Center on Rural Addiction UNIVERSITY OF VERMONT



Innovative Interventions for Adults with Opioid Use Disorder

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Outline

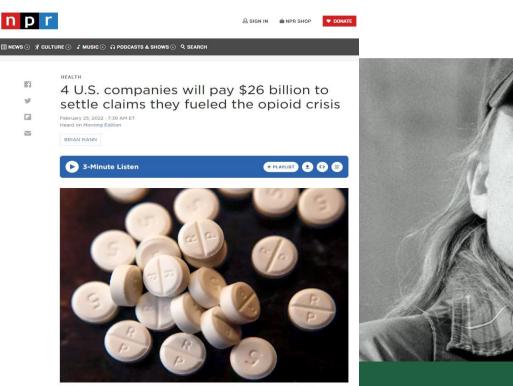
- Summarize recent epidemiological data on the opioid crisis in the United States
- Describe and compare efficacious pharmacological treatment approaches
- Examine common barriers to treatment in rural areas
- Demonstrate a novel, low-barrier, technology-assisted buprenorphine dosing protocol that can be useful for promoting opioid abstinence in rural settings
- Present new data supporting the use of prolonged exposure therapy for PTSD in individuals with opioid use disorder
- Characterize ongoing dissemination efforts through the University of Vermont Center on Rural Addiction

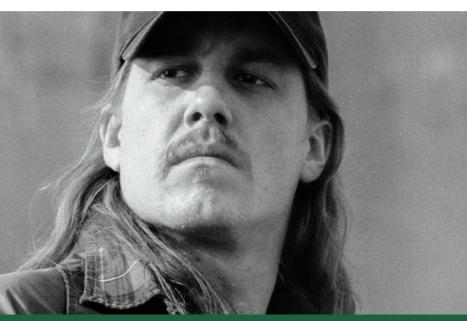


The Ongoing Opioid Crisis

- Prescription opioid misuse and heroin use are urgent concerns in the United States and worldwide
- A great deal of media attention and research has been devoted to the ongoing opioid crisis over recent years









Epidemiology – Opioid Use & Overdose Deaths

- In 2020:
 - 72 million U.S. adults used prescription pain relievers
 - 9.5 million reported misusing prescription pain relievers
 - 902,000 reported using heroin
 - 2.1 million met criteria for opioid use disorder (OUD)
 - Nearly 92,000 died from drug-involved overdose
 - 68,630 died from opioid-involved overdose

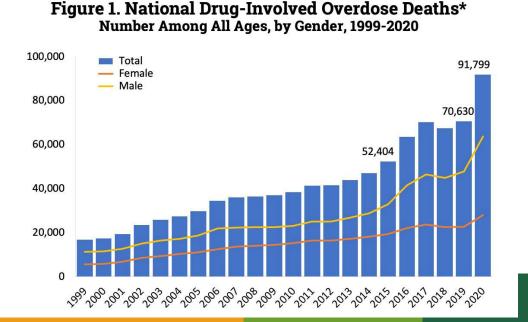
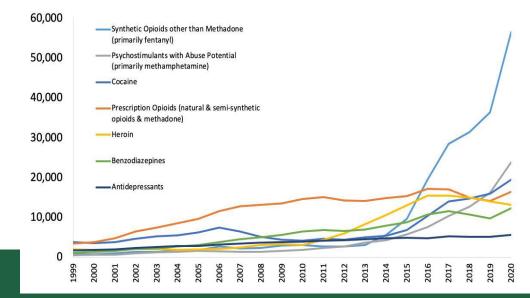
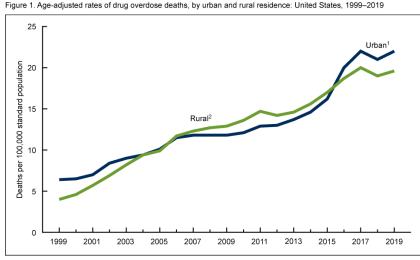


Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2020





- From 1999-2019, rate of drug overdose deaths increased from 4.0 per 100,000 to 19.6 in rural counties
- In 2019, overdose rates in rural counties were higher than in urban counties in CA, CT, NC, VT, and VA

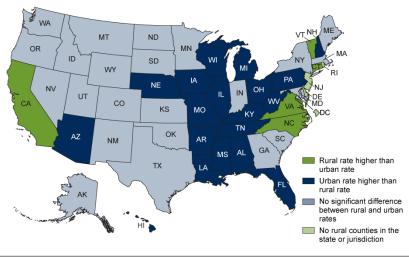


¹Significant increasing trend from 1999 to 2017, with different rates of change over time; stable trend from 2017 through 2019, p < 0.05²Significant increasing trend from 1999 through 2019, with different rates of change over time, p < 0.05.

NOTES: Drug vertices and yield from 1959 anticidate of the second classification of Diseases, 10th Revision underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Age-adjusted death rates were calculated using the direct method and the 2000 U.S. standard population. Decedent's county of residence was classified as urban or rural based on the 2013 NCHS Urban–Rural Classification Scheme for Counties. Access data table for Figure 1 at: https://www.cds.gov/nchs/data/data/tets/idv0-3-tables-508.ptf#1.

SOURCE: National Center for Health Statistics, National Vital Statistics System, Mortality.

Figure 2. Urban–rural differences in age-adjusted rates of drug overdose deaths, by jurisdiction of residence: 2019



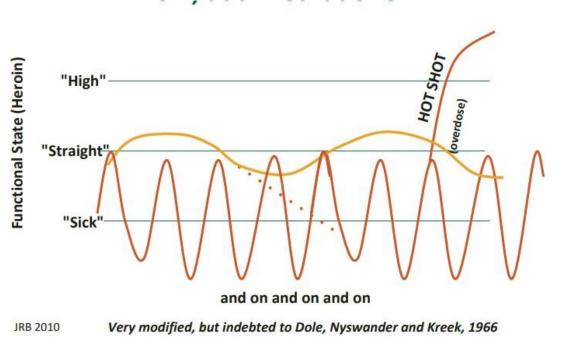
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Hedegaard & Spencer, 2021



Medications for Opioid Use Disorder (MOUD)

- Medications for opioid use disorder (MOUD) represent the most efficacious treatment for OUD
- MOUD involves administration of controlled amounts of longer-acting opioids with less euphoric effects
 - Long-term treatment is recommended and associated with better outcomes
- Two most common and effective forms of MOUD are methadone and buprenorphine



Gowing et al., 2017; Larochelle et al., 2018; Mattick et al., 2014



Methadone

- Long-acting full opioid agonist that binds to and occupies mu-opioid receptors, which prevents or reverses withdrawal symptoms and reduces craving for opioids
- More effective than non-pharmacological approaches in:
 - Retaining patients in treatment
 - Suppression of heroin use as measured by self-report and urine/hair analysis
 - Compared with no MOUD, methadone associated with reduced all-cause and opioid-related mortality
- Limitations
 - Produces/maintains dependence on opioids
 - Full opioid agonist
 - Relatively strict rules for dispensing
 - Risk of overdose death for non-tolerant individuals

Dole, 1969; Jaffe, 1990; Larochelle et al., 2018; Mattick et al., 2009; Ward, 1992





- Partial opioid agonist that is associated with less euphoria and sedating effects in comparison to full agonists (e.g., methadone)
- Buprenorphine associated with less craving and illicit opiate use compared to placebo
- Rates of adverse events similar to placebo
- Similarly effective as moderate doses of methadone on primary outcomes of:
 - Treatment retention
 - Rates of opioid-positive urines
 - Self-reports of craving and illicit-opioid use
- Available without rigid regulatory regulations and daily observation of dosing





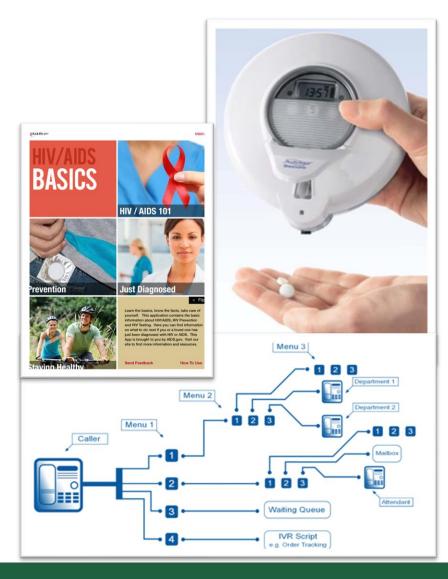
- Demand for opioid treatment exceeds available capacity in many areas of the country, with **96% of states having OUD rates that exceed their capacity**
- Insufficient treatment capacity is especially urgent in rural areas
 - Methadone clinic: Lengthy waitlists
 - In Vermont, we reached a **1.9 year waitlist**
 - <u>Office-based buprenorphine</u>: Insufficient number of providers and low density of patients among providers
 - More than **one-third** of all rural and **more than half** of small and remote rural counties lack a buprenorphine-authorized physician
 - In Vermont, most providers are treating a small handful of patients, translating to a current **utilization rate of 10%**
- Innovative approaches are urgently needed to expand access to evidence-based treatments for OUD

Andrilla et al., 2021; Jones et al., 2015; Sigmon, 2014, 2015



Interim Buprenorphine Treatment (IBT)

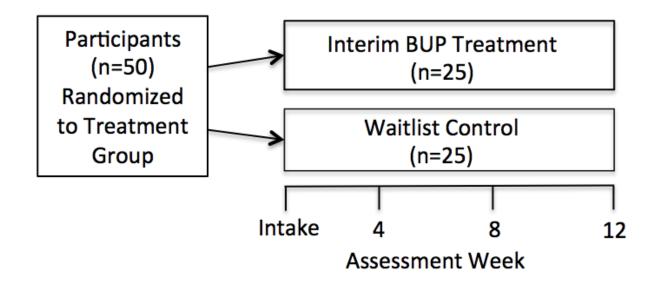
- Novel approach to reducing risk of overdose and illicit opioid use among Vermonters stuck on waitlists
- Treatment components:
 - Automated medication dispensing Buprenorphine dispensed in a secure computerized device to support medication administration while minimizing nonadherence
 - Daily monitoring Nightly calls from an automated Interactive Voice Response (IVR) phone system to assess any opioid use, withdrawal and craving
 - Random call-backs Participants contacted by IVR on random schedule to return to the clinic for UA, pill count, dose ingestion under nurse observation
 - Automated HIV and HCV Education Interactive educational application delivered via iPad





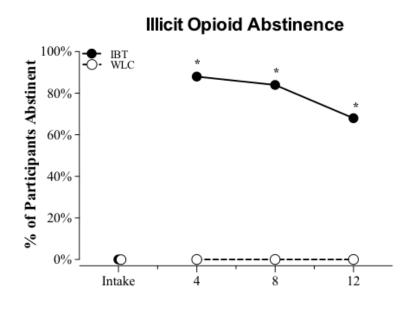
IBT Randomized Pilot Trial

- 12-week outpatient randomized pilot study to evaluate initial efficacy
- Participants (n = 50)
 - \geq 18 years old
 - Meet DSM-V criteria for OUD
 - Provide opioid-positive urine at intake
 - Currently waitlisted for opioid treatment



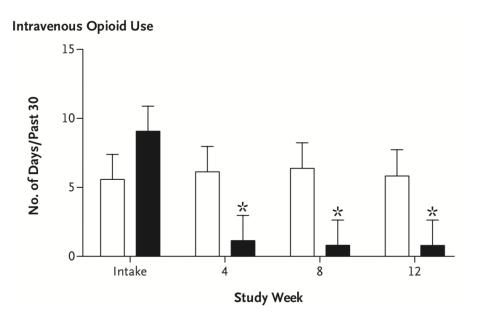
- **IBT** Visited clinic every 2 weeks to ingest dose, provided UA, and received their remaining doses via Med-O-Wheel. Daily monitoring of recent drug use, craving and withdrawal. Random call-backs (~2x/mo). Monthly follow-ups at Weeks 4, 8, and 12.
- Waitlist Control Remained on waitlist but completed Week 4, 8, and 12 follow-ups





Center on

- Participants randomized to IBT achieved significantly greater abstinence from illicit opioids
- At 4-, 8- and 12-week assessments, 88%, 84% and 68% of IBT participants abstinent vs. 0%, 0% and 0% of WLC participants



IBT participants demonstrated greater reductions in IV opioid use

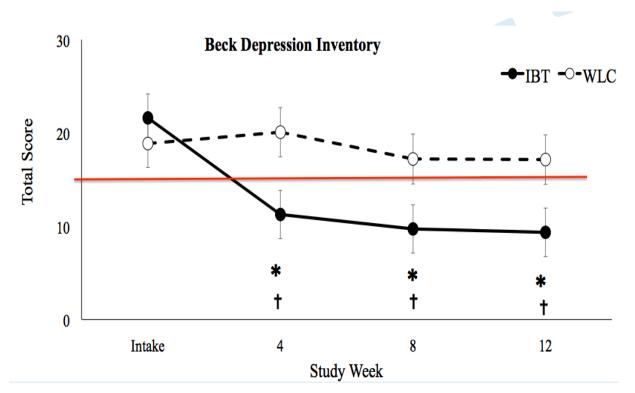
The NEW ENGLAND JOURNAL of MEDICINE

Interim Buprenorphine vs. Waiting List for Opioid Dependence

N ENGL J MED 375;25 NEJM.ORG DECEMBER 22, 2016



IBT – Secondary Outcomes

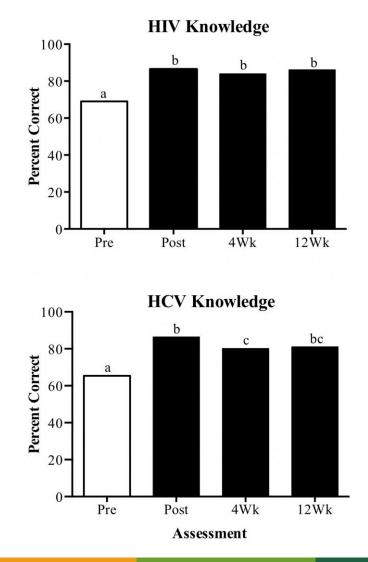


- Participants in both groups presented with elevated depression severity
- No change in WLC participants
- Depression symptoms decreased significantly among IBT participants

Streck et al., 2018, Experimental and Clinical Psychopharmacology



IBT – Secondary Outcomes



- IBT participants demonstrated significant improvements in HIV and HCV knowledge
- These improvements persisted throughout the 12week study, without additional educational sessions

Ochalek et al., 2018, Drug and Alcohol Dependence



Recently-Completed Randomized Trial

- Our recently-completed, larger-scale trial expands on the pilot in several key ways:
 - Increases duration from 3 to 6 months
 - Extends to individuals residing in rural, medically-underserved geographic areas
 - Includes a new component to address opioid overdose risk



Opioid Overdose Education

- Pre-test assessments of overdose (OD) knowledge (Dunn et al., 2016)
- Interactive educational application and video, delivered via iPad:
 - Four opioid overdose education modules (Created by Dunn et al., 2017)
 - Brief Narcan video (Adapt Pharmaceuticals)
- All participants receive Narcan with brief instructions
- Post-test assessments of OD-related knowledge and monitoring of Narcan use

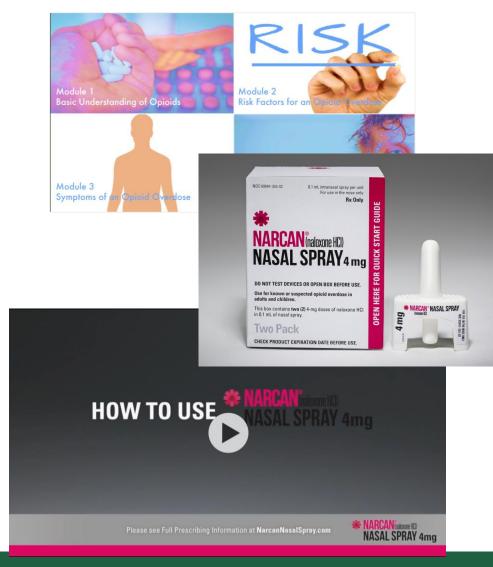
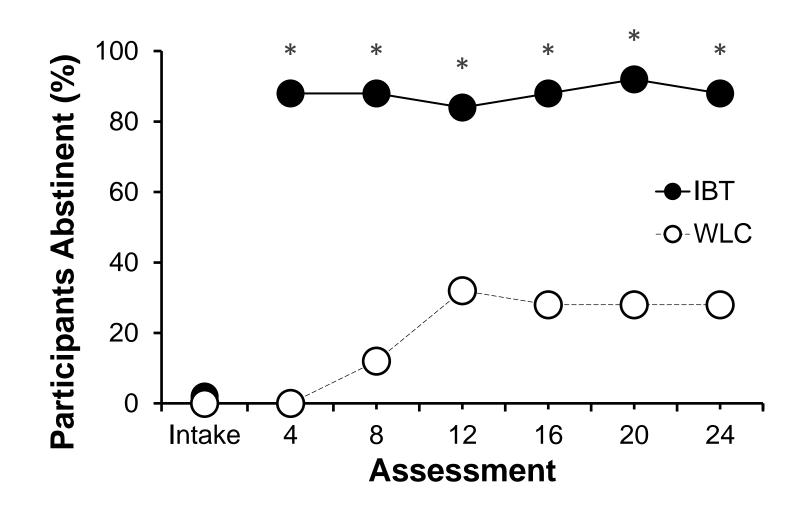




Table 1. Participant Characteristics	Total (n=50)	IBT (n=25)	WLC (n=25)	<i>p</i> -value
Age, yrs	40.3 <u>+</u> 10.8	39.3 <u>+</u> 10.0	41.3 <u>+</u> 11.5	.52
Male, %	30 (60.0)	18 (72.0)	12 (48.0)	.08
Non-Hispanic white, %	45 (90.0)	23 (92.0)	22 (88.0)	.99
Education, yrs	12.4 <u>+</u> 1.8	12.8 <u>+</u> 2.1	12.0 <u>+</u> 1.5	.12
Employed full time, %	26 (52.0)	17 (68.0)	9 (36.0)	.02
Primary past year opioid of abuse, %				.99
Heroin	4 (8.0)	2 (8.0)	2 (8.0)	
Prescription opioids	46 (92.0)	23 (92.0)	23 (92.0)	
Primary past year route, %				.15
Oral/sublingual	34 (68.0)	14 (56.0)	20 (80.0)	
Intranasal	11 (22.0)	8 (32.0)	3 (12.0)	
Inhalation	1 (2.0)	0 (0.0)	1 (4.0)	
Intravenous	4 (8.0)	3 (12.0)	1 (4.0)	
Duration of regular use, yrs	9.5 <u>+</u> 6.1	9.2 <u>+</u> 6.2	9.8 <u>+</u> 5.9	.71
Past-month cocaine use, %	13 (26.0)	7 (28.0)	6 (24.0)	.75
Ever used IV, %	22 (44.0)	10 (40.0)	12 (48.0)	.57
Ever used heroin, %	33 (66.0)	16 (64.0)	17 (68.0)	.77
Ever overdosed on opiates, %	13 (26.0)	5 (20.0)	7 (28.0)	.51



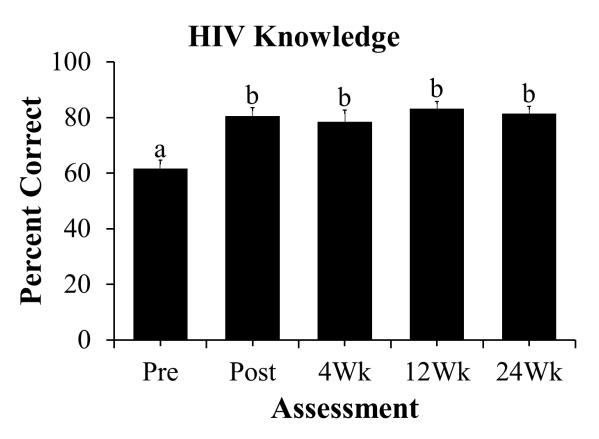
Illicit Opioid Abstinence





HIV Knowledge

- Participants answered 50 questions assessing HIV general knowledge, sexual risk behaviors, and drug risk behaviors
- Participants answered an average of 61.6% of items correctly on the baseline (Pre-test at intake) HIV knowledge assessment
- Immediately after receiving the educational intervention, participants were assessed again (Post) and answered an average of 80.5% of items correctly
- This acquired knowledge was sustained through study weeks 4, 12, and 24, during which participants answered an average of 78.6%, 83.3%, and 81.4% of items correctly, respectively.

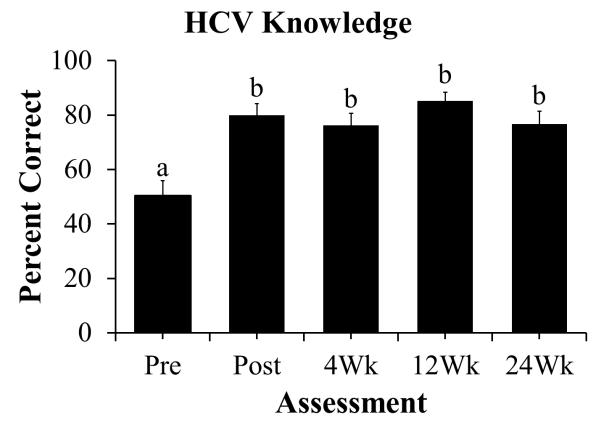


Mean percent of correct items on the HIV knowledge assessment. Data bars sharing a common letter are not significantly different (Fisher's LSD, p < .05).



Hepatitis-C Knowledge

- Participants answered 17 questions assessing HCV knowledge
- Participants answered an average of 50.4% of items correctly on the baseline (Pre-test at intake) HCV knowledge assessment
- Immediately after receiving the educational intervention, participants were assessed again (Post) and answered an average of **79.9%** of items correctly
- This acquired knowledge was sustained through study weeks 4, 12, and 24, during which participants answered an average of 76.2%, 85.1%, and 76.7% of items correctly, respectively.

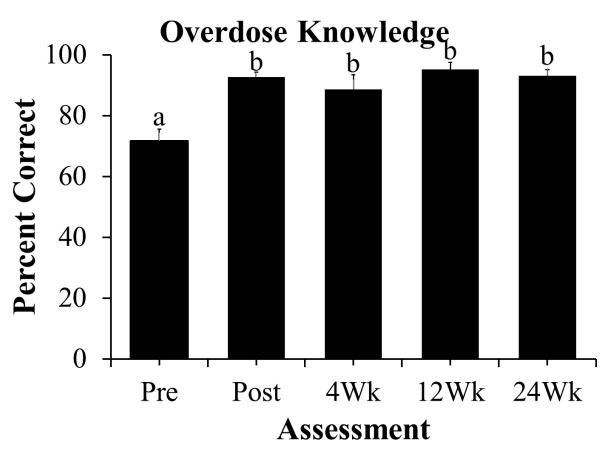


Mean percent of correct items on the HCV knowledge assessment. Data bars sharing a common letter are not significantly different (Fisher's LSD, p < .05).



Opioid Overdose Knowledge

- Participants answered 12 questions assessing knowledge of opioids generally, opioid overdose, and how to respond in the event of an opioid overdose
- Participants answered an average of 71.7% of items correctly on the baseline (Pre-test at intake) opioid knowledge assessment
- Immediately after receiving the educational intervention, participants were assessed again (Post) and answered an average of 92.7% of items correctly
- This acquired knowledge was sustained through study weeks 4, 12, and 24, during which participants answered an average of 88.6%, 95.2%, and 93.1% of items correctly, respectively.

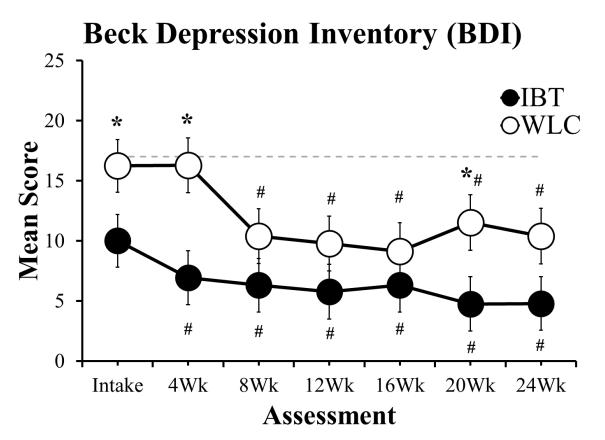


Mean percent of correct items on the HCV knowledge assessment. Data bars sharing a common letter are not significantly different (Fisher's LSD, p < .05).



Depressive Symptoms

- WLC participants begin with significantly more severe symptoms of depression
- Participants in both groups achieve significant reductions in BDI-II scores that are sustained across the 6-month study period
- No significant differences in depression at 24-weeks post-randomization



Asterisks denote significant differences between groups at each time point. Hash marks indicate that the change from intake to assessment timepoint significantly differed within group.

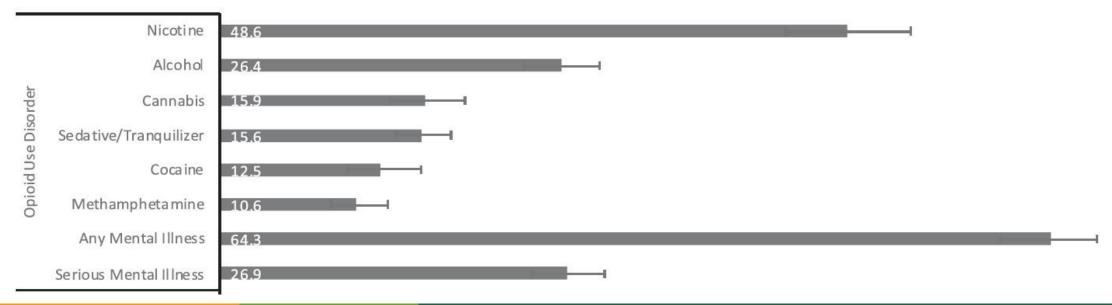


- In our efforts to replicate and further build upon the initial promising results of the pilot trial, we have observed similarly high levels of illicit opioid abstinence that are sustained over the longer 6-month duration
- We are also observing significant increases in HIV, HCV, and opioid OD knowledge, as well as decreases in depression symptoms, sustained across the 6-month study period



MOUD & Psychiatric Comorbidities

- MOUD represent the most efficacious treatment for OUD Gowing et al., 2017; Larochelle et al., 2018; Mattick et al., 2014
- Psychiatric comorbidities are prevalent among individuals with OUD and has been linked to increased risk for opioid misuse and overdose Brooner et al., 1997; Campbell et al., 2018; Conway et al., 2006; Gros et al., 2013; Johnson et al., 2013; Jones et al., 2019; Kidorf et al., 2004; Roncero et al., 2016; Strain, 2002





MOUD & Posttraumatic Stress Disorder (PTSD)

 Almost all individuals (~90%) with OUD report lifetime trauma exposure and one-third of these individuals meet criteria for PTSD

Lifetime prevalence of trauma and PTSD in the general population vs. those with OUD						
	Trauma Exposure PTSD					
General Population	60.7%	6.8%				
OUD	87.8%	33.2%				
Kessler et al., 1995; Kessler et al., 2008; Mills et al., 2006						



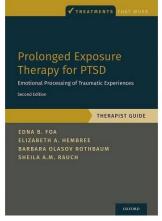
- **MOUD & PTSD**
- PTSD is defined as a psychiatric disorder that occurs in people who have experienced or witnessed a traumatic event (e.g., natural disaster, sexual violence, physical assault)
- In addition to trauma exposure, individuals must exhibit symptoms from each of the following four symptom clusters in order to meet criteria for DSM-defined PTSD:
 - Intrusion symptoms (e.g., intrusive thoughts, nightmares)
 - Avoidance of internal and external stimuli associated with the trauma •
 - Negative alterations in cognitions and mood •
 - Arousal and reactivity (e.g., hypervigilance, irritability)
- MOUD patients with PTSD generally experience worse outcomes
 - Continued psychiatric distress
 - Greater MOUD treatment dropout ۲
 - Relapse to illicit opioid use

Havens et al., 2011; Meshberg-Cohen et al., 2021; Mills et al., 2005; Peirce et al., 2016; Schiff et al., 2010



Prolonged Exposure (PE) Therapy

- PE is an empirically supported and highly-efficacious intervention that is regarded as a first-line treatment for PTSD Foa et al., 1999, 2005, 2008; Jonas et al., 2013; Powers et al., 2010; Schnurr et al., 2007
- PE disrupts the cycle of anxiety and avoidance that characterizes PTSD by deconditioning fear responses to trauma-related stimuli via sustained imaginal and invivo exposure exercises
 - Prolonged, imaginal exposure to the trauma memory (revisiting, recounting, and processing)
 - Repeated in vivo exposure to safe situations that are avoided because of trauma-related fear (Foa et al., 2019)





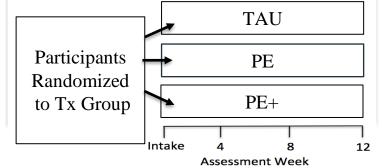
Prolonged Exposure (PE) Therapy

- Recent studies suggest that PE is associated with reductions in PTSD symptom severity in patients receiving treatment for co-occurring OUD Peck et al., 2018; Schacht et al., 2017; Schiff et al., 2015
- As with other behavioral interventions, poor attendance often limits the efficacy of PE Belleau et al., 2017; Hein et al., 2009; McGovern et al., 2015
- MOUD is associated with significant reductions in psychiatric symptoms Dean et al., 2004; Falcon et al., 2015, 2016; Fingleton et al., 2015; Lake et al., 2019; Streck et al., 2018
- It is unclear to what extent improvements in PTSD severity were a function of PE versus the effects of MOUD



Overview of Randomized Trial

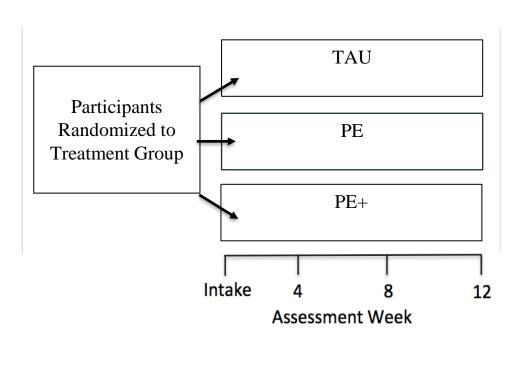
- 12-week randomized trial to evaluate the feasibility of a novel PE protocol for improving PE session attendance and reducing PTSD symptoms among OUD patients with co-occurring PTSD
- Participants:
 - > 18 years old
 - Maintained on buprenorphine or methadone > 1 month
 - Meet DSM-V PTSD criteria



- <u>Treatment as usual (TAU)</u>: Continue to receive buprenorphine or methadone from current provider. Follow-ups at Weeks 4, 8, and 12
- **Prolonged exposure therapy (PE):** Continue to receive MOUD. Follow-ups at Weeks 4, 8, and 12. Twelve 60-minute individual sessions of PE
- **Prolonged exposure therapy + attendance-contingent financial incentives (PE+):** Continue to receive MOUD. Follow-ups at Weeks 4, 8, and 12. Twelve 60-minute individual sessions of PE. Financial incentives contingent on completion of PE sessions



Overview of Randomized Trial



PE+ Incentive Program					
Session	Incentive	Bonus			
1	\$20				
2	\$25	\$50			
3	\$30				
4	\$35	\$50			
5	\$40				
6	\$45	\$50			
7	\$50				
8	\$55	\$50			
9	\$60				
10	\$65	\$50			
11	\$70				
12	\$75	\$100			
Total earnings	\$570	\$350			
		• *			

Maximum possible total earnings: \$920



	Total	TAU	PE	PE+	
Measure	(n = 30)	(n = 10)	(n = 10)	(n = 10)	p-value
Age, years	38.1 (7.9)	44.7 (8.9)	33.8 (4.6)	35.9 (5.2)	.002
Female, N (%)	19 (63.3)	7 (70.0)	6 (60.0)	6 (60.0)	>.999
White, N (%)	29 (96.7)	10 (100)	9 (90.0)	10 (100)	>.999
Education, years	13.3 (1.5)	13.6 (2.0)	13.6 (1.3)	12.8 (1.1)	.410



	Total	TAU	PE	PE+	
Measure	(n = 30)	(n = 10)	(n = 10)	(n = 10)	p-value
Duration of illicit opioid use. years	7.4 (7.3)	9.1 (8.9)	4.6 (4.6)	8.2 (7.4)	.379
OAT medication					>.999
Buprenorphine, N (%)	17 (56.7%)	6 (60.0%)	6 (60.0%)	5 (50.0%)	
Daily dose, mg	15.6 (5.6)	17.0 (6.2)	16.3 (5.7)	13.2 (5.0)	.525
Methadone, N (%)	13 (43.3%)	4 (40.0%)	4 (40.0%)	5 (50.0%)	
Daily dose, mg	92.2 (42.3)	103.8 (44.2)	55.8 (17.3)	112.0 (44.4)	.118
Duration of OAT, years	4.5 (4.1)	5.2 (5.2)	5.3 (4.4)	3.0 (2.2)	.410



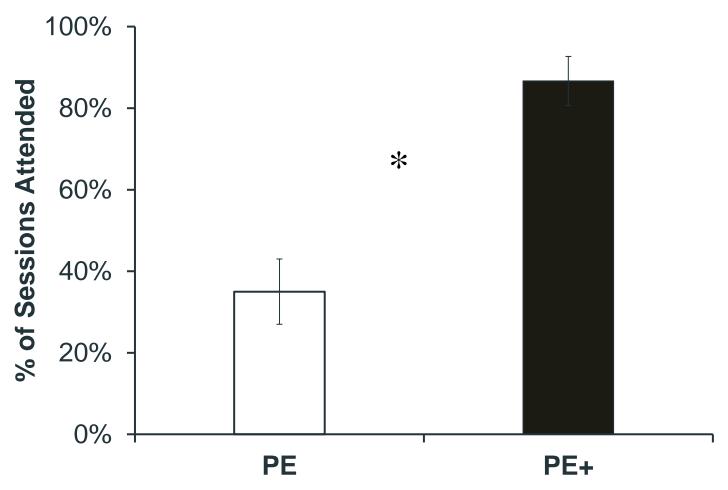
	Total	TAU	PE	PE+	
Measure	(n = 30)	(n = 10)	(n = 10)	(n = 10)	p-value
Index trauma					.556
Sexual assault, N (%)	10 (33.3%)	4 (40.0%)	2 (20.0%)	4 (40.0%)	
Physical assault, N (%)	8 (26.7%)	4 (40.0%)	3 (30.0%)	1 (10.0%)	
Witnessed injury/death, N (%)	4 (13.3%)	1 (10.0%)	1 (10.0%)	2 (20.0%)	
Learned ab injury/death, N (%)	3 (10.0%)	1 (10.0%)	0 (0%)	2 (20.0%)	
Accident, N (%)	2 (6.7%)	0 (0%)	1 (10.0%)	1 (10.0%)	
Combat, N (%)	1 (3.3%)	0 (0%)	1 (10.0%)	0 (0%)	
Other, N (%)	2 (6.7%)	0 (0%)	2 (20.0%)	0 (0%)	
History of PTSD treatment, N (%)	18 (60.0%)	5 (50.0%)	5 (50.0%)	8 (80.0%)	.348



	Total	TAU	PE	PE+	
Measure	(n = 30)	(n = 10)	(n = 10)	(n = 10)	p-value
Lifetime Suicide Attempt	17 (56.7%)	6 (60.0%)	5 (50.0%)	6 (60.0%)	>.999
Generalized Anxiety Disorder Dx	15 (50.0%)	6 (60.0%)	3 (30.0%)	6 (60.0%)	.467
Major Depressive Disorder Dx	13 (43.3%)	4 (40.0%)	5 (50.0%)	4 (40.0%)	>.999
CAPS-5	41.5 (8.1)	38.9 (8.7)	41.4 (8.6)	44.1 (6.9)	.369
BAI	26.2 (11.8)	31.7 (11.3)	21.5 (9.6)	25.3 (13.1)	.149
BDI-II	32.3 (9.9)	34.4 (8.8)	29.7 (6.5)	32.8 (13.4)	.572

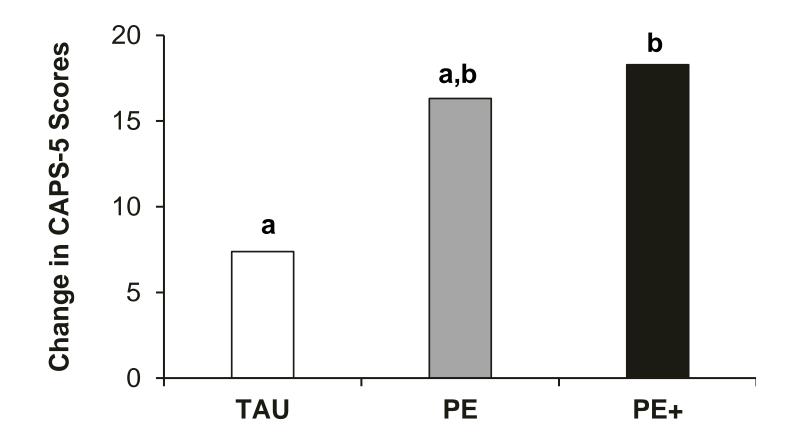


PE Session Attendance



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Change in PTSD Symptoms





Illicit Substance Use

- Urine samples submitted by PE & PE+ participants were significantly less likely than TAU participants to test positive for illicit opioids during treatment (0% vs. 22%; p=.007).
- Participants in the two PE conditions also submitted numerically fewer urine specimens that were positive for non-opioid illicit drugs (i.e., cocaine, benzodiazepines, amphetamines) during treatment compared to the TAU condition (20% vs. 44%).





- Pilot data suggests that individuals with co-occurring OUD and PTSD are much more likely to attend PE sessions if they are incentivized to do so
- Individuals in the PE+ group reported greater reductions in PTSD symptoms than those who received TAU
- PE may be associated with less illicit substance use than SUD treatment alone
- Despite these promising findings, only half of all individuals with co-occurring mental health diagnoses and OUD received past-year mental health treatment (Jones et al., 2019) and individuals in rural communities may be even less likely to access mental health treatment due to workforce shortages Jones et al., 2019; Thomas et al., 2009
- We are currently preparing an R01 submission that examines the efficacy of PE+ delivered via telemedicine



UVM Center on Rural Addiction

CORA MISSION

To expand addiction-treatment capacity in rural communities by providing evidence-based technical assistance, consultation, resources and education to healthcare providers and other staff









SURVEILLANCE & EVALUATION

- Conduct baseline needs assessments to identify real-time barriers in rural practices
- Assist providers and practices with establishing & improving data systems
- Monitor drug use patterns in rural communities

BEST PRACTICES

•

- Provide in-person & remote technical assistance to implement evidence-based practices
- Provide hardware, software, resources and training in new or expanded models of care and delivery

CLINICIAN ADVISORY BOARD

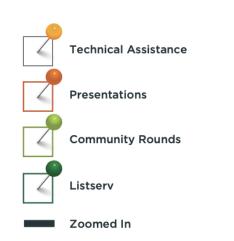
- Provide expertise & consultation in evidencebased treatment and patient-centered care coordination
- Individual peer mentoring with expert providers
- Best Practices Scholarship Program

EDUCATION & OUTREACH

- Provide education & outreach in science-based best practices
- Community Rounds Webinar Series with CMEs
- On-site Learning Lunches
- Resource Library & Online Learning Collaborative

UVM CORA GEOGRAPHICAL REACH

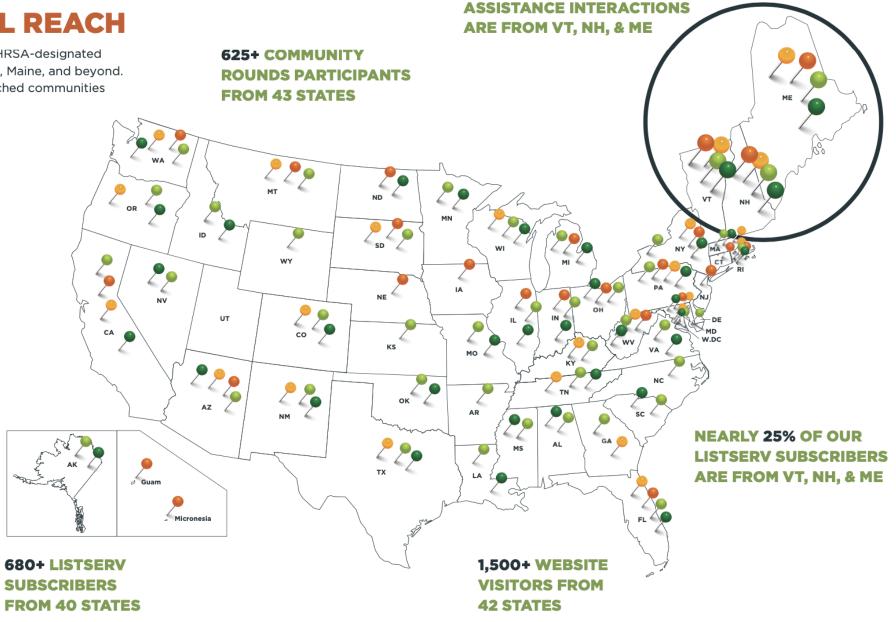
UVM CORA's mission is to serve the HRSA-designated counties of Vermont, New Hampshire, Maine, and beyond. Our evidence-based efforts have reached communities across the United States.



165 TECHNICAL ASSISTANCE INTERACTIONS FROM 22+ STATES

Top 3 areas:

Psychostimulant use
COVID-related equipment
Complex patient support



64% OF OUR TECHNICAL



UVM Center on Rural Addiction

- Since our inception:
 - We have completed > 600 technical assistance interactions and delivered > 99,000 individual supplies
 - > 2,000 people have attended our webinars and > 1,600 people have viewed our webinars on YouTube





- Rates of opioid use, misuse, and overdose remain high nationally and in rural communities
- Methadone and buprenorphine represent the most efficacious treatments for OUD
- Access to MOUD and mental health treatment is often limited in rural areas
- Innovative approaches to treatment such as low-barrier, technology-assisted buprenorphine dosing can be useful for promoting illicit opioid use in rural settings
- Pilot data provides strong preliminary support for the efficacy of PE+ for improving PE attendance and PTSD symptoms in individuals with co-occurring PTSD and OUD
- UVM CORA is committed to delivering evidence-based support to rural treatment providers as they treat substance use disorders in their communities



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