Update on Addiction Treatment

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Shepherd Hill – Newark, Ohio

Definition of Terms

- **Addiction:**
- Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Models of Addiction

- As clinicians how we treat a disorder is dependent on how we model the disorder. In other words, the model we use to define and diagnose addiction, drives the way we treat it.

Importance of Recognition of Addiction as a Separate Disease

Models of Addiction

- **Impaired Model**, or *Alcoholics Can't Change*
- **Psychoanalytic Model**, or *The Addictive Personality*
- **Old Medical Model**, or *Alcoholism is Caused by Drinking Too Much*
- **Dry Moral Model**, or *Denouncing the Demon Rum*
- **Wet Moral Model**, or *Social Drinking*
- **AA Model**, or *Living Without Alcohol*

Importance of Recognition of Addiction as a Separate Disease

Models of Addiction

- **Modern Medical Model**, or

  . . . It Really Is a Disease

Disease of Addiction

- As a DISEASE it has:
  - Symptoms
  - A Natural History
  - Diagnostic Criteria
  - Approved Medical Management
  - Effective Treatment
  - A progressive and potentially relapsing course

Alcohol and Drug Addiction:

Stigma and Ignorance

Stigma and Ignorance

- Stigma and ignorance are the major barriers to obtaining effective treatment
- Includes false beliefs, unwillingness to accept available medical evidence
- Brands the ill as shameful, contemptible, evil, stupid, condemned, almost non-people
- Stigmatizing this disease decreases access to care, resulting in more risk to the person and to the community
- Past examples: Epilepsy, Hansen's Disease (leprosy), Cancer, Tuberculosis, Schizophrenia, AIDS, and currently Alcoholism and Drug Addiction

The Facts about Addiction

- ‘Biopsychosocial’ disease
- Genetic and environmental influences
- A brain disease, manifested as aberrant behaviors
- A chronic disease, in which relapse and remission can recur episodically
- Treatment works! Permanent remission is possible.

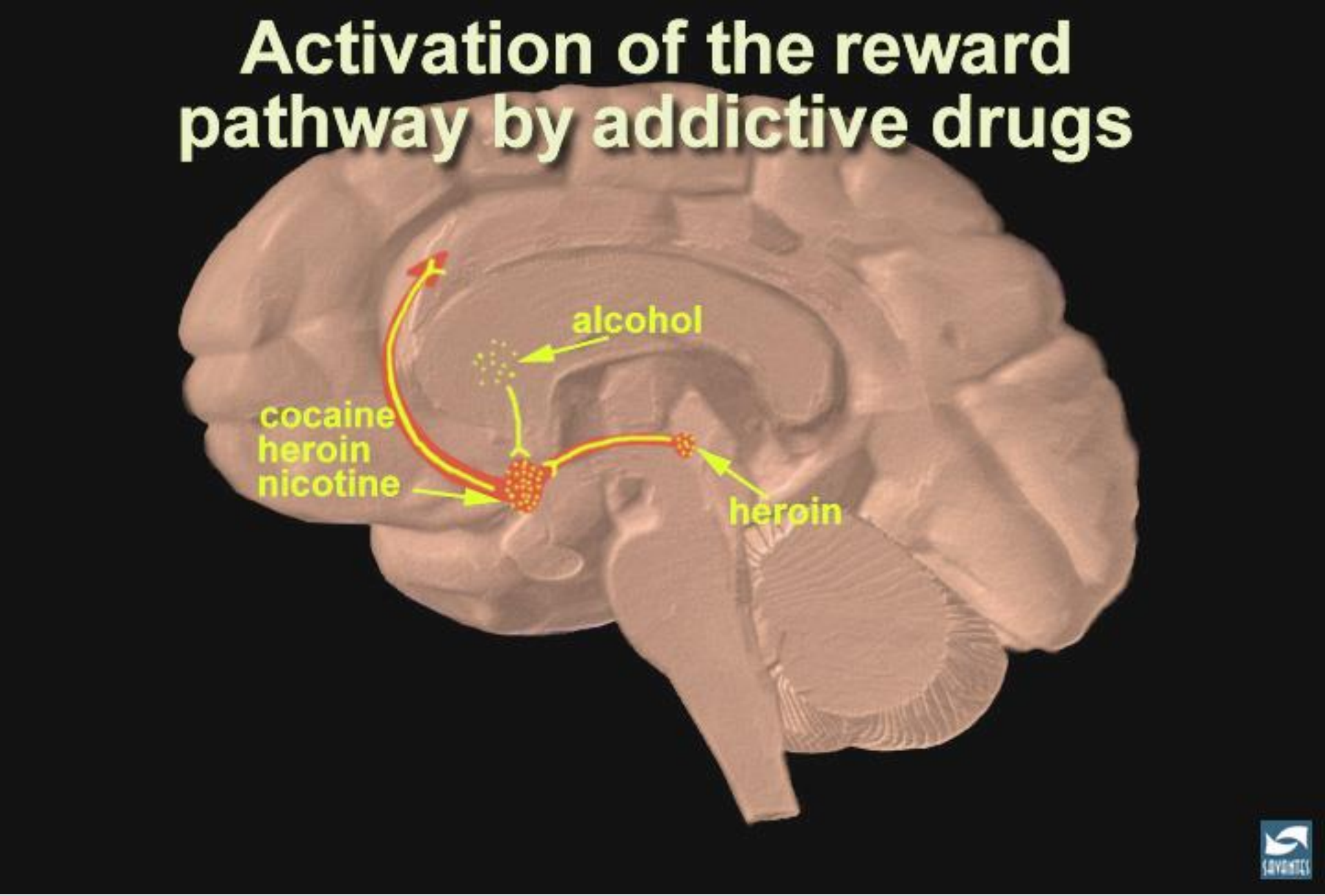
Key Features of Addiction

- Control, loss of
  - inability to consistently limit use
- Craving
  - preoccupation with drinking, procurement
- Compulsive use
- Cognitive changes
  - Narrowed scope of interests, denial
- Consequences of use
- Continued use
  - despite consequences

Natural Rewards

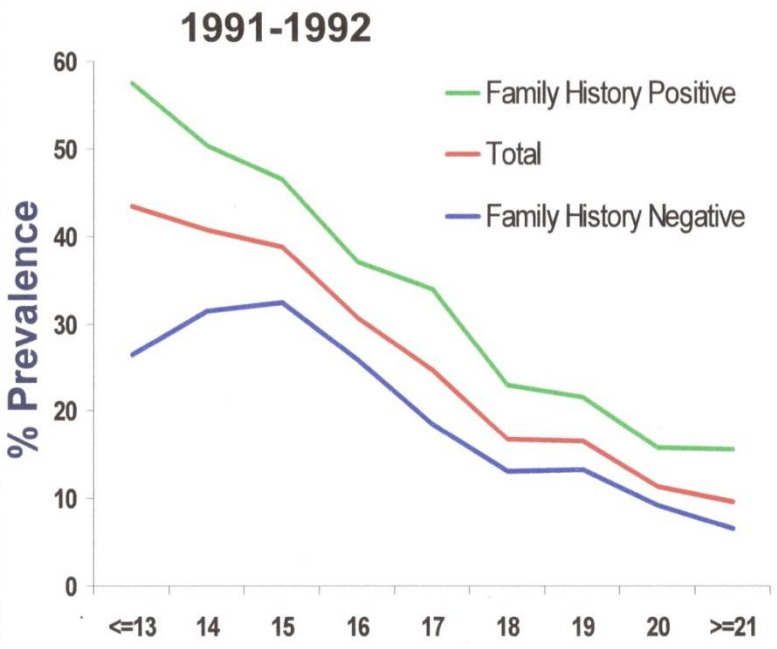
Food
Water
Sex
Nurturing

Activation of the reward pathway by addictive drugs

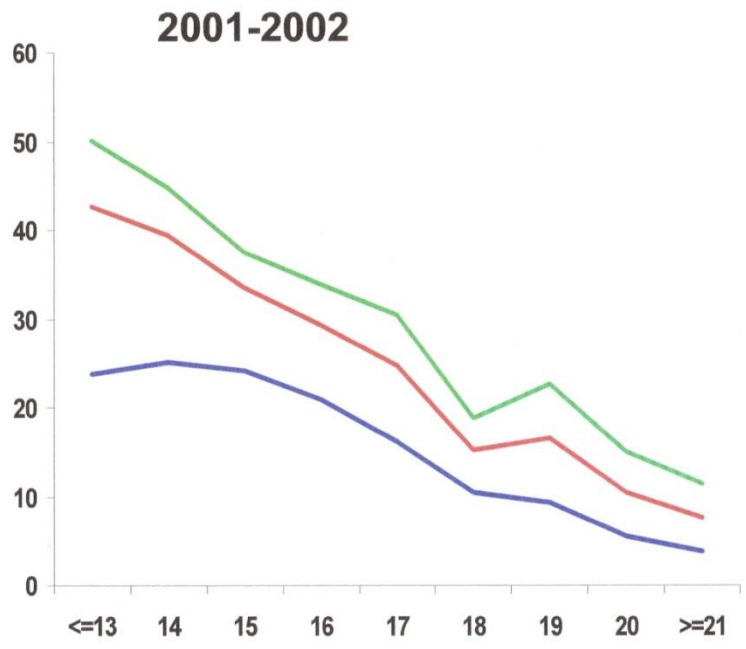


National Institute on Alcohol Abuse and Alcoholism

Prevalence of Lifetime Alcohol Dependence by Age of First Alcohol Use



Source: Grant and Dawson. *J Subst Abuse.* 1998. 10(2):163-73.



Source: 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions

CAGE

- **C**ut down, **A**nnoyed, **G**uilt, **E**ye-opener
- Positive test $\geq$ 2 yes answers
- Sensitivity → 50-80%
- Specificity → ~ 80%
- Doesn't screen for hazardous drinking

Physical Exam

- Hypertension common in patients that drink more than 3 drinks per day
- Hepatomegaly
- Splenomegaly
- Peripheral Neuropathy

Laboratory Evaluation

- Blood tests
- Change with heavy sustained alcohol use
  - Gamma-glutamyl transferase (GGT)
  - Carbohydrate Deficient Transferrin (CDT)
  - CBC w/Mean Corpuscular Volume (MCV)
  - Aspartate transaminase (AST)
  - AST/ALT > 2 suggests alcoholic hepatitis

Manage At Risk Patients: SBIRT

☑Screening

☑Brief Intervention

☑Referral to Treatment

Medications for Alcohol Use Disorder

- Antabuse® (disulfiram)
- Naltrexone - ReVia®

  Vivitrol®
- Campral® (acamprosate)
- Anticonvulsants
- Other agents

Naltrexone: Purported Mechanism

- Competitive antagonist at *mu* opioid receptor
- Blocks endogenous-opioid-mediated release of dopamine in the nucleus accumbens in response to EtOH, thus blocking EtOH-induced euphoria
- Blunts rewarding effects of alcohol in humans
- Reduces subjective cravings and reduces return to heavy drinking

Campral® (acamprosate)

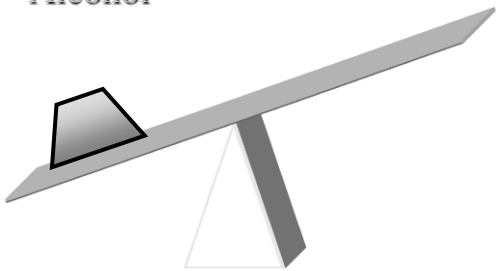
Neuroadaptation: Potential for Relapse

Normal

Inhibition (GABA) **Excitation (Glutamate)**

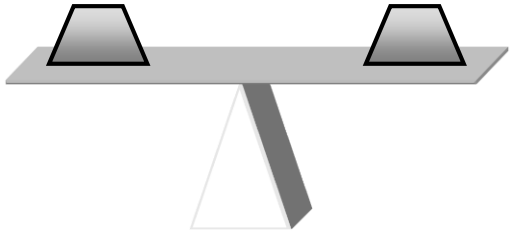
Acute Alcohol Intake

Alcohol



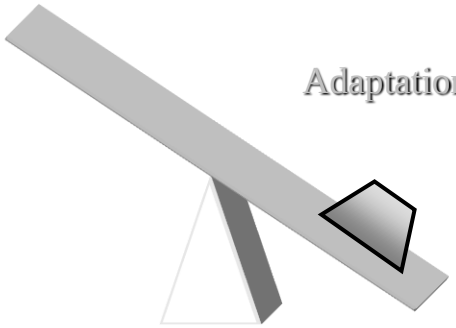
Tolerance

Alcohol Adaptation

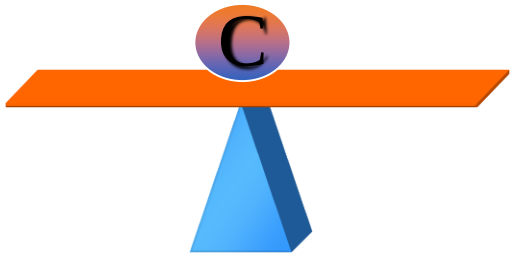


Acute Withdrawal

Adaptation



Post-Acute Withdrawal and Cue-Induced Responses



Campral® (acamprosate calcium) may balance glutamate over-activity, thus reducing the potential for relapse

Other Agents

- Gabapentin

Gabapentin and Detox

Alcohol Clin Exp Res. Author manuscript; available in PMC 2010 Sep 1.
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Published in final edited form as:
NIHMSID: NIHMS152162
Alcohol Clin Exp Res. 2009 Sep; 33(9): 1582–1588.
Published online 2009 May 26. doi: 10.1111/j.1530-0277.2009.00986.x

A DOUBLE BLIND TRIAL OF GABAPENTIN VS. LORAZEPAM IN THE TREATMENT OF ALCOHOL WITHDRAWAL

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Gabapentin and Detox

Results

CIWA-Ar scores decreased over time in all groups; high-dose gabapentin was statistically superior but clinically similar to lorazepam (p=0.009). During treatment, lorazepam-treated participants had higher probabilities of drinking on the first day of dose decrease (day 2) and the second day off medication (day 6) as compared to gabapentin-treated participants (p=.0002). Post-treatment, gabapentin-treated participants had less probability of drinking during the follow-up post-treatment period (probability=.2 for 900 mg and probability=.3 for 1200mg) compared to the lorazepam-treated participants (probability=.55). The gabapentin groups also had less craving, anxiety, and sedation compared to lorazepam.

Conclusions

Gabapentin was well tolerated and effectively diminished the symptoms of alcohol withdrawal in our population especially at the higher target dose (1200mg) used in this study. Gabapentin reduced the probability of drinking during alcohol withdrawal and in the immediate post-withdrawal week as compared to lorazepam.

Gabapentin for Maintenence

- Gabapentin has been found to be helpful in reducing relapse to alcohol
- Primary effects include reduction in anxiety, improved sleep and reduction of cravings for alcohol
- Acts by increasing GABA synthesis and attenuating Glutamate at NMDA receptors

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Gabapentin Treatment for Alcohol Dependence: A Randomized Controlled Trial

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Abstract

Importance—Approved medications for alcohol dependence are prescribed for fewer than 9% of US alcoholics.

Objective—To determine if gabapentin, a widely-prescribed generic calcium channel/GABA modulating medication, increases rates of sustained abstinence and no heavy drinking, and decreases alcohol-related insomnia, dysphoria and craving, in a dose-dependent manner.

Design, Participants and Setting—A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women over 18 years of age with current alcohol dependence, conducted 2004–2010 at a single-site outpatient clinical research facility adjoining a general medical hospital.

Interventions—Oral gabapentin (0, 900, 1800 mg/d) and concomitant manual-guided counseling.

Main Outcome Measures—Rates of complete abstinence and no heavy drinking (co-primary) and changes in mood, sleep and craving (secondary) over the 12-week study.

Gabapentin for Maintenence

- **Results** Gabapentin significantly improved the rates of abstinence and no heavy drinking. The abstinence rate was 4.1% (95% CI, 1.1%-13.7%) in the placebo group, 11.1% (95% CI, 5.2%-22.2%) in the 900-mg group, and 17.0% (95% CI, 8.9%-30.1%) in the 1800-mg group ($P = .04$ for linear dose effect; number needed to treat [NNT] = 8 for 1800 mg). The no heavy drinking rate was 22.5% (95% CI, 13.6%-37.2%) in the placebo group, 29.6% (95% CI, 19.1%-42.8%) in the 900-mg group, and 44.7% (95% CI, 31.4%-58.8%) in the 1800-mg group ($P = .02$ for linear dose effect; NNT = 5 for 1800 mg). Similar linear dose effects were obtained with measures of mood ($F_2 = 7.37$; $P = .001$), sleep ($F_2 = 136$; $P < .001$), and craving ($F_2 = 3.56$; $P = .03$). There were no serious drug-related adverse events, and terminations owing to adverse events (9 of 150 participants), time in the study (mean [SD], 9.1 [3.8] weeks), and rate of study completion (85 of 150 participants) did not differ among groups.

Other Agents

- Ondansetron (Zofran)
  - Most effective for early onset alcoholics (age 25 or less)
  - Low dose compared to anti-nausea dose

Opiates

- 4000 BC opium papaver somniferum
- 1805 morphine
- 1874 heroin (diacetylmorphine)
- 1940s synthetic opioids
- 1973 stereospecific binding sites
- 1975 endogenous opioids


VAPOR-OL
TREATMENT
No. 6
Contains not more than
45% ALCOHOL,
OPIUM 3 Grs.
TO EACH FLUID
OUNCE
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PRICE - - 50 CENTS
Prepared expressly for
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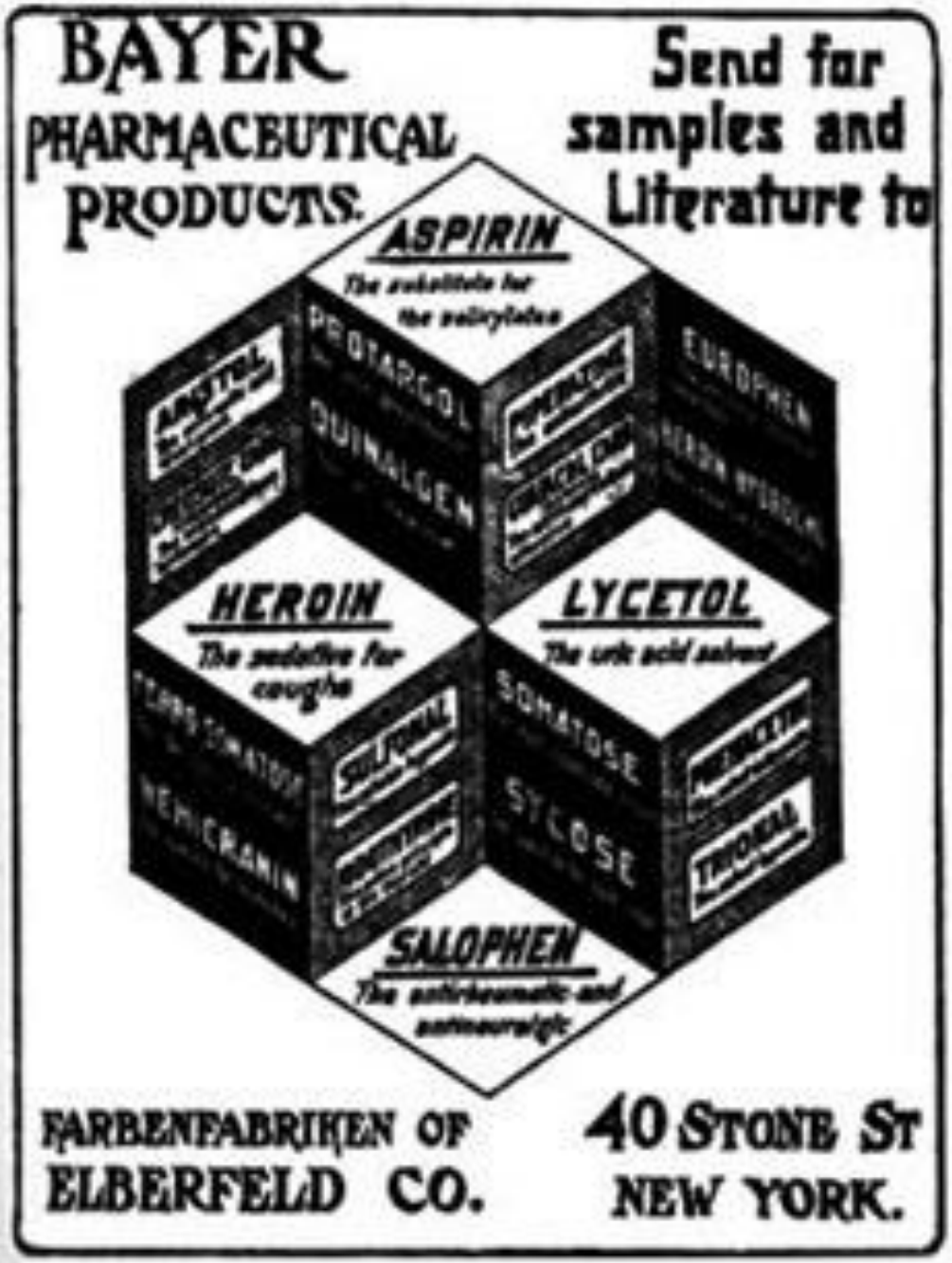
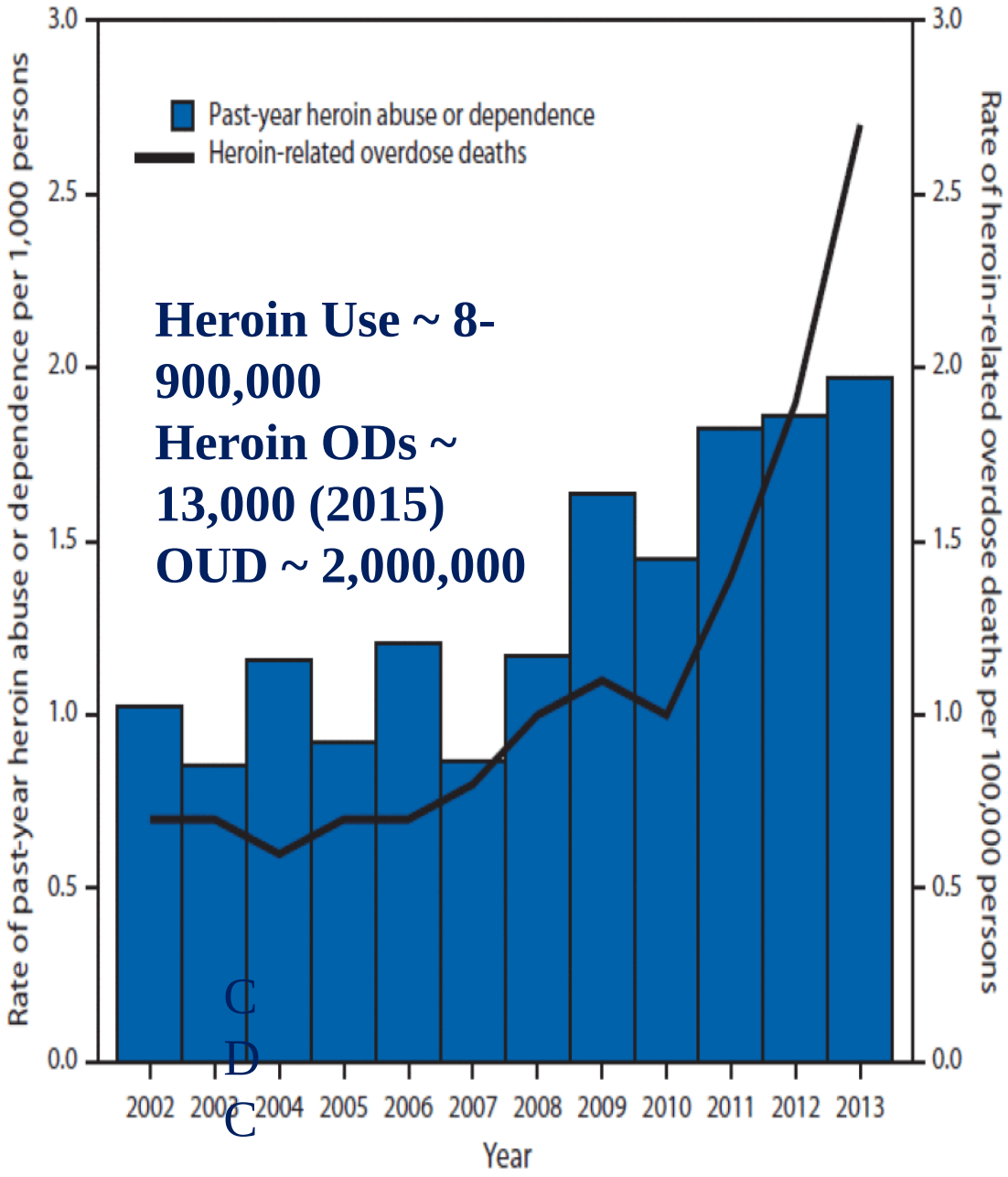
Heroin


BAYER
PHARMACEUTICAL
PRODUCTS.
Send for
samples and
Literature to
ASPIRIN
The substitute for the salicylates
PEPTARGOL
QUINALGEN
EUROPHEN
HEROIN
The sedative for coughs
LYCETOL
The uric acid solvent
SOMATOSE
STYLOSE
SALOPHEN
The antirheumatic and antineuralgic
FARBENFABRIKEN OF
ELBERFELD CO.
40 STONE ST
NEW YORK.


Past-year heroin abuse or dependence
Heroin-related overdose deaths
Heroin Use ~ 8-900,000
Heroin ODs ~ 13,000 (2015)
OUD ~ 2,000,000
Rate of past-year heroin abuse or dependence per 1,000 persons
Rate of heroin-related overdose deaths per 100,000 persons
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Year

Boonshoft School of Medicine
WRIGHT STATE UNIVERSITY

Montgomery County Coroner
Miami Valley Crime Laboratory

RESEARCH UPDATE ON FENTANYL OUTBREAKS IN THE DAYTON, OH AREA:

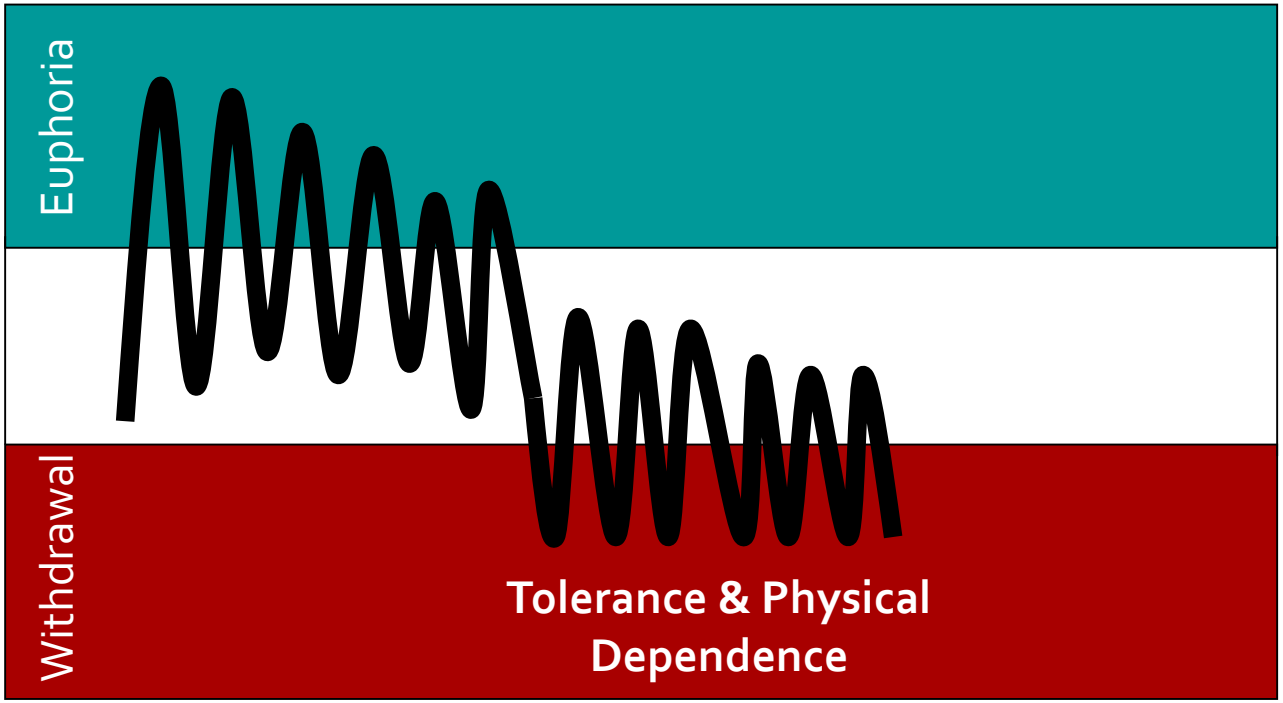
Acryl Fentanyl and Furanyl Fentanyl Commonly Found In Overdose Death Cases

UPDATE 04/28/2017

DAYTON, OHIO. The Dayton area (Montgomery County, Ohio) has recently experienced dramatic increases in heroin and other opioid-related problems. Unintentional drug overdose deaths increased significantly from 127 in 2010 to 264 in 2014. In 2016, there were 349 overdose deaths in Montgomery County, and 251 of them screened positive for fentanyl. Preliminary data from 2017 indicate continuing increases in overdose deaths.

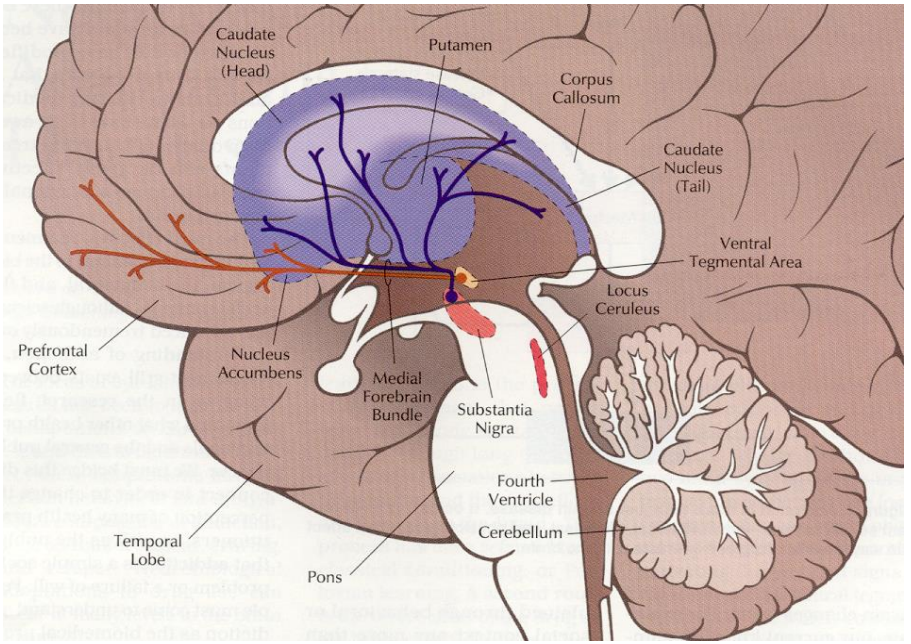
Synthetic opioids/fentanyl analogues/metabolites	A. All cases (N=100)	B. Acryl Fentanyl Positives (N=56)	C. Furanyl Fentanyl Positives (N=39)
Fentanyl	99 (99%)	56 (100%)	39 (100%)
Norfentanyl	64 (64%)	39 (70%)	26 (67%)
Acryl fentanyl	56 (56%)		25 (64%)
Despropionylfentanyl	46 (46%)	26 (46%)	32 (82%)
Furanyl Fentanyl	39 (39%)	25 (45%)	
Carfentanil	3 (3%)	2 (4%)	1 (2.6%)
Acetyl Fentanyl	2 (2%)	1 (2%)	1 (2.6%)
Butyryl/Isobutyrylfentanyl	1 (1%)	0 (0%)	0 (0%)
Furanyl Norfentanyl	1 (1%)	1 (2%)	1 (2.6%)
U47700	1 (1%)	1 (2%)	1 (2.6%)

Natural History of Opioid Use Disorder



Reward/Reinforcement

- Reward/Reinforcement is in part controlled by mu receptors in the Reward Pathway:
  - Ventral Tegmental Area (VTA)
  - Nucleus Accumbens with projections to Prefrontal Cortex
  - Dopaminergic system



Buprenorphine

Treatment
Medications
Efficacy and Safety

Medically Supervised Withdrawal
"Opioid Detoxification"

- Low rates of retention in treatment
- High rates of relapse post-treatment
  - < 50% abstinent at 6 months
  - < 15% abstinent at 12 months
- "Detox" is not treatment, it is just the start of treatment

- Increased rates of overdose due to decreased tolerance

Reasons for Relapse

- Protracted abstinence syndrome (chronic withdrawal)
  - Generalized malaise, fatigue, insomnia
  - Poor tolerance to stress and pain
  - Opioid craving
- Conditioned cues (triggers)
- Priming with small dose of drug

Medications to Treat Opioid Use Disorder

- Goals
  - Alleviate signs/symptoms of physical withdrawal
  - Opioid receptor blockade
  - Diminish and alleviate drug craving
  - Normalize and stabilize perturbed brain neurochemistry
- Options
  - **Opioid Antagonist**
    - **Naltrexone** (full opioid antagonist)
  - **Opioid Agonist**
    - **Methadone** (full opioid agonist)
    - **Buprenorphine** (partial opioid agonist)

Oral Naltrexone Efficacy

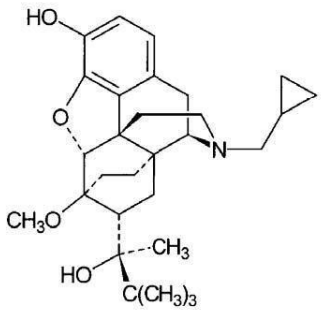
- Oral naltrexone
  - Duration of action 24-48 hours
  - FDA approved 1984
- 10 RCTs ~700 participants to naltrexone alone or with psychosocial therapy compared with psychosocial therapy alone or placebo
  - No clear benefit in treatment retention or relapse at follow up
- Benefit in highly motivated patients
  - Impaired physicians > 80% abstinence at 18 months

Injectable Naltrexone (XR-NTX)*

- Multicenter (13 sites in Russia) Funded by Alkermes
- DB RPCT, 24 wks, n=250 w/ opioid dependence
- XR-NTX vs placebo, all offered biweekly individual drug counseling
- Increased weeks of confirmed abstinence (90% vs 35%)
- Increased patients with confirmed abstinence (36% vs 23%)
- Decreased craving (-10 vs +0.7)

*No Black Box LFTs Warning Label for IM formulation

Buprenorphine



- Metabolism
  - In liver with N-dealkylation by cytochrome P450 3A4 enzyme system into an active metabolite norbuprenorphine
    - Norbuprenophine undergoes further glucuronidation
- Elimination
  - Excreted hepatobiliary (70%) and urine (30%)
    - Mean elimination half-life = 37 hours
  - Commercial screening urine drug test for parent compound.
  - Does NOT show as opiate positive on standard screen

Buprenorphine Formulations

- **Sublingual forms** (tablets and films)
    - **"Combo"** (buprenorphine/naloxone): Tablets and Films (SL & Buccal)
    - **"Mono"** (buprenorphine only): Generic Tablets
    - "Mono" 6 mos implantable rods
  - Approved for mod to severe OUDs
  - Can be used **OFF LABEL** for pain

- **Parenteral, Transdermal Patches and Buccal Film formulations**
- Approved for pain but **NOT** OUDs
- **Can NOT be used OFF LABEL** for OUDs: Violates DATA 2000

Purpose of Naloxone in "combo"

- Naloxone has limited bioavailibility PO or SL, but is active parenterally, e.g. injected SQ, IM or IV
- The combo product, if crushed, dissolved and injected the:
  - Naloxone may cause initial withdrawal if the person is opioid physically dependent.
    - Decreasing diversion and misuse
  - Naloxone will block, or attenuate, the opioid agonist effect of the buprenorphine
  - Therefore safer if diverted

Buprenorphine/Naloxone Bioavailability

- If dissolved sublingually
  - Buprenorphine is active
  - Naloxone is not active
- If swallowed
  - Buprenorphine not active (minimal oral bioavailability)
  - Naloxone not active
- If injected
  - Buprenorphine active, but
  - Naloxone active x 20 minutes so attenuates the parenteral "rush"
- Not time-released so tablets/film strip can be split

Buprenorphine Efficacy Summary

- Studies (RCT) show buprenorphine more effective than placebo and equally effective to moderate doses (80 mg) of methadone on primary outcomes of:
  - Abstinence from illicit opioid use
  - Retention in treatment
  - Decreased opioid craving

Johnson et al. *NEJM.* 2000.

Fudala PJ et al. *NEJM.* 2003.

Kakko J et al. *Lancet.* 2003.

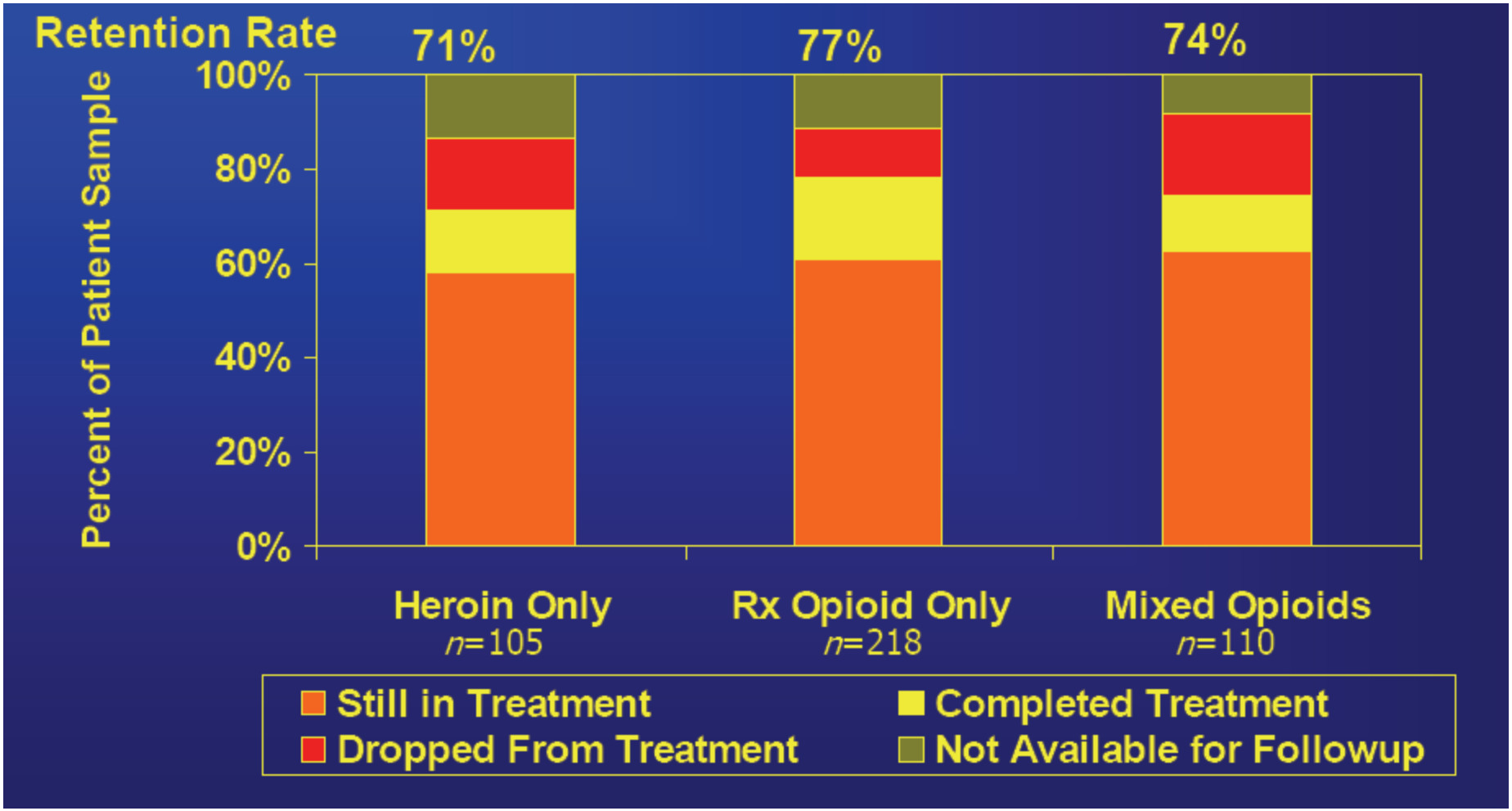
Overdose Risk Minimal

- Low risk of clinically significant problems
- Pre-clinical studies suggest high doses of buprenorphine should not produce respiratory depression
- No reports of respiratory depression in clinical trials
- Overdose and misuse (e.g., injecting) of buprenorphine combined with other CNS depressants result in respiratory depression and risk overdose
- France experience…
  - IV buprenorphine + high potency benzodiazepines → deaths

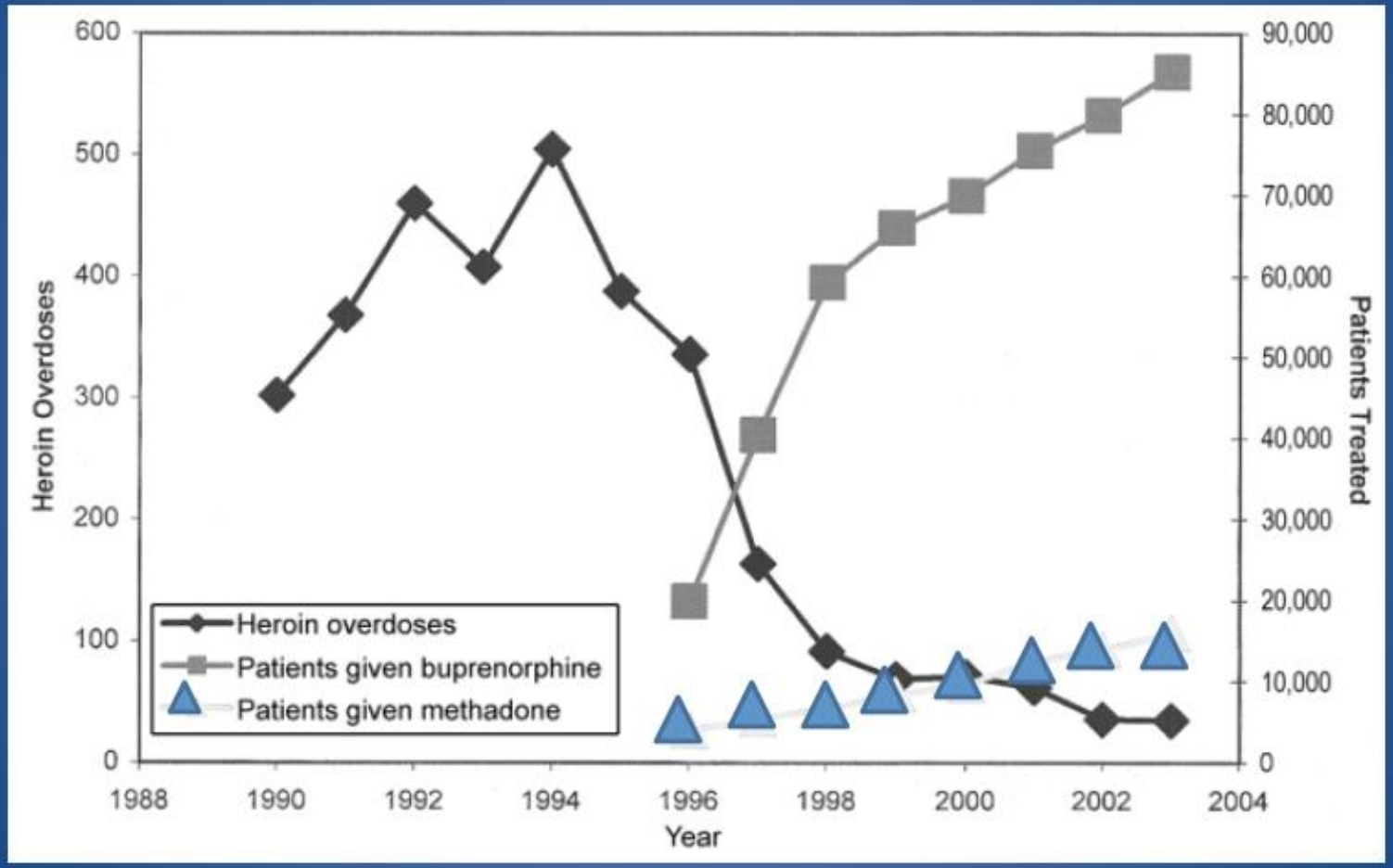
Buprenorphine Advantages

- More favorable safety profile and long duration of action than other opioid medications
- Newer option, and may engender less fear of stigma than methadone
- More accessible over a wide geographic area due to its availability in office-based primary-care
- May be more appropriate as an early intervention strategy for those with short dependence histories (e.g., adolescents) or those with less physical dependence[10]

Buprenorphine: Retention in Treatment at 6 Months



Fatal Poisonings in France Decreases with Availability of Opiate Treatment



Source:Carrieri PM, 2006, Clin Infect Dis, 43: S197-215, data from Emmanueli, et al.

New Preparation
Sublocade

Sublocade

- Once monthly Injection of depot buprenorphine
- Available April 2018 (at last estimate)
- Reduces likelihood of diversion and misuse
- Remarkably quick approval – limited study data to date

Sublocade

- Recommended dosage is 300 mg per month for 2 months then 100 mg per month
- First injection given after no less than 7 days of sublingual buprenorphine.
- Limited information on insurance coverage at this time.

Substance Use Disorders in Perspective

- Alcohol Use Disorder: ~ 20 million affected
- Alcohol Related Deaths: ~100,000 per year
- Tobacco Use Disorder: ~20% population > 18yo
- Tobacco Related Deaths: ~450,000 per year

Resources for Help or Information

- Shepherd Hill – Assessments

  Cindy Barbour, RN (740) 348-4877

  Eric Hockenberry, RN (740) 348-4898

- Shepherd Hill – Educational Sessions

  ‘Ask-the-Doc’

  Second and Fourth Saturdays at 9:00 AM,

  SH Auditorium

  Free and open to the public

Licking Memorial Hospital

Behavioral Health Services

Located at Shepherd Hill