1

Disclosures

Employment

-406 Recovery (Montana nonprofit) - CEO and co-founder.

-Consultant w/ Community Medical Services and MPCA

Off-label / products

Will discuss off-label use of gabapentin for treatment of alcohol use disorder given this is evidence-based treatment.

Public role: 406recovery.care/our-team/robert-g-sise/ | No One Point Care affiliation on this activity. | FDA/FTC: no medication efficacy claims in this session.

2

Objectives

1. Appreciate the evidence for Medication for Alcohol Use Disorder (MAUD)
2. Assess clinical appropriateness of different forms of MAUD based on their mechanisms of action
3. Understand how MAUD benefits both patients seeking abstinence as well as those engaged in harm reduction programs

3

Patient Case

Meet Ms. CS, 33 y/o woman with hepatitis C (thinks she contracted it over a year ago- yet to receive treatment) active IV meth and EtOH abuse.

She has long standing alcohol use of 2-3 bottles of wine daily. She has a history complicated by PTSD from a traumatic experience involving her first child, was hypervigilant and afraid he would stop breathing. Began drinking to calm her intrusive thoughts and states "It's the only thing that has worked to help my anxiety."

She wishes to pursue abstinence from all substances.

LFTs: ALT- 101, AST- 143

What treatment can we offer her?

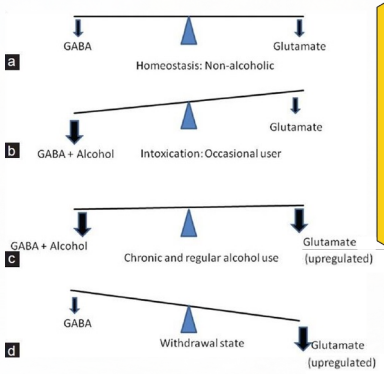
4

Abbreviated Pathophysiology

- Alcohol interferes with 2 neurotransmitters:
  - Gamma-aminobutyric acid A (**GABA-A**) agonist
  - N-methyl-d-aspartate (**NMDA**)-glutamate antagonist

Alcohol Use	Alcohol Quantity	Neuronal Effects		Clinical Effect
		GABA Receptors	NMDA-Glutamate Receptors	
Naïve/Sober	No Alcohol			Baseline
Acute		Enhanced inhibition	Blocked excitation	Intoxication/ Sedation
Chronic/ Tolerance		Down-regulation	Up-regulation	New baseline
Abstinent		Loss of inhibition	Uncontrolled excitation	Withdrawal/ Autonomic instability

= alcohol; = no alcohol; = GABA receptor; = NMDA-glutamate receptor; = Blocked excitation



Simplified model: *Alcohol affects GABA, glutamate, dopamine, opioid, serotonin, norepinephrine, endocannabinoid, and cholinergic systems; GABA/glutamate are emphasized here for their central role in tolerance and withdrawal.*

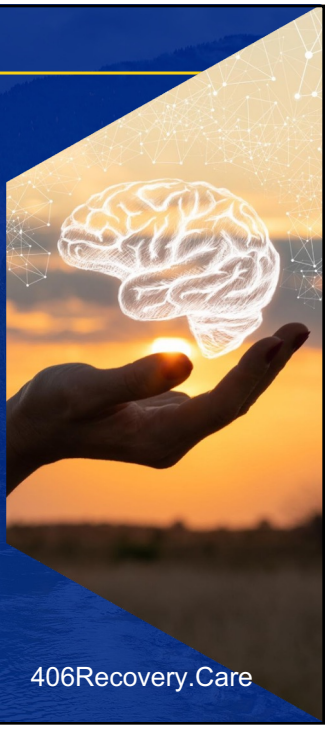
Neuropsychopharmacology 2010; 35: 217-38.; Alcohol and alcoholism. Harrison's principles of internal medicine, 18th ed. Columbus: McGraw-Hill; 2012.

5

Medication Assisted Treatment (MAT) is available for most SUDs

- **Opioid Use Disorder (OUD)**: methadone, buprenorphine, naltrexone
- **AUD**: naltrexone, gabapentin, disulfiram, acamprosate
- **Stimulant Use Disorder**: Case management, motivational interviewing, Vivitrol (naltrexone IM) + bupropion for meth use (perhaps disulfiram for cocaine use)
- **Kratom**: buprenorphine

*Note for most SUDs: motivational interviewing & 12-step facilitation (i.e. AA, NA) = crux of tx



406Recovery.Care

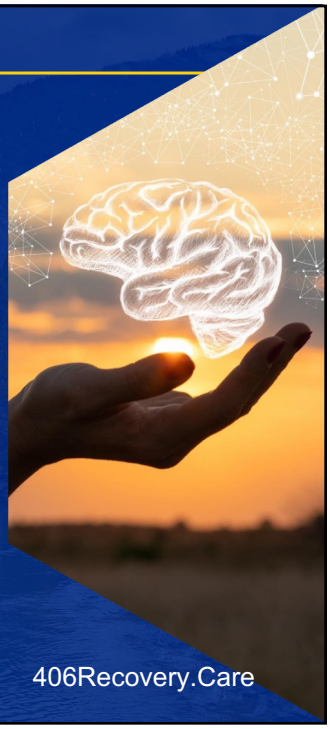
6

Medication for Alcohol Use Disorder (MAUD)

7

Systems as Targets for Pharmacologic Intervention in Substance Use Disorders

- Metabolizing Enzymes
- Dopamine Reward System
- Endogenous Opioid System
- Gamma Amino Butyric Acid (GABA) System
- Excitatory Amino Acid System

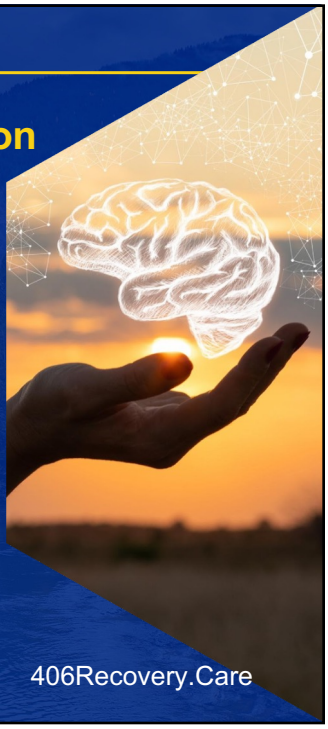


406Recovery.Care

8

Pertinent Systems For Today's MAUD Discussion

- Metabolizing Enzymes
- Dopamine Reward System
- Endogenous Opioid System
- Gamma Amino Butyric Acid (GABA) System
- Excitatory Amino Acid System



406Recovery.Care

9

Medication for Alcohol Use Disorder

- Disulfiram (Antabuse)
- Acamprosate (Campral)
- Naltrexone (ReVia, Vivitrol)
- Gabapentin

FDA Approved

406Recovery.Care

10

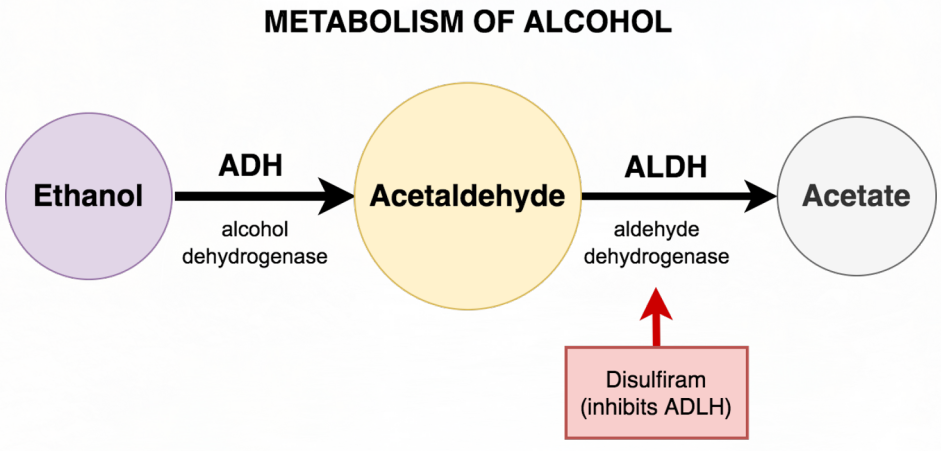
Disulfiram

Tetraethylthiuram Disulfide

- first synthesized in 1881
- widely used by 1900 in the production of rubber
- In 1937 E. E. Williams, a physician working at an American rubber plant, described:
  - workers processing tetramethylthiuram monosulfide and disulfide became sick when they ingested alcohol

11

Mechanism of Action



12

Disulfiram-Alcohol Reaction = Deterrent Effect

Related to acetaldehyde buildup

- Flushing
- Sweating
- Nausea and Vomiting
- Headache
- Tachycardia
- Sometimes hypotension
- Sometimes dyspnea

406Recovery.Care

13

Sounds compelling… what could go wrong?

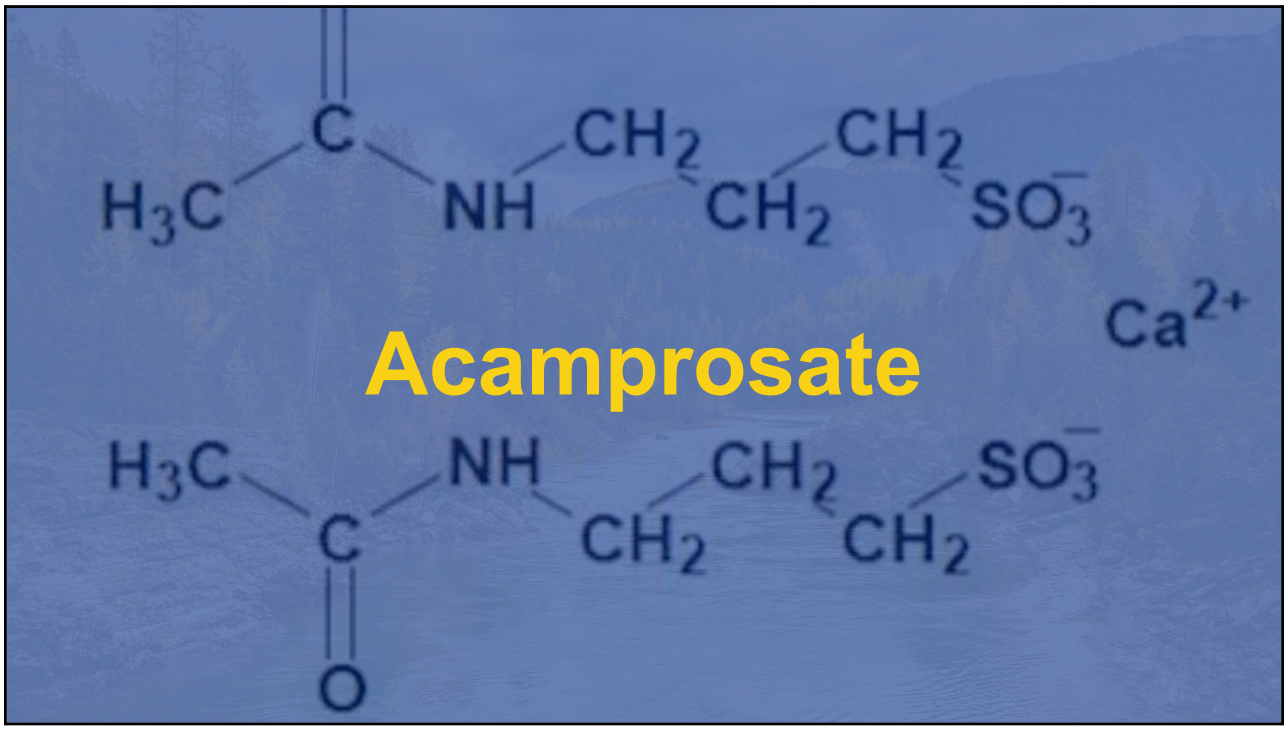
NO WAY- Only works in settings where other parties ensure adherence/ patients have incentive to remain adherent

Clinical trials support the efficacy of disulfiram in patients with alcohol use disorder in patients with supervised medication ingestion to ensure adherence*, **

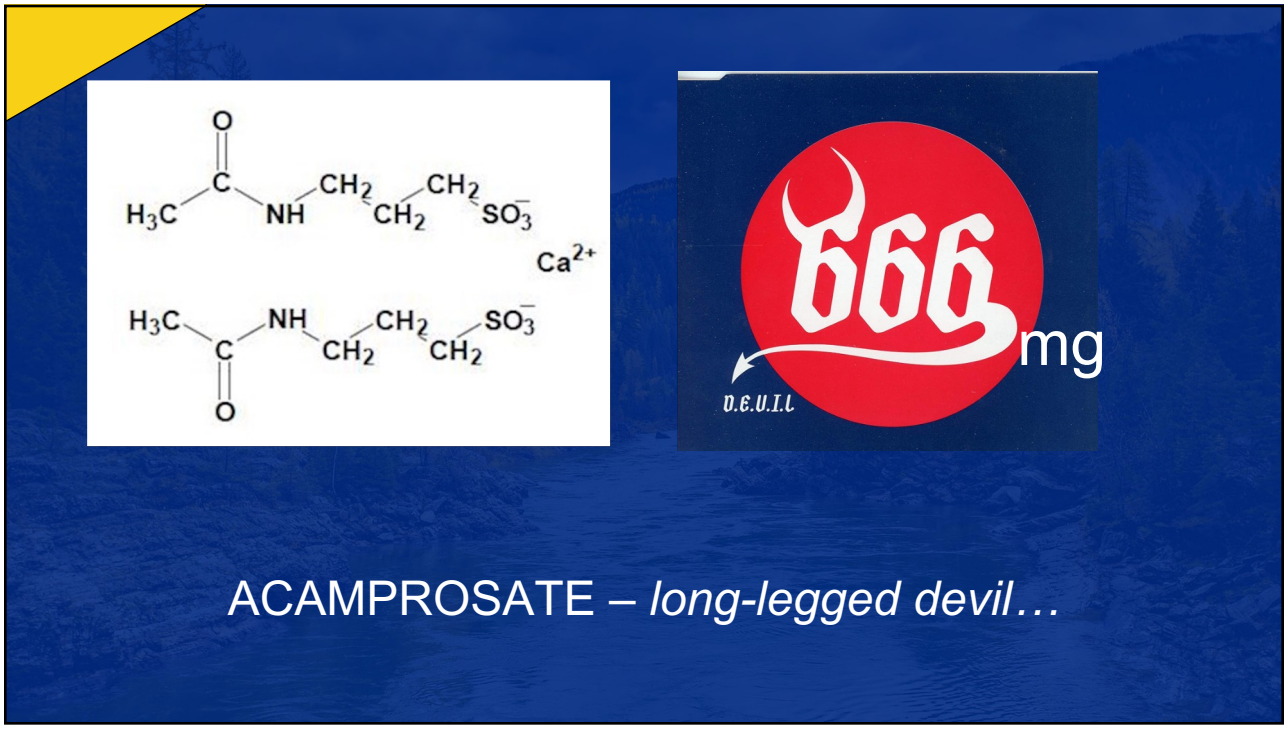
*Azrin NH. Improvements in the community-reinforcement approach to alcoholism. Behav Res Ther 1976; 14:339.
**Azrin NH, Sisson RW, Meyers R, Godley M. Alcoholism treatment by disulfiram and community reinforcement therapy. J Behav Ther Exp Psychiatry 1982; 13:105.

406Recovery.Care

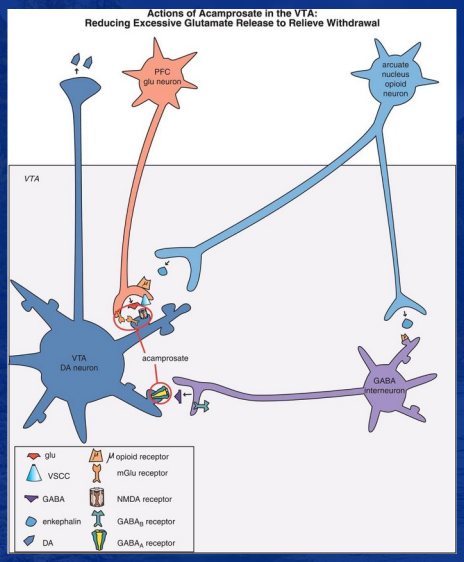
14

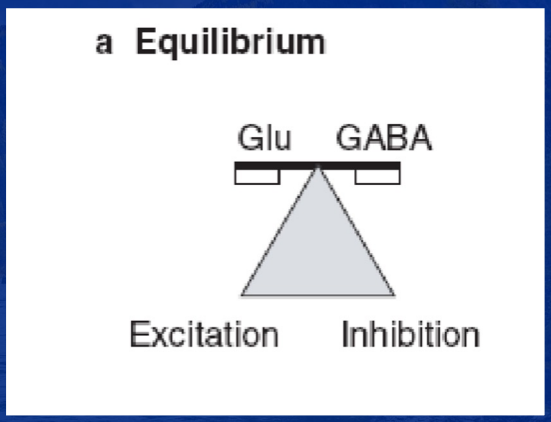


15



16





17

Acamprosate Side Effects and Metabolism

Diarrhea 10-20%

Rash < 5%

Renally cleared: contraindicated in renal failure

406Recovery.Care

18

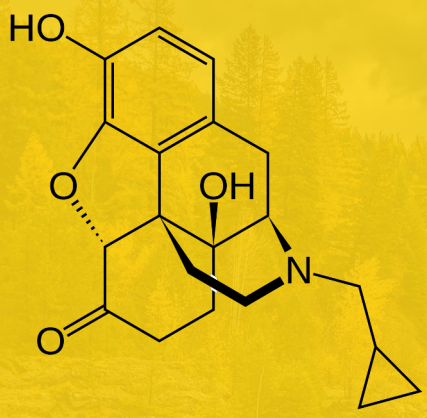
COMBINE Study:
- Randomized Intervention Model
- 1375 participants
- Examined Acamprosate, Naltrexone and cognitive behavioral interventions

 acamprosate showed no evidence of efficacy, with or without CBI*

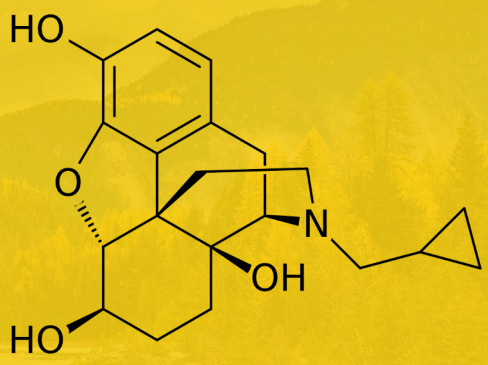
ACAMPROSATE – *long-legged devil… THAT DOESN'T OUTPERFORM PLACEBO IN US STUDIES*

*Anton, Raymond F., et al. "Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. " Jama 295.17 (2006): 2003-2017.

19

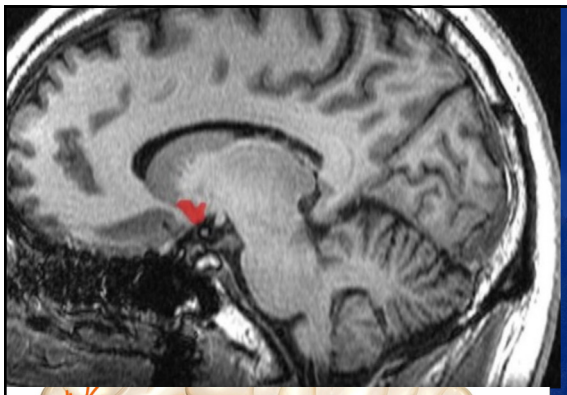


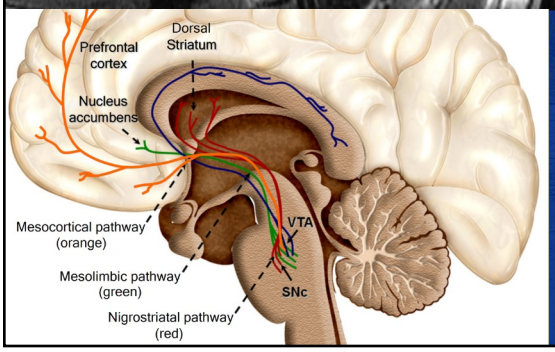
Naltrexone



6β-Naltrexol

20



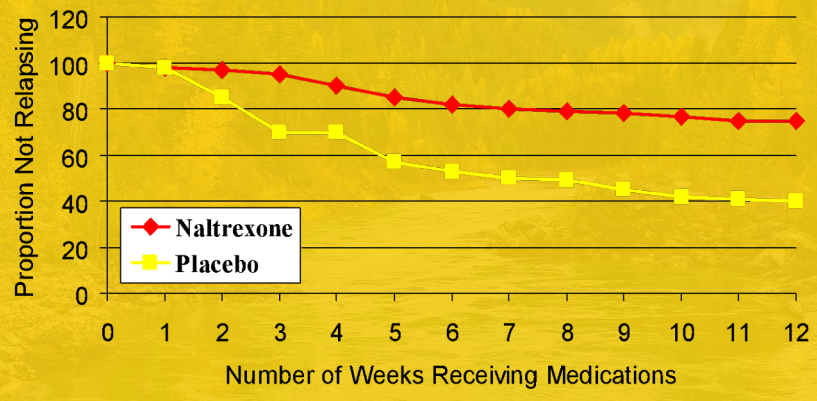


Site of Action:

Nucleus Accumbens

21

Effects of Naltrexone on Relapse Rates among Alcohol Dependent Outpatients



Volpicelli, et al., 1992

24

Meta-Analysis Oral Naltrexone vs. Placebo: Relapse to Heavy Drinking

Study or subcategory (first-named author)	Naltrexone n/N	Placebo n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Number of subjects with relapses					
Volpicelli (1992)	8/35	19/35		9.72	0.42 (0.21–0.83)
Oslin (1997b)	3/23	8/21		3.73	0.34 (0.10–1.12)
Volpicelli (1997)	17/48	26/49		16.74	0.67 (0.42–1.06)
Anton (1999)	26/68	38/63		22.18	0.63 (0.44–0.91)
Gastpar (2002)	34/84	36/87		22.31	0.98 (0.68–1.40)
Guardia (2002)	8/101	19/101		7.82	0.42 (0.19–0.92)
Latt (2002)	19/56	27/51		17.50	0.64 (0.41–1.00)
Subtotal (95% CI)	415	407		100.00	0.64 (0.51–0.82)

Total events: 115 (naltrexone), 173 (placebo)
Test for heterogeneity: $\chi^2 = 8.86$, df = 6 ($p = 0.18$), $I^2 = 32.3\%$
Test for overall effect: $Z = 3.65$ ($p = 0.0003$)

Srisurapanont & Jarusuraisin, 2006

406Recovery.Care

25

Naltrexone Side Effects

Nausea/Diarrhea
Headache
Insomnia
Dizziness
Possible Hepatic toxicity
Opioid analgesics will not be effective

406Recovery.Care

27

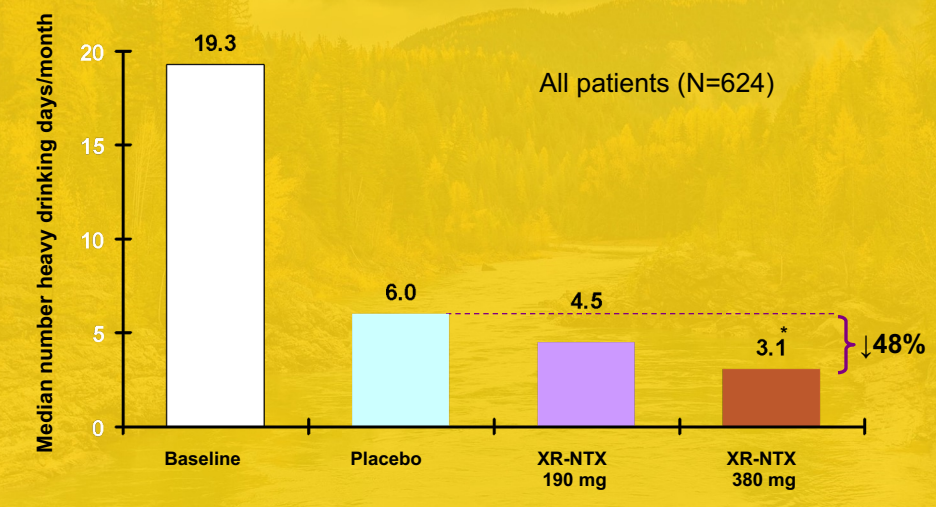
Long-Acting Injectable Naltrexone Clinical Trial

- 24-week multicenter, randomized, double-blind, placebo-controlled study
- 624 alcohol-dependent patients (DSM-IV)
  - Subgroup abstinent prior to treatment initiation
    - 82 patients (13.1%) abstinent for 4 days
    - 53 patients (8.5%) abstinent for 7 days
  - Patients who were abstinent for 7 days were stratified for equal distribution across treatment groups
- Treatment consisted of 12 sessions of low-intensity psychosocial intervention (BRENDA) plus 6 monthly IM injections of either:
  - Placebo, XR-NTX 190 mg, or XR-NTX 380 mg

406Recovery.Care

29

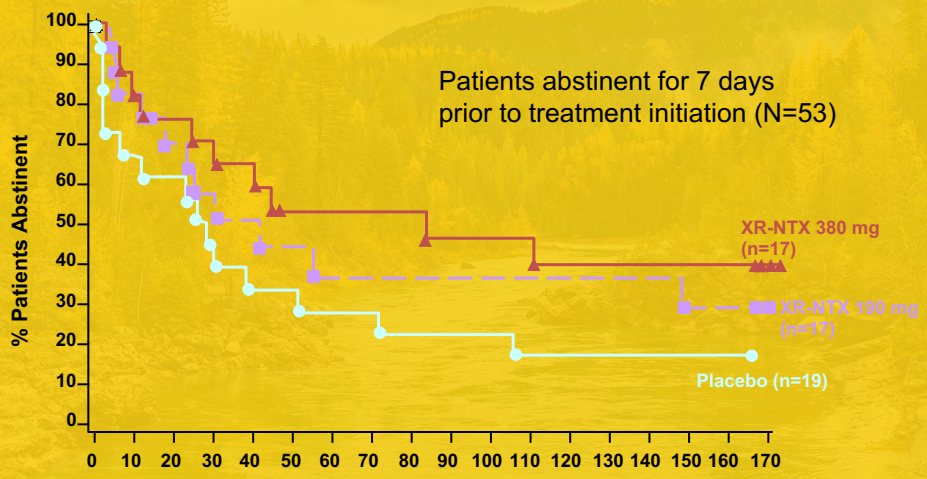
Reduction in Heavy Drinking Days



*P<0.05 vs placebo.

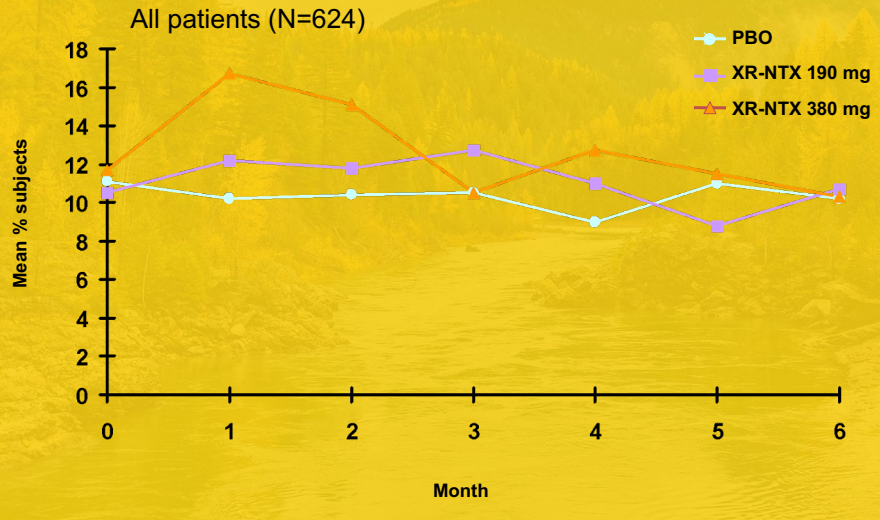
30

Maintenance of Abstinence



31

Monthly Rate of Self-Help Meeting Attendance



32

Naltrexone Contraindications

Acute hepatitis (Canadian Labeling)

Hepatic failure - only absolute contraindication

Note for cirrhosis

- ***Need to dose adjust in cirrhosis***

406Recovery.Care

35

Naltrexone in Harm Reduction

SUBSTANCE ABUSE, 36: 21–33, 2015
Copyright © Taylor and Francis Group, LLC
ISSN: 0889-7077 print / 1547-0164 online
DOI: 10.1080/08897077.2014.904838

Routledge
Taylor & Francis Group

Extended-Release Naltrexone and Harm Reduction Counseling for Chronically Homeless People With Alcohol Dependence

Susan E. Collins, PhD,[1] Mark H. Duncan, MD,[1] Brian F. Smart, MD,[1] Andrew J. Saxon, MD,[1,2] Daniel K. Malone, MPH,[3] T. Ron Jackson, MSW,[4] and Richard K. Ries, MD[1]

406Recovery.Care

36

Naltrexone in Harm Reduction

12-week studying XR-NTX administration and harm reduction counseling for homeless w/ EtOH Use D/O

31 subjects from 2 community-based agencies (including UW-HMC), 24 complied with all study procedures

Measures included self-reported alcohol craving, quantity/frequency, problems, and biomarkers (ethyl glucuronide [EtG], liver transaminases).

XR-NTX and harm reduction counseling were administered monthly over the 3-month treatment course.

406Recovery.Care

37

Naltrexone in Harm Reduction

Outcomes = decreases in:

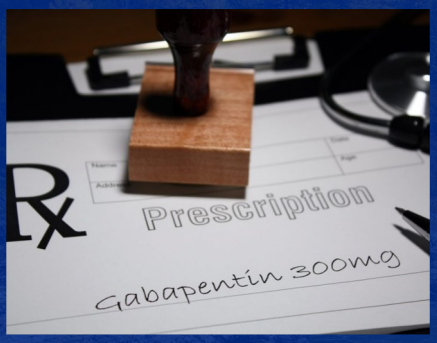
- alcohol craving (33%)
- typical (25%) and peak use (34%)
- frequency (17%)
- medical complications/ED visits (60%)

- **Corroborated reported changes in use with changes in EtG from the baseline to the 12-week follow-up (Ps < .05)**

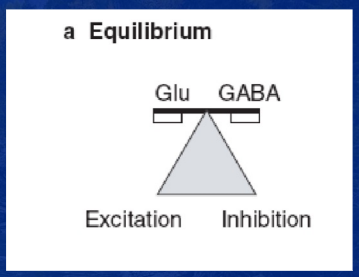
406Recovery.Care

38

Gabapentin as MAUD

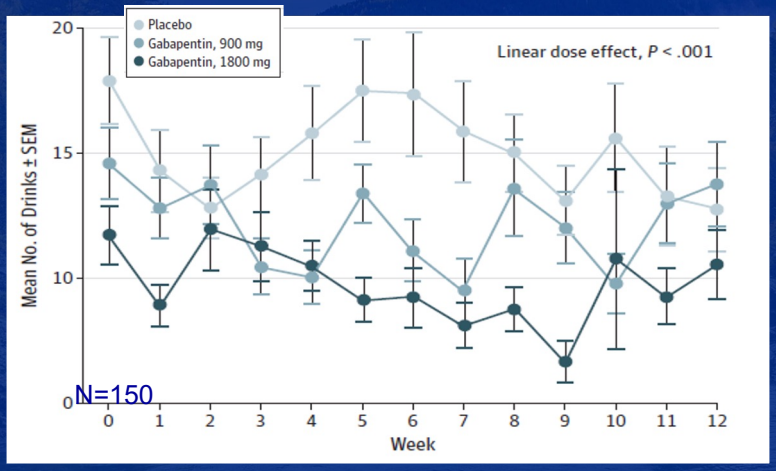


- GABA Analog
- May also serve to ↓ glutamate production
- Facilitates normalization of GABA vs. glutamate tone in early abstinence from alcohol



39

Gabapentin as MAUD

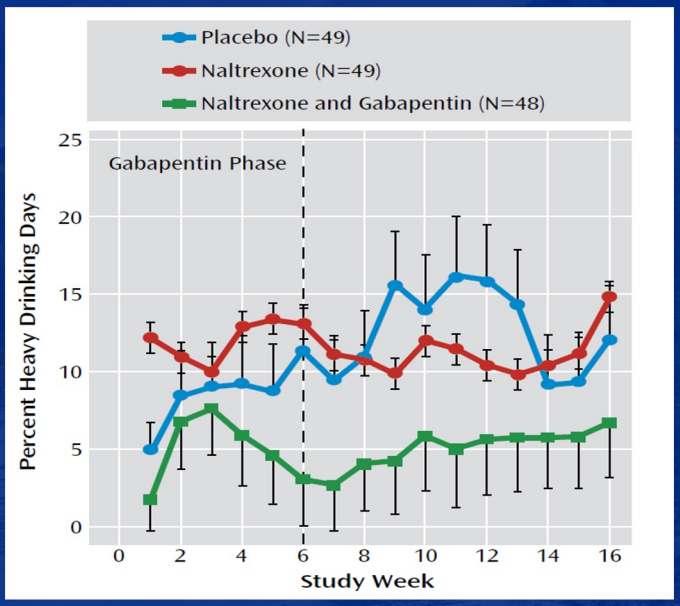


Mason et al., 2013

40

p=0.0002

Gaba-Ntx Combo?



Anton, Myrick, et al., 2011: Gabapentin (up to 1200 mg/d) Combined with Naltrexone (50 mg/d) for Treatment of Alcohol Dependence

p=0.0002

41

406 RECOVERY

Patient Case

406Recovery.Care

42

Patient Case

Meet Ms. CS, 33 y/o woman with hepatitis C (thinks she contracted it over a year ago- yet to receive treatment) active IV meth and EtOH abuse.

She has long standing alcohol use of 2-3 bottles of wine daily. She has a history complicated by PTSD from a traumatic experience involving her first child, was hypervigilant and afraid he would stop breathing. Began drinking to calm her intrusive thoughts and states "It's the only thing that has worked to help my anxiety."

She wishes to pursue abstinence from all substances.

LFTs: ALT- 101, AST- 143

What treatment can we offer her?

43

Patient Case

Naltrexone

Oral: 25 mg PO qday *7 days, then
50 mg PO qday thereafter
(vs. 380 mg IM q 28 days)

+

Gabapentin:

300 mg PO TID, may ↑ to
600 mg PO TID as tolerated

+

Sertraline:

25 mg PO qAM*7 days, then
50 mg PO qAM thereafter

What treatment can we offer her?

44

Patient Case

*Note: psychosocial interventions are the most important form of treatment, including:

- Motivational Interviewing
- 12-step facilitation

What treatment can we offer her?

45

TAKEAWAYS re MAUD

- Naltrexone (especially IM) is very rarely contraindicated and has robust evidence supporting it's use in treating patients:
  - Who pursue abstinence
  - Who wish to reduce use/adverse outcomes
- Gabapentin is a helpful adjunct over the first 6-12 weeks
- Acamprosate doesn't work
  - *Unless maybe you are a moderate drinking German… Austrian?*

406Recovery.Care

46

Questions?

Contact Us:

406Recovery.Care

robert.sise@406recovery.care

47