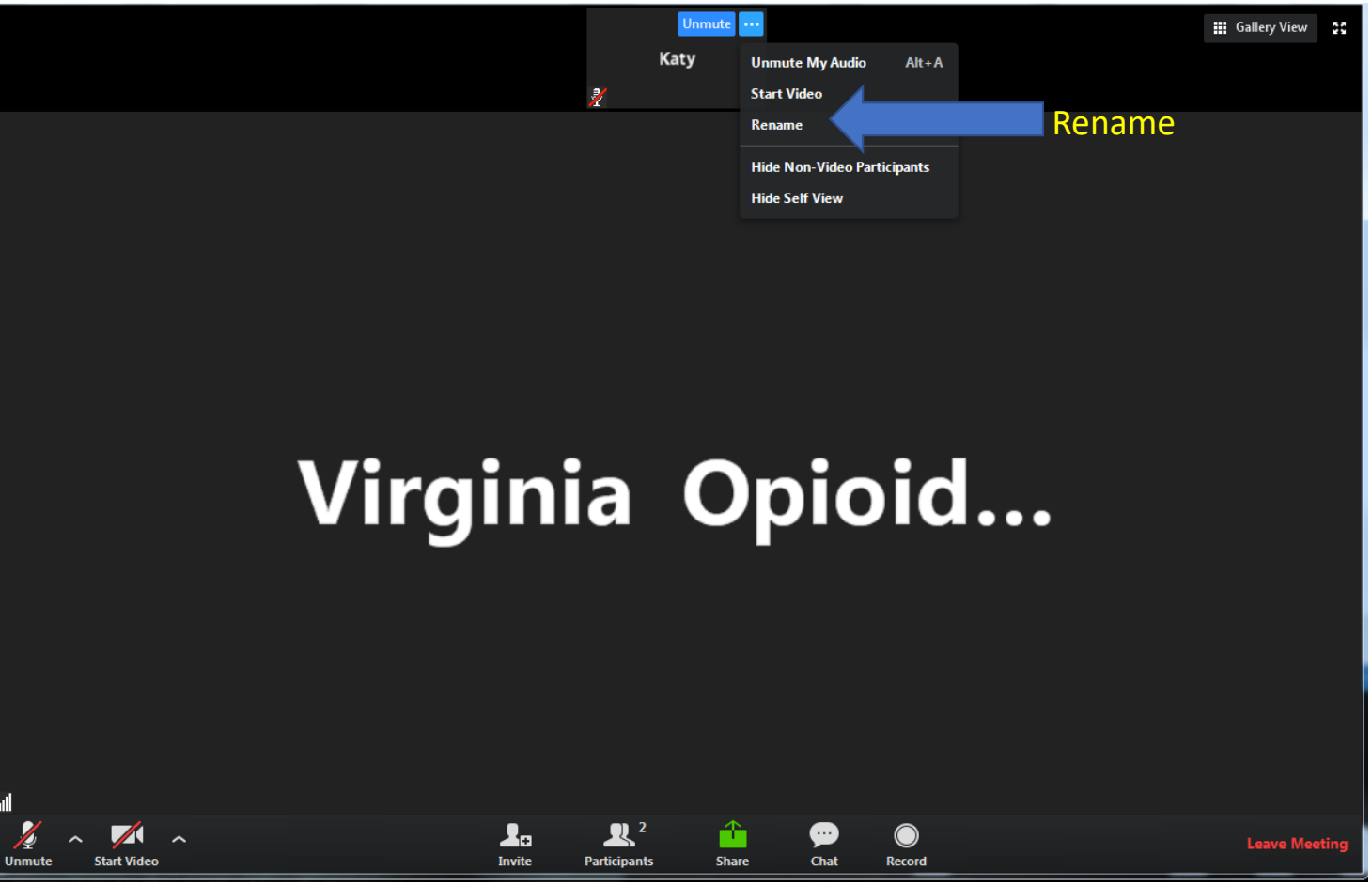
Virginia Opioid Addiction ECHO* Clinic

November 1, 2019

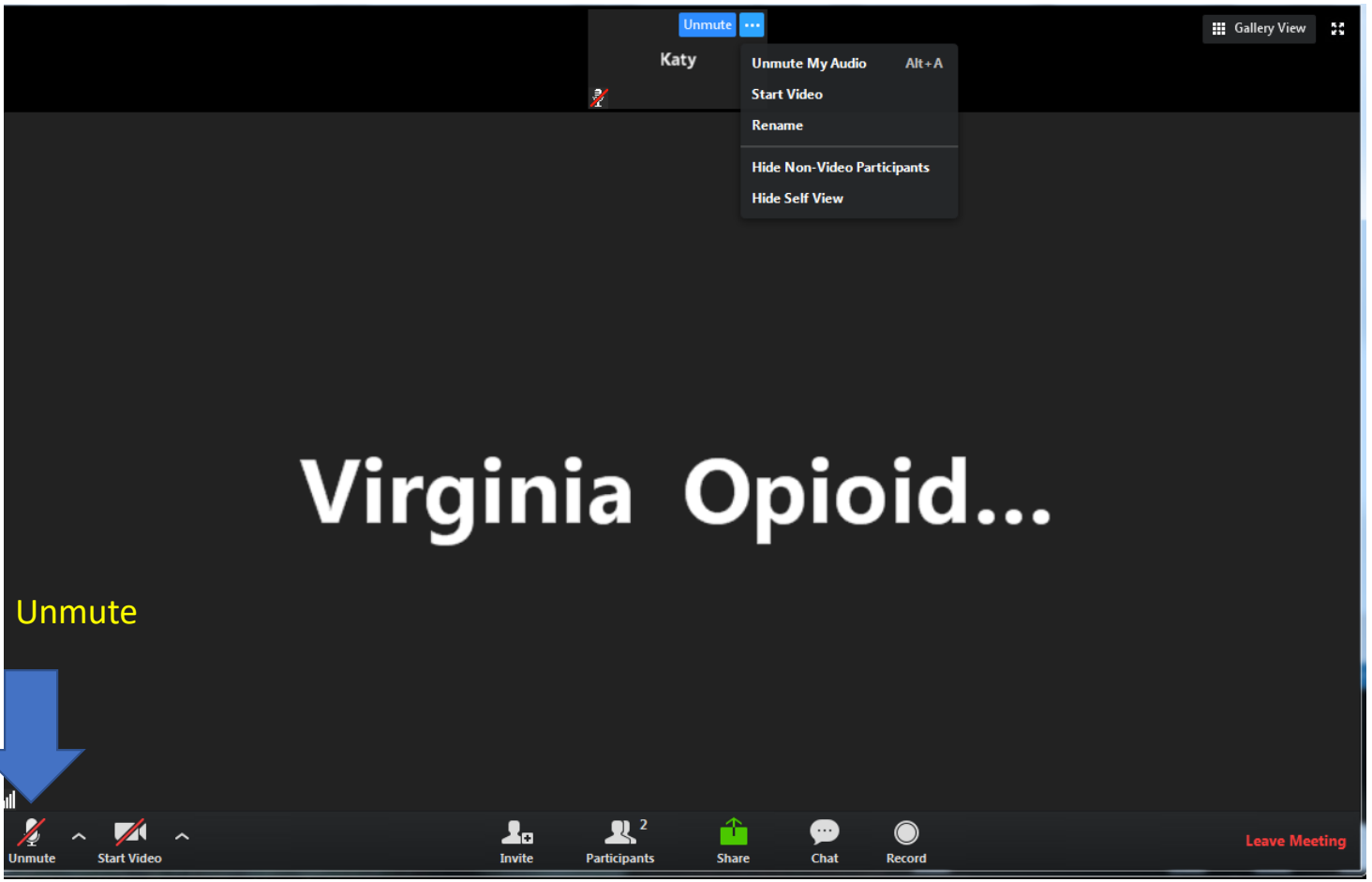
*ECHO: Extension of Community Healthcare Outcomes

Helpful Reminders



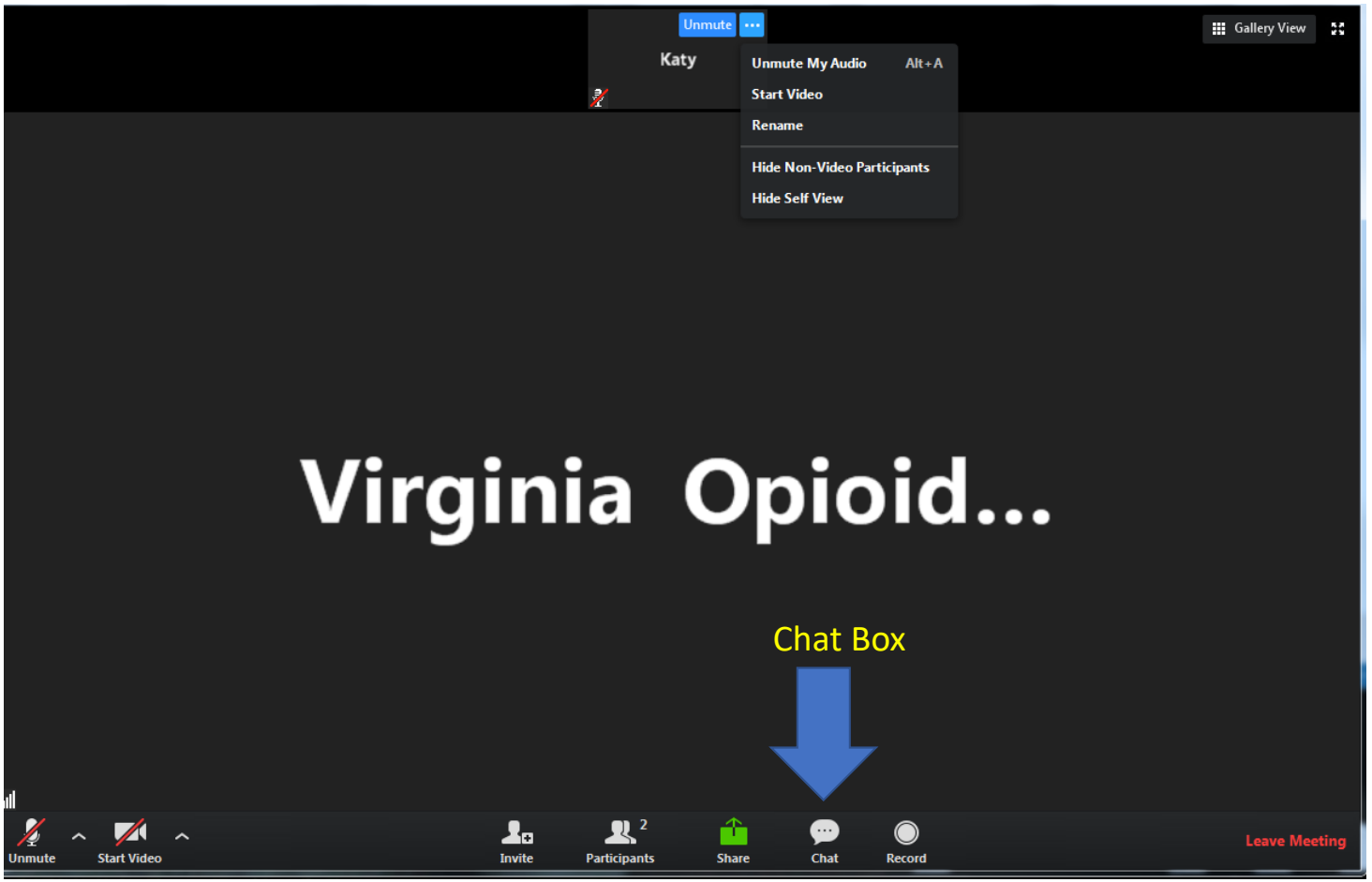
- Rename your Zoom screen, with your name and organization

Helpful Reminders



- You are all on mute please unmute to talk
- If joining by telephone audio only, *6 to mute and unmute

Helpful Reminders



- Please type your full name and organization into the chat box
- Use the chat function to speak with IT or ask questions

VCU Opioid Addiction ECHO Clinics

VCU Health
VCU School of Medicine

VDH Virginia Department of Health | VDHLiveWell.com

Virginia Department of Behavioral Health & Developmental Services

- Bi-Weekly 1.5 hour tele-ECHO Clinics
- Every tele-ECHO clinic includes a 30 minute didactic presentation followed by case discussions
- Didactic presentations are developed and delivered by inter-professional experts
- Website Link: www.vcuhealth.org/echo

Hub Introductions

VCU Team	
Clinical Director	Gerard Moeller, MD
Administrative Medical Director ECHO Hub and Principal Investigator	Vimal Mishra, MD, MMCi
Clinical Expert	Lori Keyser-Marcus, PhD Courtney Holmes, PhD Albert Arias, MD Kanwar Sidhu, MD
Didactic Presentation	Albert Arias, MD
Program Manager	Bhakti Dave, MPH
Practice Administrator	David Collins, MHA
IT Support	Vladimir Lavrentyev, MBA

Introductions:

- Name
- Organization

Reminder: Mute and Unmute to talk
*6 for phone audio
Use chat function for Introduction

What to Expect

I. Didactic Presentation
   I. **Albert Arias, MD**
II. Case presentations
   I. Case 1
      I. Case summary
      II. Clarifying questions
      III. Recommendations

   II. Case 2
      I. Case summary
      II. Clarifying questions
      III. Recommendations

III. Closing and questions

Lets get started!
Didactic Presentation

Incorporating Pharmacotherapy for Alcohol Use Disorder into Your Practice:

The Basics of What You Need to Know…

Albert J. Arias, M.D., M.S.
Associate Professor, Department of Psychiatry,
Associate Division Chair, Addiction Psychiatry
Institute of Drug and Alcohol Studies
Virginia Commonwealth University School of Medicine (aka MCV)

Disclosures

- No drug company research support
- Not on speakers bureaus
- No financial disclosures
- Will discuss OFF-LABEL use of medications (e.g., topiramate for AUD)
- Research Support from:
  - NIAAA R01 AA024466
  - NIAAA R21
  - NIDA SBIR II (Subaward)

Learning Objectives

- Learn about available pharmacotherapies for AUD and how to use them (cover the main 5)
- Learn about the evidence base supporting the use of these medications
- To learn about new clinical biomarkers for alcohol use and how they can increase diagnostic authority for clinicians
- Not going to talk about withdrawal

Why Care? Impact of AUDs

- **US DSM-5 AUD: about 29% lifetime, 14% last year**
- Alcohol Use Disorder: Excessive drinking >$250 billion/year impact (Sacks et al., 2010)
- Top 3 “actual” causes of death (preventable/modifiable behaviors, Mokdad et al., 2004)

Barriers to Treatment with AUD Medications

- Most AUD patients don't ever receive meds:
  - VA study <5%, US total <10%
- Physicians' perceptions of limited effectiveness
- Difficulty "seeing" an impact of the medication
- Poor information dissemination
- Medication adverse effects
- Inadequate time available to physicians for patient management
- Patient reluctance to take medications
- High prices of medication

Mark et al., 2003a, 2003b, 2003c, 2009,Thomas et al., 2003, Harris et al., 2010, 2012, 2013, Grant et al., 2015

Comparison of Healthcare Utilization Among Patients Treated With Alcoholism Medications

- 2977 patients receiving any alcoholism medication
  - Naltrexone XR
  - Oral Naltrexone
  - Disulfiram
  - Acamprosate
- 2977 patients receiving no alcoholism medication
- Measured outcomes
  - Detoxification admissions
  - Alcoholism- related admissions (admissions with a principal diagnosis of alcohol dependence
  - Non-alcoholism-related admissions.
  - Utilization measured as the % of patients with admissions and the total inpatient days

Mark et al., 2010

Mark et al., 2010

Table 2. Healthcare Utilization in the Groups Receiving Any vs No Alcoholism Medication

Variable	Receipt of Alcoholism Medication			
	Any (n = 2977)		None (n = 2977)	*P* Value
Inpatient services utilization		*		
% With detoxification admission	8.7	*	13.4	<.001
No. of detoxification days per 1000 patients, mean (SD)	706 (3422)	*	1163 (4552)	<.001
% With alcoholism-related admission	6.8	*	11.2	<.001
No. of alcoholism-related days per 1000 patients, mean (SD)	650 (3790)		1086 (5006)	<.001
% With nonalcoholism-related admission	11.4		11.6	.78
No. of nonalcoholism-related days per 1000 patients, mean (SD)	862 (4730)		967 (4703)	.39
Inpatient costs per 1000 patients, $		*		
Detoxification days	1,890,882	*	3,113,389	<.001
Alcoholism-related days	1,818,292		3,037,374	<.001
Alcoholism-related ED visits				
% With visit	8.3	*	10.3	.007
No. of visits per 1000 patients, mean (SD)	127 (553)		171 (657)	.005
Substance abuse and mental health visits		*		
% With substance abuse diagnosis	62.8	*	94.9	<.001
No. of substance abuse visits, mean (SD)	5.4 (8.6)	*	7.7 (9.0)	<.001
% With combined substance abuse and mental health diagnosis	80.8		97.3	<.001
No. of combined substance abuse and mental health visits, mean (SD)	9.0 (10.9)		10.5 (10.7)	<.001

VCU

Oslin et al., 2013 – RCT of Alcohol Care Management in Primary Care

- 26 week single blind randomized clinical trial
- 163 alcohol dependent veterans were randomly assigned to **ACM** or **standard outpatient treatment**
- Primary Outcome Measures
  - Amount of alcohol consumed
    - Recorded heavy drinking days as well as standard drinking days
    - Recorded 60 days prior to intervention and during intervention
  - Engagement in clinical services tracked by
    - VA electronic medical record
    - Questionnaire of services received outside the VA

Oslin et al., 2013

Key Features of Alcohol Care Management (ACM)

- BASED ON AN INTEGRATED CARE MODEL
- Patients met weekly with their Behavioral Health Provider for 30 minutes, over the phone if necessary
- The BHP assessed alcohol used, offered support, encouraged , and educated the patient about the pharmacology, dosing regimen, and drug side effects
- Promotes goal of abstinence but allows participants to set own goals with abstinence as one option
- Participants were offered treatment with naltrexone (50 mg)
- Use of naltrexone was not a requirement
- Naltrexone was prescribed in 56/85 (65.9%) of the ACM participants

Oslin et al., 2013

Key Features of the Specialty Care Addictions Treatment

- Treatment was based on a 12 step model
- Interventions included evaluations, detox, counseling, and pharmacotherapy
- All participants started an IOP consisting of 2-4 half day sessions for up to 6 weeks
- Promotes goal of abstinence
- After IOP participants began group therapy 1-2 times a week
- Naltrexone, acamprosate and disulfiram was available
- Naltrexone was prescribed to 9/78 (11.5% of patients)

Oslin et al., 2013

Results

- Average number of visits made
  - 6.43 visits- Specialty Care Group
  - 11.31 visits- ACM group
  - Significant main effect for the intervention p<.0001
- Significant main effect of the ACM group more likely to refrain from heavy drinking

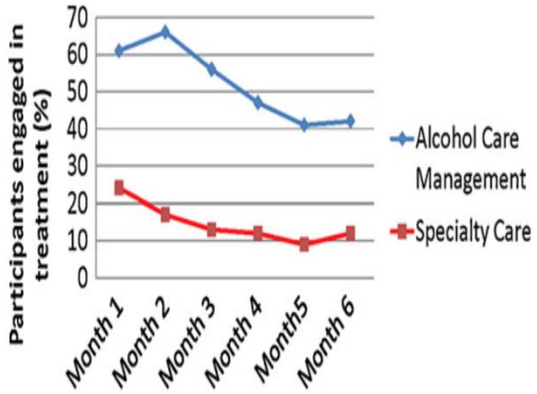


Figure 2. Treatment engagement as determined by the percentage of participants who had two or more addiction-related treatment visits in a given month.

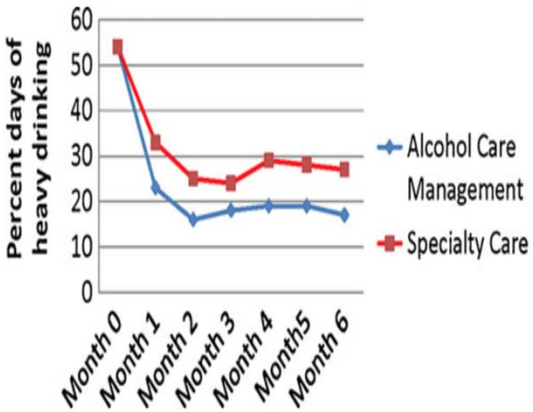


Figure 3. Group means of the percent days of heavy drinking from baseline throughout treatment.

Oslin et al., 2013

Your Role, Responsibilities

- Target population for primary care:
  - Mild to moderate AUDs
  - Regular Heavy Drinkers ("At Risk Drinkers") with co-occurring medical illness or uncomplicated psychiatric illness
  - Know when to refer, and specialized tx

- FOR GENERAL PSYCHIATRISTS:
  - All the above plus…
  - Manage partially stabilized patients with all levels of severity and dual diagnosis
  - Know when specialized treatment settings and higher level of care indicated, work with addiction specialists
  - Need to be comfortable with pharmacotherapies for alcohol dependence

- For trained sub-specialists (ABAM/ABPN);
  - All of the above plus…
  - Consult to colleagues, referrals
  - The most difficult alcoholism cases

Unmet Treatment Needs

- Only a minority of adults with alcohol abuse or dependence receive treatment
- Many with alcohol dependence will relapse if they only receive psychosocial/behavioral tx
- Medications still not widely prescribed, though many would benefit

Cohen et al., 2006, Johnson et al., 2010, Swift et al., 1999, Harris et al., 2012

Etiology of Alcohol Use Disorders

- Heritablility 50-60% Alcoholism
- Similar for drug dependence
- Etiology: Complex disorder; genes and environment
  - Early Life Adverse Experiences
- Neuromodulation-changes in the brain
- Changes in the stress response system
- Allostatic changes hedonic setpoint

AUD: A Molecular Disease

- Chronic heavy alcohol exposure effects neurons on the molecular level
- Huge alterations in levels of many transmitters and changes to receptors (GABA, Glutamate, Serotonin, Dopaminergic etc)
- Active at Level of Gene Regulation: Changes in transcription of many genes
- Subunit Substitution Hypothesis: GABA-A receptors
- Changes glutamatergic receptor subunits and localization also
- Changes in levels of CREB, activity of Kinases
- Targets: BDNF, NPY, CRF (levels affected)
- Profound changes in neuronal physiology in various brain regions
- Epigenetic changes-

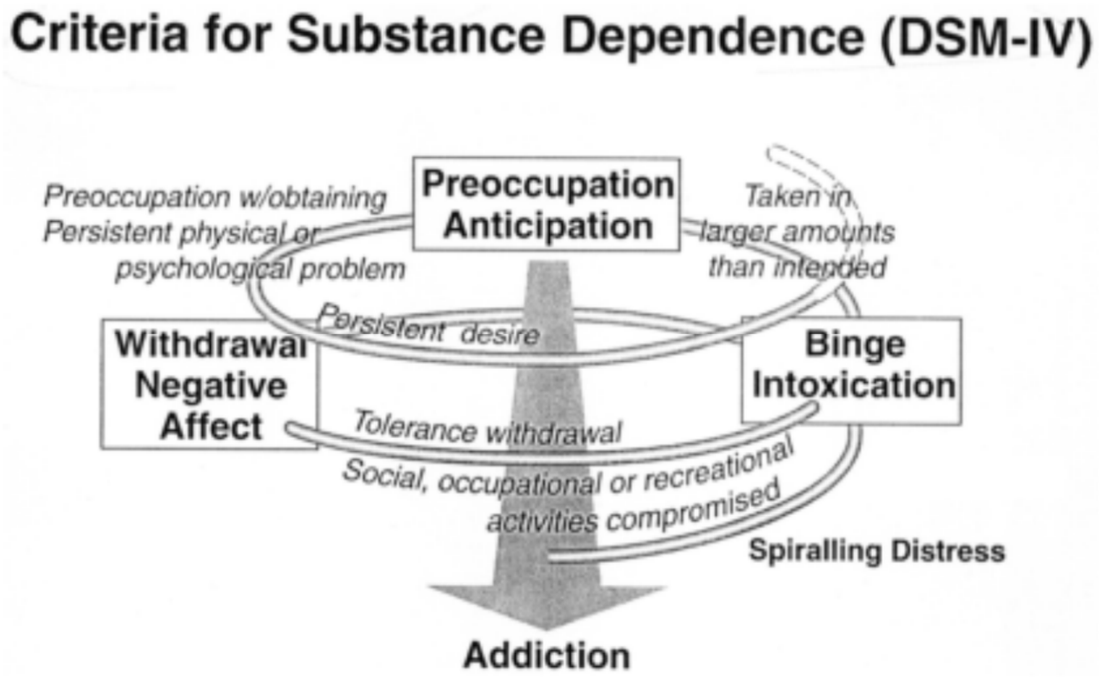
Moonat et al., 2009, Kalivas and O'Brien 2008

DSM 5 AUD- at least 2 in last 12 months.

- Had times when you ended up drinking more, or longer than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over the aftereffects?
- Experienced craving — a strong need, or urge, to drink?
- Found that drinking — or being sick from drinking — often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- Continued to drink even though it was causing trouble with your family or friends?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
- Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?
- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or sweating? Or sensed things that were not there?

- Mild: 2-3 symptoms, Moderate: 4-5 symptoms, Severity 6+ symptoms

Koob and LeMoal 2001



A DISEASE OF ALLOSTATIC CHANGES: A CHANGE IN HEDONIC AND REWARD SETPOINT

Neural substrates of addiction

- Emotional-motivational reward and reinforcement, incentive learning
- “Cortical-Basal Ganglia Circuit”
- Prefontal Cortex and Cingulate areas
- Mesolimbic Dopaminergic system
- VENTRAL STRIATUM (the heart of it)
  - Ventral Tegmentum
  - Nucleus Accumbens
- Limbic Areas: hippocampus, amygdala

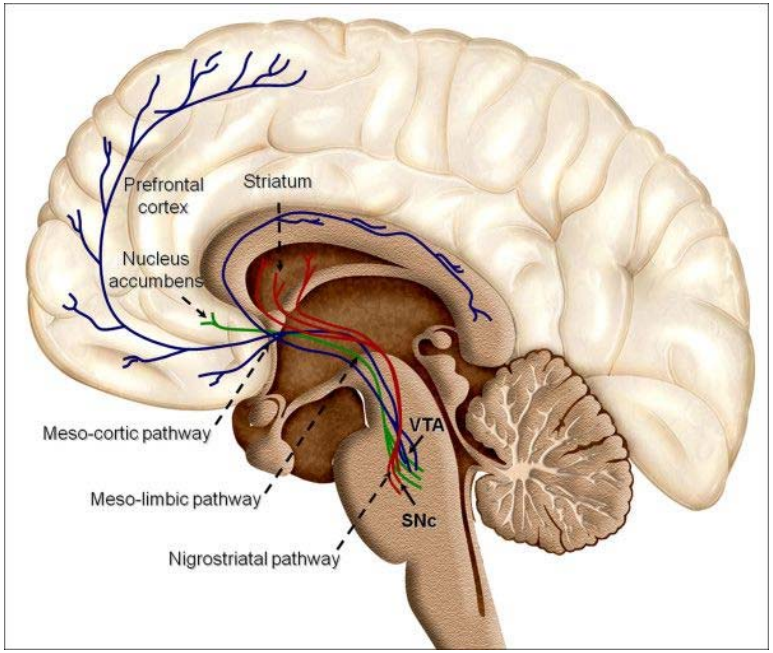


Image from Arias-Carillion et al., 2010

Haber and Knutson, 2010, Koob and Volkow, 2010

Protracted Abstinence Syndrome

- Important concept in Addiction Medicine
- Allostatic State: a new setpoint for hedonic function and reward function- biological basis
- A pathological state, slow to return to normal (scale of months to years)
- AFTER ACUTE DETOX- cause return to use even months later
- Without alcohol/drug… dysphoric, more anxious and easily stressed, unable to motivate for normal rewards, unable to inhibit impulse to seek or use drugs

Koob 2003, Kalivas and O'Brien

Generalized Pharmacotherapeutic Mechanisms

- Multiple **targets for pharmacologic treatment;**
  1. Block or attentuate acute positively reinforcing effects (including blocking the drug from reaching the brain)
  2. Reduce negative reinforcement (reward generated by the removal of painful or stressful conditions or events) from the "protracted abstinence syndrome", and acute withdrawal
  3. Aversive reaction, conditioning (punishment)
  4. Reduce the learned anticipation of alcohol effects (URGE/CRAVING- positive and negative)
  5. Promote beneficial neuroplasticity (prevent the neuromodulatory slide into the dependent state, and help shift it back toward normal if already changed, normalize stress response and reverse protracted abstinence syndrome

To whom should you offer medication?

- Consider Medication for:
  - those with an AUD
  - frequent heavy drinkers “at risk/problem”
- Consider 12 step and other Psychosocial therapies for heavy drinkers and AUD
  - with or without medication
- For more severe patients or with complicated dual medical/psych dx; refer

Treatment Goals

- Prevent worsening of/into AUD,
- Prevent drinking related consequences psychosocial consequences and problems
- Eliminate heavy drinking, or prevent relapse to
- Long term reduce risks of increased morbidity and mortality.
- Ask patient if they want abstinence or reducing to non-harmful levels
- Most don’t want abstinence (really)
- Some have tried non-harmful with treatment, and have failed, consider abstinence goal and referral

The most used first and second line medications

- FDA Approved for AUD:
  - Disulfiram (approved 1949)
  - Naltrexone (approved 1994), (PO and IM)
  - Acamprosate (approved 2004)
- Not FDA Approved for AUD:
  - Topiramate (good evidence)
  - Gabapentin (mediocre evidence)

Acamprosate

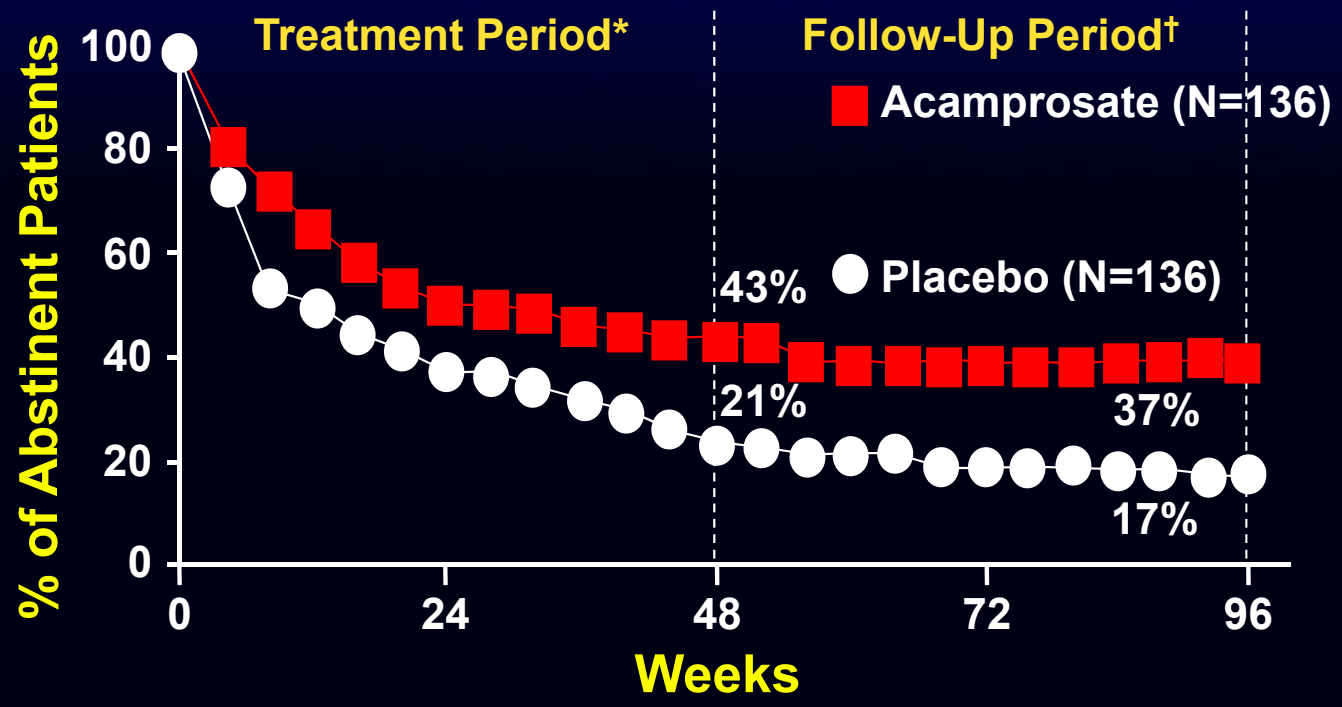
- mGluR5 antagonist
- Indirectly modulates NMDA receptor
- Acts as an NMDA antagonist, may + GABA
- Efficacy for abstinent alcoholics to prevent relapse, goal of total abstinence (Meta-analysis)
- Effectiveness demonstrated, primary care (Kiritz-Topor et al., 2004, European)
- Cost-effectiveness demonstrated also (Poldrugo et al. 2005)
- Best suited for those with abstinence as goal.
- Efficacy substantiated by meta-analysis, but famous for large negtive US trial

Rosner et al., 2009, Maisel et al., 2013

2012 Individual Patient Level Meta-Analysis (Mason and Lehert)

- N of about 6,000
- Broad efficacy for decreasing heavy drinking days, increasing abstinent days, also on total abstinence and abstinence from heavy drinking
- Worked for women and men

Sass et al. Study



*p=0.001; †p=0.003; 272 patients were entered into the study over 2 years; Kaplan-Meier survival analysis (survival function estimate). Continuous abstinence for the treatment and follow-up periods. Sass et al., Arch Gen Psychiatry, 1996

Dosing and SE's

- 666mg TID no titration needed
- Renally excreted, half life 20-33 hrs, adjustment required moderate impairment, contraindicated for severe renal impairment
- No adjustment for food, but poor bioavailability 11%
- Very well tolerated overall, no interactions
- GI upset (diarrhea, nausea)
- Rare: suicidal behavior more vs placebo

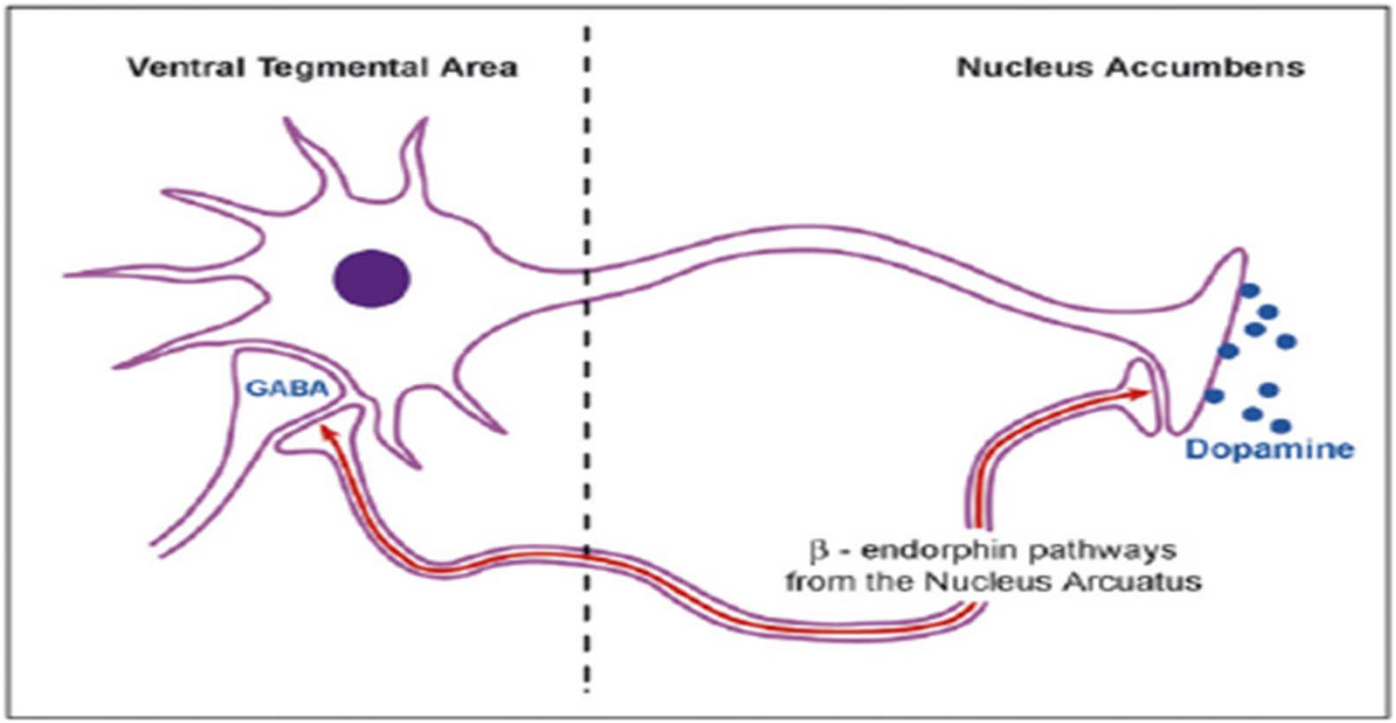
Naltrexone oral

- Opioid Receptor Antagonist
- Modulates dopaminergic transmission NAcc, Reward Circuitry
- Clearly Efficacious, many trials and meta-analyses, small effect size (approximate NNT=7-12)
- Reduces heavy drinking and relapse to heavy drinking, (smaller effect size- abstinent days)
- Probably works by MOA 1 and 3, maybe 5
- 50mg daily dose (25mg-150mg daily)

Rosner et al., 2008, Kranzler and VanKirk 2001,

Bouza et al., 2004, Srisurapanont M, Jarusuraisin N, 2005

From Johnson, 2008



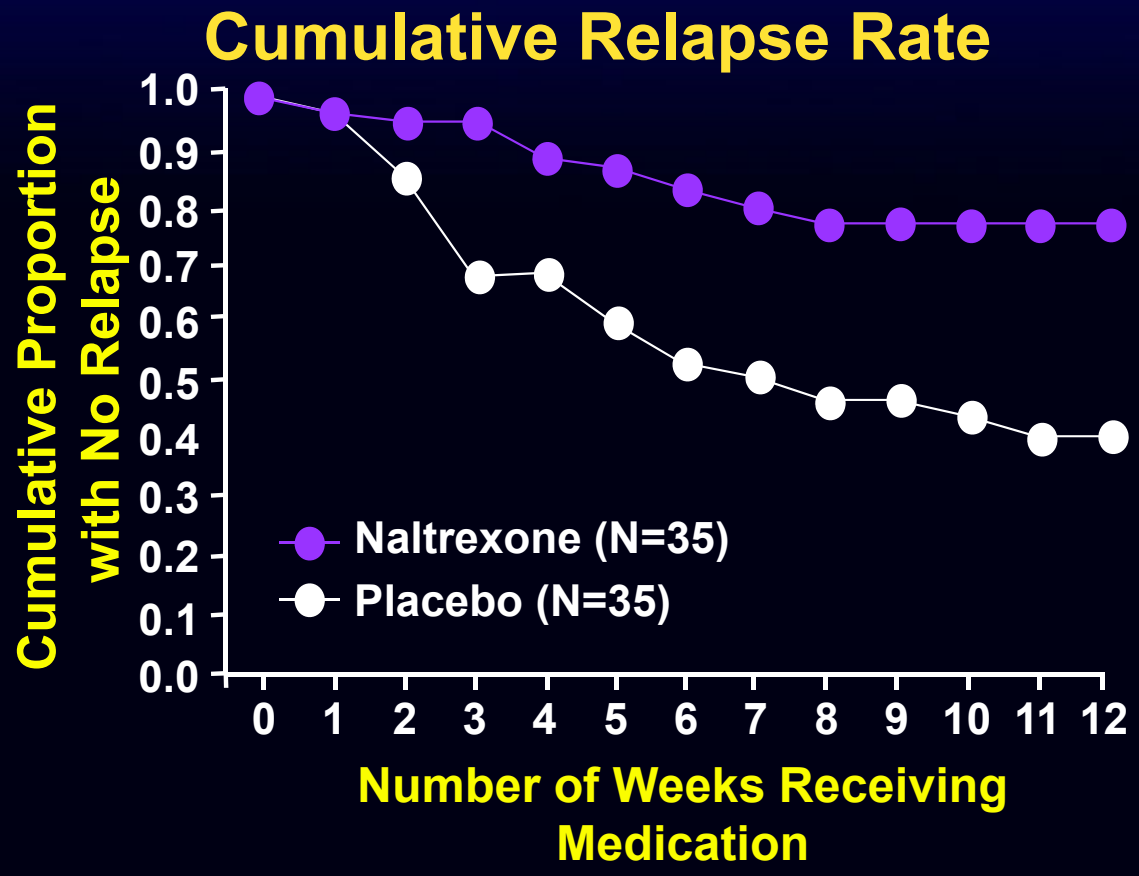
Naltrexone dosing, SE's

- 50mg daily (range 25mg-150)
- Metabolized in Liver mainly-
  - dihydrodiol dehydrogenase
  - Cytosolic enzymes, Conjugation
- Renal excretion occurs esp. for metabolite
- PO dosing half life is about 4 hours, (range of 2-10 hours reported),
- 6-beta naltrexol has a longer half-life (range of about 7.5-13 hours) and may accumulate (Porter et al., 2002)
- IM- less metabolite, half life ~5-10 days, depending on polymer erosion
- Probably no need to adjust for renal impairment

Naltrexone SE's

- Nausea, Vomiting, anorexia
- Headache, Dizziness
- Arthralgias, muscle cramps
- Uncommon but > placebo: depression (IM)
- Rare: suicidality (IM), liver toxicity, eosinophilic pneumonia, injection site reactions (IM)
- Contraindicated in severe liver disease
- Rare hepatotoxicity- black box
- Probably no need to adjust for renal impairment

Naltrexone in the Treatment of Alcohol Dependence

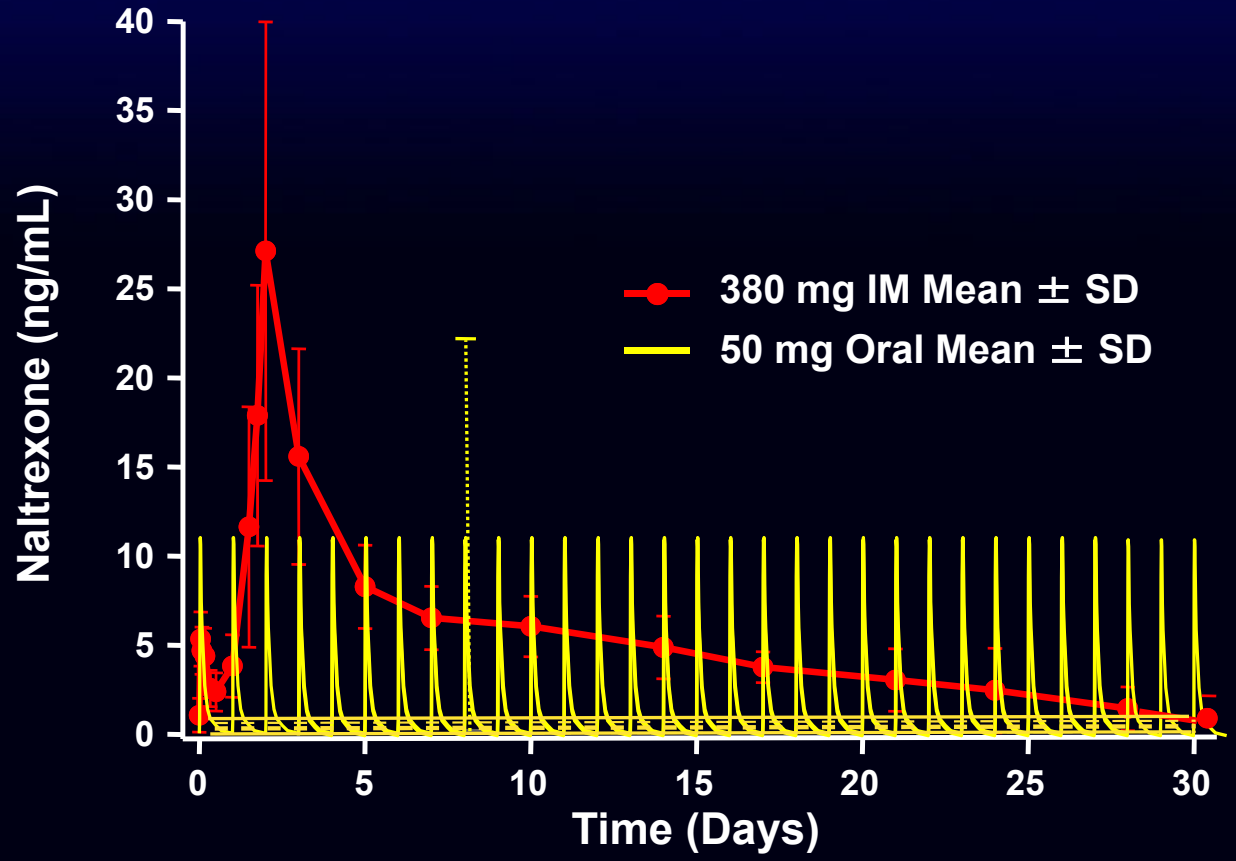


Volpicelli et al., Arch Gen Psychiatry, 1992

Risks with IM

- Injection site reactions
- Eosinophili Pneumonia
- Depression/SI- not common but probably greater than placebo by 5/1%
- Note that in most naltrexone studies these are rare side effects- Revia FDA labeling not greater than placebo
- NTX safe to use in dual diagnosis/depressed patients with adequate follow up

Mean Steady State Naltrexone Concentration Following XR-NTX 380 mg Compared to Daily Oral Dosing



Phase III Trial Design

- Objectives: evaluate safety & efficacy of XR-NTX
- 624 DSM-IV alcohol dependent subjects
  - > 2 Heavy Drinking Days (HDD) / week during prior month
- 24 centers
- Treatment duration: 24 weeks
- Dose: XR-NTX 190 mg, XR-NTX 380 mg, matching placebo doses by volume
  - Once a month intramuscular injection

IM Naltrexone Efficacy Trial

- 24 week multicenter RCT, N=624 Alcohol dependent subjects, 380mg and 190mg dose, placebo controlled
- Concomitant BRENDA therapy to all
- **Overall significant reduction in event rate of heavy drinking for 380mg subjects vs. placebo (25% reduction, p = 0.02)**
- Significant statistical interactions with treatment group and sex, ability to be abstinent to alcohol for 7 days prior to therapy
- Dropout rate similar to oral naltrexone studies, similar side effect profile

Secondary Analysis

- Of the subset that achieved 7 days abstinence prior to start of treatment…
- Higher rates of abstinence at the end of treatment but not statistically significant
- GGT levels reduced in all groups, no difference
- FDA approved labeling: indicated for alcohol dependent patients able to achieve some abstinence before treatment initiation (how long not specified)- 4 days sufficient though

Garbutt et al., 2005

Table 3. Analyses of Primary and Secondary Efficacy Outcomes*

	Population	Naltrexone 380 mg vs Placebo		Naltrexone 190 mg vs Placebo	
		Hazard Ratio (95% CI)	*P* Value	Hazard Ratio‡ (95% CI)	*P* Value
Primary outcome					
Heavy drinking	624	0.75 (0.60-0.94)	.03	0.83 (0.68-1.02)	.07
Sex					
Men	423	0.56 (0.41-0.77)	<.001	0.83 (0.64-1.07)	.16
Women	201	1.23 (0.85-1.78)	.28	1.07 (0.73-1.58)	.72
Goal of total abstinence					
Yes	270	0.72 (0.48-1.08)	.11	0.88 (0.61-1.28)	.50
No	354	0.79 (0.59-1.05)	.10	0.91 (0.70-18)	.48
Lead-in drinking					
Yes	571	0.79 (0.62-1.00)	.05	0.93 (0.75-1.15)	.48
No	53	0.20 (0.07-0.62)	.005	0.05 (0.02-0.15)	<.001
Secondary outcomes					
Risky drinking†	624	0.90 (0.76-1.07)	.23	0.95 (0.81-1.13)	.58
Nonabstinent days	624	0.96 (0.83-1.11)	.58	0.98 (0.85-1.14)	.80

*For the primary end point (heavy drinking), the Hochberg method was used to adjust multiple comparisons. As specified a priori, the secondary outcomes (drinking more than the National Institute on Alcohol Abuse and Alcoholism–specified level of risky drinking and nonabstinent days) are included for informational purposes, and no adjustments were made.

†National Institute on Alcohol Abuse and Alcoholism–specified level of risky drinking is more than 2 drinks per day for men and more than 1 drink for women.

‡Treatment effect size is derived from the estimate of the hazard ratio (HR) for each individual treatment relative to placebo: HR = 1 indicates no treatment effect (ie, treatment effect size = 0); HR = 0.75 is a 25% reduction of heavy drinking relative to placebo (ie, treatment effect size relative to placebo = 0.25); HR = 1.25 is a 25% increase of heavy drinking relative to placebo (ie, treatment effect size relative to placebo = 1.25).

Disulfiram

- Approved by FDA before efficacy requirement
- **Irreversibly** Inhibits Acetaldehyde dehydrogenase:
  - Interferes with the breakdown of acetaldehyde,
    a toxic byproduct of alcohol metabolism

  Ethanol → Acetaldehyde → Acetate
- The Disulfiram-Ethanol Reaction: aversive reaction
- Sweating, flushing, nausea/vomiting, headache, tachycardia, hypotension

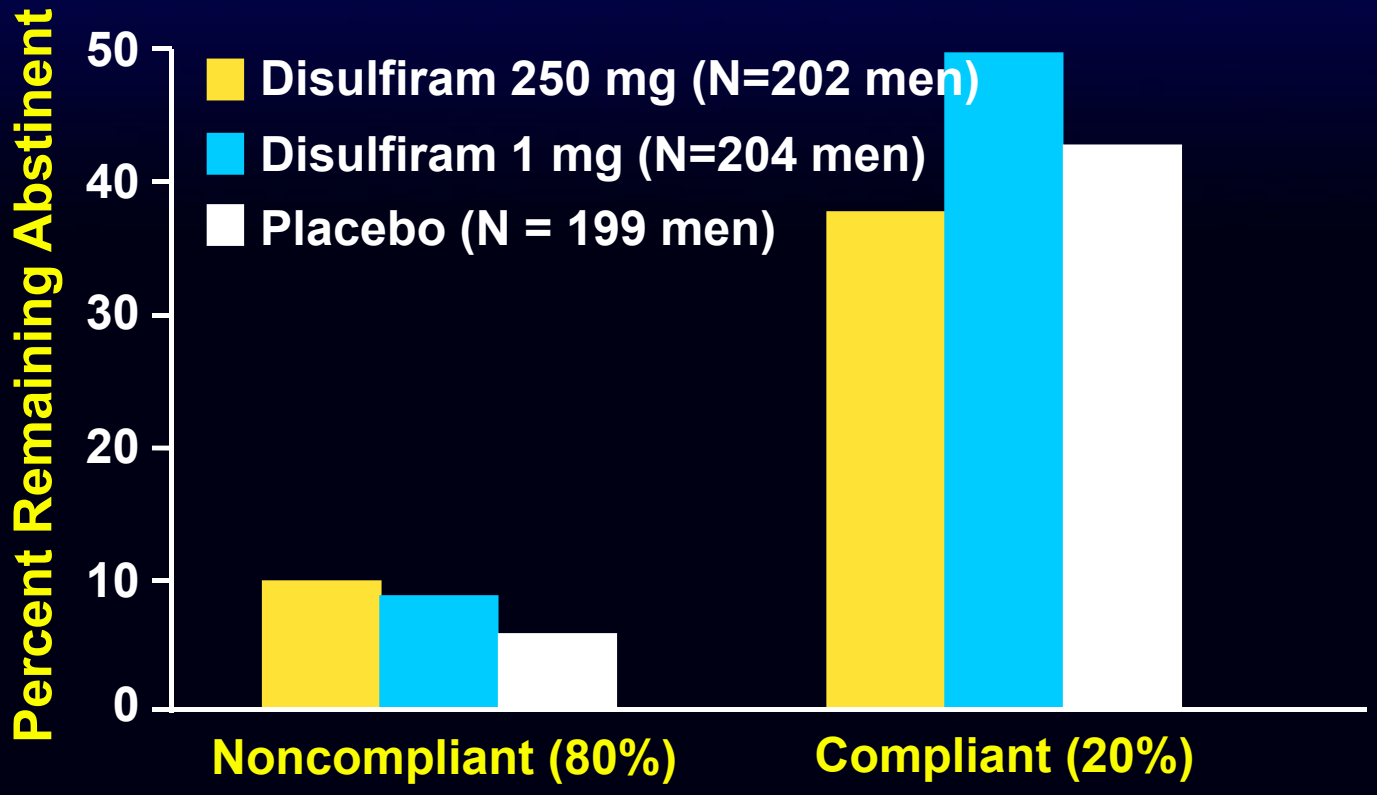
Disulfiram- Effective under the right conditions

- Not proven efficacious versus placebo,or blinded, or when dosing unsupervised/non-contingent
- Can help some patients under certain conditions
- Highly motivated, supervised, contingent (e.g. observed disulfiram as part of methadone program)
- Disulfiram contract and supervision: social, family pressure for observed dosing may improve effectiveness
- Critical times, short-term, dual diagnosis
- Effectiveness supported also by studies of active controls, naturalistic design, open trials, meta-analysis (Skinner et al., 2014)

Disulfiram Dosing/Side Effects

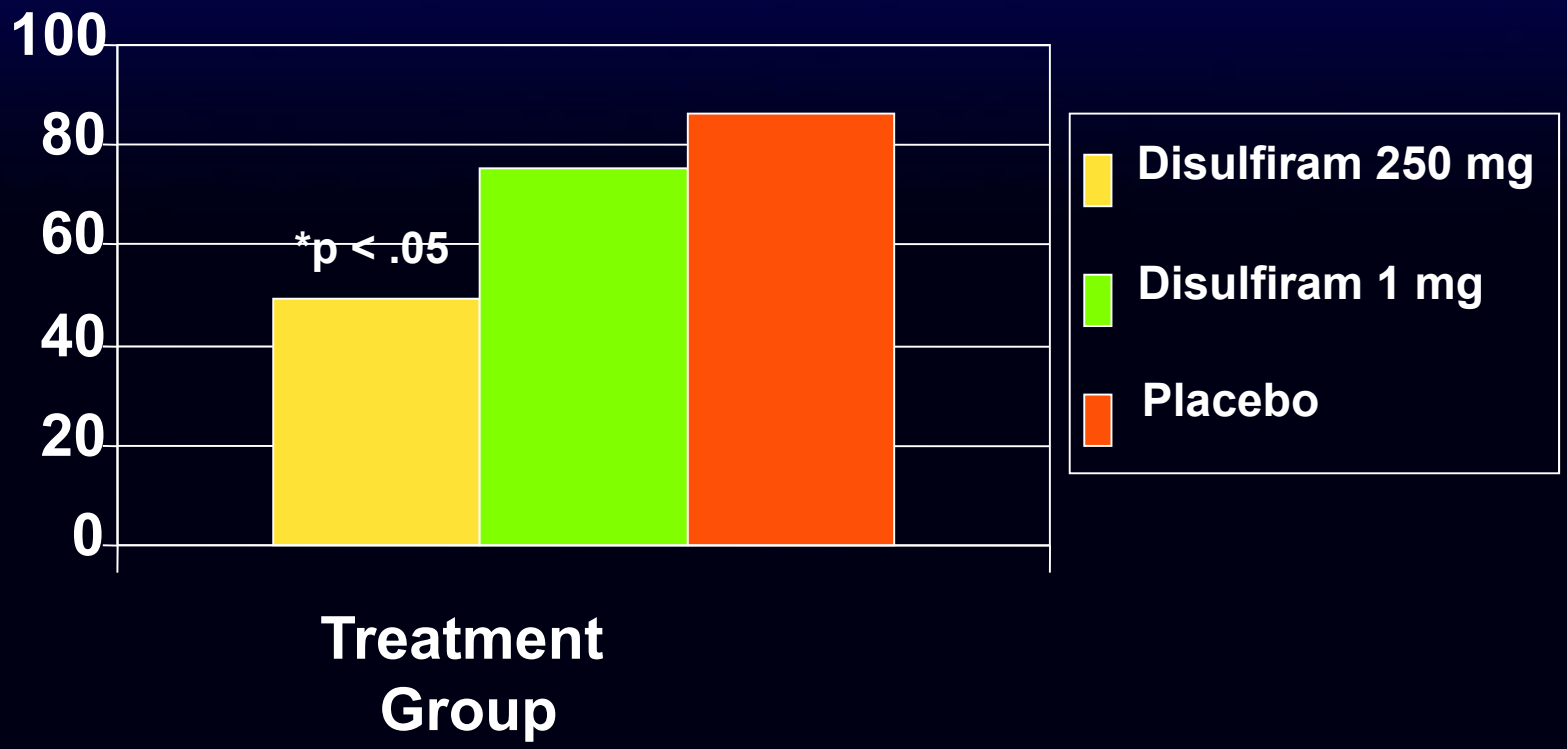
- Dosing Range 125mg-500mg daily, Start with 250mg
- Metabolized by Liver, also excreted, t1/2= 12 hrs (effect up to 14 days)
- Uncommon but serious: Liver toxicity, Seizures, arrhythmias, peripheral neuropathy, psychosis
- Many drug interactions; warfarin, metronidazole, (inhibits CYP450 enzymes)
- LFTs 2wks, 4wks, q3-6months
- Contraindicated in : cardiac disease, pregnancy,
- relative in liver disease and psychosis
- Common: HA, fatigue, sleepiness, anxiety

Disulfiram and Abstinence Rates



Fuller RK et al. JAMA. 1986(Sep);256(11):1449-1455

Drinking Days Among Those Who Drank



Fuller RK et al. JAMA. 1986; 256:1449-1455

Topiramate (not FDA approved for AUD)

- Mostly renally cleared, some hepatic metabolism
- Elimination half-life is 18-24 hours
- Common SE's: paresthesias, memory-language problems, weight loss, other cognitive
- Uncommon: psychiatric, Suicidal behavior
- Warnings (Rare): kidney stones and acute angle closure glaucoma, metabolic acidosis, hyperammonemia, birth control (theoretical)
- Titrated to target dose over about 5-6 weeks

Mechanism Of Action

- GABA-A Receptor allosteric modulator (potentiates transmission at non-benzodiazepine site)
- AMPA and Kainate glutamate receptor antagonism
- Limitation of L-type calcium channels and calcium dependent 2nd messenger systems
- Limitation of activity dependent depolarization and excitability of voltage-dependent sodium channels
- Activation of potassium conductance
- Weak inhibition of Carbonic Anhydrase (II and IV)
- Which are the ones that matter?...
- How does that translate into treatment response clinically?

Clinical MOA

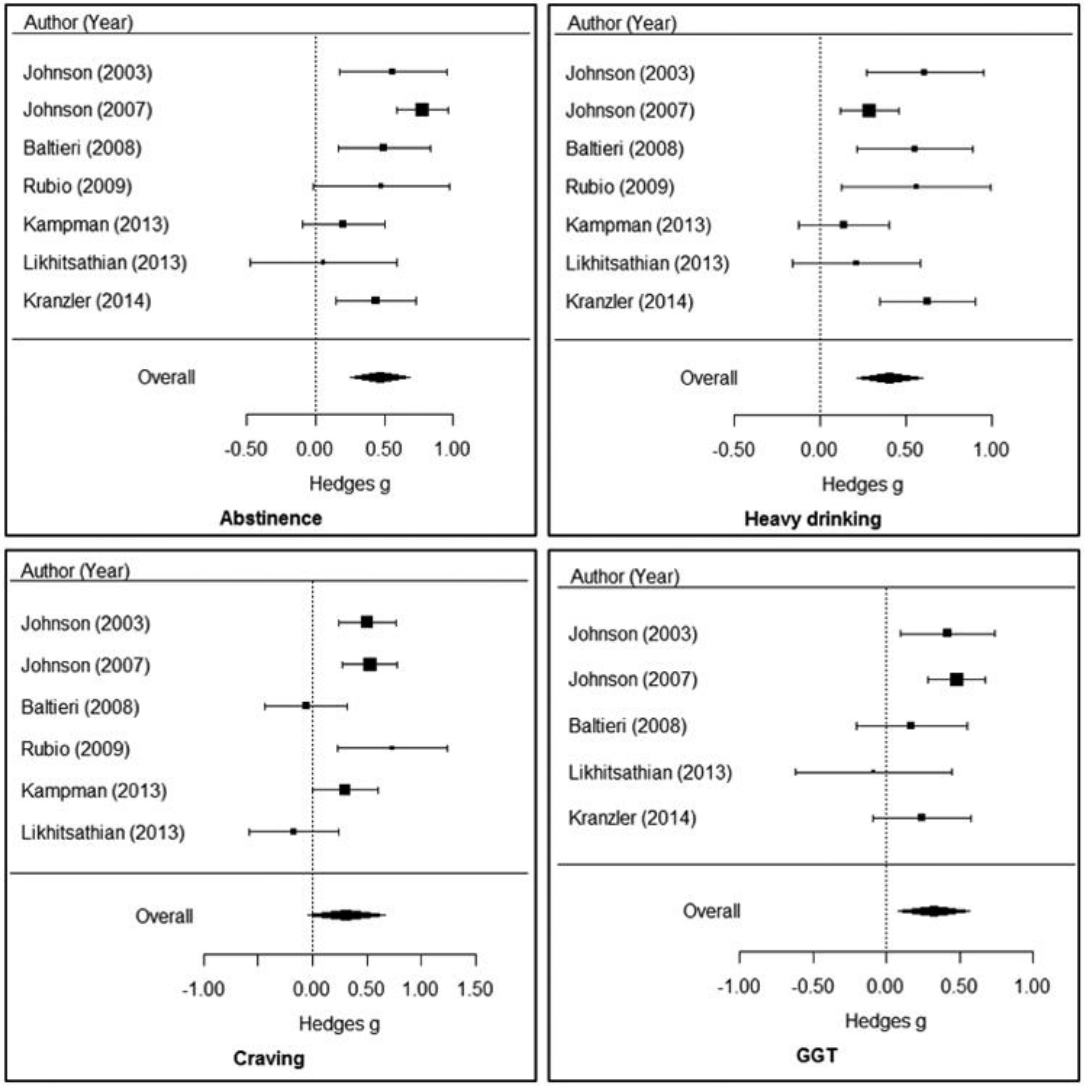
- Probably reduces craving/desire/urge to drink - especially once people start drinking
- May reduce the positively reinforcing effects of alcohol
- Effect mediated by self-efficacy: increases the belief in ability to resist heavy drinking
- May in some patients reduce anxiety and help with protracted abstinence (possibly)

(Miranda, et al., 2016, 2008, Kranzler et al., 2014)

Major Placebo-Controlled Topiramate Treatment Trials

- Single-site, 12-week study in 150 patients, with an ultimate goal of abstinence (Johnson et al. 2003)
- 17-site, 14-week study in 371 patients with an ultimate goal of abstinence (Johnson et al. 2007)
- Single-site,12-week study in 138 patients with a goal of reduced drinking, not abstinence (Kranzler et al., 2014)
- Meta-analysis of all reasonably relavent trials was very positive

Topiramate AUD meta-analysis (Blodgett et al., 2014)



Significant advantage for topiramate on:

-abstinence measures

-heavy drinking measures

-GGT level

-trend for reducing craving

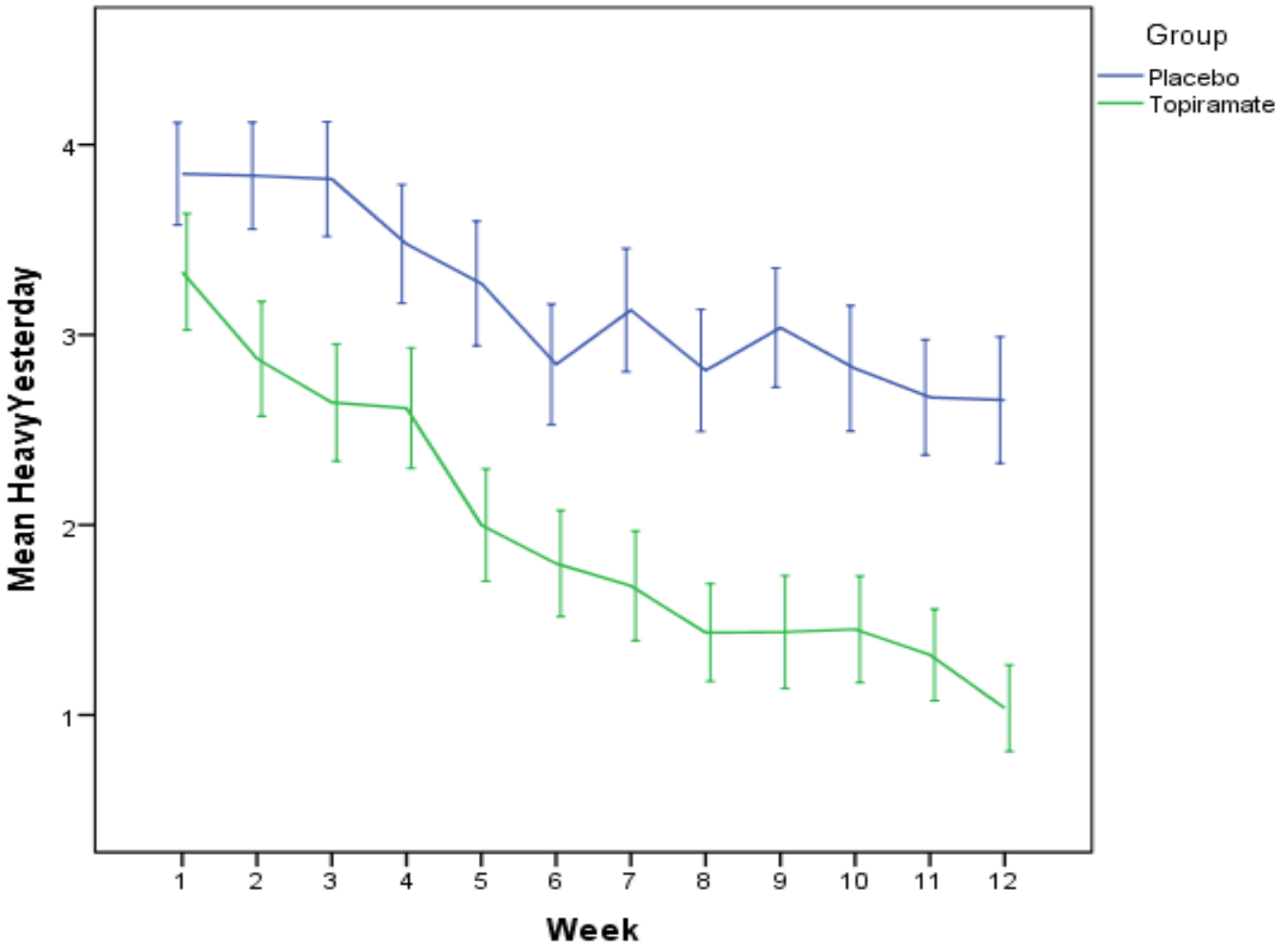
Kranzler et al., 2014: Moderate Dose 200mg Topiramate

- Is it efficacious?
- What if the goal is to just reduce instead of quit drinking?
- In previous studies goal was to quit…
- What about including "at risk" problem drinkers (more of a DSM-5 AUD vs just Dependence)?
- Lower rates side effects and discontinuation with moderate dose?
- Does genetic variation at *GRIK1* predict response?
- Mediators of response?

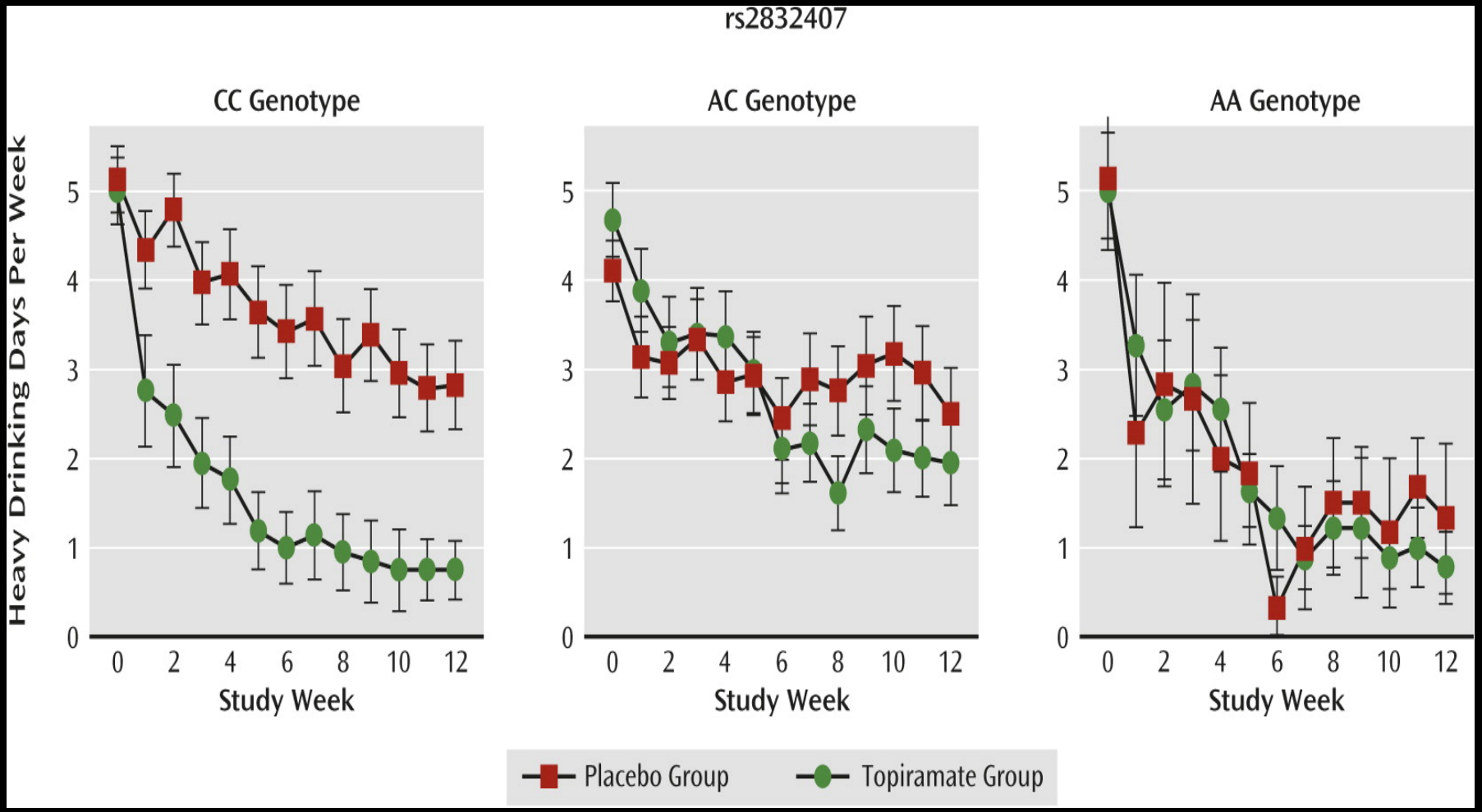
GRIK1

- Encodes Glutamate Receptor, Ionotropic, Kainate 1 subunit (*GRIK1*),
- SNP rs2832407- not known if functional
- Has been implicated as an AD risk allele in an association study
- One prior study found a possible association with topiramate side effects severity and this SNP (Ray et al., 2009)

Within-Treatment Heavy Drinking Days



Heavy Drinking Days by Medication and Genotype Groups



Kranzler et al., Am J Psychiatry, 2014a

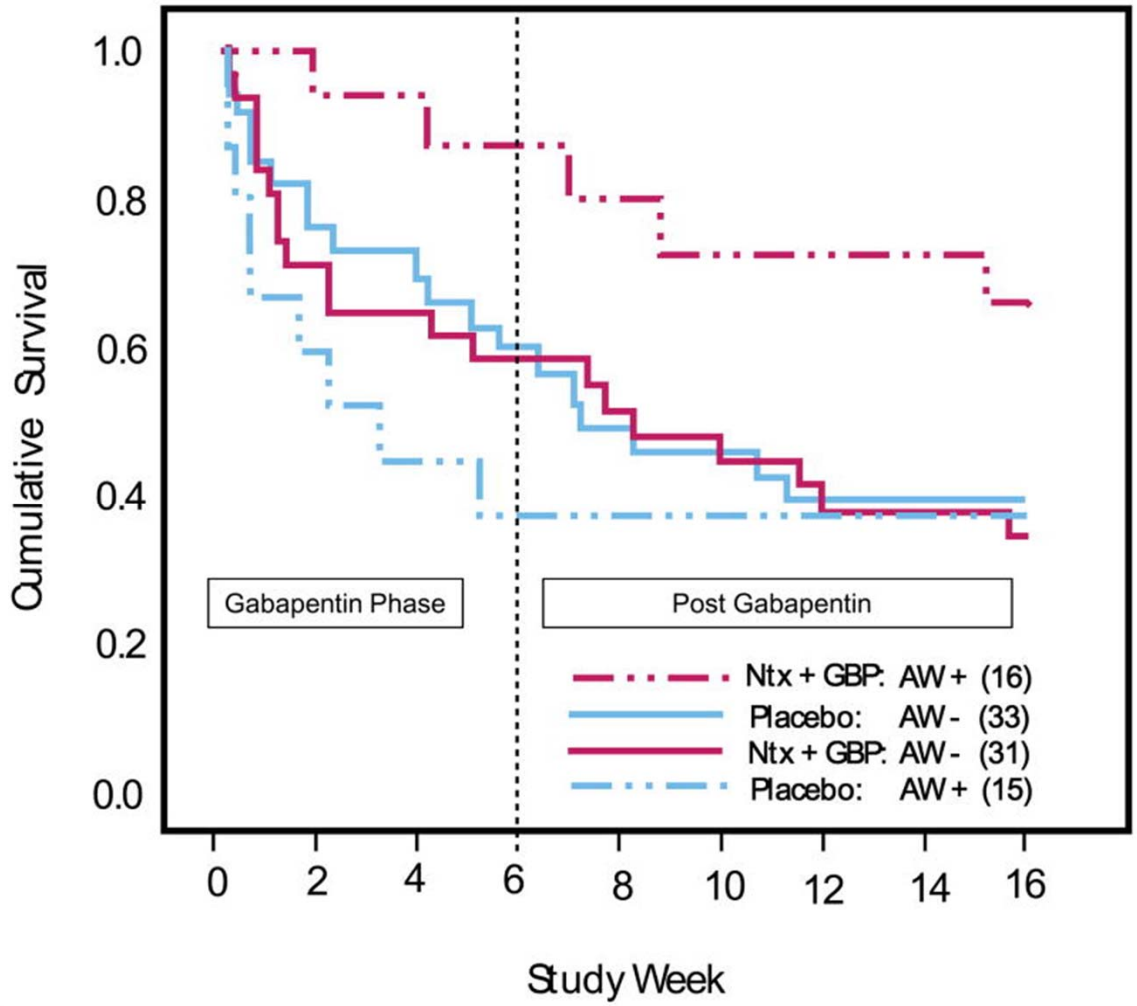
Summary

- Rs2832407 moderates the therapeutic response to topiramate, but not its adverse effects.
  - C-allele homozygotes are significantly more responsive to topiramate than A-allele carriers
  - Relevant to ~40% of European Americans
- These findings require replication. About 50 CC, half on med vs plc

Gabapentin for reducing risk relapse and harmful drinking

- Monotherapy: recent medium size trial; very positive (Mason et al., 2013) but high dropout rate
- 1800MG daily target dose
- Benefits in all drinking outcomes, protracted abstinence (mood, sleep)
- Smaller trials support use
- Added to naltrexone- probably improves outcomes (Anton et al., 2011)
- Relatively safe and well tolerated

Anton et al., 2011

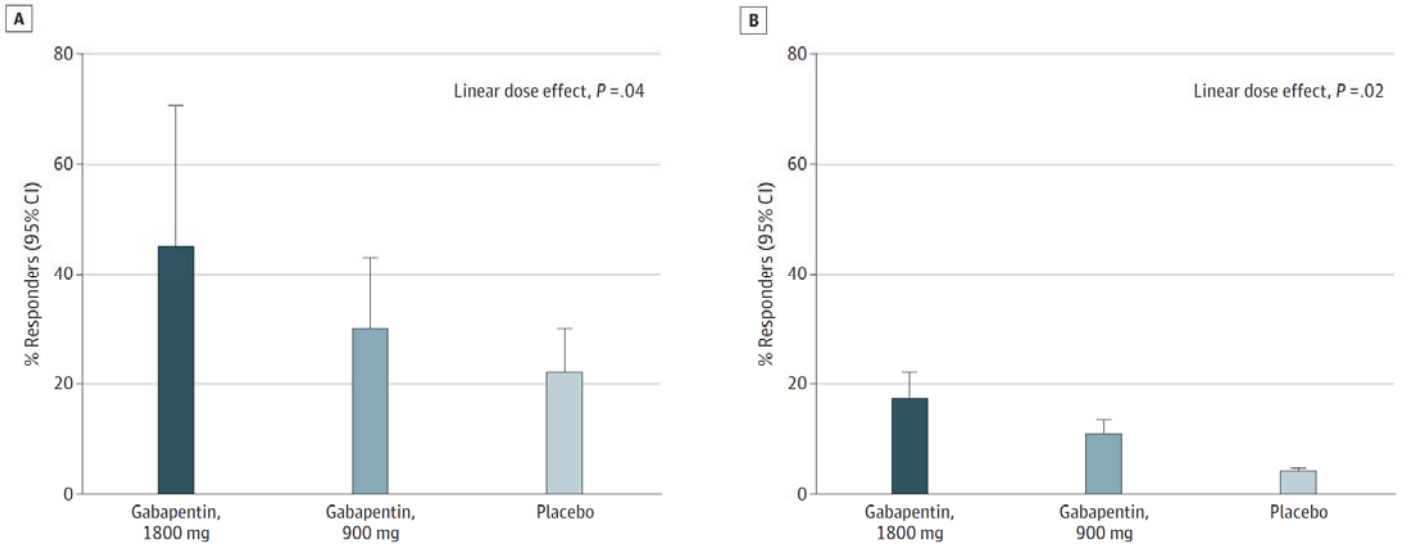


Mason et al., 2013

- N= 150, 3 groups; PLC, 900mg, 1800
- 1800mg daily most effective (600mg TID)
- Titrated over 4-6 days to target dose
- Works on alpha-2d subunit VGCC, indirectly facilitates GABA
- Well tolerated across groups and no serious AE's
- A relatively "clean" sample, not a dual dx or a veteran sample

Mason et al., 2013

Figure 2. Gabapentin Effects on Rates of No Heavy Drinking and Complete Abstinence During the 12-Week Study in the Intention-to-Treat Population



A, No heavy drinking; B, complete abstinence. Error bars indicate 95% confidence intervals. (N = 150.)

VCU

Summed up in 3-5 Meta-Analyses:

- Jonas et al., 2104, Maisel et al., 2013, Blodgett et al., 2014, Kranzler and VanKirk 2001), Cochrane database,
- NTX NNT- probably between 7-12, small effect on reducing heavy drinking amount and relapse
- ACAMP- NNT 9-12, has small effect on preventing relapse to any drinking, no clear effect on reducing heavy drinking in those who drink
- Both work poorly if patient can't get about 4 days abstinence on their own, or go for a detox first.
- Naltrexone probably better suited for those that want to cut down, acamprosate probably better for abstinence goal
- Topiramate: NNT probably 5-7, for HD measures: reduces or eliminates heavy drinking in actively heavy drinking patients without need for detox/clean time, increases abstinence outcomes (Feinn et al., 2016)

Biomolecules and Biomarkers Used in Diagnosis of Alcohol Drinking and in Monitoring Therapeutic Interventions

- Various biomarkers used to assess alcohol consumption patterns
  - Breath test
  - Ethyl glucuronide
  - Ethyl Sulfate
  - GGT, Liver Enzymes, MCV
  - Phosphatidylethanol
  - Carbohydrate-deficient transferrin
  - Fatty acid Ethyl Ester

Breath Test

- Ashdown et al. questions the sensitivity of commercial breathalyzers
  - 3 different commercial breathalyzers showed 89.5%, 94.7% and 26.3% sensitivity
- A study conducted in 88 hospitalized patients (35 women and 53 men) showed that estimating BAC from BrAC (2100:1 ratio) leads to underestimation of BAC by 26%
- Breathing patterns and food can influence breath alcohol pharmacokinetics
  - Hyperventilation or deep breathing lowers BrAC
  - BrAC maximum concentration was highest in fasting subjects and lowest in subjects who consumed a light meal

Nanau and Neuman, 2015

The classic blood biomarkers

- GGT, AST/(ALT), MCV
- Not that sensitive for AUD/HD
- MCV sens 30-76%, spec 79-98% to detect AUD or self reported heavy drinking
- AST elevation:
  - Sens: 6-33%
  - Spec: 92-98%

Alcohol Biomarkers

Source	Test	Detects	Sens%	Spec%	window
Blood	GGT	Frequent HD	40-73	63-91	4 wks
	CDT	Frequent HD	40-63	80-93	3 wks
	Both		90	98	?
Urine *	EtG	Heavy drinking >.445 mg/L (exact level)	80.5	78.7	1-3 days

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CSAT 2006, Wurst et al., 2004, Fleming et al., 2003

Ethyl Glucuronide and Ethyl Sulfate in Urine

- EtG and EtS are metabolites of alcohol that represent short term biomarkers of alcohol use
- A good correlation exists between self reported drinking and urinary EtG ($r = 0.662$, $p < 0.001$) and EtS ($r = 0.716$, $p < 0.001$) levels
- Post mortem analysis showed EtG concentrations in urine were significantly higher in individuals with a history of alcohol abuse(339 ± 389 mg/L, $p < 0.001$)
- Mouthwash, hand sanitizer and non alcholic beers can lead to a positive EtG in individuals who deny drinking
  - 55.6% of individuals testing positive for low levels of urinary EtG or EtS denied drinking
    - 70% of the time a negative PEth supported the subjects claim of alcohol abstinence
    - 20% of the time a positive PEth test contradicted the subjects claim

Nanau and Neuman, 2015

Phosphatidylethanol

- PEth is used primarily to identify chronic excessive drinking
  - Heavy drinkers (>60 g/day)- PEth Level- **3.897 µmol/L**
  - Social drinkers -PEth Level- **0.288 µmol/L**
- PEth has a half life of 3.5-9.0 days but remains detectable for up to 14 days in alcoholics admitted for detox
- An association between days since the last heavy drinking day and PEth level was observed
  - 1-4 days preceding heavy drinking- PEth levels significantly correlated **($p < 0.001$)**
  - >5 days preceding heavy drinking- PEth levels were not significantly correlated **($p > 0.2$)**

Nanau and Neuman, 2015

Ethyl Glucuronide and Fatty Acid Ethyl Esters

- Hair EtG is an important marker of long term alcohol consumption
- Meta-analysis of hair EtG levels showed
  - Social drinkers- EtG concentrations (**mean 7.5 pg/mg**, 95% CI 4.7–10.2, $p < 0.001$),
  - Heavy Drinkers (**mean 142.7 pg/mg**, 95% CI 99.9–185.5, $p < 0.001$)
  - History of chronic excessive drinking- (**mean 586.1 pg/mg**, 95% CI 177.2–995.0, $p < 0.01$
- FAEEs were assessed in a large sample of 1057 autopsy cases
  - Social drinkers- Median FAEEs levels were **0.302 ng/mg** (range 0.008–14.3 ng/mg)
  - Alcohol abusers- Median FAEEs levels **were 1.346 ng/mg** (range 0.010–83.7 ng/mg)

Nanau and Neuman, 2015

Carbohydrate-Deficient Transferrin

- CDT is an biomarker for moderate to heavy alcohol consumption and a useful indirect marker for initial screening as well as relapse
- CDT preforms better in non-cirrhotic than cirrhotic patients
  - Among abstinent individuals,
    - Subjects with liver disease CDT level- **.9%**
    - Control subject CDT level- **0.5%**
- Post mortem analysis showed
  - Positive CDT in **60%** of samples with positive BAC
  - Positive CDT was found in **66.7%** of individuals with severe liver disease
- CDT levels were significantly associated with the body mass index (p = 3.71 × 10−9), female gender (p = 2.30 × 10−9) and smoking (p = 8.28 × 10−8
  - Usefulness of CDT is reduced in overweight or obese subjects

Nanau and Neuman, 2015

Oslin et al., 2013 – RCT of Alcohol Care Management in Primary Care

- 26 week single blind randomized clinical trial
- 163 alcohol dependent veterans were randomly assigned to **ACM** or **standard outpatient treatment**
- Primary Outcome Measures
  - Amount of alcohol consumed
    - Recorded heavy drinking days as well as standard drinking days
    - Recorded 60 days prior to intervention and during intervention
  - Engagement in clinical services tracked by
    - VA electronic medical record
    - Questionnaire of services received outside the VA

Source	Test	Detects	Sens %	Spec %	Window
Serum	%CDT	Freq HD	40-63	96.6	1-2 weeks
	GGT	Freq HD	32-85	89-97	3 weeks
	Both +	Freq HD	90	98	*
Urine	EtG	HD	89.3	98.9	< 80 hrs
Hair	EtG	-any	76.0	91.0	<6 months
Blood	PEth	HD Active HD in AUD	91+ 99	77+ 100	Up to 2+ wks

Travakoli et al., 2011,
Staufer and Yegles, 2016
Nanau and Neuman, 2015,
CSAT 2006,
Wurst et al., 2004,
Fleming et al., 2003,
Hietala et al., 2006

Questions?

Case Presentation #1
Sunny Kim, NP

- 12:35-12:55 [20 min]
  - 5 min: Presentation
  - 2 min: Clarifying questions- Spokes
  - 2 min: Clarifying questions – Hub
  - 2 min: Recommendations – Spokes
  - 2 min: Recommendations – Hub
  - 5 min: Summary - Hub

Reminder: Mute and Unmute to talk
*6 for phone audio
Use chat function for questions

Case Presentation #1

Please state your main question(s) or what feedback/suggestions you would like from the group today?

Potential seizure vs stability

Case History

Attention: Please DO NOT provide any patient specific information nor include any Protected Health Information!

Demographic Information (e.g. age, sex, race, education level, employment, living situation, social support, etc.)

26 yo Caucasian male pt with 12 th grade education. Currently working for a roofing company. Pt was living with his maternal grandparents but about a year ago he moved out with his wife and 3 yo daughter. Early onset of bipolar and manic episode and it's been on a disability since he was a late teen. Good support from his family but still makes poor decisions. Recently lost his disability and struggling financially.

Reminder: Mute and Unmute to talk
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Use chat function for questions

Case Presentation #1

Physical, Behavioral, and Mental health background information (e.g. medical diagnosis, reason for receiving opioids, lab results, current medications, current or past counseling or therapy treatment, barriers to patient care, etc.)

Strong family history of SMI. Mother bipolar with opioid use disorder. Biological father schizophrenia and alcohol use disorder. Pt grow up with mother and step farther and 2 step sisters. Pt does not know much about his biological father. Only met him on mother's funeral.

Pt's mother died opioid overdose when pt was 16 yo. When mother past pt attempt to commit suicide by hanging himself but grandparents found him in time to save him. After this attempt pt started experimenting with substances. Started abusing various substances. Transitioned to prescription opioids when he was 17 then quickly transitioned to heroin. Occasional IV use but mostly IN use only. Luckily no OD.

Pt moved in with grandparents when he was 23 and girlfriend got pregnant as well. Continued substance use until birth of his child then pt decided it was time for him to stop. Initiate MAT with a provider that was only taking cash payment. Stable on MAT for nearly 2 yo with 16 mg of buprenorphine.

Pt transitioned to MOTIVATE January of 2018. Stable in remission quickly earned 4 wks prescription privilege. Occasional participation with 1:1 therapy at the clinic but minimal community recovery group participation. Pt continuing his psych care with his psych provider and on risperidone 2 mg daily, bupropion 150 mg BID.

March 2018 pt started overusing BUP as he started working at Wawa. BUP increased to 24 mg

Pt moved out of grandparents' house May of 2018. Pt still working. Maintained sobriety with minimal participation for therapies.

July 2018 pt MIA for unknown reason. Unable to contact pt.

November 2018 pt returned to clinic states that he lost his disability and insurance. Unable to afford to come to the clinic. Pt admits that he was using various substances to compensate with withdrawal symptoms. UDS positive for methamphetamine, methadone, amphetamine, cocaine, opioid and THC. Pt also using alcohol and BAC testing 0.03. pt now with Medicaid and wishes to resume his treatment.

Pt could not maintain sobriety after this point

Reminder: Mute and Unmute to talk
*6 for phone audio
Use chat function for questions

Case Presentation #1

What interventions have you tried up to this point ?
Additional case history (e.g. treatments, medications, referrals, etc.)

Pt started coming in with UDS that is positive for various substances. Pt also started test negative for BUP. Started bad cycle of resuming BUP, stable until interval increase, status decline, shortening interval, and doesn't come to the clinic on time.

With in-depth conversation pt reveals that his vehicle is not in a great condition and has hard time leaving the job for the clinic visit. Pt also talks about financial strains since he lost his disability. Pointed out to pt that he complains of financial strain yet he spends significant amount of his income to buy various substances and educated pt about the Medicaid transport. Encouraged pt to resume his behavioral health treatment but he does not follow through. Pt continue struggling.

May 2019 informed pt that we will transition him to sublocade. Due to insurance complications unable to get sublocade until July 2019. First sublocade given to pt August 2019. Pt does not return to 1 wk follow up.

September 2019 pt returned to clinic. Pt claims that after first sublocade he had severe nausea/vomiting and could not hold any food down. 3rd day after sublocade pt claims that he had a seizure and went to ER. Pt was discharged with ondansetron which resolved his nausea. Pt claims when he was taking 4 mg of ondansetron BID he felt "normal" and was able to function. Ondansetron lasted for 2 wks then pt started using methamphetamine for a week to compensate with this nausea before returning to the clinic.

Pt wishes to stay on sublocade if we provide month long ondansetron prescription

---

What is your plan for future treatment? What are the patient's goals for treatment?

Resumed ondansetron and gave small dose of SL BUP as sublocade depot still remains with pt. pt claims that he had total of 3-4 seizures in his life and never been severe enough nor got treatment. Unclear if seizure was caused by electrolyte imbalance because pt could not eat and vomited for 3 days before seizure. Pt wishes to resume sublocade because it was "perfect" with ondansetron but wife very oppose to that idea as she witness the seizure. Concerns remain with SL BUP as pt could not break through the cycle.

End of Case Study

Case Presentation #2
Susan Cecere, MD

- 12:55pm-1:25pm [20 min]
  - 5 min: Presentation
  - 2 min: Clarifying questions- Spokes (participants)
  - 2 min: Clarifying questions – Hub
  - 2 min: Recommendations – Spokes (participants)
  - 2 min: Recommendations – Hub
  - 5 min: Summary - Hub

Reminder: Mute and Unmute to talk
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Use chat function for questions

Case Presentation #2

Please state your main question(s) or what feedback/suggestions you would like from the group today?

I have a client who was recently able to legally apply for and receive a medical card to be prescribed marijuana. There are numerous dispensaries opening up in January 2020. How are other SA treatment programs handling this issue?

Case History

Attention: Please DO NOT provide any patient specific information nor include any Protected Health Information!

Demographic Information (e.g. age, sex, race, education level, employment, living situation, social support, etc.)

Female, 45, Caucasian, less than 4 yrs of college, unemployed, lives with fiance and 5 of her 9 children. She is very involved with NA and has a very large support system. She reports a history of crack addiction and alcohol abuse but reports that she has abstained from these for approximately 10 years. Several years ago, she had her leg crushed in a motorcycle accident and was afraid to use pain medication for fear she would become addicted. She reports that Marijuana is the only thing that helps her pain. When she came to our agency, she was on probation for an old, non-drug related charge. She kept testing + for THC and was in danger of violating probation. When she was able to receive a legal medical marijuana card, her PO said that she no longer had to go to SA treatment because THC was the only thing she tested + for.

Reminder: Mute and Unmute to talk
*6 for phone audio
Use chat function for questions

Case Presentation #2

Physical, Behavioral, and Mental health background information (e.g. medical diagnosis, reason for receiving opioids, lab results, current medications, current or past counseling or therapy treatment, barriers to patient care, etc.)

This Client has been in and out of services for many years for treatment of her addictions. She was able to sustain her abstinence from crack and alcohol for approximately 10 years. In the past 2-3 years, she has come through the agency a couple of times due to being on probation and testing + for THC. The last time she came through, her PO had told her that if she gave 3 consecutive, negative screens, she could complete treatment. She was able to accomplish this but then her probation was extended and she tested + for THC again and was sent back to us. in between her assessment and her orientation appt. she was able to get her medical marijuana card, so she was released from treatment. She has never tested + for anything other than THC. Her diagnosis is cannabis dependence. She is not motivated to stop using marijuana.

What interventions have you tried up to this point ?
Additional case history (e.g. treatments, medications, referrals, etc.)

This Ct. tried CBD oil for a while and reported "some" relief from pain. She was also able to use other forms of coping with the pain by Epson salt baths, massage and exercise/stretching. She also reported drinking alcohol on several occasions. she reports that she has a strong support system and she attends regular NA meetings and has a sponsor.

What is your plan for future treatment? What are the patient's goals for treatment?

This is where my dilemma comes into play. If our clients are able to get medical marijuana, have no motivation to stop using, what are our options for treatment?

End of Case Study

Reminder: Mute and Unmute to talk
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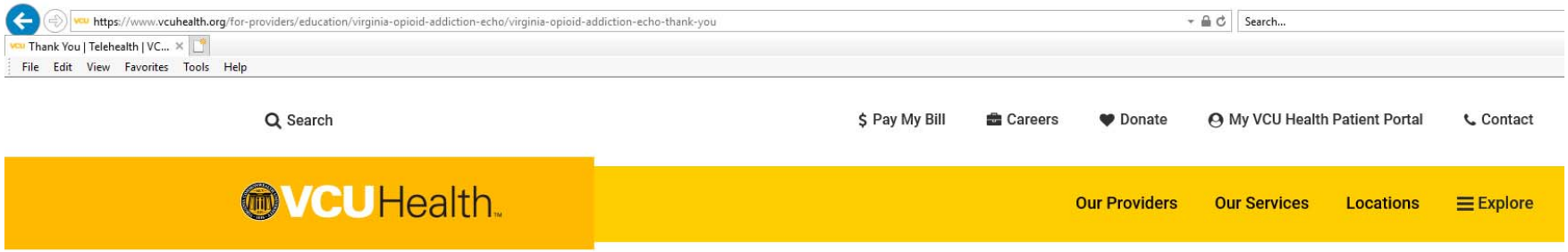
Case Studies

- Case studies
  - Submit: www.vcuhealth.org/echo
  - Receive feedback from participants and content experts
  - Earn **$150** for presenting



Thank You

The success of our telehealth program depends on our participants and those who submit case studies to be discussed during clinics. We recognize the following providers for their contributions:

- **Michael Bohan, MD** from Meridian Psychotherapy
- **Diane Boyer, DNP** from Region Ten CSB
- **Melissa Bradner, MD** from VCU Health
- **Michael Fox, DO** from VCU Health
- **Shannon Garrett, FNP** from West Grace Health Center
- **Sharon Hardy, BSW, CSAC** from Hampton-Newport News CSB
- **Sunny Kim, NP** from VCU Health
- **Thokozeni Lipato, MD** from VCU Health
- **Caitlin Martin, MD** from VCU Health
- **Faisal Mohsin, MD** from Hampton-Newport News CSB
- **Stephanie Osler, LCSW** from Children's Hospital of the King's Daughters
- **Jennifer Phelps, BS, LPN** from Horizons Behavioral Health
- **Crystal Phillips, PharmD** from Appalachian College of Pharmacy
- **Tierra Ruffin, LPC** from Hampton-Newport News CSB
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- **Barbara Trandel, MD** from Colonial Behavioral Health
- **Bill Trost, MD** from Danville-Pittsylvania Community Service
- **Art Van Zee, MD** from Stone Mountain Health Services
- **Sarah Woodhouse, MD** from Chesterfield Mental Health

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- www.vcuhealth.org/echo

- Claim CME credit for today's session
- Feedback
  - Overall feedback related to session content and flow?

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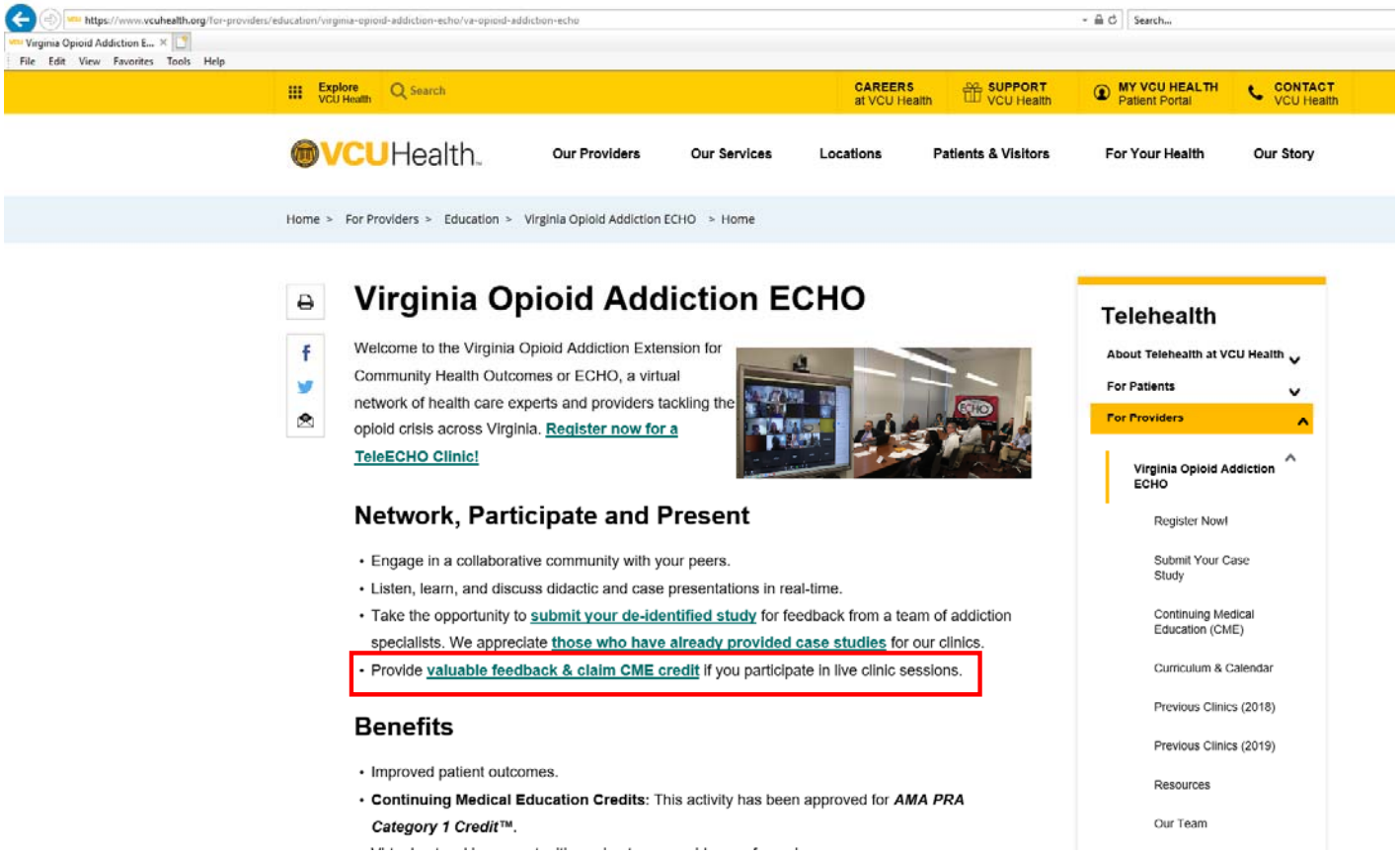

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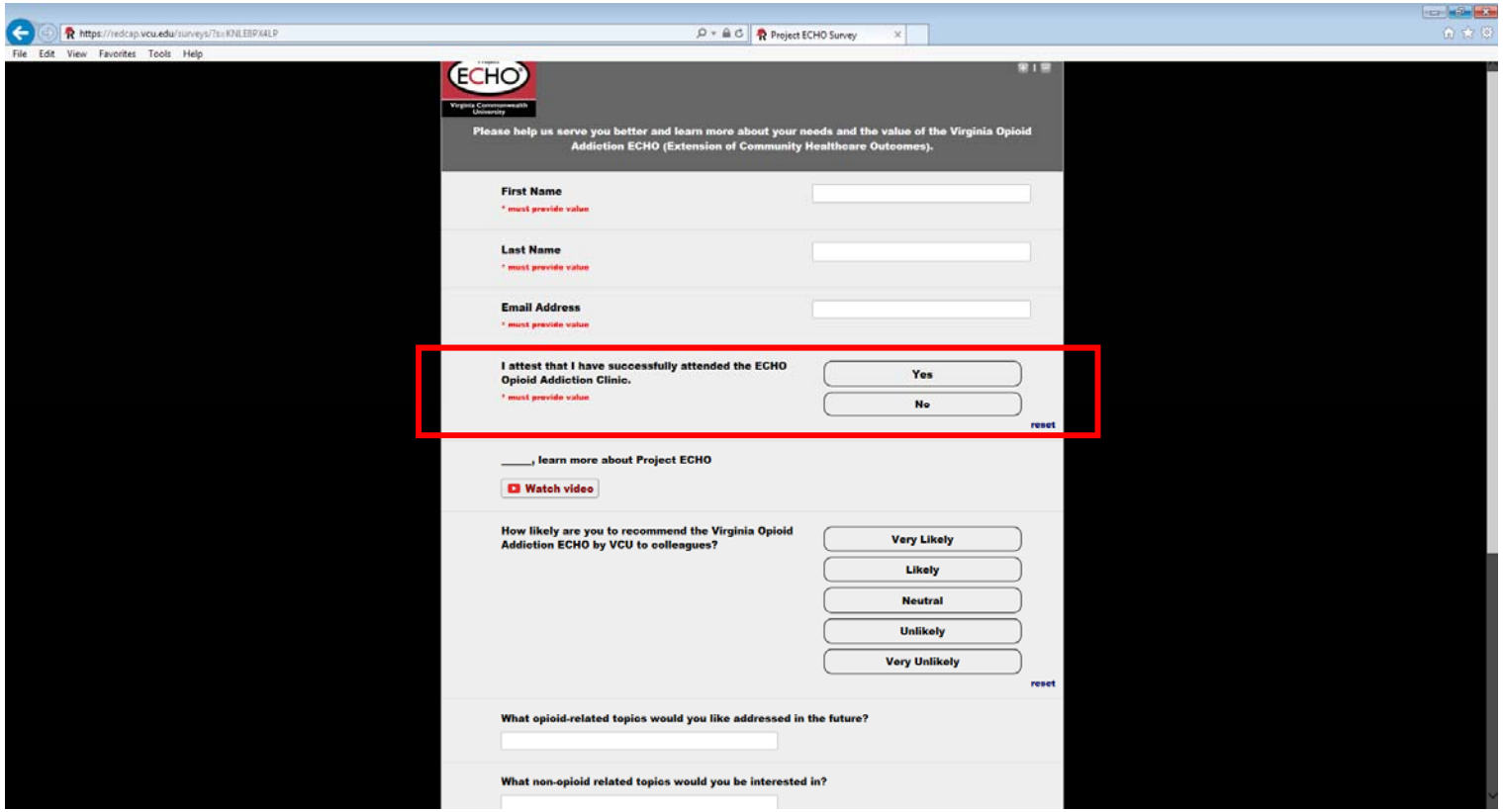

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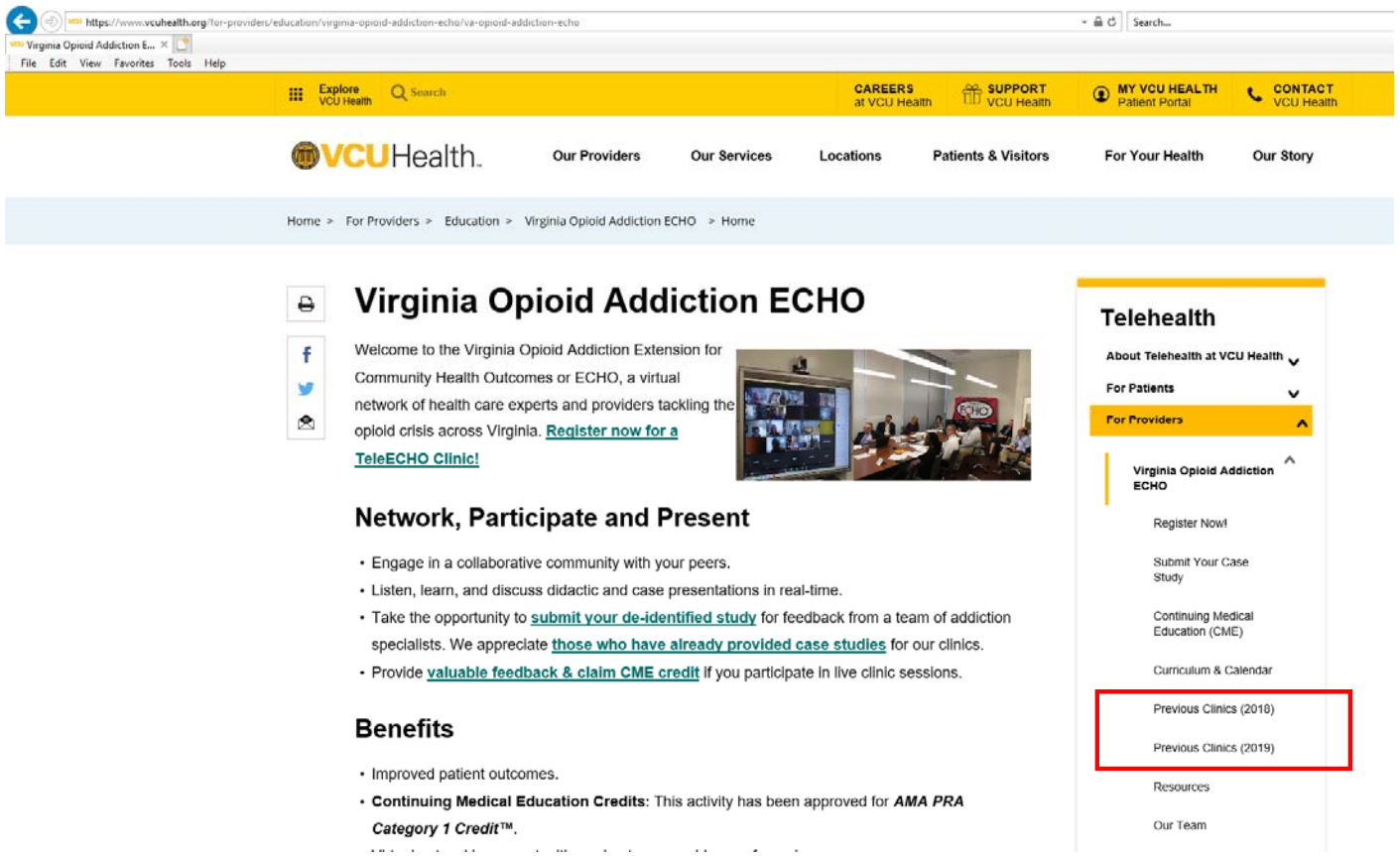

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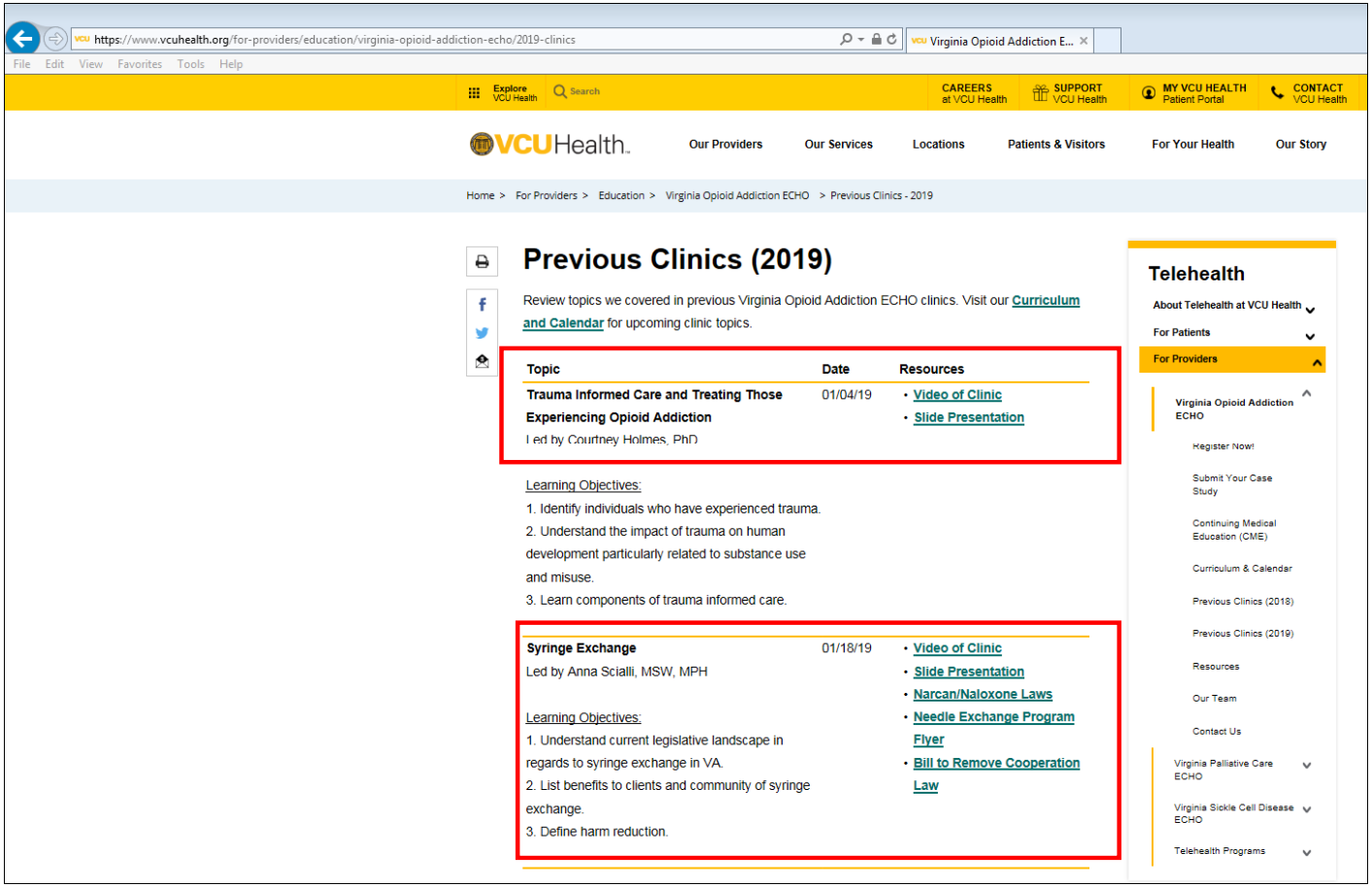

VCU Virginia Opioid Addiction TeleECHO Clinics

Bi-Weekly Fridays - 12-1:30 pm

Mark Your Calendar --- Upcoming Sessions

Nov 15:	USDOJ Diversion Guidelines	Oliva Norman
Dec 6:	Managing Patient Trauma	Anika Alvanzo, MD

Please refer and register at vcuhealth.org/echo

THANK YOU!

Reminder: Mute and Unmute to talk
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Resources

Feinn, R., Curtis, B., & Kranzler, H. R. (2016). Balancing risk and benefit in heavy drinkers treated with topiramate: implications for personalized care. *The Journal of clinical psychiatry*, *77*(3), e278.

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