Housekeeping

• You will be muted automatically upon entry. Please keep your phone line muted for the duration of the webinar.
• Webinar is being recorded and will be archived for future viewing at www.pcssNOW.org within 2 weeks.
• Submit questions in the Q&A box at the bottom of your screen.
Sarah S. Kawasaki, MD
Director of Addictions Services, Pennsylvania Psychiatric Institute (PPI)
Assistant Professor of Psychiatry and Internal Medicine, Penn State Hershey Medical Center
Disclosures

- I have nothing to disclose.

The content of this activity may include discussion of off label or investigative drug uses. The faculty is aware that it is their responsibility to disclose this information.
Target Audience

• The overarching goal of PCSS is to train healthcare professionals in evidence-based practices for the prevention and treatment of opioid use disorders, particularly in prescribing medications, as well for the prevention and treatment of substance use disorders.
Educational Objectives:
Co-morbid Opioid and Alcohol Use

- At the conclusion of this activity participants should be able to:
  - Understand the prevalence and health risks
  - Identify treatment implications
  - Examine the benefits of integrated care
  - Discuss strategies to support long-term recovery
Outline

1. Case
2. Neurobiology of AUD and OUD
3. Prevalence of OUD and AUD comorbidity
4. Medical considerations
5. Evidence-based management: OUD
6. Evidence-based management: AUD
7. Opioid agonist therapy and alcohol use, impact and evidence
8. Case follow-up
9. Summary
Case Discussion

63 yo man, with chronic DJD, CKD, CAD and a h/o OUD, on methadone treatment at 180mg daily, admits to drinking ten 12oz beers daily. He cites pain as the primary reason for drinking. Doesn’t have etoh abstinence periods and denies a h/o withdrawal seizures.

For pain, he currently takes:
- pregabalin 200mg TID
- duloxetine 60mg daily
- tizanidine 4mg TID

Other medications:
- Lisinopril-HCTZ 20-25mg
- ASA 81mg
- metoprolol succinate, 25mg daily

How would you manage his alcohol use disorder?
Neural Pathways of Addiction

**Binge/intoxication:**
- Ventral Striatum (VS), nucleus accumbens: *euphoria, reward*
- Dorsal Striatum (DS) *habits, perseveration*
- Global Pallidus (GP) *habits, perseveration*
- Thalamus (Thal) *habits, perseveration*

**Withdrawal/Negative affect**
- Amygdala (AMG), bed nucleus of the stria terminalis (BNST), “extended amygdala” *malaise, dysphoria, negative emotional states*
- Ventral Striatum (VS): *decreased reward*

**Preoccupation/anticipation**
- Anterior cingulate (AC)
- Prefrontal cortex (mPFC), orbitofrontal cortex (OFC) *subjective effects of cravings, executive function*
- Basolateral nucleus of the amygdala *conditioned cues*  
- Hippocampus (Hippo) *Conditioned contextual cues*

Koob et al, 2008
Alcohol: Mechanism of Action

Diagram showing the mechanism of action of GABA, benzodiazepines, ethanol, neurosteroids, and barbiturates.
Opioids: Mechanism of Action

- Binds to the Mu opioid receptor
- Inhibits the release of GABA
- Lack of GABA receptor stimulation leads to release of dopamine from neighbor
Analgesic Mechanisms of Mu Opiate Drugs (Heroin, Vicodin, Morphine)

Slide courtesy of Nora Volkow, Director of NIDA, ASAM Plenary 2016
How bad is it?

Source: SAMHSA, 2020 National Survey on Drug Use and Health, 2021

- Heavy etoh use: >5 drinks on >5/30 days
  - Contributes to 5% of global disease burden
  - 4th leading cause of preventable death in the US
How bad is it?

Figure 27. People Aged 12 or Older with a Past Year Substance Use Disorder (SUD); 2020

Source: SAMHSA, 2020 National Survey on Drug Use and Health, 2021

Note: The estimated numbers of people with substance use disorders are not mutually exclusive because people could have use disorders for more than one substance.
How bad is it?

Source: SAMHSA, 2020 National Survey on Drug Use and Health, 2021
Prevalence and patterns:

- **National Survey of Drug Use and Health**
  - 2006: all drinkers were >70% more likely to have used opioids.
  - 2014: >50% of 4 million people using prescription opioids were binge drinkers.
  - 2017, among 2 million Americans with OUD, 25% had comorbid AUD.

- **Hood et al, 2020**
  - Etoh use is common in patients with chronic pain.
  - Chronic pain patients with heavy drinking report greater pain levels.
  - KP surveyed 12K patients prescribed opioids:
    - 12% reported etoh use
    - 32% reported concurrent sedatives
    - 3% reported all three used

- **Soyka et al, 2015**
  - 30% of people on methadone treatment have problematic etoh use.
  - Health care costs are greater than OUD alone.
Dangers:

- Mortality (Hood et al, 2020)
  - Increased risk of respiratory failure and death: CNS depressants
  - Linked to opioid overdoses
  - 130 people die daily from opioid overdoses and 20% involved alcohol
  - AUD diagnosis predicts higher risk of opioid overdose, accidents and injuries

- Morbidity (Hood et al, 2020)
  - Etoh associated with 20% of opioid related hospitalizations in young adults
  - Concurrent use interferes with treatment for chronic pain.
  - Higher disease burden, higher rates of multiple medical comorbidities
  - HCV risk much higher; cirrhosis risk much higher (Murrill et al 2002)
  - BZD use concurrently with opioids and etoh is also a problem
  - Higher psychiatric disorder comorbidity: including suicidality
    - (Lloyd et al 2007)
Methadone treatment and etoh use:

- Zador et al, 2000: number and causes of death at an MMT in Australia
  - Drug related death was 44%, etoh use 3rd most common after benzos and other opioids
- New York longitudinal study looking at active and discharged methadone patients: excessive etoh use was 35% cause of death for active participants (Joseph et al, 1985)
- Methadone initiation is a time of increased risk of mortality, especially with concurrent etoh use

How bad is it?
SUD and COVID-19

1. Addiction: (from SAMHSA) Strong desire to use, inability to control use, continued use despite obligations, social functioning, impaired health, the need to use more and more to achieve the same effect, spending a lot of time obtaining and using opioids.

2. Dependence: Withdrawal symptoms after stopping or reducing use.

3. DSM-V: Substance use disorder used for abuse AND dependence.
What are the Treatment Options: Opioids

1. **Methadone**
2. **Buprenorphine**
3. **Naltrexone**:

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Comparison between agonist & antagonist:

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What does the evidence say: Methadone

a. Reduction in death rates:

Fig. 1. Twenty-year survival estimates for cohorts 1–3 (solid line) and 8-year survivals in the control group (dotted line) with 95% confidence intervals.

166 MMT vs 115 controls over 8 years

Fig. 3. Cohort 2 (voluntary discharge; upper solid line) contrasted to cohort 3 (involuntary discharge; lower solid line) and controls (dotted line).

34 VD vs 53 NVD vs 115 controls
b. Retention in Treatment:

Newman et al, Lancet 1979:
- 100 heroin addicts randomized:
  - Detox/placebo
  - Maintenance
- 76% retention rate at 32 weeks in MMT
- 10% in placebo
- 56% retention rate at 3 years
  - 2% in placebo

**Figure 1**—Proportion of subjects retained in study.
Admission to the study occurred over 7 months; at least 128 weeks passed between admission of last subject and conclusion of the study.
c. Reduction in recidivism rates:

![Cartoon of people and text: "Stop the cycle, reform the system."

Figure 1. Reincarceration of Treated and Untreated (Control) Subjects as a Function of Time after Release from Jail.

Dole et al, NEJM 1969
d. Reduced Disease transmission:

**Gowing et al, JGIM 2005:**
- 28 studies
- 7900 methadone patients
- Results: methadone significantly reduces the high-risk behaviors of HIV transmission (e.g., IVDU, high risk sex) and seroconversion
What does the evidence say: Buprenorphine

a. Reduction in death rates

**Agonist Treatment Reduced Heroin OD Deaths**
Baltimore, Maryland, 1995-2009

![Graph showing reduction in overdose deaths](image)

**Buprenorphine Reduced Heroin OD**
France 1995-1999 (75% reduction)

![Graph showing reduction in opioid deaths](image)

_Schwartz RP et al., Am J Public Health 2013._

_Ling et al. J Subst Abuse Tx 2002;23:87-92._
_Auriacombe et al. JAMA 2001;285:45._

_Slide courtesy of Nora Volkow, Director of NIDA, ASAM plenary, 2016_
b. Retention in Treatment:

- 255 patients
- 56% retained at 1 year
- Those with polysubstance use were more likely to adhere to treatment
- 64% were opioid negative in tox screens for >6 months

Fig. 1. Patient retention and percentage of patients in treatment classified as opioid-negative over 12 months.

Soeffing et al, JSAT 2009
c. Reduction in recidivism rates:

- Criminal charges compared between methadone maintenance and office-based buprenorphine
- 2 years prior to treatment vs 2 years after initiating treatment
- Significant reductions in the methadone group in all charges and drug charges
- No significant reductions in the buprenorphine group

<table>
<thead>
<tr>
<th>Table 2. Overall charges and drug charges in the 2 years before and 2 years after enrollment in methadone maintenance (METH) or office-based buprenorphine (BUP).</th>
</tr>
</thead>
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<tr>
<td>2 years before treatment initiation</td>
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<tr>
<td><strong>BUP</strong></td>
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<tr>
<td>Number of subjects with a charge</td>
</tr>
<tr>
<td>Mean number of cases per subject</td>
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<tr>
<td>Mean number of cases among subjects in treatment at 12 months</td>
</tr>
<tr>
<td>Drug charges</td>
</tr>
<tr>
<td>Number of subjects with a drug charge</td>
</tr>
<tr>
<td>Mean number of drug cases per subject</td>
</tr>
<tr>
<td>Mean number of drug cases among subjects in treatment at 12 months</td>
</tr>
</tbody>
</table>

^a p-Value for comparison of BUP and METH subjects

^b p-Value for comparison of 2 years before and 2 years after enrollment

^c Wilcoxon signed ranks test

^d Mann-Whitney U test

Rastegar, Kawasaki et al, Substance use and misuse 2016
d. Reduced Disease transmission:

- Compares two methods: 15 day detox (2x) and 21 therapy sessions with Bup/naloxone
- Every 3 day dosing of Bup/naloxone for 48 weeks with 21 therapy sessions
- In 4 high-risk communities in Thailand and China
- Followed for 52 weeks after treatment
- Long-Term (LT) buprenorphine rx associated with less heroin and injection drug use by nearly 3x as much as short-term detox
- Dramatically reduced rates of HIV-risk behavior

Metzger et al, 2015 J Acquir Immune Defic Syndr
What does the evidence say: **Naltrexone**

**a. Reduction in death rates**

**Improving Treatments for Addiction:**

Naltrexone Trial in CJ Populations

- **Participants:** parolees/probationers with opioid addiction
  - all volunteers – received either
    - Monthly injections of extended release naltrexone for 6 months
    - Community treatment, including methadone or Suboxone (encouraged)

- *Note: These patients VOLUNTARILY wanted naltrexone*

- *Note: No patient continued injections after 24-week trial*

![Relapse Frequency](image)

*Overdoses in 78 weeks:
  - Control: 7
  - Naltrexone: 0*

*Lee et al. NEJM March 31, 2016.*

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Slide courtesy of Nora Volkow, Director of NIDA, ASAM plenary, 2016
What does the evidence say: Naltrexone

b. Retention in Treatment:

SJ Cousins et al. JSAT, 2016

Those who identified as homeless, injected heroin or having mental illness were less likely to stay in treatment.
c. Reduction in recidivism rates:

- One small study
- Non-randomized
- 27 incarcerated individuals with OUD in the year prior to incarceration
- Received 1 injection prior to release and 6 injections in the community
- 10 (37%) retained in treatment
- Those completing treatment less likely to test positive for opiates
- Those who didn’t were more likely to be re-arrested
  - Did not reach level of statistical significance.
d. Reduced Disease transmission:

- Has not been studied specifically
- We do know it is more effective at negative urine drug screens than placebo
Mattick et al, 2014, Cochrane Review: buprenorphine vs methadone vs placebo

- 31 studies, ~5500 participants
- Methadone better at retention in treatment (52 weeks) (RR 1.12) vs buprenorphine
- Buprenorphine much better than placebo for 52-week retention (16mg) (RR 1.88)
What does the evidence say:
Comparison Studies

b. Buprenorphine vs Naltrexone:

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, with 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=1474). XR-NTX = extended-release naltrexone. BUP-NX = buprenorphine-naloxone.

Figure 3. Opioid craving during the trial:
Craving was self-reported with an opioid craving VAS, range 0–100. VAS = Visual Analogue Scale. XR-NTX = extended-release naltrexone. BUP-NX = buprenorphine-naloxone.

Lee et al. Lancet, 2018
What are the treatment options: Alcohol

1. Acamprosate
2. Disulfiram
3. Oral Naltrexone
4. IM Naltrexone
Acamprosate

How Does Acamprosate Work?

- After one stops consuming alcohol, the glutamate system continues to be overactive as it readjusts by down regulating the glutamate receptors.
- During this time, the individual continues to feel anxiety and agitation that can lead to relapse. Acamprosate helps to re-regulate the glutamate system.
- Only proven after detox for relapse prevention
- Expensive
- TID dosing
“20% …[of those]… who finished the study were judged compliant”

Fuller et al, JAMA 1986
## Oral Naltrexone

Figure 9. Forest plot of comparison: NTX versus PBO, outcome: 1.5 Consumed amount per drinking day.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NTX</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
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<tr>
<td>Artt et al. 1999</td>
<td>401</td>
<td>53</td>
<td>80</td>
<td>58.7</td>
</tr>
<tr>
<td>Artt 2006</td>
<td>401</td>
<td>53</td>
<td>80</td>
<td>58.7</td>
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<tr>
<td>Baslin 2003</td>
<td>51.1</td>
<td>50</td>
<td>60</td>
<td>60.7</td>
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<tr>
<td>Brown 2003</td>
<td>67.2</td>
<td>42</td>
<td>20</td>
<td>92.4</td>
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<td>Hershi 1999</td>
<td>54.5</td>
<td>51.3</td>
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<td>Johnson 2004</td>
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<td>57.3</td>
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<td>Killien 2004</td>
<td>65.9</td>
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<td>Kryziu 2001</td>
<td>128.8</td>
<td>52.1</td>
<td>158</td>
<td>128</td>
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<td>88.2</td>
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<td>58</td>
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<td>O'Malley 1992</td>
<td>56.7</td>
<td>51.9</td>
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<td>OSIP 2008</td>
<td>169</td>
<td>86.1</td>
<td>158</td>
<td>211.4</td>
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<td>Pahlevi 2004</td>
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<td>57.1</td>
<td>16</td>
<td>30.3</td>
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<td>Petch 2008b</td>
<td>65.7</td>
<td>54.8</td>
<td>10</td>
<td>81.7</td>
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<tr>
<td>Schmitt 2004</td>
<td>85</td>
<td>136.4</td>
<td>10</td>
<td>54.8</td>
</tr>
</tbody>
</table>

| Total (95% CI)    | 960 | 817 | 100.0% | -16.33 (-19.69, -12.97) |
|                   |     |     |        |                               |

Heterogeneity: Tau² = 1.72; Q = 195.98, df = 15 (P < 0.0001), I² = 68%
Test for overall effect Z = 2.40, (P = 0.02)


www.cochranelibrary.com
ER Naltrexone

**Figure 2.** Primary Efficacy Analysis: Mean Heavy Drinking Event Rate

Intention-to-treat analysis shows the cumulative mean event rate of heavy drinking during the study by treatment group. The participant retention rates are shown at 4-week intervals through 24 weeks, which was the intended duration of the treatment.

**Figure 3.** Median Heavy Drinking Days per Month for Each Treatment Group Overall and by Sex

In addition to injections of study treatment, all patients received standardized, low-intensity psychosocial support. This represents an intention-to-treat analysis with the last observation carried forward. The bars represent interquartile range.
What are the off-label treatment options:

Alcohol

1. Gabapentin
2. Topiramate
3. Baclofen
Abstinence rate: 17% and no “heaving drinking” 44%
Gabapentin

Gabapentin Combined with Naltrexone for the Treatment of Alcohol Dependence

Raymond F. Anton, M.D., Hugh Myrick, M.D., Tara M. Wright, M.D., Patricia K. Latham, Ph.D., Alicia M. Baros, Ph.D., L. Randolph Waid, Ph.D., and Patrick K. Randall, Ph.D.
Medical University of South Carolina, Institute of Psychiatry

- Used in first 6 weeks of abstinence combined (50mg daily naltrexone, max 1200mg daily gabapentin)
- Found statistically significantly superior to naltrexone alone in the following areas:
  - Longer delay to heavy drinking
  - Less total heavy drinking days
  - Less drinks/drinking days
- Results didn’t last after gabapentin stopped after 6 weeks…so why stop?
Topiramate

- 25mg-300mg/day over 5 weeks
- Final dose 300mg/day divided

Baclofen

Addolorato et al Lancet 2007

42 etoh cirrhotic patients 10mg TID for 12 weeks

*caution! Has potential for withdrawal seizures, and don’t use if patient is suicidal!
How does OAT impact etoh use?

- Effect of Initiation of OAT
  - Mixed results: Caputo et al 2002, short-term rx associated with reduction in etoh, but long-term resulted in increased consumption
  - Nava et al, 2008: 12-month study with OUD and AUD showed both methadone and buprenorphine associated with a reduction in ETOH use, buprenorphine more efficacious
  - Meta-analysis: 15 studies with no clear pattern (Srivastava et al, 2008)
What is the uptake of etoh Rx on OAT?

• Nolan et al, 2016
  • Treatment is widely ignored
  • At one OTP in NYC, 21% had AUD, but only 5% engaged in etoh detox and 7% in psychosocial intervention
  • Many programs require termination of MOUD as terms of acceptance
    • Magnitude for risk of OD for treatment of AUD in those on MOUD may be overblown*
    • *watch out for precipitated withdrawal if co-administering phenobarbital and methadone
  • All MOUD participants should be offered treatment
Evidence for OAT and etoh rx?

• Disulfiram
  • Making methadone contingent on taking disulfiram was effective (Bickel et al, 1988)
  • Adding disulfiram to methadone without contingencies was not (Ling et al, 1983)
Evidence for OAT and etoh rx?

- ER naltrexone
  - Found safe, feasible in a small pilot in HIV clinic (Korthuis et al, 2017) but only 8 individuals in pilot
Evidence for OAT and etoh rx?

- Non-pharmacologic
  - Collaborative care intervention (Watkins et al, 2017)
    - 377 primary care patients with either AUD, OUD +/- AUD
    - 6 sessions of brief psychotherapy by psychologist with addiction expertise—intervention
    - TAU: referral to community programs
    - Those in intervention twice as likely to get treatment and greater rates of abstinence
    - Rates of those with both AUD and OUD were low, failed to report numbers or any subgroup differences
  - Mindfulness
    - Effective in polysubstance use, pain
  - CBT
    - Effective in ETOH and SUDs (Magill and Ray, 2009)
Prognosis?

- Comorbidity may reduce efficacy of available treatments.
- Opioid misuse tied to poorer AUD treatment outcomes and vice versa.
- There are no specific treatment approaches, pharmacological or non-pharmacological, that effectively treat co-morbid AUD and OUD.
- It can complicate treatment of chronic pain.
- Research is lacking, especially the role pain plays.
Case Discussion

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- metoprolol succinate, 25mg daily

How would you manage his alcohol use disorder?
Case Follow-Up

- Naltrexone and gabapentin contraindicated
- Acamprosate and disulfiram with lackluster evidence
- Initiated topiramate and titrated up to 100mg daily
- Offering broad support: AA, SMART recovery, counseling

- Reduced drinking to 2 beers daily
Etoh and opioid therapy is understudied
Treatment can be given simultaneously
Determine best treatment milieu
Different SUDs call for different treatment
Screen in the UDS at your OTP
Thank you!

Sarah S. Kawasaki, MD
Pennsylvania Psychiatric Institute (PPI) and
Penn State Hershey Medical Center
skawasaki@pennstatehealth.psu.edu
PCSS Mentoring Program

- PCSS Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid use disorder.

- PCSS Mentors are a national network of providers with expertise in addictions, pain, evidence-based treatment including medications for opioid use disorder (MOUD).
  - 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
  - No cost.

For more information visit: https://pcssNOW.org/mentoring/
PCSS Discussion Forum

Have a clinical question?

Ask a Colleague

A simple and direct way to receive an answer related to medications for opioid use disorder. Designed to provide a prompt response to simple practice-related questions.

http://pcss.invisionzone.com/register
**PCSS** is a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) in partnership with:

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<th>American Society for Pain Management Nursing</th>
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Educate. Train. Mentor

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