

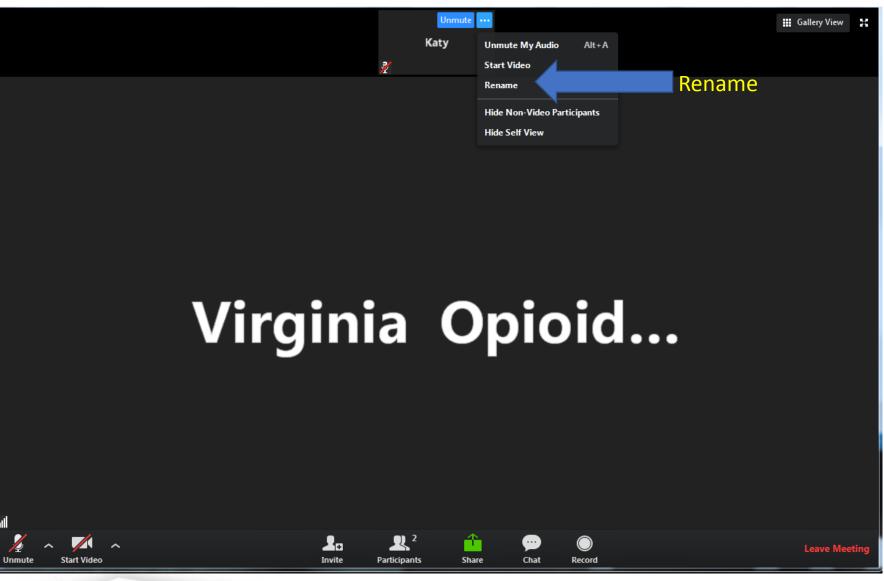
# Virginia Opioid Addiction ECHO\* Clinic

February 15, 2019

\*ECHO: Extension of Community Healthcare Outcomes



### **Helpful Reminders**

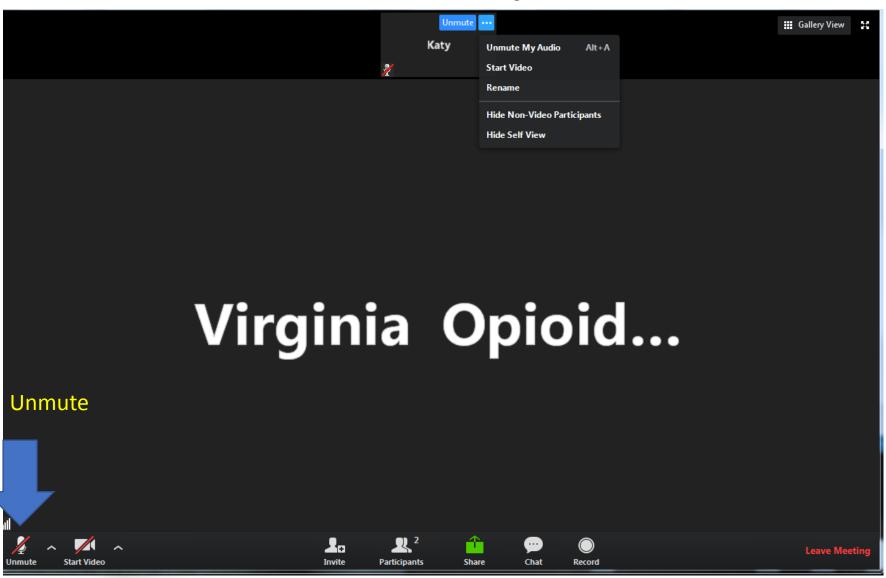




 Rename your Zoom screen, with your name and organization



### **Helpful Reminders**

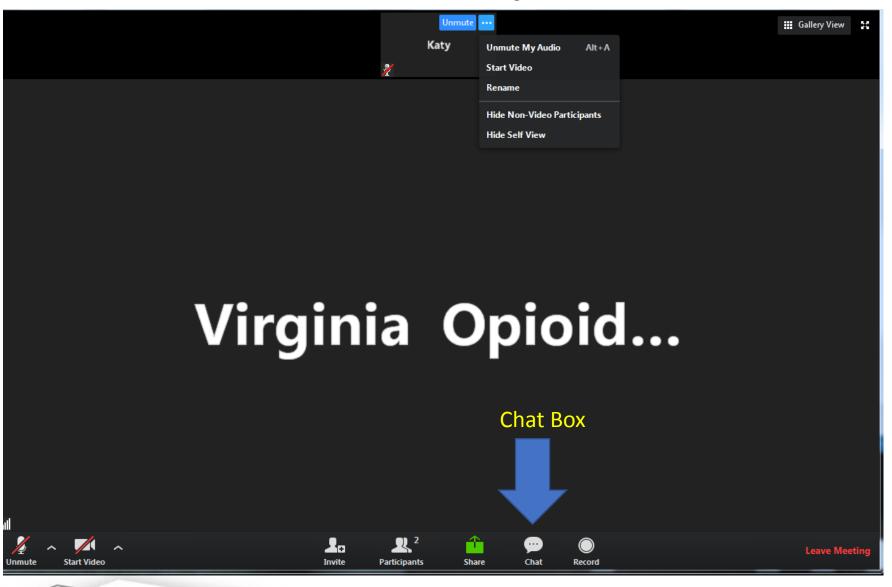




- You are all on mute please unmute to talk
- If joining by telephone audio only, \*6 to mute and unmute



### **Helpful Reminders**





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



### **VCU Opioid Addiction ECHO Clinics**











- 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 in substance use disorder
- Website Link: www.vcuhealth.org/echo



### **Hub Introductions**

| VCU Team  |   |  |  |  |  |
|---|---|--|--|--|--|
| Clinical Director   | Mishka Terplan, MD, MPH, FACOG, FASAM           |  |  |  |  |
| Administrative Medical Director ECHO Hub and Principal Investigator | Vimal Mishra, MD, MMCi                          |  |  |  |  |
| Clinical Expert   | Lori Keyser-Marcus, PhD<br>Courtney Holmes, PhD |  |  |  |  |
| Didactic Presentation   | Mishka Terplan, MD                              |  |  |  |  |
| Program Manager   | Bhakti Dave, MPH                                |  |  |  |  |
| Practice Administrator  | David Collins, MHA                              |  |  |  |  |
| IT Support  | Vladimir Lavrentyev, MBA                        |  |  |  |  |







### Introductions:

### Poll Question #1:

- Name
- Organization

 What is your current comfort level with Naltrexone?

Reminder: Mute and Unmute to talk

\*6 for phone audio

Use chat function for Introduction



### What to Expect



- I. Didactic Presentation
  - . Naltrexone
  - II. Mishka Terplan, 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







# Project ECHO Naltrexone





### Naltrexone

- Opioid antagonist (at mu and kappa receptors)
- Can be prescribed by anyone
- Does not cause dependence or euphoria
- "Detox Hurdle" precipitated withdrawal if not detoxed from opioids
- Oral formulation approved 1984 (OUD) and 1995 (AUD), SQ approved 2006 (AUD) and 2010 (OUD)
- Cost: 50 mg tablet=\$0.74/day, 380mg Injection=\$41.20/day
- Hepatic Metabolism



### Injectable Naltrexone (XR-NTX)\*

- Multicenter (13 sites in Russia) Funded by Alkermes
- ❖ DB RPCT, 24 wks, n=250 w/ opioid dependence
- XR-NTX vs placebo, all offered biweekly individual drug counseling
- Increased weeks of confirmed abstinence (90% vs 35%)
- Increased patients with confirmed abstinence (36% vs 23%)
- Decreased craving (-10 vs +0.7)

\*No Black Box LFTs Warning Label for IM formulation

Krupitsky E et al. Lancet. 2011.



# Oral Naltrexone Efficacy

- Oral naltrexone
  - Duration of action 24-48 hours
  - FDA approved 1984
- 10 RCTs ~700 participants to naltrexone alone or with psychosocial therapy compared with psychosocial therapy alone or placebo
  - No clear benefit in treatment retention or relapse at follow up
- Benefit in highly motivated patients
  - Impaired physicians > 80% abstinence at 18 months

Cochrane Database of Systematic Reviews 2006





Cochrane Database of Systematic Reviews

### Oral naltrexone maintenance treatment for opioid dependence (Review)

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A

### Analysis 1.2. Comparison I naltrexone versus placebo or no pharmacological treatments, Outcome 2 retention and abstinence, all patients.

Review: Oral naltrexone maintenance treatment for opioid dependence

Comparison: I naltrexone versus placebo or no pharmacological treatments

Outcome: 2 retention and abstinence, all patients

| Study or subgroup                     | naltrexone                     | placebo/no pharm                  | Risk Ratio<br>M-<br>H.Random,95% | Weight        | Risk Ratio<br>M-<br>H,Random,95% |
|---------------------------------------|--------------------------------|-----------------------------------|----------------------------------|---------------|----------------------------------|
|                                       | n/N                            | n/N                               | Cl                               |               | Cl                               |
| Curran 1976                           | 2/19                           | 2/19                              | <del></del>                      | 9.1 %         | 1.00 [ 0.16, 6.38 ]              |
| Krupitsky 2004                        | 12/27                          | 4/25                              | -                                | 17.8 %        | 2.78 [ 1.03, 7.49 ]              |
| Krupitsky 2006                        | 25/70                          | 7/70                              | -                                | 20.9 %        | 3.57 [ 1.65, 7.71 ]              |
| Lemer 1992                            | 9/15                           | 8/16                              | +                                | 22.8 %        | 1.20 [ 0.63, 2.28 ]              |
| San 1991                              | 4/28                           | 8/22                              | -                                | 16.8 %        | 0.39 [ 0.14, 1.14 ]              |
| Schottenfield 2008                    | 4/43                           | 3/39                              | -                                | 126%          | 1.21 [ 0.29, 5.07 ]              |
| Total (95% CI)                        | 202                            | 191                               | •                                | 100.0 %       | 1.43 [ 0.72, 2.82 ]              |
| Total events: 56 (naltrexon           | ne), 32 (placebo/no p          | harm)                             |                                  |               |                                  |
| Heterogeneity: Tau <sup>2</sup> = 0.4 | $2$ ; $Chi^2 = 13.40$ , $df =$ | 5 (P = 0.02); I <sup>2</sup> =63% |                                  |               |                                  |
| Test for overall effect: Z =          | 1.03 (P = 0.30)                |                                   |                                  |               |                                  |
|                                       |                                |                                   |                                  | 7             |                                  |
|                                       |                                |                                   | 0.01 0.1 1 10 10                 | 0             |                                  |
|                                       |                                | Favou                             | rs psychotherapy Favours naître  | expine + psyc |                                  |





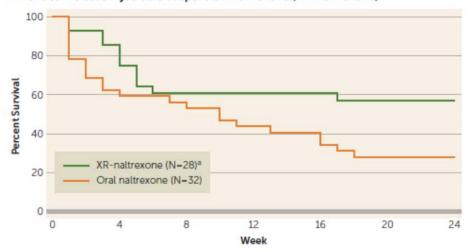
#### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON (Explane

| Patient or population: p<br>Settings:<br>Intervention: naitrexone | •                   | lependence<br>no pharmacological treatments                        | 8                           |                            |
|---|---------------------|--|-----------------------------|----------------------------|
| Outcomes  | Illustrative compar | rative risks* (95% CI)   | Relative effect<br>(95% CI) | No of Participar (studies) |
|   | Assumed risk        | Corresponding risk   |                             |                            |
|   | Control             | naitrexone versus<br>placebo or no pharma-<br>cological treatments |                             |                            |
| retention and absti-<br>nence, all patients                       | Study population    |  | RR 1.43                     | 393                        |
|   | 168 per 1000        | 240 per 1000<br>(121 to 474)                                       | (0.72 to 2.82)              | (6 studies)                |
|   | Medium risk popul   | ation  |                             |                            |
|   | 133 per 1000        | <b>190 per 1000</b> (96 to 375)                                    |                             |                            |
| abstinence at follow up   | Study population    |  | RR 1.28                     | 116                        |
|   | 340 per 1000        | <b>435 per 1000</b> (272 to 697)                                   | (0.8 to 2.05)               | (3 studies)                |
|   | Medium risk popul   | ation  |                             |                            |
|   | 364 per 1000        | 466 per 1000<br>(291 to 746)                                       |                             |                            |

### A Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder

Maria A. Sullivan, M.D., Ph.D., Adam Bisaga, M.D., Martina Pavlicova, Ph.D., Kenneth M. Carpenter, Ph.D., C. Jean Choi, M.S., Kaitlyn Mishlen, M.A., Frances R. Levin, M.D., John J. Mariani, M.D., Edward V. Nunes, M.D.

FIGURE 2. Time to Dropout for Participants Receiving Oral Naltrexone or Extended-Release Injectable Suspension Naltrexone (XR-Naltrexone)<sup>a</sup>

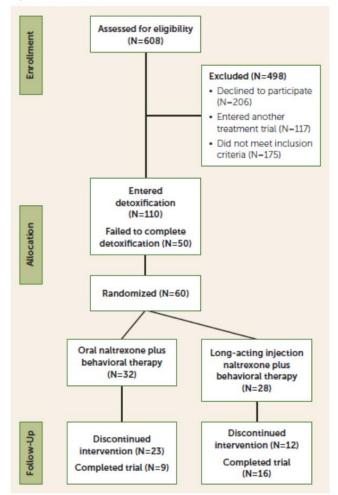


|                               |        |       |       | Week  |       |       |       |
|-------------------------------|--------|-------|-------|-------|-------|-------|-------|
| Percent Survival (N survived) | 0      | 4     | 8     | 12    | 16    | 20    | 24    |
| XR-naltrexone (N=28)          | 100.0% | 85.7% | 60.7% | 60.7% | 60.7% | 57.1% | 57.1% |
|                               | (28)   | (24)  | (17)  | (17)  | (17)  | (16)  | (16)  |
| Oral naltrexone (N=32)        | 100.0% | 62.5% | 53.1% | 43.8% | 40.6% | 28.1% | 28.1% |
|                               | (32)   | (20)  | (17)  | (14)  | (13)  | (9)   | (9)   |

<sup>&</sup>lt;sup>a</sup> Time to dropout was significantly higher in the XR-naltrexone group relative to the oral naltrexone group (Kaplan-Meier nonparametric log-rank test, χ<sup>2</sup>=4.64, df=1, p=0.03).



FIGURE 1. CONSORT Diagram for a Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder





### Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial www.thelancet.com Vol 377 April 30, 2011

Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman

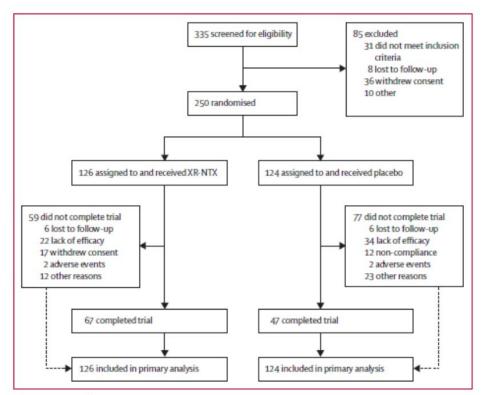


Figure 1: Trial profile

XR-NTX=extended-release naltrexone.



| XR-NTX<br>(n=126) | Placebo<br>(n=124)  |
|-------------------|---|
| 29-4 (4-8)        | 29-7 (3-6)  |
| 113 (90%)         | 107 (86%)   |
| 124 (98%)         | 124 (100%)  |
| 9-1 (4-5)         | 10-0 (3-9)  |
| 18 (9)            | 18 (7)  |
| 18 (23)           | 22 (24)   |
| 51 (40%)          | 52 (42%)  |
| 111 (88%)         | 117 (94%)   |
|                   | (n=126)<br>29·4 (4·8)<br>113 (90%)<br>124 (98%)<br>9·1 (4·5)<br>18 (9)<br>18 (23)<br>51 (40%) |

Table 1: Demographics and baseline clinical characteristics

Data are mean (SD) or number (%). XR-NTX=extended-release naltrexone.



# Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial www.thelancet.com Vol 377 April 30, 2011

Evgeny Krupitsky, Edward V Nunes, Walter Ling, Ari Illeperuma, David R Gastfriend, Bernard L Silverman

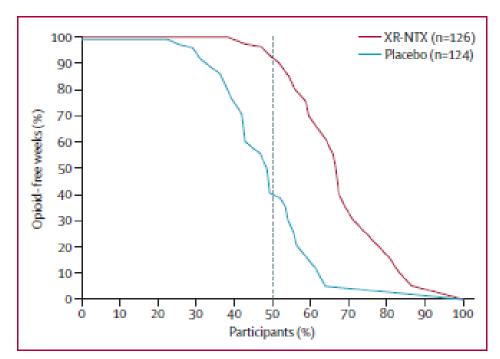


Figure 2: Percent of confirmed opioid-free weeks (cumulative) among participants treated with XR-NTX compared with placebo XR-NTX=extended-release naltrexone



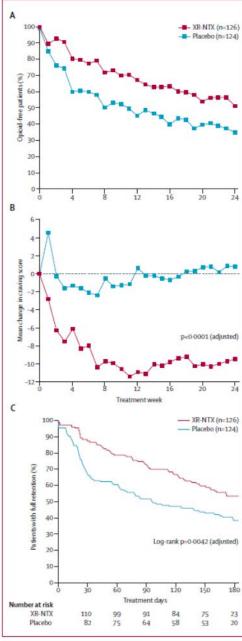


Figure 3: Key secondary efficacy outcomes

(A) Proportion of opioid-free patients by timeline follow-back self-report.
(B) Mean change from baseline in craving, p value is based on a generalised estimating equation model assuming normal distribution and autoregressive correlation structure. (C) Time-to-discontinuation of study treatment. p values for analyses of craving (B) and retention (C) are adjusted for multiplicity.
XR-NTX-extended-release naltroxone.



# Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence A Randomized Clinical Noninferiority Trial

JAMA Psychiatry December 2017 Volume 74, Number 12

Lars Tanum, MD, DMSci; Kristin Klemmetsby Solli, MSc; Zill-e-Huma Latif, MD; Jūratė Šaltytė Benth, PhD; Arild Opheim, MSc; Kamni Sharma-Haase, MD; Peter Kraici, MD, PhD; Nikolai Kunøe, MSc, PhD

Figure 1. CONSORT Flowchart for Inclusion of Participants 232 Assessed for eligibility 73 Excluded 9 Did not meet inclusion criteria 51 Refused to participate 6 Failed detoxification 7 Other reasons 159 Randomized 80 Randomized to receive extended-79 Randomized to receive release naltrexone buprenorphine-naloxone 71 Received extended-release 72 Received buprenorphinenaltrexone as randomized naloxone as randomized 9 Did not receive extended-7 Did not receive release naltrexone buprenorphine-naloxone 5 Dropped out 1 Dropped out 3 Failed detoxification 6 Never received study drug 1 Developed acute Illness 15 Lost to follow-up 23 Lost to follow-up 11 Dropped out 17 Dropped out 4 Discontinued owing to 6 Discontinued owing to adverse effects adverse effects 49 Completed 12 weeks of 56 Completed 12 weeks of extended-release naltrexone buprenorphine-naloxone 56 Included in analysis 49 Included in analysis



Table 1. Lifetime and Baseline Clinical Characteristics of Participants Randomized Into Treatment Groups<sup>a</sup>

| Lifetime Characteristic                       | Extended-Release<br>Naltrexone <sup>b</sup><br>(n = 80) | Buprenorphine-<br>Naloxone <sup>b</sup><br>(n = 79) |
|---|---|---|
| Age, mean (SD), y                             | 36.4 (8.8)  | 35.7 (8.5)  |
| Sex, No. (%)                                  |   |   |
| Male  | 61 (76.3)   | 54 (68.4)   |
| Female  | 19 (23.6)   | 25 (31.6)   |
| White, No. (%)                                | 72 (90.0)   | 70 (88.6)   |
| Injecting (intravenous) users,<br>No. (%)     | 72 (90.0)   | 64 (81.0)   |
| HIV positive, No. (%)                         | 2 (2.5)   | 2 (2.5)   |
| Hepatitis C seropositive,<br>No. (%)          | 44 (55.0)   | 42 (53.2)   |
| Years of substance use,<br>mean (SD)          |   |   |
| Heavy opioid use                              | 8.9 (7.8)   | 9.6 (10.5)  |
| Heroin  | 6.9 (5.8)   | 6.7 (5.2)   |
| Other illicit opioids                         | 2.4 (5.1)   | 3.2 (7.0)   |
| Cannabis                                      | 9.0 (7.3)   | 10.2 (9.0)  |
| Amphetamines                                  | 6.7 (7.3)   | 6.3 (6.6)   |
| Cocaine                                       | 1.4 (3.1)   | 1.7 (2.8)   |
| Benzodiazepines                               | 5.1 (6.0)   | 5.9 (8.7)   |
| Alcohol for intoxication                      | 3.5 (4.8)   | 2.9 (4.1)   |
| Use during past 30 d<br>(baseline), mean (SD) |   |   |
| Heroin  | 7.6 (11.0)  | 12.0 (12.9)   |
| Other illicit opioids                         | 8.2 (11.1)  | 14.5 (13.2)   |
| Cannabis                                      | 8.2 (11.1)  | 10.2 (12.6)   |
| Amphetamines                                  | 3.4 (7.4)   | 5.4 (9.1)   |
| Cocaine                                       | 0.2 (0.7)   | 1.3 (3.9)   |

a Intention-to-treat sample, 159.



<sup>&</sup>lt;sup>b</sup> Naltrexone, naloxone, and buprenorhine were all administered as the hydrochloride form.

# vs Daily Buprenorphine-Naloxone for Opioid Dependence Effectiveness of Injectable Extended-Release Naltrexone A Randomized Clinical Noninferiority Trial

No. at risk

Buprenorphine-naloxone group 78 Extended-release naltrexone group 78

Figure 2. Survival Curves for Retention in Treatment and Estimated Mean Number of Days for the Use of Heroin, Other Illicit Opioids, and Major Secondary Outcomes

60

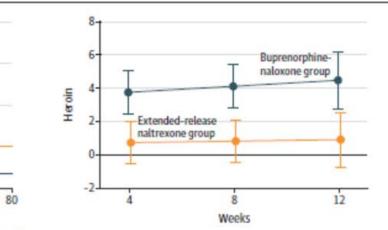
52 60

50 56

Extended-release naltrexone group

Cumulative Retention 9.0.9

0.6-





| Table 2. Days of Use of | Heroin and Other | r Illegal Substances | Assessed at Weeks   | 4 8 and 12a   |
|-------------------------|------------------|----------------------|---------------------|---------------|
| rable 2. Days or use or | neroill and othe | lilegal Juustalites  | wasessen or Liceva. | T, O, allu 12 |

Days Since Randomization

59 64

Buprenorphine-naloxone group

20

73

| Extended-Release Nalt | rexone   | Buprenorphine-Naloxone  |  | Extended-Release Naltrexone<br>vs Buprenorphine-Naloxone  |  |  |
|-----------------------|--|---|--|---|--|--|
| No. of Participants   | Mean (SD) <sup>b</sup>                             | No. of Participants   | Mean (SD)b   | Mean Difference (95% CI) <sup>c</sup>   | P Value  |  |
|                       |  |   |  |   |  |  |
| 63                    | 0.8 (1.5)  | 65  | 3.7 (7.4)  | -3.0 (-4.9 to -1.2)   | .001   |  |
| 59                    | 0.8 (1.9)  | 55  | 4.4 (9.1)  | -3.3 (-5.1 to -1.5)   | <.001  |  |
| 57                    | 1.1 (2.3)  | 50  | 4.1 (8.4)  | -3.6 (-6.0 to -1.2)   | .003   |  |
| ioids Use             |  |   |  |   |  |  |
| 63                    | 1.2 (2.2)  | 65  | 4.2 (7.9)  | -2.9 (-4.8 to -0.9)   | .004   |  |
| 59                    | 1.8 (4.7)  | 55  | 4.0 (8.5)  | -2.6 (-4.6 to -0.7)   | .007   |  |
| 57                    | 2.0 (5.0)  | 50  | 4.4 (8.7)  | -2.4 (-4.9 to 0.1)  | .06  |  |
|                       | No. of Participants  63  59  57  ioids Use  63  59 | 63 0.8 (1.5)<br>59 0.8 (1.9)<br>57 1.1 (2.3)<br>ioids Use<br>63 1.2 (2.2)<br>59 1.8 (4.7) | No. of Participants Mean (SD) <sup>b</sup> No. of Participants  63 0.8 (1.5) 65  59 0.8 (1.9) 55  57 1.1 (2.3) 50  ioids Use  63 1.2 (2.2) 65  59 1.8 (4.7) 55 | No. of Participants         Mean (SD) <sup>b</sup> No. of Participants         Mean (SD) <sup>b</sup> 63         0.8 (1.5)         65         3.7 (7.4)           59         0.8 (1.9)         55         4.4 (9.1)           57         1.1 (2.3)         50         4.1 (8.4)           ioids Use         63         1.2 (2.2)         65         4.2 (7.9)           59         1.8 (4.7)         55         4.0 (8.5) | Extended-Release Naltrexone   Buprenorphine-Naloxone   No. of Participants   Mean (SD) <sup>b</sup>   No. of Participants   Mean (SD) <sup>b</sup>   Mean Difference (95% CI) <sup>c</sup> |  |



# Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence A Randomized Clinical Noninferiority Trial

JAMA Psychiatry December 2017 Volume 74, Number 12

Lars Tanum, MD, DMSci; Kristin Klemmetsby Solli, MSc; Zill-e-Huma Latif, MD; Jüraté Šaltyté Benth, PhD; Arild Opheim, MSc; Kamni Sharma-Haase, MD; Peter Krajci, MD, PhD; Nikolaj Kunøe, MSc, PhD



|                                    | No. (%)                              |                                    |                      |  |
|------------------------------------|--------------------------------------|------------------------------------|----------------------|--|
| Outcome                            | Extended-Release Naltrexone (n = 71) | Buprenorphine-Naloxone<br>(n = 72) | P Value <sup>b</sup> |  |
| Deaths                             | 0                                    | 0                                  |                      |  |
| Nonserious AE                      | 43 (60.6)                            | 22 (30.6)                          | <.001                |  |
| Serious AE <sup>c</sup>            | 6 (8.5)                              | 3 (4.2)                            | .33                  |  |
| Pneumonia-related                  | 2 (2.8)                              | 0                                  |                      |  |
| Withdrawal-related                 | 3 (4.2)                              | 0                                  |                      |  |
| Acute pain                         | 1 (1.4)                              | 1 (1.4)                            |                      |  |
| Opioid overdose                    | 0                                    | 1 (1.4)                            |                      |  |
| Planned surgery                    | 0                                    | 1 (1.4)                            |                      |  |
| Insomnia                           | 8 (11.3)                             | 3 (4.2)                            | .13                  |  |
| Anxiety and depression symptoms    | 12 (16.9)                            | 6 (8.3)                            | .14                  |  |
| Injection site problems            | 4 (5.6)                              | 0                                  |                      |  |
| Withdrawal-related AE <sup>d</sup> | 28 (39.4)                            | 10 (13.9)                          | <.001                |  |



Abbreviation: AE, adverse event.



<sup>&</sup>lt;sup>a</sup> Naltrexone, naloxone, and buprenorhine were all administered as the hydrochloride form.

<sup>&</sup>lt;sup>b</sup> Determined with Fisher exact test; empty cells indicate not applicable.

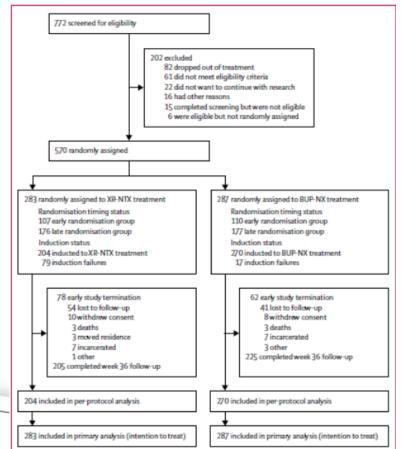
<sup>&</sup>lt;sup>c</sup> Two participants reported 2 serious AEs each.

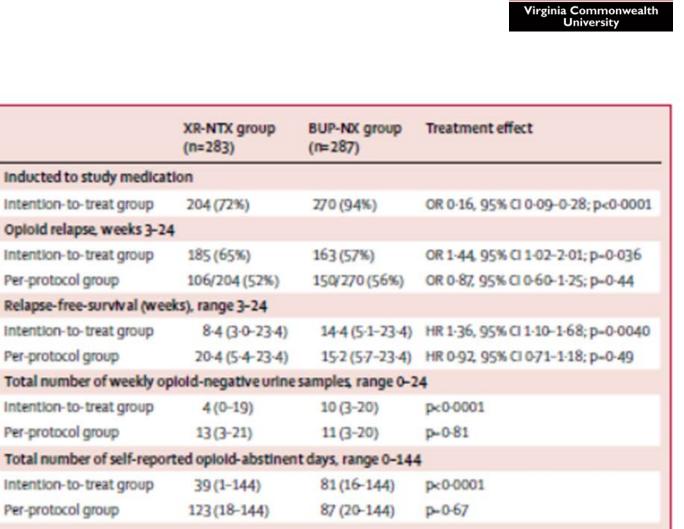
d Thirty-seven participants reported 2 or more withdrawal-related events.

### Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Lancet 2018: 391: 309-18

Joshua D Lee, Edward V Nunes Jr., Patricia Novo, Ken Bachrach, Geniel Bailey, Snehal Bhatt, Sarah Farkas, Marc Fishman, Phoebe Gauthier, Candace C Hodgkins, Jacquie King, Robert Lindblad, David Liu, Abigail G Matthews, Jeanine May, K Michelle Peavy, Stephen Ross, Dagmar Salazar, Paul Schkolnik, Dikla Shmueli-Blumberg, Don Stablein, Geetha Subramaniam, John Rotrosen







Data are n (%), n/N (%), or median (IQR).XR-NTX-extended-release naltrexone. BUP-NX-buprenorphine-nalexone.

#### Table 2: Oploid treatment outcomes

Per-protocol group

Per-protocol group

Per-protocol group

Per-protocol group



XR-NTX=extended-release naltrexone. BUP-NX=buprenorphine-naloxone

# Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

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|  | XR-NTX group<br>(n=283)  | BUP-NX group<br>(n=287) | Treatment effect                    |
|--|--|-------------------------|-------------------------------------|
| Inducted to study medical  | tion   |                         |                                     |
| Intention-to-treat group   | 204 (72%)  | 270 (94%)               | OR 0-16, 95% CI 0-09-0-28; p<0-0001 |
| Optoid relapse, weeks 3-2  | 4  |                         |                                     |
| Intention-to-treat group   | 185 (65%)  | 163 (57%)               | OR 1-44, 95% CI 1-02-2-01; p=0-036  |
| Per-protocol group   | 106/204 (52%)  | 150/270 (56%)           | OR 0-87, 95% CI 0-60-1-25; p=0-44   |
| Relapse-free-survival (wee                                       | eks), range 3-24   |                         |                                     |
| Intention-to-treat group   | 8-4 (3-0-23-4)   | 14-4 (5-1-23-4)         | HR 1-36, 95% CI 1-10-1-68; p=0-0040 |
| Per-protocol group   | 20-4 (5-4-23-4)  | 15-2 (5-7-23-4)         | HR 0-92, 95% CI 0-71-1-18; p=0-49   |
| Total number of weekly o   | piold-negative urine   | samples, range 0-2      | 4                                   |
| Intention-to-treat group   | 4 (0-19)   | 10 (3-20)               | pc0-0001                            |
| Per-protocol group   | 13 (3-21)  | 11 (3-20)               | p-0-81                              |
| Total number of self-repor                                       | rted oploid-abstinen   | t days, range 0-144     | •                                   |
| Intention-to-treat group   | 39 (1-144)   | 81 (16-144)             | pc0-0001                            |
| Per-protocol group   | 123 (18-144)   | 87 (20-144)             | p-0-67                              |
| Oata are n (%), n/N (%), or med<br>OR-odds ratio. HR-hazard rati | The second secon | ended-release naitrex   | one. BUP-NX-buprenorphine-naloxone. |





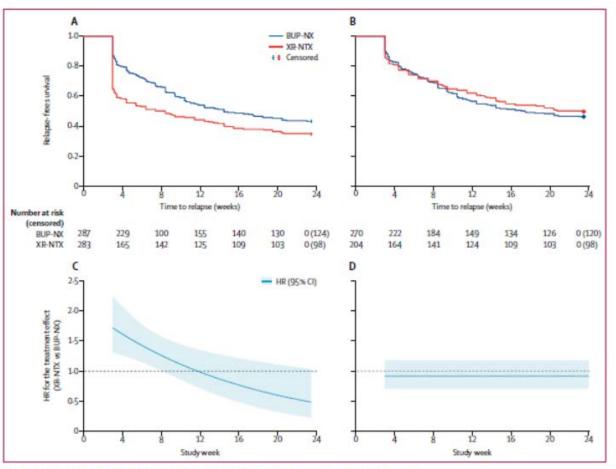


Figure 2: Relapse-free survival and treatment effect over time for the XR-NTX and BUP-NX treatment groups

Survival (A) and HRs and corresponding 95% Cis from the non-proportional hazards Cox model (time by treatment interaction included in the model; (C) assessed in the intention-to-treat population (n=570). Survival (B) and HRs by time (D) in the per-protocol population (n=474). XR-NTX=extended-release nailtrexone. BUP-NX=buprenorphine-nailoxone. HR=hazard ratio.

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial

Joshua D Lee, Edward V Nunes Jr, Patricia Novo, Ken Bachrach, Genie L Bailey, Snehal Bhatt, Sarah Farkas, Marc Fishman, Phoebe Gauthier, Candace C Hodqkins, Jacquie King, Robert Lindblad, David Liu, Abiqail G Matthews, Jeanine May, K Michelle Peavy, Stephen Ross, Dagmar Salazar,

Paul Schkolnik, Dikla Shmueli-Blumberg, Don Stablein, Geetha Subramaniam, John Rotrosen

Induction Failure in naltrexone arm led to relapse in 70 of 79 (89%)

Overdose events not statistically different, however study not powered for overdose

|   | XR-NTX group<br>(n=283) | BUP-NX group<br>(n=287) |
|---|-------------------------|-------------------------|
| Treatment-emergent adverse events                               |                         |                         |
| Participants with one or more treatment-emergent adverse event* | 111 (54%)               | 141 (52%)               |
| Number of treatment-emergent adverse events                     | 247                     | 334                     |
| Study medication discontinued due to adverse event              | 6                       | 8                       |
| Type of treatment-emergent adverse event                        |                         |                         |
| Injection site reaction, mild or moderate                       | 46                      | NA                      |
| Gastrointestinal  | 34                      | 59                      |
| Psychiatric disorders   | 30                      | 29                      |
| Injury, poisoning, and procedural complications                 | 23                      | 25                      |
| Infections and infestations                                     | 22                      | 27                      |
| Nervous system disorders  | 22                      | 28                      |
| Treatment-emergent serious adverse events                       |                         |                         |
| Participants with one or more serious adverse event             | 29 (14%)                | 29 (11%)                |
| Number of treatment-emergent serious adverse events             | 39                      | 35                      |
| Type of treatment-emergent serious adverse event                |                         |                         |
| Psychiatric disorders   | 9                       | 11                      |
| Infections and Infestations                                     | 5                       | 6                       |
| Pregnancy   | 3                       | 4                       |
| Death   | 3                       | 4                       |
| Overdose events   |                         |                         |
| Participants with one or more overdose event (all)†             | 15                      | 8                       |
| Participants with one or more overdose event (per protocol)‡    | 9                       | 7                       |
| Number of overdose events (all)§                                | 18                      | 10                      |
| Number of overdose events (per protocol)                        | 10                      | 9                       |
| Fatal overdose events   |                         |                         |
| Number of fatal overdose events (all)                           | 2                       | 3                       |
| Number of fatal overdose events (per protocol)                  | 2                       | 3                       |

Data are n (%) or N. NA-not applicable. XR-NTX-extended-release naltrexone. BUP-NX-buprenorphine-naloxone. 
\*Treatment emergent is defined as any adverse events that occurred after the study day of induction for those participants inducted onto study medication. †p=0.14 (Fisher's exact). †p=0.31 (Fisher's exact). Shour participants reported more than one overdose event. Three of the four participants were randomly assigned to XR-NTX (two of these induction failures, one successfully inducted); each reported two overdose events. One of the four was randomly assigned to BUP-NX (successfully inducted) and reported three overdose events. None of these nine overdoses were fatal.

Table 3: Adverse events and serious adverse events





#### SHORT COMMUNICATION



# Project Brown and the state of the state of

### Review of Case Narratives from Fatal Overdoses Associated with Injectable Naltrexone for Opioid Dependence

Roxanne Saucier<sup>1</sup> · Daniel Wolfe<sup>1</sup> · Nabarun Dasgupta<sup>2</sup>

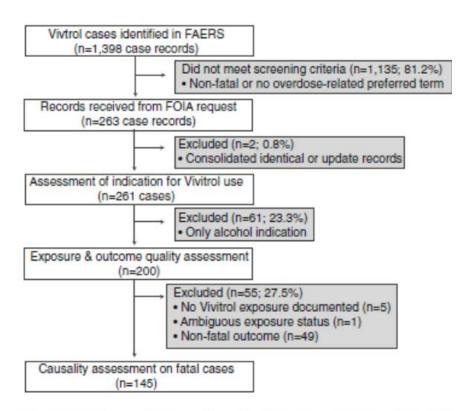


Fig. 1 Selection criteria schematic for case identification. The figure represents the selection criteria and major data processing steps for identifying case records involving Vivitrol as a primary suspect drug from the US Food and Drug Administration Advers Event Reporting System (FAERS), 1 October, 2010 through 3 March, 2016. FOIA Freedom of Information Act

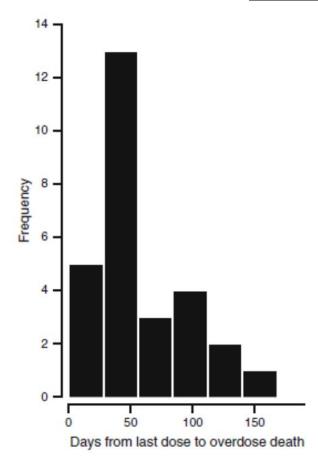


Fig. 3 Histogram of time from last known Vivitrol injection to opioid overdose death. Time to death was known for 28 out of 52 fatal overdose cases that were assessed for causality involving Vivitrol as a primary suspect drug from the US Food and Drug Administration Adverse Event Reporting System, 1 October, 2010 through 31 March, 2016. Bin width is 28 days because that is the labeled duration of effect





### Conclusions

- "Induction Hurdle" for naltrexone and high rate of relapse among induction failures
- However after induction both bupe/nal and xr naltrexone are similar
- Patient selection and ancillary supports to keep individuals engaged in care





# Questions?







• 12:35pm-12:55pm [20 min]

• 5 min: Presentation

• 2 min: Clarifying questions- Spokes (participants)

• 2 min: Clarifying questions – Hub

• 2 min: Recommendations – Spokes (participants)

• 2 min: Recommendations – Hub

• 5 min: Summary - Hub



Reminder: Mute and Unmute to talk
\*6 for phone audio



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

How can we help retain the patient in treatment? We would like for her to:

- 1. Give us negative urine screens
- 2. Take Suboxone as prescribed
- 3. Stay engaged in counselling
- 4. Make necessary lifestyle changes conducive to her recovery.

#### **Case History**

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

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

29 yr. separated, currently unemployed Caucasian female. Did not finish high school. No GED. Has 2 children but does not have custody. Lives with her father who drives a tow truck. Stays home much of the time.

She was referred to us for follow up from a local Psychiatric Hospital where she had been started on Suboxone for her opioid use disorder. She was on 8mg-2mg twice daily when she was initially enrolled into our OBOT program.





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

History of Hepatitis C. Reports she was treated with Harvoni last year and virus was eradicated. Has not had any follow ups since.

Psychiatric Diagnosis include Recurrent Major Depressive Disorder and Generalized Anxiety Disorder. Is prescribed Venlafaxine XR 225 mg daily, Buspirone 10 mg three times daily and Trazodone 200 mg bedtime for sleep.

#### Substance Use Disorder:

Started abusing heroin around age 16. Has been using intravenously for the most part. Has "speedballed" as well. Using on average about 4-5 bags of heron daily. Presently prescribed a total Suboxone dose of 18mg daily; 8mg-2mg BID and 2mg-0.5mg in the afternoon.

Has a history of snorting cocaine and also i.v. use.

Alcohol: started drinking liquor regularly in her late adolescence. This had escalated to approximately a fifth of rum daily for the last 2 years. Has reportedly significantly cut back on her drinking since starting OBOT.

Urine screens are done weekly and randomly. UDS is usually positive for Oxys, Opi, Methamphetamines, Cocaine or THC. She has denied using Crystal Meth or any amphetamine based stimulants. Denies using any OTC medications such as decongestants, etc.

2 weeks ago, Buprenorphine level was 1 ng/ml and Norbuprenorphine level was 5ng/ml. The cutoff on LC/MS is 0.5 ng/ml.

Last week, on a random drug screen, UDS was positive for THC, Coc, Methamphetamines, and Oxys. However, negative for Buprenorphine.

Has been enrolled in weekly SA groups. Attendance has been inconsistent.





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

Medication Assisted Treatment includes Suboxone. Total dose at present is 18 mg-4.5mg per day. Attends weekly. Is offered counselling every visit.

Has also been referred to Peer driven Recovery groups. Has also been urged to attend AA and NA meetings.

Recommendations have also been made for her to seek employment or volunteer work to stay busy and structured throughout the day.

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

Patient's stated goal earlier in the treatment was to pursue full recovery from all substances. However, during the entire period of treatment, her mood has been apathetic and attitude passive. Is praised and positive reinforcement offered whenever she tests negative for Opioids and Oxys.

- 1. She is now on a Behavioral contract. Must give negative urine screens by the end of 2 weeks, after which a second and final contract will be instituted.
- Increase counselling sessions to 2 per week.
- Possibly increase the Suboxone dose to 20mg-5mg daily. But inconsistent compliance with this medication, repeated use of other substances and possibility of diversion, make this the least preferred option at this time.
- 4. Referral to the Methadone program or Residential based services is another option if unsuccessful in completing the Behavioral contract. We do not at the present time have an IOP.





#### Other relevant information

States she sometimes skips Suboxone for up to three days at a time during which she will use heroin and other substances. On some occasions she will take more than the daily prescribed dose. Cannot explain why.

Denies any diversion. December last year, on an LC/MS confirmation, she was negative for Norbuprenorphine, but Buprenorphine was measured at 6.0 ng/ml. Cutoff is 0.5 ng/ml.

Is uninsured. On a time limited SAMHSA grant which could be extended if it is shown that she has been compliant with her treatment and making progress in her recovery goals.

Transportation is sometimes an issue.

Has provided Buprenorphine only positive screens on two occasions only. This was earlier in the treatment.

REMINDER: Please ensure that NO patient specific identifiable information (PHI) is included in this submission. Please read, sign, and click SUBMIT when completed.









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



Reminder: Mute and Unmute to talk
\*6 for phone audio



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

How to manage or engage a client with high SI and continued polysubstance use and failed treatment recommendations in MAT?

#### **Case History**

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

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

22 yr old white male originally born in Russia history of was adopted twice in Russia and returned before finally getting adopted and came to the US to live. Lived in Delaware till this year, moved with parents to Virginia was court ordered into Substance Abuse treatment. Resides with his parents lives in the county rural area, transportations often an issue has limited social support and limited peer interaction. When he has mentioned dating often dates older women; by 10 or 15 years his senior. Has significant history of abuse from childhood, has high school education some trade skill training, has worked as a firefighter in Delaware, now works as a tele marker. Receives Medicaid, has applied for disability.





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

Has genetic and environmental; birth defect was born in highest pollution area in Russia, born without a leg, very defensive over this, and hides this very well, for first 3 months staff was not aware of this and actually got his physical from a PCP without notice of this. His mother is a nurse and came in shared this information with staff. Client was told he has a traumatic Brain Injury from childhood by the orphanage in Russia, has paperwork with limited information about this, there was signification physical and sexual abuse prior to age of 3. Client current diagnosis F31.81 Bipolar II disorder, F90.2 Attention-deficit.hyperactivy disorder combined presentation; F42.2 Obsessive-compulsive disorder; F11.20 Opioid dependence, F12.1 cocaine, abuse. Client has had individual therapy in the past, stated, "It doesn't help it's pointless". Client has SI daily and presents flat and struggles to find hope daily, client struggles to engage in groups or therapy, clients fights treatment and often is his own barrier to success and has insight to see this, but struggles to overcome this. Client has had multiple positive UDS screens 2-4-19 \_ + BUP, + AMP ( takes VAYVANSE) + THC 1-7-19 + BUP + COC + THC MEDS: Suboxone 8 mg 2 mg SL place 2 film SL g D

Rexulti 0.5 mg tab 1 po q am (took himself off this reported on 2-11-19) Seroquel 200 mg tab 1 po g HS

VYVANSE 50 mg 1 po q AM





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

Client was started on MAT 4-5-18, client is seen weekly and has been weekly since starting treatment due to non compliance with treatment and continue positive UDS for THC, COC. Client was recommended for IOP did not engage, Client was referred for Individual therapy did not engage, Client was talked to after repeated positive UDs screens, discussed psych med management, linked to a PCP for PX medically cleared. Client reported struggling with focus started on VAYAVSE. Client reported stressors of girlfriend and recent abortion as trigger for COC use, client has not relapsed on heroin during this time clients drug of choice is heroin. Client reports that it is a struggle daily to feel anything, a struggle daily to find a reason to keep going. Client continues to come weekly for MAT and Case Management.

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

Client is seen weekly for Case management
Client is seen weekly for OBOT MAT
Client is seen for psych med management to monitor his SMI
refer to therapy as needed
continues to asses client's willingness and motivation for therapy and link to services as client is ready to engage.





#### Other relevant information

Client present with SI daily, client has made significant progress in that he come to office weekly, he engages with Case manager and OBOT MD he talks with both for 20 mins each, weekly he is open and honest about his use and has reached a point of trust in that he listens openly to feedback from both. Case manager weekly redirects and encourages client to consider therapy and we discuss the importance and value of therapy and why it would help the client move past some of his issues that might beholding him back. Client has complied with every demand and treatment recommendation even if he has not fully engaged in the process. He did go to the therapy appointments that where required, he just did not engage and then he missed and cancelled several of them before being disagreed. Client continues to use COC and THC on occasion as coping skills.

REMINDER: Please ensure that NO patient specific identifiable information (PHI) is included in this submission. Please read, sign, and click SUBMIT when completed.







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  - Overall feedback related to session content and flow?
  - Ideas for guest speakers?





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To claim CME credit for today's session







### **Virginia Opioid Addiction ECHO**



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

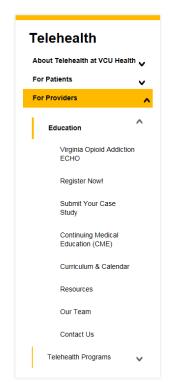


#### Network, Participate and Present

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- · Listen, learn, and discuss didactic and case presentations in real-time
- Take the opportunity to <u>submit your de-identified study</u> for feedback from a team of addiction specialists.
- Provide <u>valuable feedback & claim CME credit</u> if you participate in live clinic sessions.

#### **Benefits**

- · Improved patient outcomes.
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  recording and claim credit.









| ♦ https://redcap.vcu.edu/surveys/?s=KNLE8PX4LP | Project ECH  | 10 Survey ×                            |       | <del></del> |
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| Virgins Common Units                           | noonwallb<br>only<br>ase help us serve you better and learn more about your nee<br>Addiction ECHO (Extension of Community He | eds and the value of the Virginia Opio | id    |             |
|  | First Name  * must provide value   |  |       |             |
|  | Last Name * must provide value   |  |       |             |
|  | Email Address * must provide value   |  |       |             |
|  | I attest that I have successfully attended the ECHO Opioid Addiction Clinic.  * must provide value                           | Yes                                    |       |             |
|  | * must provide value   | No                                     | reset |             |
|  | , learn more about Project ECHO  Watch video   |  |       |             |
|  | How likely are you to recommend the Virginia Opioid Addiction ECHO by VCU to colleagues?                                     | Very Likely                            |       |             |
|  |  | Likely                                 |       |             |
|  |  | Neutral                                |       |             |
|  |  | Unlikely                               |       |             |
|  |  | Very Unlikely                          | reset |             |
|  | What opioid-related topics would you like addressed in th  | ne future?                             |       |             |
|  | What non-opioid related topics would you be interested in  | 1?                                     |       |             |

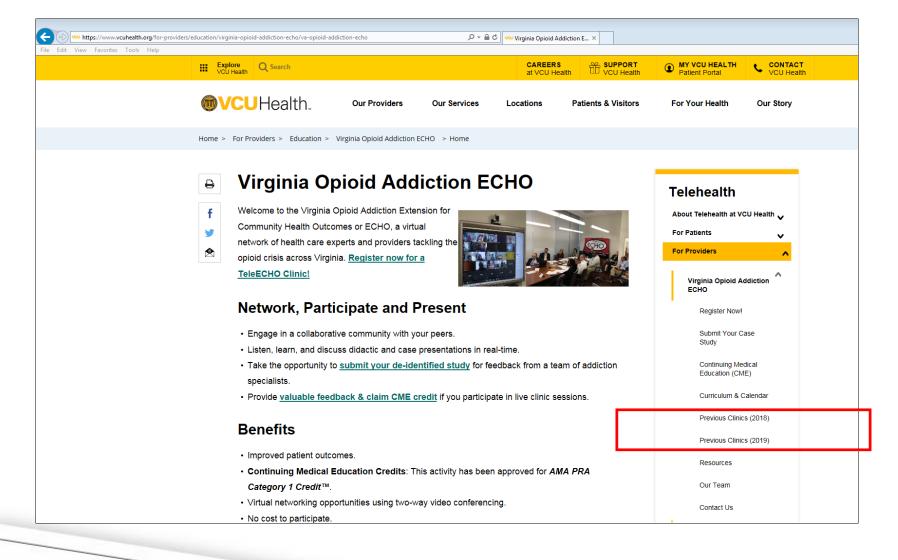




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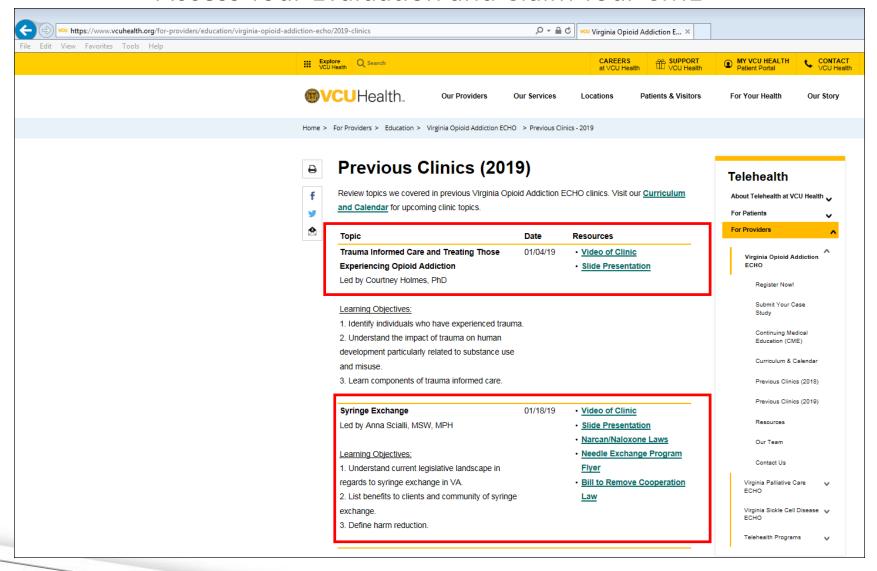
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### VCU Virginia Opioid Addiction TeleECHO Clinics

Bi-Weekly Fridays - 12-1:30 pm

### **Mark Your Calendar --- Upcoming Sessions**

03/01 Pharmacotherapy for Co-Occuring SUD Gerard Moeller, MD

03/15 Policy with Maternal Substance Use Disorder Valerie L'Herrou, JD

Please refer and register at <u>vcuhealth.org/echo</u>





### THANK YOU!



Reminder: Mute and Unmute to talk
\*6 for phone audio

Use chat function for questions

#### **Resource Materials**

Review of Case Narratives from Fatal Overdoses Associated with Injectable Naltrexone for Opioid Dependence

Authors: Roxanne Saucier, Daniel Wolfe, Nabarun Dasgupta

https://doi.org/10.1007/s40264-018-0653-3

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial Author: Dr. Joshua Lee, et al

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5806119/