Pharmacotherapy for Opioid Use Disorder: Who, what, when, where, why and how

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June 2020 Webinar

CROP+TR
Center for Rural Opioid Prevention, Treatment & Recovery

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Purpose

- This is a brief overview of pharmacotherapy use for opioid use disorder for the non-prescriber, focusing on buprenorphine products
- Discussion of common questions and links to resources will be provided.

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Harm Reduction Framework

- Harm reduction refers to policies, programs and practices that aim to minimize negative health, social and legal impacts associated with drug use, drug policies and drug laws.
- Harm reduction is grounded in justice and human rights - it focuses on positive change and on working with people without judgement, coercion, discrimination, or requiring that they stop using drugs as a precondition of support.

Credit: https://www.hri.global/what-is-harm-reduction

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Harm Reduction Framework

What are the principles of Harm Reduction in health care?

https://www.hri.global/what-is-harm-reduction

How do we do this?

Offer people help

Keep people alive

Harm reduction tool and self-assessment:
https://equip2013.files.wordpress.com/2017/06/harm-reduction-tool-may-10-2017.pdf

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Opioid Use Disorder

Commonly Asked Questions about Pharmacotherapy for Opioid Use Disorder

- Aren't you just replacing one drug with another?
- How can patients get clean if you are not promoting abstinence?
- How can I be sure patients won't just sell their medications?
- What if a patient doesn't want help?

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Pharmacotherapy

FDA Approved Pharmacotherapy for Opioid Use Disorder

- Methadone (no approval or established use for children or adolescents, used for neonatal abstinence syndrome but not FDA approved)
- Naltrexone (off label use age 16 and older for OUD and alcohol use disorder)
- Buprenorphine (approved for age 16 and older for OUD, age 2 and up for pain)

Pharmacotherapy

- Methadone—binds to opioid receptors producing analgesia and sedation (opioid agonist). Half life 8-59 hours.
- Buprenorphine—binds to opioid receptors but produces agonism at some (delta), partial agonism at others (mu), and antagonism at kappa receptors (opioid agonist-antagonist). Half life 20-44 hours.
- Naltrexone—antagonizes opioid receptors. Half life 4-5 hours (parent drug).

Naloxone

- Naloxone is an opioid reversal agent which antagonizes opioid receptors
- It is used intranasally and injectably for opioid overdose
- Buprenorphine is a mixed opioid agonist/antagonist which is long acting and can have opioid like effects
- The use of naloxone in buprenorphine products blocks the effects of buprenorphine if it is injected, where the naloxone becomes highly bioavailable

FDA Approved Buprenorphine Products

- Generic Buprenorphine/naloxone sublingual tablets
- Buprenorphine sublingual tablets (Subutex™)
- Buprenorphine/naloxone sublingual films (Suboxone™)
- Buprenorphine/naloxone) sublingual tablets (Zubsolv™)
- Buprenorphine/naloxone buccal film (Bunavail™)
- Buprenorphine implants (Probuphine™)
- Buprenorphine extended-release injection (Sublocade™)

Who

- Children and adolescents
- Pregnant women
- Elderly patients
- Patients with chronic pain
- Medical co-morbidities

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Children and Adolescents

Opioids and Fentanyl: Children and Adolescents

- Morphine, Methadone – The safety and efficacy in patients less than 18 years have not been established
- Hydromorphone – Pharmacokinetics of hydromorphone have not been evaluated in children
- Fentanyl – The safety and efficacy of in children under two years of age has not been established
- Oxycodone, Hydrocodone – Have some pediatric dosing information (Shenoi, AAP)

Adolescents

- In 2016 the American Academy of Pediatrics published guidance for Medication Assisted Treatment of Opioid Use Disorders
- The AAP recommends that pediatricians consider offering medication-assisted treatment to their adolescent and young adult patients with severe opioid use disorders or discuss referrals to other providers for this service.

Adolescents

- One randomized trial of detoxification (14-day taper) vs. treatment with buprenorphine/naloxone in patients age 18-21 which included weekly individual or group counseling demonstrated:
  - At week 12, 21 detox patients had positive urine opioid results (51%; 95% CI=35%-67%) vs 21 12-week buprenorphine-naloxone patients (43%; 95% CI=29%-57%
  - BUT those using buprenorphine/naloxone had less frequent use, less injecting, and were more likely to still be in treatment (16 of 78 detox patients (20.5%) remained in treatment vs 52 of 74 12-week buprenorphinenaloxone patients (70%; 2 1=32.90, P.001).

Adolescents

- Another study compared clonidine with buprenorphine in a double-blind study with adolescents age 13-18 with diagnosed opioid dependence
- A significantly greater percentage of adolescents who received buprenorphine were retained in treatment (72%) relative to those who received clonidine (39%) (P.05). For those in the buprenorphine group, a significantly higher percentage of scheduled urine test results were opiate negative (64% vs 32%; P=.01).

Adolescents are underserved

- Among 13,585 addiction treatment facilities in the U.S., 3,537 (26.0%) offered adolescent programs. Adolescent-serving facilities were half as likely to offer maintenance MOUD as adult-focused facilities (odds ratio, .53; 95% confidence interval, .49–.58), which was offered at 23.1% (816) of adolescent-serving versus 35.9% (3,612) of adult-focused facilities.
- Among adolescent-serving facilities, characteristics associated with increased unadjusted odds of offering maintenance MOUD were nonprofit status, hospital affiliation, accepting insurance (particularly, private insurance), accreditation, Northeastern location, or offering inpatient services.

Adolescents

- Evidence based programs for adolescents with opioid use disorder are lacking, none found for children
- https://strengtheningfamiliesprogram.org/ is one evidence-based program with longitudinal use nationally and internationally, though not specific to opioids

Pregnancy

- Only about 50% of women in treatment for OUD and other substance use disorders (including alcohol) are using contraception
- Women currently on treatment for OUD do not have to stop their medication during pregnancy
- Medication doses will need to be adjusted during pregnancy due to physiologic metabolic changes
- Initiation with buprenorphine (without naloxone) or methadone during pregnancy are recommended

https://store.samhsa.gov/product/Clinical-Guidance-for-Treating-Pregnant-and-Parenting-Women-With-Opioid-Use-Disorder-and-Their-Infants/SMA18-5054

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Pregnancy

- Healthcare professionals may want to reassure women that, to date, research has not shown that buprenorphine and methadone can cause an increase in birth defects (Committee on Healthcare for Underserved Women, ASAM, & American College of Obstetricians and Gynecologists, 2017; Holbrook & Rayburn, 2014) and has minimal long-term neurodevelopmental impact (ASAM, 2015).
- About 50% of neonates *will* have neonatal abstinence syndrome, worse with methadone and this needs to be anticipated and managed

Breastfeeding

- Naltrexone is not recommended for use during pregnancy but can be used while breastfeeding
- Breastfeeding is possible and encouraged in most protocols while women are treated with buprenorphine or methadone

Elderly Patients

- Methadone has renal and hepatic decreased dosing and may be used with significantly reduced renal function (Epocrates, 2020)
- Naltrexone does not have well defined renal or hepatic dosing (Epocrates, 2020)
- Buprenorphine does not require different dosing for renal impairment, severe hepatic impairment requires a reduction of up to 50%
- Slower titration up of any medication is suggested for elderly patients to monitor effects
- Pain management with buprenorphine is effective and well tolerated in the elderly and comorbid OUD and pain can be treated with buprenorphine

Take Home Message

- Most of your patients, regardless of age, health status, or pregnancy are potential candidates for buprenorphine treatment
- Do not miss the opportunity to discuss and encourage this option in your interactions with them

What

- What we are treating is opioid use disorder and the associated risk to health and well-being
- Buprenorphine and methadone are used to treat symptoms of craving and withdrawal so that patients can focus on engaging in positive changes in their health and well being
- Medications for OUD need to be appropriately prescribed within a network of support which promotes behavioral health
- OUD is a chronic health condition and data indicates treatment with pharmacotherapy is both cost effective and cost beneficial over the long term

What

- The TIP expert panel (Treatment Improvement Protocol/SAMHSA) recommends that healthcare professionals screen patients for alcohol, tobacco, prescription drug, and illicit drug use at least annually.
- Buprenorphine does not treat alcohol, tobacco, or prescription drug use other than opioids (more than 80% of patients who are opioid dependent smoke cigarettes)
- Naltrexone can be used to treat concurrent alcohol and opioid use disorder, BUT since it does not alleviate withdrawal symptoms patients must be free of alcohol and opioids for 7-10 days

https://www.samhsa.gov/medication-assisted-treatment/treatment/naltrexone

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PRESCRIBING CONSIDERATIONS	METHADONE	NALTREXONE	BUPRENORPHINE
Mechanism of Action at mu-Opioid Receptor	Agonist	Antagonist	Partial agonist
Phase of Treatment	Medically supervised withdrawal, maintenance	Prevention of relapse to opioid misuse, following medically supervised withdrawal	Medically supervised withdrawal, maintenance
Route of Administration	Oral	Oral, intramuscular extended-release	Sublingual, buccal, subdermal implant, subcutaneous extended release injection
Possible Adverse Effects	Constipation, hyperhidrosis, respiratory depression, sedation, QT prolongation, sexual dysfunction, severe hypotension including orthostatic hypotension and syncope, misuse potential, neonatal abstinence syndrome	Nausea, anxiety, insomnia, precipitated opioid withdrawal, hepatotoxicity, vulnerability to opioid overdose, depression, suicidality, muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders **Intramuscular:** Pain, swelling, induration (including some cases requiring surgical intervention)	Constipation, nausea, precipitated opioid withdrawal, excessive sweating, insomnia, pain, peripheral edema, respiratory depression (particularly combined with benzodiazepines or other CNS depressants), misuse potential, neonatal abstinence syndrome **Implant:** Nerve damage during insertion/removal, accidental overdose or misuse if extruded, local migration or protrusion **Subcutaneous Injection:** Injection site itching or pain, death from intravenous injection
Regulations and Availability	Schedule II; only available at federally certified OTPs and the acute inpatient hospital setting for OUD treatment	Not a scheduled medication; not included in OTP regulations; requires prescription; office-based treatment or specialty substance use treatment programs, including OTPs	Schedule III; requires waiver to prescribe outside OTPs **Implant:** Prescribers must be certified in the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program. Providers who wish to insert/remove implants are required to obtain special training and certification in the REMS Program **Subcutaneous Injection:** Healthcare settings and pharmacies must be certified in the Sublocade REMS Program and only dispense the medication directly to a provider for administration

Adapted with permission.[18] Copyright 2017. UBM Medica. 131265:0917SH

When

- Methadone and Buprenorphine= may be used as part of medically supervised withdrawal from opioids to change a patient over to naltrexone
  - OR started when patient has recently used opioids but should be monitored carefully (particularly methadone which has overdose risk)
- Naltrexone= can only be used after medically supervised withdrawal, exerts no opioid effects and cannot cause overdose.

No evidence favors one treatment over the other, but they differ in use, administration and legal requirements

EXHIBIT 2.13. DSM-5 Criteria for OUD[73]

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period of time than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused by or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that's likely to have been caused or exacerbated by the substance.
10. Tolerance,* as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect
    b. A markedly diminished effect with continued use of the same amount of an opioid
11. Withdrawal,* as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome
    b. The same—or a closely related—substance is taken to relieve or avoid withdrawal symptoms

*This criterion is not met for individuals taking opioids solely under appropriate medical supervision.

Severity: mild = 2–3 symptoms; moderate = 4–5 symptoms; severe = 6 or more symptoms

Where

- Methadone is a controlled substance that can only be dispensed by a federally certified opioid treatment facility
- Buprenorphine is a controlled substance which can be prescribed for a patient by a qualified clinician. Telehealth is currently a federally allowed method for evaluating a patient and authorizing a prescription for buprenorphine (not methadone)
- Naltrexone is not a controlled substance and can be administered in any clinical setting or prescribed without special certification to a pharmacy

https://tinyurl.com/y7u6pesz

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Why

Aren't you just replacing one drug with another?

In this case you are replacing very dangerous and lethal drugs with a very safe and controlled medication called buprenorphine. There are very few side effects with this medication and in fact most people have no side effects except mild constipation. When patients are on this medication, they will be able to taper to a lower dose as time goes on. Some patients can even taper completely off the medication although that is not a high priority. The highest priority is to treat this chronic relapsing disease of the brain and keep people alive long enough for their brains and mental health to heal.

Credit: Deborah Wachtel, MPH, DNP
Nurse Practitioner, Vermont

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Why

How can patients get clean if you are not promoting abstinence?

Only 13 percent of patients who tapered from methadone had successful outcomes (no treatment reentry, death, or opioid-related hospitalization within 18 months after taper). Clinical trials of extended release naltrexone versus treatment without medication also found increased risk of returning to illicit opioid use after discontinuing medication.

Continued buprenorphine improves treatment retention and reduced illicit prescription opioid use compared with buprenorphine dose taper (SAMSHA, 2020). Initial stabilization with buprenorphine/naloxone vs. tapering lead to long term abstinence from opioids (42 months) of 80% vs. 51%. This is IF they made it to 18 months.

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Why

How can I be sure patients won't just sell their medications?

The vast majority of patients seeking help for their addiction are desperately wanting to get their lives back. They are very motivated to recover from this disease and want their medication. It is up to society to identify the social determinants of health that might cause someone to NEED to sell their medication and assist with improving their food, housing, and job insecurities. It is also widely recognized that buprenorphine is very safe and life-saving and many people with OUD started their own recovery (when they could not get into treatment program) by purchasing buprenorphine off the streets.

Credit: Deborah Wachtel, MPH, DNP

Nurse Practitioner, Vermont

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Why

What if a patient doesn't want help?

- Many patients are conflicted about their own health and habits. This is no different than patients I see every day in primary care. Trusted health professionals create safe space where patients can explore their ambivalence and find motivation for change.
- Meet the patient where they are and be there for them.

How

- Medications for OUD can be prescribed by:
  - MD/DO
  - Physician Assistant
  - Nurse Practitioner
  - Clinical Nurse Specialists, Certified Registered Nurse Anesthetists, Certified Nurse Midwives

Specific registration with the Drug Enforcement Administration is required for buprenorphine and is site specific.

https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/treatment-practitioner-locator

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Questions?

- Questions and Feedback

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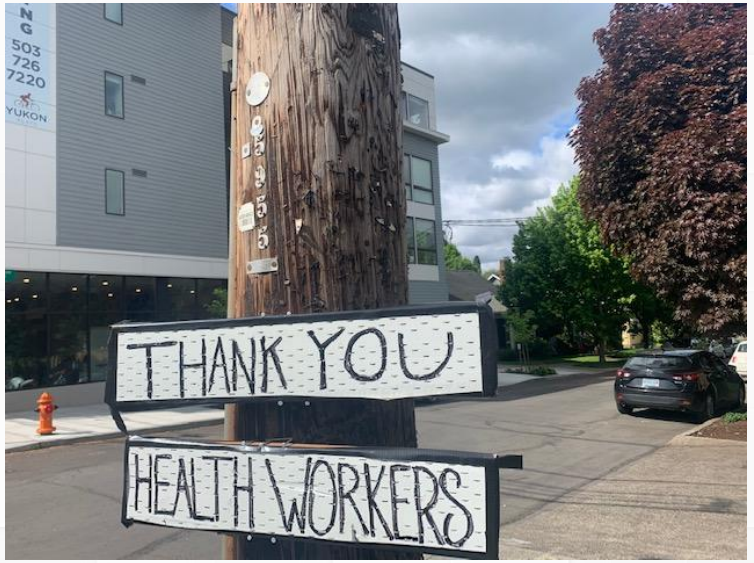
- https://labs.wsu.edu/tracy-klein/



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