Treatment of Opioid Use Disorder

Samuel Martin, MD
Assistant Clinical Professor
Department of Psychiatry and Behavioral Sciences
Oklahoma State University Center for Health Sciences

Disclosure Information

- Samuel Martin, MD
  - No disclosures

Objectives

- Review history of opioid addiction treatment in the United States
- Discuss the role of naloxone rescue kits in outpatient practice
- Review outpatient medication assisted treatment options for opioid addiction

Opioid History in the 1800s

- Opium extracts used in medications as early as the 18th century
- First apparent concern of an “opioid problem” in the U.S. began in the early 19th century in the form of smoking opium
- Morphine was compounded in the early 19th century
- First apparent concern of an “opioid problem” in the U.S. began in the early 19th century in the form of smoking opium
- Invention of the hypodermic needle in the 1840s allowed for a new form of administration
- Physicians began to recognize the habit-forming behaviors associated with morphine in 1870 following extensive use in the American Civil War
- By 1900 there were an estimated 300,000 opioid addicted individuls in the U.S.
- Morphine maintenance clinics were established in 44 cities across the United States in response to the epidemic

Opioid History in the Early 1900s

- An uprise in the number of opioid related crimes occurred in the 1920s likely due to the Harrison Act's mandatory closure of morphine maintenance clinics
- Congress appointed two treatment facilities in Fort Worth, Texas, and Lexington, Kentucky, in 1929 called "narcotic farms"
  - Allowed for individuals to voluntary detoxify from opioid within the facility
  - Served as facilities for Federal court mandated prison inmates who had opioid addiction
  - Atmosphere was "prison-like" and relapse rates were 93-97% within 5 years
- Heroin epidemic began in New York City following World War II
  - Riverside Hospital for adolescents with addiction disorders was established in 1952
  - Relapse rated were high (~86% within 2 years)

Early Regulatory Legislation

- Pure Food and Drug Act of 1906 created the Food and Drug Administration
  - Required manufacturers to label products that contained "dangerous substances" including opium, cocaine, alcohol, and marijuana
  - Failure to comply lead to seizure and destruction of the goods as well as a public posting of the violation
- Importation of smoking opium prohibited in 1909
- Harrison Narcotics Tax Act of 1914 placed strict controls on opioids and cocaine
  - Manufacturers, pharmacists, and physicians were required to to licensed, keep records for inspection, and pay fees to the US Department of Treasury
  - Mandated that physicians and dentists only dispense or distribute opioids to patients inside their practice
  - Prohibited prescribing opioids to persons with addiction to maintain their addiction
  - Legislation's position stated that addiction was not a disease, thus, the person with addiction was not a patient

Opioid History in the Early 1900s

- An uprise in the number of opioid related crimes occurred in the 1920s likely due to the Harrison Act's mandatory closure of morphine maintenance clinics
- Congress appointed two treatment facilities in Fort Worth, Texas, and Lexington, Kentucky, in 1929 called "narcotic farms"
  - Allowed for individuals to voluntary detoxify from opioid within the facility
  - Served as facilities for Federal court mandated prison inmates who had opioid addiction
  - Atmosphere was "prison-like" and relapse rates were 93-97% within 5 years
- Heroin epidemic began in New York City following World War II
  - Riverside Hospital for adolescents with addiction disorders was established in 1952
  - Relapse rated were high (~86% within 2 years)

Opioid History in the Mid-1900s

- Heroin related deaths in New York City increased from 7.2 to 35.8 per 10,000 deaths between 1950 and 1961
- In 1958 the American Bar Association and the American Medical Association issued a report recommending outpatient facility prescribing of opioids to treatment addiction
- By 1965 heroin related mortality became the leading case of death for young adults in New York City from ages 15 to 35
- Dr. Vincent Dole published a paper on the efficacy of methadone maintenance in 1965
- Controlled Substance Act of 1970 required all manufacturers, distributors, and practitioners who prescribe or dispense controlled substances register with the DEA
- The Narcotic Addict Treatment Act of 1974 amended the Controlled Substance Act to allow opioid drugs to treat opioid addiction in federally approved facilities

Amended Controlled Substance Act

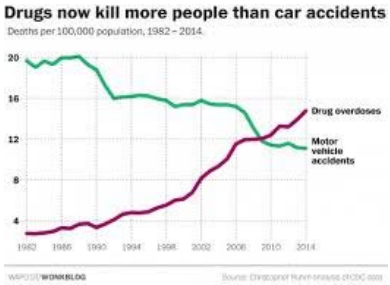
- Drug Addiction Treatment Act of 2000: “Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment”
- Revision in legislation allows a physicians to prescribe narcotic drugs in schedules III, IV, V, or combinations of such drugs for the treatment of opioid dependence
- Drugs and practitioner must meet certain requirements

Practitioner Requirements

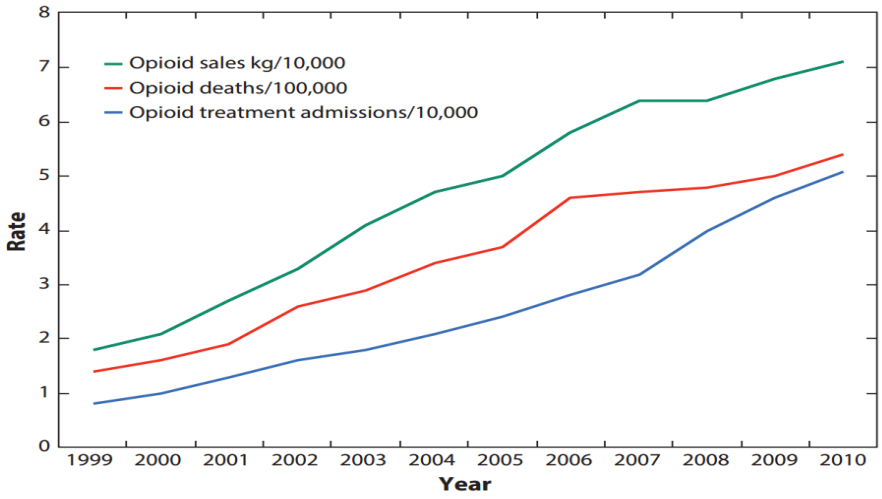
- Be a “qualifying physician”
- Nurse practitioners and physician assistants allowed to prescribe since 2016
- Have capacity to refer patients for appropriate counseling and ancillary services
- No more than 30 patients the first year (can be expanded to 100 patients after the first year)
- Physicians holding certification in Addiction Medicine or Addiction Psychiatry were authorized to treat up to 275 patients via the Comprehensive Addiction Recovery Act (2016)
- Notify the Secretary of HHS in writing of name, DEA registration, practice location, qualifying criteria, capacity to refer to appropriate ancillary services

MODERN OPIOID HISTORY

- Project Lazarus begins in 2007 in North Carolina to help reduce opioid overdose death
- Naltrexone is approved by the FDA for treatment of opioid addiction in 2010
- CDC declares epidemic of overdose deaths in 2011
- Oklahoma mandates PMP monitoring for opioids, benzodiazepines, and carisoprodol



OPIOID SALES, DEATHS, AND TREATMENT ADMISSIONS



Kolodny, A., et al. Annual Rev Public Health

CDC Guidelines

CDC Opioid Guidelines of 2016

- Developed without input from experts with ties to opioid pharmaceutical industry
- Defined greater than 50 mg morphine equivalents as high dose and greater than 90 mg morphine equivalents to be avoided
- Stated that three days or less will often be sufficient for treatment of acute pain
- Stated that non-pharmacologic therapy and non-opioid pharmacologic therapies are preferred for chronic pain

Naloxone Rescue Kits

- Naloxone rescue can be prescribed to help reduce mortality from opioid overdose
- Proven effective in reducing community overdose deaths in North Carolina and Massachusetts[1]
- Recommended for the following:[2]
  - Individuals with suspected or known opioid or heroin addiction
  - Individuals with opioid overdose history
  - Individuals taking greater than 50 morphine equivalents per day
  - Individuals on concurrent opioid and benzodiazepine use

Oklahoma Overdose Prevention Naloxone Initiative

- Oklahoma ranks fifth in the United States in overdose deaths from prescription medications
- ODMHSAS has made free naloxone rescue training available to all first responders
- ODMHSAS has also provided funding for pharmacies and facilities to provide free Narcan Nasal Spray to eligible facilities
- Dispensing pharmacies and facilities can be found at takeasprescribed.org

NARCAN NASAL SPRAY

- FDA approved for intranasal use
- No assembly required
- Manufacturer: Adapt Pharma
- Strength: 4 mg/0.1 mL
- Total Package Volume: 8 mg/0.2 mL
- Cost: $$

NARCAN NASAL SPRAY

- Rx: #1 two-pack of two 4 mg/0.1 mL intranasal devices
- Sig: Spray 0.1 mL into one nostril. Repeat with second device into other nostril after 2-3 minutes if no or minimal response.
- Refills: 2

EVZIO

Figure 1. Evzio Auto-injector. Image courtesy of Kaleo, Inc.
Source: Reference 16.

- FDA approved for intranasal use
- Manufacturer: kaleo
- No assembly required
- Strength: 0.4 mg/0.4 mL
- Total Package Volume:0.8 mg/0.8 mL
- Cost: $$$

EVZIO

Figure 1. Evzio Auto-injector. Image courtesy of Kaleo, Inc.
Source: Reference 16.

- Rx: #1 two-pack of two 0.4 mg/0.4 mL prefilled auto-injector devices
- Sig: Inject into outer thigh as directed by voice-prompted 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.
- Refills: 2

NALTREXONE

Oral Naltrexone

Injectable Naltrexone

NALTREXONE

- Oral naltrexone (ReVia) was approved for treatment of alcohol addiction in 1994 and has seen increased use for opioid addiction since the approval of the long-acting version for opioid addiction
- Long-acting naltrexone (Vivitrol) was approved for treatment of alcohol dependence in 2006 and opioid addiction in 2010
- Blockades mu opioid receptorsand prevents opioid agonists from binding

Clinical Use of Oral Naltrexone

- Administered orally in tablet form
- Available in 50 mg tablets
- Generic form is available
- FDA approved dosage in 50 mg daily (give an initial 25 mg dosage to assure the individual has completed withdrawal and then continue 25 mg daily for 3-7 days to decrease side effect potential)
- Clinically used in dosages up to 150 mg daily (can increase dosage by 25 mg every 3-7 days until desired effect)

Clinical Use of Oral Naltrexone

- Common Side Effects: nausea and other gastrointestinal disturbances, headache, dizziness, lightheadedness, weakness
- Side effects are usually transient and are best dealt with by delaying or avoiding dosage increases
- Rare Common Side Effect: black box warning on hepatotoxicity
- Monitor LFTs at baseline and quarterly after initiation
- Will block opioid action at the mu receptor and cause precipitated withdrawal in individuals who are physiologically dependent on opioids

Clinical Use of Injectable Naltrexone

- Administered intramuscularly in prepackaged solution
- Available in 380 mg IM solution
- No generic form available
- FDA approved dosage in 380 mg IM every 4 weeks in the buttocks
- Must be opioid free for 7-10 days prior to administration to prevent precipitated withdrawal
- Consider naloxone challenge test of risk of withdrawal is suspected

Clinical Use of Injectable Naltrexone

- Common Side Effects: nausea and other gastrointestinal disturbances, headache, dizziness, lightheadedness, weakness, pain and inflammation at injection site
- Rare Common Side Effect: black box warning on hepatotoxicity (appears to be less so than oral version)
- Individuals have option to carry a card in their wallet, wear a wrist band, or wear a dog tag identifying use of Vivitrol in case emergency situations warrant surgery and/or pain relief

Characteristics of Buprenorphine Mu Receptor Binding

- Buprenorphine is a partial agonist of the mu receptor
- Buprenorphine has a high mu receptor affinity
  - Therefore, it will displace most full mu agonists
- Buprenorphine has slow mu receptor dissociation
  - Therefore, it will remain on the receptor a long time and prevents binding of full mu agonists
  - Despite slow dissociation it has relatively short analgesics effects

Full Mu Receptor Agonists vs Partial Mu Receptor Agonists

Full Agonist

- Activates the mu receptor
- Is highly reinforcing
- Results in high level of abuse
- Includes morphine, methadone, hydromorphone, codeine, fentanyl, heroin, oxycodone, and hydrocodone

Partial Agonist

- Activates the mu receptor at lower levels
- Is relatively less reinforcing
- Results in less abuse
- Includes buprenorphine

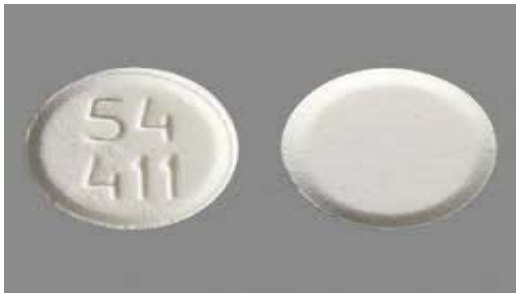
Buprenorphine for Maintenance Treatment

- Buprenorphine is more effective than placebo in decreasing positive opioid drug screens
- Buprenorphine is equally effective as moderate doses of methadone (up to 60mg daily)
- There is unclear data comparing buprenorphine effectiveness to high doses of methadone (>80mg daily)

Submucosal Buprenorphine Products

- Buprenorphine sublingual tablet
- Buprenorphine/naloxone sublingual tablets
- Buprenorphine/naloxone sublingual films
- Buprenorphine/naloxone buccal films

Buprenorphine Sublingual Tablets



- Previously marketed under trade name Subutex
- Available only as generic medication now
- Orange citrus flavor
- Sublingually absorbed
- Dosages Available: 2 and 8 mg SL tablets

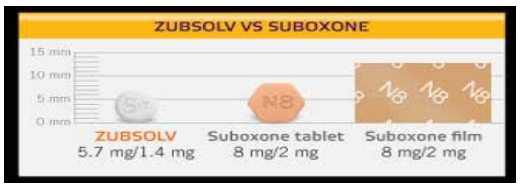
BUPRENORPHINE/NALOXONE SUBLINGUAL TABLET

- Previously marketed under trade name Suboxone
- Available only as generic medication now
- Orange citrus flavor
- Sublingually absorbed
- Dosages Available: 2-0.5 and 8-2 mg SL tablets

BUPRENORPHINE/NALOXONE SUBLINGUAL FILM

- Marketed under trade name Suboxone Film
- No generic available
- Orange citrus flavor
- Sublingually absorbed
- Dosages Available: 2-0.5, 4-1, 8-2 and 12-3 mg SL strips

BUPRENORPHINE/NALOXONE MENTHOL SUBLINGUINAL TABLET



- Marketed under trade name Zubsolv
- No generic available
- Mint flavor
- Sublingually absorbed
- Dosages Available: 0.7-0.18, 1.4-0.36, 2.9-0.71, 5.7-1.4, 8.6-2.1 and 11.4-2.9 mg SL tablets

BUPRENORPHINE/NALOXONE BUCCAL STRIPS

- Marketed under trade name Bunavail
- No generic available
- Buccally absorbed
- Citrus flavor
- Dosages Available: 2.1-0.3, 4.2-0.7, and 6.3-1 mg SL buccal strips

ADVANTAGES OF COMBINED BUPRENORPHINE/NALOXONE

- Sublingual naloxone has relatively poor bioavailability
- Doses of up to 1-2 mg of sublingual naloxone do not precipitate opioid withdrawal
- Combination tablet containing buprenorphine and naloxone has predominant buprenorphine effects if taken sublingually
- However, if combination pill is dissolved and injected it will have a predominant naloxone effect resulting in precipitated opioid withdrawal

Buprenorphine Implant

- Marketed as Probuphine
- No generic available
- Four 80 mg rods are implanted under the skin of the inner side of the upper arm
- Lasts for 6 months
- Requires training course for certification of use

Buprenorphine Extended-Release Injection

- Marketed as Sublocade
- No generic available
- Administered subcutaneously in the abdomen every 4 weeks by health care professionals after at least a 7 day induction period with sublingual buprenorphine
- Recommended dosage is 300 mg the first 2 months followed by 100 mg afterwards

Buprenorphine Safety Issues

- Primary side effects are the same as other mu agonist opiates (eg. nausea, constipation)
- No significant disruption in cognitive or psychomotor performance
- Potential for transaminase elevation in individuals with hepatitis C
- No reports of teratogenic effects but there is only a minimal number of studies
- Low risk of overdose on buprenorphine alone but this is increased with combination with other medications (eg. opiates, benzodiazepines)

Initial Evaluation: Factors that Decrease Office Based Success

- Dependence on high doses of benzodiazepines, alcohol, and other CNS depressants
- Significant psychiatric comorbidities
- Active or chronic suicidal or homicidal ideations/attempts
- Multiple previous treatments and relapses
- Non-response to buprenorphine in the past

Initial Evaluation: Factors that Decrease Office Based Success

- High level of physical dependence
- Patient needs cannot be addressed with existing office-based resources
- Pregnancy
- Poor support system

Peer Support Groups for Addiction

- Alcoholics Anonymous (AA)
- Narcotics Anonymous (NA)
- Cocaine Anonymous (CA)
- Crystal Meth Anonymous (CMA)
- Dual Recovery Anonymous (DRA)
- SMART Recovery
- Celebrate Recovery
- Secular Organization of Sobriety (SOS)

Peer Support Groups for Family Members of Addicts

- Al-Anon
- Alateen
- Nar-Anon

References

- Davis, C., Walley, A., Bridger, C. Lessons learned from the expansion of naloxone access in Massachusetts and North Carolina. J Law Med Ethics J Am Soc Law Med Ethics. 2015; 43 (Suppl 1): 19-22.
- Kerensky, T., Walley, A. Opioid overdose prevention and naloxone rescue kits: what we know and what we don't. Addiction Science and Clinical Practice. 2017; 12:4.