Managing Opioid Use Disorder

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<table>
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<th>Disclosure Category</th>
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<td>Stock Equity</td>
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Objectives

• Emphasize opioid use disorder (OUD) is a chronic brain disease

• Discuss medication treatments for OUD

• Discuss use of medication treatment in inpatient and outpatient settings

• Discuss process for obtaining buprenorphine waiver
Substance use disorders (SUDs) are **chronic brain diseases.**
Clinical symptoms of SUDs— including loss of control and continued compulsive use despite negative consequences— are associated with significant, pathologic neurochemical changes.

As with other chronic diseases, relapse in SUDs is common.

Although OUD is a chronic disease, the disease course has become increasingly short.

- More than 120 persons per day die from an opioid-related overdose
- Drug overdoses (majority of which are opioid-related) are leading cause of death for persons under 50 years of age

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released January, 2020

RESULTS The primary cohort included 76,325 adults and 66,736 person-years of follow-up. During the first year after nonfatal opioid overdose, there were 5194 deaths, the crude death rate was 778.3 per 10,000 person-years, and the all-cause SMR was 24.2 (95% CI, 23.6-24.9). The most common immediate causes of death were substance use-associated diseases (26.2%), diseases of the circulatory system (13.2%), and cancer (10.3%). For every cause examined, SMRs were significantly elevated, especially with respect to drug use-associated diseases (SMR, 132.1; 95% CI, 125.6-140.0), HIV (SMR, 45.9; 95% CI, 39.5-53.0), chronic respiratory diseases (SMR, 41.1; 95% CI, 36.0-46.8), viral hepatitis (SMR, 30.6; 95% CI, 22.9-40.2), and suicide (SMR, 25.9; 95% CI, 22.6-29.6), particularly including suicide among females (SMR, 47.9; 95% CI, 39.8-52.3).
People with OUD are **almost 25 times** more likely to die within a year than persons without OUD.
What about in Missouri?

In 2018, one of every 56 deaths in Missouri was attributed to an opioid-related overdose.

https://health.mo.gov/data/opioids/death-toll.php
Missouri opioid-related deaths continue to increase, largely driven by fentanyl
Black males are disproportionately more likely to die of an overdose death compared to women and white males.

https://health.mo.gov/data/opioids/death-toll.php
Medication Treatment for OUD
Importantly, we have medication treatment for OUD!

• Often called “MAT” or “MOUD”
  • Previously: “Medication-Assisted Treatment”
  • Currently: “Medication for Addiction Treatment” or “Medication for Opioid Use Disorder”
  • One day: “treatment” ?????
Medications for OUD

- Detoxification
  - Buprenorphine
  - Methadone

- Maintenance
  - Buprenorphine
  - Methadone
  - Naltrexone (oral and extended-release depot)

- Overdose reversal
  - Naloxone
  - *EVERY PERSON WITH OUD SHOULD BE GIVEN NALOXONE SCRIPT*
Naltrexone

- **Antagonist** at mu-opioid receptor
  - Blocks rewarding properties of opioids
- Oral and extended-release formulations
  - Oral formulation most commonly dosed daily (usually 50 mg)
  - Extended-release depot injection (Vivitrol) dosed monthly (380 mg)
- No risk of physical dependence
- Any licensed physician can prescribe
- Should not initiate until patient is opioid free for several days, due to concern for precipitated withdrawal
  - MAJOR challenge for many with OUD
- Extended-release depot formulation is (often prohibitively) expensive

Methadone

- **Full agonist** at mu-opioid receptor
  - Important to be cognizant of potential side effects
    - Sedation
    - Drug-drug interactions
    - Potential for physical dependence
- Long half-life (days)
  - Eliminates the cycle of intoxication and withdrawal
  - Must be slowly uptitrated
- Target maintenance dose = minimization of opioid cravings without negative side effect
- Highly regulated due to DEA Schedule II classification
  - Outpatient: Must be administered through Opioid Treatment Programs (OTPs) certified by SAMHSA
    - Often daily dosing for first 90 days of treatment
  - Inpatient: Any licensed physician with DEA registration can prescribe for OUD so long as OUD is not primary reason for admission
Buprenorphine

- **Partial agonist** at mu opioid receptor
  - High affinity for receptors, decreased stimulation relative to commonly abused opioids
  - Potential for physical dependence
  - Fewer drug-drug interactions compared to methadone
- Ceiling effect decreases likelihood of sedating side effects
- Buprenorphine monoprodut = Subutex; buprenorphine + naloxone = Suboxone
  - Naloxone inactive when taken sublingually → protects against misuse
- Sublingual tablets and films; long-acting injection; implant
- Half-life ~ 24 hours
Buprenorphine, continued

- Schedule III classification
- Can be prescribed in outpatient setting by any licensed physician with DEA registration who has “X” Waiver (8 hours of training and test) – does not require OTP status
- Can be prescribed in the inpatient setting without a waiver, so long as patient’s primary admission diagnosis is not OUD
Do these medications work?
Oral Naltrexone

From the FDA:

Treatment of Opioid Addiction

REVIA has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other non-opioid drugs of abuse.

There are no data that demonstrate an unequivocally beneficial effect of REVIA on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018932s017lbl.pdf
Reference ID: 3383348
Extended-release depot naltrexone

Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (XNOR): a multicenter, open-label, randomized clinical trial

Findings: Between Jan 30, 2014, and May 25, 2016, we randomly assigned 570 participants to receive XR-NTX (n=283) or BUP-NX (n=287). The last follow-up visit was Jan 31, 2017. As expected, XR-NTX had a substantial induction hurdle: fewer participants successfully initiated XR-NTX (204 [72%] of 283) than BUP-NX (270 [94%] of 287; p<0.0001). Among all participants who were randomly assigned (intention-to-treat population, n=570) 24 week relapse events were greater for XR-NTX (185 [65%] of 283) than for BUP-NX (163 [57%] of 287; hazard ratio [HR] 1.36, 95% CI 1.10–1.68), most or all of this difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures. Among participants successfully inducted (per-protocol population, n=474), 24 week relapse events were similar across study groups (p=0.44). Opioid-negative urine samples (p<0.0001) and opioid-abstinent days (p<0.0001) favoured BUP-NX compared with XR-NTX among the intention-to-treat population, but were similar across study groups among the per-protocol population. Self-reported opioid craving was initially less with XR-NTX than with BUP-NX (p<0.0012), then converged by week 24 (p=0.20). With the exception of mild-to-moderate XR-NTX injection site reactions, treatment-emergent adverse events including overdose did not differ between treatment groups. Five fatal overdoses occurred (two in the XR-NTX group and three in the BUP-NX group).

Interpretation: In this population it is more difficult to initiate patients to XR-NTX than BUP-NX, and this negatively affected overall relapse. However, once initiated, both medications were equally safe and effective. Future work should focus on facilitating induction to XR-NTX and on improving treatment retention for both medications.

Funding: NIDA Clinical Trials Network.
Extended-release depot naltrexone

Participants were 18 years or older, spoke English, had Diagnostic and Statistical Manual of Mental Disorders-5 opioid use disorder, and had used non-prescribed opioids in the past 30 days. We excluded participants if they had other serious medical, psychiatric, or substance use disorders; transaminase concentrations were more than 5 times the upper limit of normal; were suicidal or homicidal; had allergy or sensitivity to XR-NTX or BUP-NX; had methadone maintenance treatment (≥30 mg/day); had chronic pain requiring opioids; had a legal status precluding study completion; and were not able to have safe intramuscular XR-NTX treatment. We excluded women if they were pregnant, breastfeeding, planning conception, or unwilling to use birth control.
Background: Opioid overdose survivors have an increased risk for death. Whether use of medications for opioid use disorder (MOUD) after overdose is associated with mortality is not known.

Objective: To identify MOUD use after opioid overdose and its association with all-cause and opioid-related mortality.

Design: Retrospective cohort study.

Setting: 7 individually linked data sets from Massachusetts government agencies.

Participants: 17,568 Massachusetts adults without cancer who survived an opioid overdose between 2012 and 2014.

Measurements: Three types of MOUD were examined: methadone maintenance treatment (MMT), buprenorphine, and naloxone. Exposure to MOUD was identified at monthly intervals, and persons were considered exposed through the month after last receipt. A multivariable Cox proportional hazards model was used to examine MOUD as a monthly time-varying exposure variable to predict time to all-cause and opioid-related mortality.

Results: In the 12 months after a nonfatal overdose, 2,040 persons (11%) enrolled in MMT for a median of 5 months (interquartile range, 2 to 9 months), 3,022 persons (17%) received buprenorphine for a median of 4 months (interquartile range, 2 to 8 months), and 1,099 persons (6%) received naloxone for a median of 1 month (interquartile range, 1 to 2 months). Among the entire cohort, all-cause mortality was 4.7 deaths (95% CI, 4.4 to 5.0 deaths) per 100 person-years and opioid-related mortality was 2.1 deaths (CI, 1.9 to 2.4 deaths) per 100 person-years. Compared with no MOUD, MMT was associated with decreased all-cause mortality (adjusted hazard ratio [AHR], 0.47 [CI, 0.32 to 0.71]) and opioid-related mortality (AHR, 0.41 [CI, 0.24 to 0.70]). Buprenorphine was associated with decreased all-cause mortality (AHR, 0.63 [CI, 0.46 to 0.87]) and opioid-related mortality (AHR, 0.62 [CI, 0.41 to 0.92]). No associations between naltrexone and all-cause mortality (AHR, 1.44 [CI, 0.84 to 2.46]) or opioid-related mortality (AHR, 1.42 [CI, 0.73 to 2.70]) were identified.

Limitation: Few events among naltrexone recipients preclude confident conclusions.

Conclusion: A minority of opioid overdose survivors received MOUD. Buprenorphine and MMT were associated with reduced all-cause and opioid-related mortality.

Primary Funding Source: National Center for Advancing Translational Sciences of the National Institutes of Health.

For author affiliations, see end of text.
This article was published at Annals.org on 19 June 2018.
Conclusions:

• Buprenorphine associated with ~40% decreased risk of all-cause mortality at one year

• Methadone associated with ~50% decreased risk of all-cause mortality at one year

• Underpowered to comment with confidence re: naltrexone
Fig. 1. Unadjusted overdose rates are calculated for time on and off treatment as overdose events per 100-person years. There were 1,683 overdoses during 35,776 person-years spent off treatment (not counting the first four weeks after MOUD discontinuation) for a rate of 4.70 per 100-person years (95% CI 4.48-4.93). There were 15 overdoses observed while on XR-NTX, 100 while on oral NTX, and 620 while on buprenorphine during 390, 1,617, and 29,628 person-years, respectively, resulting in overdose rates of 3.85 per 100 person-years (95% CI 2.31-6.37) while on XR-NTX, 6.18 per 100-person years while on oral naltrexone (95% CI 5.08-7.52), and 2.09 per 100-person years while on buprenorphine. In the first four weeks after MOUD discontinuation, there were 16 overdoses among those discontinuing XR-NTX, 81 among those discontinuing oral NTX, and 200 among those discontinuing buprenorphine over 153, 739, and 5,188 person-years, respectively, resulting in overdose rates of 10.46 per 100 person-years after discontinuing XR-NTX (95% CI 6.40-17.06), 10.96 per 100 person-years after discontinuing medications for opioid use disorder; XR-NTX = extended-release injectable naltrexone; NTX = naltrexone; CI = confidence interval.
Summary

- Buprenorphine and methadone are associated with improved retention and **DECREASED MORTALITY** among persons with OUD.

- Extended-release naltrexone may improve retention but as has **NOT** been shown to have mortality benefit.

- Oral naltrexone may *increase* risk of overdose.

- Therefore, opioid agonist therapy with either buprenorphine or methadone is often recommended first-line for OUD maintenance treatment.

- Although similarly effective, because of fewer restrictions and fewer side effects, buprenorphine is more commonly prescribed than methadone.
A word about physical dependence vs addiction

• Different concepts but commonly conflated
  • Conflating may be barrier to opioid agonist treatment with buprenorphine or methadone, both of which can result in physical dependence

• Addiction: continued compulsive use despite negative consequences
  • Use interferes with life

• Physical dependence: tolerance and withdrawal-- may occur with or without addiction
  • Occurs with MANY medications when taken chronically including those without addictive potential
    • Exs: SSRI medications for depression or anxiety

• Most research suggests opioid agonist treatments are not commonly misused– on the contrary, they allow persons with OUD to live meaningful lives
  • Associated with decreased recidivism, improved social functioning, and decreased infectious complications

OVERVIEW OF CONCLUSIONS

To read the full text of the committee’s conclusions, visit nationalacademies.org/OUDtreatment.

1. Opioid use disorder is a treatable chronic brain disease.
2. FDA-approved medications to treat opioid use disorder are effective and save lives.
3. Long-term retention on medications to treat opioid use disorder is associated with improved outcomes.
4. A lack of availability of behavioral interventions is not a sufficient justification to withhold medications to treat opioid use disorder.
5. Most people who could benefit from medication-based treatment for opioid use disorder do not receive it, and access is inequitable across subgroups of the population.
6. Medication-based treatment is effective across all treatment settings studied to date. Withholding or failing to have available all classes of FDA-approved medication for the treatment of opioid use disorder in any care or criminal justice setting is denying appropriate medical treatment.
7. Confronting the major barriers to the use of medications to treat opioid use disorder is critical to addressing the opioid crisis.
And yet, a minority of persons with OUD receive medication treatment...

It has been estimated fewer than 10% of persons with OUD receive medication treatment.

What can we do to improve uptake of evidence-based treatment for OUD in inpatient and outpatient settings?
Hospitalizations have been underutilized as a setting in which to initiate treatment for OUD, but offer many potential advantages

- Patients with OUD may be particularly motivated for treatment if admitted for a drug-related complication

- Waiver not required to prescribe buprenorphine in the inpatient setting (can also prescribe methadone in inpatient setting)

- Close monitoring during dose titrations
A historical problem of initiating someone on MAT during hospitalization: Bridge to nowhere
A potential resource: EPICC (with two Cs!)

- Engaging Patients In Care Coordination (EPICC) funded by State Targeted Response (STR) and State Opioid Response (SOR) grants from Substance Abuse and Mental Health Services Administration
  - [https://mocep.org/about/epicc/](https://mocep.org/about/epicc/)

- Able to link persons to outpatient waivered provider or OTP quickly
  - Peer counselor contacts patient during hospitalization/ER visit and arranges follow-up appointment with waivered buprenorphine provider within days of discharge
But we need more waivered providers!

2018:

Obtaining a buprenorphine waiver
Buprenorphine X Waiver training is an important **first step** to treating persons with OUD

- Drug Addiction Treatment Act of 2000
- Must have DEA registration
- 8 hours of additional training for physicians, 24 hours for NPs or PAs
  - Online or in-person
- [https://pcssnow.org/medication-assisted-treatment/](https://pcssnow.org/medication-assisted-treatment/)
- After obtaining waiver, can prescribe buprenorphine for up for 30 persons at a time for first year (up to 100 persons after that)
- Allows inpatient providers to bridge someone from hospital discharge to outpatient appt
- Outpatient providers can initiate and/or continue buprenorphine in clinic
Why aren't physicians prescribing more buprenorphine?

Andrew S. Huhn, Kelly E. Dunn *

Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Table 2

<table>
<thead>
<tr>
<th>Reason</th>
<th>Nonwaivered respondents (N = 74)</th>
<th>Waivered and not prescribing to capacity (N = 272)</th>
<th>(χ², p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No time for more patients (%)</td>
<td>12.2</td>
<td>36.0</td>
<td>15.51, &lt;0.001</td>
</tr>
<tr>
<td>Reimbursement insufficient (%)</td>
<td>5.4</td>
<td>15.4</td>
<td>5.08, = 0.02</td>
</tr>
<tr>
<td>Concerned about diversion (%)</td>
<td>25.7</td>
<td>10.3</td>
<td>11.73, = 0.002</td>
</tr>
<tr>
<td>Don't want to be inundated with suboxone requests (%)</td>
<td>29.7</td>
<td>8.8</td>
<td>22.06, &lt;0.001</td>
</tr>
<tr>
<td>Don't believe in agonist treatment (%)</td>
<td>13.5</td>
<td>2.9</td>
<td>13.16, = 0.001</td>
</tr>
<tr>
<td>Concerned about precipitating withdrawal (%)</td>
<td>12.2</td>
<td>1.5</td>
<td>18.40, &lt;0.001</td>
</tr>
<tr>
<td>Not educated enough about Opioid Use Disorder (%)</td>
<td>14.6</td>
<td>1.1</td>
<td>28.38, &lt;0.001</td>
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<tr>
<td>Don't know how to get waiver (%)</td>
<td>9.5</td>
<td>&lt;1</td>
<td>21.29, &lt;0.001</td>
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<tr>
<td>No problem in my community (%)</td>
<td>2.7</td>
<td>&lt;1</td>
<td>3.70, = 0.12</td>
</tr>
</tbody>
</table>

Respondents who were waived and prescribing to capacity did not answer these questions.

Degrees of freedom = 1 for all comparisons.
Why aren't physicians prescribing more buprenorphine?

Andrew S. Huhn, Kelly E. Dunn *

Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, Baltimore, MD, United States

Table 3
What resources will increase receipt of waiver or prescribing to capacity.

<table>
<thead>
<tr>
<th>Program that will most increase prescribing (%)</th>
<th>Nonwaivered respondents (N = 74)</th>
<th>Waivered and not prescribing to capacity (N = 272)</th>
<th>(χ², p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing will increase my willingness</td>
<td>33.8</td>
<td>54.8</td>
<td>10.26, =0.001</td>
</tr>
<tr>
<td>Information about local counseling resources</td>
<td>27.0</td>
<td>18.4</td>
<td>2.96, 0.10</td>
</tr>
<tr>
<td>Being paired with experienced provider</td>
<td>35.1</td>
<td>12.5</td>
<td>20.79, &lt;0.001</td>
</tr>
<tr>
<td>More CME courses for opioid use disorder</td>
<td>33.8</td>
<td>9.2</td>
<td>28.46, &lt;0.001</td>
</tr>
<tr>
<td>Financial assistance for waiver</td>
<td>24.3</td>
<td>2.9</td>
<td>38.27, &lt;0.001</td>
</tr>
</tbody>
</table>

Waivered respondents who were prescribing to capacity did not answer these questions.

CME = continuing medical education. Degrees of freedom (df) = 1 unless otherwise stated.

* Percent of respondents initially endorsing that >1 program would increase prescribing.
Introduction: Opioid abuse has reached epidemic levels. Evidence-based treatments such as buprenorphine maintenance therapy (BMT) remain underutilized. Offering BMT in primary care settings has the potential to reduce overall costs of care, decrease medical morbidity associated with opioid dependence, and improve treatment outcomes. However, access to BMT, especially in rural areas, remains limited. This article will present a review of barriers to adoption of BMT among family physicians in a primarily rural area in the USA.

Methods: An anonymous survey of family physicians practicing in Vermont or New Hampshire, two largely rural states, was conducted. The survey included both quantitative and qualitative questions, focused on BMT adoption and physician opinions of opioids. Specific factors assessed included physician factors, physicians’ understanding of patient factors, and logistical issues.

Results: One-hundred and eight family physicians completed the survey. Approximately 10% were buprenorphine prescribers. More than 80% of family physicians felt they regularly saw patients addicted to opiates. The majority (70%) felt that they, as family physicians, bore responsibility for treating opiate addiction. Potential logistical barriers to buprenorphine adoption included inadequately trained staff (88%), insufficient time (80%), inadequate office space (49%), and cumbersome regulations (37%). Common themes addressed in open-ended questions included lack of knowledge, time, or interest; mistrust of people with addiction or buprenorphine; and difficult patient population.

Conclusions: This study aims to quantify perceived barriers to treatment and provide insight expanding the community of family physicians offering BMT. The results suggest family physicians are excellent candidates to provide BMT, as most report regularly seeing opioid-addicted patients and believe that treating opioid addiction is their responsibility. Significant barriers remain, including inadequate staff training, lack of access to addiction experts, and perceived efficacy of BMT. Addressing these barriers may lower resistance to buprenorphine adoption and increase access to BMT in rural areas.
Table 2: Physician perception of personal and patient barriers to buprenorphine adoption

<table>
<thead>
<tr>
<th>Statement</th>
<th>Total sample (N=108)</th>
<th>Buprenorphine prescribers (n=11)</th>
<th>Buprenorphine non-prescribers (n=97)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) agree with statement</td>
<td>No. (%) agree with statement</td>
<td>No. (%) agree with statement</td>
<td></td>
</tr>
<tr>
<td>Treating patients with opioid addiction is difficult</td>
<td>101 (94)</td>
<td>9 (82)</td>
<td>92 (95)</td>
<td>0.10</td>
</tr>
<tr>
<td>I am confident in my ability to prescribe buprenorphine in accordance with accepted standards</td>
<td>27 (25)</td>
<td>11 (100)</td>
<td>16 (16)</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>I am confident in my ability to treat the psychiatric co-morbidities in patients with opioid addiction</td>
<td>30 (28)</td>
<td>5 (45)</td>
<td>25 (26)</td>
<td>0.17</td>
</tr>
<tr>
<td>Buprenorphine is an effective treatment for opioid addiction</td>
<td>61 (56)</td>
<td>10 (91)</td>
<td>51 (53)</td>
<td>0.015*</td>
</tr>
<tr>
<td>My patients with opioid addiction are motivated to discontinue use</td>
<td>44 (41)</td>
<td>9 (82)</td>
<td>35 (36)</td>
<td>0.003</td>
</tr>
<tr>
<td>My patients with opioid addiction would be satisfied with BMT.</td>
<td>44 (41)</td>
<td>10 (91)</td>
<td>34 (36)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Cost of buprenorphine is a barrier for my patients.</td>
<td>96 (89)</td>
<td>7 (64)</td>
<td>89 (92)</td>
<td>0.005**</td>
</tr>
<tr>
<td>My patients are concerned about confidentiality;</td>
<td>16 (15)</td>
<td>2 (18)</td>
<td>14 (15)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

We need to increase knowledge of MAT (and treatment for all SUDs) EARLY in medical education and training

- WashU awarded 3-year grant from Substance Abuse and Mental Health Services Administration (2019-2022)
  - PIs: Sarah Hartz, MD, PhD (Psychiatry), David Liss, MD (Emergency Medicine)

- Goals:
  - Improve medical school curriculum so that all graduating WUMS will have obtained required training to apply for X-waiver
  - Psychiatry and Emergency Medicine residents required obtain X-waiver during training
Conclusions

• **OUD is a chronic brain disease.** It continues to be a lethal, both nationally and in Missouri.

• **We have effective, life-saving medication treatment for OUD** that can be initiated in the inpatient or outpatient setting.

• **Obtaining the buprenorphine waiver is an important initial step** to increasing knowledge and comfort with prescribing buprenorphine.
Questions????

• Thank you!

• mintzc@wustl.edu