#CHAIR2017

10TH ANNUAL CHAIR SUMMIT

neuroscience CME

Master Class for Neuroscience Professional Development

November 16 - 18, 2017 | Hotel Monteleone | New Orleans, LA

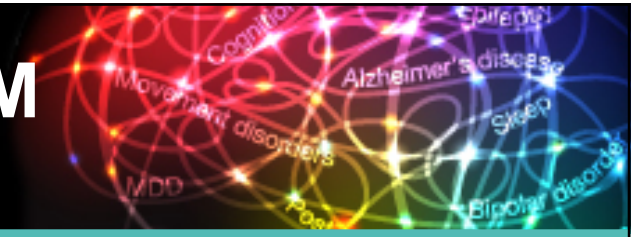
Provided by CME Outfitters

What's Next After Naloxone Rescue?

Mark S. Gold, MD, DLFAPA, DFASM
Adjunct Professor, Washington University School of Medicine St. Louis, MO
17th University of Florida Distinguished Alumni Professor
Chairman, Scientific Advisory Board, RiverMend Health

Mark S. Gold, MD, DLFAPA, DFASAM

Disclosures



- ***Consultant:*** Chairman, Scientific Advisory Board for RiverMend Health

Learning Objective 1

Review the impact of the expanding opioid crisis.

Learning Objective 2

Match individuals with opioid use disorder with the appropriate evidence-based mediation assisted treatment (MAT) for their addiction.

Learning Objective 3

Explore the linkage between drug overdoses and suicide attempts among individuals with opioid use disorder.

The Opioid Epidemic in the U.S.

In 2015...

12.5 million
People misused prescription opioids[1]

2.1 million
People misused prescription opioids for the first time[1]

33,091
People died from overdosing on opioids[2]

2 million
People had prescription opioid use disorder[1]

15,281
Deaths attributed to overdosing on commonly prescribed opioids[2,3]

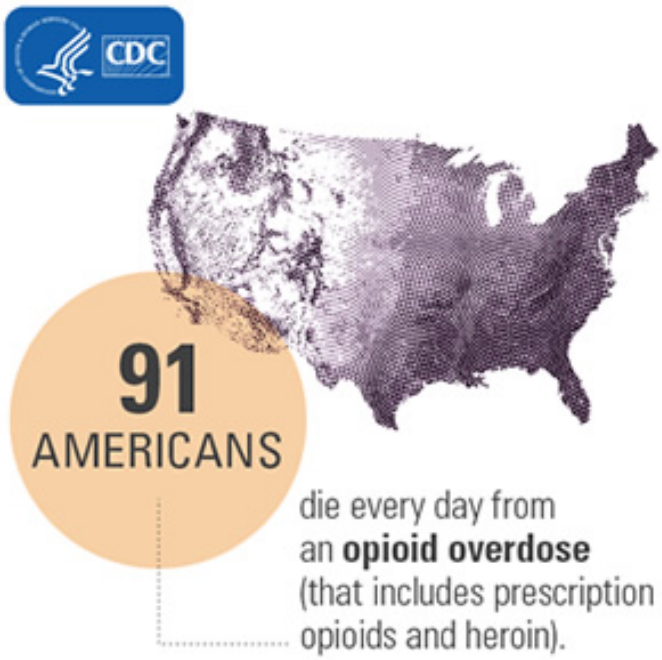
828,000
People used heroin[1]

9,580
Deaths attributed to overdosing on synthetic opioids[2,5]

135,000
People used heroin for the first time[1]

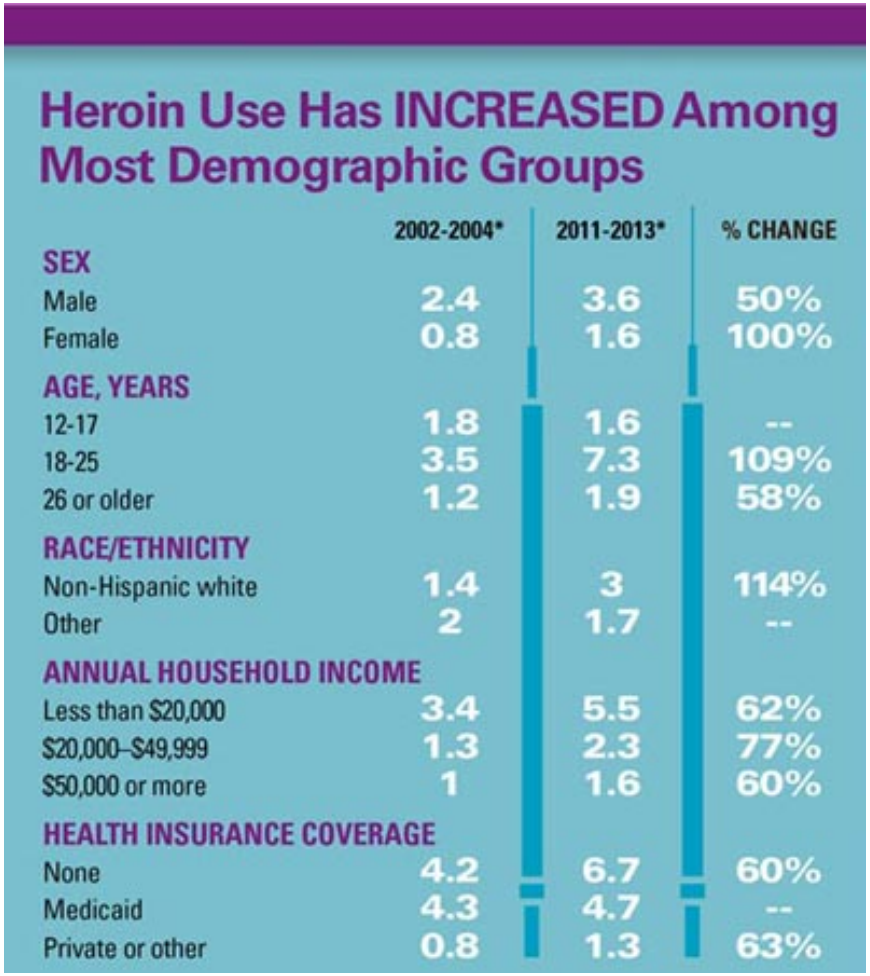
12,989
Deaths attributed to overdosing on heroin[2,4]

$78.5 billion
In economic costs (2013 data)[6]



U.S. Department of Health and Human Services [HHS]. The U.S. opioid epidemic. https://www.hhs.gov/opioids/about-the-epidemic/index.html. Reviewed June 15, 2017; 2. Center for Behavioral Health Statistics and Quality. *2015 National Survey on Drug Use and Health*: *Detailed Tables*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2015. SAMHSA Website. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf; 3. Rudd R, et al. *MMWR Morb Mortal Wkly Rep.* 2016;65(5051):1445-1452.; 4. Centers for Disease Control and Prevention [CDC]. Prescription opioid overdose data. https://www.cdc.gov/drugoverdose/data/overdose.html. Reviewed August 1, 2017.; 5. CDC. Heroin overdose data. https://www.cdc.gov/drugoverdose/data/heroin.html. Reviewed January 26, 2017.; 6. CDC. Synthetic opioid data. https://www.cdc.gov/drugoverdose/data/fentanyl.html. Reviewed December 16, 2016.

Heroin Impact Across Demographic Groups

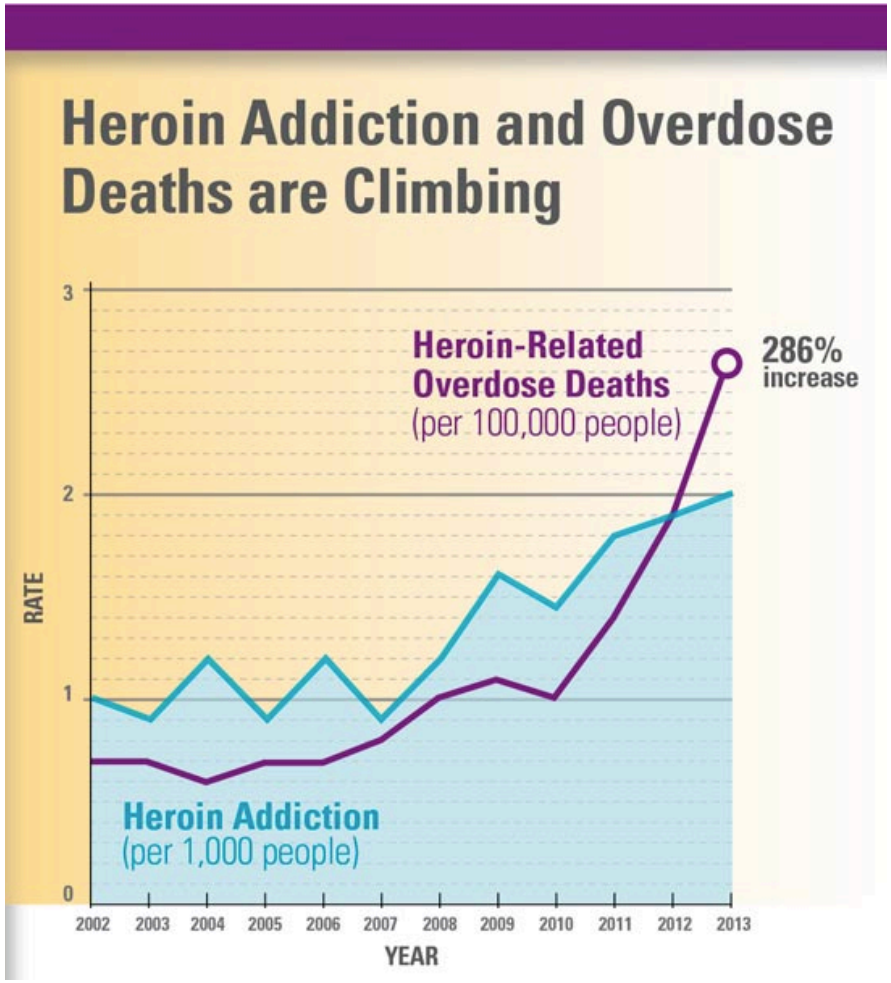


Heroin Use Has INCREASED Among Most Demographic Groups

	2002-2004*	2011-2013*	% CHANGE
SEX			
Male	2.4	3.6	50%
Female	0.8	1.6	100%
AGE, YEARS			
12-17	1.8	1.6	--
18-25	3.5	7.3	109%
26 or older	1.2	1.9	58%
RACE/ETHNICITY			
Non-Hispanic white	1.4	3	114%
Other	2	1.7	--
ANNUAL HOUSEHOLD INCOME			
Less than $20,000	3.4	5.5	62%
$20,000–$49,999	1.3	2.3	77%
$50,000 or more	1	1.6	60%
HEALTH INSURANCE COVERAGE			
None	4.2	6.7	60%
Medicaid	4.3	4.7	--
Private or other	0.8	1.3	63%

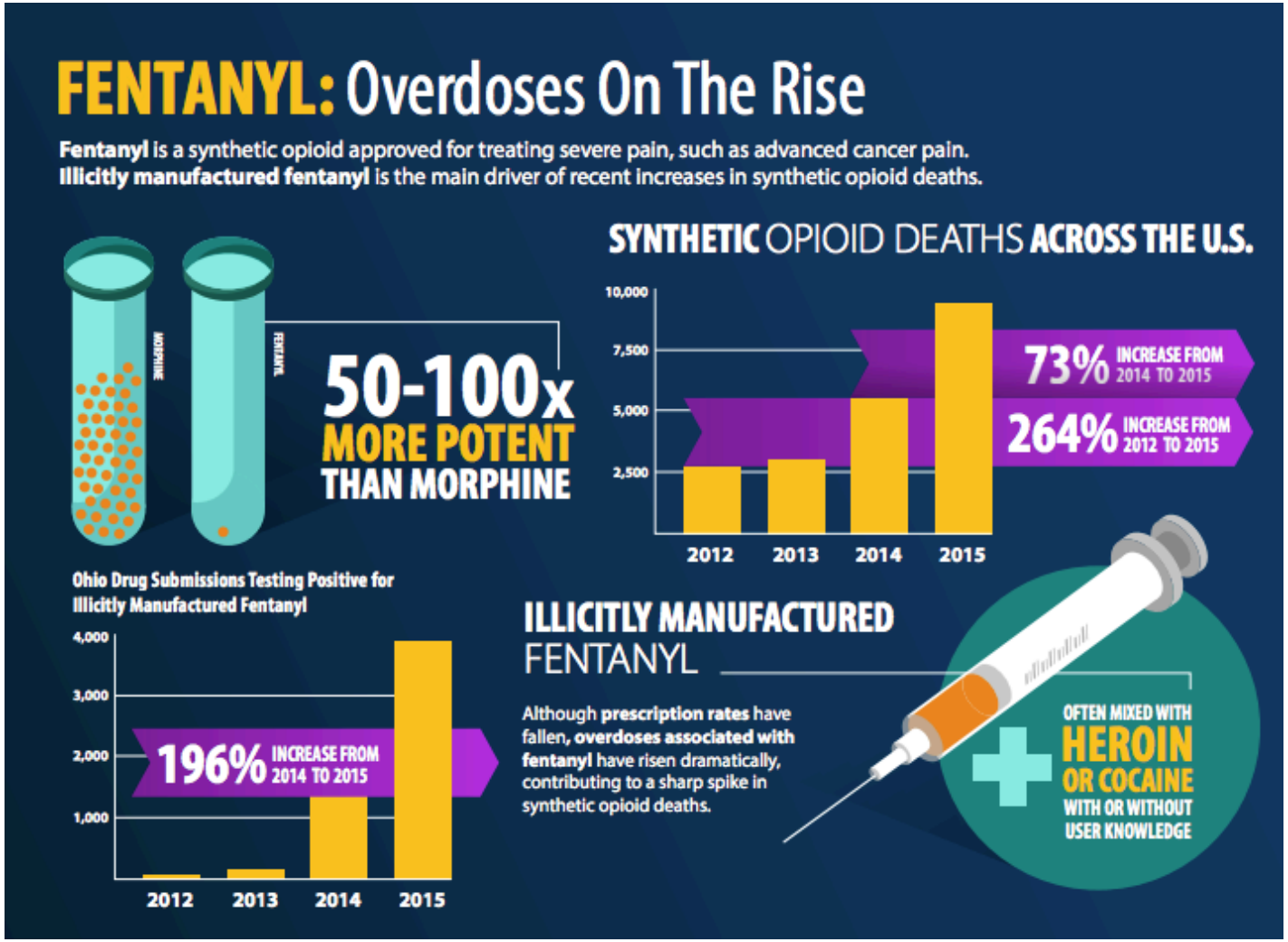
CDC/NCHS, National Vital Statistic System, Mortality. CDC WONDER, Atlanta, GA: US Department of Heath and Human Services, CDC; 2016.
https://www.cdc.gov/vitalsigns/heroin/infographic.html#graphic

Heroin and Overdoses



National Vital Statistic System, 2002-2013. CDC https://www.cdc.gov/vitalsigns/heroin/infographic.html#graphic. Accessed November 8, 2017.

Fentanyl: Overdoses on the Rise

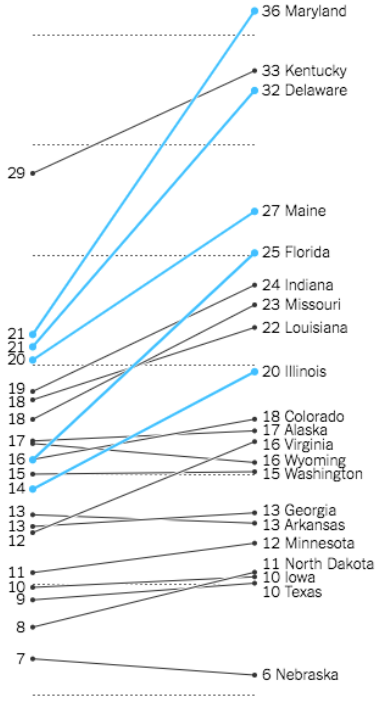


Prescription Behavior Surveillance System Issue Brief. CDC National Center for Injury Prevention and Control. Available at https://www.cdc.gov/drugoverdose/pdf/pbss/PBSS Report-072017.pdf. July 2017. Accessed October 31, 2017.

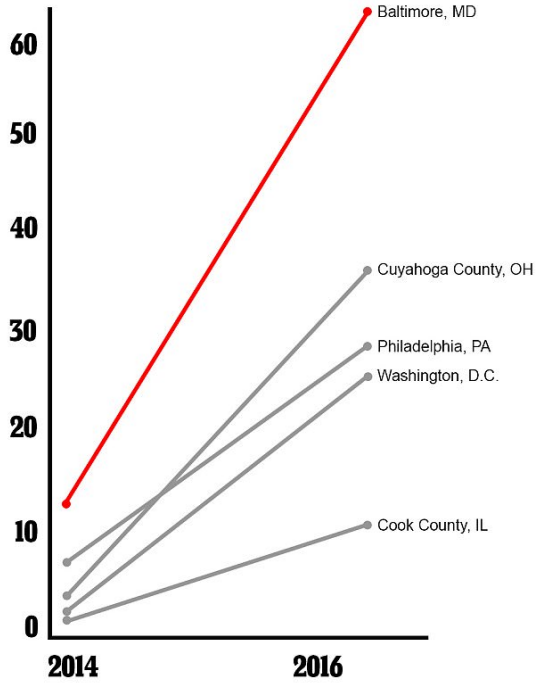
Steep Rise in East Coast Overdoses

- The rate of deaths in US cities related to fentanyl overdoses increased 600% from 2014 to 2016
- The synthetic opioid can be ordered from China or bought from Mexico and is 50 times stronger than heroin

Drug Overdoses per 100,000 Residents in 2015 and 2016[1]



5 Cities with Highest Historic Rates of Fentanyl Deaths[2]



1. Provisional Counts of Drug Overdoses, as of 8/6/17. Available at https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf.
2. Lewis N, et al. *Washington Post*. Published August 15, 2017. Available at https://www.washingtonpost.com/graphics/2017/national/fentanyl-overdoses/?utm_term=.50d494f36deb

Beyond Addiction

CDC Reports 294% Increase in New HCV Infections in the US Between 2010-2015

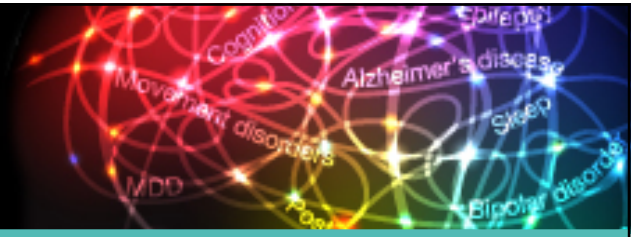
1. New reported infections increased from 850 n 2010 to 2436 in 2015. CDC estimates 2015 number closer to 34,000
2. Highest rates among individuals 20-29 years old who are injection drug users (IDU)
3. States with rates twice the national average: IN, KY, ME, MA, NM, TN, WV
4. States with infection rates above the national average: AL, MT, NJ, NC, OH, IK, PA, UT, WA, WI

Hepatitis Awareness Month and Testing Day — May 2017. *MMWR Morb Mortal Wkly Rep.* 2017;66:465.

Naloxone for Overdoses

- 1971: Naloxone hydrochloride received FDA approval. Over the next 40 years, injectable naloxone became the standard of care used by first responders and within the hospital setting
- 1996: Successful use in pilot programs
- 2013: SAMHSA Opioid Overdose Toolkit is published
- 2014: The first and only naloxone auto-injector is approved by the FDA
- 2016: Inhaled naloxone available

Intranasal Naloxone Protocol for Opioid Overdoses



- Assess ABC's – Airway, Breathing, Circulation
- For pulseless patients, proceed to ACLS guidelines
- Apnea with pulse – Establish oral airway and begin bag ventilation with 100% oxygen
- Load syringe with 2 mg (2 ml) of naloxone and attach nasal atomizer
- Place atomizer within the nostril
- Briskly compress syringe to administer 1 ml of atomized spray.
- Remove and repeat in other nostril, so all 2 ml (2 mg) of medication are administered
- Continue ventilating patient as needed
- If no arousal occurs after 5-10 minutes, proceed down standard unconscious protocol including injectable naloxone and secure airway if necessary

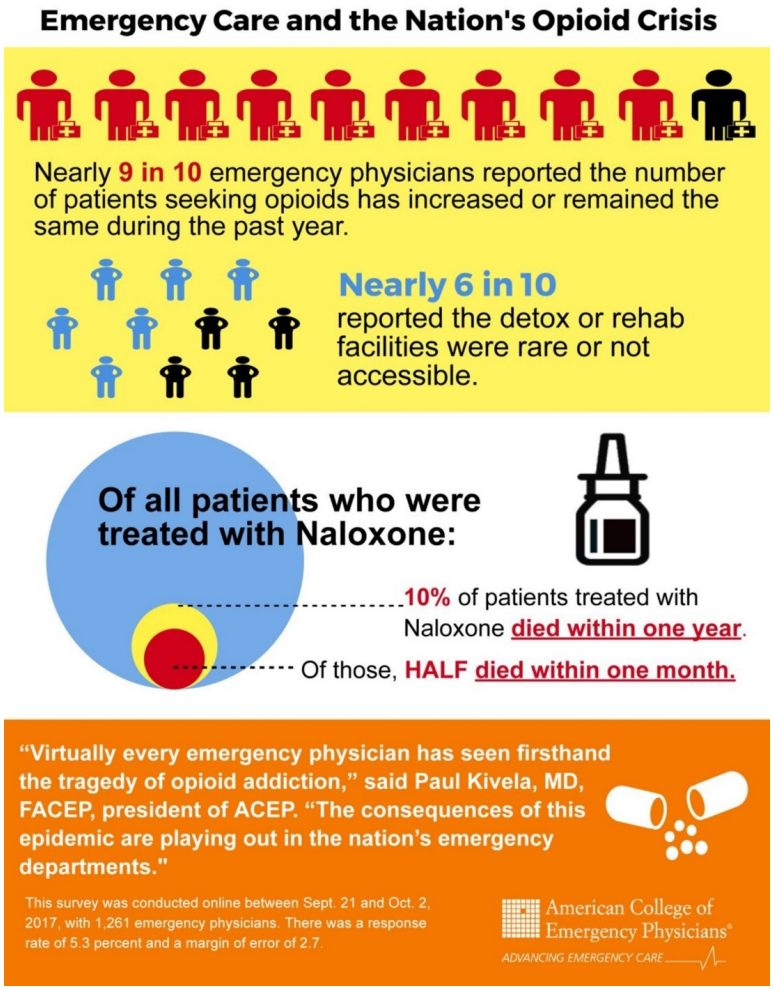
ACLS = Advanced Cardiac Life Support

http://intranasal.net/Treatmentprotocols/Naloxoneprotocol/Naloxoneprotocol.htm. Accessed November 8, 2017.

Naloxone Rescue: Now What?

Abstinence is ideal, but is it realistic?

- Naloxone is 93% effective, but approximately 10% of patients in Massachusetts who received naloxone died within 1 year, 50% of these individuals died within 1 month[1]
- 60% of emergency MDs reported detox or rehab facilities were rare or not accessible[2]
- ”Patients who survive opioid overdoses are by no means ‘out of the woods’”[2]
- Repeat rescue

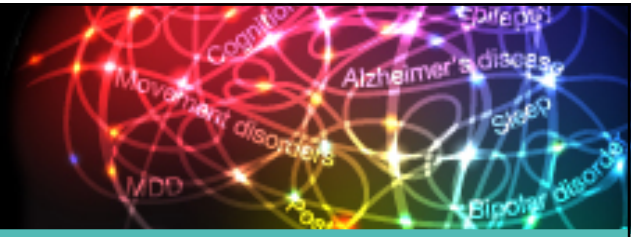


1. Weiner SG, et al. Presented at the ACEP17 Scientific Assembly. Washington, DC. October 30, 2017.
2. ACEP survey of 1,261 emergency physicians. Available at https://www.morningstar.com/news/pr-news-wire/PRNews_20171030DC25652/research-offers-new-insights-into-the-opioid-crisis.html.

Yale Psychiatry in the 1970s: Abstinence vs. Medication Assisted Treatment (MAT)

- MAT began as we tried to match patients to the treatments available
- Historically, substance dependence has focused on the manifestation of an abstinence syndrome upon abrupt cessation of drug self administration characterized by physical signs and autonomic hyperactivity
- Clonidine detox allowed us to separate withdrawal and treatment
- Depression, dysphoria, boredom, irritability, anhedonia are sufficiently negative to drive relapse in some people

MAT Barriers and Challenges



- Only 5% in the past year, and only 17% of individuals with OUD received treatment, including medication and behavioral counseling[1]
- Only ~25% of veterans treated at VA hospitals receive MAT[2]
- Per Federal Bureau of Justice, of nation's 5,100 jails and prisons, fewer than 30 have methadone or buprenorphine programs[3]
- In a national survey of 50 state and Federal Department of Corrections' medical directors found a general preference for abstinence-based policies vs. MAT[4]
  - Misconceptions about addiction
  - Incorrect association of forced detoxification with curing opiate dependence
  - Ignoring risk to relapse
  - Lack of education

1. National Institute on Alcohol Abuse and Alcoholism [NIAAA]. Rates of nonmedical prescription opioid use and opioid disorder doubles in 10 years. NIAAA Website. https://www.niaaa.nih.gov/news-events/news-releases/rates-nonmedical-prescription-opioid-use-and-opioid-use-disorder-double-10. Published June 22, 2016. Accessed November 1, 2017.; 2. Olivia EM, et al. *Am J Drug Alcohol Abuse*. 2013;39(2):103-107.; 3. Williams T. Opioid users are filling jails. Why don't jails just treat them. *The New York Times* Website. https://www.nytimes.com/2017/08/04/us/heroin-addiction-jails-methadone-suboxone-treatment.html. Published August 4, 2017. Accessed November 1, 2017.; 4. Nunn A, et al. *Drug Alcohol Depend*. 2009;105(1-2):83-88.

Comparison of FDA-Approved Medications to Treat Opioid Use Disorder with Physiological Opioid Dependence

Medication	MOR intrinsic activity MOR binding	Differential pharmacology affecting MOR activation at therapeutic dose	Mechanism of relapse preventions
Buprenorphine	Partial agonist High affinity K_i[1] = 0.2 nM	• Slow MOR dissociation allows 3x/wk sublingual dosing and possibility of weekly formulation • Highest known MOR affinity makes rescue from overdose by naloxone less effective; rapid precipitation of withdrawal if full agonists present	• Reduces opioid craving, withdrawal, and stress reactivity • Competitively blocks or reduces the reinforcing effects of other opioids
Methadone	Full agonist High affinity K_i[1] = 3.4 nM	• Long terminal half-life (up to 120 hrs) with delayed steady-state efficacy poses increased MOR toxicity risk during induction phase • Multiple drug-drug interactions pose both opioid-toxicity and withdrawal risks	• Reduces opioid craving, withdrawal, and stress reactivity • Reduces reinforcing effects of other opioids
Naltrexone ER	Antagonist High affinity K_i[2] = 0.26 – 0.34 nM	• Lack of MOR agonism associated with delayed stabilization of opioid craving • Safety concern based on rodent data demonstrating chronic naltrexone exposure increases respiratory depression risk upon opioid agonist reexposure	• Competitive blocks reinforcing effects of opioid agonists • Reductions in craving are psychologically mediated (reduced anticipatory expectancies)

MOR, mu-opioid receptor; ER, extended release; nM, nanomoles

1. Equilibrium dissociation constant for the test compound and relative values are from Volpe DA, et al. *Regul Toxicol Pharmacol*. 2011;59:385-390.; 2. Equilibrium dissociation constant is from Yuan T, et al. *J Med Chem*. 2013;56:9156-9169. 3. Connery HS. *Harv Rev Psychiatry*. 2015;23(2):63-75.

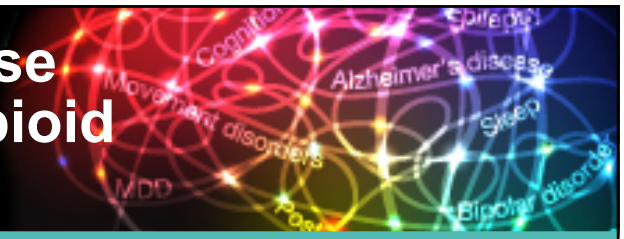
Opioid Abstinence Rates with Medication Compared to Nonmedication

Medication	% Opioid Free on Medication	% Opioid Free on Placebo/Detoxification	Study
Naltrexone ER	36%	23%	Krupitsky et al. 2011
Buprenorphine/naloxone	20%-50%	6%	Fudala et al. 2003 Weiss et al. 2011[a]
Buprenorphine/naloxone	60%	20%	Woody et al. 2008[b]
Methadone	60%	30%	Mattick et al. 2009

- Randomized, controlled clinical trials summarized paired medication maintenance with evidence-based treatments and opioid use self-report data confirmed with urine toxicology
- Predominantly adult opioid use disorder populations, with majority being heroin dependent or having mixed dependence on heroin and prescription opioids

[a]Population was prescription opioid-dependent patients
[b]Population was youth aged 14-21 years
Connery HS. *Harv Rev Psychiatry*. 2015;23(2):63-75.

Comparative Effectiveness of Extended-Release Naltrexone vs Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT)



- 24 week, open-label, randomized controlled, comparative effectiveness trial at 8 community-based inpatient services and followed up as outpatients
  - Participants 18 years or older meeting *DSM-5* criteria for OUD
  - Had not been prescribed opioids in past 30 days
  - Block design with random equally weighted block sizes of 4 and 6 for randomization (1:1) to receive extended-release naltrexone (XR-NTX) monthly intramuscular injections or daily administered buprenorphine-naloxone (BUP-NX) sublingual film
  - XR-NTX had a substantial induction hurdle: fewer participants successfully initiated XR-NTX (204 [72%] of 283) than BUP-NX (270 [94%] of 287; $p < 0{\cdot}0001$)

Lee JD, et al. *Lancet* 14 Nov 2017 DOI: http://dx.doi.org/10.1016/S0140-6736(17)32812-X.

Results

- Among all participants randomly assigned (intent-to-treat population, n = 570) 24 week relapse events were greater for XR-NTX (185 [65%] of 283) than for BUP-NX (163 [57%] of 287
  - Hazard ratio [HR] 1.36, 95% CI 1.10–1.68), most or all of difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures
  - Among participants successfully inducted (n = 474), 24 week relapse events were similar across study groups (p = 0.44).
  - Opioid-negative urine samples (p < 0.0001) and opioid-abstinent days (p < 0.0001) favored BUP-NX compared with XR-NTX among the intent-to-treat population, but were similar across study groups among the per-protocol population
  - Self-reported opioid craving was initially less with XR-NTX than with BUP-NX (p = 0.0012), then converged by week 24 (p = 0.20)

Lee JD, et al. *Lancet* 14 Nov 2017 DOI: http://dx.doi.org/10.1016/S0140-6736(17)32812-X.

What's Next?


Schizophrenia
ADHD
Tardive dyskinesia
Cognition
Epilepsy
Alzheimer's disease
Movement disorders
Sleep
MDD
Bipolar disorder
Post-partum Depression
MS

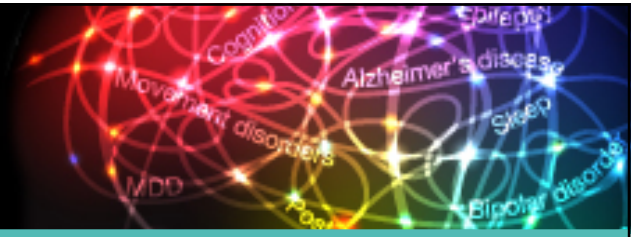
Anti-Drug Vaccine

Rehabilitating the Addicted Brain with Transcranial Magnetic Stimulation- NIDA's New TMS Group

- Substance use disorders (SUDs) are one of the leading causes of morbidity and mortality worldwide. In spite of considerable advances in understanding the neural underpinnings of SUDs, therapeutic options remain limited.
- Recent studies have highlighted the potential of transcranial magnetic stimulation (TMS) as an innovative, safe and cost-effective treatment for some SUDs
- Repetitive TMS (rTMS) influences neural activity in the short and long term by mechanisms involving neuroplasticity both locally, under the stimulating coil, and at the network level, throughout the brain
- The long-term neurophysiological changes induced by rTMS have the potential to affect behaviors relating to drug craving, intake and relapse

Diana M, et al. *Nat Rev Neurosci*. 2017;18(11):685-693.

Injectable Naltrexone



- Longer acting than 1 month
- Trials suggest 3 months possible but still hurdles with safety , drug metabolism, drug-drug interactions and potential need for opioids

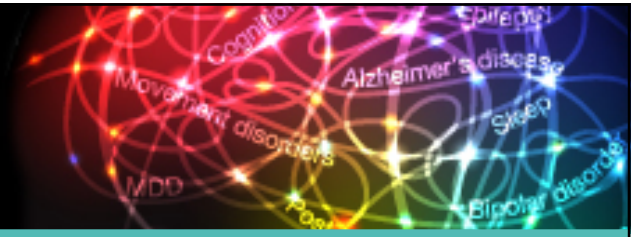
RBP-6000 Injectable Buprenorphine for Opioid Use Disorder

- RBP-6000, injectable, sustained-release (28 days) formulation of buprenorphine recommended for FDA approval for opioid use disorder (OUD) on October 31, 2017*
- Demonstrated clinically and statistically significant differences ($p < 0.0001$) in % abstinence and treatment success, defined as any subject with ≥ 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from Weeks 5 to 24, compared to placebo
  - 300 mg/300 mg: 41.3%
  - 300 mg/100 mg: 42.7%
  - Placebo: 5.0%
- RBP-6000 was generally well tolerated, with a safety profile consistent with transmucosal buprenorphine except for injection site reactions

*Recommendation for FDA approval is non-binding, not currently FDA-approved for OUD

Vijapura A, et al. Data presented in a late-breaking research oral presentation at the 79th Annual Scientific Meeting of the College on Problems of Drug Dependence (CPDD) meeting in Montreal. June 21, 2017.

Novel Delivery Formulation: Buprenorphine Implant



- Depot formulation lasting 6 months
- Novel formulations can impact nonadherence
- Nonfluctuating blood levels compared with variable levels associated with sublingual dosing
- Lower risk of diversion compared with daily-dosed formulations
- Because requires surgical insertion, only medical professionals who have been trained by the *Probuphine Risk Evaluation and Mitigation Strategy (REMS)* program can administer the implant

Rosenthal RN, Goradia VV. *Drug Des Devel Ther*. 2017;11:2493-2505.
Gold MS. http://www.rivermendhealth.com/resources/new-sub-dermal-buprenorphine-implant-approved-fda-opioid-addiction/#sthash.yWe2WNmU.dpuf

FDA Approves NSS-2 Bridge: First Device for Use in Reducing Symptoms of Opioid Withdrawal

- Small electrical nerve stimulator placed behind the ear containing a battery-powered chip that emits electrical pulses to stimulate branches of certain cranial nerves. Stimulations may provide relief from opioid withdrawal symptoms.
- Device can be used for up to 5 days during the acute physical withdrawal phase
- Single-arm clinical study of 73 patients undergoing opioid physical withdrawal. The study evaluated patients' clinical opiate withdrawal scale (COWS) score, which is a clinical assessment conducted by a health care professional that measures opioid withdrawal symptoms such as resting pulse rate, sweating, pupil size, gastrointestinal issues, bone and joint aches, tremors and anxiety.
  - COWS scores range from 0 to more than 36 — the higher the number, the more severe the withdrawal symptoms are to a patient

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585271.htm. Published November 15, 2017.

Post-Naloxone Rescue: Was the Overdose Accidental or Suicide?

Overdose Considered Accidental in Origin Until Proved Otherwise

- How many accidental drug overdoses are suicide attempts?
- 50% of patients with OUD have histories of MDD which may drive suicidal thoughts and behaviors
- Could depression and suicide be post SUD co-morbidities on the basis of drug-related damage to the brain's: reward system-threshold, pleasure-mood systems?

Srivastava AB, Gold MS. *Clinical Psychiatry News*. http://www.mdedge.com/clinicalpsychiatrynews/article/145653/addiction-medicine/missed-opportunities-opioid-overdoses-and. Published August 29, 2017. Accessed November 2, 2017.

Accidental Overdose or Suicide

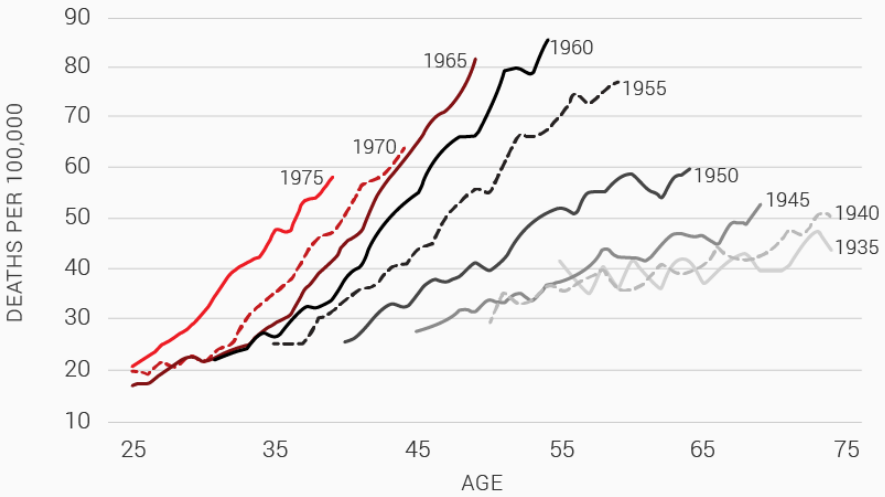
- Secondary analysis of 41,053 participants of the 2014 National Survey of Drug Use and Health found that prescription opioid misuse was associated with[1]
  - 40%-60% increase in suicidal ideation
  - Those reporting at least weekly opioid misuse were at much greater risk for suicide planning and attempts than those who used less often
  - 75% more likely to make plans for a suicide and made suicide attempts at a rate 200% greater than those unaffected by opioid misuse
- A study of nearly 5M veterans reported that presence of a diagnosis of *any* substance use disorder and *specifically* diagnoses of OUD led to increased risk of suicide for both males and females[2]
  - Risk for suicide death was over 2-fold for men
  - More than 8-fold in women

1. Ashrafioun L, et al. *J Psychiatr Res*. 2017;92:1-7.; 2. Bohnert KM, et al. *Addiction*. 2017;112(7):1193-1201.

“Deaths of despair” — or Suicide, Alcoholism, and Drug Overdoses, Particularly From Opioid Painkillers — Are a Growing Problem for Midlife White People

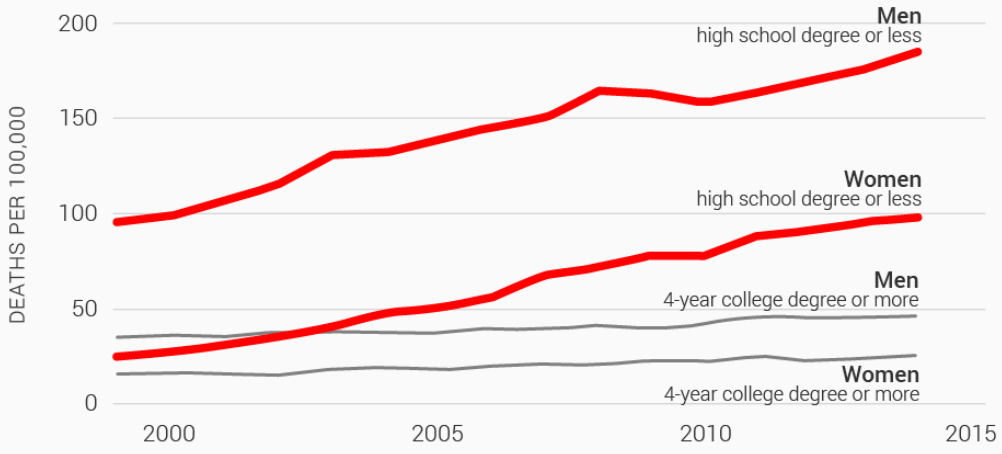
White non-Hispanic mortality from “deaths of despair” in U.S. by birth cohort

Men and women, deaths by drugs, alcohol, and suicide



White non-Hispanic midlife mortality from “deaths of despair” in the U.S. by education

Ages 50-54, deaths by drugs, alcohol, and suicide



Case A, Deaton A. Brookings Papers on Economic Activity. Spring 2017

Call to Action

- After a naloxone overdose rescue, develop a strategy for individuals with OUD to match them to the appropriate MAT strategy that will promote abstinence and decrease relapse
- Evaluate patients with OUD post-overdose to separate accidental overdose from suicide attempt in order to treat an underlying mood disorder

Most Cited MSG Articles and Citation Classics

Citation Classics

1. New concepts in cocaine addiction: the dopamine depletion hypothesis CA Dackis, MS Gold - Neuroscience & Biobehavioral Reviews, 1985 - Elsevier
2. Opiate withdrawal using clonidine: a safe, effective, and rapid nonopiate treatment MS Gold, AC Pottash, DR Sweeney, HD Kleber - Jama, 1980 - jama.jamanetwork.com
3. Problematic internet use: proposed classification and diagnostic criteria…, ST Szabo, M Lazoritz, MS Gold… - Depression and …, 2003 - Wiley Online Library
4. Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. MS Gold, DE Redmond, HD Kleber - The American journal of …, 1979 - psycnet.apa.org
5. Neurobiology of food addiction DM Blumenthal, MS Gold - Current Opinion in Clinical Nutrition & …, 2010 - journals.lww.com
6. Opiate addiction and the locus coeruleus: the clinical utility of clonidine, naltrexone, methadone, and buprenorphine. MS Gold - Psychiatric Clinics of North America, 1993 - psycnet.apa.org

High Citation Recognition:

1. Hypothyroidism and depression: evidence from complete thyroid function evaluation MS Gold, et al- Jama, 1981 - jama.jamanetwork.com
2. Comorbid cigarette and alcohol addiction: epidemiology and treatment NS Miller, MS Gold - Journal of addictive diseases, 1998 - Taylor & Francis
3. Cocaine abuse: Neurochemistry, phenomenology, and treatment MS Gold, AM, Washton, CA Dackis - Cocaine use in America: …, 1985 - books.google.com
4. Methamphetamine causes microglial activation in the brains of human abusers…, H Matsuzaki, T Ueki, N Mori, MS Gold… - The Journal of …, 2008 - Soc Neuroscience
5. Body mass index and alcohol use KD Kleiner, MS Gold, K Frostpineda… - Journal of addictive …, 2004 - Taylor & Francis
6. Setting the standard for recovery: Physicians' Health Programs…, AT McLellan, WL White, LJ Merlo, MS Gold - Journal of Substance …, 2009 - Elsevier

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.