Pharmacotherapy for Relapse Prevention

Pharmacotherapy in addiction treatment

- Treat withdrawal
- Reduce risk of relapse
- Treat co-morbid psychiatric disorders
- Treat substance-induced psychiatric symptoms
- Reverse acute overdose

Pharmacotherapy Overview

	Alcohol	Sedative/ hypnotics	Opiates	Cocaine Amphetamine	Nicotine
Detox	Benzodiazepines Thiamine (Anti-adrenergics) (Carbamazepine) (gabapentin)	Benzo or Phenobarb	Methadone* Buprenorphine** (Clonidine) NSAIDs, etc.		Nicotine Bupropion Varenicline
Relapse prevent	Disulfiram Naltrexone (po) Acamprosate Vivitrol	None	Methadone* Buprenorphine** Naltrexone (po) Vivitrol		

* *Dispensing program* requires special federal license

** *Prescribing MD* must have DEA DATA 2000 waiver

(Parentheses indicate off-label uses.)

Relapse prevention for alcohol use disorder (moderate-severe)

- Psychosocial
  - Motivational Interviewing (MI)/ Motivational Enhancement Therapy (MET)
  - Cognitive-behavioral relapse prevention (CB/RP)
  - Twelve-step facilitation (TSF) $\rightarrow$ AA
  - Behavioral Couples Therapy (BCT)
- Pharmacotherapy
  - Disulfiram
  - Naltrexone
  - Acamprosate

Naltrexone

- Alcohol affects endogenous opioid system
- Opioid antagonist - orally effective
- Reduces relapse vs. placebo
  - Multiple RCT's (positive)
  - VA Cooperative Study (negative)
  - NIAAA Project COMBINE (positive)
- FDA approved 1995.
- Reduces rewarding effects of alcohol.
- Reduces alcohol craving.
- Reduces likelihood of "slip" $\rightarrow$ full relapse.

Volpicelli et al. JAMA, 1992.

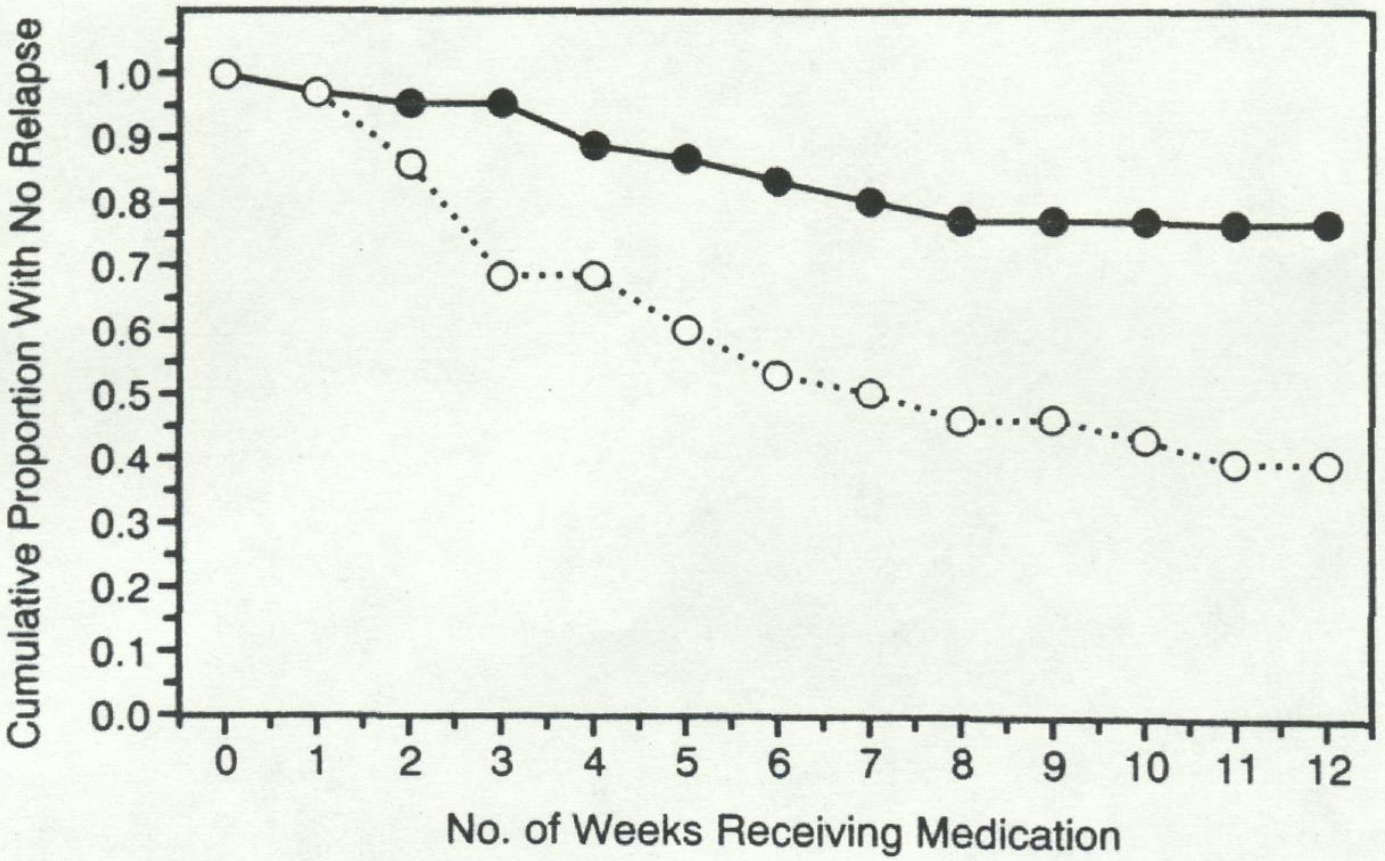


Fig 2.—*Relapse rates (as defined in the text) for the naltrexone hydrochloride- (closed circles) and placebo-treated (open circles) groups across the 12 weeks of the study.*

naltrexone

- Safe, generally well-tolerated
- Start at 25 mg, increase to 50 mg daily.
- COMBINE study used 100 mg/day.
- Infrequent nausea, dizziness, sedation
- Risk of hepatotoxicity at higher doses (≥250 mg).
- Antagonizes opioid analgesia.
- Triggers withdrawal in opioid-dependent patients.

naltrexone

- Insert: Start *after* alcohol cessation.
- Literature: May start before complete cessation.
- Routinely offer to alcohol-dependent patients as part of treatment for motivated patient.
- Treatment duration 3-12+ months
- Some patients shift from daily to prn use for high-risk situations.

Naltrexone: precautions

- Before initiating treatment, verify that patient is not physically dependent on opioids.
- If in doubt, perform UDS, naloxone challenge.
- Black box warning was removed in 2013.: Contraindicated in acute hepatitis and hepatic failure.
- Use w/ caution in less severe liver disease.
- Warn patient about symptoms of hepatitis.
- Pregnancy Category C.
- Excreted in human milk.

Naltrexone and pain management

- d/c at least 72 hours before elective, potentially painful procedure.
- Wait 7 days after last opioid analgesic use to resume naltrexone.
- Emergency surgery or trauma: be prepared to support respiration if high-dose opioids are required to override NTX.

Naltrexone injection(Vivitrol®)

- Monthly depot injection.
- FDA approved 2006.
- May help patients who are motivated for sobriety but non-compliant with oral naltrexone.
- Superior to placebo in clinical trials.

acamprosate (Campral®)

- Modulates function of excitatory NMDA-type glutamate receptor.
- Enhances GABA activity.
- Efficacious in reducing relapse in US and European randomized controlled trials.
- Not superior to placebo in COMBINE study.
- FDA approved 2004

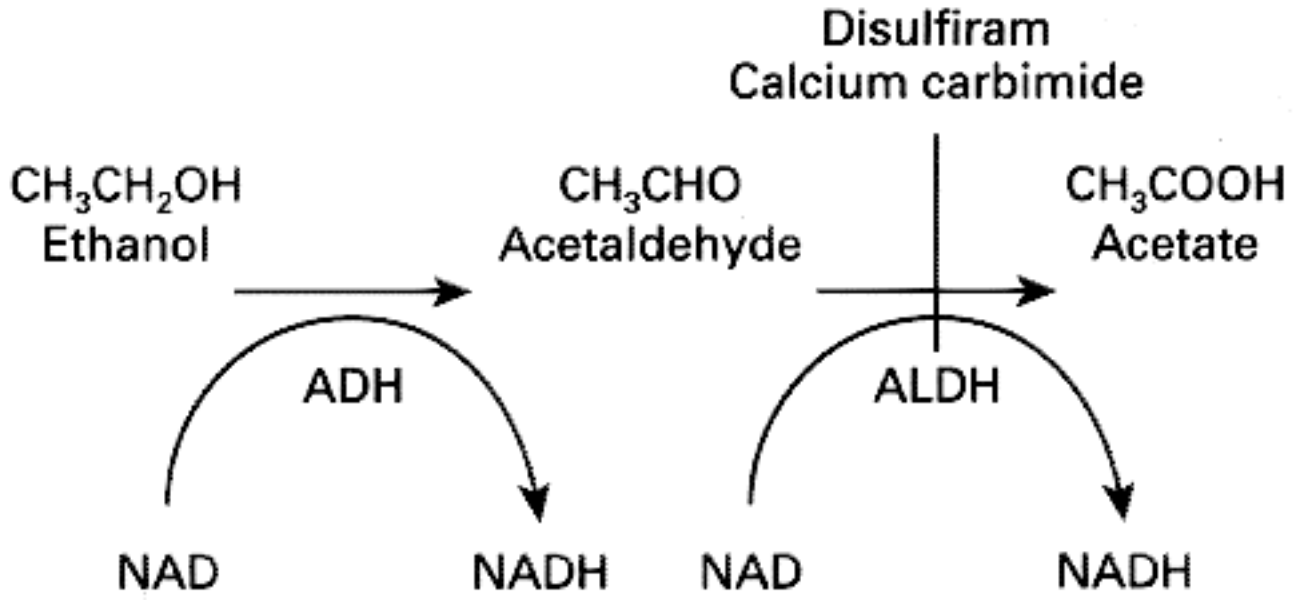
acamprosate (Campral®)

- Most common side-effect: diarrhea
- Fatigue, nausea, flatulence, pruritis
- Typical dose 666 mg tid (2 g/day)
- 3 g/day in COMBINE study
- Initiate after alcohol cessation

acamprosate (Campral®)

- No hepatic metabolism.
- Renal excretion of unchanged drug.
- BUN and Creatinine before treatment.
- Renal impairment
  - Moderate (GFR 30-50 ml/min): reduce dose
  - Severe (GFR <30 ml/min): do not prescribe
- Pregnancy category C.
- No significant drug interactions.

Disulfiram


Disulfiram
Calcium carbimide
CH_3CH_2OH
Ethanol
CH_3CHO
Acetaldehyde
CH_3COOH
Acetate
ADH
ALDH
NAD
NADH
NAD
NADH

Disulfiram

- Alcohol ingestion → acetaldehyde accumulation → aversive reaction up to 14 days after last dose
- FDA approved 1951.
- Limited efficacy in controlled trials.
- Useful in selected, motivated patients.
- Monitored administration increases efficacy.
- Typical dose 250 mg daily (range 125 - 500).

disulfiram-alcohol reaction

- Nausea and vomiting
- Abdominal pain
- Chest pain
- Hypotension
- Tachypnea
- Headache
- Fainting
- Dizziness

Disulfiram contraindications

- CAD
- CHF
- DM
- Epilepsy
- Cirrhosis
- Renal impairment
- Hypothyroidism
- Cognitive impairment

Disulfiram adverse effects

- Hepatotoxicity
- Metallic or garlic taste
- Psychosis
- Sexual dysfunction
- Optic neuritis, peripheral neuritis, polyneuritis, peripheral neuropathy
- Pustular, febrile rash

Disulfiram drug interactions

- Isoniazid (INH): psychosis
- Benzodiazepines other than oxazepam and lorazepam: increased levels
- Metronidazole: psychosis, confusion
- Phenytoin: increased levels
- Coumadin
- Others drugs metabolized by CYP2C9.

Disulfiram: lab evaluation

- Pre-treatment
  - Liver function tests
  - Renal function, electrolytes
  - CBC
- Repeat LFT's at 10-14 days
- Periodic LFT's during treatment

Patient and family education

- Nature of alcohol-disulfiram reaction
- Risk up to 14 days after last dose
- Non-beverage alcohol exposure
- Signs and symptoms of hepatitis
- Other adverse effects
- Wallet card
- Signed consent

Behavioral couples therapy (BCT) enhances disulfiram treatment.

- O'Farrell et al, Harvard Med/Brockton VAMC
- Employs behavioral contract:
  - Patient self-administers in front of partner.
  - Partner observes, expresses appreciation.
  - Minimize other discussion of drinking (i.e., nagging).
  - Couple reviews adherence with therapist.
- Improves adherence and drinking outcomes vs. standard disulfiram mgmt.

Pharmacotherapy to prevent alcohol relapse

Modestly effective.

Generally safe.

Under-utilized relative to other treatments with similar effectiveness.

No reliable predictors of response.

Prospects for improvement

- New agents with different mechanisms
- Long-acting formulations to improve adherence
- Genetic markers to identify responders

Pharmacotherapy for alcohol dependence

	FDA app	Hepatotoxicity
disulfiram	yes	Yes
naltrexone (po)	yes	At high doses. Black-box warning was removed 2013.
Vivitrol (depot naltrexone IM)	yes	Black box warning.
acamprosate	yes	Not reported.
gabapentin	no	Not reported.
topiramate	no	Rare hepatotoxicity. Possible hyperammonemia, encephalopathy.
baclofen	no	Not reported.

Relapse prevention in opioid dependence

- agonist replacement
  - methadone
  - buprenorphine
- antagonist: naltrexone
  - oral
  - sustained-release injection

Two indications for opioid agonists

- Pain
  - Any MD with full DEA license may prescribe any legal opioid (Schedule II-IV)
- Dependence (addiction)
  - Only methadone and buprenorphine
  - Restricted to certified opiate treatment programs (methadone) or waivered MD's (Suboxone)
  - Exceptions for medical necessity

Regulatory Exceptions to the General Requirement for Certification to Provide Opioid Agonist (Methadone) Treatment:

- During inpatient care, when the patient was admitted for any condition other than concurrent opioid addiction (pursuant to 21 CFR 1306.07(c)), to facilitate the treatment of the primary admitting diagnosis.
- During an emergency period of no longer than 3 days while definitive care for the addiction is being sought in an appropriately licensed facility (pursuant to 21 CFR 1306.07(b)).

Methadone

- Slow-onset, long-acting opioid agonist.
- Uses
  - chronic pain
  - opioid detoxification
  - maintenance: opioid agonist therapy (OAT), methadone maintenance therapy (MMT)
- Only certified programs can administer methadone for addiction.
- Recent sharp rise in methadone OD deaths.

Methadone

- Benefits, vs. “drug-free” counseling
  - Decreased mortality
  - Decreased hospitalizations
  - Decreased HIV seroconversion
  - Decreased arrests, incarceration
  - Increased employment

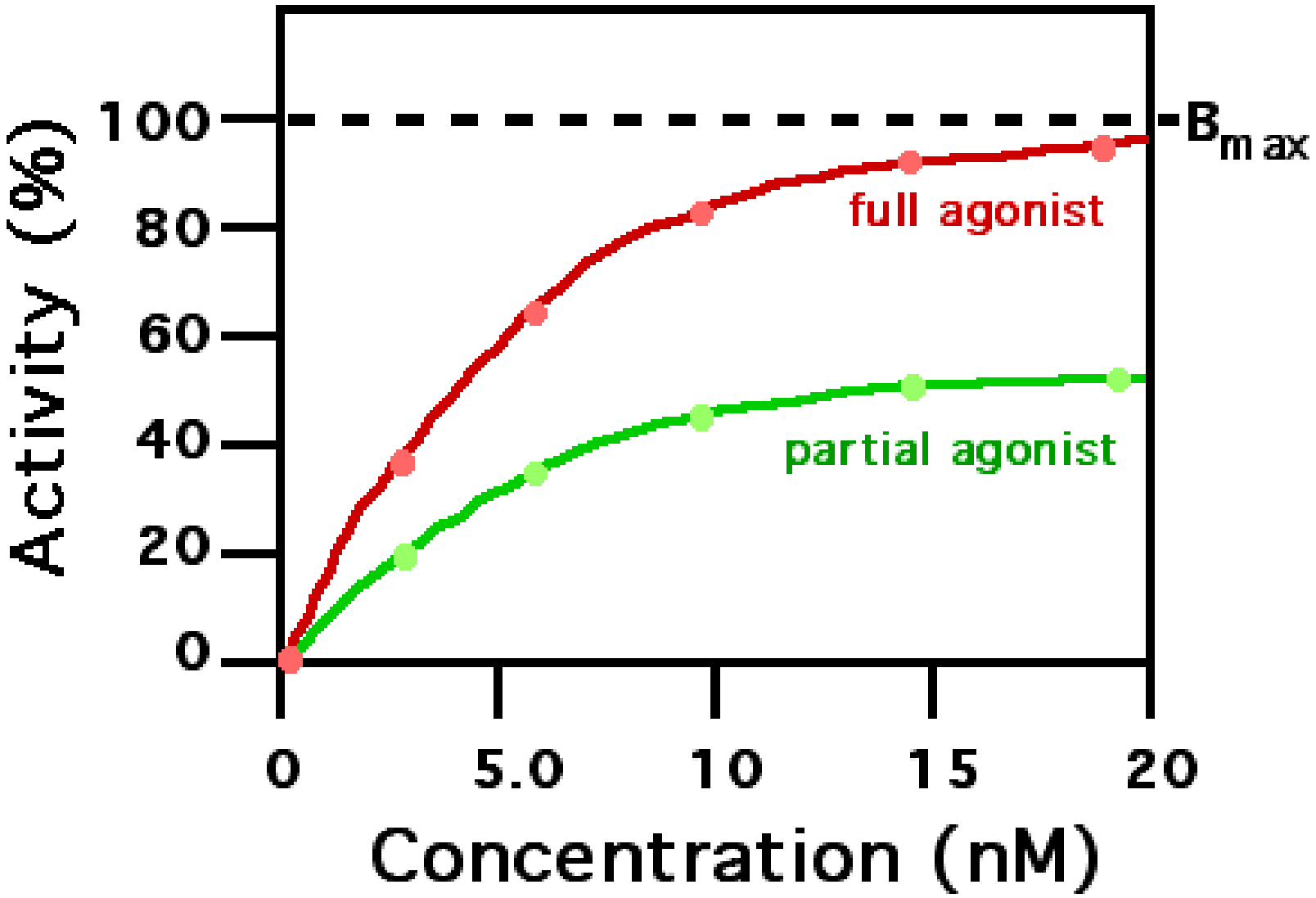
- Most effective at higher doses (80-120 mg/day), at which it blocks effect of additional opioids.

Methadone maintenance

- Administered under direct observation in MM clinic as oral liquid.
- Initially requires daily clinic attendance.
- Stable patients are allowed increasing take-home supplies.
- May continue for many months to years.

Buprenorphine

- Partial opioid agonist
- High affinity for mu opioid receptor.
- Administered sublingually.
- Lower toxicity and abuse potential relative to methadone.


Activity (%)
100
80
60
40
20
0
B_{max}
full agonist
partial agonist
0
5.0
10
15
20
Concentration (nM)

Buprenorphine

- DEA schedule III
- Prescribing MD must have “waiver” from DEA. (“X-” prefix)
- Requirements:
  - 8 hour training, available online, or
  - ASAM or AAAP certication
- Initial limit of 30 patients/MD
  - May increase to 100 (200 proposed) patients
- DEA audits for regulatory compliance

Suboxone®

- Buprenorphine + Naloxone 4:1 SL tabs or film
- Naloxone is active only if pills are diverted to parenteral abuse.
- Naloxone blocks opioid effects, can precipitate withdrawal.
- Typical dose range 4/1 - 16/4
- Generic buprenorphine/naloxone tablets

naltrexone
(oral tablets; Revia® and generic)

- Originally marketed as Trexan® for relapse prevention in opioid dependence (FDA, 1984).
- Blocks rewarding effects of opioids
- Triggers withdrawal in patient with active opioid dependence
- Useful in monitored programs, e.g., impaired physicians or probation/parole
- Oral form has limited effectiveness due to poor patient acceptance, adherence.

naltrexone
(extended-release injectable; Vivitrol®)

- Initially marketed for alcohol dependence.
- FDA approved in October 2010 for treatment of opioid dependence (following detoxification).
- IM injection given every 30 days.

Pharmacotherapy in context

No silver bullet for alcohol use disorder.

Marked benefit for opioid replacement therapy.

Medications are among several potentially effective approaches.

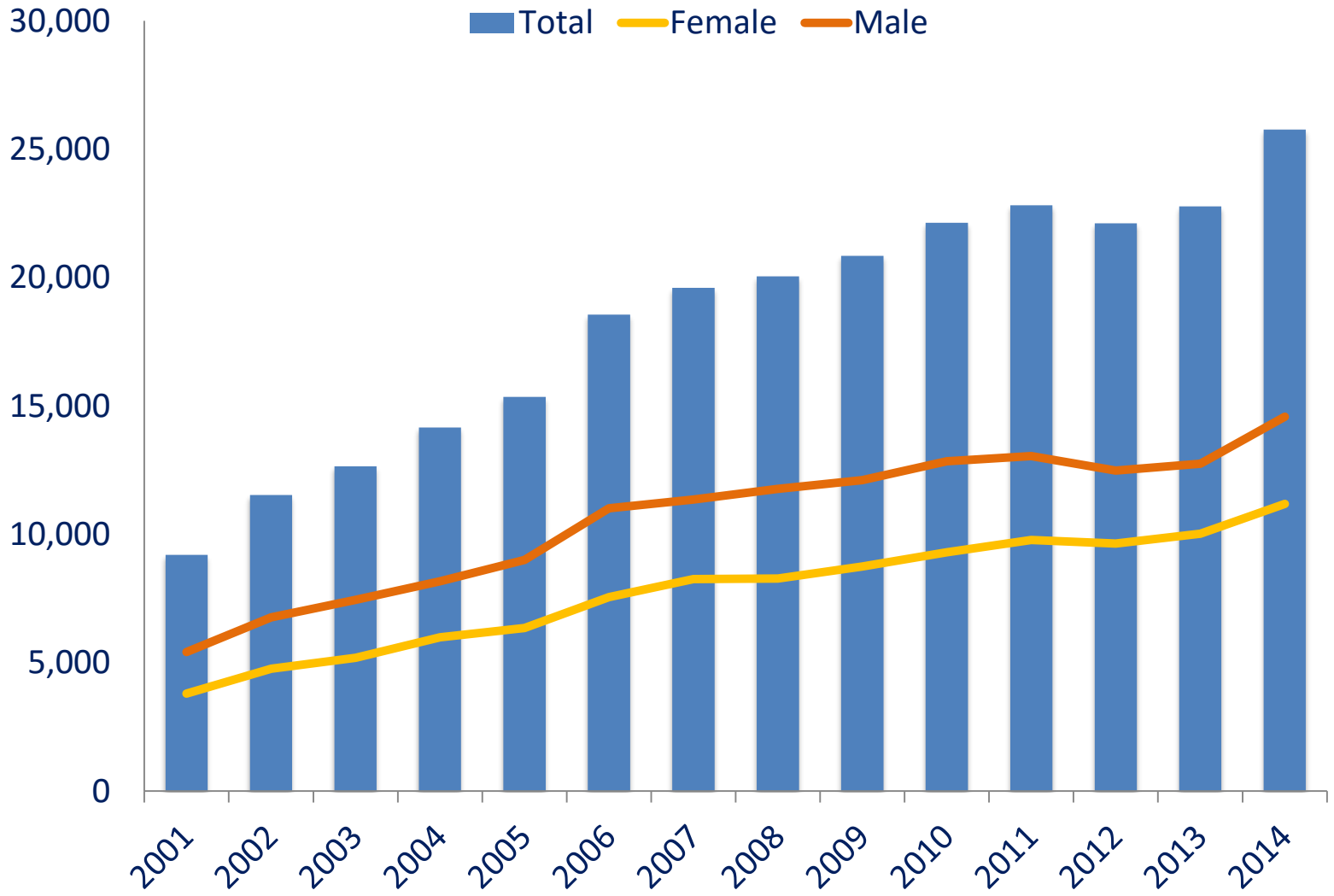
Medications should be discussed among treatment options. (“Informed *consent*” vs. “informed *choice*”)

NTX plus “office-based” brief medical counseling is viable option for alcohol-dependent patients who decline referral to a formal treatment program.

National Institute on Drug Abuse

National Overdose Deaths

Number of Deaths from Prescription Drugs

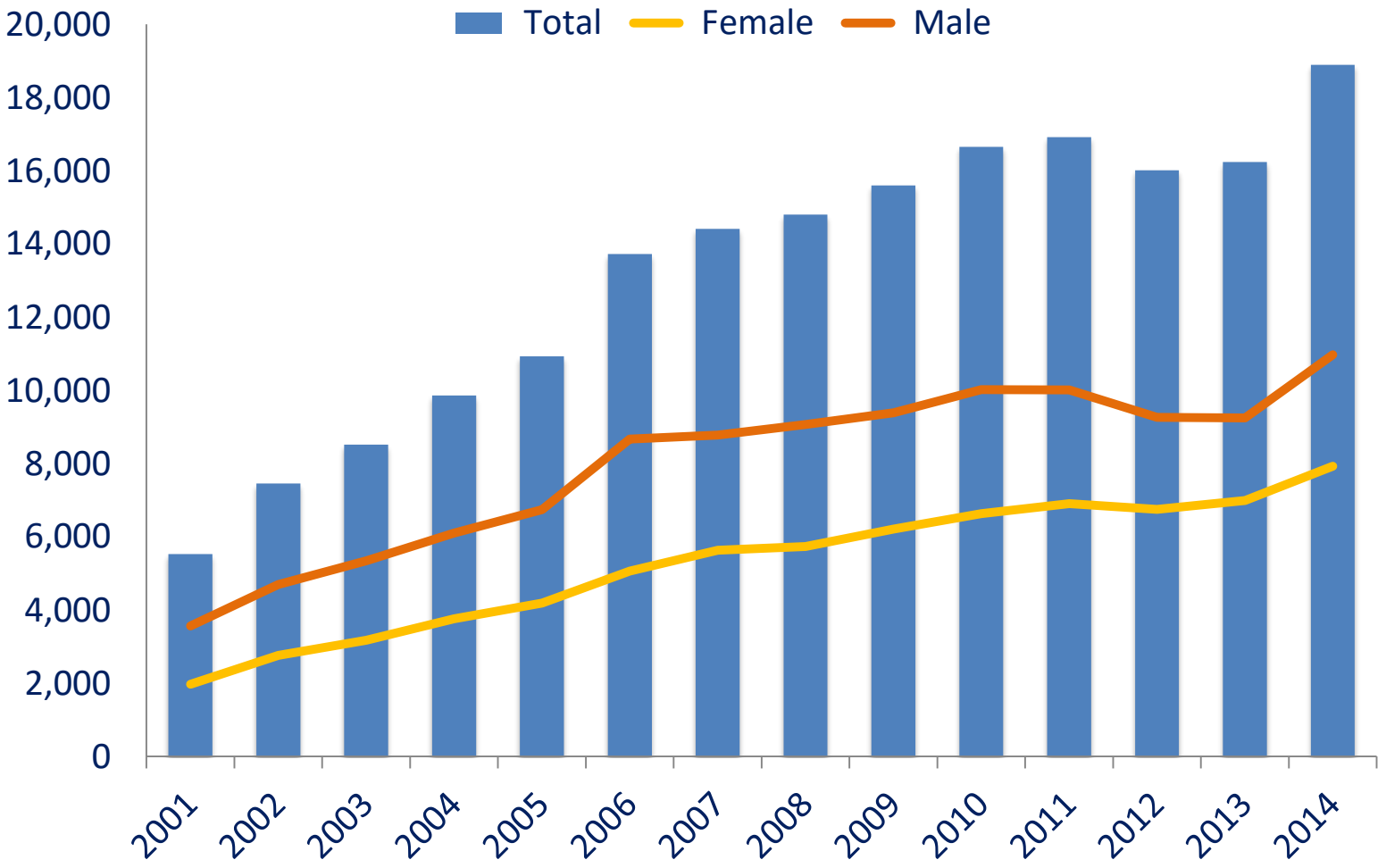


Source: National Center for Health Statistics, CDC Wonder

National Institute on Drug Abuse

National Overdose Deaths

Number of Deaths from Prescription Opioid Pain Relievers

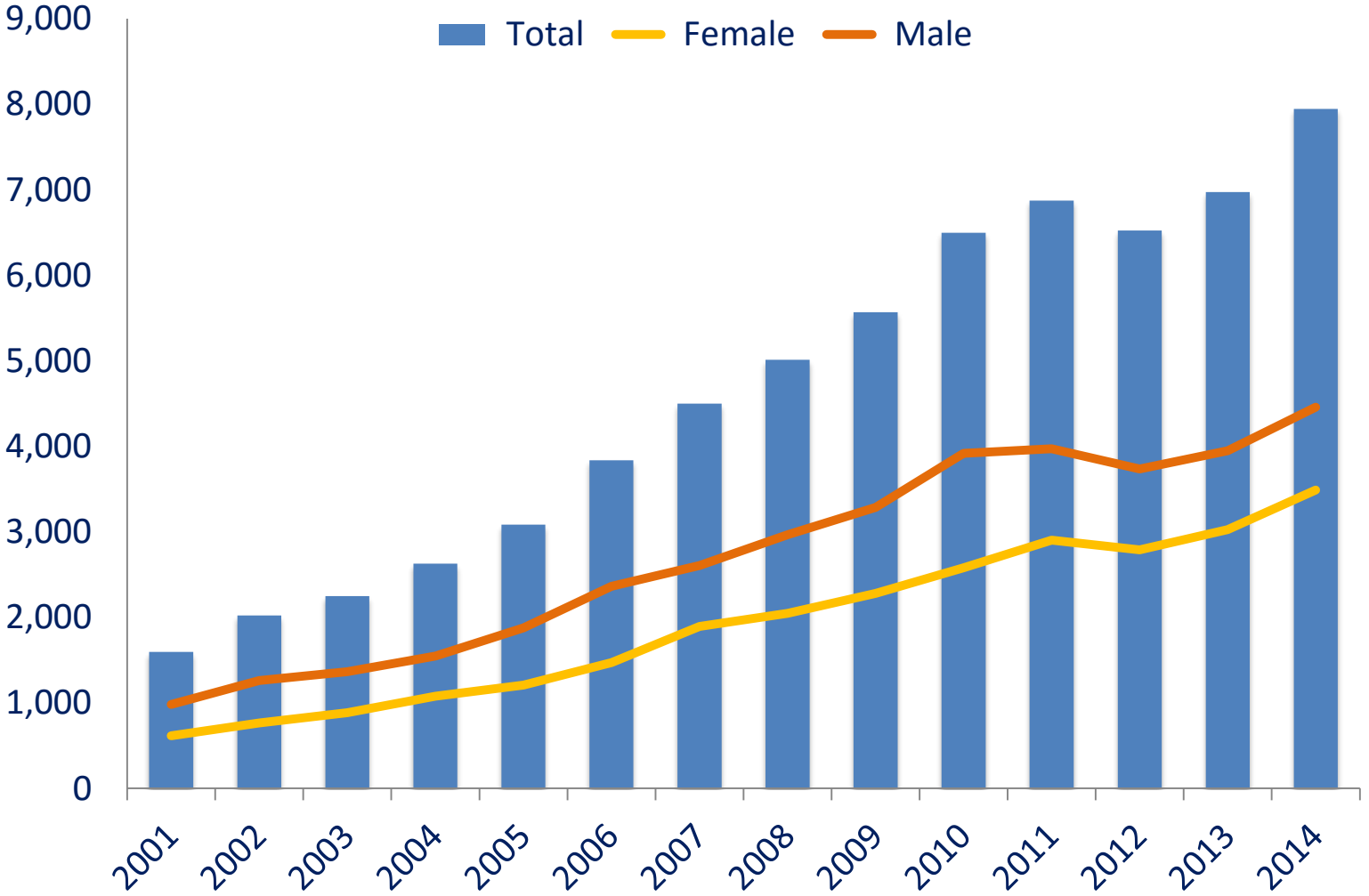


Source: National Center for Health Statistics, CDC Wonder

National Institute on Drug Abuse

National Overdose Deaths

Number of Deaths from Benzodiazepines

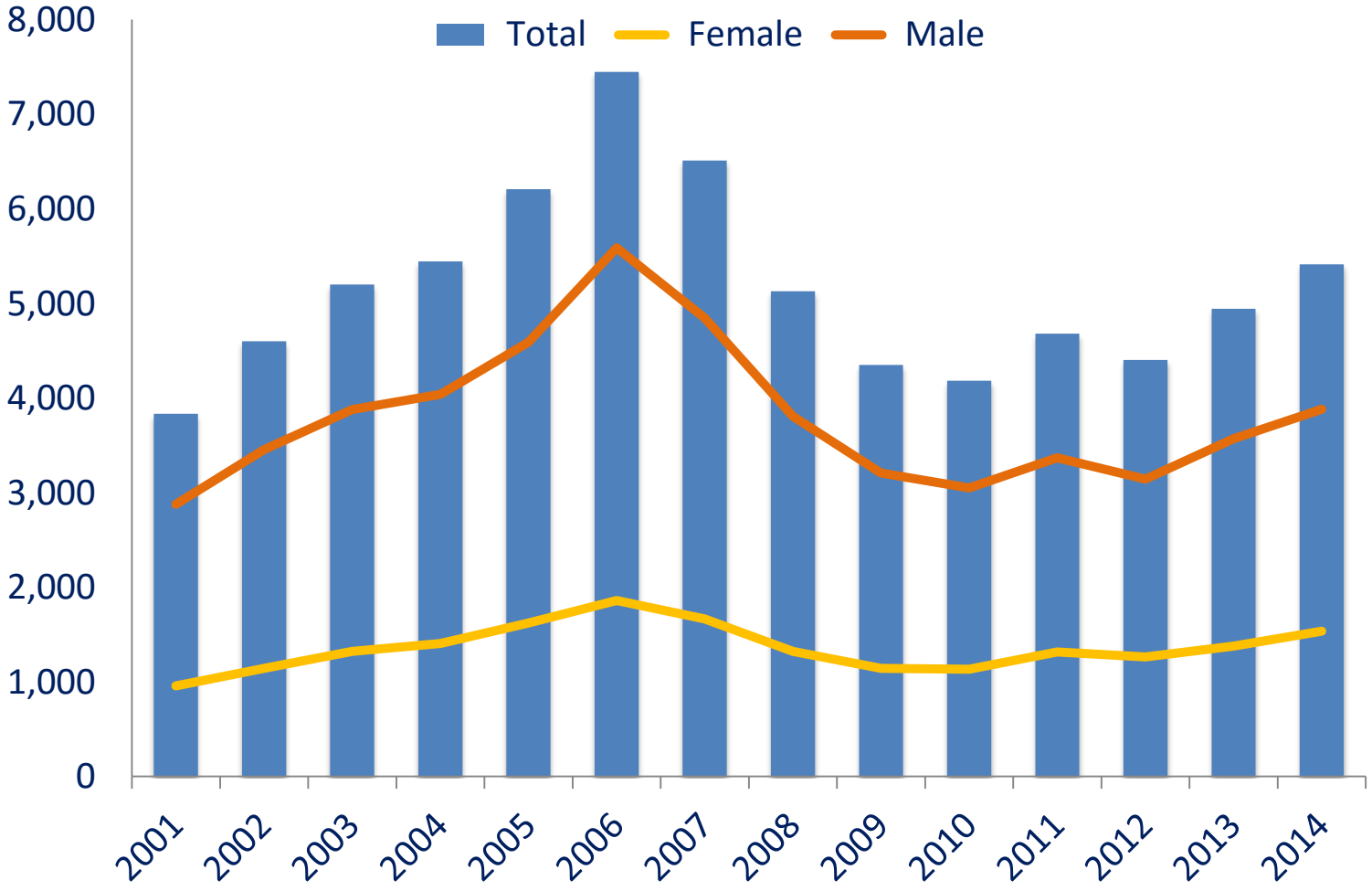


Source: National Center for Health Statistics, CDC Wonder

National Institute on Drug Abuse

National Overdose Deaths

Number of Deaths from Cocaine

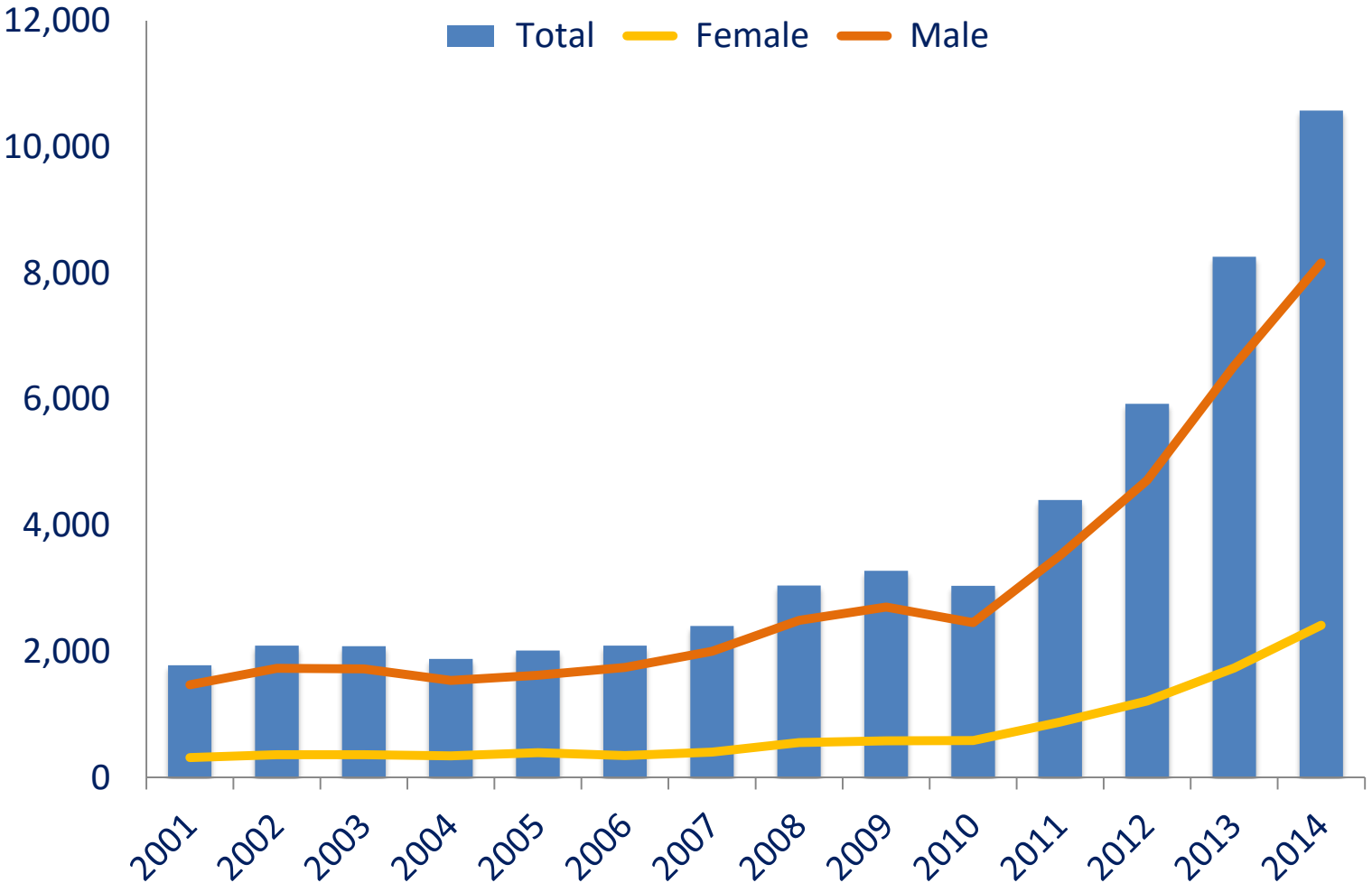


Source: National Center for Health Statistics, CDC Wonder

National Institute on Drug Abuse

National Overdose Deaths

Number of Deaths from Heroin



Source: National Center for Health Statistics, CDC Wonder

Naloxone rescue

- Injectable (IM) or intranasal kits for use by family, friends, police
- Evzio® auto-injector
- Hundreds of lives saved
- For suspected OD, call 911, administer initial dose, repeat if no response in 5 minutes.
- Good Samaritan legal protections for rescuer.

Candidates for naloxone kit

- Any pt w/ opioid use disorder, but especially:
  - h/o overdose
  - Injection use
  - Recent detox or rehab
- Pts on high-dose opioid analgesic therapy
- Family/friends/associates of above.

Walgreens Naloxone Program

- In 2016 Walgreens is making naloxone available without prescription at pharmacies in:
- North Carolina, Tennessee, Virginia
- Alabama, Arkansas, California, Colorado, Connecticut, District of Columbia, Idaho, Illinois, Indiana, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Minnesota, Mississippi, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota, Texas, Utah, Vermont, Washington, Wisconsin