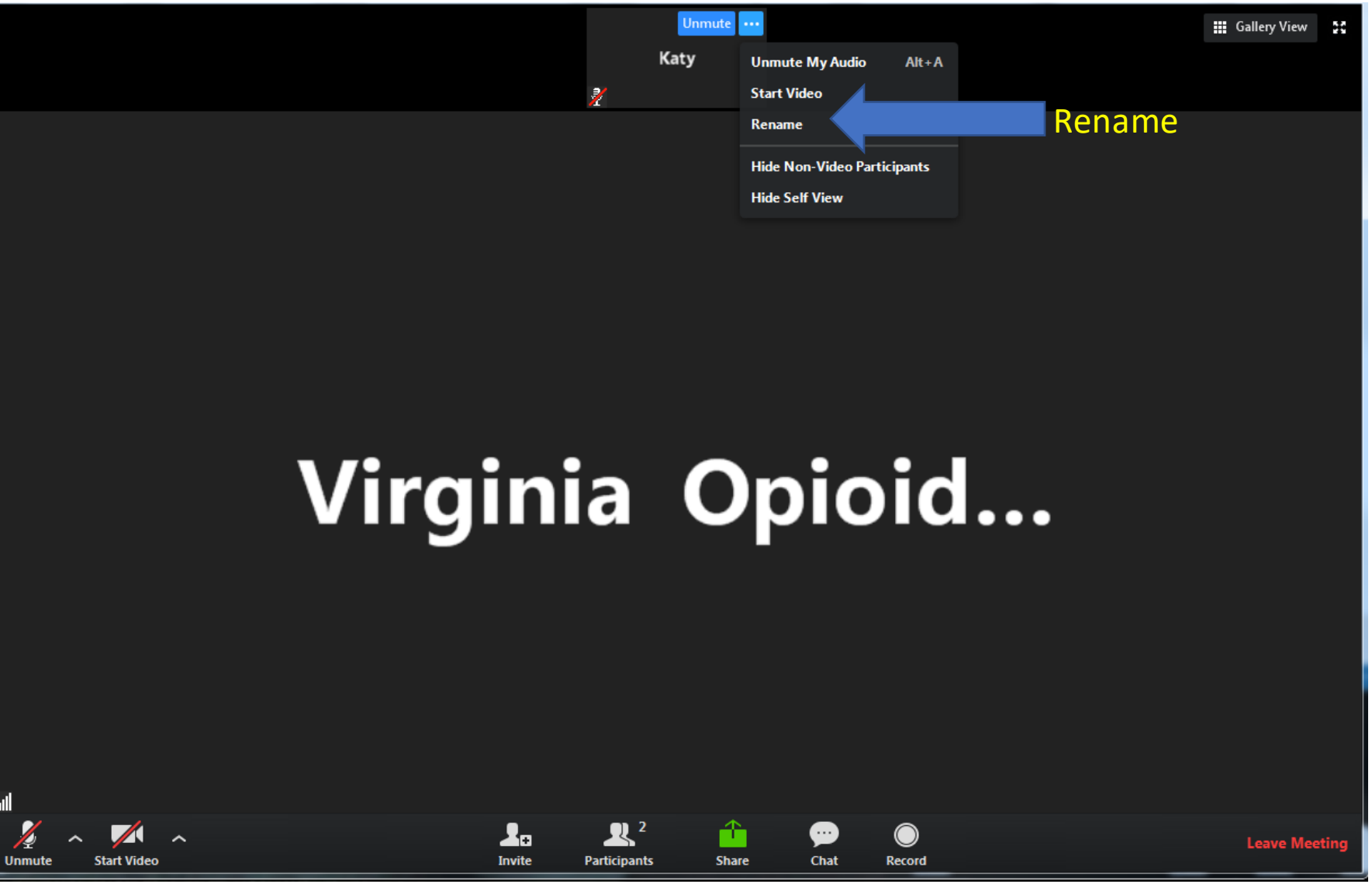
Virginia Opioid Addiction ECHO* Clinic

June 4, 2020

*ECHO: Extension of Community Healthcare Outcomes

Helpful Reminders



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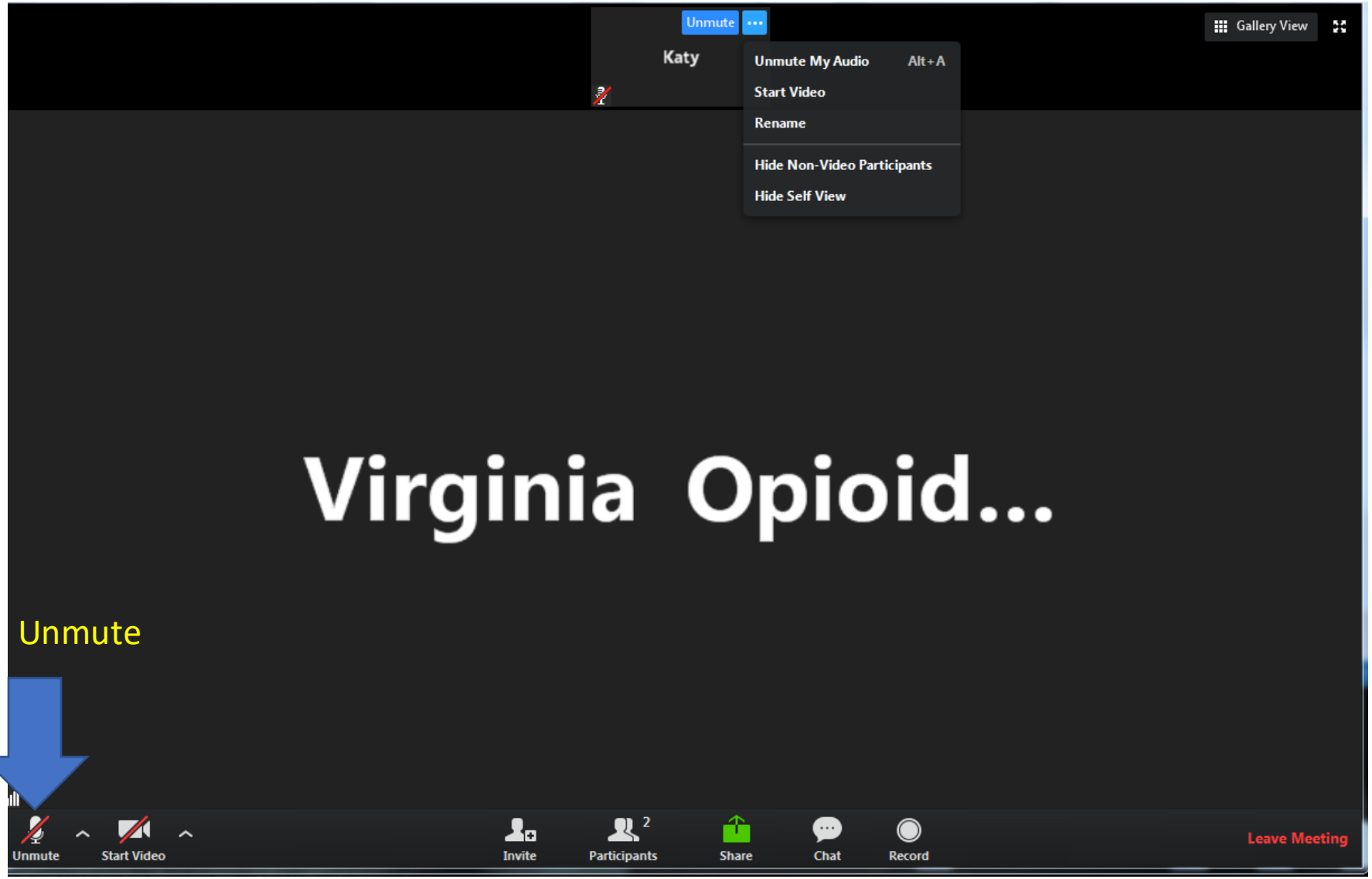
Helpful Reminders



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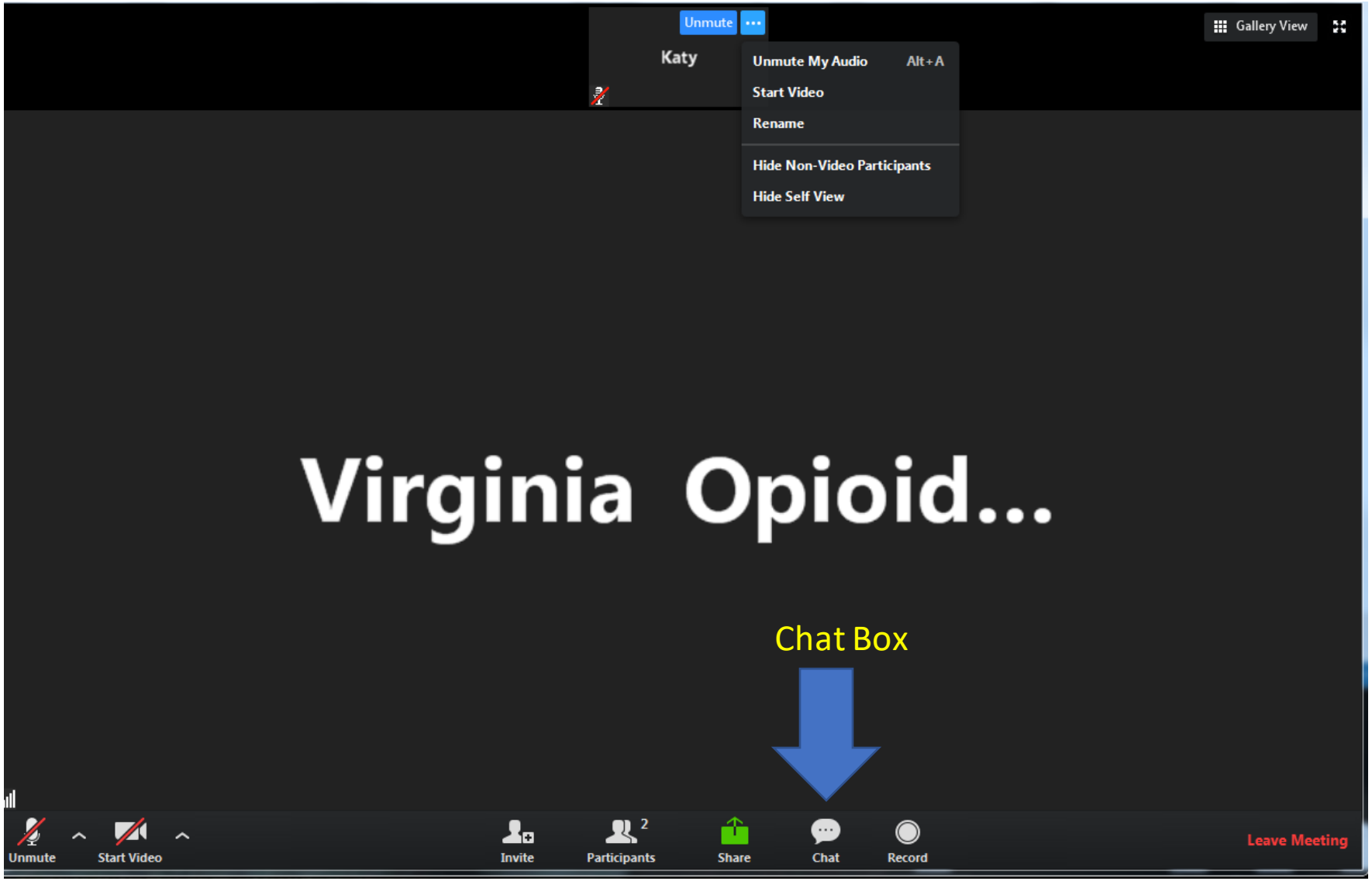
- If joining by telephone audio only, *6 to mute and unmute

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 and Participant Introductions

VCU Team	
Clinical Director	Gerard Moeller, MD
Administrative Medical Director ECHO Hub	Vimal Mishra, MD, MMCi
Clinical Experts	Lori Keyser-Marcus, PhD Courtney Holmes, PhD Albert Arias, MD Salim Zulfiqar, MD Megan Lemay, MD Katie Adams, PharmD
Didactic Presentation	Albert Arias, MD
Program Manager	Bhakti Dave, MPH
Practice Administrator	David Collins, MHA
IT Support	Vladimir Lavrentyev, MBA

- Name
- Organization

Reminder: Mute and Unmute screen 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

Novel Pharmacotherapies for Alcohol Use Disorder

VCU Opioid and Addiction ECHO

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 significant financial disclosures
  - Own 500 shares of MNMD (<$5,000) psychedelic med
- Will discuss OFF-LABEL use of medications (e.g., topiramate for AUD)
- Research Support from:
  - NIAAA/NIDA R21 AA026681,
  - UG1 DA050207

Learning Objectives

- Learn about emerging pharmacotherapies for AUD and how to use them
- Learn about the evidence base supporting the use of these medications
- Not going to discuss withdrawal today

AUD: A Molecular Disease

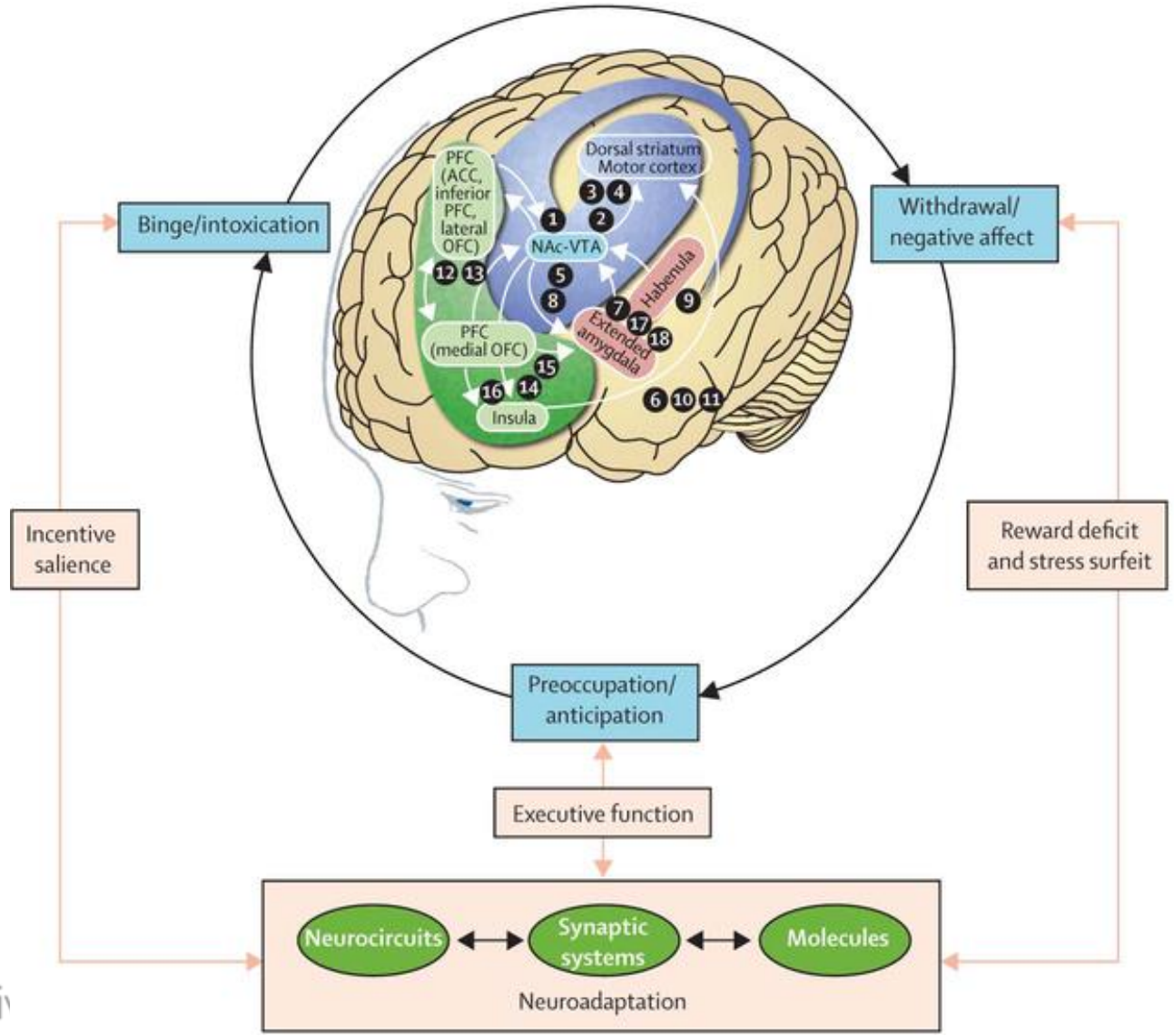
- Chronic heavy alcohol exposure effects neurons on the molecular level
- Huge alterations in levels of many transmitters and changes to receptors (GABA, Glutamate, Serotonin, Dopaminergic etc)
- Active at Level of Gene Regulation: Changes in transcription of many genes
- Subunit Substitution Hypothesis: 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-
- ALLOSTASIS- altered setpoint of brain reward and stress systems/circuits- AUD an allostatic brain disease (Koob and LeMoal)
- *ALCOHOL hijacks the brain and becomes programmed as more important than normal life rewards- without alcohol the person is easily stressed, low mood (hyperketifia)*

Koob and Volkow, 2016, Moonat et al., 2009, Kalivas and O'Brien 2008

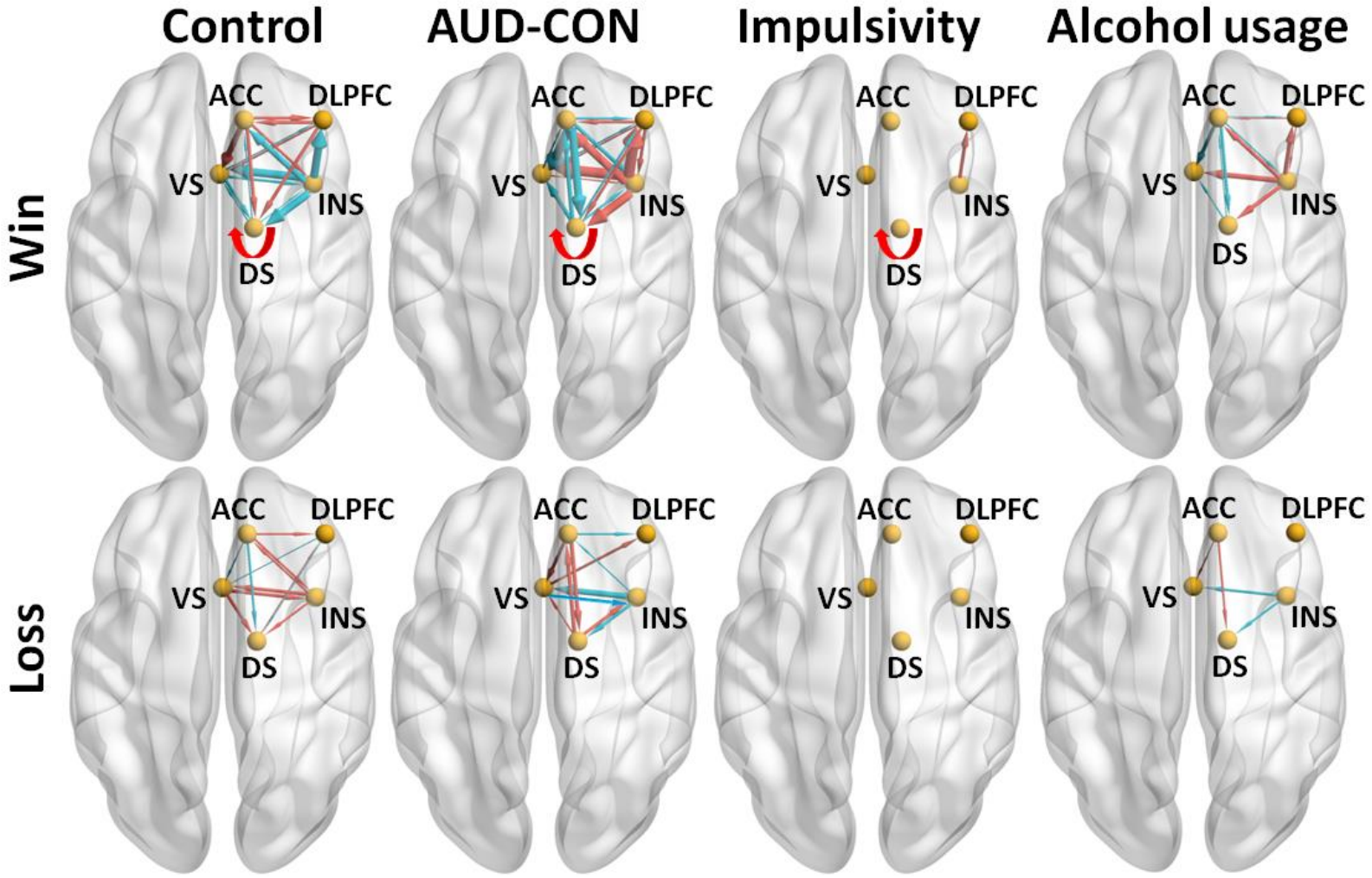
Protracted Abstinence Syndrome

- 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 and Volkow 2016



fMRI- DCM EC analysis of HCP subjects, N=78 AUD



Reward-receipt sensitivity task Delgado et al., 2000, NON-ALCOHOL REWARD Dynamic causal modeling with parametric empirical Bayesian analysis.

Individuals with AUD have disrupted EC in both instrumentally-driven and automatized cortico-striatal reward circuits during non-alcohol reward feedback. These results point to disrupted corticostriatal EC in both "top-down" and "bottom-up" pathways among individuals with AUD.

Jim Bjork, PhD

Liangsuo Ma PhD

Generalized Pharmacotherapeutic Mechanisms

- Multiple **targets for pharmacologic treatment;**
  1. Block or attenuate 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 or balance/normalize stress response and protracted abstinence syndrome; (maybe prevent the neuromodulatory slide into the dependent state, and help shift it back toward normal if already changed)

The Most Used First and Second Line Agents

FDA Approved for AUD: (WE COVERED THESE IN LAST TALK)	Not FDA Approved for AUD but frequently used:	Additional Therapies:
• Disulfiram (approved 1949) • Naltrexone (approved 1994), (PO and IM) • Acamprosate (approved 2004)	• Topiramate (good evidence) • Gabapentin (some evidence)	• Zonisamide • Baclofen • Varenacline

Non-FDA Approved for AUD

Topiramate

- Mostly renally cleared, some hepatic metabolism
- Elimination half-life is 18-24 hours
- Common SEs: paresthesias, memory-language problems, weight loss, other cognitive effects
- 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

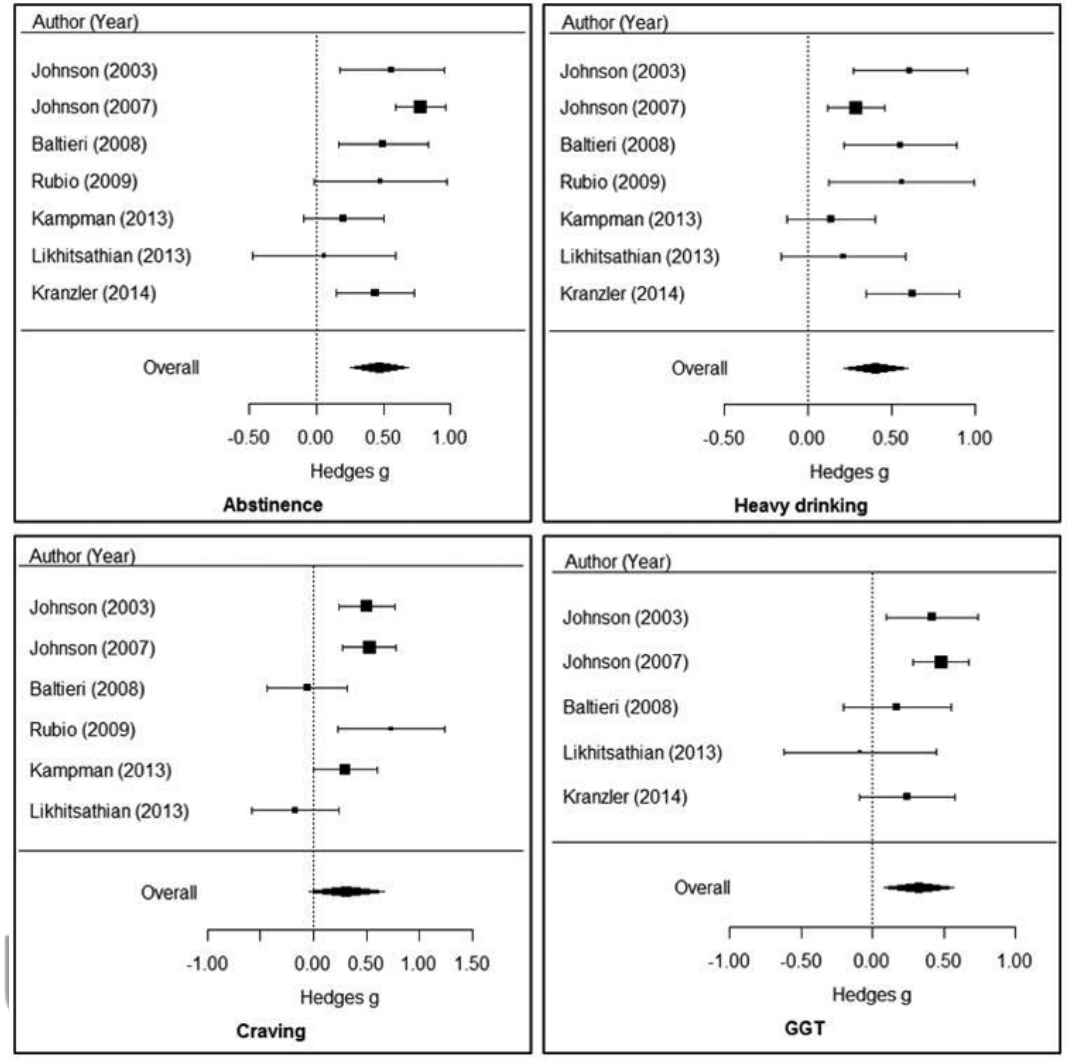
- Probably reduces craving/desire/urge to drink - especially once people start drinking
- May reduce the positively reinforcing effects of alcohol
- Effect mediated by self-efficacy: increases the belief in ability to resist heavy drinking
- May in some patients reduce anxiety and help with protracted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

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



Significant advantage for topiramate on:

-abstinence measures

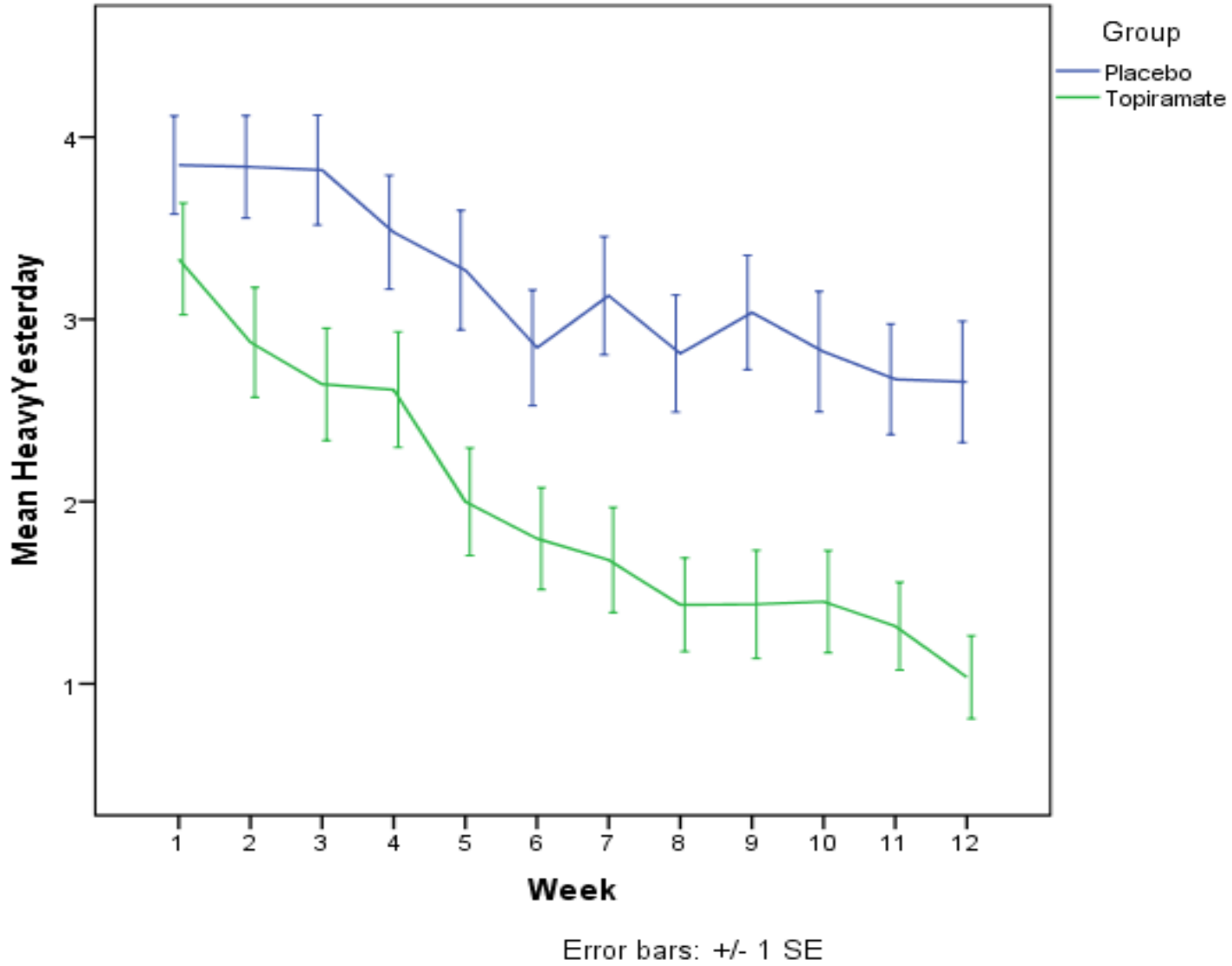
-heavy drinking measures

-GGT level

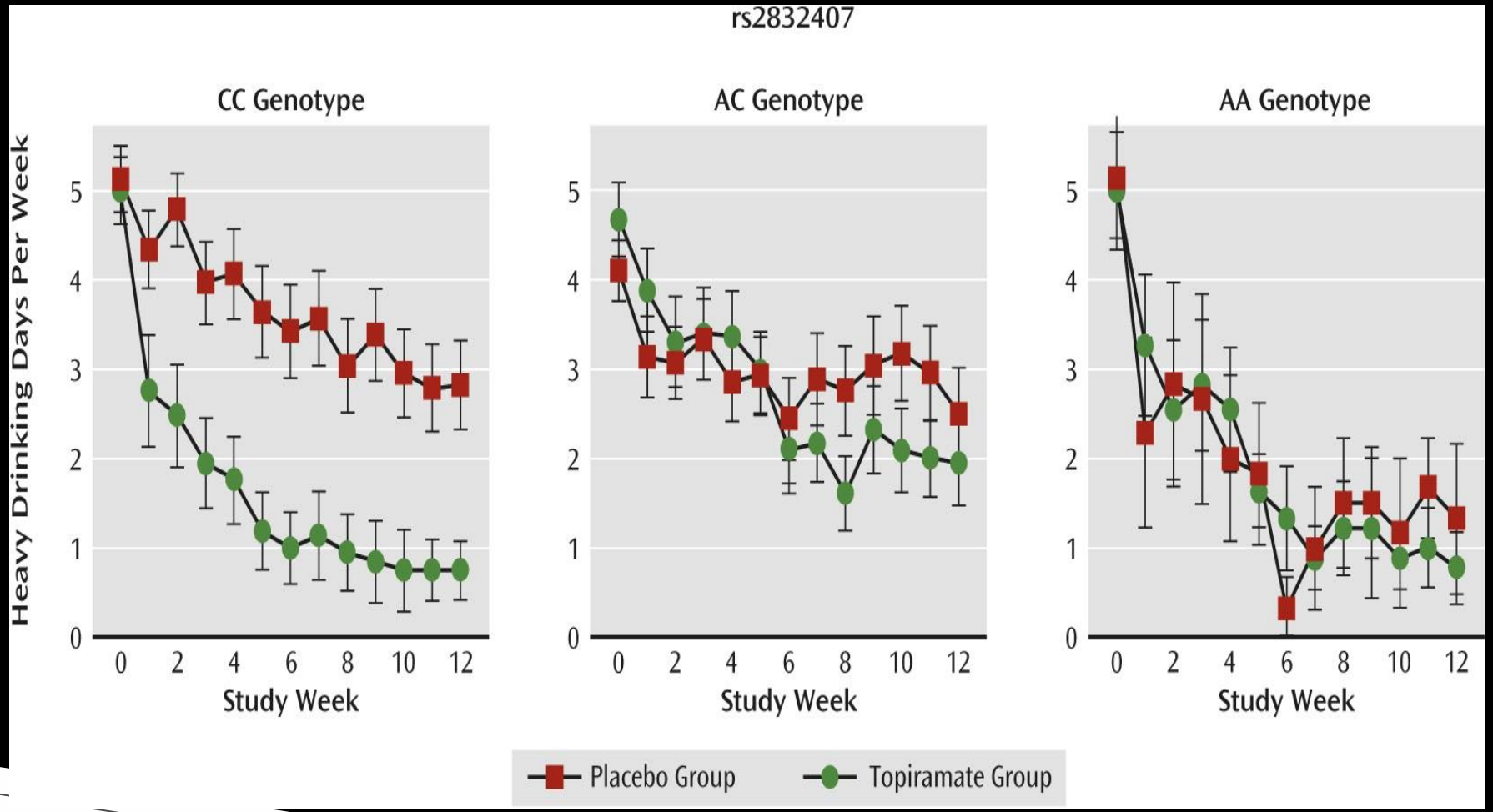
-trend for reducing craving

Kranzler et al., 2014, Within-Treatment Heavy Drinking Days

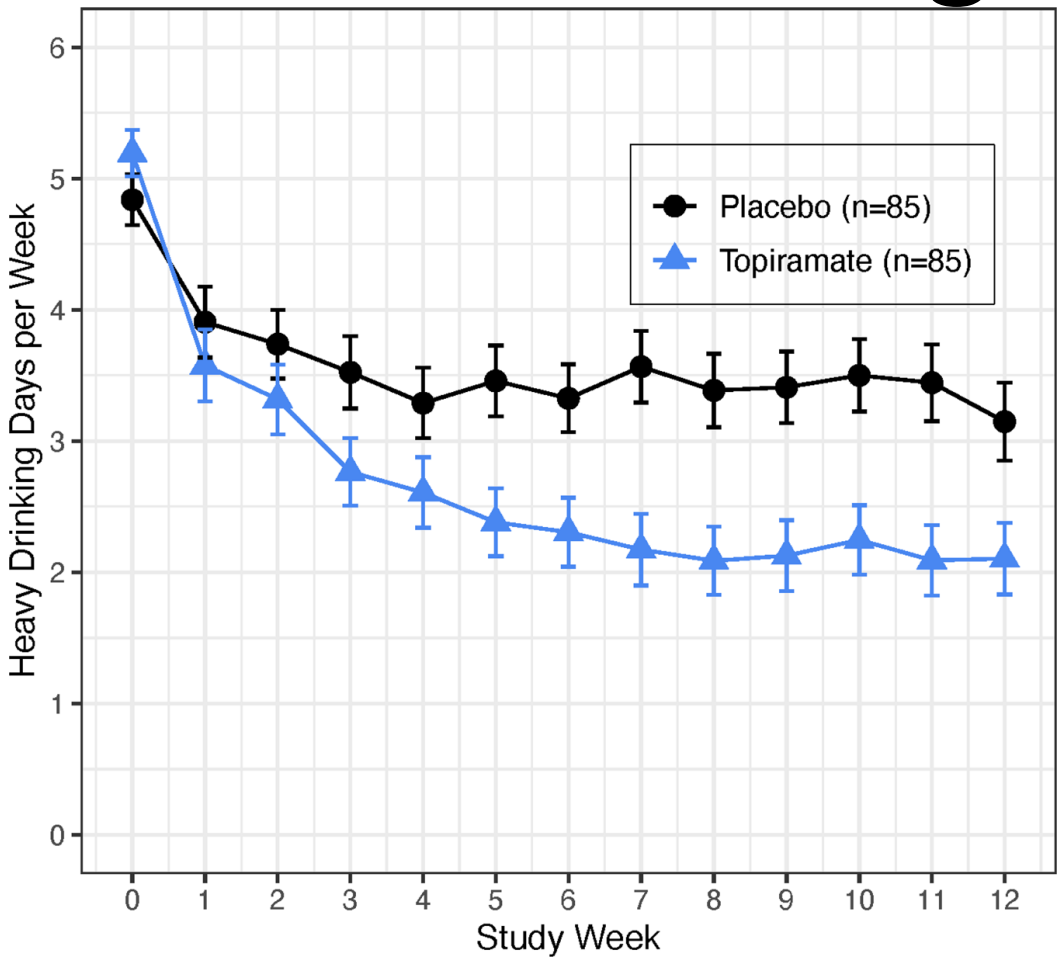
- 200mg daily



Heavy Drinking Days by Medication and Genotype Groups



Kranzler et al., 2021- replicated dose finding but *GRIK1* finding negative



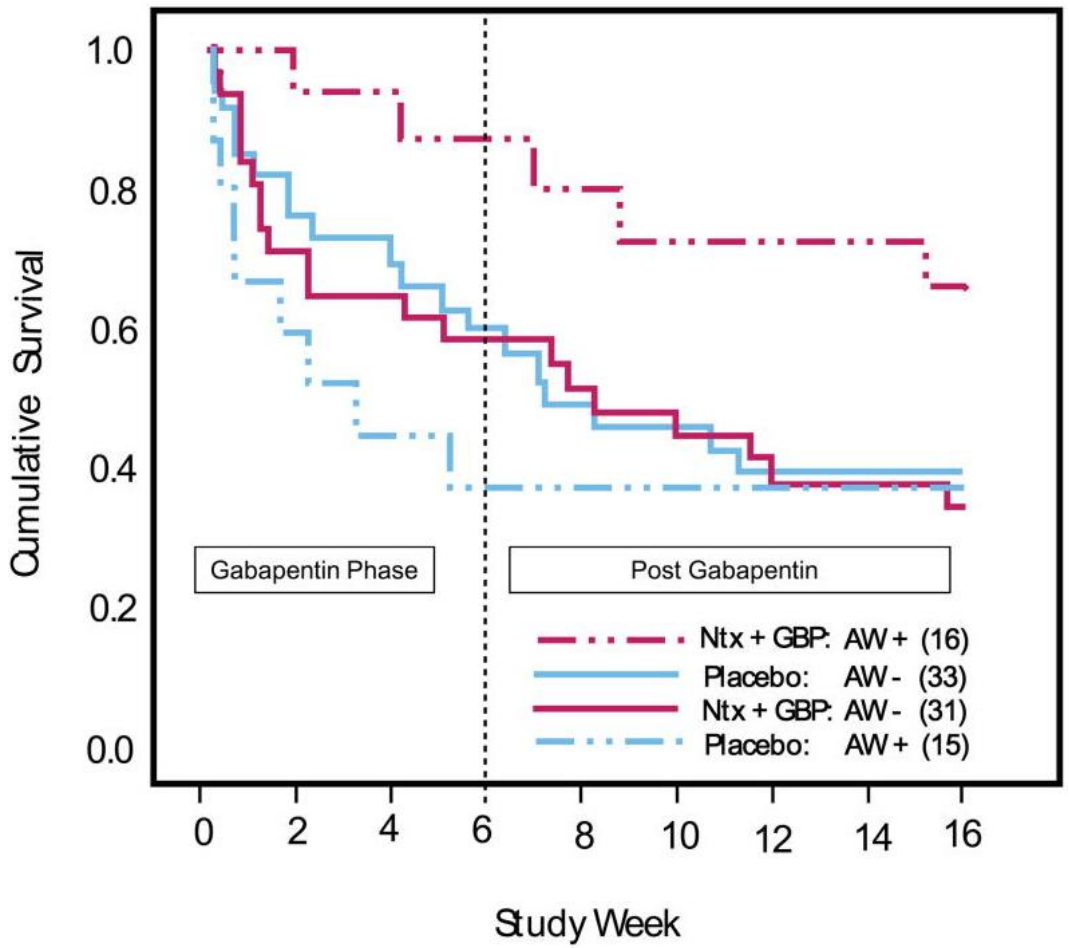
Gabapentin

- Binds to the $\alpha 2\delta$- subunit of the voltage-activated Ca^{+2} channel modulating neurotransmitter release.
- Renally excreted, no hepatic effects, no drug interactions
- Contraindications: Renal impairment
- Common SE's: Dizziness, sedation, peripheral edema
- Serious Adverse Rxn's: Rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multi-organ hypersensitivity. Suicidal ideation.
- Relatively safe and well tolerated

Gabapentin for reducing risk relapse and harmful drinking

- Monotherapy: initial 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)
- Gabapentin ER (Falk et al. 2019) RCT for AUD which did not show benefits over placebo for reduction in HDD's, craving or other other drinking related outcomes in those with AUD.

Anton et al., 2011



Kranzler et al., 2019

- Meta-analysis of the 7 placebo-controlled gabapentin monotherapy studies for AUD (N=751)
- Dosages in studies ranged from 300 to 3600 mg
- Good evidence only for decrease in percent of HDD's (moderate effect size)
- Did not significantly improve five other outcomes (GGT conc, drinks per day, percent days abstinent, relapse to heavy drinking, and complete abstinence)

Anton et al., 2020

- Medium size trial N=96 AUD subjects, RDBPCT
- Most with some recent withdrawal symptom history
- 16 weeks of treatment 1200mg daily (vs placebo)
- Gabapentin group better than placebo on NHDD and total abstinence (p=.02, NNT 5.4, and p=.04, NNT = 6.2)
- A Priori subgroup analysis: effect driven entirely by those with higher recent alcohol withdrawal symptoms on NHDD (*P* < .02; NNT, 3.1) and total abstinence (*P* = .003; NNT, 2.7)

Baclofen

- Selective $GABA_B$ agonist
- FDA-approved for the treatment of spasticity related to neurological disorders
- good safety profile and is safe in hepatic impairment, primarily excreted unchanged renally
- Common side effects include: drowsiness (especially at higher doses), dizziness, and nausea
- Baclofen should be started at a low dose (5 mg three times per day) and slowly titrated upwards (eg, 5–10 mg per day, every three days) to minimize possible side-effects, especially sedation and OD.

Baclofen

- Baclofen had shown effectiveness in multiple open label trials leading to further investigation and RCT's outlined below.
- Initial two placebo-controlled RCTs by Addolorato et al. first with AUD (N=39) and in cirrhotic patients with AUD (N=84) where roughly 70% of patients achieved abstinence over a 30-day period vs. placebo (21%). Max dose of 10 mg TID.
- Since original RCT's several other studies have been completed under varying conditions with mixed results.

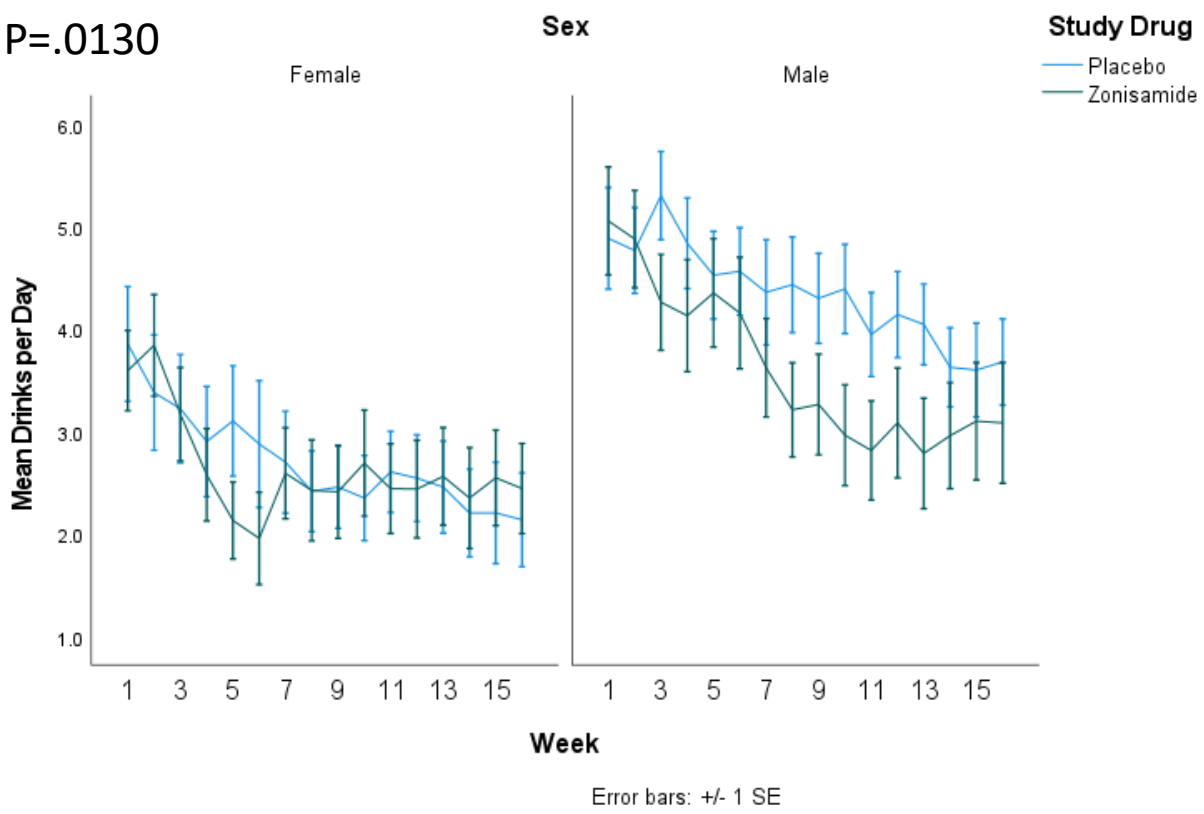
Baclofen

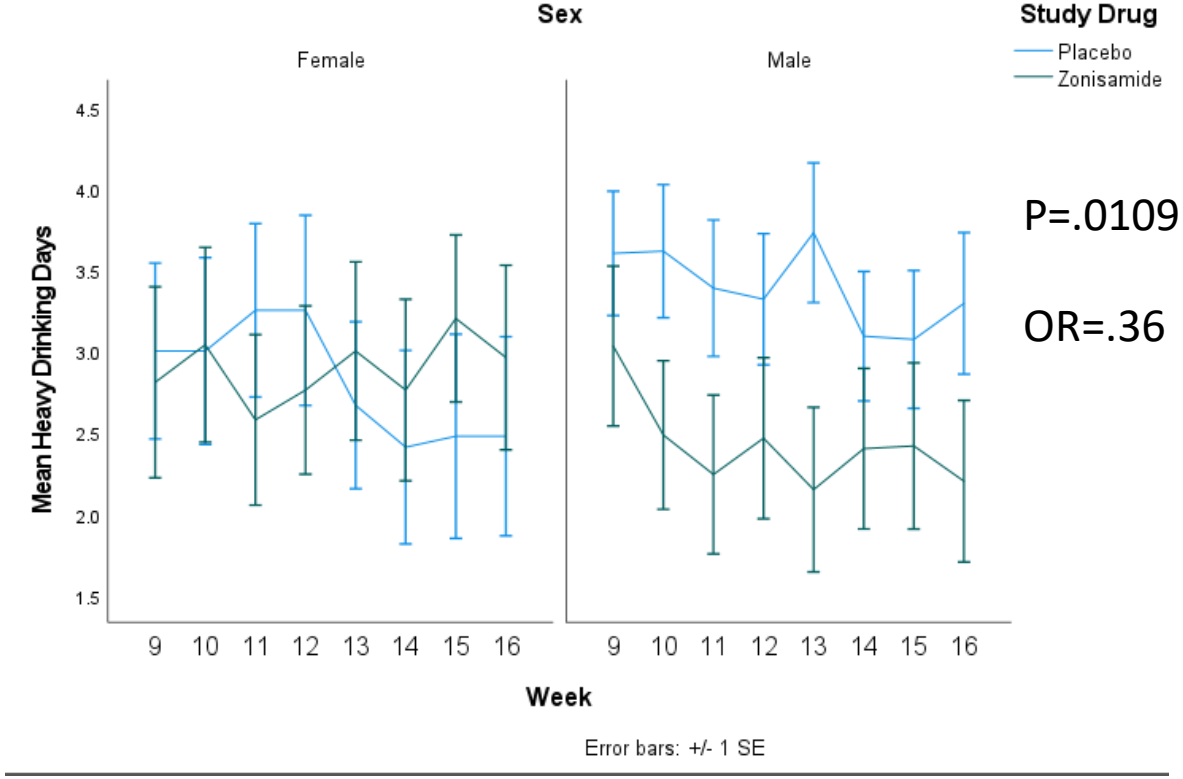
- Four meta-analyses completed in 2018
  - Rose and Jones in 2018 completed meta-analysis of 12 RCT's (N=590) showed no significant differences between baclofen and placebo on days abstinent, HDD's and craving.
    - Baclofen found to be superior for abstinence rates (CI 1.03 to 6.93).
  - Bschor et al. (14 RCT's; N=1,522) Baclofen did not outperform on primary outcomes vs placebo
  - Pierce et al. (13 RCT's; N=1,492) Low dose with better efficacy and tolerability. Better efficacy in heavier drinkers. Methodological issues.
  - Minozzi et al. (12 RCT's; N=1,128) Baclofen in those currently drinking and looking to reduce. Concluded that baclofen was not more effective than placebo on any outcome, primary or secondary.

Zonisamide- anticonvulsant similar to topiramate (SULFA)

- 2 positive pilot studies – follow up study: N=159 with AUD, 16 weeks
- Significant effect on primary outcome drinks/day (per week) and HDD/wk, about a 20% further reduction for zonisamide, significant sex effect and interaction- doesn't seem to work as well in women

P=.0130





P=.0109

OR=.36

Varenicline- O'Malley et al., 2018

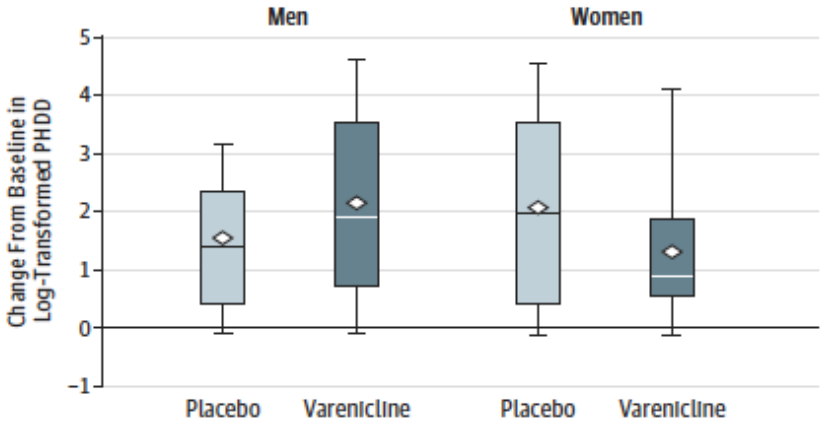
16 weeks treatment with 1mg BID

Significant effects on reducing heavy drinking in men but not women

Heavy Drinking Smokers

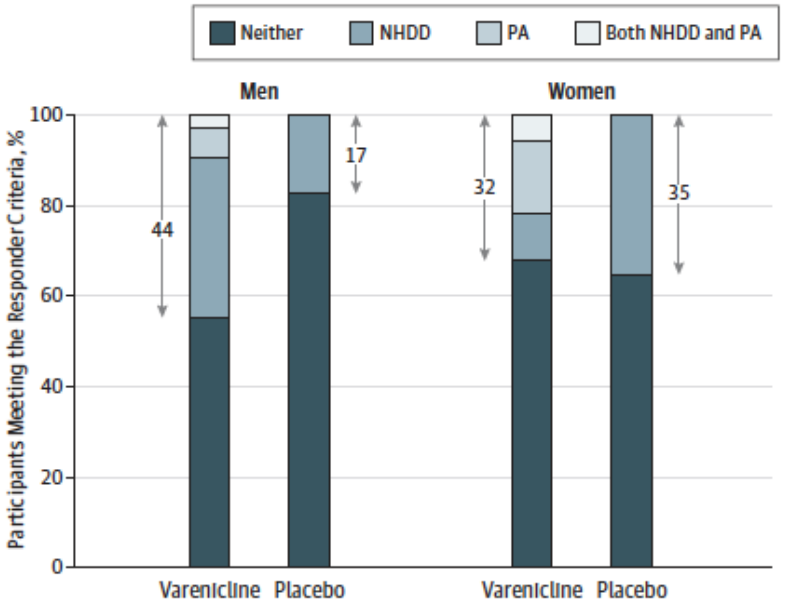
Some able to quit smoking and heavy drinking with medication but none on placebo

Figure 2. Change From Baseline to End Point in Log-Transformed Percentage of Heavy Drinking Days (PHDD) Outcome by Treatment Group and Sex



Heavy drinking days were defined as 5 or more drinks within a day for men and 4 or more drinks within a day for women. Baseline was defined as the 8 weeks prior to intake. End point was defined as the last 8 weeks of the treatment period. The horizontal line in the middle of each box indicates the median, while the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The diamonds indicate mean values. The whiskers above and below the boxes mark the minimum value and the maximum value, respectively. Varenicline was given as varenicline tartrate.

Figure 3. Percentage of Participants Meeting the Responder Criteria by Treatment Group and Sex



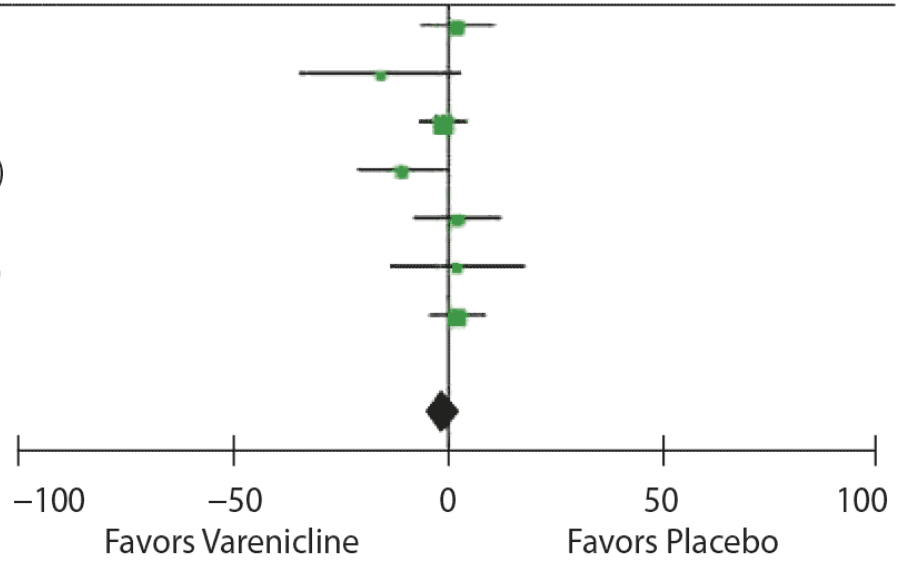
Positive response on the integrated response measure was defined as either No Heavy Drinking Days (NHDD), Prolonged Smoking Abstinence (PA), or both during the last 28 days of treatment. Percentages within the arrows correspond to the percentage who had a good response on the integrated measure. Missing data were treated as nonresponse. Varenicline treatment had a higher integrated response rate than placebo for men (Cohen h = 0.60) but not for women (Cohen h = −0.06). Varenicline was given as varenicline tartrate.

Gandhi et al., 2020 Varenicline Meta-Analysis

Figure 2. Subgroup Analysis of Percentage of Heavy Drinking Days in Those Receiving Varenicline Versus Placebo

Study or Subgroup	Varenicline Mean	Varenicline SD	Varenicline Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random (95% CI)
de Bejczy et al[18]	51	28.3	86	49	28.2	85	15.2%	2.00 (–6.47 to10.47)
Fucito et al[19]	22.7	17.5	15	38	31.2	15	4.1%	–15.30 (–33.40 to 2.80)
Hurt et al[20]	7.9	8.3	16	9.1	7.2	17	28.4%	–1.20 (–6.52 to 4.12)
Litten et al[21]	37.9	35.91	96	48.4	35.37	101	11.8%	–10.50 (–20.46 to –0.54)
O'Malley et al[23,a]	63	23	45	61	25	47	12.1%	2.00 (–7.81 to 11.81)
O'Malley et al[23,a]	65	23	19	63	25	20	5.7%	2.00 (–13.07 to 17.07)
Schacht et al[24]	60	10.8	18	58	8.4	17	22.7%	2.00 (–4.39 to 8.39)
Total (95% CI)			**295**			**302**	**100.0%**	**–1.09 (–4.86 to 2.69)**

Heterogeneity: $\tau^2 = 5.68$; $\chi^2_6 = 7.73$ ($P = .26$); $I^2 = 22\%$
Test for overall effect: $Z = 0.56$ ($P = .57$)



[a]The study by O'Malley et al[23] is included twice to show separate results for the two groups in the study.
Abbreviation: IV = inverse variation.

Second Line Medications-summary

- Topiramate has enough evidence to be first line, but there are more risks and more complicated titration vs NTX/acamp
- Gabapentin promising, may work best combined with naltrexone, can titrate quickly
- Baclofen- could consider, a lot of negative findings
- Zonisamide appears to work, similar to topiramate, at least for men, works in patients actively heavy drinking at initiation (in contrast to NTX/acamp)
- Varenicline- consider in a male patient with low psychiatric comorbidity and also a smoker

Discussion/Comments

Case Presentation #1
Dawn Merritt, QMHP-A

- 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
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Use chat function for questions

Main Question

Ways to help individual that I may not have thought of

Patient Demographics

30y/o white male, GED, works odd jobs, lives on family property in camper,

Background Information

No current medications, no MH diagnosis, all sud diagnosis. Minimal therapy as non compliant.

Previous Interventions

He was given suboxone on multiple occasions. He has been to treatment, discharged prior to 45 days no given reason by either facility or client. That facility won't take him back. He has been in and out of services with our agency. Has pending court matters. Recently lost contact with him from March up until this week.

Plan for Future Treatment/ Patient Goals

Client wants to resume treatment, no efforts made to do so. States he wants vivitrol. I advised he needs treatment again. No plans as to what he is going to do differently.

Other Relevant Information

Prior overdose, recent loss of a girlfriend (who was also possibly using) Minimal contact with me, which historically is odd as he has always kept in contact with me regardless of use.

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

Case Presentation #2
Megan Lemay, 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
*6 for phone audio
Use chat function for questions

Main Question

Advice on weaning current treatment and other potential treatment strategies.

Patient Demographics

35 year old man, currently a student, lives with supportive parents.

Background Information

History of Bipolar I which is well controlled with a long-standing psychiatrist
Alcohol use disorder in remission, with some overuse of benzos and briefly opioids in the past. None current.
Was having increased anxiety 6 months ago and found Phenibut online to treat this. Escalated his use to 8 g daily.
Unable to cut back, began experiencing withdrawal. Discussed with his psychiatrist who referred to addiction medicine.

Previous Interventions

He has actually successfully weaned off of phenibut using baclofen, which he tolerates very well. Weaned 0.5 g weekly.
He titrated up to 10 tid of baclofen and is currently taking 10 bid.

Plan for future treatment/ Patient Goals

Plan to wean baclofen

Case Studies

- Case studies
  - Submit: www.vcuhealth.org/echo
  - Receive feedback from participants and content experts
  - Earn **$100** 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:

- **Ademola Adetunji, NP** from Fairfax County CSB
- **Tara Belfast-Hurd, MBA-PA** from Department of Behavioral Health and Developmental Services
- **Michael Bohan, MD** from Meridian Psychotherapy
- **Ramona Boyd, NP** from Health Wagon
- **Diane Boyer, DNP** from Region Ten CSB
- **Melissa Bradner, MD** from VCU Health
- **Kayla Brandt, B.S.** from Crossroads Community Service Board
- **Susan Cecere, LPN** from Hampton Newport News
- **Michael Fox, DO** from VCU Health
- **Shannon Garrett, FNP** from West Grace Health Center
- **Sharon Hardy, BSW, CSAC** from Hampton-Newport News CSB
- **Kara Howard, NP** from Southwest Montana Community Health Center
- **Sunny Kim, NP** from VCU Health
- **Heidi Kulberg, MD** from Meridian Health
- **Thokozeni Lipato, MD** from VCU Health
- **Caitlin Martin, MD** from VCU Health
- **Maureen Murphy-Ryan, MD** from AppleGate Recovery
- **Faisal Mohsin, MD** from Hampton-Newport News CSB
- **Stephanie Osler, LCSW** from Children's Hospital of the King's Daughters
- **Winona Pearson, LMSW** from Middle Peninsula Northern Neck CSB
- **Jennifer Phelps, BS, LPN** from Horizons Behavioral Health
- **Crystal Phillips, PharmD** from Appalachian College of Pharmacy
- **Jashanda Poe, MA** from Rappahannock Area CSB
- **Tierra Ruffin, LPC** from Hampton-Newport News CSB
- **Manhal Saleeby, MD** from VCU Health Community Memorial Hospital
- **Jenny Sear-Cockram, NP** from Chesterfield County Mental Health Support Services
- **Elizabeth Signorelli-Moore, LPC** from Region 1 CSB
- **Daniel Spencer, MD** from Children's Hospital of the King's Daughters
- **Linda Southall, QMHP** from Alleghany Highlands CSB
- **Cynthia Straub, FNP-C, ACHPN** from Memorial Regional Medical Center
- **Saba Suhail, MD** from Ballad Health
- **Barbara Trandel, MD** from Colonial Behavioral Health
- **Bill Trost, MD** from Danville-Pittsylvania Community Service
- **Art Van Zee, MD** from Stone Mountain Health Services
- **Ashley Wilson, MD** from VCU Health
- **Sarah Woodhouse, MD** from Chesterfield Mental Health
- **Susan Mayorga, BA, CBIS** from Community Health Center of the New River Valley
- **Jordan Siebert, Peer Recovery Specialist** from Daily Planet Health Services

Claim Your CME and Provide Feedback

- www.vcuhealth.org/echo

- To claim CME credit for today's session
- Feedback
  - Overall feedback related to session content and flow?
  - Ideas for guest speakers?

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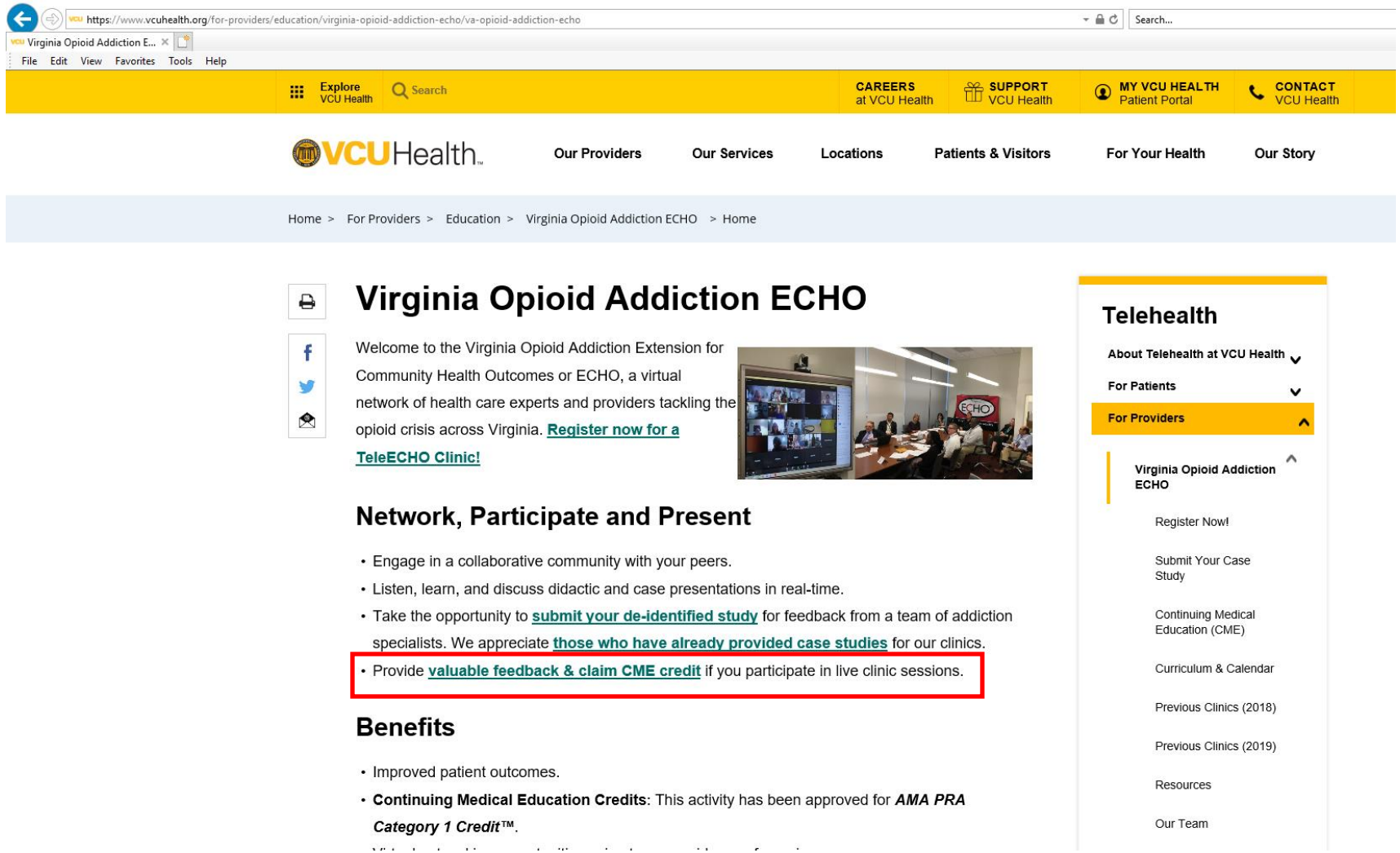

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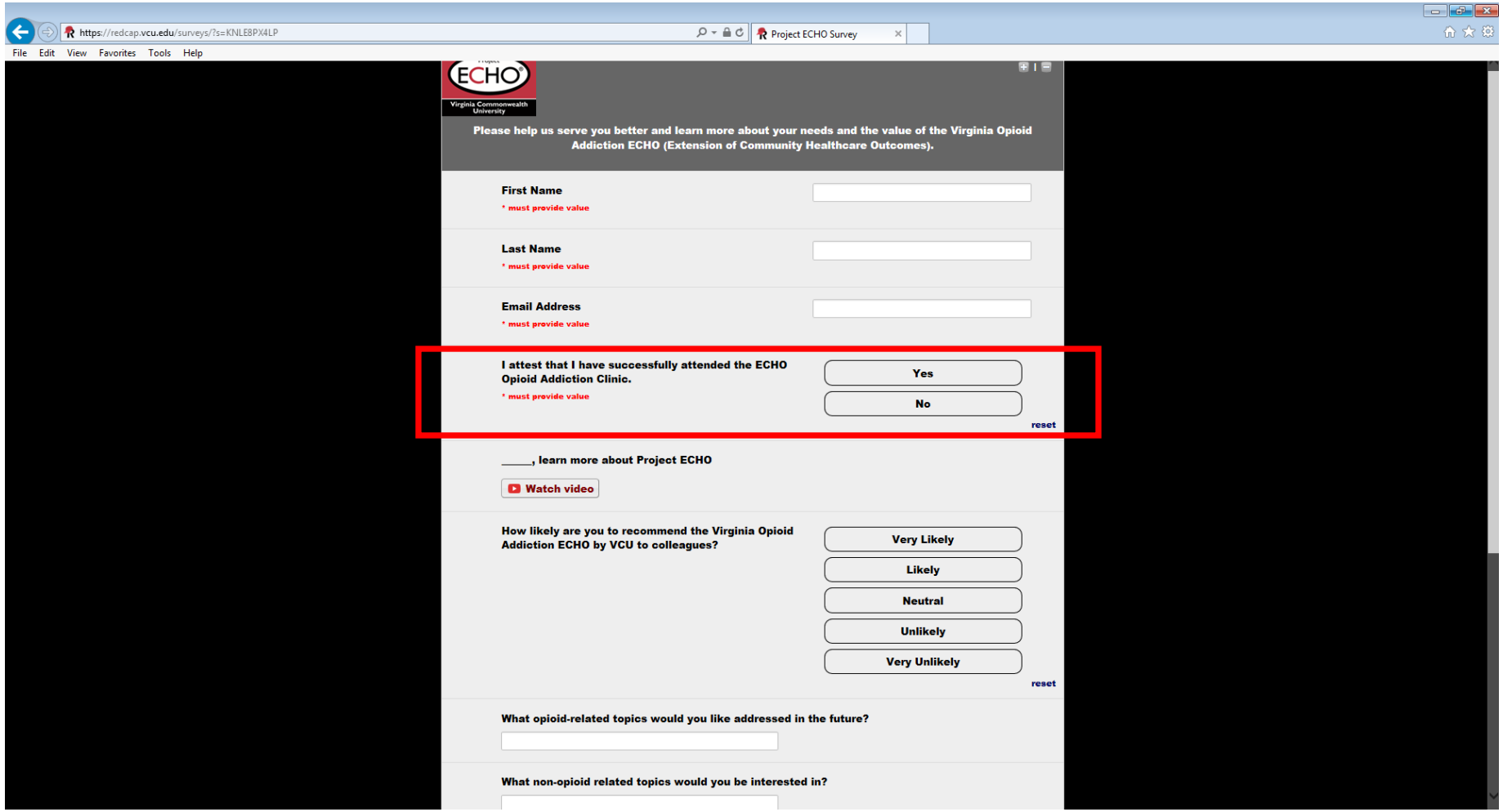

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- www.vcuhealth.org/echo
  - To view previously recorded clinics and claim credit

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Virginia Opioid Addiction ECHO

Welcome to the Virginia Opioid Addiction Extension for Community Health Outcomes or ECHO, a virtual network of health care experts and providers tackling the opioid crisis across Virginia. Register now for a TeleECHO Clinic!

Network, Participate and Present

- Engage in a collaborative community with your peers.
- Listen, learn, and discuss didactic and case presentations in real-time.
- Take the opportunity to submit your de-identified study for feedback from a team of addiction specialists. We appreciate those who have already provided case studies for our clinics.
- Provide valuable feedback & claim CME credit if you participate in live clinic sessions.

Benefits

- Improved patient outcomes.
- **Continuing Medical Education Credits**: This activity has been approved for ***AMA PRA Category 1 Credit™***.
- Virtual networking opportunities using two-way video conferencing.
- No cost to participate.
- **If unable to attend a live clinic session**, learn how to access the CME website to view the recording and claim credit.

Content posted within the Virginia Opioid Addiction ECHO is made by possible, in part, by funding from the Virginia Department of Health.

Project ECHO

Virginia Commonwealth University

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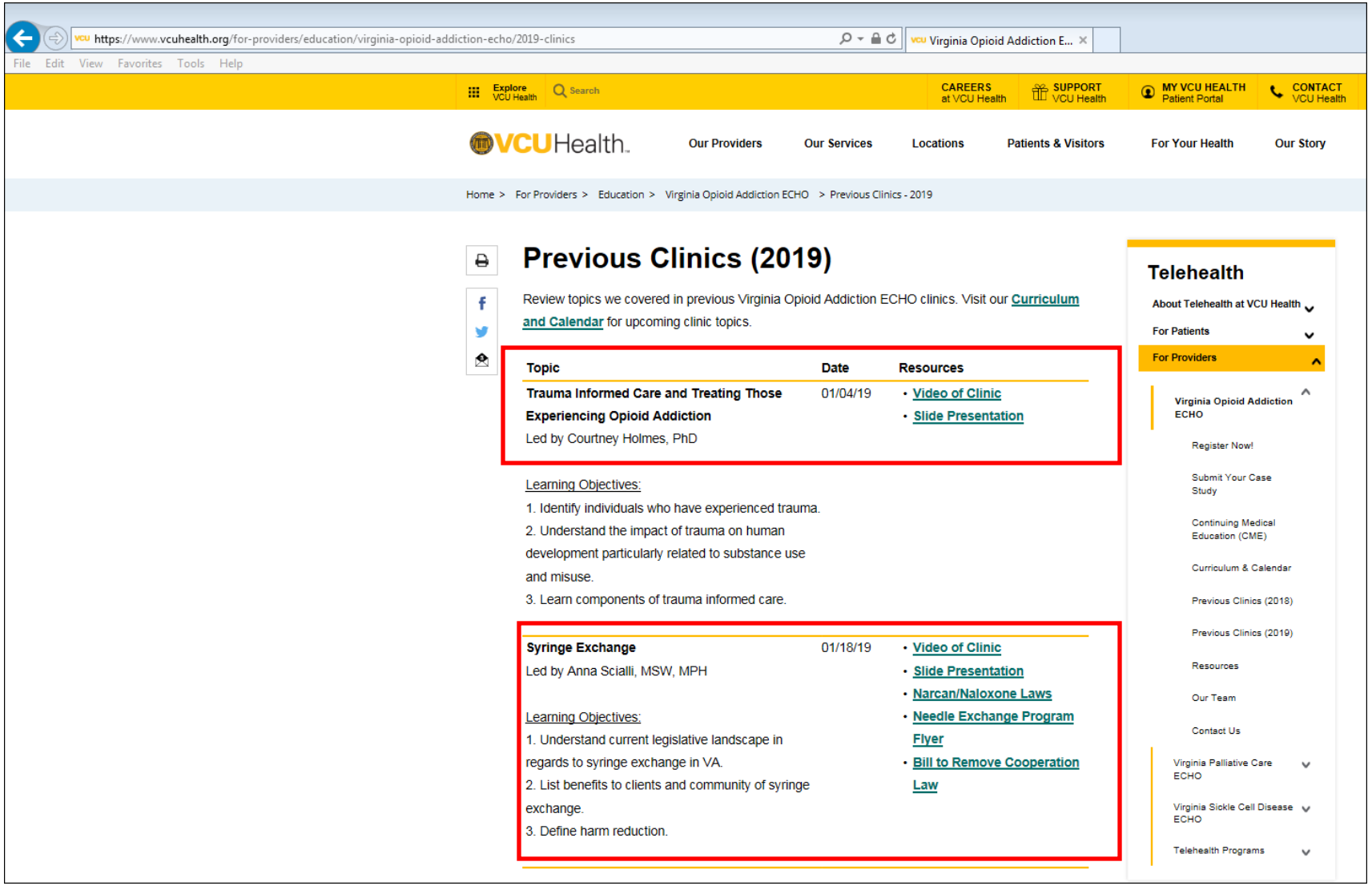

VCU Virginia Opioid Addiction TeleECHO Clinics

Bi-Weekly Fridays - 12-1:30 pm

Mark Your Calendar --- Upcoming Sessions

June 25: Novel Pharmacotherapy in SUD — Gerry Moeller, MD

July 16: Panel Discussion: Re-Entry from Incarceration — TBD

Please refer and register at vcuhealth.org/echo

Project ECHO®
Virginia Commonwealth University

THANK YOU!

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

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