UW PACC
Psychiatry and Addictions Case Conference
UW Medicine | Psychiatry and Behavioral Sciences

05/23/2019

WELCOME!

Today's Topic:

Medication Assisted Treatment Update

What medications should I consider for the treatment of alcohol use disorders?

Daniel Magliozzi, MD

PANELISTS:

MARK DUNCAN, MD, RICK RIES, MD, KARI STEPHENS, PHD, AND BARB MCCANN, PHD

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

ALCOHOL USE DISORDER: MEDICATION-ASSISTED TREATMENT

DANIEL MAGLIOZZI: ADDICTION PSYCHIATRY FELLOW - UNIVERSITY OF WASHINGTON

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

GENERAL DISCLOSURES

UW PACC is also supported by Coordinated Care of Washington

SPEAKER DISCLOSURES

✓None

UW PACC

SPEAKER DISCLOSURES

✓ No conflicts of interest

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose:

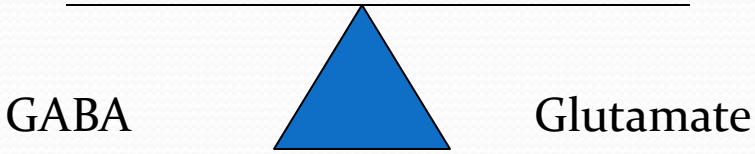
Mark Duncan MD
Barb McCann PhD
Anna Ratzliff MD PhD
Rick Ries MD
Kari Stephens PhD
Niambi Kanye
Betsy Payn
Diana Roll
Cara Towle MSN RN

UW PACC

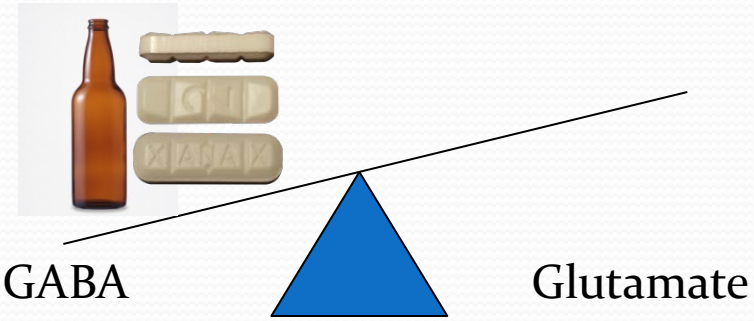
OBJECTIVES

- Discuss FDA approved medications for alcohol use disorder
- Discuss other evidence-based medications for alcohol use disorder
- Practice clinical decision-making as it relates to alcohol use disorder through case presentations

UW PACC

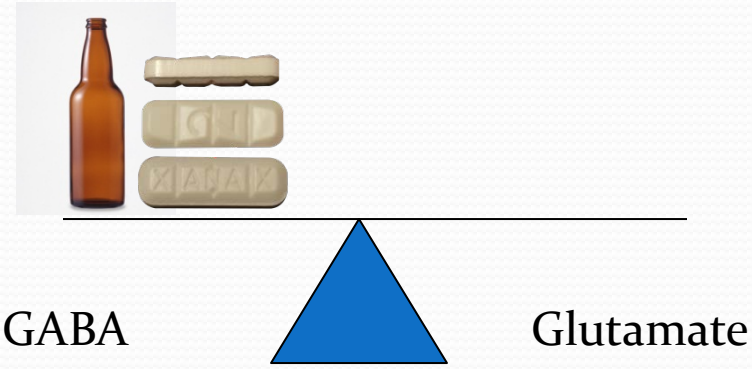


Homeostasis

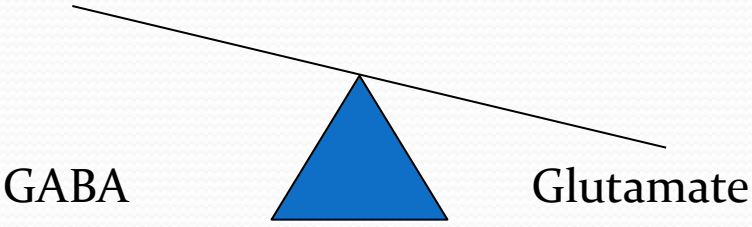


Intoxication/Occasional Alcohol Use

Sedation, psychomotor retardation



Neuroadaptation-chronic alcohol use :
Up regulation of Glutamate
and down regulation of GABA



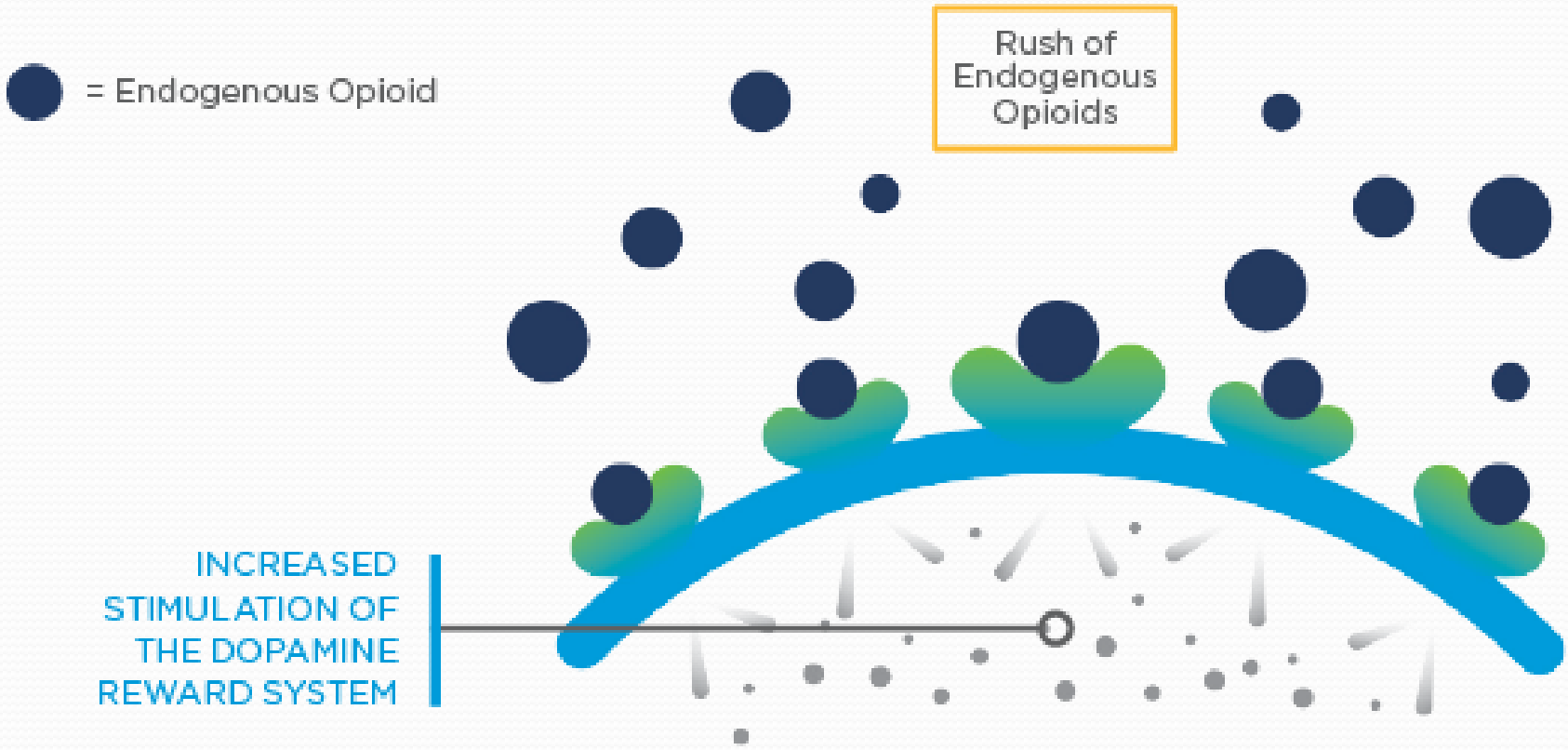
Withdrawal State:
Unopposed Glutamate up regulation
without alcohol mediated GABA stimulation

Anxiety, Insomnia, psychomotor agitation

Alcohol Use Disorder

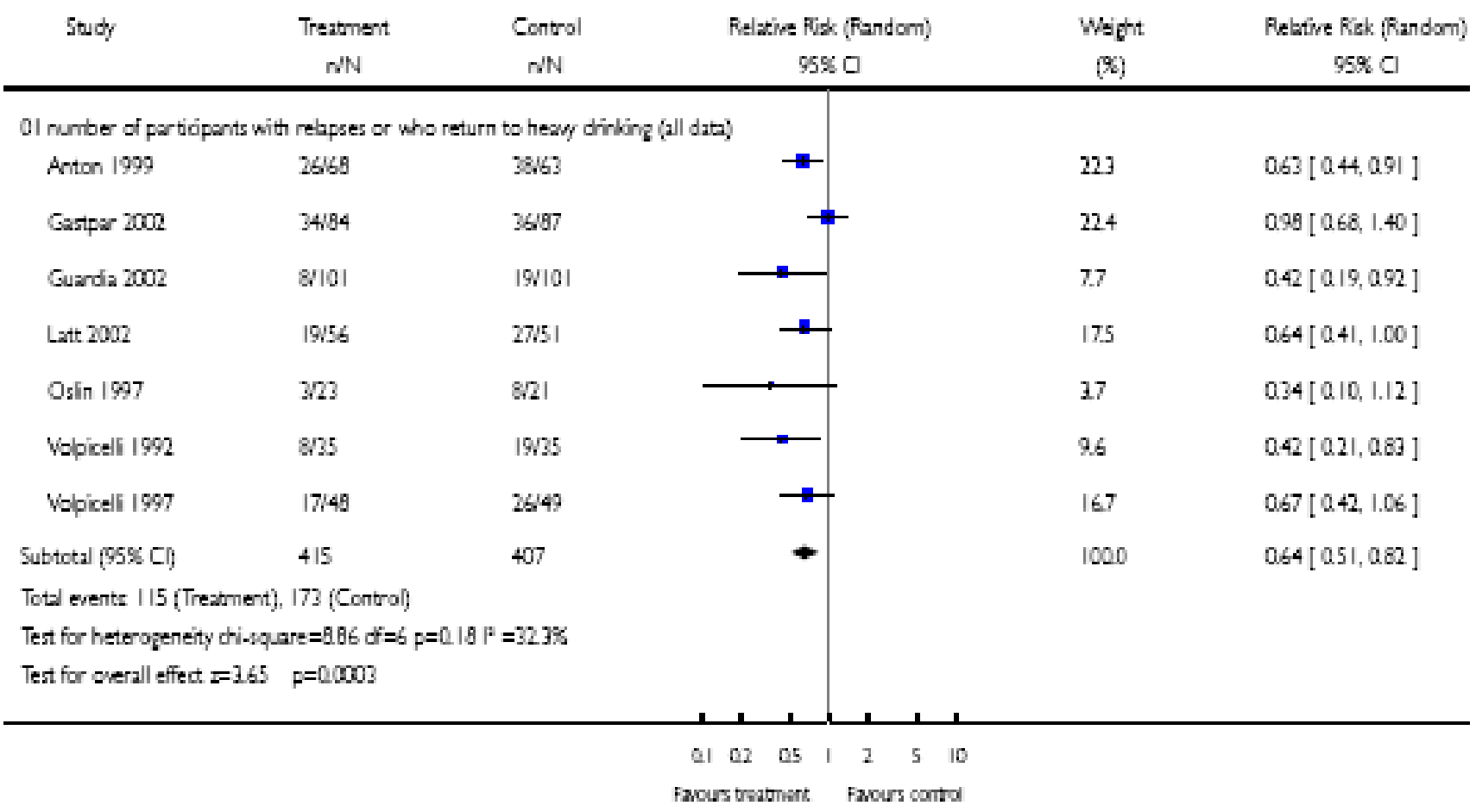
- FDA Approved Medications:
  - Naltrexone
  - Disulfiram
  - Acamprosate
- Others:
  - Gabapentin
  - Anticonvulsants
  - More…

Naltrexone


= Endogenous Opioid
Rush of Endogenous Opioids
INCREASED STIMULATION OF THE DOPAMINE REWARD SYSTEM

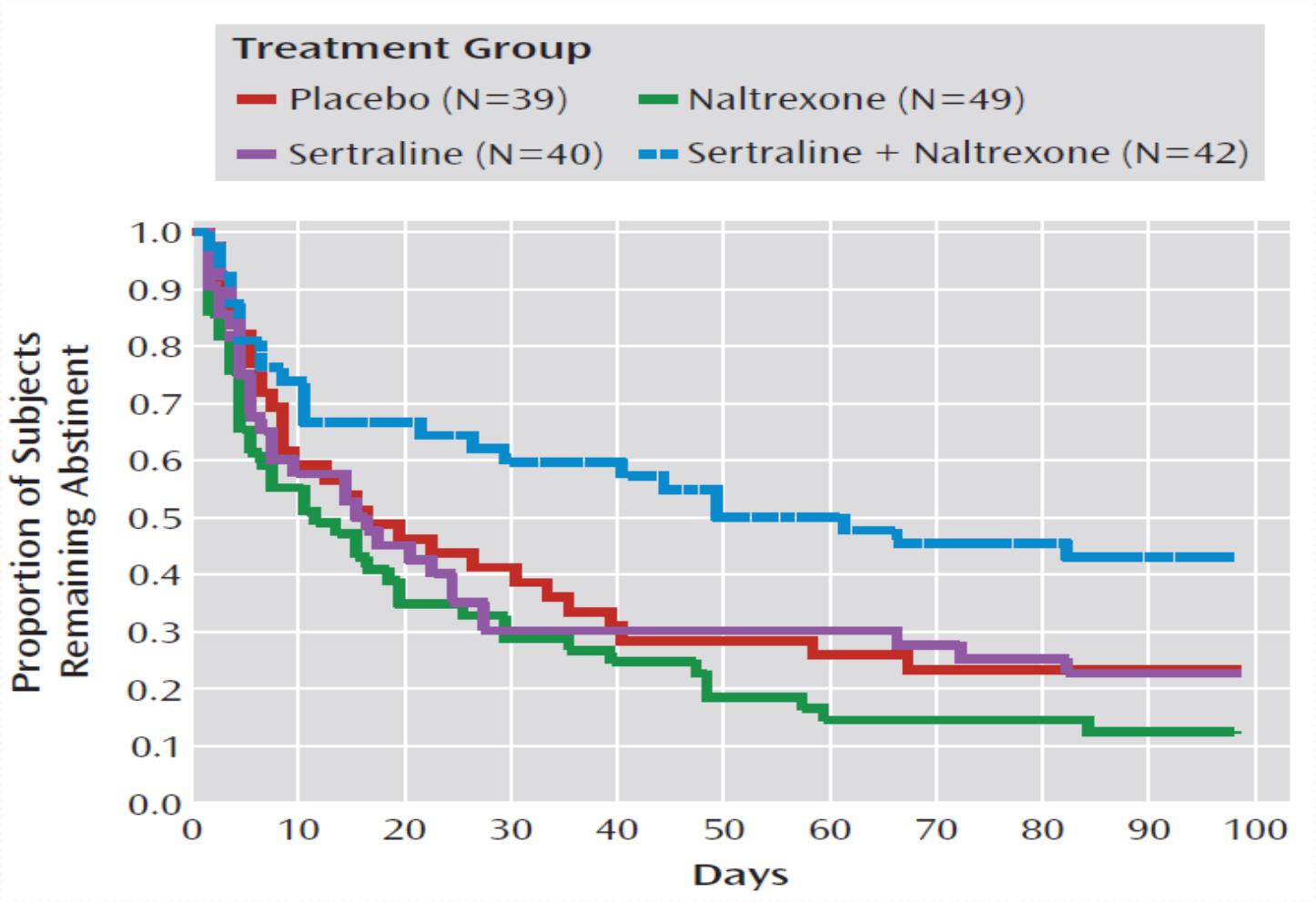
Naltrexone (PO)

Meta-analysis: Oral naltrexone vs. placebo – participants returning to heavy drinking



Srisurapanont & Jarusuraisin, 2006

Naltrexone in Co-occurring Depression



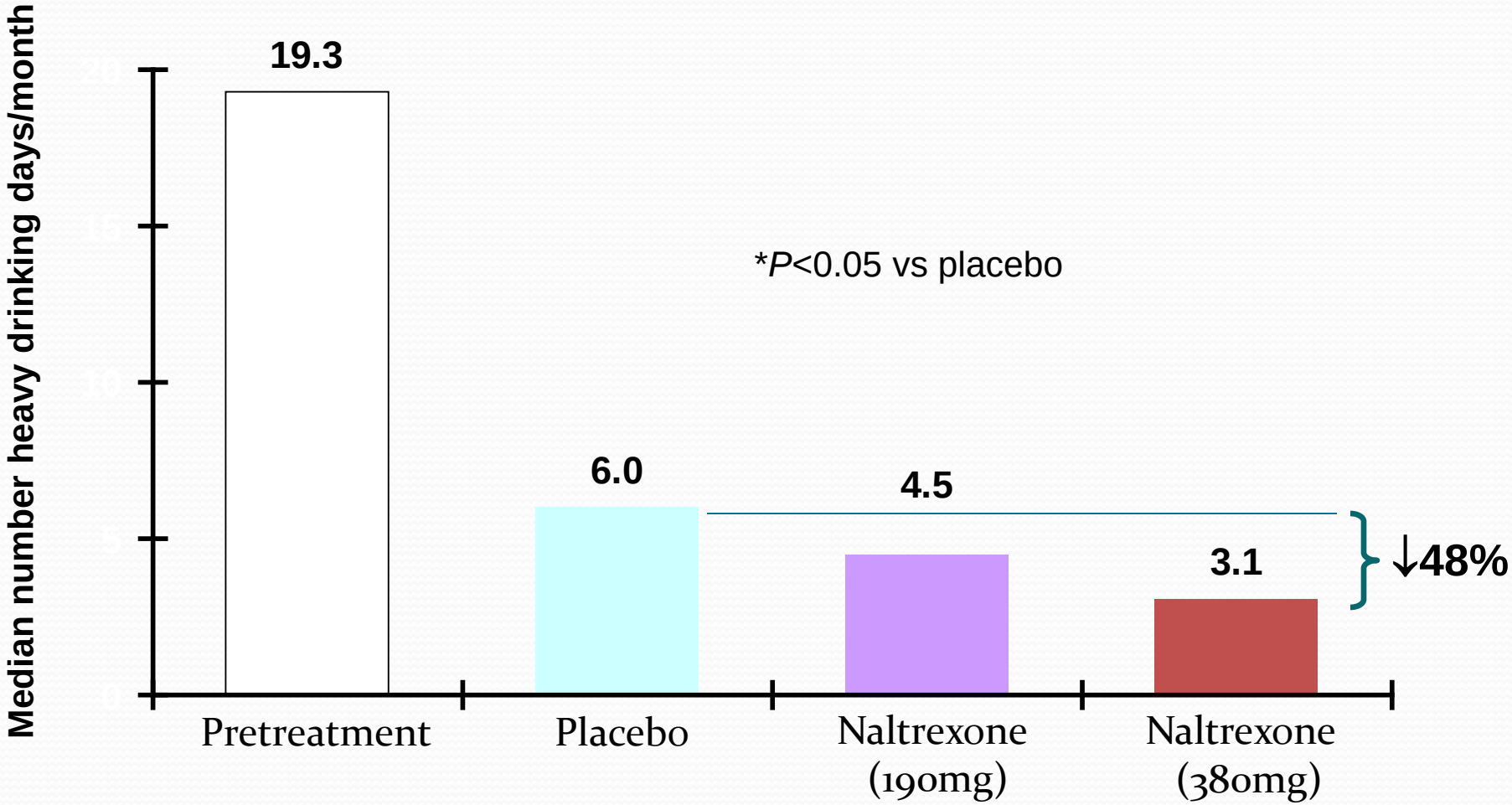
Pettinati et al., 2009. Combining Sertaline (200 mg/d) and Naltrexone (100 mg/d) for Co-occuring Depression and Alcohol Dependence

Extended Release IM Naltrexone

- 24-week multicenter, randomized, double-blind, placebo-controlled study
- 624 alcohol-dependent patients (DSM-IV)
- Treatment consisted of 12 sessions of low-intensity psychosocial intervention (BRENDA) plus 6 monthly IM injections of either:
  - Placebo
  - XR-NTX 190 mg
  - XR-NTX 380 mg

Garbutt et al, 2005. Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial

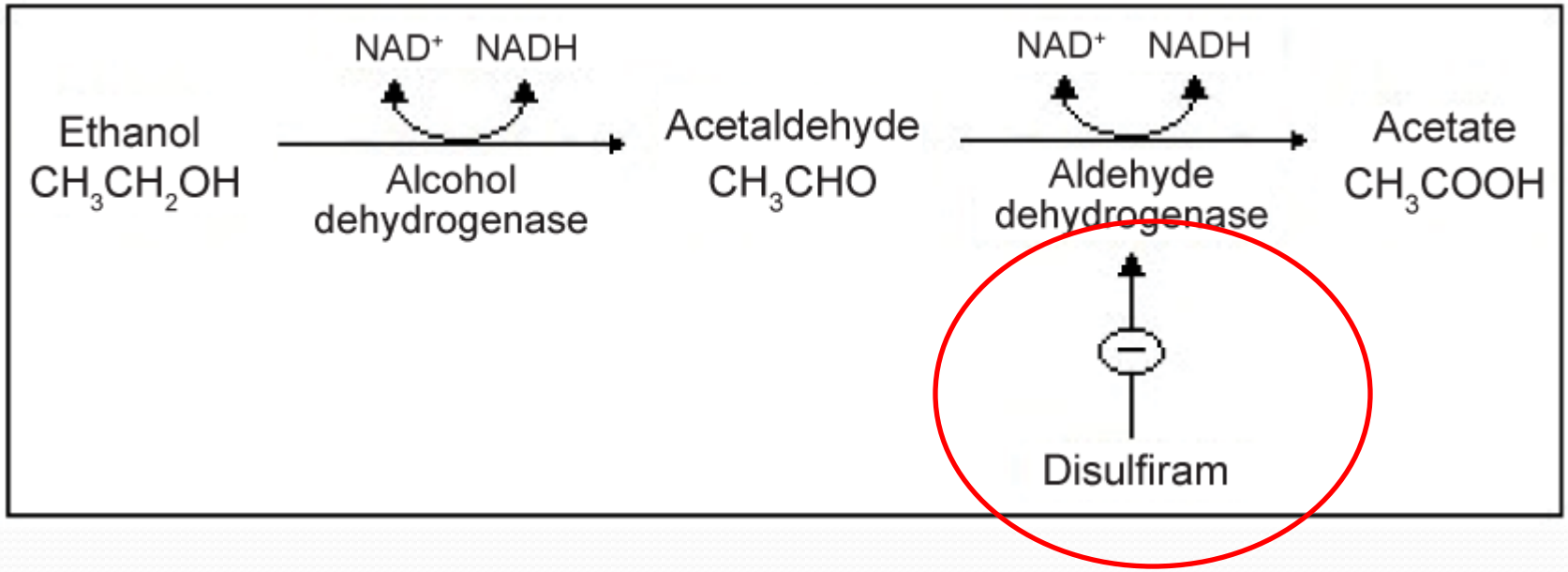
Extended Release IM Naltrexone



Naltrexone

- Decreases cravings and amount of alcohol consumed during binges
- PO 50-150mg daily; IM 380mg q28days
- Pros:
  - IM version available in US
  - Good for harm reduction
  - Generally well-tolerated
- Cons:
  - Common SEs: nausea, diarrhea, HA, insomnia, dizziness
  - Can't use with opiates
  - Caution if hepatic impairment

Disulfiram


NAD+ NADH
Ethanol
CH3CH2OH
Alcohol
dehydrogenase
Acetaldehyde
CH3CHO
NAD+ NADH
Aldehyde
dehydrogenase
Acetate
CH3COOH
Disulfiram

Disulfiram

Fuller *et al*., 1986: Partially blinded, RCT in 9 VA's

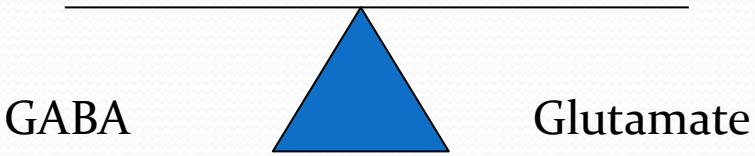
Alcohol Consumption During the Study

	250 mg	1 mg	None
Drinking Days Reported by Subjects	49.0±8.4	75.4±11.9	86.5±13.6
Drinking Days Reported by SO's	68.0±11.2	108.7±14.7	116.4±16.3

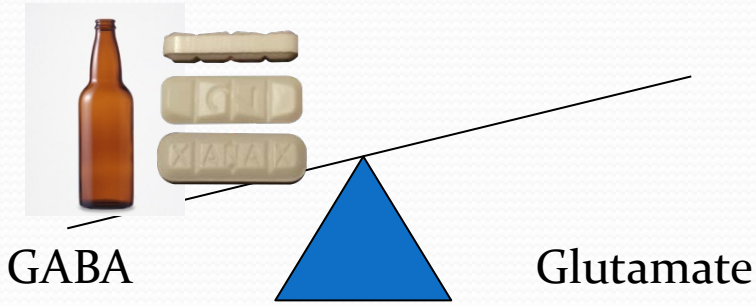
Disulfiram

- Causes disulfiram-alcohol reaction to deter alcohol use
  - Flushing, sweating, N/V, HA, tachycardia
- 250mg daily
- Pros:
  - Generally well-tolerated
  - Demonstrated efficacy (when actually taking)
  - Some evidence to also reduce cocaine cravings
- Cons:
  - Risk of hepatotoxicity (1/25,000 patient-years of tx)
  - Poor compliance (works better if someone monitors)
  - Can't use any products containing alcohol
  - Cannot use for harm-reduction

Acamprosate

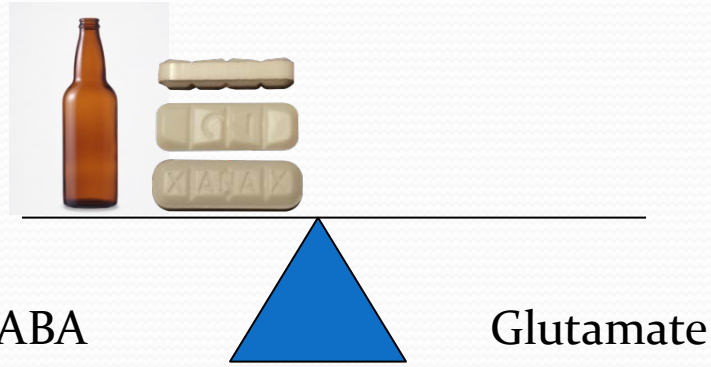


Homeostasis

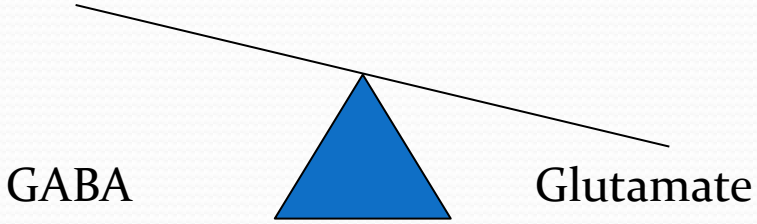


Intoxication/Occasional Alcohol Use

Sedation, psychomotor retardation



Neuroadaptation-chronic alcohol use:
Up regulation of Glutamate
and down regulation of GABA



Withdrawal State:
Unopposed Glutamate up regulation
without alcohol mediated GABA stimulation

Anxiety, Insomnia, psychomotor agitation

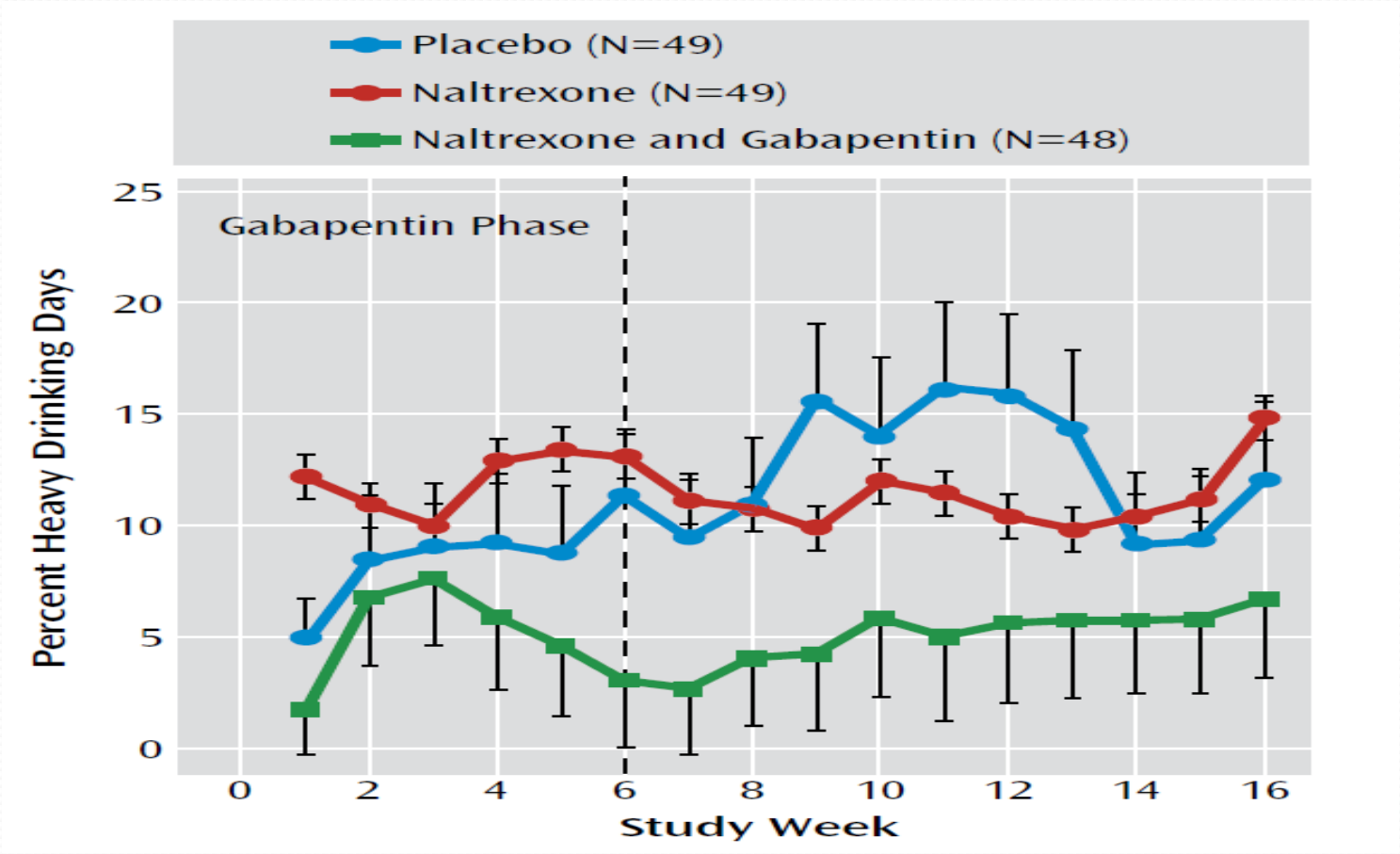
Acamprosate

- ?Restores balance of GABA/glutamate activity
- 666mg (two 333mg Tabs) TID
- Pros:
  - Generally well-tolerated (diarrhea 10-20%, rash <5%)
  - Good option in people with hepatic disease
  - Can be used for harm-reduction
- Cons:
  - Caution in renal impairment (renally excreted)
  - Difficult dosing schedule
  - Studies showing efficacy mostly done in Europe

Gabapentin

- Some studies demonstrate improvements in abstinence rate, time to first drink, number of heavy drinking days, and drinks per heavy drinking day
- 1 recent RCT shows gabapentin XR not as effective as IR
- Dose 600mg TID (this may vary)
- Pros:
  - Makes for a smooth transition from detox
  - Helps with insomnia and negative affect from prolonged withdrawal
- Cons:
  - Uncertain efficacy
  - Difficult dosing schedule

Gabapentin with Naltrexone



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

Anticonvulsants

- Topiramate
  - Some evidence for efficacy in abstinence, time to first drink, heavy drinking days, and drinks per heavy drinking day
  - Mixed evidence in ability to treat cocaine use disorder
  - Main limitation is cognitive slowing
  - Dose: 100-150mg BID
- Valproic Acid
  - Some evidence for decrease in heavy drinking days and drinks per heavy drinking day
  - Dose: 500mg TID
- Carbamazepine
  - Some evidence for benefits similar to topiramate
  - Dose: 800mg-1200mg per day

Baclofen

Drug	Dosage	Mechanism	Metabolism	Excretion	ALD patients
FDA approved for AUD					
Disulfiram	250-500 mg q.d.	Acetaldehyde dehydrogenase inhibitor	Hepatic	Hepatic	No
Naltrexone	50 mg q.d. (oral) 380 mg monthly i.m.	μ and k-opioid receptor antagonis	Hepatic	Renal	No
Nalmefene	18 mg as needed	μ and δ-opiod receptor antagonist k-opioid receptor partial-agonist	Hepatic	Renal	No data
Acamprosate	666 mg t.i.d.	N-metil-D-aspartate receptor antagonist	Minimal	Renal	Limited data, probably yes
Not FDA approved for AUD					
Sodium oxybate	50 mg/kg/day	GABAB receptor agonist	Hepatic	Hepatic	Limited data, probably yes
Topiramate	300 mg q.d.	Facilitates GABAA transmission reduces glutamatergic activity	Hepatic	Renal	No data, probably yes
Ondansetron	1-16 μg/kg b.i.d.	5-HT3 receptor antagonist	Hepatic	Renal	No data, probably yes
Baclofen	10-20 mg t.i.d.	GABAB receptor agonist	Minimal	Renal	Yes
Gabapentin	900-1800 mg t.i.d.	GABA transmission modulator	Minimal	Renal	No data, probably yes
Varenicline	2 mg q.d.	Nicotinic acetylcholine receptor partial agonist	Minimal	Renal	No data, probably yes
Metadoxine	500 mg t.i.d.	Acetaldehyde dehydrogenase activity enhancer	Oxidative	Metabolic	Yes

Addolorato G, Mirijello A, Barrio P, Gual A. Treatment of alcohol use disorders in patients with alcoholic liver disease. *J Hepatol*. (2016) 65:618–30. doi: 10.1016/j.jhep.2016.04.029

Other Meds Used

- Grade C Evidence for:
  - Varenicline
  - Prazosin
  - Oxcarbazapine
  - Lamotrigene
  - Pregabalin
  - Tiagabine
  - Levetiracetam
  - Ondansetron

Case #1

- 39yo M w/ h/o severe alcohol/cocaine use disorder and depression; no medical problems or h/o complicated withdrawal
- Alcohol use disorder
  - Currently on naltrexone 100mg daily
  - Still drinks 2-3 beers most nights, with occasional nights where he binges up to “10 beers and a couple shots”
    - Previously was drinking nearly a case per day
  - Patient’s stated goal: complete abstinence

Case #1 Continued

- Cocaine use disorder
  - Currently using almost daily with significant cravings
  - Engaged in substance use group therapy/NA
  - Never tried MAT
- Depression
  - Taking 200mg sertraline daily
  - Has ongoing mild depressive symptoms
- Homeless with minimal social support

What medication changes would you make next?

A. Add disulfiram 250mg daily to further treat alcohol use disorder and reduce cocaine cravings

B. Start disulfiram 250mg daily and stop naltrexone as combination therapy is not effective

C. Switch to long-acting injectable naltrexone for improved compliance

D. Augment sertraline with bupropion, as this can help reduce cocaine cravings and better treat depression

E. Start topiramate, titrate to 100mg BID, and stop naltrexone, as this can treat both alcohol and cocaine use

What medication changes would you make next?

**A. Add disulfiram 250mg daily to further treat alcohol use disorder and reduce cocaine cravings

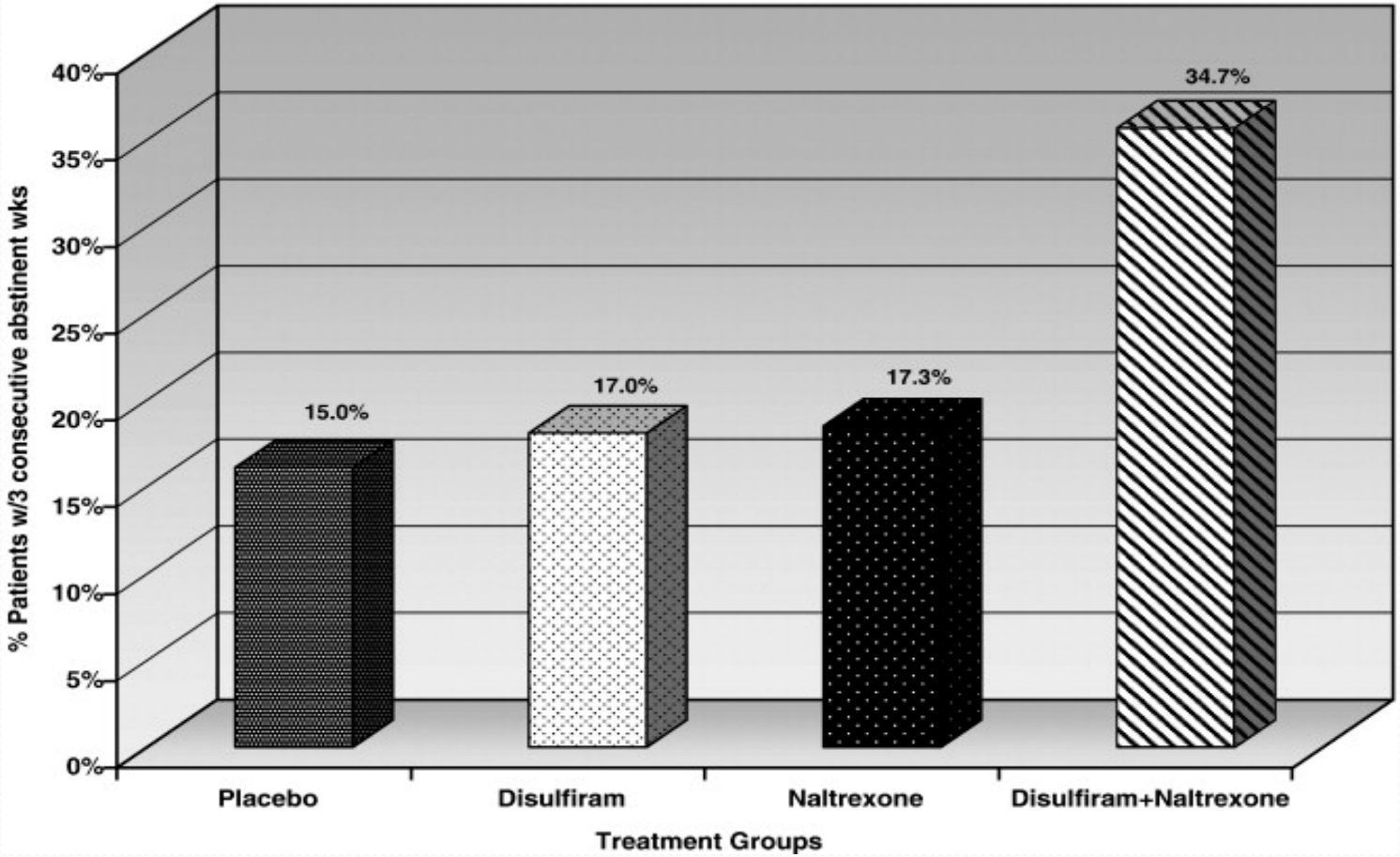
B. Start disulfiram 250mg daily and stop naltrexone as combination therapy is not effective

C. Switch to long-acting injectable naltrexone for improved compliance

D. Augment sertraline with bupropion, as this can help reduce cocaine cravings and better treat depression

E. Start topiramate, titrate to 100mg BID, and stop naltrexone, as this can treat both alcohol and cocaine use

Percent of cocaine/alcohol use disorder patients with 3+ consecutive weeks of abstinence from both cocaine/alcohol in an 11-week clinical trial:



Pettinati HM et al. Addict Behav. (2008)

Case #2

- 63 y/o white female with metastatic hepatocellular carcinoma (HCC) with vascular involvement, cirrhosis, HCV, unspecified cognitive impairment, and severe EtOH use disorder
- Alcohol use:
  - Use disorder for several decades
  - Five months of sobriety prior to HCC diagnosis
  - Relapse after diagnosis
  - Uncertain amount
  - She and her partner downplay drinking
  - Opiate pain meds withdrawn given ongoing alcohol use, and patient's goal is to get pain meds back

Case #2 Continued

- Hepatocellular carcinoma:
  - Diagnosed in January 2018
  - Received debulking surgery in March 2018
  - Now on palliative Nivolumab (has alcohol in the IV fluid)
- Unspecified cognitive impairment
  - Hepatic encephalopathy vs. alcohol-related vs. multifactorial
  - Grossly normal LFT's but INR was 1.4-1.7

What would you recommend?

A. Naltrexone (oral or long acting injectable)

B. Disulfiram

C. Alcoholics Anonymous

D. Gabapentin

E. Baclofen

F. Topiramate

What would you recommend?

A. Naltrexone (oral or long acting injectable)

B. Disulfiram

C. Alcoholics Anonymous

D. Gabapentin

**E. Baclofen

F. Topiramate

Baclofen

Drug	Dosage	Mechanism	Metabolism	Excretion	ALD patients
FDA approved for AUD					
Disulfiram	250-500 mg q.d.	Acetaldehyde dehydrogenase inhibitor	Hepatic	Hepatic	No
Naltrexone	50 mg q.d. (oral) 380 mg monthly i.m.	μ and k-opioid receptor antagonis	Hepatic	Renal	No
Nalmefene	18 mg as needed	μ and δ-opiod receptor antagonist k-opioid receptor partial-agonist	Hepatic	Renal	No data
Acamprosate	666 mg t.i.d.	N-metil-D-aspartate receptor antagonist	Minimal	Renal	Limited data, probably yes
Not FDA approved for AUD					
Sodium oxybate	50 mg/kg/day	GABAB receptor agonist	Hepatic	Hepatic	Limited data, probably yes
Topiramate	300 mg q.d.	Facilitates GABAA transmission reduces glutamatergic activity	Hepatic	Renal	No data, probably yes
Ondansetron	1-16 μg/kg b.i.d.	5-HT3 receptor antagonist	Hepatic	Renal	No data, probably yes
Baclofen	10-20 mg t.i.d.	GABAB receptor agonist	Minimal	Renal	Yes
Gabapentin	900-1800 mg t.i.d.	GABA transmission modulator	Minimal	Renal	No data, probably yes
Varenicline	2 mg q.d.	Nicotinic acetylcholine receptor partial agonist	Minimal	Renal	No data, probably yes
Metadoxine	500 mg t.i.d.	Acetaldehyde dehydrogenase activity enhancer	Oxidative	Metabolic	Yes

Addolorato G, Mirijello A, Barrio P, Gual A. Treatment of alcohol use disorders in patients with alcoholic liver disease. *J Hepatol*. (2016) 65:618–30. doi: 10.1016/j.jhep.2016.04.029