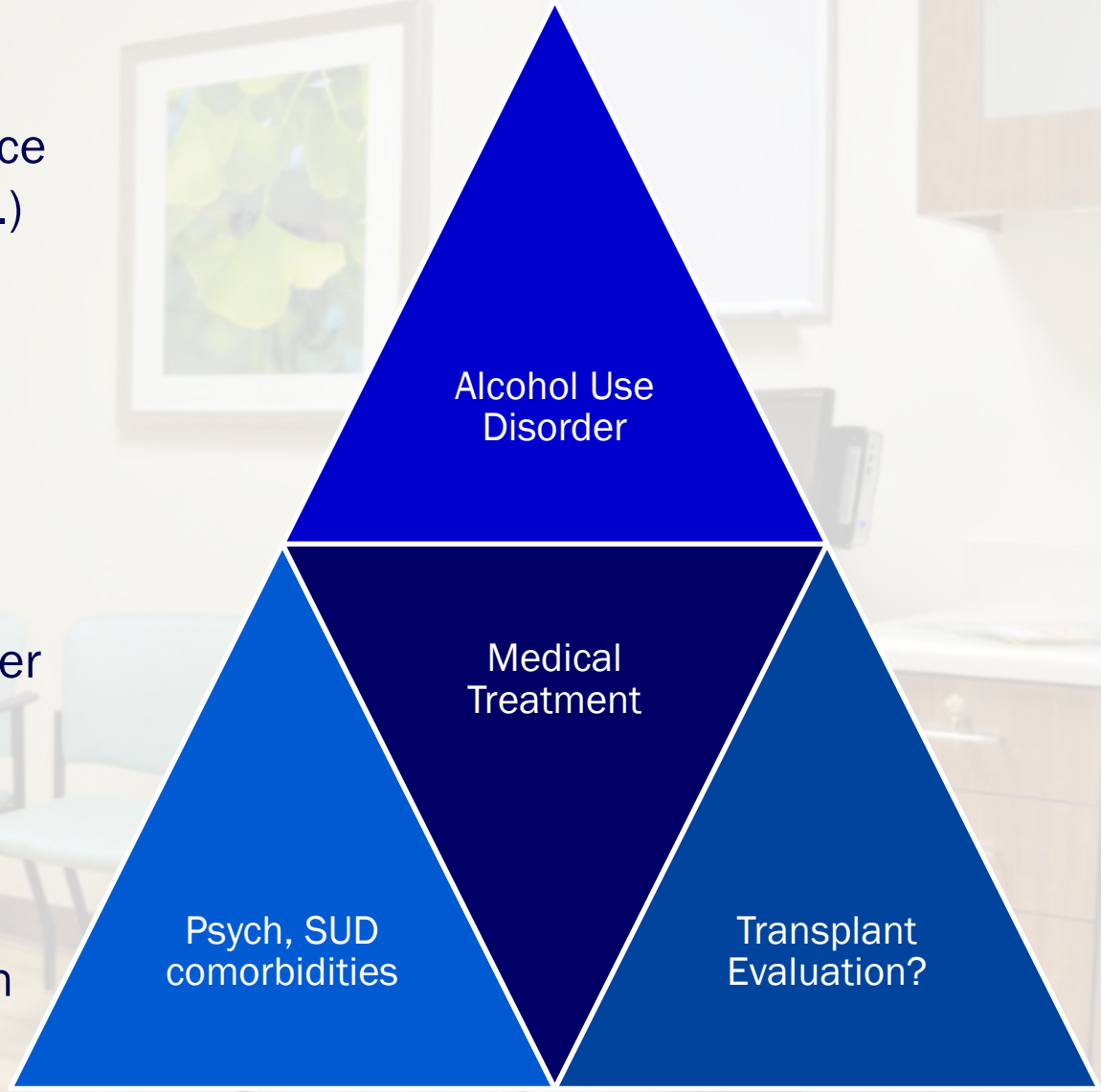
- Establish diagnosis, gather past history (what tx worked?), elicit preferences, query insurance coverage, gauge motivation, make realistic tiered recommendations given medical acuity, engage patient psychotherapeutically (e.g., MI) at bedside
- Based on liver and kidney function and clinical trajectory, consider AUD Rx

Transplant Eval?

- Is AMS evidence of hospital delirium, alcohol withdrawal, liver failure?
- Expedite psychosocial evaluation if AMS worsens, deemed aspect of ALF
- Less likely to use AUD Rx inpatient during early LT for AAH

Outpatient AUD/ALD

- **Medical treatment**
  - Stage of liver disease, kidney & liver function, presence of HE, other medical problems (HTN, obesity, DM, etc.)
- **Alcohol use disorder**
  - Medications, insight & motivation, treatment preferences, tier of recommended treatment
- **Psych, SUD comorbidities**
  - Mood, anxiety, psychosis, suicide, polysubstance, other compulsive behaviors
- **Transplant evaluation?**
  - Extra domains of evaluation, abstinence rather than harm reduction, assertive psych/SUD treatment given rigor and stress of transplant



Outpatient AUD/ALD

51yo male with a history alcohol-related pancreatitis and steatohepatitis and AUD

Normal renal function, preserved liver synthetic function

Last drink 2 months ago immediately prior to alcohol-related hospital admission (detox, ↑LFTs)

Reports frequent ongoing urges and dreams about drinking

Does not believe he has an “alcohol addiction,” alludes to drinking in moderation in the future

Not engaged in any AUD treatment, no affiliation with the recovery community

Outpatient AUD/ALD

Medical Treatment

- Outside EtOH withdrawal window
- Unlikely to need psych-SUD Rx adjustments
- Convey current, future *medical* risks regarding alcohol use
- Track toxicology

AUD Treatment

- Diagnostic AUD interview, careful drinking history
- Motivational interviewing
- Past tx, preferences
- Assertive Rx treatment (naltrexone)
- *Establish alliance!*

Transplant Evaluation?

- Likelihood of future decompensation?
- Prognosis to need a transplant?
- Adjust strength & type of recs by perceived transplant likelihood

Outpatient AUD/ALD with substantial comorbidities

55yo female with decompensated alcohol-related cirrhosis (HE, ascites, current MELD 21, Childs-Pugh C), DM (neuropathy, nephropathy), obesity, psychiatric hospitalizations for MDD and suicide attempts

Can’t remember last drink (positive PEth from last week [126 ng/mL])

Actively smoking nicotine and cannabis (latter for pain)

Patient and family report mood and confusion have been worse recently

Reports daily anxiety

Outpatient AUD/ALD with substantial comorbidities

Medical Treatment	AUD Treatment	Comorbidity Considerations	Transplant Evaluation?
• Assess withdrawal risk • Adjust psych/SUD Rx doses • Careful of sedation given HE • Clear understanding of liver disease severity & etiology • Convey current & future alcohol risks • Track toxicology	• Diagnostic AUD interview, careful drinking history • Motivational interviewing vs. confrontation • Past AUD treatment, preferences • Assertive AUD treatment (acamprosate, gabapentin, baclofen) • *Establish alliance!*	• Recent alcohol & cannabis use, neuropathy, anxiety, protracted EtOH withdrawal? (renally-dosed gabapentin) • Alcohol use, obesity (renally-dosed topiramate) • Nicotine use (renally-dosed varenicline) • CTP-C (avoid naltrexone) • Mood, anxiety (SSRI)	• Likelihood of transplant need? • Adjust strength, type of recs by transplant need • Center policies re: cannabis, nicotine, sobriety length • Mandatory AUD treatment per center policy? • Likelihood of psych sx recurrence?

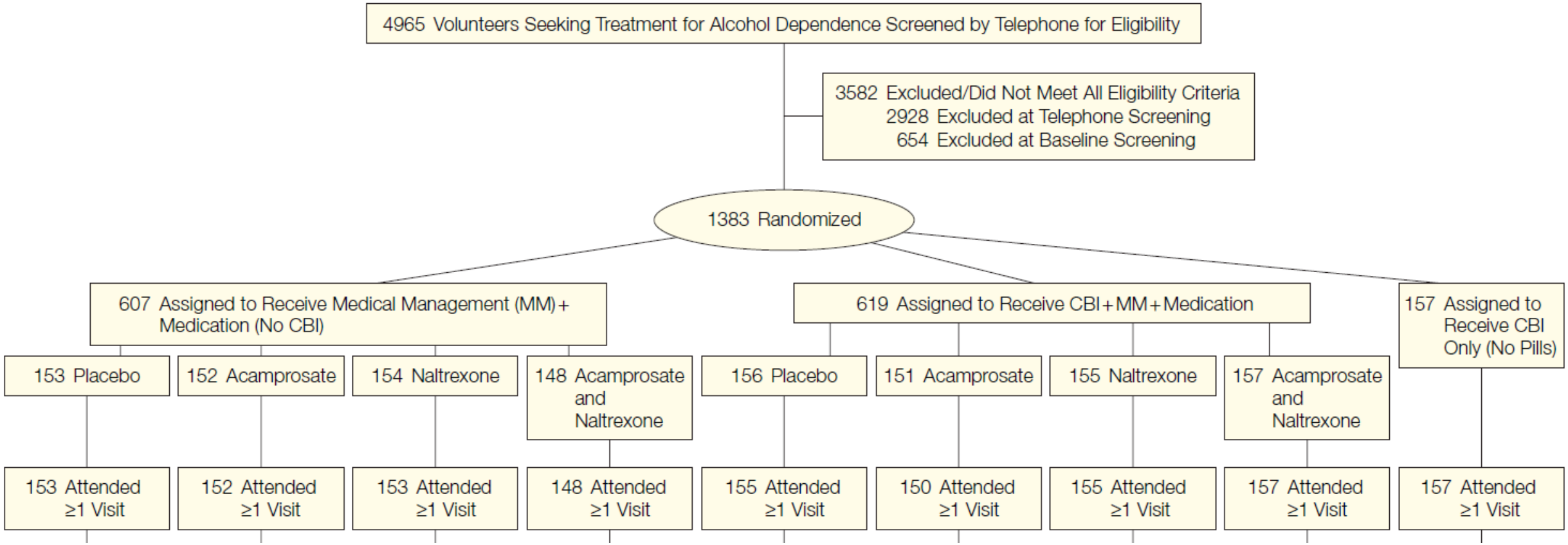
Combining AUD Psychotherapy & Medication

Does combining AUD Rx and therapy work?

MM – medical management
CBI – combined behavioral intervention

Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence

The COMBINE Study: A Randomized Controlled Trial



Anton RF et al. COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006 May 3;295(17):2003-17

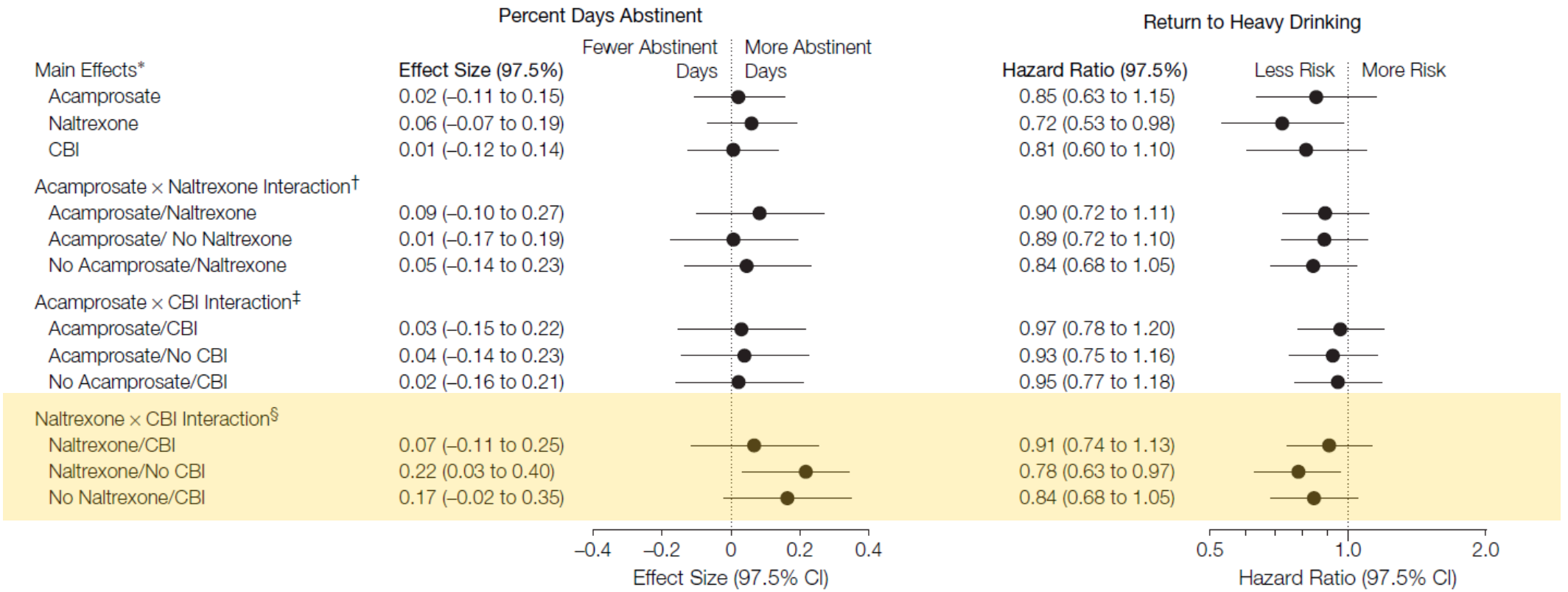
Does combining AUD Rx and therapy work?

CBI – combined behavioral intervention

Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence

The COMBINE Study: A Randomized Controlled Trial

Figure 2. Effect Size Estimates and Hazard Ratios for Primary Outcomes



Anton RF et al. COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006 May 3;295(17):2003-17

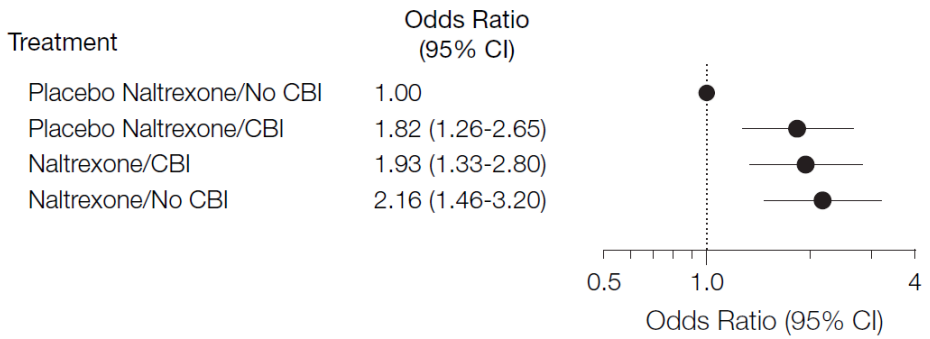
Does combining AUD Rx and therapy work?

CBI – combined behavioral intervention

Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence

The COMBINE Study: A Randomized Controlled Trial

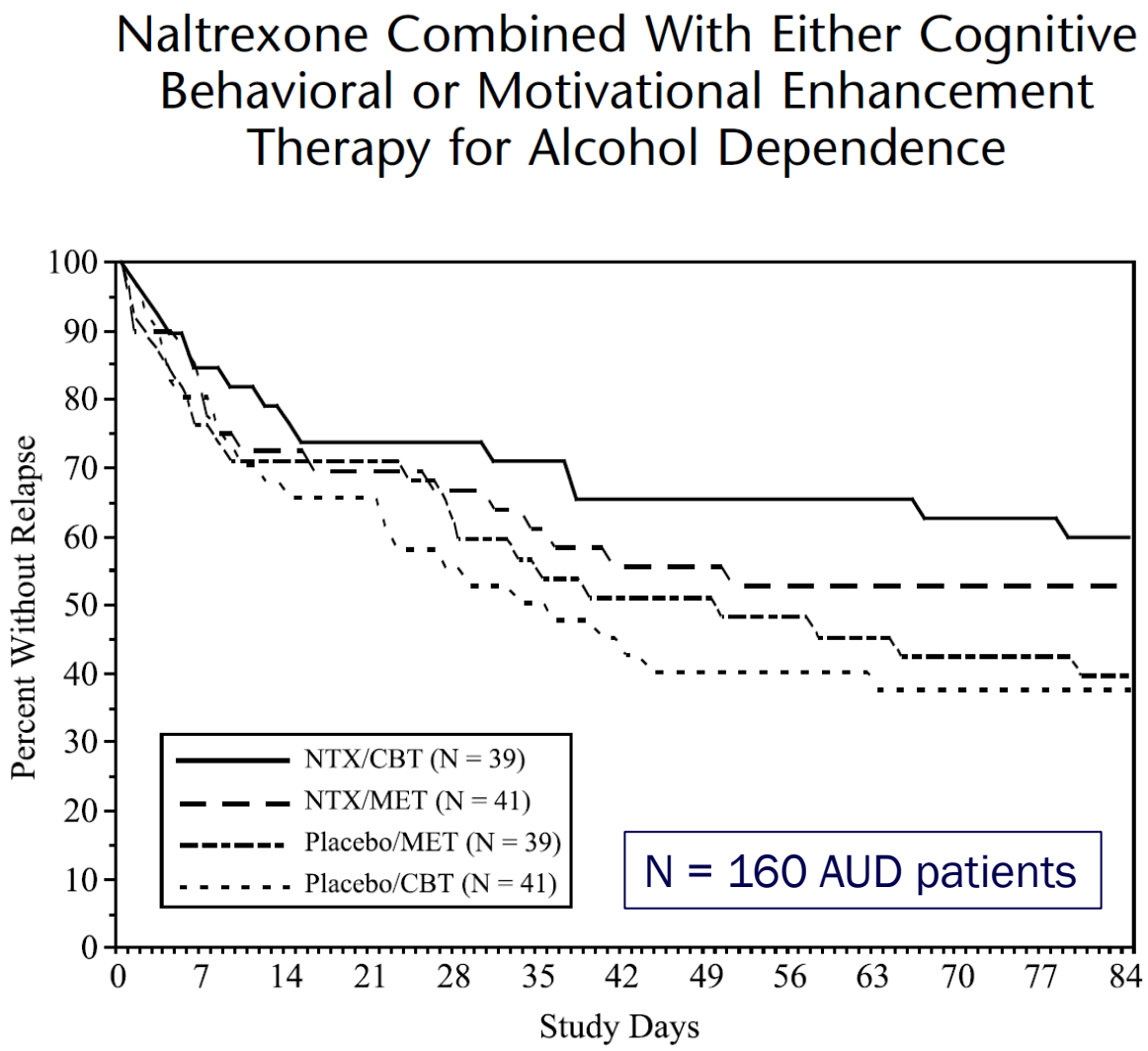
Figure 4. Odds Ratios for Good Composite Clinical Outcome at End of Treatment Compared With Placebo Naltrexone/No Combined Behavioral Intervention (CBI)



- More relapse in CBI alone
  - Adding pills, med mgmt more effective
- Acamprosate ☒ effect on drinking
  - No efficacy w/ naltrexone
- Naltrexone + CBI was *not* more effective together than alone
- Sex didn't affect treatment response

Anton RF et al. COMBINE Study Research Group. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006 May 3;295(17):2003-17

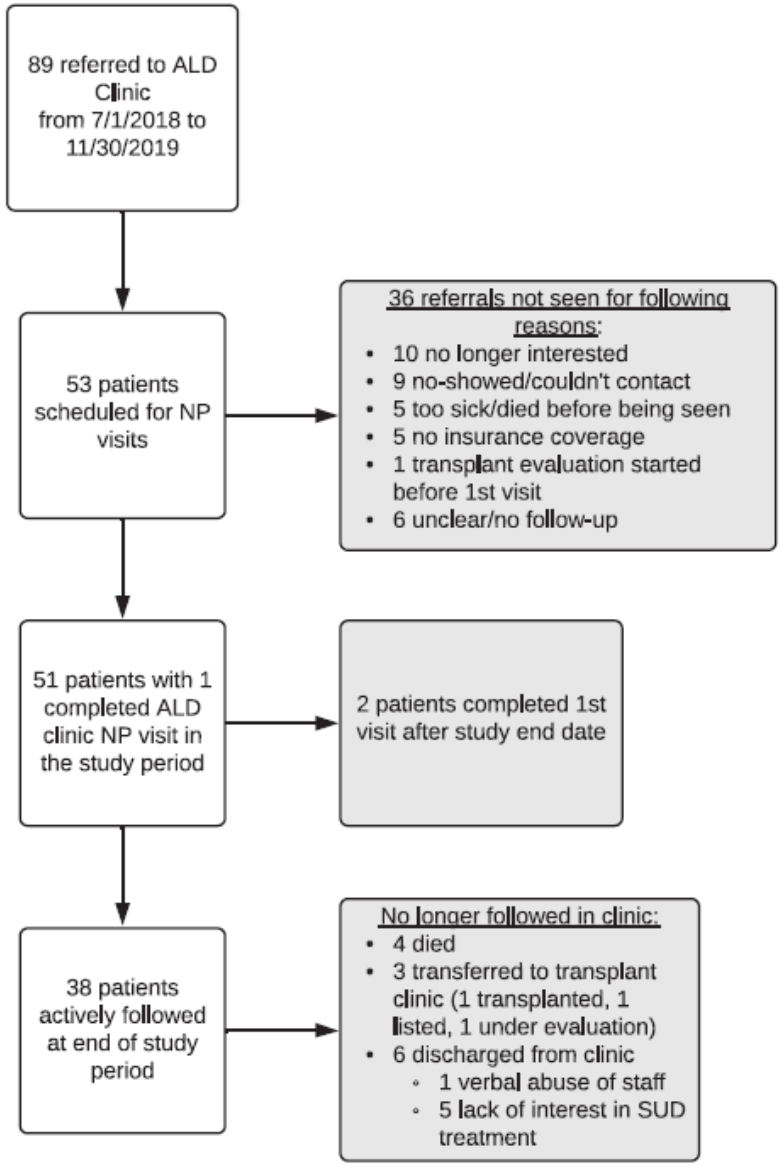
Does combining AUD Rx and therapy work?



- 12 weeks of treatment
- Naltrexone increased time-to-first-drink
- Naltrexone + CBT performed better
  - Fewer relapses overall
  - Relapses more sparse

Anton RF, et al. Journal of clinical psychopharmacology. 2005 Aug 1;25(4):349-57.

Does combining AUD Rx and therapy work?



Feasibility and early experience of a novel multidisciplinary alcohol-associated liver disease clinic

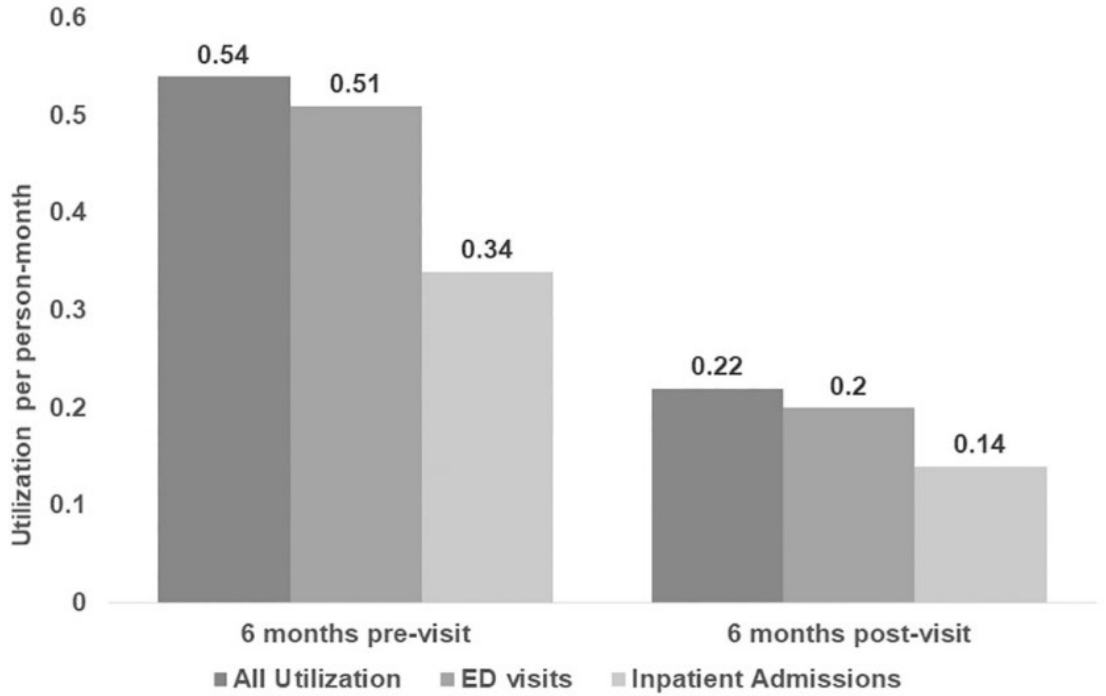


Fig. 4. Rates of hospital admissions and ER utilization per person-month follow-up.

Mellinger JL et L. Feasibility and early experience of a novel multidisciplinary alcohol-associated liver disease clinic. Journal of Substance Abuse Treatment. 2021 Nov 1;130:108396.

Other Relevant Medications

Do we need to treat AUD comorbidities?

- **‘Negative affect’** → robust statistically significant effect on relapse
  - 25 studies (n=10,139) VS. 8 studies (n=724)
- **‘Life events,’ trauma, ‘stress’** → ↑ relapse risk
- Comorbid **‘substance use disorder’** significantly associated with relapse
  - 20 studies (n=45,382) VS. 3 studies (n=310)
- Co-occurring **‘smoking’** → ↑ relapse risk
  - 15 studies (n=20,092) VS. 5 studies (n=456)

- Insomnia prevalent, costly in AUD
- Tx improves depression, sleep quality, ☒ abstinence
  - Behavioral >> Rx

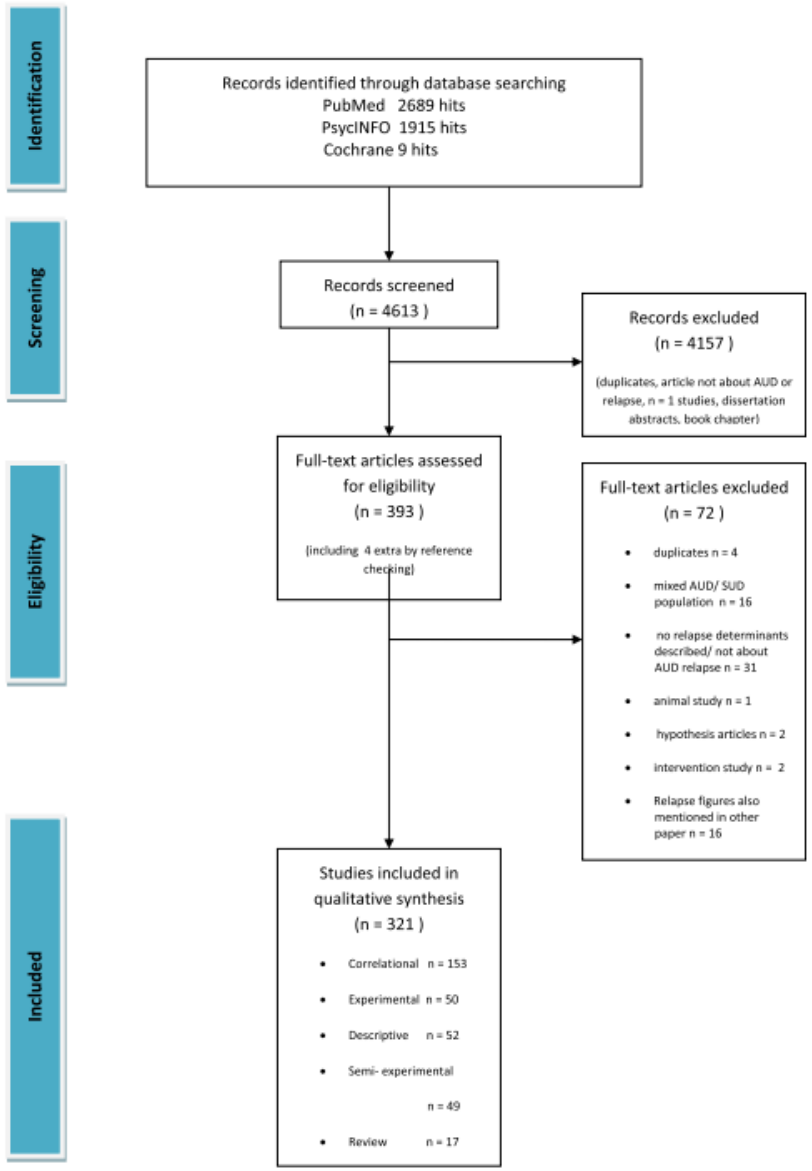


Fig. 1. Flowchart (Prisma based).

Sliedrecht W, de Waart R, Witkiewitz K, Roozen HG. Alcohol use disorder relapse factors: A systematic review. Psychiatry research. 2019 Aug 1;278:97-115

Miller MB, Donahue ML, Carey KB, Scott-Sheldon LA. Insomnia treatment in the context of alcohol use disorder: a systematic review and meta-analysis. Drug and alcohol dependence. 2017 Dec 1;181:200-7.

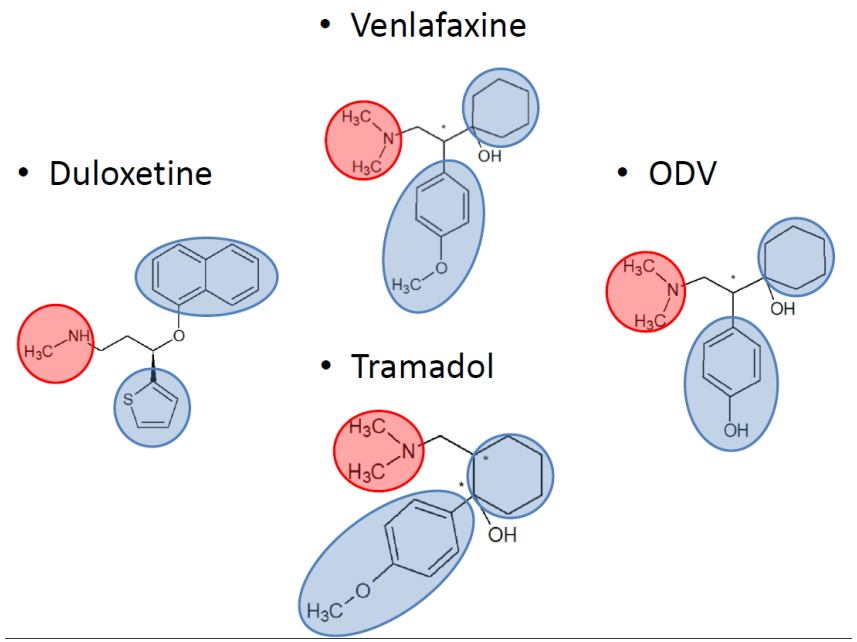
Antidepressants, anxiolytics

- **Fluoxetine**
  - 0.5% incidence of ↑LFTs
  - ≥17 cases of DILI
- **Paroxetine**
  - ≥11 cases of liver injury
- **Sertraline**
  - 0.8% incidence of ↑LFTs
- **Fluvoxamine, citalopram**
  - Rare, sporadic cases
- **Buspirone**
  - Infrequent LFT elevations

- **Nefazodone**
  - 2003 - withdrawn 2/2 liver effects
    - Mitochondrial toxicity
  - Generic still available w/ **BBW** ☠
  - Death or txp 1/250,000 pt years
- **Mirtazapine**
  - Generally safe
- **Bupropion**
  - ↑LFTs <1% & self-limited; rare injury/fatality
- **MAOIs**
  - Rare cases of liver damage with each
  - Older drug (iproniazid) limited by hepatic necrosis (1% incidence, 20% fatality rate)

Sedky K et al General hospital psychiatry. 2012 Jan 1;34(1):53-61
Lucena MI et al. Expert opinion on drug safety. 2003 May 1;2(3):249-62
Selim K, Kaplowitz N. Hepatology. 1999 May;29(5):1347-51
Mauri MC et al. Pharmacokinetics of antidepressants in patients with hepatic impairment. Clin Pharmacokinet. 2014;53(12):1069-1081.

SNRIs up close



ODV = o-desvenlafaxine

- **Venlafaxine**
  - Case reports of idiosyncratic toxicity
  - DILI 1.8/100,000 pt years
- **Duloxetine**
  - DILI 26.2/100,000 pt years
    - Compared to nefazodone: 28.96/100,000
    - No **BBW** ☠
  - 3x ↑LFTs 0.9-1.7% of pts
  - 74% liver injury within 16 weeks
    - 60mg >> 30mg
- **Desvenlafaxine**
  - ↓ dose in Childs-Pugh B, C

Graphic courtesy of Amy Vandenberg PharmD

Sedky K et al General hospital psychiatry. 2012 Jan 1;34(1):53-61
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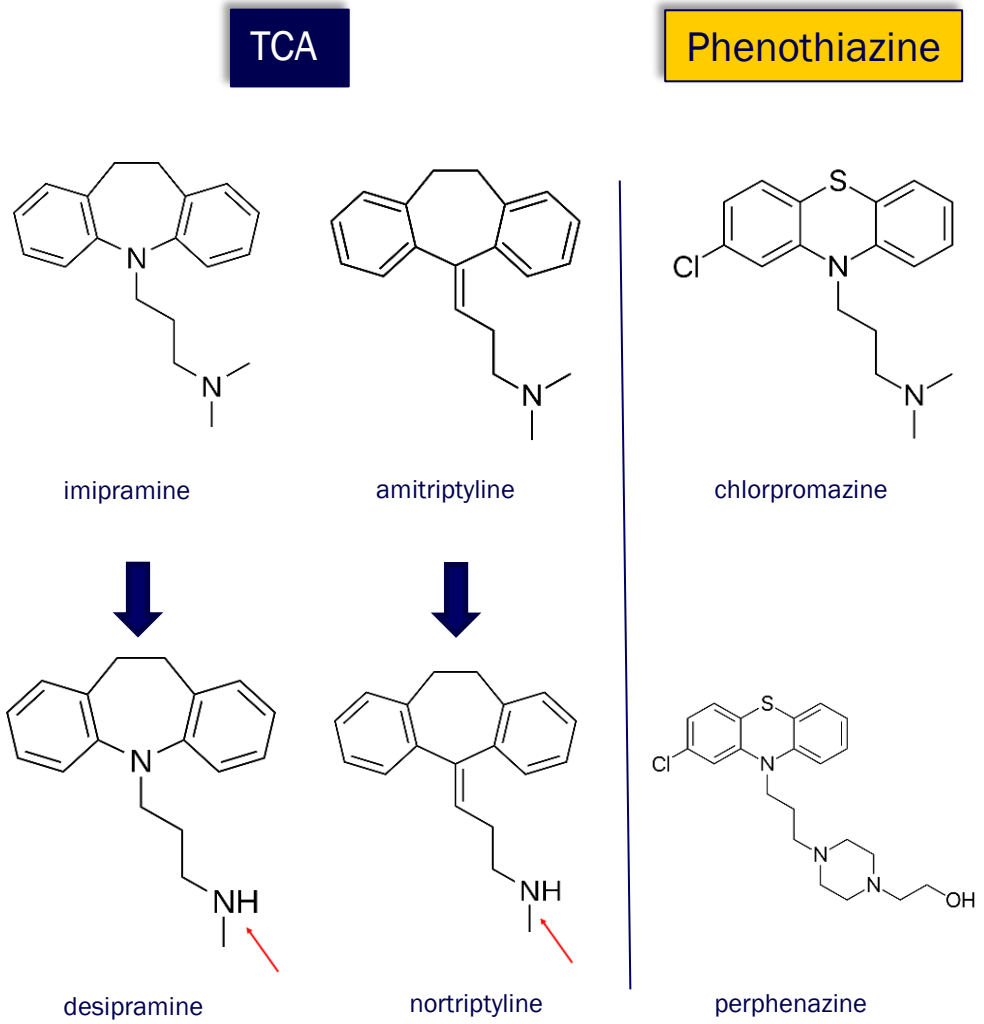
Tricyclic antidepressants (TCA)

- Cases severe hepatitis & fulminant failure, usually early in course
  - Rare acute rxn 4/100,000
- Imipramine ⟶ cholestatic jaundice, ↑LFTs 20% pts, uncommon >3x
- Amitriptyline ⟶ ↑ALT 2-10% pts (asymptomatic), uncommon >3x
  - Rare cholestasis
- Nortriptyline ⟶ rare hepatitis
- Cross-hepatotoxicity?
  - Rechallenge TCA ⟶ reinjury
  - Rechallenge pheno ⟶ reinjury



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Lucena MI et al. Expert opinion on drug safety. 2003 May 1;2(3):249-62
livertox.nlm.nih.gov

Sleep aids

- **Trazodone**
  - Similar to nefazodone in structure, action
  - Modest LFT elevations w/o need for intervention
  - Rare instances of acute liver failure
- **Non-BZD sedative-hypnotics**
  - Zolpidem, eszopiclone, zaleplon
  - Rare liver injury, if at all
- **Melatonin receptor agonists**
  - Melatonin – not linked to liver injury
  - Ramelteon – rare liver injury
    - single case of worsening liver disease in ALD patient
- **Benzodiazepines**
  - Rare ALT elevations & liver injury
  - General caution advised
    - Worsening hepatic encephalopathy
    - Dependence
    - Misuse

livertox.nlm.nih.gov
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Fourman LT, Robert Meyer B. Autoimmune hepatitis in association with ramelteon. J Clin Gastroenterol 2013; 47: 651-4

Other SUD medications

Table 2
Pharmacotherapy for SUD.

Drug	Dose	Mechanism	SUD Indication	Metabolism	Excretion	Use in end-stage disease	Use in transplant patients
Disulfiram	250–500 mg daily	Acetaldehyde dehydrogenase inhibitor	Alcohol[a], cocaine[b]	Hepatic	Hepatic	Not recommended in liver dz; rare cases of liver failure	Caution in LT recipients; interacts with immunosuppressants
Naltrexone	50 mg daily oral; 380 mg IM monthly	Mu receptor antagonist	Alcohol[a], opioids[a]	Hepatic	Renal	Elevated transaminases documented; rarely hepatotoxic	Not studied in LT recipients; interferes with perioperative pain control
Acamprosate	666 mg three times daily	NMDA receptor antagonist	Alcohol[a]	Minimal	Renal	Reduce dose in kidney dz	
Gabapentin	900–1800 mg three times daily	GABA transmission modulator	Alcohol[b], marijuana[b]	Minimal	Renal	Reduce dose in kidney dz and dialysis	
Topiramate	300 mg daily	enhances GABA-A activity, glutamate receptor antagonist	Alcohol[b], cocaine[b]	Minimal	Renal	Reduce dose in kidney dz and dialysis	
Baclofen	10–20 mg three times daily	GABA-B receptor agonist	Alcohol[b]	Hepatic	Renal	Only AUD treatment studied in cirrhosis	
Varenicline	1 mg twice daily	Nicotinic acetylcholine receptor partial agonist	Nicotine[a], alcohol[b]	Minimal	Renal	Reduce dose in kidney dz and dialysis	
Bupropion	150–300 mg daily	Poorly understood; weak NE and DA reuptake inhibitor	Nicotine[a]	Hepatic	Renal	Caution in kidney dz (extended-release not recommended); dosing reductions in liver dz	Interacts with prednisone
Methadone	80–120 mg daily	Opioid receptor agonist	Opioids[a]	Hepatic	Renal	Reduce dose in kidney dz	OUD maintenance should be continued through LT course; interacts with tacrolimus (QT prolongation risk)
Buprenorphine-naloxone	Various doses depending on formulation: buccal film, SL film, SL tablet, implants, injection	Buprenorphine (B): mu receptor partial agonist Naloxone (N):	Opioids[a]	B: Hepatic N: Hepatic	B: Hepatic N: Renal	Rare cases of hepatotoxicity in liver dz	Interferes with perioperative pain control

Winder GS et al. Best Practice & Research Clinical Gastroenterology. 2020 Sep 14:101685.

Thank you.

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