BUPRENORPHINE

for Opioid Use Disorder

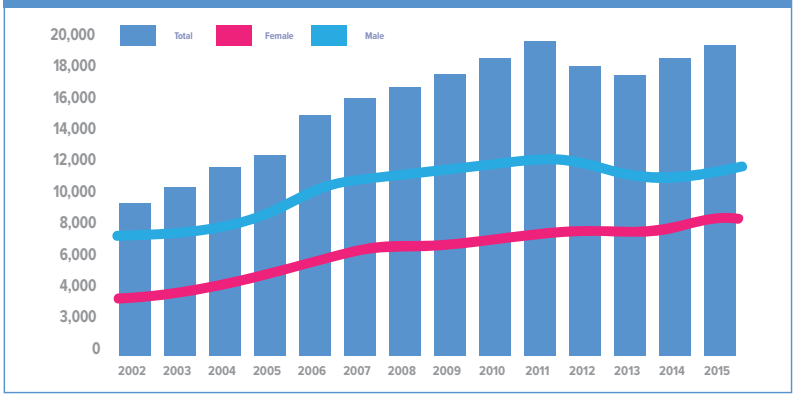
Introduction

The United States is in the midst of an epidemic of opioid overdose and overdose deaths, driven by misuse of opioids.[1,2]

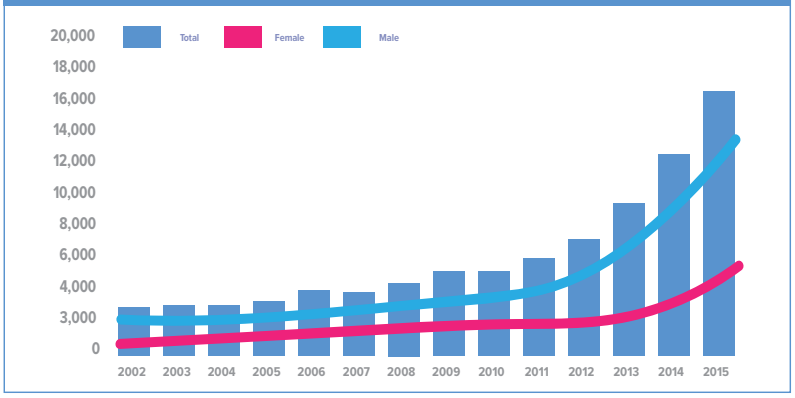
National Overdose Deaths

National prescription opioid and heroin/non-methadone synthetics overdose deaths: 2002-2015.[1]

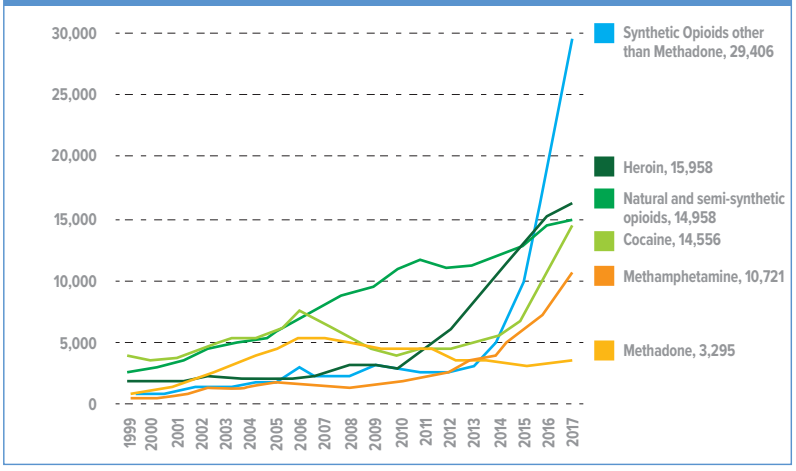
Number of Deaths from Prescription Opioid Pain Relievers (excluding non-methadone synthetics)



Number of Deaths from Heroin and Non-Methadone Synthetics (includes illicit opioids)

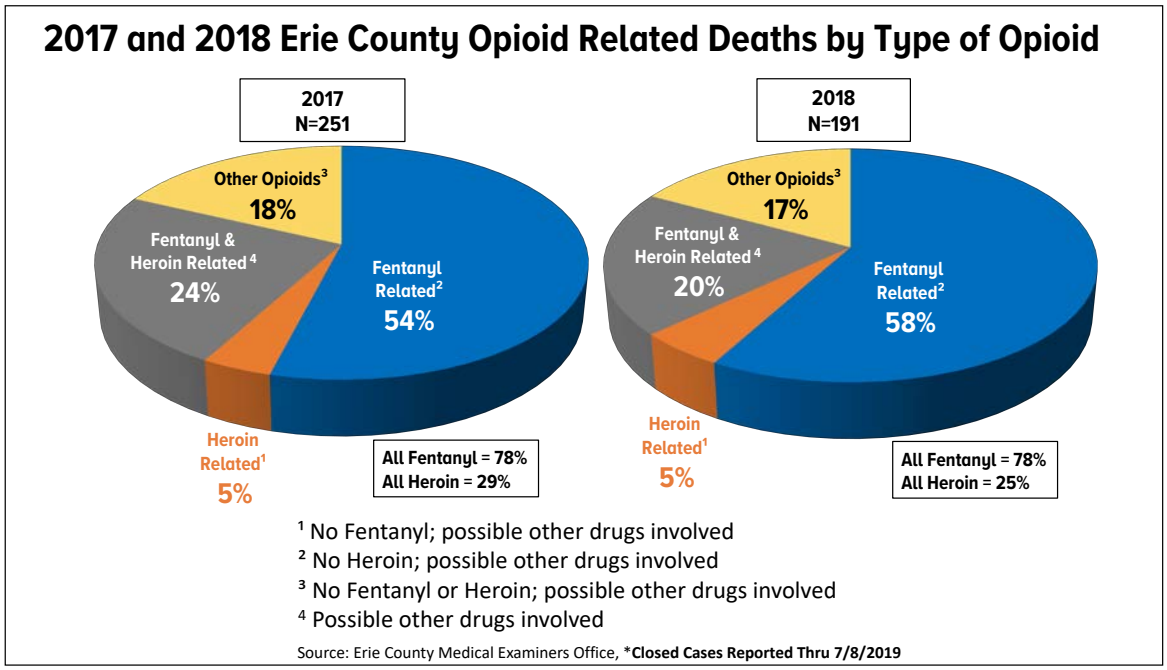


Drugs Involved in U.S. Overdose Deaths, 2000 to 2017



The opioid overdose death epidemic is accelerating, fueled primarily by overdose deaths from illicit opioids. Provisional CDC data indicate that the number of deaths from heroin and other opioids exceeded 53,000 in 2016.[2]

Fentanyl



- The synthetic opioid fentanyl has been implicated in this accelerating wave of opioid overdose deaths. Fentanyl (50-100 times more potent than morphine) is commonly found as an adulterant in the "heroin" sold on the street. Fentanyl derivatives, such as carfentanil, (50-100 times more potent than morphine) have been found episodically in the illicit drug supply as well. **The unpredictability of the concentration of these potent synthetic opioids makes the epidemic increasingly deadly, and the need for effective treatment more urgent.**
- These opioid overdose deaths are preventable.
- Opioid Use Disorder (OUD) is a treatable condition.[5]
- Effective treatment is available.[8,5]
- Opioid Agonist Treatment (OAT) is not "substituting one addiction with another".[6]

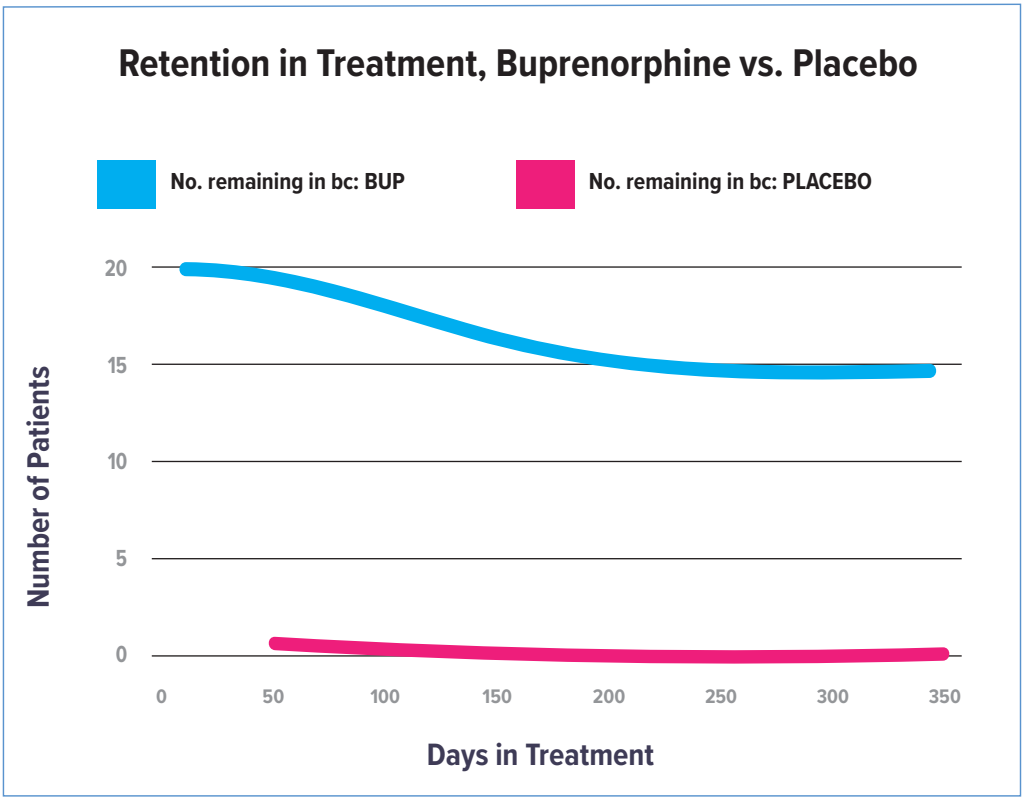
Opioid Use Disorder (OUD) Treatment

- Effective treatment is available to help control OUD and help prevent overdose and death.
- There are three Food and Drug Administration (FDA) - approved medications for use in treatment of OUD. Multiple products are available - see separate handout for the details.
  - Buprenorphine (with and without naloxone)
  - Methadone
  - Naltrexone
- **The choice of medication should be based on effectiveness, safety, patient preference, clinical parameters, affordability, and treatment goals.**
- When considering medication options for treatment of OUD, clinicians should be aware that, at present, the weight of evidence and clinical experience is considerably greater for the efficacy of the agonist medications buprenorphine and methadone, compared to that of naltrexone.[13]

Opioid Agonist Treatment (OAT)

OAT refers to treatment with buprenorphine (with or without naloxone) or methadone.

- OAT works by stopping withdrawal symptoms, decreasing craving, and by blocking the use of other opioids.[5]
- OAT does not "substitute one addiction for another".[6]
- OAT promotes a return to normal biologic, psychologic, and social function.[5]
- OAT decreases crime, improves employment, decreases disease transmission, increases access to health care and housing, decreases overdoses, and saves lives.[14,15]



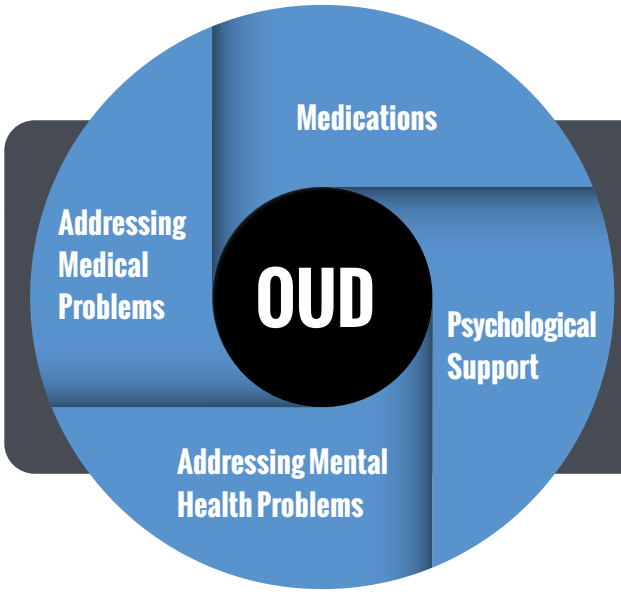
Retention in treatment is better in the buprenorphine group: risk ratio 58.7 (95% CI 7.4-467.4); P=0.0001

Four patients in the placebo group died during the treatment period; there were no deaths in the buprenorphine group (p=0.015).

Agonist treatment with buprenorphine can be extremely effective in promoting abstinence from illicit opioids and retention in treatment.

Potential components of OUD treatment:[17]

Psychosocial support can improve quality of life and outcomes from Substance Use Disorder (SUD) treatment, but is not an absolute requirement for patients on medication for OUD. Providing referral options based on the needs of the patient is sufficient and should be documented.[18]



Psychosocial treatment may include:[18]

- Supportive counseling
- Links to existing family supports
- Referrals to community services
- Cognitive behavioral therapy
- Self-help groups

Risk of misuse is lower with buprenorphine than with full opioid agonists.

- The partial agonist effect of buprenorphine reduces euphoria and decreases the potential for misuse.[5]
- The buprenorphine-naloxone co-formulations are designed to deter injection. When taken as directed (sublingually), there is minimal absorption of the naloxone component. If injected, the naloxone (a pure opioid antagonist) will attenuate the potential euphoric effect. Naloxone, as well as buprenorphine, could precipitate withdrawal in individuals who are physically dependent on opioids.[5,19]
- **When buprenorphine is diverted for illicit use, it is usually for the purpose of trying to self-medicate and manage withdrawal symptoms, often in areas where there is limited access to OAT.[20]**
- When considering medication options for treatment of OUD, clinicians should be aware that, at present, the weight of evidence and clinical experience is considerably greater for the efficacy of the agonist medications buprenorphine and methadone, compared to that of naltrexone.[13]

Taking a Patient-Centered and Public Health Oriented Approach

- People with SUD are often stigmatized, which creates obstacles to effective treatment. Understanding the underlying problem as a health issue rather than a moral failing can reduce stigma and improve access to care.[7]
- Primary care providers are in a unique position to identify substance use problems at an earlier stage in their patients when treatment may be more effective, and in a less stigmatizing environment.[8,9]

Stop the Stigma

- Respectful language can help create an effective, therapeutic environment.
- Non-judgmental terminology and person-first, supportive language are recommended.[10-12]

SAY:

Substance Use Disorder (SUD)
Person with SUD/People Who Use Drugs
Positive or Negative Toxicology

RATHER THAN:

Addiction
Drug Addict
"Clean" or "Dirty" Toxicololgy

Medications for Treatment of OUD[19,21-23]

MEDICATION	SCHEDULE	FORMULATIONS	PHARMACOLOGY	TREATMENT SETTINGS
BUPRENORPHINE	C-III	SL tablet, extended-release SC injection, implant	Partial mu-opioid agonist	Clinician's office, OTP, or other health care setting
BUPRENORPHINE/ NALOXONE	C-III	SL tablet, SL film, buccal film	Partial mu-opioid agonist + full mu-opioid antagonist	Clinician's office, OTP, or other health care setting
METHADONE	C-II	Oral solution liquid concentrate, tablet/ diskette, powder	Full mu-opioid agonist	OTP
NALTREXONE	N/A	Tablet, extended-release IM injection	Full mu-opioid antagonist	Clinician's office, OTP, or other health care setting

All above medications are FDA-approved for OUD treatment. SL=sublingual, SC=subcutaneous, IM=intramuscular, N/A=not applicable, OTP=opioid treatment program. Table adapted from SAMHSA TIP 63.[5]

Key Points

Buprenorphine/Buprenorphine-Naloxone[19,22]

- Buprenorphine should be used cautiously with other Central Nervous System (CNS) depressants, including benzodiazepines, alcohol and other sedative drugs. Deaths have been reported when benzodiazepines are misused, particularly when combined with alcohol.[23,24]
- Effective in controlling OUD, decreasing use of illicit opioids, and decreasing overdose deaths.
- Formulation with naloxone may minimize diversion potential. Partial agonist "ceiling effect" reduces potential for respiratory depression and overdose.
- DEA waiver training required.
- May be useful for treatment of concurrent chronic pain and OUD.
- If interactions with other medications that induce or inhibit CYP enzymes occur, the patient must discontinue other opioid agonists long enough to experience mild-moderate withdrawal symptoms before induction of buprenorphine therapy.
- May be used in office-based treatment of OUD.

Key Points (continued)

Methadone[21]

- Concomitant use of alcohol or other sedative-hypnotics (especially benzodiazepines) may lead to respiratory depression, overdose, and death.
- Use caution in patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse.
- Effective in controlling OUD, decreasing use of illicit opioids, and decreasing overdose deaths.
- Absence of antagonist effect can facilitate transition from illicit opioids.
- May be helpful in patients with more severe OUD or where buprenorphine has not been effective.[15]
- Potential for QT interval prolongation at higher doses.
- Interactions with other medications that induce or inhibit CYP enzymes.
- Not for office-based treatment of OUD. Dispensed in federally-approved Opioid Treatment Programs (OTPs).

Naltrexone[25]

- Contraindicated with concurrent use of opioid analgesics, including methadone or buprenorphine.
- Will precipitate acute opioid withdrawal if administered to a person dependent on opioids.
- Blocks reinforcing effects of opioids.
- No tolerance or withdrawal symptoms upon discontinuation.
- May be useful in stable patients with strong motivation and established recovery programs, or in patients who are required to discontinue OAT.
- Has been found to be useful in treatment of alcohol use disorder.[26]
- Need to stop all opioids for at least 7-10 days before starting treatment, to avoid precipitated withdrawal.
- Increased potential for overdose after discontinuation.[27,28]

Adverse Effects[19,21,22,24]

Buprenorphine

- Adverse effects are similar to those of other opioids: constipation, nausea, vomiting, headache, anxiety and sleep disturbances.

Methadone

- Adverse effects are similar to those of other opioids: constipation, nausea, vomiting, headache, anxiety and sleep disturbances.

Naltrexone

- Adverse effects may include: insomnia, lack of energy/sedation, anxiety, nausea, vomiting, abdominal pain/cramps, headache, cold symptoms, and joint and muscle pain.
- Injection site reactions may be reported for injectable naltrexone.

References

1. NIH, National Institute on Drug Abuse. Overdose Death Rates. Available at https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates. Accessed February 18, 2018.
2. CDC, National Center for Health Statistics. Provisional Counts of Drug Overdose Deaths, as of 8/6/2017. Available at https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf. Accessed October 19, 2017.
3. George AV, Lu JJ, Pisano MV, Erickson TB. Carfentanil–an ultra potent opioid. *Am J Emerg Med.* 2010;28(4):530-32.
4. NIH, National Institute on Drug Abuse. Fentanyl. Available at https://www.drugabuse.gov/publications/drugfacts/fentanyl. Accessed October 19, 2017.
5. Substance Abuse and Mental Health Services Administration. Medications To Treat Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63, Full Document. HHS Publication No. (SMA) 18-5063FULLDOC. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2018.
6. U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: *The Surgeon General's Report on Alcohol, Drugs, and Health.* Washington, DC: HHS, November 2016.
7. Livingston JD, Milne T, Fang ML, Amari E. The effectiveness of interventions for reducing stigma related to substance use disorders: a systematic review. *Addiction.* 2012;107(1):39-50.
8. Bonhomme J, Shim RS, Gooden R, Tyrus D, Rust G. Opioid addiction and abuse in primary care practice: a comparison of methadone and buprenorphine as treatment options. *J Natl Med Assoc.* 2012;104(7-8):342-350.
9. Sterling S, Valkanoff T, Hinman A, Weisner C. Integrating substance use treatment into adolescent health care. *Curr Psychiatry Rep.* 2012;14(5):453-461.
10. Broyles LM, Binswanger IA, Jenkins JA, et al. Confronting inadvertent stigma and pejorative language in addiction scholarship: a recognition and response. *Subst Abus.* 2014;35(3):217-221.
11. Kelly JF, Saitz R, Wakeman S. Language, substance use disorders, and policy: the need to reach consensus on an "Addiction-ary". *Alcohol Treat Q.* 2016;34(1):116-123.
12. Kelly JF, Westerhoff CM. Does it matter how we refer to individuals with substance-related conditions? A randomized study of two commonly used terms. *Int J Drug Policy.* 2010;21(3):202-7.
13. National Institute on Drug Abuse. Efficacy of Medications for Opioid Use Disorder. Available at https://www.drugabuse.gov/publications/research-reports/medications-to-treat-opioid-addiction/efficacy-medications-opioid-use-disorder. Accessed October 19, 2017.
14. Thomas CP, Fullerton CA, Kim M, et al. Medication-assisted treatment with buprenorphine: assessing the evidence. *Psychiatr Serv.* 2014;65(2):158-170.

References

15. Fullerton CA, Kim M, Thomas CP, et al. Medication-assisted treatment with methadone: assessing the evidence. *Psychiatr Serv.* 2014;65(2):146-157.
16. Kakko J, Svanborg KD, Kreek MJ, Heilliq M. 1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled *trial. Lancet.* 2003;361(9358):662-668.
17. Substance Abuse and Mental Health Services Administration. Treatments for Substance Use Disorders. Available at https://www.samhsa.gov/treatment/substance-use-disorders. Accessed October 19, 2017.
18. American Society of Addiction Medicine. ASAM National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use. Available at https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed October 19, 2017.
19. Buprenorphine and naloxone tablet [package insert]. Parsippany, NJ: Actavis Pharma, Inc.; 2016.
20. PCSS. MAT Training: Adherence, Diversion and Misuse of Sublingual Buprenorphine. Available at http://pcssmat.org/wp-content/uploads/2014/02/PCSS-MATGuidanceAdherence-diversion-bup.Martin.pdf. Accessed October 19, 2017.
21. Dolophine® [package insert]. Eatontown, NJ: West-ward Pharmaceuticals Corp.; 2017.
22. Buprenorphine hydrochloride tablet [package insert]. Parsippany, NJ: Actavis Pharma, Inc.: 2016.
23. Hakkinen M, Launianinen T, Vuori E, Ojanpera I. Benzodiazepines and alcohol are associated with cases of fatal buprenorphine poisoning. *Eur J Clin Pharmacol.* 2012;68:301-309.
24. Selden T, Ahlner J, Druid H, Kronstrand R. Toxicological and pathological findings in a series of buprenorphine related deaths. Possible risk factors for fatal outcome. *Forensic Sci Int.* 2012;220:284-90.
25. Vivitrol® [package insert]. Waltham, MA: Alkermes, Inc.; 2015.
26. Soyka M, Muller CA. Pharmacotherapy of alcoholism – an update on approved and off-label medications. *Expert Opin Pharmacother.* 2017;18(12):1187-1199.
27. Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug Alcohol Rev.* 2007;33(12):405-410.
28. Kjome KL, Moeller FG. Long-acting injectable naltrexone for the management of patients with opioid dependence. *Subst Abuse.* 2011;5:1-9.

This project is supported by 1 NU17CE002742 (Prescription Drug Overdose Prevention), funded by the Centers for Disease Control and Prevention. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Department of Health and Human Services.

Notes:

NEW YORK STATE | Department of Health

0110

10/19