Introduction

- The speaker is an employee of Pear Therapeutics®. Information provided constitutes scientific exchange, including information on:
  - reSET® an FDA-authorized prescription digital therapeutic for Substance Use Disorder (SUD) intended to provide cognitive behavioral therapy (CBT) as an adjunct to a contingency management system, for patients 18 years of age and older who are currently enrolled in outpatient treatment under the supervision of a clinician
  - reSET-O® an FDA-authorized prescription digital therapeutic (PDT) for Opioid Use Disorder (OUD) intended to increase retention of patient in outpatient treatment by providing cognitive behavioral therapy (CBT), as an adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management, for patient 18 years of older who are currently under the supervision of a clinician.
- This presentation is not intended to provide medical advice. There are no data on the use of reSET® or reSET-O® in the incarcerated population.

Dr. Audrey Kern, MD, FASAM
Global Medical Director, SUD/OUD
Pear Therapeutics®
## Agenda | Today’s Goal and Discussion Topics

### Today’s Agenda

- Introduction
- The Unmet Medical Need in the Incarcerated Population
- Barriers to treatment for Substance Abuse in this population
- Evidence Based Approaches for Effective Treatment
- Prescription Digital Therapeutics
- Clinical Data

### Today’s Goal

Understand the potential utility of Prescription Digital Therapeutics for substance use disorder and opioid use disorder in individuals with a history of incarceration
Unmet Medical Need in Substance Abusing Offenders in the Criminal Justice System

- Offenders engage in disproportionately high rates of substance use while in the community.

- **53% of state and 45% of federal prisoners meet criteria for a Substance Use Disorder** compared with only 3% of the general U.S. population\(^1\)

- **83% of prisoners report lifetime drug use and more than two thirds report regular use**\(^1\)

- **50% of male and 33% of female inmates** with Substance Use Disorders **require substance abuse treatment services** in prison; However, the best available estimates show that while incarcerated, **only 20% to 25% of those in need of treatment actually receive it**\(^1\)

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Unmet Medical Need in Substance Abusing Offenders in the Criminal Justice System

Some evidence-based practice treatment approaches are difficult to provide for patients in an outpatient setting.

**Community Reinforcement Approach (CRA):**
- Focuses on managing behavior related to substance use, to help patients adopt a healthier lifestyle without alcohol or drug use.
- Psychosocial support to support behavioral change and emotional wellbeing.

**Contingency Management (CM):**
- An evidence-based adjunct to counseling that uses positive reinforcement to support treatment goals.
- Offers rewards for desired behaviors, designed to weaken drug use by helping replace the ‘reward’ patients previously received from substance use.

**Cognitive-Behavioral Therapy (CBT) for SUD:**
- Helps patients learn to identify and correct behaviors that lead to substance use.
- Helps patients learn how to deal with problems related to substance use and teaches strategies to encourage abstinence.
- Each lesson ends with Fluency Training to promote learning and improve retention.

### US Treatment Facilities Therapeutic Approach offerings

<table>
<thead>
<tr>
<th>Approach</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance abuse counseling</td>
<td>99%</td>
</tr>
<tr>
<td>Relapse prevention</td>
<td>96%</td>
</tr>
<tr>
<td>Cognitive-Behavioral therapy</td>
<td>94%</td>
</tr>
<tr>
<td>Motivational interviewing</td>
<td>93%</td>
</tr>
<tr>
<td>Anger Management</td>
<td>83%</td>
</tr>
<tr>
<td>Brief Intervention</td>
<td>82%</td>
</tr>
<tr>
<td>Trauma Counseling</td>
<td>79%</td>
</tr>
<tr>
<td>12-step facilitation</td>
<td>73%</td>
</tr>
<tr>
<td>Contingency management</td>
<td>56%</td>
</tr>
<tr>
<td>Dialectical behavioral therapy</td>
<td>54%</td>
</tr>
<tr>
<td>Rational emotive behavioral therapy</td>
<td>46%</td>
</tr>
</tbody>
</table>

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3. David, D. The Community Reinforcement Approach An Update of the Evidence Front Psychiatry. 2018
Cognitive Behavioral Therapy (CBT) for SUD

CBT is intended to treat SUD by

- Understanding the connection between thoughts and behaviors
  - Functional analysis to identify triggers and understand consequences of use
  - Identify factors that promote/maintain use

- Modifying cognitive barriers to change
  - Identify rationalizing, giving up, overgeneralizations, or personalizing in thinking
  - Use cognitive restructuring to evaluate and alter negative thinking

- Improving behavioral strategies
  - Enhanced coping skills
  - Drug refusal skills
  - Problem solving skills
  - Enhanced social experiences


Cognitive Behavioral Therapy (CBT) for SUD

CM: Contrived Contingencies¹,²
- Promote initial abstinence.
- Put in place explicitly and exclusively for therapeutic purposes; Monetary/other gift tied to defined abstinence endpoints.
- Allows time for the therapist and patient to work toward reestablishing naturalistic contingencies.

CRA: Naturalistic Contingencies¹,²
- Promote sustained long-term abstinence once the contrived reinforcers are discontinued.
- Systematically increasing the availability and frequency of alternative reinforcing activities (stable family life, job, participation in self-help, etc.).
- Use aversive events or the loss of reinforcing event as a consequence of drug use.

Prescription Digital Therapeutics (PDTs)
A new class of therapies that are being integrated into standard of care

“Software as therapeutics” that treat serious diseases with high unmet medical need

PDTs meet stringent regulatory requirements related to:

- Safety and effectiveness clinical data \(^{1,2}\)
- Regulatory labeling\(^3\)
- Payers to evaluate coverage based on traditional therapeutic coverage mechanisms

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**What Does Regulatory Authorization Mean in The Context of Digital Therapeutics?**

Evidence of clinical effectiveness, patient safety, and GMP quality that is reviewed and authorized by a regulatory body to support quality, safety and treatment claims.

Regulatory Authorization follows a rigorous review of a therapy’s:
- Safety
- Effectiveness
- Instructions for Use

Authorization enables licensed providers to prescribe and gives payers the level of confidence in PDT quality, value, and effectiveness given to other FDA-regulated therapies they cover.

Scrutiny from regulatory bodies has resulted in millions of dollars in fines and settlements for companies unable to substantiate effectiveness claims.

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1. Evidence of effectiveness, patient safety, and GMP quality that is reviewed and authorized by a regulatory body to support quality, safety and treatment claims.


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**Acronyms:**
- FDA: Food and Drug Administration
- PDT: Prescription Digital Therapeutic
- GMP: Good Manufacturing Practice
**reSET® | Mechanism of Action**

An FDA-authorized Prescription Digital Therapeutic (PDT) for SUD

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivers therapy based on the community reinforcement approach (CRA), an intensive form of validated neurobehavioral therapy for SUD, along with contingency management and fluency training to enhance learning.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on the Therapeutic Education System (TES)</td>
</tr>
<tr>
<td>Comprised of 62 interactive modules: 32 core modules and 30 supplemental modules</td>
</tr>
<tr>
<td>Core modules focus on key CRA concepts, building skills to support behavior change and prevent relapse</td>
</tr>
<tr>
<td>Supplemental modules provide more in-depth information on specific topics such as relationship skills or living with Hepatitis C</td>
</tr>
<tr>
<td>Each module can be completed in approximately 10-20 minutes</td>
</tr>
</tbody>
</table>
**reSET® | Indications for Use**

reSET® is the only therapy approved for marijuana and stimulant patients

<table>
<thead>
<tr>
<th>Indication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- reSET® is intended to provide cognitive behavioral therapy, as an adjunct to a contingency management system, for patients 18 years of age and older, enrolled in outpatient treatment under the supervision of a clinician</td>
</tr>
<tr>
<td>- 12-week prescription duration</td>
</tr>
<tr>
<td>- Patient population: Patients with SUD, under treatment for the following:</td>
</tr>
<tr>
<td>- Stimulants</td>
</tr>
<tr>
<td>- Alcohol + another substance</td>
</tr>
<tr>
<td>- Marijuana</td>
</tr>
<tr>
<td>- Cocaine</td>
</tr>
<tr>
<td>- Opioids (when not primary substance of abuse)</td>
</tr>
<tr>
<td>- All other substances</td>
</tr>
<tr>
<td>- Not indicated for patients who are on opioid replacement therapy, or abusing alcohol solely, or abusing opioids as their primary substance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effectiveness Data</th>
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</thead>
<tbody>
<tr>
<td>- Pivotal study demonstrated significant improvements in abstinence and treatment retention(^1)(^2)</td>
</tr>
</tbody>
</table>

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2. Pear Internal data and Pear regulatory submission. DEN160018

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reSET® is intended for patients whose primary language is English and who have access to an Android/iOS tablet or smartphone. reSET is intended only for patients who own a smartphone and are familiar with use of smartphone apps (applications).

Clinicians should not use reSET to communicate with their patients about emergency medical issues. Patients should be clearly instructed not to use reSET to communicate to their clinician any urgent or emergent information.

reSET® is not to be used for emergencies. In case of an emergency, patients should dial 911 or go to the nearest emergency room.

The long-term benefit of treatment with reSET on abstinence has not been evaluated in studies lasting beyond 12-weeks in the Substance Use Disorder (SUD) population. The ability of reSET to prevent potential relapse after treatment discontinuation has not been studied.
reSET® Clinical Data | Pivotal Trial Summary

Pivotal Trial Overview¹
- 399 patients with SUD (alcohol, cannabis, cocaine, stimulants) received either:
  - Treatment-as-Usual (TAU), consisting of intensive face-to-face therapy
  - Reduced TAU and reSET (rTAU + reSET®) for 12 weeks¹
- Patients provided urine samples twice per week to objectively monitor abstinence
- Co-primary study endpoints
  - Abstinence in weeks 9-12
  - Retention in treatment

### Study Results²

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>rTAU+reSET®</th>
<th>TAU</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence: all patients</td>
<td>40.3%</td>
<td>17.6%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Abstinence: non-abstinent at study start</td>
<td>16.1%</td>
<td>3.2%</td>
<td>0.0013</td>
</tr>
<tr>
<td>Retention in treatment: all patients</td>
<td>76.2%</td>
<td>63.2%</td>
<td>0.0042</td>
</tr>
</tbody>
</table>

² Pear Internal data and Pear regulatory submission. DEN160018
## reSET® | Additional Clinical Data Highlights

### Highlights

#### Abstinence
- Among patients whose primary addiction was not opioids, adding reSET® to outpatient therapy more than doubled abstinence rates (40% vs. 18%).

#### Retention Rates
- Among all patients, adding reSET® to outpatient therapy improved rates of retention (76% vs. 63%).
- Patients who adhered to reSET® module completion in the first six weeks of the trial were 7x more likely to complete treatment than those who did not.

#### Treatment Attendance
- Clinical trial data revealed a positive correlation between module completion and appointment attendance.

#### Safety
- reSET® did not demonstrate a significant difference in unanticipated adverse events.

#### Module Completion
- Average Core Modules Completed: 38^2^ (of 48)
- Number of reSET® modules completed correlated with abstinence (R^2^=0.21, p<.001 with n=206)^2^

### Clinical Outcomes Summary

<table>
<thead>
<tr>
<th>Abstinence</th>
<th>Retention Rates</th>
<th>Treatment Attendance</th>
<th>Safety</th>
<th>Module Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Among patients whose primary addiction was not opioids, adding reSET® to outpatient therapy more than doubled abstinence rates (40% vs. 18%).</td>
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<td>• Clinical trial data revealed a positive correlation between module completion and appointment attendance.</td>
<td>• reSET® did not demonstrate a significant difference in unanticipated adverse events.</td>
<td>• Average Core Modules Completed: 38^2^ (of 48) • Number of reSET® modules completed correlated with abstinence (R^2^=0.21, p&lt;.001 with n=206)^2^</td>
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### Safety

- reSET® did not demonstrate a significant difference in unanticipated adverse events.

### Module Completion

- Average Core Modules Completed: 38^2^ (of 48)
- Number of reSET® modules completed correlated with abstinence (R^2^=0.21, p<.001 with n=206)^2^

### Abstinence Rates by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Percentage of patients who completed the 12-week study</th>
</tr>
</thead>
<tbody>
<tr>
<td>reSET® + rTAU</td>
<td>76%</td>
</tr>
<tr>
<td>TAU</td>
<td>63%</td>
</tr>
</tbody>
</table>

### Retention

<table>
<thead>
<tr>
<th>Retention Rates by Treatment Group</th>
<th>Percentage of patients who completed the 12-week study</th>
</tr>
</thead>
<tbody>
<tr>
<td>reSET® + rTAU (n=255)</td>
<td>76%</td>
</tr>
<tr>
<td>TAU (n=252)</td>
<td>63%</td>
</tr>
</tbody>
</table>

1. Among patients whose primary addiction was not opioids.

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1. Pear Internal data and Pear regulatory submission, DEN160019
2. Ludmer HF, Campbell ANC, Nunes EV, Marich YA. A Digital Therapeutic for SUD, reSET®, Demonstrates a Correlation Between Dose and Treatment Outcomes. Poster presented at: 29th Annual Meeting of the American Academy of Addiction Psychiatry; December 6-9, 2018; San Diego, CA.
reSET-O® | Capabilities and Functionality
Used in conjunction with Medication Assisted Treatment, under clinician supervision

**ENTER** drug and alcohol screen results, to guide conversation and inform clinicians

**SEE** the intensity of patient-reported cravings and triggers. Each metric can be expanded for greater detail— increasing transparency in patient-HCP dialogue

**FOLLOW** patient-reported cravings, triggers, buprenorphine use, and substance use; track lesson completion, progress over time, and appointment compliance

**VIEW** patient summary, personal information, prescription status, and drug screen results

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**Intervention**
- Medication Reminders & Tracking
- Craving & Trigger Assessment
- CBT Module Delivery
- Fluency Training
- Contingency Management

**Insight**
- Abstinence & Appointment Attendance Tracking
- CBT Module Completion Tracking
- Fluency Training
- Contingency Management
- Cravings & Triggers Reporting

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**PATIENT**

**CLINICIAN**
### reSET-O® | Mechanism of Action
An FDA Cleared Digital Therapy for OUD

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Product Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Delivers addiction-specific form of CBT, fluency training, and contingency management for opioid use disorder (OUD)</td>
<td>▪ Based on the Therapeutic Education System (TES)</td>
</tr>
<tr>
<td>▪ Based on the Therapeutic Education System (TES)</td>
<td>▪ Comprised of 67 interactive modules: 31 core modules and 36 supplemental modules</td>
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<tr>
<td>▪ Supplemental modules provide more in-depth information on specific topics such as relationship skills or living with hepatitis</td>
<td>▪ Each module is lasts approx. 10-20 minutes</td>
</tr>
<tr>
<td>▪ Each module is lasts approx. 10-20 minutes</td>
<td>▪ Voluntary buprenorphine check-in feature to support buprenorphine use</td>
</tr>
</tbody>
</table>
### reSET-O® | Indications for Use

<table>
<thead>
<tr>
<th>Indication(s)</th>
<th>reSET-O® is intended to increase retention of patients with opioid use disorder (OUD) in outpatient treatment by providing cognitive behavioral therapy, as an adjunct to outpatient treatment that includes transmucosal buprenorphine and contingency management, for patients 18 years or older who are currently under the supervision of a clinician.</th>
</tr>
</thead>
</table>
|                       | - 12-week prescription duration  
|                       | - indicated as a prescription-only Mobile Medical Application                                                                                                                                 |
| Intended Use          | Intended for use in combination with buprenorphine pharmacotherapy                                                                                                                                                                                        |
| Effectiveness Data    | Pivotal study demonstrated significant improvements in retention in treatment²                                                                                                                                                                          |
reSET-O® is intended for patients whose primary language is English and who have access to an Android/iOS tablet or smartphone. reSET-O® is intended only for patients who own a smartphone and are familiar with use of smartphone apps (applications).

Clinicians should not use reSET-O® to communicate with their patients about emergency medical issues. Patients should be clearly instructed not to use reSET-O® to communicate to their clinician any urgent or emergent information.

The long-term benefit of treatment with reSET-O® on abstinence has not been evaluated in studies lasting beyond 12-weeks in the Opioid Use Disorder (OUD) population. The ability of reSET-O to prevent potential relapse after treatment discontinuation has not been studied.
Pivotal Trial Overview

- 170 patients were randomized to receive either:
  - Treatment-as-Usual (TAU), consisting of Contingency Management + buprenorphine or
  - TAU + reSET-O® (academic name Therapeutic Education System, or TES) + Contingency Management + buprenorphine
- All patients received 30 mins. of face-to-face counseling every other week.
- Patients provided urine samples 3x per week to objectively monitor abstinence.
- Co-primary endpoint analysis
  - Abstinence/Negative urine drug screens in weeks 9-12
  - Retention in treatment

Study Results

- 170 patients were randomized to receive either:
  - Treatment-as-Usual (TAU), consisting of Contingency Management + buprenorphine or
  - TAU + reSET-O® (academic name Therapeutic Education System, or TES) + Contingency Management + buprenorphine
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  - Retention in treatment

<table>
<thead>
<tr>
<th></th>
<th>TAU + reSET-O®</th>
<th>TAU</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinence (Opioids)</td>
<td>77.3% (n=91)</td>
<td>62.1% (n=79)</td>
<td>0.0248</td>
</tr>
<tr>
<td>Retention (All)</td>
<td>82.4%</td>
<td>68.4%</td>
<td>0.0224</td>
</tr>
</tbody>
</table>
reSET-O® | Additional Clinical Data Highlights

<table>
<thead>
<tr>
<th>Highlights</th>
<th>Clinical Outcomes Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention Rates</td>
<td>• Adding reSET-O® to outpatient treatment using buprenorphine increased retention of patients with OUD almost 15%</td>
</tr>
</tbody>
</table>
| Safety                      | • The observed adverse events (AE) were of type and frequency as anticipated in a large population of patients with OUD, or associated with buprenorphine pharmacotherapy, particularly during the induction phase.  
• The AEs observed were not adjudicated to be device related. |
| Module Completion           | • reSET-O® vs TAU did not demonstrate any significant safety differences between the cohorts |

**Treatment Retention Rate¹**  
Patients Retained at 12-week endpoint

- TAU: 68.4%
- TAU + reSET-O®: 82.4%

P = .0224
A Comparative Study of the Therapeutic Education System for Incarcerated Substance-Abusing Offenders:

• Objectives and Design
  • Study compared the effectiveness of the Therapeutic Education System (TES) vs. Standard of Care on measures of crime (including re-incarceration at 12 months), drug use, and HIV risk behavior 3 and 6 months after prison release.
  • Participants were randomized into two study groups, Standard of Care (C) (n=255) and E-TES (n=258)
  • Note: These data were not the basis for reSET® or reSET-O® FDA review/authorization. The incarcerated population were not specifically studied in the pivotal trials used as the basis for authorization There are no data on the use of reSET® or reSET-O® in the incarcerated population.

• Randomized into two study groups: Standard of Care (C) (n=255) and E-TES (n=258)
• Treatment conditions included 48 interactive modules: once a week for two hours or twice a week for one hour
• Standard of Care: Group activities 1 day per week for 2 hours a day over 8-12 weeks.
• Outcomes: Results showed TES and standard treatment were equally effective across facilities in reducing criminality, relapse to drug use, and HIV risk behavior.
  • In prisons, where a majority of substance-using offenders do not receive treatment, identifying an equally effective high-volume alternative such as TES can greatly expand access to quality psychosocial interventions.
• Objective: comparing TES with standard care in a sample of substance-abusing offenders in prison

Technology Enabled Behavioral Therapy
Clinical Data in Incarcerated Substance Abuse Offenders*

Clinical Outcomes:

- Analysis indicated similar rates of re-incarceration for the two groups overall and separately for new offenses or for re-incarceration; no statistical significance (181.8 days for E-TES vs 225.1 days for C).
- The degree of change was statistically similar for drug use (54% E-TES; 54% C) and alcohol intoxication (54% E-TES; 57% C) fell more than half and the number of days of abstinent increased by nearly 3 months (80 E-TES; 85 C).
- Computer-based treatment required much less therapist time.

Key Takeaway: There was no significant difference between groups, indicating that E-TES is equally effective compared with standard of care.

*There are no data on the use of reSET® or reSET-O® in the incarcerated population.
Thank You!

Dr. Audrey Kern
Audrey.Kern@peartherapeutics.com