Considerations for Evzio® (naloxone) and Suboxone® (buprenorphine and naloxone) Use

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Dr. Broder indicated no potential conflict of interest to this presentation. She does not intend to discuss any unapproved/investigative use of a commercial product/device.

Objectives

• Naloxone: how to prescribe it and who needs it
• Buprenorphine: pharmacology, side effects, and contraindications
• Special considerations for buprenorphine use
• Office-based opioid treatment
Naloxone

Steve’s Law

- Named after Steve Rummler, who died of an overdose in Minnesota in 2011
- Provides immunity to those who call 911
- Allows law enforcement and the public to access and administer naloxone
- Providers can prescribe to third parties if they may witness an overdose

- prescribetoprevent.org
Naloxone Prescribing

- Naloxone is an opioid antagonist used to treat opioid overdoses
- Should be prescribed to anyone at risk for an overdose
  - History of overdose
  - Any suspicion of non-medical use
  - On methadone or buprenorphine (Suboxone®)
  - Taking the equivalent of 50 mg of morphine or more per day
  - Age >65, Smoking, COPD, emphysema, asthma, sleep apnea, respiratory infection, or other respiratory illness or potential obstruction, renal dysfunction, hepatic disease, cardiac illness, HIV/AIDS
  - Known or suspected concurrent alcohol use
  - Concurrent benzodiazepine or other sedative prescription
  - Known recent suicidal ideation

Naloxone Prescribing

- Narcan® Nasal Spray
  - Very easy
  - Relatively inexpensive
    - ($75 for 2)
  - 4mg/0.1mL
  - 2 per package
  - Spray 0.1mL into one nostril
  - May repeat with second device in 2-3 minutes if little or no response
Naloxone Prescribing

• Evzio® Auto-Injector
  • Very Easy
  • 0.4mg/4mL
  • 2 per box (and trainer)
  • Very expensive
    • $3-4,000
  • Button speaks directly to you
  • Inject into outer thigh as directed by English voice-prompt system. Place black side firmly on outer thigh and depress and hold for 5 seconds. Repeat with second device in 2-3 minutes if no or minimal response.

Naloxone Prescribing

• Med and MAD
  • Assembly
  • Relatively cheap
  • 1mg/mL
  • #2 2 mL Luer-Jet™ Luer-Lock needleless syringe plus #2 mucosal atomizer devices (MAD-300)
  • Spray 1 ml (1/2 of syringe) into each nostril. Repeat after 2-3 minutes if no or minimal response.
Naloxone Prescribing

• Med and Needle
  • Assembly
  • Very cheap
  • 0.4mg/mL
  • #2 single-use 1 ml vials PLUS #2 3 mL syringe w/ 23-25 gauge 1-1.5 inch IM needles
  • Inject 1 mL in shoulder or thigh. Repeat after 2-3 minutes if no or minimal response

Suboxone® (Buprenorphine and Naloxone)
Intro to Buprenorphine

• Buprenorphine is a partial opioid agonist used in treatment of opioid use disorder and chronic pain
• Suboxone® is a combination of buprenorphine and naloxone
  • Zubsolv® sublingual tablet
  • Suboxone® sublingual film
  • Bunavail™ buccal film
  • Generics
• Naloxone is ineffective when used sublingually or orally but has excellent bio-availability when injected, blocking the high and potentially precipitating withdrawal from full opioid agonists

Intro to Buprenorphine

• Slow onset, long-acting μ opioid partial agonist
  • Relieves withdrawal from other opioids
  • Controls cravings
• Effects increase only to a certain point with increased dose, and level off at moderate doses (less abuse)
• Ceiling effect on respiratory depression
• Mildly reinforcing (improves treatment adherence)
• Very high affinity for and slow dissociation from μ receptors
  • Buprenorphine partially or totally blocks the effects of abusable opioids, such as heroin and oxycodone
  • Can precipitate withdrawal
Indications for Buprenorphine:
Opioid Use Disorder

• Problematic pattern of opioid use leading to clinically significant impairment or distress – DSM 5 criteria
• Heroin addicts
• Prescription opioid abuse
  • Obtaining pills illegally
  • Fabricating or exaggerating pain
  • Legitimate pain but using pills in excess of what is needed to treat the pain

Why Use Buprenorphine

• Buprenorphine has been shown in multiple studies to be as effective as methadone in suppressing opioid misuse
• Ceiling effect for respiratory depression with buprenorphine
• Somewhat less risk of abuse compared to methadone
• Methadone can only be prescribed by specially accredited opioid treatment programs for the treatment of opioid use disorder
• With extra training, non-addiction specialists can obtain a waiver from the DEA to prescribe buprenorphine to treat opioid use disorder
  • 8 hours for physicians, 24 hours for NPs and PAs
Pharmacokinetics

- Bioavailability depends on route of administration
  - Oral: Rapidly metabolized
  - Transmucosal: Skips first-pass metabolism
- Primarily metabolized in GI tract and the liver, using the CYP 3A4 system
- Most metabolites are excreted fecally rather than renally -> relatively safe for patients with renal insufficiency

Effects of Buprenorphine

- Buprenorphine treatment maintains physical dependence
- Tolerance and physical dependence develop more slowly but patients still experience withdrawal
  - Somewhat less severe than withdrawal from a full agonist, however, withdrawal from buprenorphine still can be severe and prolonged even with a taper
  - Relapse rates after tapering from buprenorphine are very high
Buprenorphine Side Effects

• Safe when used as indicated.
• Side effects are rare, usually minor, and similar to side effects of other opioids. Some of the most commonly reported side effects of Suboxone® include:
  • Headaches
  • Withdrawal syndrome (Consider whether withdrawal may have been precipitated)
  • Pain
  • Nausea and vomiting
  • Constipation
  • Insomnia
  • Sweating
  • Numb mouth and painful tongue

Buprenorphine Side Effects

• An evaluation of waiver programs found that only 0.4% inducted onto buprenorphine ever experienced severe adverse reactions. The specific reactions reported were:
  • Withdrawal (n=103)
  • Allergic reactions (12)
  • Respiratory depression (9)
  • Drug interactions (9)
  • Liver problems (2)
  • Renal insufficiency or aggravation of it (2)
  • Unspecified (80)
Buprenorphine Side Effects

- Other less common side effects seen in opioids are also seen with buprenorphine
  - Sleep disordered breathing.
  - Included in several safety warnings for all opioids
    - Serotonin syndrome
    - Adrenal insufficiency
    - Decreased sex hormone levels with chronic use
    - Less common with buprenorphine compared to other full agonist opioids

Contraindications

- Patients who have suffered a head injury or have intracranial lesions.
- Patients with a history of hypersensitivity to buprenorphine.
- Patients with elevated liver function testing 3-5 times greater than normal.
- Patients with moderate to severe hepatic impairment.
- Patients who indicate benzodiazepine abuse.
- Patients with at risk alcohol use or alcohol use disorder.
Drug Interactions

- Benzodiazepines, alcohol, sedative-hypnotics, tranquilizers, other opioids, muscle relaxants, gabapentin
- Anticholinergics (including inhaled)
- Drugs metabolized by the CYP 3A4 system:
  - Azole antifungals
  - Macrolide antibiotics
  - HIV protease inhibitors
  - Antidepressants (e.g., fluoxetine, fluvoxamine, and amitriptyline)
  - Antiseizure meds (e.g., phenobarbital, carbamazepine, phenytoin)
  - Rifampicin

Special Populations

- **Pregnancy:** Use buprenorphine only
- **Adolescents:** Adolescents who are over age 16 and have had opioid use disorder for a year or more may be suitable for office-based treatment
- **Elderly:** May be used in elderly; consider lower dose
Phases of Buprenorphine Treatment

- **Induction:** Start buprenorphine treatment when the patient is in an appropriate state of withdrawal and to find the patient’s ideal daily dose (minimizes both side effects and drug craving).
- **Stabilization:** Eliminate opioid use other than buprenorphine. Continues until your patient is no longer experiencing withdrawal symptoms or intense cravings.
- **Maintenance:** Continue daily dose of buprenorphine to prevent relapse. Likely indefinite.

Office-Based Opioid Treatment in Primary Care

- There is a large, unmet need for treatment of opioid use disorder.
  - Only 10 to 15% of individuals who have opioid use disorder receive treatment
- Incorporating treatment into primary care increases availability and accessibility of treatment.
  - Reaches patients who would otherwise not seek treatment
- It’s effective
Prevalence of Buprenorphine Use

- Approximately 36,000 providers were waivered to prescribe buprenorphine at the end of 2016 (around 6% of the physicians and surgeons in the US)
- There are more than twice as many people maintained on buprenorphine as methadone
- 9.3 million buprenorphine prescriptions were filled in the U.S. in 2012

Special Considerations – Chronic Pain

- Many patients with opioid use disorder have chronic pain
- An ASAM Consensus Panel on buprenorphine treatment determined that there is insufficient data to recommend the use of buprenorphine for the treatment of acute or chronic pain in patients with a history of opioid use disorder
- A panel of experienced prescribers noted that patients having continuing chronic pain and opioid use disorder can be more challenging to treat in office-based opioid treatment
- Twice daily dosing may help
Special Considerations – Postoperative or Acute Pain

• Continue buprenorphine
• Provide regional anesthesia, increase the buprenorphine dose, add a high-potency opioid such as fentanyl (1 mg Suboxone® = 75-90 mg morphine)

If Your Patient is on Buprenorphine...

• They will (should) likely be on it indefinitely
• There are many medication interactions
• Be aware of common side effects (e.g., constipation)
• Be aware of potential serious adverse events (sedation, hepatitis)
• Special considerations for acute pain (injuries, accidents, surgery)
  • Probably will be managed by buprenorphine prescriber
  • High enough doses of full opioid agonists will work
• Concurrent psychosocial treatment is very important
If You Want to Prescribe Buprenorphine...

• Non-addiction specialists can obtain a waiver to prescribe
  • 8 hours for physicians (online)
    • https://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training
  • 24 hours for NPs and PAs (in process) – may take initial 8 hours online now
    • pcssmat.org
• Must have capacity to provide or refer patients for counseling

• Can prescribe buprenorphine for hospitalized patients without a DEA waiver

Resources/References
• steverummlerhopenfoundation.org
• Prescribetoprevent.org
• Substance Abuse and Mental Health Services: www.samhsa.gov
• Provider’s Clinical Support System for Medication Assisted Therapy: pcssmat.org
• Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Mattick et al. Cochrane Database Syst Rev. 2014 Feb 6;(2):CD002207


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