

Naloxone and Medically Assisted Treatment (MAT) for Opioid Dependence

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Disclaimer

- The opinions and conclusions expressed today are those of the author and do not necessarily represent the views of the Department of Health and Human Services, US Public Health Service, the Indian Health Service or the Ho-Chunk Nation.
- No financial disclosures to report.

Objectives

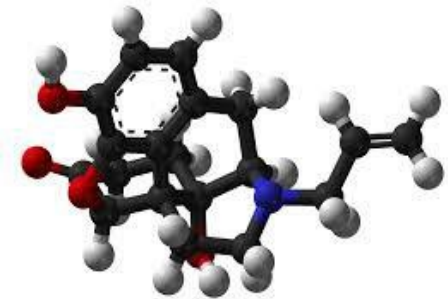
- Identify the indication and clinical application of naloxone treatment for opioid overdose reversal
- Differentiate between the various medically assisted treatment options for opioid dependence substance use disorders
- Formulate most appropriate medication assisted treatment plan based on patient parameters
- Integrate alcohol and other drugs of abuse (AODA) and mental health psychotherapy into medically assisted treatment plans

Epidemiology of Opioid Overdose

- Opioid prescribing has almost doubled since late 1990's due to pain treatment initiatives and guidelines
- Drug overdose death rates increased 102% in the US between 1999 and 2010
 - 60% drug overdose deaths related to pharmaceuticals and 75% involve prescription opioids
- Tightening of opioid prescribing trends have been correlated with increased heroin use and heroin overdose

Naloxone HCl 0.4 mg/ml (Narcan)

- Drug Class: opioid antagonist
 - Essentially pure opioid antagonist
 - Synthetic congener of oxymorphone
- FDA indication: emergency treatment of known or suspected opioid overdose, characterized by decreased breathing or heart rates, or loss of consciousness¹
- Route of Administration: Intravenously (IV), Intramuscularly (IM) or Subcutaneously (SQ)
 - Generally administered by healthcare professional (Paramedic, RN, MD, etc.)



Naloxone HCl 0.4mg Auto-injector (Evzio)

- FDA indication: emergency treatment of known or suspected opioid overdose, characterized by decreased breathing or heart rates, or loss of consciousness¹
- Designed to deliver a dose of naloxone for administration outside of the healthcare setting
- Route of Administration: Intramuscularly or Subcutaneously
- Device provides verbal instruction similar to automated defibrillators
 - Trainer device to assist family/caregivers with familiarity of use
- Estimated out-of-pocket expense is approximately \$600



Intranasal Naloxone 2mg/2ml

- Designed to deliver a dose of naloxone for administration outside of the healthcare setting by lay



- Exhibits opioid antagonist effects almost as rapidly as the IV route with bioavailability approaching 100%¹
- Benefits:
 - No need to learn how to administer an injection or sterile method techniques
 - Elimination of needle stick risk
- Cost per kit: b/t \$12 and \$50+

<http://intranasal.net/OpiateOverdose/#Introduction>



Naloxone Clinical Applications

- Consider prescriptions for patients at high risk of overdose due to high dose prescription opioids
 - 20% overdoses occur in patients prescribed < 100 mg morphine¹
 - 40% overdoses occur in patients prescribed > 100mg morphine¹
- Known or suspected opioid intravenous drug users (IDU) or their caregivers/family members
- Emergency Services and First Responders
 - Ambulances, Paramedics, and [Police](#)

Naloxone General Considerations

- *Repeat Administration:*
 - Repeated doses may be required due to opioid duration of action may exceed that of naloxone
 - Naloxone half life ($t_{1/2}$) ranges from 30-81 minutes¹
- *Withdrawal Precipitation:*
 - Symptoms: body aches, diarrhea, tachycardia, fever, rhinorrhea, piloerection, diaphoresis, yawning, nausea/vomiting, restlessness and irritability, tremors, abdominal cramps, increased blood pressure.
- *Seek immediate medical attention after administration*
- *Third Party Prescribing:* www.prescribetoprevent.org
 - Resource to determine if your state allows prescribing to an individual other than the patient (caregiver/family member)

Medically Assisted Treatment (MAT)

- The goals of treatment for opioid dependence include a decrease in illicit opioid use, decreased mortality, and reductions in criminal activity.¹
- Three main categories:
 - Opioid Agonist
 - Methadone
 - Mixed Opioid Partial Agonist/Antagonist
 - Buprenorphine (Subutex[®])
 - Buprenorphine/naloxone (Suboxone[®])
 - Opioid Antagonist
 - Naltrexone (Revia[®], Vivitrol[®])

MAT: Methadone

- Federal law restricts dispensing of methadone to Federal and State approved opioid treatment programs (OTPs)
- OTPs are licensed and accredited opioid agonist treatment programs
 - Dispense methadone according to highly structured protocols as determined by the Federal and State Government including
 - U.S. DHHS
 - U.S. DEA
 - Various State Agencies
- Medical providers and pharmacies are prohibited to prescribe and dispense methadone for opioid dependence
 - Treatment for pain management indications only is authorized outside of OTPs

MAT: Methadone

- Used in treatment of opioid dependence for almost 50 years¹
- Full opioid agonist binds to cells in the brain and fully activates receptors²
- Used for induction therapy (initial management of withdrawal symptoms to help wean patients from illicit opioid use) or for maintenance treatment²
- Risk of abuse and overdose are substantial challenges with methadone treatment²

Tetrault JM, Fiellin DA. Current and potential pharmacological treatment options for maintenance therapy in opioid-dependent individuals. *Drugs*. 2012;72(2):217-228.

Nosyk B, Anglin MD, Brissette S, et al. A call for evidence-based medical treatment of opioid dependence in the United States and Canada. *Health Aff (Millwood)*. 2013;32(8):1462-1469.

MAT: Methadone

- Pharmacokinetics:
 - $T_{1/2}$ - 8-59 hours
 - Chronic use: may be retained in the liver and then slowly released, prolonging the duration of action despite low concentration levels
- Can cause serious cardiac conduction effects, including prolonged QT interval and Torsades de Pointes
- Exercise caution in dosing frequency and titration
 - Risk of unintentional overdose at prescribed doses

MAT: Buprenorphine and Buprenorphine/naloxone

- Office based opioid replacement therapy with buprenorphine or buprenorphine/naloxone is also restricted by Federal and State Regulations
- Federal Drug Addiction Treatment Act (DATA) of 2000 allows qualified physicians to obtain a waiver (known as an “X” license) to prescribe and/or dispense after receiving special training.
 - Initial waiver restricts treatment to 30 patient concurrently
 - After 1 year, a second waiver may be obtained to increase to a 100 patient at one time maximum

MAT: Buprenorphine and Buprenorphine/naloxone

- Buprenorphine is a partial opioid agonist/antagonist
- Combination Buprenorphine/naloxone
 - 4:1 ratio
 - Naloxone deters diversion and abuse
 - Poor absorption into the body but causes withdrawal symptoms when injected intravenously
- Activates opioid receptors similar to methadone, but activity is diminished as a partial agonist
 - ‘ceiling effect’ limits efficacy at high doses

MAT: Buprenorphine and Buprenorphine/naloxone

- May be used for induction therapy as well as maintenance treatment
- Pharmacokinetics
 - $T_{1/2}$ - 3-44 hours
 - Sublingual (SL) administration due to extensive first pass effect leading to low bioavailability in oral (PO) form
- Target maintenance dose is 16mg/4mg
 - Doses higher than 24mg/6mg have not been demonstrated to provide clinical advantage

Clinical Pearls and Considerations: Methadone and Buprenorphine

- Methadone and Buprenorphine require special lab tests
 - Will not be detected on a standard urine toxicology screen
- Very long half-life of each agent complicate induction and taper to abstinence treatment plans
 - Delayed and prolonged opioid withdrawal syndromes
- Diversion potential
 - High risk for selling or trading for illicit drugs

MAT: Naltrexone

- Complete opioid antagonist
 - Producing blockade at receptors in the brain and preventing euphoria from opioid use
 - Synthetic congener of oxymorphone with no agonist properties
- Oral formulation (Revia[®])
 - Once daily dosing
 - Associated with hepatotoxicity and GI adverse effects
- Long-acting injectable formulation (Vivitrol[®])
 - 380mg once a month (every 28 days) intramuscular dorsogluteal injection
 - Most common adverse effect is local injection site reaction
- Must be opioid free (indicated by absence of opioids on urine toxicology results)
 - Precipitation of immediate and severe opioid withdrawal

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s005s010lbl.pdf

<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=od929bf5-2eaa-4679-8334-1ac159b2b55c>

MAT: Naltrexone

- Pharmacokinetics:
 - Oral formulation $T_{1/2}$ - 4 hours (naltrexone) and 13 hours (6- β -naltrexol; active metabolite)
 - Caution in renal impairment due to primary metabolite excreted in the urine
 - Injectable formulation: concentrations slowly decline after 14 days post administration

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s005s010lbl.pdf

<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=od929bf5-2eaa-4679-8334-1ac159b2b55c>

MAT: Naltrexone Clinical Observations

- Anecdotal observations and patient reports:
 - Significant reduction and elimination of cravings from first dose for both oral and injectable formulations
 - Waning after 3 weeks after injection may cause return of cravings
 - Bridge with oral daily therapy x 1 week or inject earlier than 28 days
- Inpatient detox vs. Outpatient Detox
 - Inpatient detox services are limited
 - Not a medical emergency- often discharged from ER same day
 - Funding limitations
 - Outpatient detox feasible but challenging
 - Refer to Ho-Chunk Nation Primary Care Evidence Based Addiction Withdrawal Supportive Care Treatment Protocol (see attachment)

Comprehensive Integrated Treatment Plan

- All forms of MAT ***must*** be paired with mandatory Alcohol and Other Drugs of Abuse (AODA) and/or
 - Mental Health psychotherapy for effective outcomes
 - Medications are tools to assist the individual achieve
 - sobriety and recovery
- Consider recommending social support groups such as NA and AA to the individual as part of the recovery plan
- Referrals to social services when appropriate to assist with social elements of recovery such as employment and education assistance.

General Concepts

- Realistic and “rapid” opioid tapers with opioid full or partial agonists should be the goal of treatment and discussed at every visit
- No MAT option is a “one size fits all”
 - “Meet the patient where they are at” in their motivational stage for recovery (precontemplation, contemplation, preparation, action, maintenance.)
 - Determine risk to benefit of medically managed addiction with opioid agonists vs. addiction ‘removal’ with opioid antagonist.
- Addiction is not a linear process
 - Expect relapses and set-backs
 - Most important thing is to be available and compassionately firm with every attempt at sobriety
- Addiction is a complicated bio-psycho-social chronic brain disorder
 - Brain is hijacked and aberrant behavior is often out of the individual's control

General Concepts

- Get comfortable with thinking outside the box
 - May need to incorporate parole officers or family members into the treatment plan
- Integrated collaboration is essential
 - Addiction requires an integrated multi-disciplinary team patient centered care approach for successful outcomes
- Case management
 - Medical and Behavioral Health (AODA and Mental Health) professionals need to communicate routinely and share minimum essential information
 - Releases of information and consent forms



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