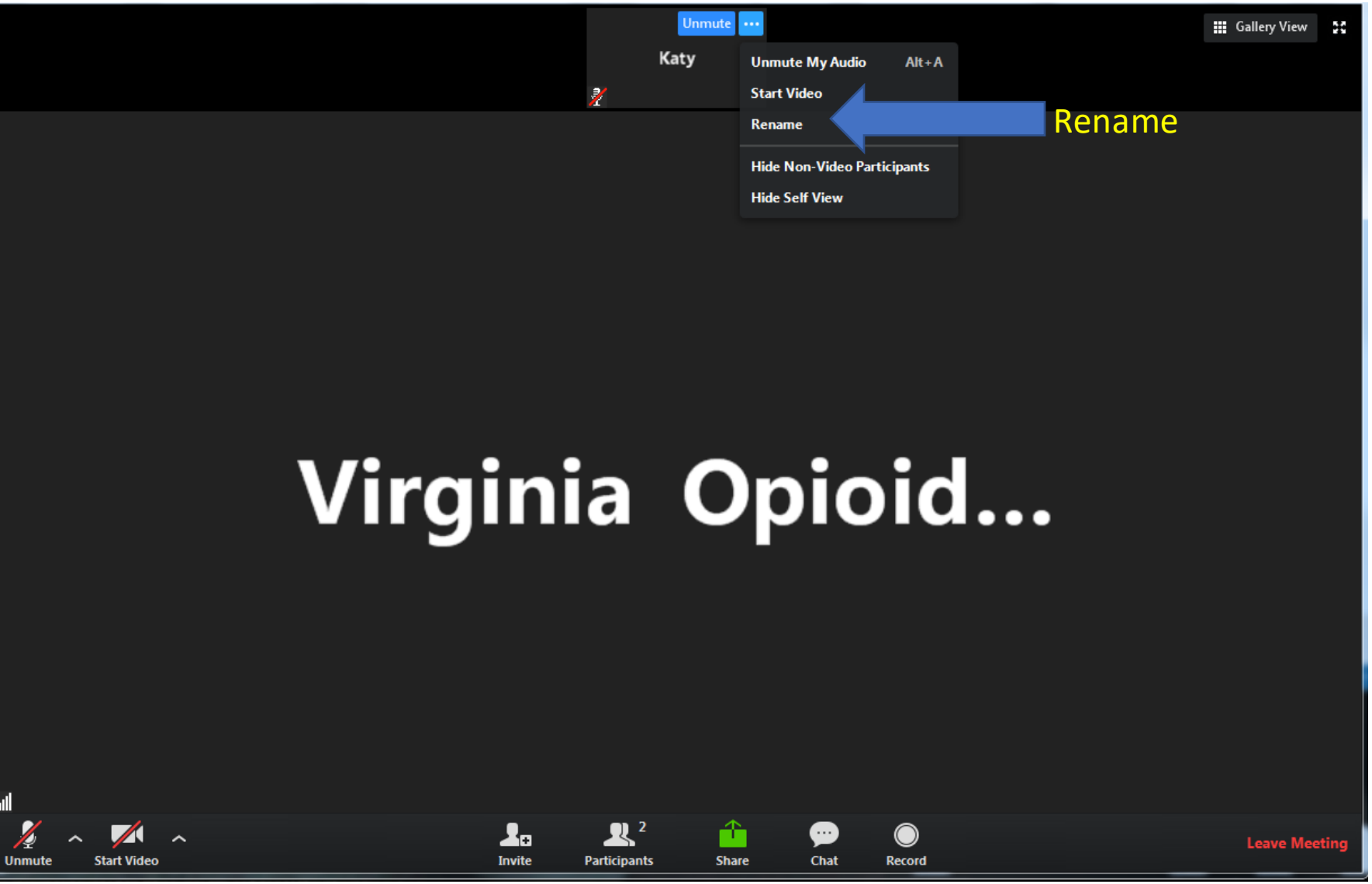
Virginia Opioid Addiction ECHO* Clinic

June 24, 2021

*ECHO: Extension of Community Healthcare Outcomes

Helpful Reminders



- Rename your Zoom screen, with your name and organization

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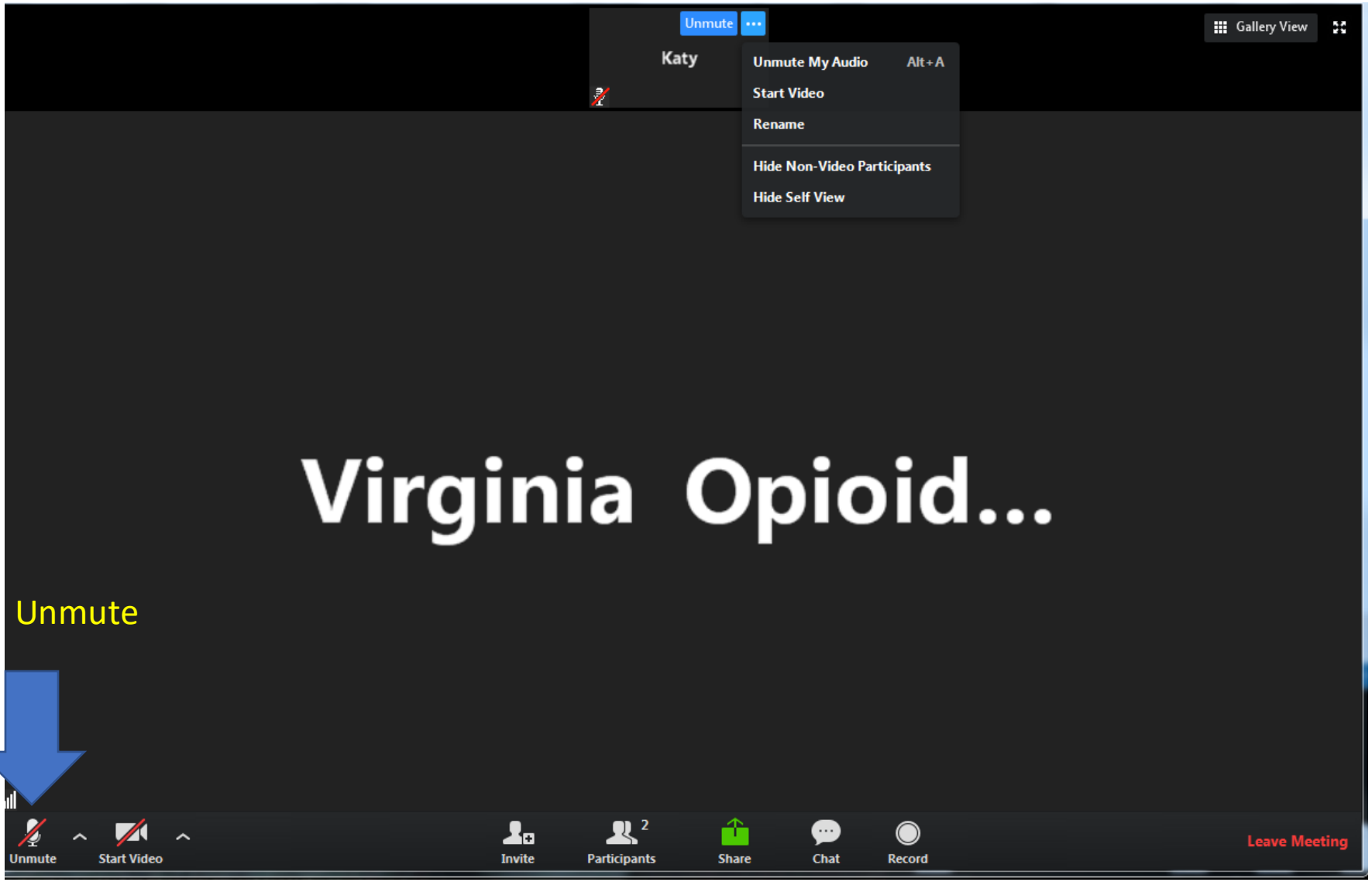

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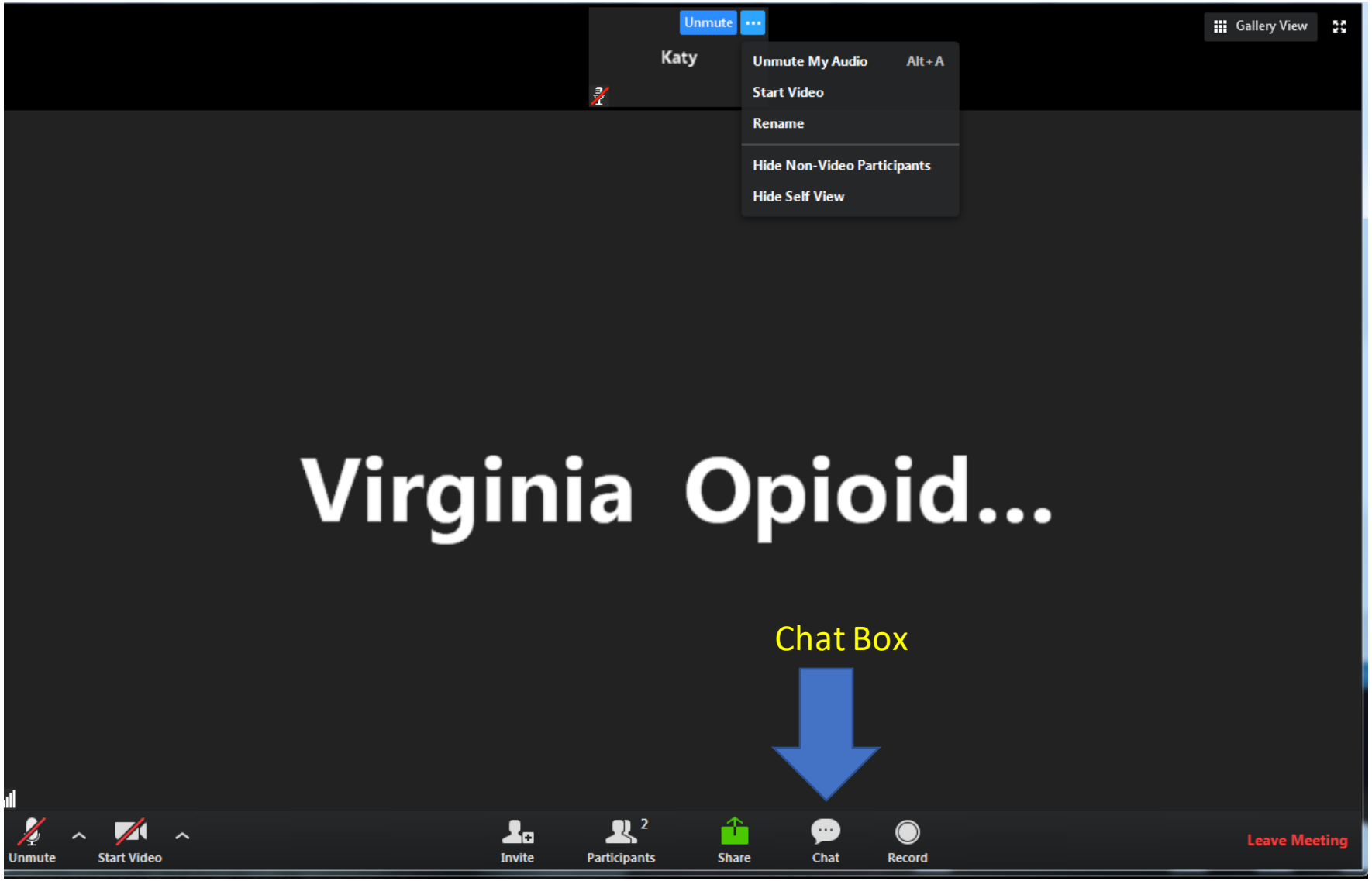
Helpful Reminders



- 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 Megan Lemay, MD Salim Zulfiqar, MD Katie Adams, PharmD
Didactic Presentation	Gerry Moeller, 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. **Gerry Moeller, 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 Pharmacotherapy in OUD

F. Gerard Moeller, M.D.
Professor and Director, VCU Institute for Drug and Alcohol Studies

Disclosures

- Past grant funding: Indivior pharmaceuticals
- Consulting: Indivior, Astellas, Boehringer Ingelheim, Virginia Catalyst
- Grant funding and consulting are unrelated to this work
- Some of the medications to be discussed are not FDA approved for opioid use disorder

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Current FDA Approved Medications for Opioid Use Disorder

- Maintenance Treatment
  - Buprenorphine (partial agonist at mu opioid receptor, antagonist at kappa opioid receptor)
    - Buprenorphine and naloxone (buccal or sublingual film, sublingual tablet)
    - Probuphine (buprenorphine) implant for subdermal administration
    - Sublocade (buprenorphine extended-release) injection for subcutaneous use

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Current FDA Approved Medications for Opioid Use Disorder

- Maintenance Treatment
  - Methadone: full agonist at mu opioid receptor
  - Vivitrol (depot injectable naltrexone): antagonist at mu opioid receptor

Current FDA Approved Medications for Opioid Use Disorder

- Opioid Withdrawal
  - Lucemyra (lofexidine): alpha-2 adrenoreceptor agonist
  - Approved in 2018 for treatment of opioid withdrawal symptoms
  - From FDA "While Lucemyra may lessen the severity of withdrawal symptoms, it may not completely prevent them and is only approved for treatment for up to 14 days. ***Lucemyra is not a treatment for opioid use disorder (OUD), but can be used as part of a broader, long-term treatment plan for managing OUD***."
  - Can be used to aid in transition to depot naltrexone

Why do we need new medications for OUD treatment?

- The US opioid epidemic has reached an alarming scale, with more than 72,000 drug overdose deaths occurring across the US in 2017, and the majority of these deaths due to opioids (CDC 2018).
- Medication treatment utilizing methadone, buprenorphine, or naltrexone in addition to behavioral interventions has proven to be effective at reducing all-cause mortality and overdose deaths in patients with opioid use disorder (Ma, Bao et al. 2018).

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Why do we need new medications for OUD treatment?

- However, retention in medication treatment is problematic, with controlled trials showing a 20-30% patient dropout rate or more in the first 12 weeks of treatment (Johnson, Chutuape et al. 2000, Tanum, Solli et al. 2017).
- Factors associated with dropout from treatment include continued opioid and other drug use, as well as behavioral factors, including insomnia, impulsivity and anxiety (Marcovitz, McHugh et al. 2016, Hui, Weinstein et al. 2017, Zhu, Evans et al. 2018).

How to Choose Medications for OUD

- Top priority is reducing opioid use/protecting against opioid overdose
- Currently approved mu agonist, partial agonist, antagonist show clear benefit for these issues
- Most likely use of novel pharmacotherapies is as adjunctive medication in addition to FDA approved meds

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Potential Reasons for Adjunctive Medications

- Continued opioid use
- Continued use of other illicit substances
- Comorbid psychiatric illness / symptoms

Potential Reasons for Adjunctive Medications

- Continued opioid use
  - Have you maximized current treatment?
    - Dose of medications
    - Length of trial of medications
    - Type of medications
    - Compliance with medications (consider depot formulations)
    - ASAM levels of care
    - Counseling/behavioral therapy

Potential Reasons for Adjunctive Medications

- Continued use of other illicit substances
  - Have you considered currently approved medications (alcohol use disorder)?
    - ASAM levels of care
    - Counseling/behavioral therapy

Potential Reasons for Adjunctive Medications

- Comorbid psychiatric illness
  - Has the patient had a comprehensive psychiatric evaluation?
    - Mood stabilizing medications for Bipolar disorder
    - Antidepressants for Major Depressive Disorder
    - Antipsychotic medications for Schizophrenia/Schizoaffective disorder
    - Counseling/behavioral therapy

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Other Options and How to Choose Them

- Study of over 72 million electronic health records
- Evaluating currently approved medications and link to diagnosis of OUD in remission

Molecular Psychiatry
https://doi.org/10.1038/s41380-020-01011-y

ARTICLE

Drug repurposing for opioid use disorders: integration of computational prediction, clinical corroboration, and mechanism of action analyses

Mengshi Zhou[1,2] · QuanQiu Wang[1] · Chunlei Zheng[1] · A. John Rush[3,4,5] · Nora D. Volkow[6] · Rong Xu[1]

Received: 10 September 2020 / Revised: 11 December 2020 / Accepted: 17 December 2020

Abstract
Morbidity and mortality from opioid use disorders (OUD) and other substance use disorders (SUD) is a major public health crisis, yet there are few medications to treat them. There is an urgency to accelerate SUD medication development. We present an integrated drug repurposing strategy that combines computational prediction, clinical corroboration using electronic health records (EHRs) of over 72.9 million patients and mechanisms of action analysis. Among top-ranked repurposed candidate drugs, tramadol, olanzapine, mirtazapine, bupropion, and atomoxetine were associated with increased odds of OUD remission (adjusted odds ratio: 1.51 [1.38–1.66], 1.90 [1.66–2.18], 1.38 [1.31–1.46], 1.37 [1.29–1.46], 1.48 [1.25–1.76], p value < 0.001, respectively). Genetic and functional analyses showed these five candidate drugs directly target multiple OUD-associated genes including BDNF, CYP2D6, OPRD1, OPRK1, OPRM1, HTR1B, POMC, SLC6A4 and OUD-associated pathways, including opioid signaling, G-protein activation, serotonin receptors, and GPCR signaling. In summary, we developed an integrated drug repurposing approach and identified five repurposed candidate drugs that might be of value for treating OUD patients, including those suffering from comorbid conditions.

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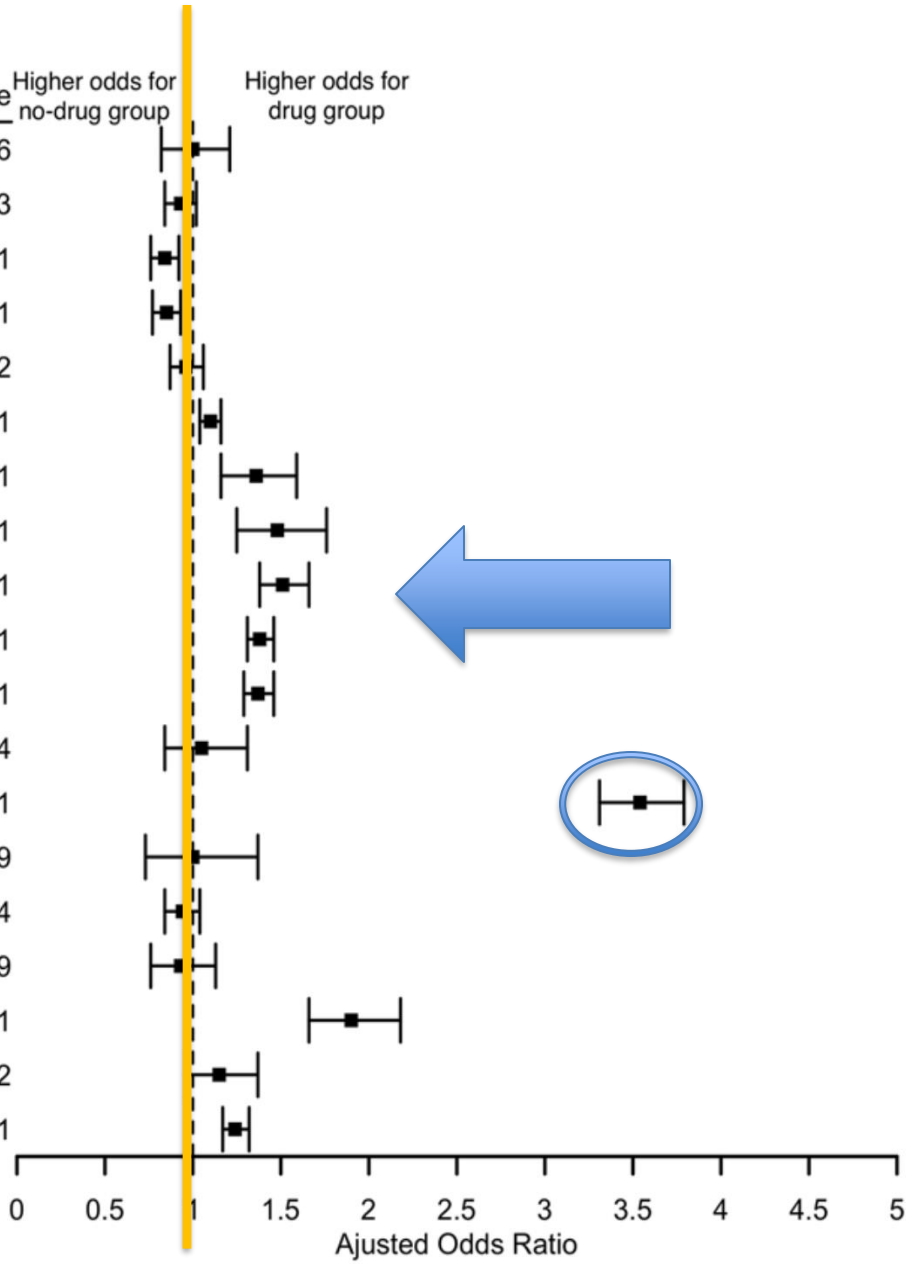
Drug	Class	Treatment	Rank	AOR(95% CI)	P-value
pregabalin	other	diabetic neuropathy	1	1 (0.82,1.21)	0.96
fentanyl	opioid analgesic	pain	2	0.93 (0.84,1.02)	0.13
morphine	opioid analgesic	pain	3	0.84 (0.76,0.92)	<0.0001
oxycodone	opioid analgesic	pain	4	0.85 (0.77,0.93)	<0.0001
hydromorphone	opioid analgesic	pain	5	0.96 (0.87,1.06)	0.42
citalopram	other	depression	6	1.10 (1.04,1.16)	<0.0001
ziprasidone	other	schizophrenia	7	1.36 (1.16,1.59)	<0.0001
atomoxetine	other	ADHD	8	1.48 (1.25,1.76)	<0.0001
tramadol	opioid analgesic	pain	9	1.51 (1.38,1.66)	<0.0001
bupropion	other	depression	10	1.38 (1.31,1.46)	<0.0001
mirtazapine	other	depression	11	1.37 (1.29,1.46)	<0.0001
cortisol	other	rheumatoid arthritis	12	1.05 (0.84,1.31)	0.74
naltrexone	opioid addiction treatment	opioid addiction	13	3.54 (3.31,3.79)	<0.0001
tapentadol	opioid analgesic	pain	14	1 (0.73,1.37)	0.99
amphetamine	other	ADHD	15	0.94 (0.84,1.04)	0.24
methylprednisolone	other	rheumatoid arthritis	16	0.93 (0.76,1.13)	0.49
olanzapine	other	schizophrenia	18	1.90 (1.66,2.18)	<0.0001
topiramate	other	seizures	19	1.15 (0.97,1.37)	0.12
fluoxetine	other	depression	20	1.24 (1.17,1.32)	<0.0001



From Zhou et al., 2021

Serotonin (5-HT) 2A Receptor Antagonists

- Mirtazapine has 5-HT_{2A}R Antagonist effects
- Reduce cue induced reinstatement of cocaine and economic demand for opioids in preclinical studies (Sholler et al., 2019, Martin et al., 2021)
- Reduce premature responding (impulsivity) in rodents
- Does mirtazapine reduce the response to drug cues in humans?

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A Biobehavioral Signature of Functional Connectivity and Pharmacogenetics in Cocaine Use Disorder Participants

- 28 Cocaine Use Disorder Participants underwent fMRI scans on two separate days following placebo or mirtazapine (15mg) administration while performing cocaine Stroop task
- Interaction with 5-HT_{2C}R rs6318 polymorphism on ACC to Hippocampus effective connectivity examined using Dynamic Causal Modeling in SPM

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Ma et al., Under Review

Imaging Targets for Cocaine Cue Reactivity in Humans

- Cocaine Stroop task
- Name the colors (Red, Green, Blue) but ignore meaning of the words
- 300 trials: 60 practice trials + 240 test trials
- Block design
  - Cocaine-related words: 2 blocks, 30 trials / block
  - Neutral words: 6 blocks, 30 trials / block
- Attentional Bias: difference of reaction time to cocaine-related and neutral words over session or over blocks

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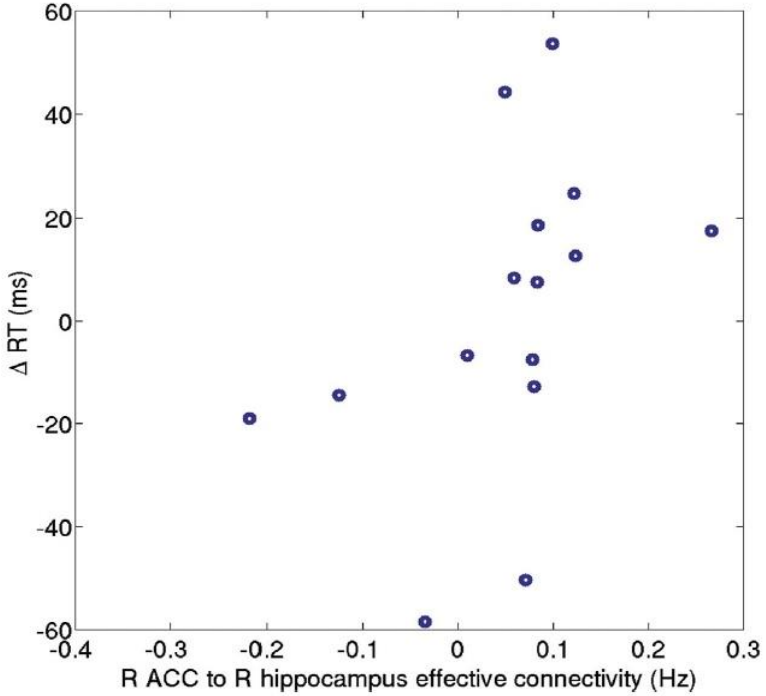
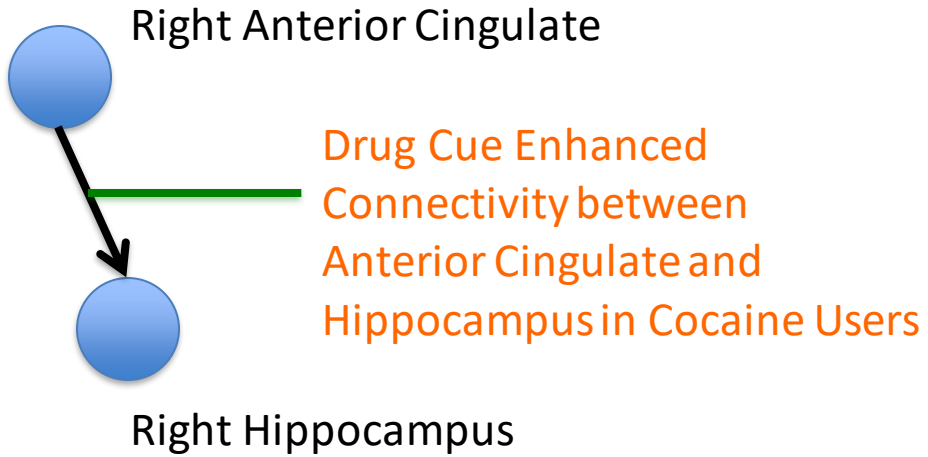
Previous Research Showed that ACC to Hippocampus Effective Connectivity Related to Attentional Bias in Cocaine and Opioid Users



Correlation between ACC to Hippocampus Connectivity and Attentional Bias on Cocaine Stroop Task



Anterior Cingulate plays a Central Role in Drug Cue related Brain Connectivity in Cocaine Users similar to mPFC in Rodents

Ma et al., 2018, 2019

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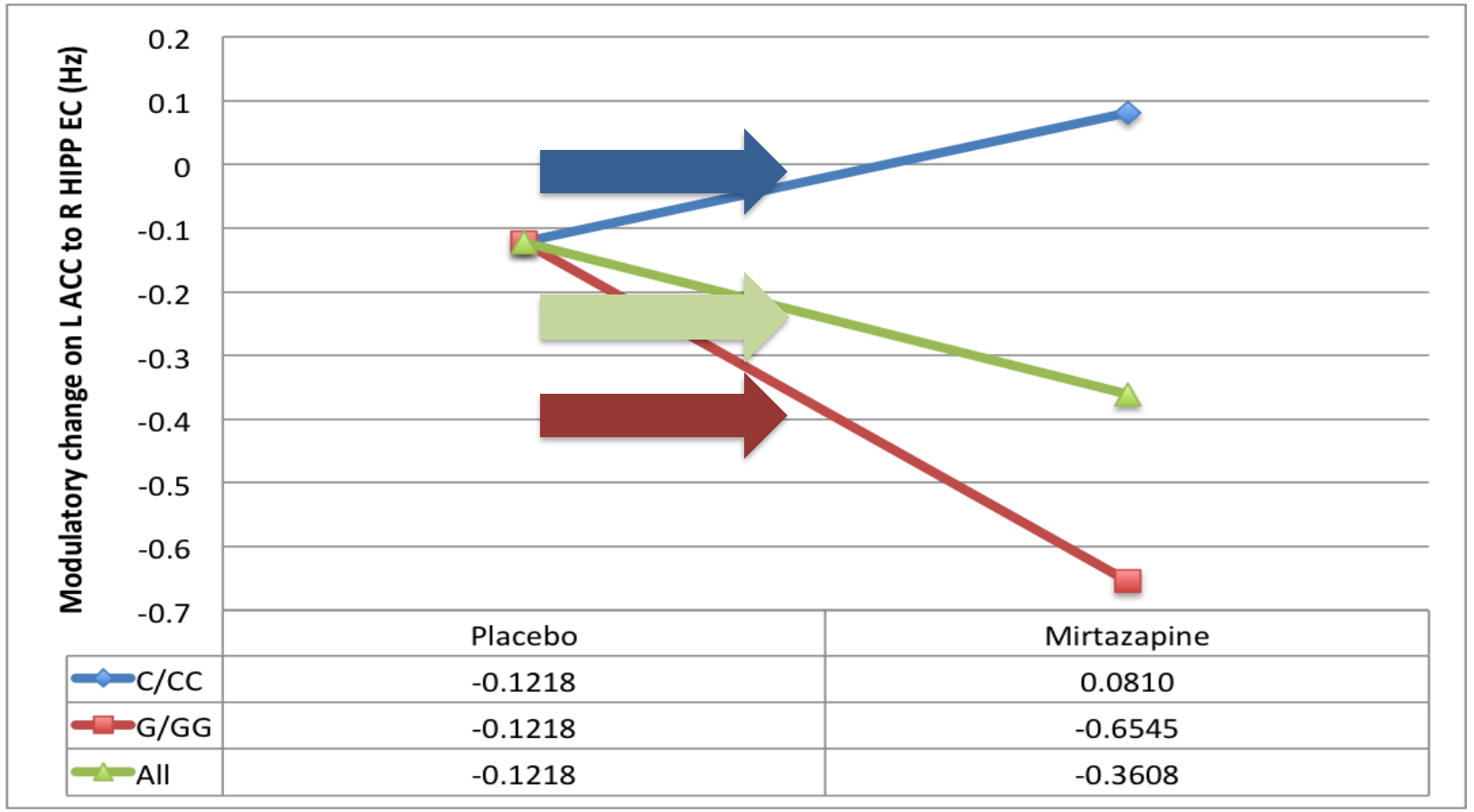
Interaction Between Mirtazapine and 5-HT_{2C}R Polymorphism on Cocaine Cue Related Brain Connectivity

- Overall: Mirtazapine Reduced ACC-Hippocampus Effective connectivity
- Effect showed interaction With 5-HT_{2C}R polymorphism Primarily G/GG rs6318 Participants
- Suggests mirtazapine reduces cocaine cue Related brain connectivity and Interaction with 5-HT_{2C}R



	Placebo	Mirtazapine
C/CC	-0.1218	0.0810
G/GG	-0.1218	-0.6545
All	-0.1218	-0.3608

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Mirtazapine Clinical Results (Coffin et al., 2019)

- Mirtazapine significantly reduced methamphetamine positive urine drug screens in 12-week clinical trial vs. placebo
- End of study abstinence not significantly different between mirtazapine (18%) vs. placebo (8%) (p = 0.11)
- Mirtazapine reduced depression insomnia scores but not craving
- Low medication adherence for mirtazapine (38.5%) and placebo (39.5%)

Research

JAMA Psychiatry | Original Investigation

Effects of Mirtazapine for Methamphetamine Use Disorder Among Cisgender Men and Transgender Women Who Have Sex With Men

A Placebo-Controlled Randomized Clinical Trial

Phillip O. Coffin, MD, MIA; Glenn-Milo Santos, PhD, MPH; Jaclyn Hern, MPH; Eric Vittinghoff, PhD; John E. Walker, MSN; Tim Matheson, PhD, MS; Deirdre Santos, RN, MSN; Grant Colfax, MD; Steven L. Batki, MD

Supplemental content

IMPORTANCE Methamphetamine use is increasingly prevalent and associated with HIV transmission. A previous phase 2a study of mirtazapine demonstrated reductions in methamphetamine use and sexual risk behaviors among men who have sex with men.

OBJECTIVE To determine the efficacy of mirtazapine for treatment of methamphetamine use disorder and reduction in HIV risk behaviors.

DESIGN, SETTING, AND PARTICIPANTS This double-blind randomized clinical trial of mirtazapine vs placebo took place from August 2013 to September 2017 in an outpatient research clinic in San Francisco, California. Participants were community-recruited adults who were sexually active; cisgender men, transgender men, and transgender women who (1) had sex with men, (2) had methamphetamine use disorder, and (3) were actively using methamphetamine were eligible. Participants were randomized to receive the study drug or placebo for 24 weeks, with 12 more weeks of follow-up. Data analysis took place from February to June 2018.

Other Reasons Mirtazapine may be Helpful as an Adjunctive Medication

- In addition to 5-HT_{2A}R antagonism, mirtazapine is a potent H_1 antagonist
- One area receiving increased attention as a target for SUD prevention, assessment, treatment and recovery is sleep (Valentino and Volkow 2020).

Sleep and Addictions

- Acutely drugs of abuse disrupt sleep latency, duration, and quality.
- With chronic drug use sleep becomes more disturbed, driving drug craving, increasing impulsivity.
- Current medication therapies for opioid, alcohol, or nicotine addiction do not reverse sleep dysfunction associated with addictions.
- Most FDA approved medications for insomnia have abuse potential which limits use in OUD patients

From Valentino and Volkow, 2020

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Mirtazapine for Insomnia in Methadone Maintained Patients

- Pilot study in methadone maintained patients
- Mirtazapine compared to zolpidem and combination of mirtazapine and zolpidem
- ***Mirtazapine by itself showed greatest increase in sleep***
- No negative side effects noted

TABLE 1. Estimated Difference in Mean Sleep Outcomes for Active Medication Protocols Minus Placebo

Sleep Outcome	Estimated Differences		
	Mirtazapine-placebo, Mean Difference (95% CI)	Zolpidem-placebo, Mean Difference (95% CI)	Combo-placebo, Mean Difference (95% CI)
Sleep-minutes	23.1 (−15.2; 61.4)	−16.1 (−57.7; 25.6) $LR^2 = 4.82$, d.f. = 3, $P = 0.186$	17.4 (−23.0; 57.8)
Wake-minutes	−23.4 (−58.2; 11.4)	20.7 (−17.1; 58.6) $LR^2 = 6.13$, d.f. = 3, $P = 0.105$	−5.8 (−42.5; 30.9)
Sleep efficiency	3.2 (−2.0; 8.4)	−3.7 (−9.4;1.9) $LR^2 = 7.02$, d.f. = 3, $P = 0.071$	1.3 (−4.2; 6.7)
Sleep latency	−9.7 (−27.7; 8.3)	7.5 (−12.0; 27.0) $LR^2 = 6.82$, d.f. = 3, $P = 0.078$	12.6 (−6.3; 31.5)
Wake after sleep onset	−13.6 (−39.3; 12.0)	20.2 (−7.6; 48.0) $LR^2 = 7.97$, d.f. = 3, $P = 0.047$	−11.3 (−38.3; 15.6)

Differences adjusted for sequential week of administration and sequential day within week of administration using fixed-effects regression (n = 10 persons observed on 254 days). CI, confidence interval; d.f., degree of freedom; LR^2, likelihood ratio chi-square results.

From Stein et al, 2020

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Mirtazapine Summary

- Mirtazapine reduces drug cue related brain connectivity compared to placebo
- Human study in methamphetamine users also shows promise
- Computational study in patients treated with mirtazapine also showed increased odds of remission for Opioid Use Disorder
- Mirtazapine not selective 5-HT_{2A}R Antagonist (significant effects at H_1, Alpha $_{2A}$)
- Improvement in sleep also noted with mirtazapine in pilot study with methadone maintained patients
- Mirtazapine may be useful adjunctive medication for OUD, especially in patients who complain of difficulty with sleep

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Novel medications for OUD: Future directions

- 2018 Review by National Institute on Drug Abuse Medication Development Division
- Highlights medication types that might be useful for future medication development for opioid use disorder

Neuropsychopharmacology www.nature.com/npp

COMMENT OPEN

NIDA's medication development priorities in response to the Opioid Crisis: ten most wanted

Kurt Rasmussen[1], David A. White[1] and Jane B. Acri[1]

Neuropsychopharmacology (2018) 0:1–3; https://doi.org/10.1038/s41386-018-0292-5

The United States is in the midst of a horrific problem. The rampant misuse of opioid drugs (both prescribed and illegal), now known as the Opioid Crisis, has had grave effects on both the public health and the well-being of our society. In 1 year, 2017, it is estimated that almost as many Americans died from opioid-related overdose as died in the entire Vietnam War [1]. In response to the problem, the White House has declared the Opioid Crisis a national Public Health Emergency under federal law [2].

The causes of the Opioid Crisis are complex and multifaceted and a solution will require a Herculean, integrated effort from disparate components of society. Changes in both the public and private sectors (e.g., revisions in: health care policy; medical education; business regulation; deployment of existing medications; local and state justice systems) will be needed to address this crisis. In an effort to leverage science to help address the problem, the National Institutes of Health (NIH) has launched the HEAL (Helping to End Addiction Long-term) Initiative, an aggressive, trans-agency effort to speed scientific solutions to the Opioid Crisis [3]. This initiative will nearly double funding for research on opioid misuse/addiction and pain. As part of the NIH, the National Institute on Drug Abuse (NIDA) is devoted to addressing this crisis in multiple ways. NIDA will coordinate four overarching research projects around the country: the Focused Opioid Use Disorder (OUD) Medications Development Research Project; the HEALing Communities Study; the Clinical Trials Network OUD Research Enhancement Project; and the Justice Community Opioid Innovation Network [4]. The medication development component of this four-pronged effort includes aiding the development of novel pharmacotherapies, behavioral therapies and devices for the treatment of opioid overdose and OUD.

Our science can have political, economic and social ramifications. Indeed, the introduction of safe and effective therapeutics, while unlikely to be a panacea, has the potential to transform not only health outcomes for individual patients, but anachronistic societal attitudes towards diseases, especially brain diseases. In this regard, we hope that the introduction of new safe and effective medications for OUD will enlighten the public discourse around opioid addiction and those suffering from it. In an effort to specifically speed the development of pharmacotherapies for the treatment of OUD and reach NIDA's stated goal of 15 Investigational New Drugs (INDs) and 5 New Drug Applications (NDAs) submitted to the Food and Drug Administration (FDA), NIDA's Division of Therapeutics and Medical Consequences (DTMC) has created a list of medication development priorities.

The mechanisms listed in Table 1 are NIDA's DTMC highest priority pharmacological targets for the development of novel therapeutics to treat opioid overdose and OUD *in the near term*. The list does not include mechanisms of existing OUD medications and the mechanisms are listed in no particular order. While the existing medications (e.g., buprenorphine, methadone, naloxone, naltrexone, lofexidine) have demonstrable utility in the treatment of OUD, they are not without limitations. Indeed, problematic residual symptoms and discontinuation rates plague these treatments [5, 6], leaving a deceptively cavernous un-met medical need that could be addressed, at least in part, by new medications.

Our goal is to help deliver new treatment options to the millions of patients and physicians battling OUD. At this point in time, we feel compounds with the mechanisms-of-action listed in Table 1 have the highest probability of a path to FDA approval for the treatment of some aspect of OUD *in the near term*. An important component of this list are allosteric modulators. Based on their suppression/augmentation of endogenous responses, negative allosteric modulators (NAMs) and positive allosteric modulators (PAMs) may provide more physiologically relevant effects compared with agonists and antagonists acting on the same receptor, which may ultimately result in improved clinical outcomes [7]. It is important to note that due to the complexity of the addiction cycle, different stages of the disease (e.g., transition from sporadic to chronic use, acute withdrawal, delayed relapse) are likely to have different (albeit overlapping) pathophysiologies [8]. Thus, there is unlikely to be a "silver bullet" among these mechanisms for the treatment of OUD and medications with these mechanisms-of-action are likely to be useful at different stages of the addiction cycle. In addition, it is important to remember, as has been clearly demonstrated from the treatment of major depressive disorder [9], pharmacotherapies can have greater impact when paired with effective psychosocial interventions. Indeed, two key components of NIDA's treatment development efforts are the development of novel behavioural and device treatments. Ultimately, we anticipate multiple medications, integrated with both psychosocial interventions and potentially devices, employed in an orchestrated fashion, will be needed to achieve truly effective treatments "tailored" for maximal efficacy in different individuals.

We have determined our "most wanted" mechanisms based on data from published literature and internal studies that we feel have the most direct relevance to desirable treatment effects and clinical endpoints for OUD. Importantly, most of these mechanisms are active in more than one model, and for more than one drug of abuse, which presents the intriguing

[1]Division of Therapeutics and Medical Consequences, National Institute on Drug Abuse, 6001 Executive Blvd, Bethesda, MD 20892, USA
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SPRINGER NATURE

Table 1. NIDA's DTMC ten most wanted pharmacological mechanisms for the rapid development of therapeutics in response to the Opioid Crisis

NIDA's DTMC ten most wanted
Orexin-1 or 1/2 antagonists or NAMs [17–19]
Kappa opioid antagonists or NAMs [20, 21]
GABA-B agonists or PAMs [22, 23]
Muscarinic M5 antagonists or NAMs [24, 25]
AMPA antagonists, NAMs or PAMs [26–28]
NOP/ORL agonists, antagonists, NAMs or PAMs [29–31]
mGluR2/3 agonists or PAMs [32–34]
Ghrelin antagonists or NAMs [35, 36]
Dopamine D3 partial agonists, PAMs, antagonists or NAMs [37, 38]
Cannabinoid CB-1 antagonists or NAMs [39, 40]

PAM positive allosteric modulator, *NAM* negative allosteric modulator, *AMPA* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA* γ-aminobutyric acid, *NOP* nociceptin opioid peptide receptor, *ORL* opioid receptor like, *mGluR* metabotropic glutamate receptor, *5HT* 5-hydroxytryptamine, *MOP* mu opioid protein

Other mechanisms of interest:
5HT2C agonists or PAMs, with or without 5HT2A antagonist/NAM activity [41, 42]
Biased Mu Opioid agonists or PAMs [43, 44]
NOP/MOP bifunctional agonists or PAMs [45, 46]
Respiratory stimulants (including nicotinic agonists) [47, 48]

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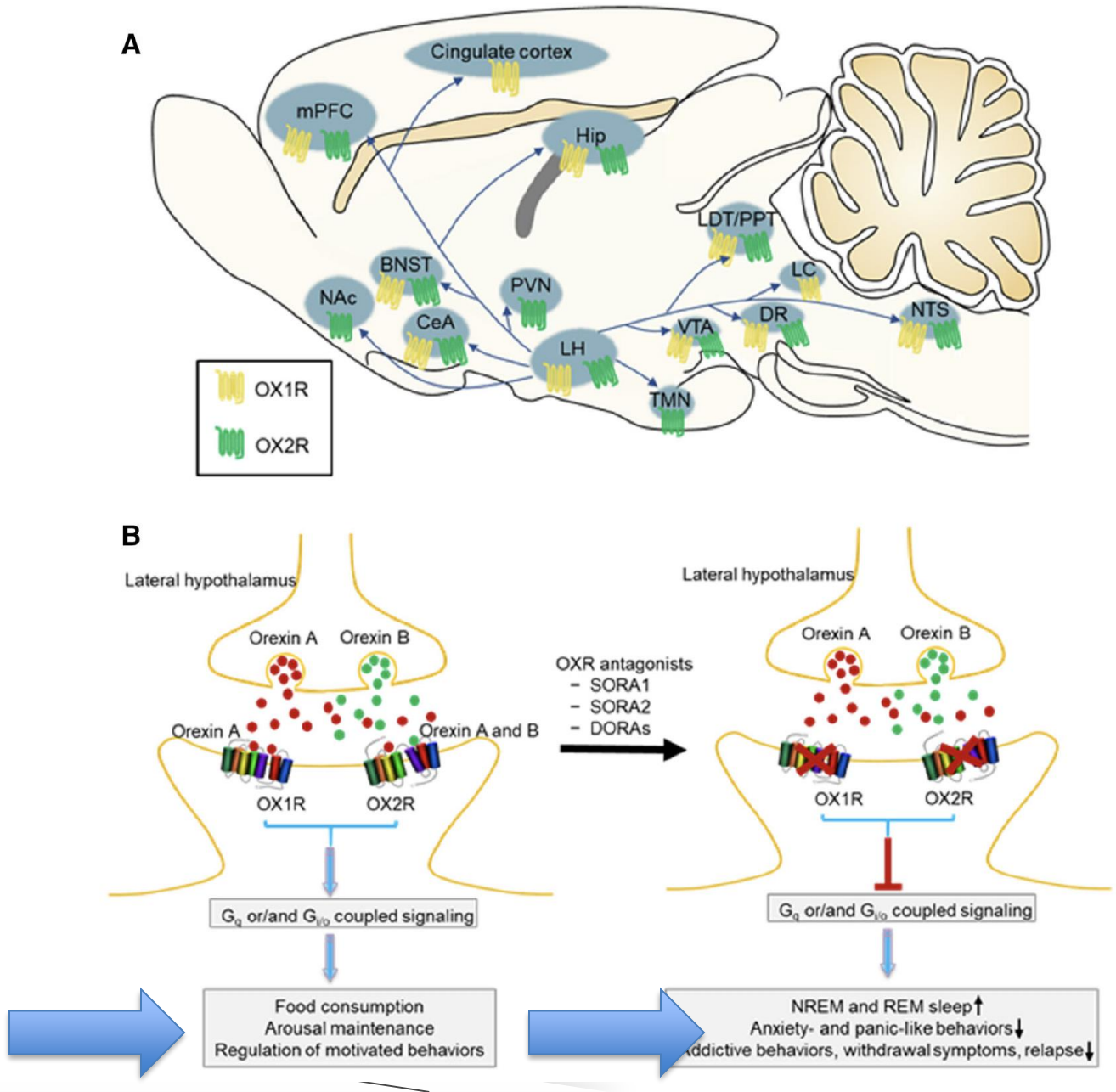
From Rasmussen et al., 2018

OX1R and OX2R And Behavior

Han et al., Neurosci Bull 2020



OX1R antagonist effects on oxycodone self-administration

Matzeu & Martin-Fardon, Neuropharmacology, 2020

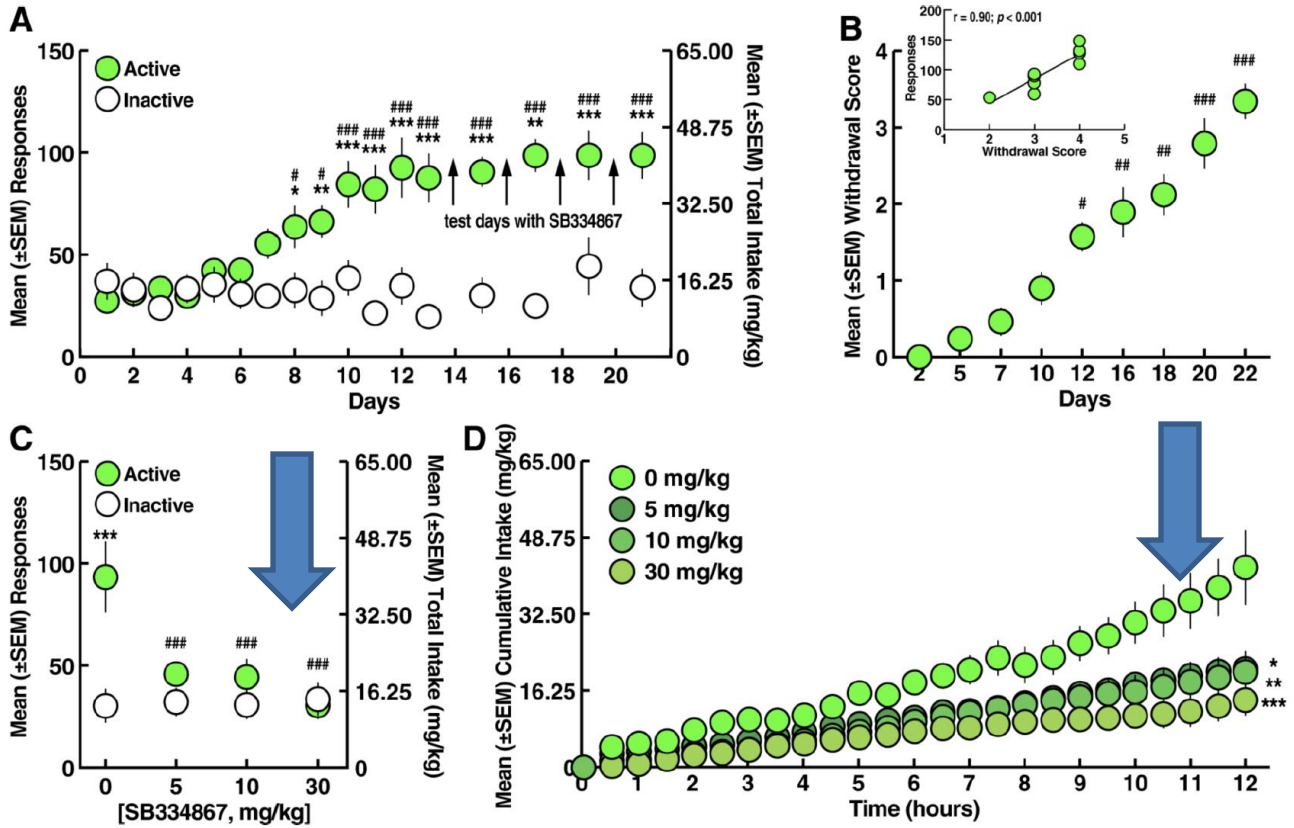


Fig. 3. Effect of SB334867 on oxycodone self-administration. **A.** Oxycodone self-administration. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, *vs.* inactive lever; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$, *vs.* day 1 (Sidak *post hoc* test). **B.** Somatic withdrawal signs. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, *vs.* day 2 (Dunn's *post hoc* test). **Inset.** Correlation plot between the somatic withdrawal score and number of oxycodone infusions. **C.** SB334867 (5, 10, and 30 mg/kg) reduced the number of oxycodone infusions. $^{***}p < 0.001$, *vs.* inactive lever; $^{\#\#\#}p < 0.001$, *vs.* vehicle (Sidak *post hoc* test). **D.** SB334867 (5, 10, and 30 mg/kg) reduced the cumulative intake of oxycodone. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, *vs.* vehicle (Sidak *post hoc* test). $n = 9$.

OX2R antagonist effects on oxycodone self-administration

Matzeu & Martin-Fardon, Neuropharmacology, 2020

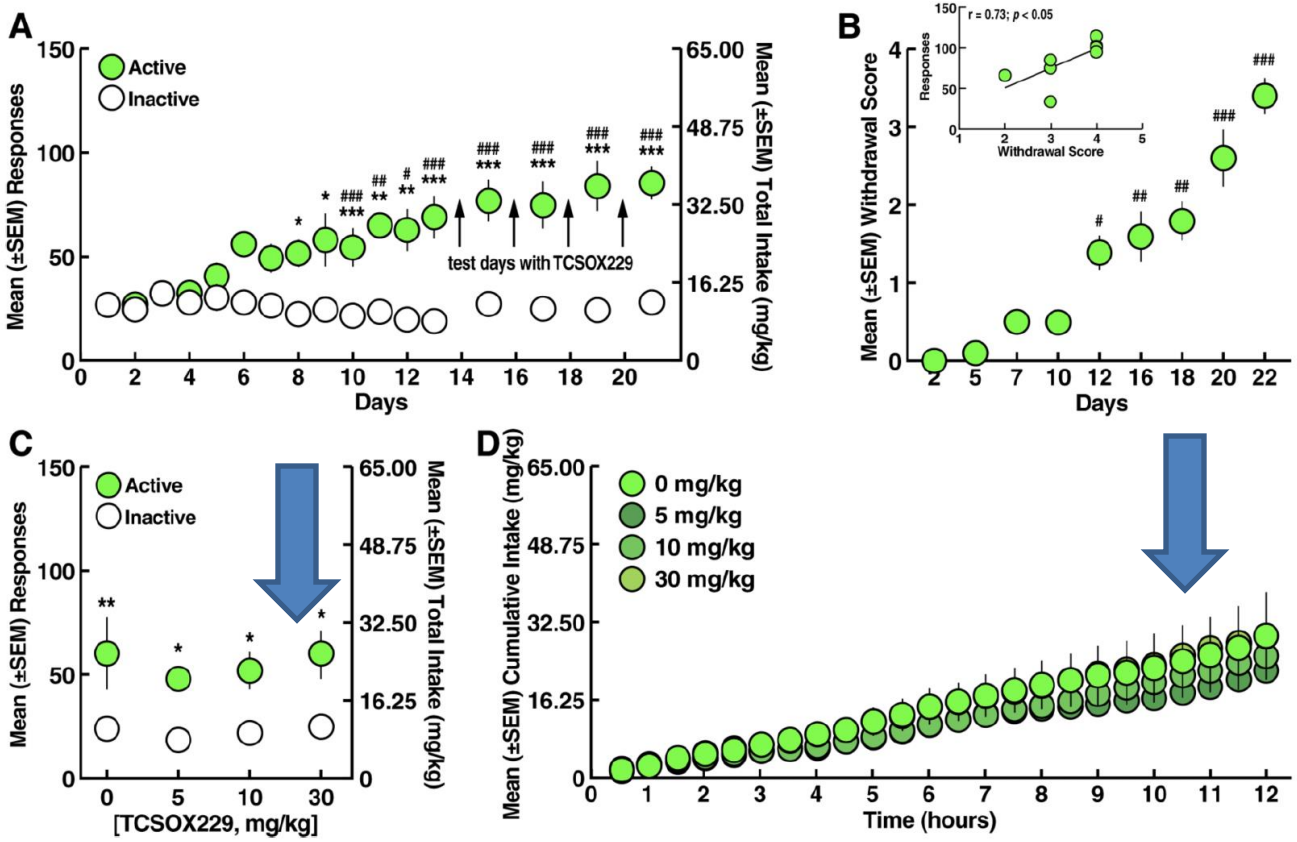


Fig. 4. Effect of TCSOX229 on oxycodone self-administration. **A.** Oxycodone self-administration. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, *vs.* inactive lever; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, *vs.* day 1 (Sidak *post hoc* test). **B.** Somatic withdrawal signs. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, *vs.* day 2 (Dunn's *post hoc* test). **Inset.** Correlation plot between the somatic withdrawal score and number of oxycodone infusions. **C.** TCSOX229 (5, 10, and 30 mg/kg) did not modify oxycodone self-administration. $^{*}p < 0.05$, $^{**}p < 0.01$, *vs.* inactive lever (Sidak *post hoc* test). **D.** TCSOX229 (5, 10, and 30 mg/kg) did not alter the cumulative intake of oxycodone. $n = 10$.

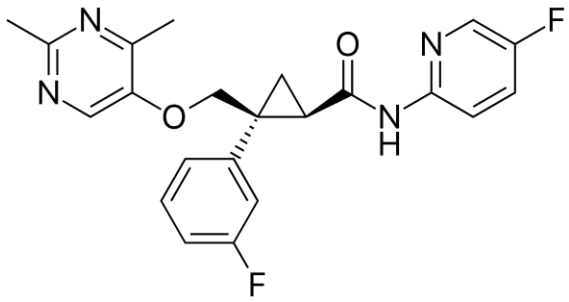
Orexin Receptor Antagonists and Opioid Use Disorder

- Orexin 1 receptor antagonists reduce opioid self administration in preclinical studies
- Orexin 2 receptor antagonists have less effects on opioid self-administration but improve sleep
- Current clinical trials underway with Orexin 1 and 1-2 receptor antagonists

VCU

Lemborexant Treatment of Addiction

- Lemborexant is a novel compound that is antagonist at Orexin 1 and 2 receptors (OX1R & OX2R)
- FDA Approved in December 2019, marketed in June 2020 for insomnia (Dayvigo)
- Good safety profile, low abuse potential
- 17-19 hour half-life



VCU

Lemborexant and OX1R vs. OX2R

- Lemborexant binds to orexin receptors OX1R and OX2R and acts as a competitive antagonist (IC50 values of 6.1 nM and 2.6 nM, respectively).
- A major metabolite of lemborexant, M10, binds with comparable affinity as the parent drug to orexin receptors OX1R and OX2R (IC50 values of 4.2 nM and 2.9 nM), respectively.

Lemborexant Safety with Alcohol

Postural Stability

- No significant differences in body sway change from baseline were observed for LEM10 with alcohol compared with alcohol alone.

Cognitive measures

- Change from baseline in Power of Attention was significantly higher (worsened) for LEM10 with alcohol compared with LEM10 alone at 0.5 hours and 6.0 hours
- Cognitive effects resolved by 9 hours

Effect of Alcohol Coadministration on the Pharmacodynamics, Pharmacokinetics, and Safety of Lemborexant

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Introduction

- Lemborexant (LEM) is a dual orexin receptor antagonist being investigated for treating insomnia and irregular sleep-wake rhythm disorder.[1]
- Several approved sleep-promoting drugs have demonstrated additive negative effects on certain pharmacodynamic (PD) assessments when administered with alcohol, including vigilance, working/episodic memory, postural stability, and alertness.[2]
- This phase 1 study (NCT03483636; E2006-A001-009) examined potential interactions between LEM and alcohol on the PD assessments of postural stability (body sway) and cognitive performance, and assessed the safety and tolerability of a single dose of LEM with or without alcohol. The effect of alcohol coadministration on LEM pharmacokinetics (PK) was also examined.

Objectives

- The primary objectives of this study were to evaluate, in healthy subjects:
  - Effects of LEM combined with alcohol vs LEM alone and vs alcohol alone on postural stability
  - Effects of the Power of Attention domain of the computerized assessment battery (CPAB)
  - Safety and tolerability of a single dose of LEM alone or in combination with alcohol.
- Secondary objectives included evaluating, in healthy subjects:
  - PK of LEM following a single oral dose of LEM alone or combined with alcohol
  - Effects of LEM combined with alcohol vs LEM alone and vs with alcohol alone on 3 additional domains of cognitive performance (Continuity of Attention, Quality of Memory, Speed of Memory).

Methods

Subjects

- Healthy males and females aged 19-55 years with a body mass index of 22-33 kg/m^2 and weighing ≥ 55 kg were enrolled in the study.
- Occasional or regular drinkers (an average of 2-14 alcohol-containing drinks per week, no more than 2 alcohol-containing drinks per day).

Study Design

- Phase 1, single-center, randomized, double-blind, placebo-controlled, single-dose, 4-way crossover study in healthy subjects.
- For each treatment period, eligible subjects were randomized into 1 of 4 treatment sequences:
  1. Alcohol + LEM placebo
     - To preserve the blind for the placebo alcohol treatment, 1 mL of supernatant 40% alcohol was floated on each aliquot of low-calorie beverage to produce some odor/taste of alcohol.
  2. LEM 10 mg (LEM10) alone + alcohol placebo
  3. Alcohol (0.6 g/kg females, 0.7 g/kg males) alone + LEM placebo
  4. LEM10 + alcohol.
- Treatment was administered approximately 2 hours following a light (low-fat) breakfast.
- Subjects were admitted to the clinic the night before administration of the study drug and remained in the clinic until 72 hours postdose.
- Subjects must have had 2 negative breath alcohol test results before being discharged.
- A washout period of ≥ 14 days was implemented between treatments.

PD Assessments

- Postural stability was assessed using an ataxiameter, which measures body sway in units of 1/3° angle of arc (units; higher values indicate more body sway, ie, less postural stability). Details of these methods have been previously presented.[3,4]
- Cognitive performance was tested using a CPAB consisting of 9 tasks assessing 4 domains of attention and memory (Power of Attention, Continuity of Attention, Quality of Memory, and Speed of Memory Retrieval).
- Assessments were conducted predose and up to 72 hours postdose.

PK Assessments

- Blood samples for determination of plasma concentrations of LEM10 were collected at predose and up to 72 hours postdose in each treatment period. Blood samples for determination of blood ethanol concentrations were collected on Day 1 of each treatment period.
- Plasma concentrations of LEM10 were quantified by liquid chromatography with tandem mass spectrometry methodology using a validated assay.

Statistical Analyses

- Body sway and CPAB analyses were conducted using the Completer Analysis Set (CAS), defined as all subjects who had no major protocol deviations that would impact PD results, had sufficient PD data to derive at least 1 PD parameter, and completed all 4 treatment periods.
- The Safety Analysis Set was defined as all participants who received ≥ 1 dose of active study drug.
- Change from baseline (CFB) in body sway and each CPAB domain were analyzed using a mixed-effect model for a crossover study.
  - The model was adjusted for treatment, period, treatment sequence, and first-order carryover effect as fixed effects, baseline (predose) measurement as a covariate (where applicable), and the default variance components variance structure block for each subject.
- PK parameters were calculated by noncompartmental analysis.

Results

Subject Disposition

- Thirty-two subjects were randomized; 18 (56.3%) completed all 4 treatments (CAS).
- The median (range) age was 38.5 years (26-54 years). The majority of subjects were male (75.0%) and white (65.6%).

Postural Stability

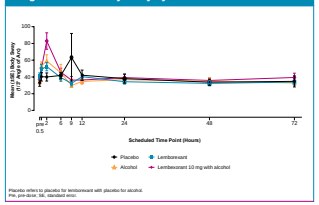
- Lower values for body sway indicate a better performance.
- No significant differences in body sway CFB were observed for LEM10 with alcohol compared with alcohol alone.
- At 2 hours postdose, the CFB in body sway was significantly higher for subjects who received LEM10 with alcohol compared with LEM10 alone. CFB in body sway was not significantly different between these groups at any other time point (Table 1).
- Body sway CFB at 2 hours was worsened by alcohol alone compared with placebo (Table 1).
- No significant differences in body sway CFB were observed for LEM compared with placebo at any time point (except at 9 hours due to 1 placebo group subject exhibiting an unusually high body sway value at this time point; Table 1).
- By 12 hours postdose, postural stability had generally returned to baseline values for all treatment groups (Figure 1).

Table 1. Postural Stability: Treatment Comparison of Change From Baseline for Body Sway[a]

Time Point, h	LEM10/ Alcohol vs Alcohol	LEM10/ Alcohol vs LEM10 mg	Alcohol vs Placebo	LEM10 vs Placebo	Synergy[c]
	Contrast Mean Difference (95% CI)				*P* Value
0.5	−5.4 (−22.8 to −12.0)	6.8 (−10.6 to 24.2)	13.0 (−4.4 to 30.5)	0.8 (−16.6 to 18.2)	0.598
2	16.8 (−1.7 to 35.2)	36.2 (17.6 to 54.7)[†]	23.7 (5.2 to 42.2)[*]	3.3 (−14.2 to 22.8)	0.395
6	−1.8 (−19.2 to 15.6)	12.5 (−4.9 to 29.9)	3.3 (−14.1 to 20.7)	−10.9 (−28.3 to 6.5)	0.481
9	3.9 (−13.5 to 21.3)	9.7 (−7.8 to 27.1)	−33.3 (−50.8 to −15.9)[‡]	−39.1 (−56.5 to −21.7)[‡]	< 0.001
12	−1.0 (−18.4 to 16.4)	1.9 (−15.5 to 19.4)	−7.0 (−24.4 to 10.5)	−9.9 (−27.3 to 7.5)	0.495
24	−0.4 (−18.4 to 17.5)	11.5 (−6.5 to 29.4)	−0.2 (−18.2 to 17.7)	−12.1 (−30.1 to 5.8)	0.371
48	−1.3 (−18.7 to 16.1)	9.6 (−7.8 to 27.0)	1.2 (−16.3 to 18.6)	−9.8 (−27.2 to 7.6)	0.517
72	4.1 (−13.3 to 21.5)	11.6 (−5.9 to 29.0)	−1.6 (−19.0 to 15.9)	−9.1 (−26.5 to 8.3)	0.308

[*]*P* < 0.05, [†]*P* < 0.01.
[a]Body sway was measured in units of 1/3° angle of arc. Lower values for body sway indicate a better performance.
[c]Synergy comparison contrast: LEM10 with alcohol – alcohol vs LEM10 – placebo.
CI, confidence interval; LEM10, lemborexant 10 mg.

Figure 1. Mean Body Sway by Time Point and Treatment



Placebo refers to placebo for lemborexant with placebo for alcohol.
Pre, pre-dose; SE, standard error.

Computerized Performance Assessment Battery

- Lower values for Power of Attention indicate a faster performance. CFB in Power of Attention was significantly higher (worsened) for LEM10 with alcohol compared with LEM10 alone at 0.5 hours and 6.0 hours (Table 2).
- CFB in Power of Attention was significantly increased for LEM10 with alcohol compared with alcohol alone, and for LEM10 compared with placebo at 0.5 hours and 2 hours.
- Higher values for Continuity of Attention indicate better performance. LEM10 with alcohol worsened performance on the CPAB domain of Continuity of Attention at the 2-hour time point compared with LEM10 alone.
- For the cognitive measure Quality of Memory, higher values indicate a better performance. LEM10 with alcohol worsened performance on the CPAB domain of Quality of Memory at 0.5 and 2 hours compared with LEM10 alone, and both conditions were worse than PBO.
- LEM10 with alcohol worsened performance on the CPAB domain of Speed of Memory at 2 hours compared with LEM10 alone.
- No statistically significant differences between treatment groups were observed at 9 hours and beyond for all domains of the CPAB (Table 2).

Table 2. Cognitive Performance: Treatment Comparison of Each CPAB Domain Change From Baseline

Time Point, h	LEM10/ Alcohol vs Alcohol	LEM10/ Alcohol vs LEM 10 mg	Alcohol vs Placebo	LEM10 vs Placebo	Synergy
	Contrast Mean Difference (95% CI)				*P* Value
Power of attention					
0.5	346.5 (131.1 to 561.9)[†]	239.2 (23.3 to 455.2)[*]	132.1 (−83.9 to 348.0)	239.3 (23.9 to 454.8)[*]	0.469
2	489.3 (246.6 to 692.0)[‡]	165.5 (−57.8 to 388.9)	127.4 (−95.9 to 350.8)	431.2 (208.5 to 653.9)[‡]	0.813
6	170.2 (−38.5 to 378.9)	234.7 (25.8 to 443.6)[*]	30.4 (−178.5 to 239.3)	−34.0 (−242.8 to 174.7)	0.152
9	−9.4 (−212.3 to 193.4)	73.1 (−129.9 to 276.2)	−3.4 (−206.5 to 199.6)	−86.0 (−288.8 to 116.8)	0.573
12	−51.8 (−254.6 to 151.1)	−21.6 (−224.7 to 181.4)	−13.1 (−216.1 to 190.0)	−43.2 (−246.1 to 159.6)	0.985
Continuity of attention					
0.5	−3.72 (−7.42 to −0.01)[*]	−1.90 (−5.61 to 1.82)	−0.96 (−4.68 to 2.75)	−2.78 (−6.49 to 0.93)	0.845
2	−10.81 (−14.64 to −6.98)[‡]	−5.96 (−9.81 to 2.11)[‡]	−4.93 (−8.77 to −1.08)[*]	−9.78 (−13.6 to −5.94)[‡]	0.875
6	−3.61 (−7.20 to −0.02)[*]	−3.44 (−7.03 to 0.16)	0.86 (−2.74 to 4.45)	0.68 (−2.91 to 4.27)	0.095
9	−1.45 (−4.94 to 2.04)	−1.29 (−4.78 to 2.20)	1.61 (−1.88 to 5.11)	1.50 (−2.04 to 4.94)	0.270
12	0.72 (−2.77 to 4.21)	1.00 (−2.50 to 4.49)	0.78 (−2.71 to 4.27)	0.51 (−2.98 to 3.99)	0.855
Quality of memory					
0.5	20.35 (−55.91 to −15.21)	−67.69 (−103.33 to −32.05)[‡]	−102.46 (−138.10 to 66.82)[‡]	−55.12 (−90.68 to −19.57)[†]	0.101
2	−77.80 (−114.56 to −41.04)[‡]	−46.84 (−83.71 to 9.97)[*]	−47.15 (−84.02 to 10.28)[*]	−78.11 (−114.86 to −41.35)[‡]	0.801
6	−26.50 (−60.95 to 7.95)	−28.43 (−62.91 to 6.05)	−1.37 (−35.85 to 33.12)	0.57 (−33.89 to 35.02)	0.185
9	−2.94 (−36.42 to 30.54)	9.45 (−24.06 to 42.97)	10.23 (−23.29 to 43.74)	−2.16 (−35.64 to 31.32)	0.987
12	−18.34 (−51.82 to 15.14)	−17.39 (−50.91 to 16.13)	−3.60 (−37.12 to 29.91)	−4.55 (−38.034 to 28.93)	0.532
Speed of memory					
0.5	959.9 (491.4 to 1428.4)[‡]	4.2 (−465.5 to 473.8)	−32.3 (−502.0 to 437.3)	923.4 (454.9 to 1391.9)[‡]	0.928
2	1227.3 (743.0 to 1711.6)[‡]	638.6 (152.8 to 1124.4)[*]	17.4 (−468.4 to 503.2)	606.1 (121.8 to 1090.5)[*]	0.129
6	495.5 (41.5 to 949.5)[*]	92.6 (−361.7 to 547.0)	−340.9 (−795.3 to 113.4)	61.9 (−392.1 to 515.9)	0.189
9	49.6 (−391.5 to 490.8)	−160.3 (−601.9 to 281.4)	−222.4 (−664.0 to 219.2)	−12.5 (−453.7 to 428.6)	0.925
12	24.3 (−416.9 to 465.5)	−161.8 (−603.4 to 279.9)	−105.9 (−547.5 to 335.7)	80.2 (−361.0 to 521.3)	0.778

[*]*P* < 0.05, [†]*P* < 0.01, [‡]*P* < 0.001.
To statistically significant differences were observed at 24, 48, and 72 hours postdose for any treatment comparisons (data not shown).
Least squares means were estimated from a mixed-effect model having treatment, period, treatment sequence, and baseline (predose) measurement as a covariate, and subject as a random effect.
Synergy comparison contrast: LEM10 with alcohol – alcohol vs LEM10 – placebo.
CI, confidence interval; CPAB, computerized assessment battery; LEM10, lemborexant 10 mg; SE, standard error.

Pharmacokinetics

- Median time to reach maximum plasma drug concentration after drug administration (t_{max}) of LEM was 1.5 hours for LEM10 administered with alcohol and 1.7 hours for LEM10 alone (Table 3).
- Coadministration of LEM10 with alcohol showed a 35% increase in maximum plasma drug concentration vs LEM10 alone.
- Coadministration of LEM10 with alcohol showed a 70% increase in area under the plasma concentration-time curve from time 0 to 72 hours after dosing vs LEM10 alone (Table 3).

Table 3. Summary of PK Parameters of Lemborexant (PK Analysis Set)

Parameter	Geometric Mean (Geometric %CV)	
	LEM10 (N = 24)	LEM10 + Alcohol (N = 18)[a]
t_{max}, hour[b]	1.7 (0.42-3.00)	1.5 (0.42-5.92)
C_{max}, ng/mL	45.17 (31.1)	58.08 (33.2)
AUC_{0-72}, ng•h/mL	250.0 (40.6)	402.3 (35.2)
CL/F, L/h	39.99 (51.2)	27.83 (38.4)

[a]Data from 1 subject in the LEM10 with alcohol group had to be excluded from the PK analysis due to vomiting within 2 hours postdose.
[b]Data shown are the median (range).
AUC_{0-72}, area under the plasma concentration-time curve from 0-72 hours; CL/F, apparent total body clearance; C_{max}, maximum plasma drug concentration; CV, coefficient of variation; LEM10, lemborexant 10 mg; PK, pharmacokinetic; t_{max}, time to reach maximum plasma drug concentration after drug administration.

Safety

- Occurrence of treatment-emergent adverse events (TEAEs) was lower with placebo compared with the other 3 treatment groups (Table 4).
- Somnolence was the most common TEAE.
- Most TEAEs were mild or moderate in severity and were considered treatment related. (One severe TEAE occurred following treatment with alcohol; Table 4).

Table 4. Summary of TEAEs (Safety Analysis Set)

	Placebo (n = 24)	LEM10 (n = 26)	Alcohol (n = 24)	LEM10/Alcohol (n = 21)
Subjects with at least 1 TEAE[a]	8 (33.3)	25 (96.2)	20 (83.3)	20 (95.2)
Subjects with at least 1 serious TEAE	0	0	0	0
Subjects with at least 1 severe TEAE[b]	0	0	1 (4.2)	0
Subjects with at least 1 related TEAE[c]	5 (20.8)	25 (96.2)	20 (83.3)	20 (95.2)
Subjects with at least 1 TEAE leading to study discontinuation	0	0	2 (8.3)	1 (4.8)

For each row, a subject with ≥ 2 events is counted in that category once.
All values are n (%), number of subjects (percentage of subjects).
[a]TEAE starting or worsening after treatment with the study drug.
[b]TEAE where the severity is severe. In cases where severity is missing, the adverse event was considered to be the highest degree of severity.
[c]Related TEAE is a TEAE categorized as related. In cases where relationship is missing, the adverse event is considered to be the highest degree of relationship: related.
LEM10, lemborexant 10 mg; TEAE, treatment-emergent adverse event.

Conclusions

- LEM10 alone did not affect postural stability. However, alcohol alone significantly worsened postural stability at 2 hours. LEM10 with alcohol did not show evidence of additivity on postural stability vs alcohol alone.
- LEM10 with alcohol had additive negative effects on cognitive measures, which corresponded with the approximate t_{max} of LEM10 (~2 hours), but these effects resolved over time.
- Exposure to lemborexant was increased when coadministered with alcohol.
- Overall, this study suggests that LEM should not be taken with alcohol.

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Disclosures

IL, NH, JA, GF, LR, and MM are employees of Eisai Inc. SD is an employee of Eisai Ltd. BS is affiliated with Syneos Health, Raleigh, NC, USA, and Department of Toxicology & Pharmacology, University of Toronto, Toronto, Canada.

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Lemborexant Abuse Potential

Preclinical Studies

- Not self-administered, no evidence of withdrawal symptoms

Human Studies

- In a human abuse potential study lemborexant 10 mg, 20 mg and 30 mg (three times the maximum recommended dose) produced responses on positive subjective measures that were statistically similar to those produced by the sedatives zolpidem (30 mg) and suvorexant (40 mg), and statistically greater than the responses on these measures that were produced by placebo.
- Suggests some abuse potential but lower than benzodiazepines

Abuse Potential Considerations for Lemborexant, a Dual Orexin Receptor Antagonist

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Introduction

- Lemborexant (LEM) is a dual orexin receptor antagonist under development for the treatment of insomnia disorder.[1,2] LEM has demonstrated efficacy on sleep onset and sleep maintenance in the pivotal phase 3 trials, SUNRISE-1 (NCT02783729; E2006-G000-304) and SUNRISE-2 (NCT02952820; E2006-G000-303).[3,4]
- LEM is structurally dissimilar to drugs associated with abuse. LEM binds selectively to orexin-1 and orexin-2 receptors with high affinity, with no evidence of off-target binding at receptors associated with abuse potential, such as the $GABA_A$ receptor.[1] In addition, LEM tablets could not readily be manipulated for the purposes of intravenous administration (data on file).
- As required for registration with the US Food and Drug Administration (FDA), the potential of abuse for LEM was assessed in animal models, phase 3 trials, and a phase 1 human abuse potential study in accordance with FDA guidelines.[5]

Methods

Animal Abuse Liability Studies

- Three nonclinical abuse liability studies were conducted in animal models (Sprague Dawley rats or rhesus monkeys). Details of these studies are summarized in Table 1.[6]
- All experimental protocols were approved by the Institutional Animal Care and Use Committees and conducted in accordance with the relevant institution requirements.

Table 1. Overview of Animal Abuse Liability Studies

Study	Study Description	Treatments
Physical dependence (Sprague Dawley rats)	• 10 male rats/group • Study drug administered orally over a 28-day period	• Vehicle • Diazepam (200, 400, 600 mg/kg)[a] • LEM (200, 600 mg/kg)[b]
Self-administration (rhesus monkeys)	• 4 catheterized rhesus monkeys (3 males and 1 female) • Fixed-ratio 5 schedule • 2 hours per day intravenous self-administration for 4-7 days per dose	• Period 1: Pentobarbital (1 mg/kg/infusion)[c] • Period 2: Vehicle[d] • Period 3: LEM (0.3, 0.1, 0.03, 0.01, 0.003 mg/kg/infusion)[e]
Drug discrimination (Sprague Dawley rats)	• 32 female rats trained with vehicle/ZOL (3 mg/kg) using a 2-level operant discrimination task under fixed-ratio 10 schedule • 6 rats/dose • Study drug administered orally 0.5-24 hours prior to operant testing session	• ZOL vehicle[f] • ZOL (0.32, 0.56, 1.0, 1.8, 3, 5.6 mg/kg)[f] • LEM vehicle[g] • LEM (10, 30, 100, 1000 mg/kg)[h] • SUV vehicle[i] • SUV (30, 100, 300, 1000 mg/kg)[i]

[a]Positive control, diazepam was dosed twice daily, 6 hours apart at escalating dose levels. [b]Administered with a 10-hour interval (100 mg/kg × 2; 300 mg/kg × 2). [c]Positive control; drug intake limited to 20 infusions/day. [d]Number of self-administrations in ± 5 for 3 consecutive days or ± 10 per day within ± 20% for 3 consecutive days. [e]Number of self-administrations are within ± 20% or ± 5 for 3 consecutive days, with ≥ 4 days/dose in a descending-dose manner. [f]Dose administered 0.5 hour before operant testing session. [g]Dose administered 1 hour before operant testing session. [h]Dose administered 1 hour or 24 hours before operant testing session. [i]Dose administered 4 hours before operant testing session.
LEM, lemborexant; SUV, suvorexant; ZOL, zolpidem.

SUNRISE-1 and SUNRISE-2 Phase 3 Studies

- Data from the pivotal SUNRISE-1 and SUNRISE-2 studies of LEM were pooled and analyzed for incidence of treatment-emergent adverse events (TEAEs) indicative of abuse by others outside of the study, as well as for potential abuse or diversion of study drug within the clinical program. Incidence and rates of potential abuse-related TEAEs were also analyzed after adjusting by duration of study drug exposure.
- Details of the SUNRISE-1 and SUNRISE-2 studies are summarized in Table 2.

Table 2. Overview of Phase 3 Studies

Study	Study Design	Treatments	Number of Subjects in Data Set
SUNRISE-1 (NCT02783729; E2006-G000-304)[3,4]	Phase 3, randomized, double-blind, PBO- and active-comparator controlled, 1-month parallel-group study in females (aged ≥ 55 years) and males (aged ≥ 65 years) with insomnia disorder	PBO ZOL 6.25 mg LEM 5 mg LEM 10 mg	1006[a]
SUNRISE-2 (NCT02952820; E2006-G000-303)[4,5]	Phase 3, randomized, double-blind, PBO-controlled (first 6 months), 12-month parallel-group study in females and males (aged ≥ 18 years) with insomnia disorder	PBO LEM 5 mg LEM 10 mg	947[a]

[a]Following an approximately 2-week PBO run-in period, subjects were randomized (4:5:5:5 ratio) to PBO, ZOL 6.25 mg, LEM 5 mg, or LEM 10 mg for 30 nights. The study drug was taken each night within 5 minutes of bedtime. [b]Safety Analysis Set (SAS), defined as randomized subjects who received ≥ 1 dose of randomized study drug and had ≥ 1 poststudee safety assessment. [c]Following an approximately 2-week PBO run-in period, subjects were randomized (1:1:1 ratio) to PBO, LEM 5 mg, or LEM 10 mg for 6 months. At the Month 6 visit, subjects receiving PBO were randomized (1:1 ratio) to LEM 5 mg or LEM 10 mg, whereas subjects receiving LEM continued on LEM at the same dose, for another 6 months. The study drug was taken each night approximately 5 minutes before bedtime. [d]SAS for the 6-month PBO-controlled portion of the study.
LEM, lemborexant; PBO, placebo; ZOL, zolpidem tartrate extended release.

Human Abuse Potential Phase 1 Study (Study 103)

Study Design

- Study 103 (NCT03158025; E2006-A001-103) was a single-center, single-dose, randomized, double-blind, 6-way crossover study in healthy, nondependent, recreational sedative users.
- During the Qualification Phase, subjects were evaluated for their ability to discriminate the effects of suvorexant 40 mg (SUV) and zolpidem 30 mg (ZOL) from placebo (PBO). Subjects who could discriminate SUV and ZOL from PBO with sufficient drug liking were eligible to move to the Treatment Phase.
- During the Treatment Phase, subjects were randomized to 1 of 6 treatment sequences, with each treatment separated by ≥ 14 days.
  - Treatments included oral doses of LEM (10 mg [LEM10], 20 mg [LEM20], 30 mg [LEM30]), PBO, and 2 active comparators with known drug liking (ZOL and SUV).

Pharmacodynamic Assessments

- Abuse potential was assessed by the peak maximum effect (E_{max}) on the 100-point bipolar "at this moment" Drug Liking visual analog scale (VAS) (primary endpoint).
  - On the bipolar VAS, a score of 0 indicates strong dislike, a score of 50 indicates neither like or dislike, and a score of 100 indicates strong liking.

Statistical Analyses

- Pharmacodynamic (PD) endpoints were assessed in the Completer Analysis Set, or the group of subjects who received all study treatments and completed all treatment periods in the Treatment Phase, and had ≥ 1 Drug Liking VAS score within 2 hours of the estimated time to reach maximum plasma drug concentration for each treatment, regardless of protocol deviations.
- PD endpoints were analyzed using a mixed-effect model, which included treatment, period, treatment sequence, and first-order carryover effect (where applicable) as fixed effects, baseline (predose) measurements as covariate (where applicable), and subject nested within treatment sequence as a random effect according to FDA guidelines.[5]
- For study validity, VAS E_{max} for Drug Liking was compared between ZOL and PBO and SUV and PBO, with a validation margin of 15 (as requested by the FDA); a supplementary analysis was also conducted using the originally intended margin of 11.

Results

Nonclinical Abuse Liability Studies With LEM

- No evidence of physical dependence was observed in Sprague Dawley rats following 28-day dosing with LEM up to 600 mg/kg/day.
- No active self-administration or gross behavioral changes that suppressed lever pressing were observed during the self-administration period with LEM, and LEM had no reinforcing effect on intravenous self-administration in rhesus monkeys.
- In a drug discrimination study, LEM at doses up to 1000 mg/kg did not cross-generalize to the zolpidem (3 mg/kg) training stimulus, whereas SUV demonstrated partial generalization to zolpidem at doses of 320 mg/kg or higher.

Abuse Liability TEAEs in Pooled Phase 3 Studies

- There was no evidence of diversion of study medication during clinical development.
- A higher incidence of abuse-related TEAEs was observed with LEM compared with PBO, which was driven by somnolence (Table 3). No euphoria was reported.
- When adjusted by duration of exposure, overall incidence and overall rates of abuse-related TEAEs were low, but they were higher for LEM 5 mg (LEM5) and LEM10 vs PBO (Table 3).

Table 3. Selected Potential Abuse-Related TEAEs and Selected Potential Abuse-Related TEAEs Adjusted by Exposure From SUNRISE-1 and SUNRISE-2 (Safety Analysis Set)[a]

	PBO (n = 528)	ZOL (n = 263)	LEM5 (n = 712)	LEM10 (n = 706)
Any selected abuse liability TEAE, n (%)	38 (7.2)	27 (10.3)	106 (14.9)	127 (18.0)
TEAEs reported in > 2% of subjects in any active treatment group and > PBO by MedDRA preferred term, n (%)[b]				
Somnolence	9 (1.7)	4 (1.5)	48 (6.7)	77 (10.9)
Fatigue	1 (0.2)	4 (1.5)	16 (2.2)	18 (2.6)
Dizziness	10 (1.9)	8 (3.0)	17 (2.4)	10 (1.4)
Total patient-years of exposure[c]	158.6	21.0	327.8	305.2
Subjects with events per total patient-years of exposure, n (subjects per patient-year)[d]				
Subjects with any selected abuse liability TEAE	38 (0.2)	27 (1.3)	106 (0.3)	127 (0.4)
Somnolence	9 (< 0.1)	4 (0.2)	48 (0.1)	77 (0.3)
Fatigue	1 (< 0.1)	4 (0.2)	16 (< 0.1)	18 (< 0.1)
Abnormal dreams	7 (< 0.1)	3 (0.1)	9 (< 0.1)	11 (< 0.1)
Dizziness	10 (< 0.1)	8 (0.4)	17 (< 0.1)	10 (< 0.1)
Events per total patient-years of exposure, n (events per patient-year)[e]				
Total events of selected TEAEs	44 (0.3)	42 (2.0)	150 (0.5)	192 (0.6)
Somnolence	9 (< 0.1)	5 (0.2)	54 (0.2)	82 (0.3)
Hypnagogic hallucination	0	0	6 (< 0.1)	22 (< 0.1)
Fatigue	1 (< 0.1)	4 (0.2)	18 (< 0.1)	18 (< 0.1)
Abnormal dreams	7 (< 0.1)	3 (0.1)	9 (< 0.1)	12 (< 0.1)
Dizziness	10 (< 0.1)	9 (0.4)	19 (< 0.1)	11 (< 0.1)
Nightmare	2 (< 0.1)	0	8 (< 0.1)	11 (< 0.1)

[a]Safety Analysis Set defined as group of subjects who received ≥ 1 dose of study drug and had ≥ 1 poststudee safety assessment. For SUNRISE-2, subjects who received different treatment during the treatment periods were counted under applicable treatment groups (eg, PBO for Period 1 and LEM for Period 2). A TEAE is defined as an adverse event with onset date on or after the first dose of study drug up to 14 days after the last dose of study drug. [b]Subjects with ≥ 2 adverse events with the same preferred term are counted only once for that preferred term. [c]Total patient-years of exposure = number of days on study drug/365.25. [d]Subjects per patient-year = number of subjects with events/total patient-years of exposure. Only TEAEs observed in ≥ 10 subjects in any active treatment group are reported here. Subjects with ≥ 2 preferred terms in the same organ class (or with the same preferred term) are counted only once for that system organ class (or preferred term). [e]Events per patient-year = number of events/total patient-years of exposure. Only TEAEs with > 10 events observed in any active treatment group are reported here.
LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; TEAE, treatment-emergent adverse event; ZOL, zolpidem tartrate extended release 6.25 mg.

Human Abuse Potential Phase 1 Study

- In total, 225 individuals were screened, 107 were randomized to the Qualification Phase, and 39 met the qualification criteria and were randomized into the Treatment Phase.
  - Of these 39 subjects (demographics summarized in Table 4), 7 discontinued early and 32 completed the study.

Table 4. Demographic Characteristics of Subjects From Study 103 (Safety Analysis Set)[a]

Parameter	N = 39
Age, years	
Mean (SD)	36.0 (8.6)
Median (range)	36.0 (18-50)
Sex, n (%)	
Male	30 (76.9)
Female	9 (23.1)
Race, n (%)	
White	29 (74.4)
Black or African American	4 (10.3)
Asian	2 (5.1)
American Indian or Alaskan Native	1 (2.6)
Other	3 (7.7)
BMI, mean (SD), kg/m²	25.5 (2.7)

[a]Safety Analysis Set defined as the group of subjects who received ≥ 1 dose of study drug during the Treatment Phase and had ≥ 1 poststudee safety assessment.
BMI, body mass index; SD, standard deviation.

- For all LEM doses, mean Drug Liking VAS E_{max} was similar and significantly higher than PBO. Mean Drug Liking VAS E_{max} was significantly higher for ZOL and SUV compared with PBO but was not significantly different from ZOL or SUV for all LEM doses (Table 5).

Table 5. Summary of Results From Study 103 (Completer Analysis Set)

	PBO (n = 32)	ZOL (n = 32)	SUV (n = 32)	LEM10 (n = 32)	LEM20 (n = 32)	LEM30 (n = 32)
Drug Liking VAS E_{max} during Treatment Phase[a]						
Mean (SE)	57.8 (2.9)	78.3 (2.8)	76.1 (3.2)	78.4 (3.3)	80.5 (3.1)	83.6 (3.0)
LSM (95% CI)	58.3 (52.3-64.3)	78.5 (72.5-84.5)	76.5 (70.5-82.5)	78.9 (72.9-84.9)	80.9 (74.9-86.9)	83.9 (77.9-89.9)
LSM (SE) difference from PBO	—	20.2 (3.7)	18.2 (3.7)	20.5 (3.7)	22.5 (3.7)	25.5 (3.7)
95% CI	—	Lower 95% CI: 14.1	Lower 95% CI: 12.2	Upper 95% CI: 26.6	Upper 95% CI: 28.6	Upper 95% CI: 31.6
P value (margin of 15)[b]	—	0.079	0.190	—	—	—
P value (margin of 11)[c]	—	0.006	0.025	—	—	—
P value (LEM vs PBO)[d]	—	—	—	0.995	0.999	1.000
LSM (SE) difference from ZOL	—	—	—	−0.3 (3.7)	−2.4 (3.7)	−5.4 (3.7)
Lower 95% CI	—	—	—	−8.4	−10.4	−13.4
P value (LEM vs ZOL)[e]	—	—	—	0.538	0.740	0.928
LSM (SE) difference from SUV	—	—	—	−2.3 (3.7)	−4.3 (3.7)	−7.3 (3.7)
Lower 95% CI	—	—	—	−8.4	−10.4	−13.4
P value (LEM vs SUV)[e]	—	—	—	0.737	0.881	0.977

[a]Drug Liking VAS is a bipolar scale assessing "at this moment" subjective perceptions, whereby a score of 0 indicates strong dislike, a score of 50 indicates neither like nor dislike, and a score of 100 indicates strong liking. LSMs were estimated from a mixed-effect model having treatment, period, and treatment sequence as fixed effects, and subject nested within sequence as a random effect. Overall treatment effect was assessed using Fréedman's test. [b]If $\mu_C - \mu_P \leq 15$ vs HA: $\mu_C - \mu_P > 15$, where C = positive control and P = PBO. For ZOL vs PBO and SUV vs PBO comparisons, a *P* value < 0.05 indicates that the treatments were different. [c]If $\mu_C - \mu_P \leq 11$ vs HA: $\mu_C - \mu_P > 11$, where C = positive control and P = PBO. For ZOL vs PBO and SUV vs PBO comparisons, a *P* value < 0.05 indicates that the treatments were different. [d]If $\mu_T - \mu_P \geq 11$ vs HA: $\mu_T - \mu_P < 11$ where T = test drug and P = PBO. For LEM vs PBO comparisons, a *P* value < 0.05 indicates that the treatments were the same, whereas a *P* value > 0.05 indicates that the treatments were different. [e]If $\mu_T - \mu_C \leq 0$ vs HA: $\mu_T - \mu_C > 0$ where C = positive control and T = test drug. For LEM vs ZOL and LEM vs SUV comparisons, a *P* value < 0.05 indicates that the treatments were different.
CI, confidence interval; E_{max}, maximum (peak) effect; LEM10, lemborexant 10 mg; LEM20, lemborexant 20 mg; LEM30, lemborexant 30 mg; LSM, least squares mean; PBO, placebo; SE, standard error; SUV, suvorexant 40 mg; VAS, visual analog scale; ZOL, zolpidem 30 mg.

- Incidence of TEAEs was higher with LEM10 (94.6% [35/37]), LEM20 (97.1% [33/34]), LEM30 (97.1% [34/35]), ZOL (97.1% [34/35]), and SUV (91.2% [31/34]) vs PBO (38.9% [14/36]).
  - The most common TEAE was somnolence (LEM10, 91.9% [34/37]; LEM20, 88.2% [30/34]; LEM30, 97.1% [34/35]; ZOL, 85.7% [30/35]; SUV, 85.3% [29/34]; PBO, 16.7% [6/36]). The high rates of somnolence were not surprising, as LEM, ZOL, and SUV are sleep-promoting drugs that were administered during the daytime.
- There were no serious TEAEs or deaths.

Conclusions

- In nonclinical abuse potential studies, LEM was not associated with physical dependence, reinforcing effects, or cross-generalization to ZOL.
- During phase 3 testing, incidence of TEAEs associated with abuse potential was low, and there was no evidence of dependence or diversion of study drug for inappropriate use.
- In the human abuse potential study, all doses of LEM appeared to have a similar abuse potential profile, which was similar to the abuse potential profiles observed for ZOL and SUV.
- Taken together, these studies provide support for the position that LEM is unlikely to be associated with a significant risk to public health from drug abuse.

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Disclosures

MM and IL are employees of Eisai Inc. SA and CB are employees of Eisai Co., Ltd. At the time of the study, BS was an employee of Syneos Health; BS is a current employee of Altasciences.

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Poster presented at the American College of Neuropsychopharmacology Congress; December 8-11, 2019; Orlando, FL

Lemborexant/Buprenorphine-Naloxone Drug Drug Interaction Study

- **NIDA funded, currently recruiting patients who are stable on buprenorphine-naloxone and have sleep problems**
- Randomized, double-blind, placebo-controlled phase 1b study
- 18 Participants (12 lemborexant, 6 placebo)
- **STUDY AIMS: Aim 1: To examine safety-tolerability and drug-drug interactions** between lemborexant and buprenorphine-naloxone in participants with opioid use disorder with insomnia who are in MAT with buprenorphine-naloxone.
- **Aim 2: To examine lemborexant early signal of efficacy (anticraving, anxiolysis, impulsivity, and reduced subjective withdrawal symptoms)** in participants with opioid use disorder who are in MAT with buprenorphine-naloxone. **Exploratory aim**: To determine behavioral profiles predict behavioral response to lemborexant when added to buprenorphine-naloxone and to measure effects of lemborexant on sleep.

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Lemborexant Next Steps

- If Phase I study shows safety with buprenorphine-naloxone, plan phase II study for insomnia
- Similar phase I study being caried out with Suvorexant

Summary on New Medications for OUD

- Currently FDA approved medications for OUD are effective, but not completely
- Strategies for improved effectiveness include:
  - maximizing compliance/dose
  - ensuring counseling/behavioral therapy
  - evaluating best level of care
  - examination of comorbidities that can be treated

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Summary on New Medications for OUD

- Medications currently approved for other indications may be helpful as adjunctive medications for OUD
- Sleep thought to be important target for adjunctive medications
- Research underway examining novel therapeutic agents as adjunctive agents

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Questions?

Case Presentation #1
Latwan Carpenter, QMPH

- 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

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Case Presentation #2
Dr. Moeller

- 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

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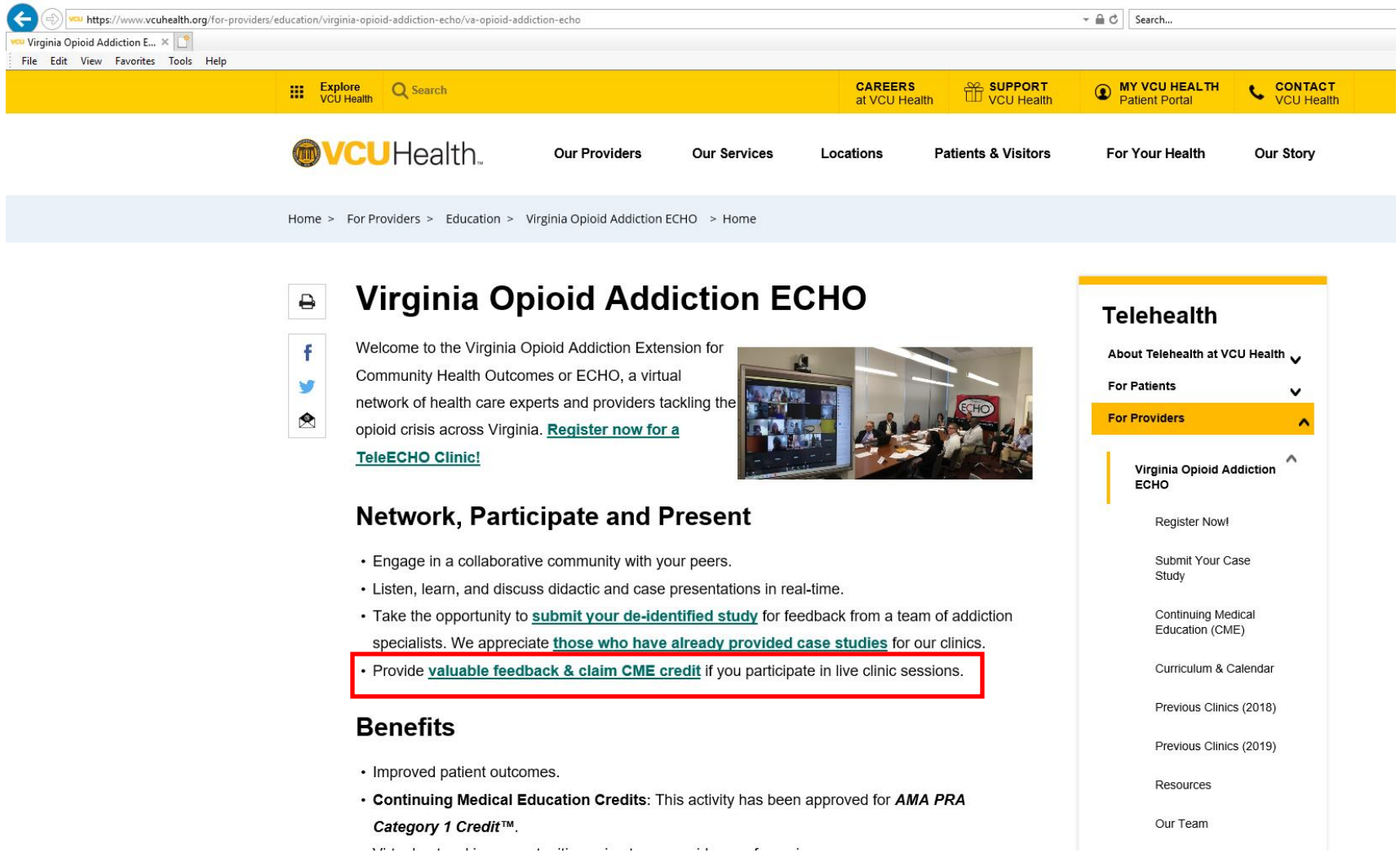

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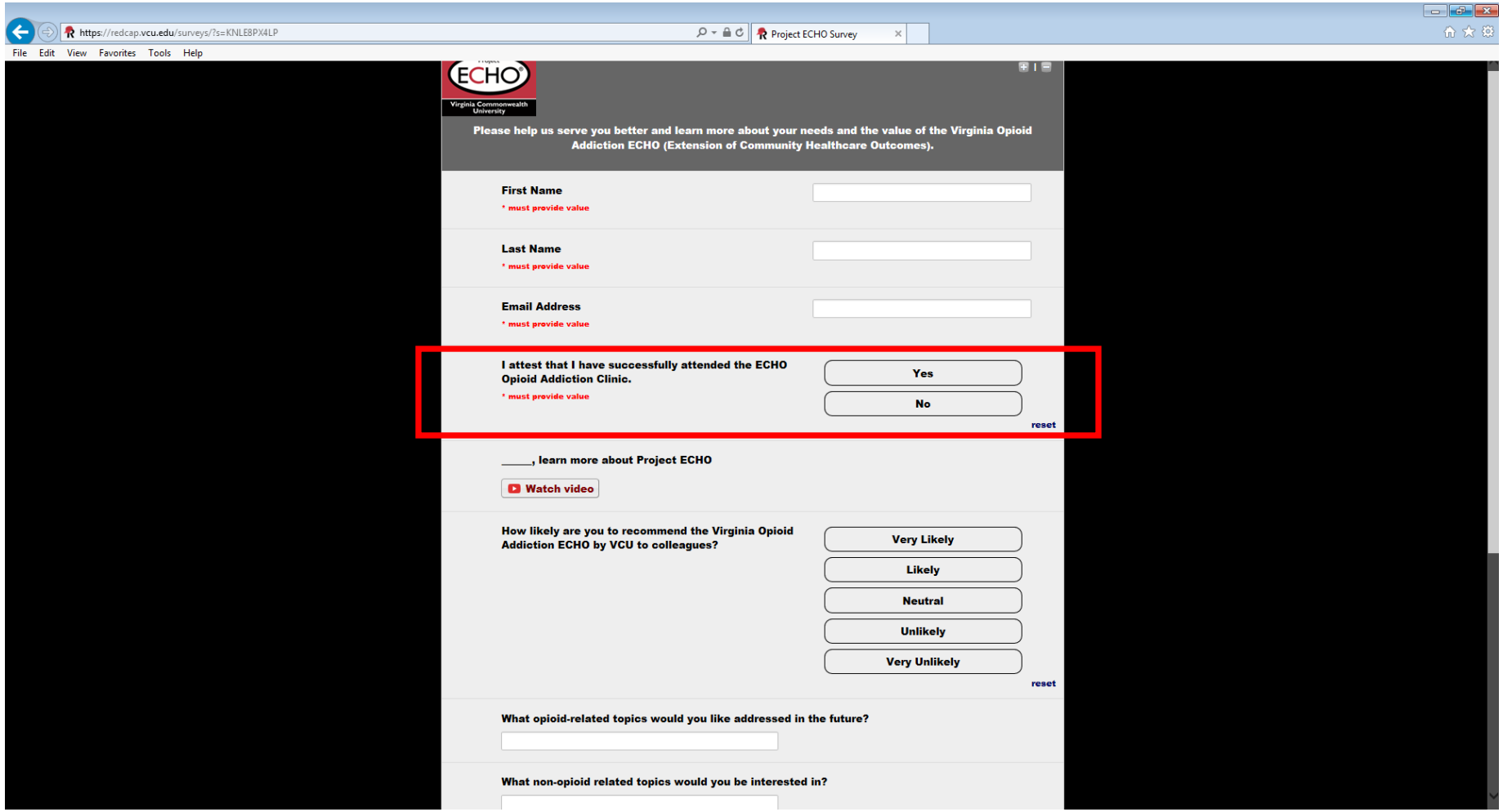

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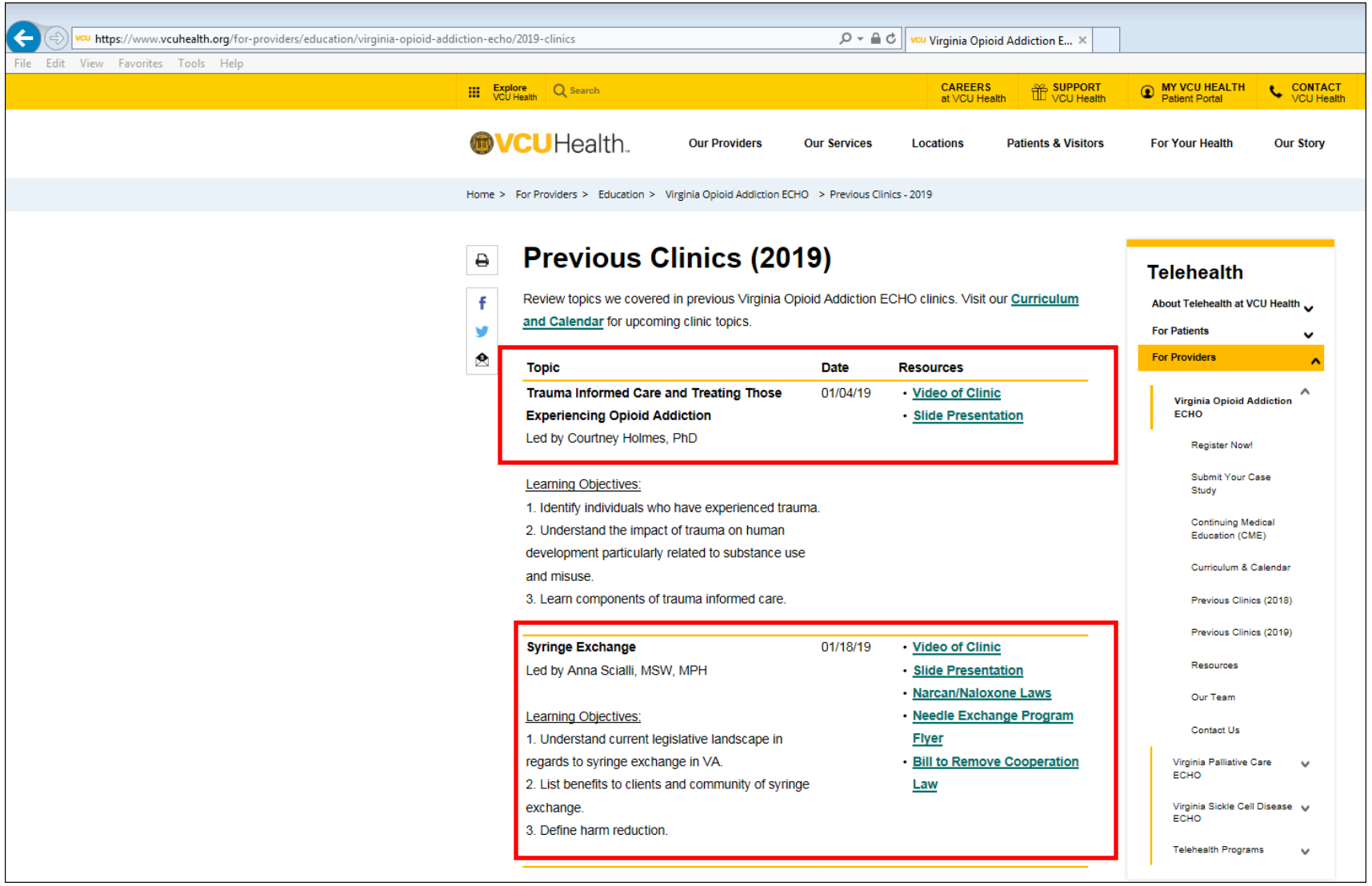

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