Methamphetamine Use Disorder: Getting Up to Speed on Trends & Treatments
Methamphetamine Use Disorder

Robrina Walker, PhD

• Associate Professor, Dept. of Psychiatry, U Texas Southwestern Medical Center

• Helped lead CTN Texas Node
  • Co-Lead Investigator of CTN-0068
  • Co-Investigator of CTN-0090

• Co-Investigator of the COMEBACK study
Methamphetamine Use Disorder: Getting Up to Speed on Trends and Treatments

Robrina Walker, PhD
Associate Professor
University of Texas Southwestern Medical Center

February 25, 2020
Disclosures

- Alkermes: Provided injectable extended-release naltrexone (Vivitrol®) for CTN-0054 ADAPT-MD
- Alkermes: Provided injectable extended-release naltrexone (Vivitrol®) and matched injectable placebo for CTN-0068 ADAPT-2

Funding

- NIDA UG1 DA020024 (PI: Trivedi)
- NIDA R34 DA045592 (PI: Nijhawan)
Opioids are a Huge and Necessary Focus...

Why fentanyl is deadlier than heroin, in a single photo

By ALLISON BOND / SEPTEMBER 29, 2016

On the left, a lethal dose of heroin; on the right, a lethal dose of fentanyl.

NEW HAMPSHIRE STATE POLICE FORENSIC LAB

April 3, 2018 -- With the nation still reeling from the opioid crisis, drug forecasting experts say a new wave of addiction is coming and the United States isn’t ready for it.

Abuse of stimulants like methamphetamine, cocaine, and even prescription drugs like Adderall and Ritalin is surging across the country, fed by cheap, potent, and plentiful supplies.

“No one is paying attention to this,” said John Eadie, coordinator for the National Emerging Threat Initiative, which provides research to the government’s High Intensity Drug Trafficking Areas program.

Experts Warn of Emerging ‘Stimulant Epidemic’

By Brenda Goodman, MA

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“No one is paying attention to this,” said John Eadie, coordinator for the National Emerging Threat Initiative, which provides research to the government’s High Intensity Drug Trafficking Areas program.

“Everyone, correctly, is focused on opioids and should be because of the known problem there. But this other problem is catching up with us very rapidly.”

April 3, 2018 -- With the nation still reeling from a new wave of addiction, a new problem is on the horizon. Abuse of stimulants like methamphetamine, cocaine, and Ritalin is surging across the country, fed by a lack of attention to this issue.

"No one is paying attention to this," said John E. Donnelly, director of the DEA's Threat Initiative, which provides research to the DEA's High Intensity Areas program.

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Gay Men Are Dying From a Crisis We’re Not Talking About

No one’s really grappling with the meth disaster.

By Jim Mangia
Mr. Mangia runs a network of community health centers in Los Angeles.

Jan. 22, 2020
Gay Men Are Dying From a Crisis We’re Not Talking About

No one’s really grappling with the meth disaster.

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Mr. Mangia runs a network of community health centers in Louisiana.

Jan. 22, 2020

HEALTH
Arkansas leads U.S. in meth use, study finds

(Source: AP)
Objectives

1. Describe trends in the use of methamphetamine
2. Describe evidence-based treatments for methamphetamine use disorder
3. Summarize current research investigating new treatments for methamphetamine use disorder
What is Methamphetamine?

- **Forms:**
  - Powder – speed; low to medium potency
  - Crystallized – crystal, glass, ice; high potency

- **Routes of administration:**
  - Smoked (most common route), injected (near-immediate euphoria)
  - Ingested, snorted
  - Dissolved sublingually, taken rectally, solubilized and consumed as a liquid
  - Long half-life (8-12 hours intranasal, oral)

Figure 70. Methamphetamine Purity and Potency.

Source: DEA Methamphetamine Profiling Program

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Purity is defined as a measure of the amount of an illicit substance present in a sample compared to other substances in the sample such as adulterants, diluents, or solvents.

Potency is defined as the measure of drug activity in terms of the dosage required to exert an effect on the body and is measured by the amount of the highly potent d-isomer present in the drug substance.

Why Methamphetamine?

- It’s a stimulant!

- Reinforcing effects:
  - eliminates fatigue, decreases appetite, focuses attention,
  - euphoria, elevated mood,
  - loss of inhibition, heightens libido

<table>
<thead>
<tr>
<th>Psychiatric</th>
<th>Neurologic</th>
<th>Cardiac</th>
<th>Other Physiological</th>
</tr>
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<td>Cardiomyopathy</td>
<td>Hyperthermia</td>
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Who?

Populations disproportionately at risk:

- Justice-involved individuals
  - Impulsive behavior, violent crime (high homicide rates), psychosis
- Women
  - Often start using for weight loss/increased energy to get things done/self-treatment of mental health problems; target of violence
- MSM
  - Injection or non-injection, risky sexual behaviors and HIV

Stimulants Fuel High-Risk Sexual Behavior

- Stimulants particularly associated with behaviors high-risk for HIV
  - Meth: heighten sexual impulses/desires/pleasure, increase energy, poor decision making, & disinhibition - increase probability of high-risk sexual behavior
- “Chemsex” – using specific drugs before/during sex to facilitate, prolong, sustain, or intensify experience and reduce inhibitions
  - Often: stimulant (meth or mephedrone) + GHB, poppers, erectile dysfunction meds (eg, sildenafil, tadalafil, vardenafil)
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- Among “non-heterosexual” individuals [(gay, lesbian, bisexual) and MSM], extensive literature on meth use associated with high-risk sexual behavior:
  - Frequency of unprotected anal sex
  - Inconsistent condom use
  - Frequency of sex with multiple partners
  - HIV infection

MSM, Meth, and HIV

- MSM have **28X higher risk acquiring HIV than heterosexual men**...HIV risk factors for this group?

- N=4684 HIV-negative high-risk MSM, 18-60yo, 1998-2002, 47 U.S. cities, HIV vaccine efficacy RCT that included HIV risk reduction counseling, followed 36 months, **excluded MSM who reported injection drug use**:

  - Use of amphetamines (aHR=1.6) linked to significantly higher risk of acquiring HIV
  - Other significant risk factors:
    - Use of amyl nitrates (poppers) (aHR=1.7)
    - 18-30yo (aHR=2.4),
    - >10 sex partners in last 6 months (aHR=2.4),
    - >1 HIV-pos partner (aHR=1.6),
    - Unprotected anal intercourse with HIV-pos/unknown partner (aHR=1.7)

Use of club drugs, particularly **methamphetamine**, is associated with high-risk sexual behaviors and increased HIV incidence among MSM.


High-Risk Sexual Behavior

- Among heterosexuals who **use** meth (compared to **non-users**):
  - 37% to 72% more likely to engage in high-risk sexual behaviors
    - Unprotected vaginal intercourse (1.37 OR)
    - Unprotected anal intercourse (1.52 OR)
    - Inconsistent condom use (1.72 OR)
  - Fast-Lane intervention – promising (reduced unprotected sex, increased protected sex) but high attrition (Mausbach et al 2007)
High-Risk Sexual Behavior

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  - 37% to 72% more likely to engage in high-risk sexual behaviors:
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    - Unprotected anal intercourse (1.52 OR)
    - Inconsistent condom use (1.72 OR)
  - Fast-Lane intervention – promising (reduced unprotected sex, increased protected sex) but high attrition (Mausbach et al 2007)

- Among heterosexuals who use meth (compared to times when not using):
  - Doubled odds of being sexually active when using meth (1.9 OR)
  - When sexually active, more likely to have:
    - Multiple partners (3.3 OR) and casual partners (3.9 OR),
    - Condomless sex with casual partners (2.6 OR)

Supply Side: Meth Availability
Manufacturing and Control of Meth

Figure 1: U.S, Canada and Mexico Federal PSE Regulations

<table>
<thead>
<tr>
<th>Year</th>
<th>Regulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>United States: Required dealers to register with DEA.</td>
</tr>
<tr>
<td>1996</td>
<td>United States: Prior regulations to include OTC and made Schedule II drugs.</td>
</tr>
<tr>
<td>2000</td>
<td>United States: Limit to 9 grams per transaction. Package size limit to 3 grams.</td>
</tr>
<tr>
<td>2003</td>
<td>Canada: Require license to import, export, produce, package, transport, sell and provide.</td>
</tr>
<tr>
<td>2005</td>
<td>United States: Limit sales to 3.6 grams per customer per day and 9 grams per customer per month. Requires OTC and logbook.</td>
</tr>
<tr>
<td>2005</td>
<td>Mexico: Limit importation and increase inspections at ports.</td>
</tr>
<tr>
<td>2006</td>
<td>Canada: Made single entity PSE a schedule II drug, only sold in pharmacies behind the counter.</td>
</tr>
<tr>
<td>2006</td>
<td>Mexico: Require pharmacies to limit sales and keep logbooks.</td>
</tr>
<tr>
<td>2007</td>
<td>Mexico: Require a prescription.</td>
</tr>
<tr>
<td>2008</td>
<td>Mexico: PSE and ephedrine banned from the country.</td>
</tr>
<tr>
<td>2010</td>
<td>United States: Retailers self-certify. Distributors only sell to DEA registered retailers.</td>
</tr>
</tbody>
</table>

Global quantity of amphetamine-type stimulants seized, 1998–2017

Methamphetamine Seizures Worldwide

Global quantity of amphetamine-type stimulants seized, 1998–2017

Seizures in N. America = Meth

**FIG. 28** Distribution by substance of the average annual quantity of amphetamine-type stimulants seized, by subregion, 2013–2017

Source: UNODC, responses to the annual report questionnaire.
Seizures in N. America = Meth

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Source: UNODC, responses to the annual report questionnaire.
Customs Intercepts $12M in Meth at Border

The methamphetamine was smuggled inside a truck carrying frozen strawberries from Mexico, CBP says.

By Megan Trimble, Digital News Editor  Feb. 20, 2019

Packages containing 905 pounds of methamphetamine seized by Customs and Border Patrol officers at the Pharr-Reynosa International Bridge cargo facility in Texas. (COURTESY OF CBP HIDALGO)

U.S. seizes record 3,800 pounds of meth intended for Australia

Authorities said the seizure would have a noticeable impact on the worldwide meth market.
February 20, 2020

Contact: National Media Affairs Office
Phone Number: (202) 307-7977

DEA announces launch of Operation Crystal Shield

Efforts will focus on main U.S. methamphetamine trafficking transportation hubs

Increase in Methamphetamine Seizures
2018 - 2019

Map of US with eight hub cities for Operation Crystal Shield

Demand Side: Drug Use Data
Annual prevalence of use of drugs in 2017 (or latest year available)

Annual Prevalence Rate Fairly Stable

FIG. 52 Methamphetamine use among the population 12 and older in the United States, 2002–2017

Reminder
Prevalence = number of cases in a population at a given time

Source: SAMHSA, National Survey on Drug Use and Health (different years).
Note: Owing to changes in the questionnaire in 2015, the trends between 2002 and 2014 and 2015 and 2017 are not comparable.
Methamphetamine Use: Significant Increase in Adults >26yo

PAST YEAR, 2015-2018 NSDUH, 12+

+ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.
FIG. 53  Methamphetamine use and non-medical use of prescription stimulants among young people aged 18–25 in the United States by sociodemographic characteristics, 2017

Ever used Methamphetamines, 2017

METH USE IN U.S. HIGH SCHOOL STUDENTS, BY SEX AND SEXUAL IDENTITY

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Gay, lesbian, bisexual</td>
<td>12%</td>
<td></td>
<td>14%</td>
</tr>
<tr>
<td>Identity: Not sure</td>
<td>14%</td>
<td>12%</td>
<td>13%</td>
</tr>
</tbody>
</table>

CDC Youth Risk Behavior Surveillance 2017.
https://www.cdc.gov/healthyyouth/data/yrbs/2017_tables/alcohol_and_drug_use.htm#t121_down
Treatment Data
FIG. 4  Trends in the primary drug of concern in drug treatment admissions, by region, 2003, 2009 and 2017

Source: UNODC, responses to the annual report questionnaire.
Meth Surpasses Cocaine Treatment Admissions in U.S.

Figure 1. Primary substance use at admission: 2007–2017

SOURCE: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through 11.21.18.
Methamphetamine Use by State

National Survey on Drug Use and Health 2018.

Differences in colors across states do not indicate significant differences in estimates.
Primary Methamphetamine Admissions by Census Region

Admissions per 100,000 population > 12 years old

Years:

Northeast  South  Midwest  West

FIG. 54  Methamphetamine use among people in the United States with opioid use disorders who were entering treatment, 2011–2017

Drugs Most Frequently Involved in Overdose Deaths

Figure 4. Age-adjusted drug overdose death rates, by opioid category: United States, 1999–2017

(Hedegaard et al. National Vital Statistics Reports. 2018. 67(9).
Hedegaard et al. National Vital Statistics Reports. 2019. 68(12.).

Yearly Rank of Fentanyl Involved Deaths:

<table>
<thead>
<tr>
<th>Year</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>10</td>
</tr>
<tr>
<td>2012</td>
<td>9</td>
</tr>
<tr>
<td>2014</td>
<td>5</td>
</tr>
<tr>
<td>2015</td>
<td>2</td>
</tr>
<tr>
<td>2016</td>
<td>1</td>
</tr>
<tr>
<td>2017</td>
<td>1</td>
</tr>
</tbody>
</table>
Drugs Most Frequently Involved in Overdose Deaths

Yearly Rank of **Fentanyl** Involved Deaths:
- 2011: 10
- 2012: 9
- 2014: 5
- 2015: 1
- 2016: 1
- 2017: 1

Yearly Rank of **Meth** Involved Deaths:
- 2011: 8
- 2013: 7
- 2015: 4
- 2016: 4
- 2017: 4

Drug overdose deaths by region

Methamphetamine was the top drug involved in overdose deaths in most of the western half of the U.S. while fentanyl pervaded the eastern half.

NOTE: Data from 2017. Deaths may include additional drugs.
SOURCE: NCHS National Vital Statistics System

Top 3 drugs most frequently involved in drug overdose deaths within each region, age-adjusted rate of overdose deaths per 100,000 people; obtained from Hedegaard et al. National Vital Statistics Reports. 2019. 68(12).
Summary of Trends

✓ Meth availability seems to be increasing, with high purity & decreased price

✓ Reports of recent use appear stable, but some groups affected more than others

✓ Treatment admissions rising
  ✓ Increases in meth use among people in tx for OUD, especially in western US, urban/suburban settings, and women

✓ Meth is becoming involved in more overdose deaths
  ✓ Heroin and fentanyl are involved in some overdose deaths attributed to meth
Factors Related to Treatment Outcomes

ASSOCIATED WITH SUCCESSFUL OUTCOMES

• Lower levels of meth use at admission (<15 days out of previous 30)
• Shorter history of meth use (<2 years)
• Retained in treatment for >90 days
• >3 consecutive weeks of abstinence during treatment

ASSOCIATED WITH POOR OUTCOMES

• Continued meth use during treatment
• Injection use
• < High school education
• Young age at admission
• Having a disability
• Polydrug use
• Childhood trauma and abuse
• Having an underlying psychiatric disorder

Keeping Patients who use Meth in Tx is Difficult

- 2019 meta-analysis of dropout rates of in-person psychosocial SUD tx
  - Dropout from treatment is a robust predictor of relapse
  - Meta-analysis aimed to estimate average dropout rates and potential predictors of dropout from in-person psychosocial SUD tx
    - If know what can predict dropout, perhaps can intervene
  - Analyzed 151 studies of in-person psychosocial SUD tx
  - Average dropout rate from all studies and all study arms was 30.4% but varied widely with population, drug of abuse, and treatment characteristics.
    - Dropout rates were highest for studies targeting cocaine, methamphetamine, all stimulants; lowest for alcohol, tobacco, heroin. But there were few studies on meth, all stimulants, and heroin.
    - Programs with more treatment sessions and greater average session length associated with higher dropout rates.

Clinical guidelines recommend psychosocial interventions as first-line treatment.

But *which* psychosocial treatment?

50 RCTs evaluating 12 psychosocial interventions (vs. TAU or active control) in 6,942 ppts.

- Outcomes: abstinence based on negative UDS, acceptability based on retention, longest duration of abstinence.
- Time points: end of treatment, 12 weeks, long-term outcome.

A: CM + Community Reinforcement

- **Contingency Management**
  - Behavioral approach
  - Contingently rewards drug-free urine samples

- **Community Reinforcement Approach**
  - Multi-layered and comprehensive behavioral intervention package
  - Functional analysis, coping-skills training, and social, familial, recreational, vocational reinforcements

Goals / Needs:

1. Medications that counteract specific acute intoxication effects
2. Medications that help initiate abstinence
3. Medications that prolong abstinence
Pharmacotherapy

- Existing FDA approved medications for all SUDs is extremely limited
  - YES: Alcohol, nicotine, opioid use disorders
  - NONE: Cannabis, cocaine, methamphetamine, etc.

<table>
<thead>
<tr>
<th>Substance and Medication</th>
<th>FDA Approval</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>Methadone</td>
<td>Treatment of opioid dependence</td>
<td>μ-Opioid receptor agonist</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Treatment of opioid dependence</td>
<td>μ-Opioid receptor partial agonist</td>
</tr>
<tr>
<td>Extended-release naltrexone</td>
<td>Treatment of opioid dependence</td>
<td>μ-Opioid receptor antagonist</td>
</tr>
<tr>
<td>Lofexidine</td>
<td>Treatment of opioid withdrawal</td>
<td>α2A-Adrenergic receptor agonist</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Reversal of opioid overdose</td>
<td>μ-Opioid receptor antagonist</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Treatment of alcohol dependence</td>
<td>NMDA antagonist, GABA-A allosteric modulator</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Treatment of alcohol dependence</td>
<td>μ-Opioid receptor antagonist</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Treatment of alcohol dependence</td>
<td>Acetaldehyde dehydrogenase inhibitor</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Used off-label to treat alcohol dependence</td>
<td>Unknown; increases GABA concentration</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Used off-label to treat alcohol dependence</td>
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<tr>
<td>Nicotine</td>
<td></td>
<td></td>
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<tr>
<td>Nicotine replacement therapy</td>
<td>Nicotine cessation</td>
<td>Nicotinic acetylcholine receptor agonist</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Nicotine cessation</td>
<td>α4β2 Nicotinic acetylcholine receptor antagonist</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Nicotine cessation</td>
<td>Dopamine and norepinephrine transporter blocker</td>
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*AMPAs=α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; FDA=U.S. Food and Drug Administration; GABA=γ-aminobutyric acid; NMDA=N-methyl-D-aspartate.*

### Medications Previously Evaluated

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<td>Methylphenidate</td>
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<td>Bupropion</td>
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Recent Atomoxetine Data

- Atomoxetine – selective norepinephrine reuptake inhibitor, for ADHD
- RCT for patients with OUD + methamphetamine use disorder
  - N=69 males (n=33 atomoxetine, 33 placebo), all received buprenorphine
  - Proportion of stimulant-negative UDS: significantly higher in atomoxetine group
  - Proportion of days abstinent: both groups significantly increased
- Tolerated, safe, some potential efficacy in population of OUD treated with buprenorphine

Recent Mirtazapine Data

Mirtazapine – antidepressant

M1.0 Study, Phase 2a trial
- N=60 MSM (30 to mirtazapine, 30 to placebo), 12 weeks, included 30 minute SUD counseling
- Reduced relative risk of meth use by more than 40% (RR=0.57), significantly reduced many sexual risk behaviors
- Adherence 48.5% by MEMS

Proportion of meth-positive UDS

Recent Mirtazapine Data

Mirtazapine – antidepressant

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- Adherence 48.5% by MEMS

M2.0 Study
- N=120 MSM (born as or identify as men) (60 to mirtazapine, 60 to placebo), 24 weeks, included 30 minute SUD counseling
- Reduced relative risk of meth use by more than 30% (RR=0.67), significantly reduced many sexual risk behaviors
- Adherence 38.5% by WisePill


Proportion of meth-positive UDS

UT Southwestern Medical Center
Current Research
Background

- Independent clinical utility of each medication for treatment of meth use disorder

- **Naltrexone** appears to:
  - Reduce reinforcing effects of amphetamine (Jayaram-Lindstrom et al., 2008)
  - Decrease craving (Ray et al., 2015)

- **Bupropion** (typically 300mg/day) appears to:
  - Reduce cue-craving (Newton et al., 2006)
  - Decrease MA use (Elkashef et al., 2008)

- Combination medication
  - One allows other to exert an effect
  - One enhances effect of another
  - Synergy between the two

Utilizing a Two-stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-daily Bupropion as a Treatment for Methamphetamine Use Disorder

Larissa J. Mooney, MD, Maureen P. Hillhouse, PhD, Christie Thomas, MPH, Alfonso Ang, PhD, Gaurav Sharma, PhD, Garth Terry, MD, PhD, Linda Chang, MD, Robrina Walker, PhD, Madhukar Trivedi, MD, David Croteau, MD, Steven Sparenborg, PhD, and Walter Ling, MD

Baseline Characteristics (N=49) % or M (SD)

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<tr>
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<td>53.1%</td>
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<tr>
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<td>39.9 (10.76)</td>
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<tr>
<td>White</td>
<td>49.0%</td>
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<tr>
<td>Hispanic</td>
<td>30.6%</td>
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<tr>
<td>High school or some college</td>
<td>63.3%</td>
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<tr>
<td>Never married</td>
<td>61.2%</td>
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<tr>
<td>Unemployed</td>
<td>49.0%</td>
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<td>METH use days prior to consent</td>
<td>27.0 (3.44)</td>
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FIGURE 2. Percentage methamphetamine-negative urine drug screen by responder status by study week. The proportion of MA-negative urines was significantly higher at each week for weeks 2 to 8 for the responder group as compared with the nonresponder group (P = 0.05). MA indicates methamphetamine.

CTN-0054 ADAPT-MD

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11 of 49 (22%) met “responder” definition → development of CTN-0068 ADAPT-2 trial


Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder

FIGURE 2. Percentage methamphetamine-negative urine drug screen by responder status by study week. The proportion of MA-negative urines was significantly higher at each week for weeks 2 to 8 for the responder group as compared with the nonresponder group (P = <0.05). MA indicates methamphetamine.
Oral Medication Adherence via Video Observed Therapy

Medication Adherence Monitoring Using Smartphone Video Dosing in an Open-label Pilot Study of Monthly Naltrexone Plus Once-daily Bupropion for Methamphetamine Use Disorder: Feasibility and Acceptability

Robrina Walker, PhD, Maureen Hillhouse, PhD, Brian Perrochet, BA, Steven Sparenborg, PhD, Larissa Mooney, MD, and Walter Ling, MD

**Likely Benefits of Providing Smartphones**

- Objective numerical indicator of lowest possible adherence rate
- Means to incentive valid dosing videos
- Reliable method of ppt contact
- Tangible reminder of study participation
- Smartphone calendar used for visit reminders
- Fostered retention because ppts could keep smartphones

Data provide low to high range of adherence rates

CTN-0068 ADAPT-2: Accelerated Development of Additive Pharmacotherapy Treatment for Methamphetamine Use Disorder

Funded by NIDA UG1DA020024
Primary Aim:
- Assess efficacy of extended-release injectable naltrexone (380 mg) + extended release oral bupropion (450 mg) as combination pharmacotherapy for methamphetamine use disorder

Secondary Aims:
- Assess safety
- Assess efficacy on other SUD outcomes, depression symptom scores, quality of life ratings
ADAPT-2 Study Design & Schema - Masked

- Double-blind, randomized, placebo-controlled, sequential parallel comparison design
- N = 403 in 8 sites
- Key Inclusion Criteria:
  - DSM-5 moderate or severe stimulant use disorder, methamphetamine type
  - Self-report using meth on most days in month prior to consent (>18/30)
  - Fairly healthy
  - No concurrent addiction treatment
- Medication Phase
  - AMC: 450 mg bupropion (dispensed weekly) and XR-NTX every 3 weeks
  - PLB: matched oral and injectable
  - Re-randomization may occur

dela Cruz et al. 2018. Rationale for combination XR-Naltrexone and bupropion XL for methamphetamine use disorder. CPDD, San Diego, CA.
Study Schema - Unmasked

Randomization

Active Medication Combination (AMC)*

- Pharmacotherapy: PLB Injections: Weeks 1 & 4
- PLB Oral: Daily

AMC Responders & Non-Responders

- AMC*
  - Pharmacotherapy: Naltrexone Injections: Weeks 7 & 10
  - Bupropion Oral: Daily

Placebo (PLB)*

- Pharmacotherapy: PLB Injections: Weeks 1 & 4
- PLB Oral: Daily

PLB Responders

- PLB*
  - Pharmacotherapy: PLB Injections: Weeks 7 & 10
  - PLB Oral: Daily

PLB Non-Responders

- Randomization

PLB*

- Pharmacotherapy: PLB Injections: Weeks 7 & 10
- PLB Oral: Daily

AMC*

- Pharmacotherapy: Naltrexone Injections: Weeks 7 & 10
- Bupropion Oral: Daily

*Also includes the following:
  - Clinic Visits: Twice weekly
  - Medical Management: Once weekly
  - Medication Adherence: Video dosing confirmation
ADAPT-2 Primary Outcomes

- **Primary efficacy outcome measure**
  - Methamphetamine negative UDS results in Medication Phase (AMC vs PLB), in the ITT population
  - "Responder": At least 3 Meth negative UDS (of possible 4), per Stage
    - Stage 1 evaluation period: Weeks 5 and 6
    - Stage 2 evaluation period: Weeks 11 and 12

- **Primary safety outcomes**: Adverse Events and Serious Adverse Events
<table>
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<th>Safety Measures</th>
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<td>▪ Adverse Events</td>
<td>▪ Urine Drug Screen</td>
</tr>
<tr>
<td>▪ Physical examination</td>
<td>▪ Timeline Followback</td>
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<tr>
<td>▪ Electrocardiogram</td>
<td>▪ Visual Analog Craving Scale</td>
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<tr>
<td>▪ Injection Site Examination</td>
<td>▪ Patient Health Questionnaire-9</td>
</tr>
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<td>▪ Clinical Laboratory Tests</td>
<td>▪ Quality of Life</td>
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<tr>
<td>▪ Concise Health Risk Tracking</td>
<td>▪ Treatment Effectiveness Assessment</td>
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<tr>
<td>▪ Urine Pregnancy Test</td>
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Adherence Measures

- Study Medication Dosing Logs (self-report + staff observation)
- Injection Administration Form (staff observation)
- Oral Study Medication Blood Levels (prior to each injection)
- Video observed therapy via AiCure app (daily)
Western States Node:
- Portland, OR - CODA, Inc.
- San Francisco, CA - SF Dept. of Public Health

Texas Node:
- Los Angeles, CA - UCLA Vine Street Clinic
- Dallas, TX - UT Southwestern
- Houston, TX - UTHealth Center for Neurobehavioral Research on Addiction

Northstar Node:
- Minneapolis, MN - Hennepin Healthcare/Berman Center for Research Outcomes

Southern Consortium:
- Pickens, SC - Behavioral Health Services

Greater New York Node:
- New York, NY - Columbia/NY State Psychiatric Institute
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Texas Node
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Angela Casey-Willingham
Kathy Shores-Wilson, PhD

UCLA
Walter Ling, MD

Clinical Coordinating Center (CCC)
Bob Lindblad, MD
Eve Jelstrom
Matthew Wright
Prashanth Parmar

Data & Statistics Center (DSC)
Gaurav Sharma, PhD
Paul Van Veldhuisen, PhD
Lauren Yesko
Anne Hoehn
Cathryn Mudrick
Ashley Case

NIDA CCTN
Udi Ghitza, PhD
With less than a month to go in the study’s 12-week drug regimen, Kim reports significant progress. She says she still uses some, but she’s down to once a week or once every other week, usually just when friends with meth show up. She recently told her old dealer not to come around any more.

“I used to really chase it, but now I don’t have those cravings,” says Kim, who’s been in rehab four times and to prison because of meth twice.

“I’m not all the way there yet,” she said, “but I don’t need to stay in bed for days at a time.”
Thank you!