Pharmacologic Treatment of Alcohol, Nicotine and Opioid Use Disorders

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Disclosures

- None

Goals and Objectives

- Review the different pharmacotherapeutic options available to treat alcohol, nicotine, and opioid use disorders
- Describe the biological mechanisms of action and rationale for using pharmacotherapy as a treatment option
- Discuss ways in which pharmacotherapy can be incorporated into a collaborative treatment model for addiction

Addiction is only one of the Substance-Related Disorders

- Substance Use Disorders (Addiction and Problematic Use)
- Intoxication States
- Withdrawal States
- Substance-Induced Medical Problems
- Substance-Induced Psychiatric Problems
- Health Problems linked to Secondary Use

Addiction in a Broad Context

- Pulmonary---Tobacco Addiction
- Gastroenterology---Alcohol(Top→Bottom),
- Infectious Disease---HIV/AIDS, Hepatitis C—IDU
- Trauma Team---Alcohol,etc.—MVA
- Psychiatry---Vulnerability/Co-morbidity
- Pediatrics---Fetal Alcohol Syndrome, Adolescents
- Ob-Gyn: Neonatal Abstinence Syndrome, Pregnancy
- Geriatrics---Alcohol as a Mimic of other diseases
- Gen. Med.---Insomnia, ↑BP, depression/anxiety weight loss, fatigue, falls, ↑LFT's etc.

Changes in DSM-5

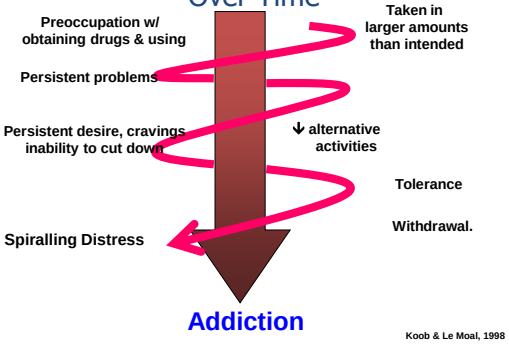
The categories of substance abuse and dependence have been combined into a new category of Substance Use Disorders. The DSM-5 Substance Use Disorder criteria combine the abuse and dependence criteria of DSM-IV with the elimination of recurrent legal problems and the addition of craving. Using the resulting 11 criteria (see following slide) the severity of the disorder – either mild (2-3), moderate (4-5), or severe (6 or more) is rated based on the number of criteria endorsed.

DSM-5 Substance Use Disorder

- Recurrent substance use in **Hazardous** conditions
- **Craving or strong desire or urge to use the substance**
- Recurrent substance use resulting in **Role failures**
- Recurrent use use despite medical, social, interpersonal **Problems**
- **T**olerance
- **W**ithdrawal
- Use greater than **I**ntended
- **S**ubstantial **t**ime spent to obtain or use substance
- Many efforts to **C**ut down
- **A**ctivities reduced
- Persistent use despite consequences

Mild: 2-3 symptoms Moderate: 4-5 symptoms
Severe: ≥6 symptoms

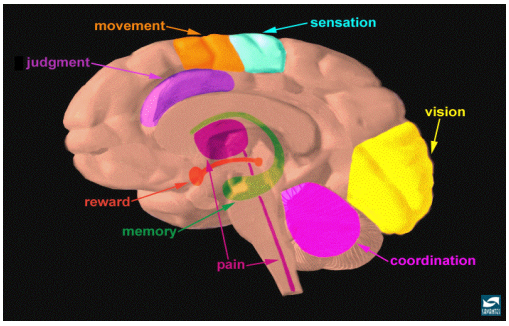
Progression of Symptoms Over Time



Koob & Le Moal, 1998

Brain Centers associated with addiction

Anatomy of the Brain



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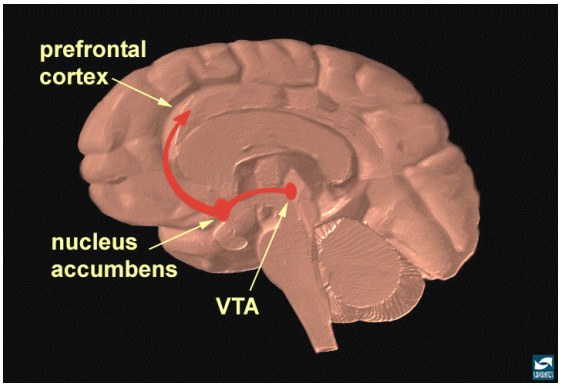

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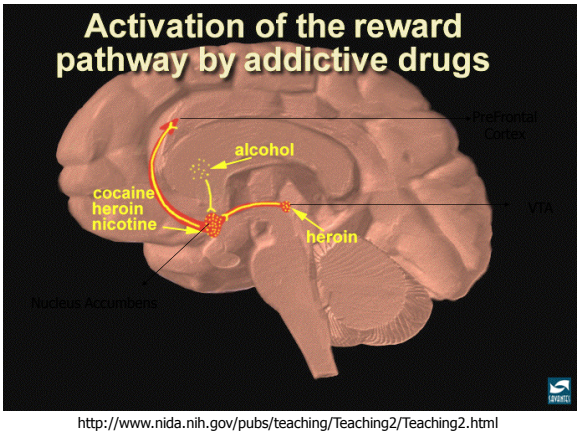

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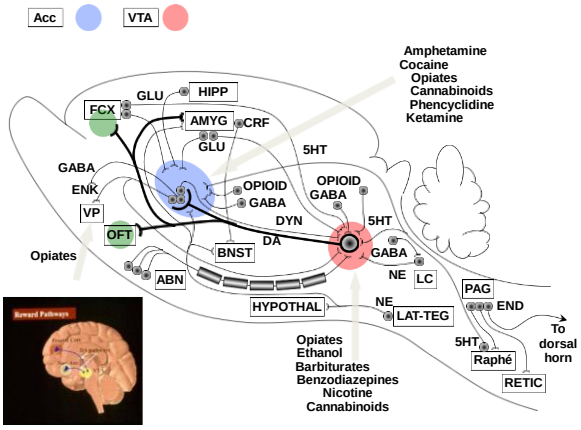
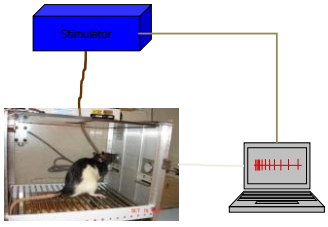


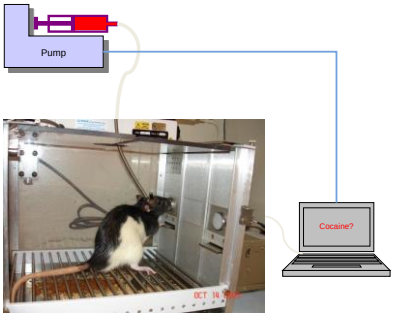
Activation of Reward Pathway

- **The nucleus accumbens (NA):** Action of amphetamines, cocaine, opiates, THC, phencyclidine, ketamine, and nicotine
- Opiates, alcohol, barbiturates and benzodiazapines stimulate neurons in the **ventral tegmental area (VTA)**
- **Prefrontal cortex (PFC)** involved in drug-related cues and drug seeking behavior
- **The final common action of most substances of abuse is stimulation of the brain reward pathway by increasing dopamine**

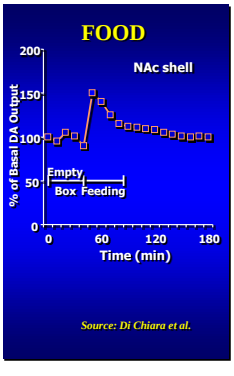
Evidence for reward pathway

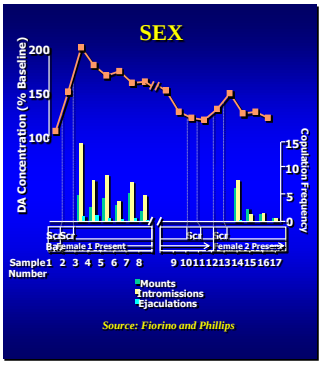
- Stimulation (electrical or chemical) of NA & VTA is intrinsically rewarding.
- Stimulation elsewhere is not rewarding
- Reward can be interrupted by
  - Severing NA-PFC fibers
  - Using dopamine blocker
- Blocking can interrupt naturally rewarded behaviors
  - Patients on drugs that block dopamine "look flat" to us and experience decreased emotions



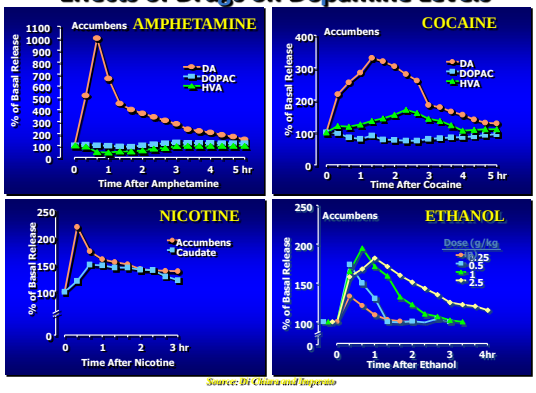


Natural Rewards Elevate Dopamine Levels





Effects of Drugs on Dopamine Levels



Source: Di Chiara and Imperato

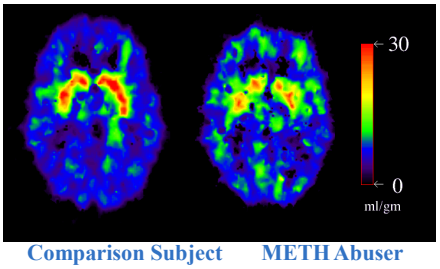
Effects of Acute Substance Use

- VTA-NA tract involved in acute substance abuse
- Dopamine increase in the NA
- Increased dopamine directs the brain to experience pleasurable activities
- Drug withdrawal leads to decreased dopamine. Natural reinforcers no longer effective. Only drugs give the same pleasurable effect

Effects of Chronic Substance Use

- Chronic drug use may cause disruption in dopaminergic activity (neurotoxicity to neurons, downregulation of receptors)
- Chronic use also leads to increased glutamate activity and stress hormones leading to increased drug seeking and intake.

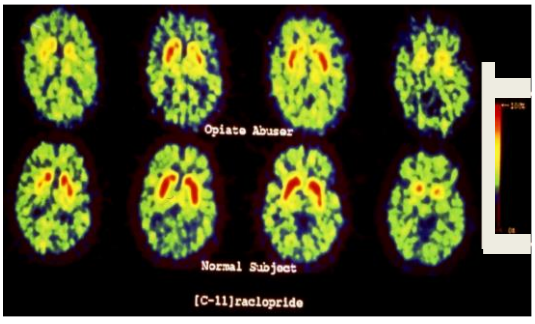
Dopamine Transporter Loss After Heavy Methamphetamine Use



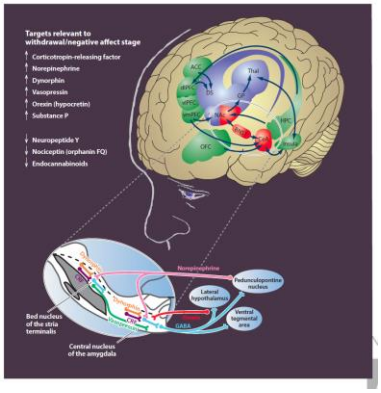
Comparison Subject METH Abuser

Volkow N. D. et al., *Am.J. Psychiatry 158(3), pp. 377-382, 2001*

Opioids Decrease D2 Receptors

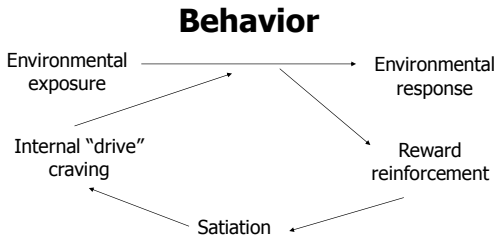


Source: Wang, G-J et al., Neuropsychopharmacology, 16(2), pp. 174-182, 1997.

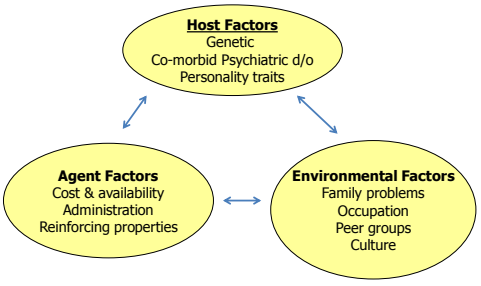


Conditioning

- Operant Conditioning: a behavior that is maintained by events occurring after the behavior. Events which increase the probability or rate of behavior are "reinforcers". Drugs of abuse are initially positive reinforcers but over time withdrawal symptoms are a negative reinforcer.
- Classical (Pavlovian) Conditioning: pairing of stimuli to elicit response or behavior. Important for patients to identify these stimuli to prevent relapse.



Factors Associated with Addiction



Characteristics of Drugs with Abuse Potential

Abuse Potential of a Drug Can Vary as a Function of:

- Route of administration (faster routes such as injecting, smoking = greater abuse potential)
- Half life (shorter half life = greater abuse potential)
- Lipophilicity (more rapidity reaches brain = greater abuse potential)

Genetics of Addiction

- **FAMILY STUDIES**:
- Children of alcoholics have 3-4 fold increase of becoming alcoholics (Shuckit 1987; Cotton 1979)
- **TWIN Studies:**
- Concordance rate of Etoh in MZ twins 60% vs 39% in DZ (Kaji 1960)
- Similar finding in male twins (Hrubec & Omenn 1981; Pickens, Svikis et al 1991; McGue et al 1992) but ess consistent in females
- Adoption studies: Sons of alcoholics 4 times likely to be Etohics whether raised by bio or nonEtoh adoptive parents * Schuckit 1972; Clononger 1981)

Genetics of Addiction

- Subjects with + family hx have less subjective feelings of intoxication, decreased body sway, less intense change in levels of cortisol, prolactin, fewer EKG changes after drinking Etoh (Schuckit 1987, 1988, 1984)
- Gene polymorphism: familial differences in GABA receptor, serotonin transporter, alcohol dehydrogenase genes may mediate level of response to alcohol and predict risk of developing alcohol dependence

Heritabilities Derived From Twin Studies

DRUG	Males	Females
Cocaine	44% (Tsuang et al., 1996) 79% (Kendler et al., 2000)	81%(Kendler et al., 1999)
Heroin (opiates)	54% (Tsuang et al., 1996)	
Sedatives	87% (Kendler, et al., 2000)	
Marijuana	33% (Tsuang et al., 1996) 58% (Kendler, et al., 2000)	79%(Kendler & Prescott, 199
Hallucinogens	79% (Kendler, et al., 2000)	
Nicotine	53% (Carmelli et al., 1990)	72%(Kendler et al., 1999)

Psychiatric Comorbidity

Brooner, 1997:

716 opioid abusers seeking methadone treatment DSM-IIIR assessments one month after admission

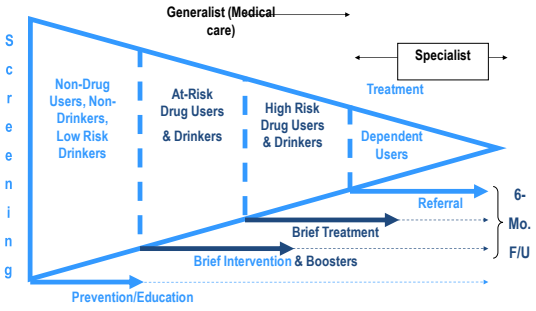
	Lifetime	Current
• Any psychiatric comorbidity	47%	39%
• Any Axis I disorder	24%	8%
• Mood disorder	19%	4%
◦ major depression	16%	3%
◦ anxiety disorder	8%	5%
• Any personality disorder		35%
– anti-social		25%
– avoidant		5%
– borderline		5%

Substance Use History

- **Substances used** (opioids, stimulants, alcohol, sedatives, marijuana, hallucinogens, tobacco, inhalants)
- **Patterns of use** (starting age, duration, frequency, last used, usual and highest amts, periods of abstinence)
- **Treatment History & Response** (detox, AA, NA, counseling, methadone, buprenorphine, other pharmacotherapies, Residential programs)
- **Medical Complications**(HIV, Hepatitis, Endocarditis, infections, OD)
- **Psychiatric Complications** (Depression, Psychosis, Anxiety)
- **Social Complications** (family/friend problems, job loss, legal problems, academic problems)

Continuum of Care

Clinically-appropriate interventions in medical settings



Addiction Treatment Modalities

- Detoxification
- Pharmacotherapy
- Relapse Prevention (Cognitive Behavioral Therapy)
- Self-help groups (12 step NA/AA; Rational Recovery)
- Treatment of co-occurring psychiatric/medical disorders
- Family Therapy

Types of Treatment Settings

- Inpatient Hospital Treatment:
  - Detox and stabilization of co-occurring psychiatric/medical diagnoses
- Residential Treatment:
  - 14-28 day programs
- Outpatient Treatment: Intensive or standard outpatient treatment
- Others: 12-step meetings, halfway houses or recovery houses

Goals of Pharmacotherapy in SUD Treatment

- Management of withdrawal syndromes
- Decrease and stop cravings and urges to use
- Prevention of relapse to compulsive use

Treatment Strategies for SUDs

- Drug antagonists
- Drug agonists
  - Full agonists
  - Partial agonists
- Neuromodulators
- Aversive agents

Pharmacotherapy:
Opioids

- Drug antagonists
  - Naltrexone
  - Naloxone (to treat overdose)
- Drug agonists
  - Methadone (full agonist)
  - Buprenorphine (partial agonist)
- Neuromodulators

Opioids

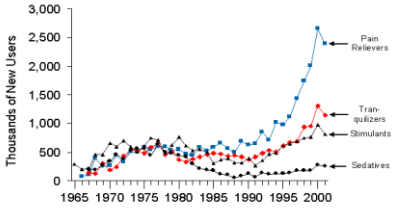
Natural opiates (alkaloids contained in opium poppy)
- morphine
- codeine
- thebaine

Semi-synthetic opiates (created from natural opiates)
- hydromorphone
- oxycodone
- heroin (diacetylmorphine)
- oxymorphone
- hydrocodone

Fully synthetic opioids
- fentanyl
- propoxyphene
- methadone
- meperidine

Endogenous opioid peptides
- endorphins
- enkaphalins
- dynorphins
- endomorphins

Annual Numbers of New Nonmedical Users of Psychotherapeutics: 1965–2001



From: 2002 National Survey on Drug Use and Health, SAMHSA

ABUSE & DEPENDENCE OF OPIOID ANALGESICS - A NEW EPIDEMIC

- **1984 to 1994: New heroin users each year ranged from 28,000 to 80,000**
- **In 1990, there were 628,000 new users of pain relievers for non-medical purposes**
- **In 2006 there were 5,200,000 users of pain relievers for non-medical purposes**
- **In 2006, 1,635,000 of this group met criteria for opioid dependence or abuse**

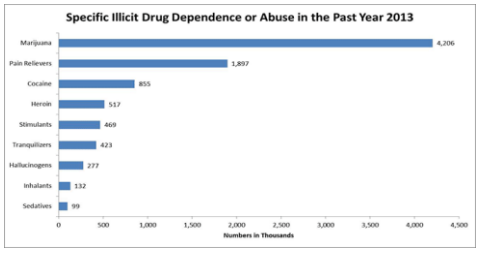
2006 National Survey on Drug Use and Health: National Findings, Office of Applied Studies, DHHS, SAMHA www. oas.samhsa.gov

ABUSE & DEPENDENCE OF OPIOID ANALGESICS
- TRACKING THE EPIDEMIC

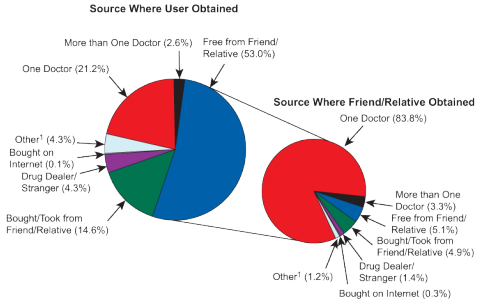
- **Since 2009 the use of pain relievers for non-medical purposes has begun to drop. This is thought to reflect:**
  - **Education of the public and physicians about the risks associated with the use of these medications**
  - **Introduction of abuse-deterrent drug formulations**
- **Unfortunately there has also been a concurrent increase in the abuse of heroin, with no significant drop in the numbers of individuals seeking treatment. Pain relievers still rank second to marijuana as the first illicit drug used by individuals 12 and older.**

2013 National Survey on Drug Use and Health: National Findings, Office of Applied Studies, DHHS, SAMHA www. oas.samhsa.gov

National Survey on Drug Use and Health (NSDUH)

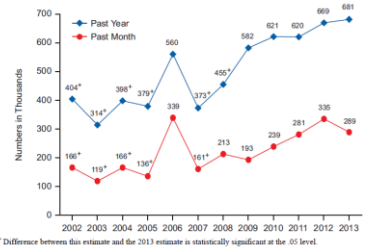


Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use Among Past Year Users Aged 12 or Older: 2012-2013



NSDUH 2013

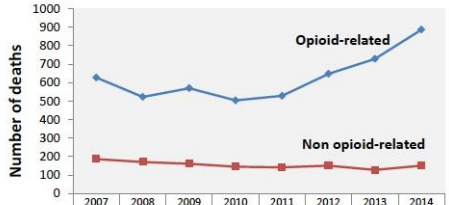
Figure 2.4 Past Month and Past Year Heroin Use among Persons Aged 12 or Older: 2002-2013



* Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.

Increasing Opioid-Related Deaths

Figure 6. Total Number of Opioid* and Non-Opioid-Related Deaths Occurring in Maryland, 2007-2014.



	2007	2008	2009	2010	2011	2012	2013	2014
Opioid-related	628	523	570	504	529	648	729	887
Non opioid-related	187	171	161	145	142	151	128	151

Function at Receptors: Full Opioid Agonists

Mu receptor — **Full agonist binding …**

❶ activates the mu receptor

❷ is highly reinforcing

❸ is the most abused opioid type

❹ includes heroin, codeine, & others

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Function at Receptors: Partial Opioid Agonists

Mu receptor — **Partial agonist binding …**

❶ activates the receptor at lower levels

❷ is relatively less reinforcing

❸ is a less abused opioid type

❹ includes buprenorphine

49

Function at Receptors: Opioid Antagonists

Mu receptor — **Antagonist binding …**

❶ occupies without activating

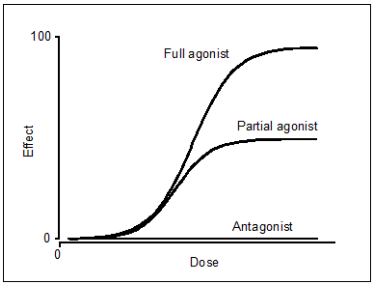
❷ is not reinforcing

❸ blocks abused agonist opioid types

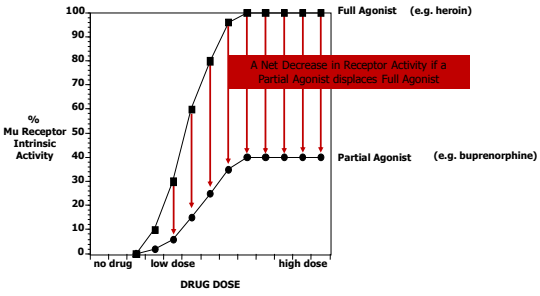
❹ includes naloxone and naltrexone

50

Efficacy: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)



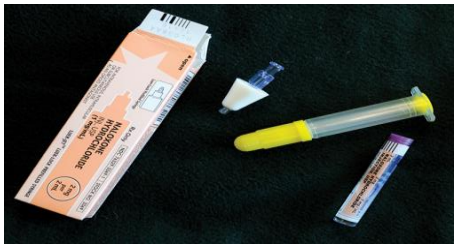
Precipitated Withdrawal

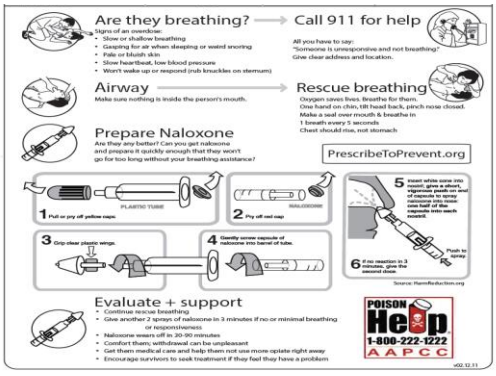


Opioid Overdose/Withdrawal

- Overdose (respiratory depression, coma, pinpoint pupils): Naloxone 0.4 -0.8 mg IV
- Withdrawal Treatment:
  - Buprenorphine/Naloxone Sublingual Tablets/Film (Suboxone/Subutex)
  - Methadone
  - Clonidine 0.3 mg orally every 6 hrs—only treats autonomic symptoms but not cravings

Intranasal Naloxone for Opioid Overdose





Source: PrescribetoPrevent.org

Methadone

- Full opioid agonist
- Patients are typically started at 30 mg/day.
- Usual doses 60 - 100 mg/day.
- Dispensed at federally regulated opioid treatment centers (OTP)
- Daily attendance initially, patients earn "take-homes" (contingency management)
- Meetings, individual counseling, other psychosocial services.

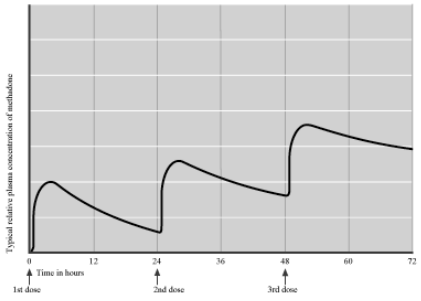
Impact of MMT

- Reduction death rates (Grondblah, '90)
- Reduction IVDU (Ball & Ross, '91)
- Reduction crime days (Ball & Ross)
- Reduction rate of HIV seroconversion (Bourne, '88; Novick '90,; Metzger '93)
- Reduction relapse to IVDU (Ball & Ross)
- Improved employment, health, & social function

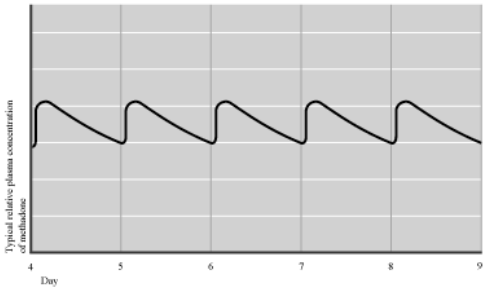
Phases of Methadone Dosing

PHASE	PURPOSE	RANGE IN MG
Initial Dose	Relieve opioid withdrawal	20-30 mg
Early Induction	Reach established tolerance level	+/- 5-10 mg every 3 days
Late Induction	Establish adequate dosing	+/- 5-10 mg every 5-10 days
Maintenance	Maintain steady state, occupation of all opiate receptors	Usual range 60-120 mg/day

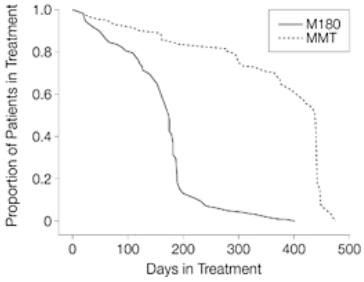
Methadone Induction Levels



Methadone Maintenance Levels

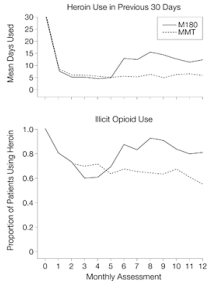


Methadone vs. detox:
Treatment retention



MMT: methadone maintenance
M180: detox followed by psychosocial rx

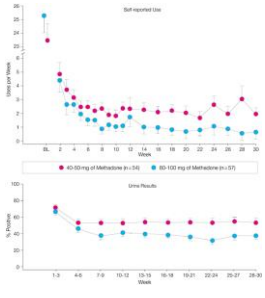
Methadone vs Detox:
Heroin use



MMT: methadone maintenance

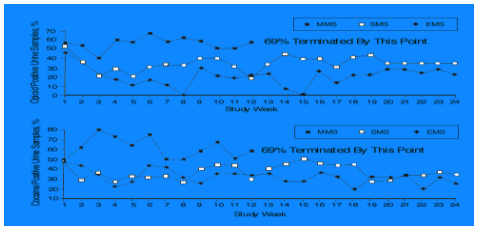
M180: detox followed by psychosocial rx

Methadone maintenance: moderate vs. high dose



Red: 40-50 mg/day
Blue 80-100 mg/day

Effect of Counseling in MMT



McLellan AT, et al. (1993) JAMA

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Methadone

Full opioid agonist.

Pros:

- Long-acting (given once daily).
- Metabolite distinct from heroin and morphine (for urine testing)
- Inexpensive

Cons:

- Use limited to licensed programs.
- QT prolongation, especially at higher dosages
- Significant drug-drug interactions

Common Myths/Misconceptions about methadone

- Methadone makes bones weak: methadone does not affect the bone system, aches and pains may be from mild opioid withdrawal
- Methadone rots your teeth: teeth decay is consequence of long term active addiction
- Methadone harms your liver: methadone metabolized by liver but does not cause liver damage; pts with hepatitis can take methadone safely
- Methadone is harder to get off than heroin: Methadone has longer half-life so withdrawal sxs last longer if pt stops it suddenly. Medically supervised withdrawal will minimize withdrawla symptoms and make it more likely for pt to stay opiate-free

Buprenorphine

- Prescribed in a variety of settings, from structured addiction-treatment programs to primary care offices.
- Typical sublingual maintenance dose ranges from 8 to 24 mg per day.
- Most often prescribed in a formulation combined with naloxone to discourage intravenous or intranasal use.

Buprenorphine has reduced the gap in the treatment of opioid dependence

- **Before the introduction of buprenorphine there were estimated to be 1,900,000 chronic opioid users. Less than 10% were in treatment.**
- **There are now over 300,000 on buprenorphine and 275,000 on methadone**

DRUG ADDICTION TREATMENT ACT OF 2000

An Amendment
to the Controlled Substances Act

Allows practitioner to prescribe FDA approved narcotic drugs in schedule III, IV, V, or combinations of such drugs, for maintenance or detoxification treatment

AMENDED CONTROLLED SUBSTANCES ACT

Drugs and practitioner must meet certain requirements

AMENDED CONTROLLED SUBSTANCES ACT

PRACTITIONER REQUIREMENTS:

- **"Qualifying physician"**
- **Has capacity to refer patients for appropriate counseling and ancillary services**
- **No more than 30 patients (individual practice) for the first year**
- **May request approval to treat up to 100 patients after the first year**

AMENDED CONTROLLED SUBSTANCES ACT

"QUALIFYING PHYSICIAN":

A licensed physician who meets one or more of the following:

1. **Certified in Addiction Psychiatry by ABPN**
2. **Certified in Addiction Medicine by ABAM**
3. **Certified in Addiction Medicine by AOA**
4. **Investigator in buprenorphine clinical trials**

AMENDED CONTROLLED SUBSTANCES ACT

"QUALIFYING PHYSICIAN" (continued):

Meets one or more of the following:

5. **Has completed 8 hours training provided by APA, AAAP, ASAM, AMA, AOA (or other organizations which may be designated by HHS)**
6. **Training/experience as determined by state medical licensing board**
7. **Other criteria established by Secretary of HHS**

AMENDED CONTROLLED SUBSTANCES ACT

PRACTITIONER:

Must notify the Secretary of HHS in writing (yellow form in syllabus):

- **His/Her name**
- **DEA registration**
- **Category for qualification (1 to 7)**
- **Certify intend to comply with law**

Notifications can be submitted by mail, fax, online (www.buprenorphine.samhsa.gov)

AMENDED CONTROLLED SUBSTANCES ACT

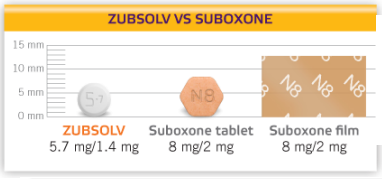
PRACTITIONER:

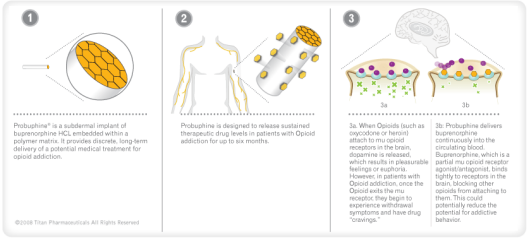
- **HHS has 45 days to determine if the physician meets all the requirements**
- **The DEA will assign an identification (DEA) number to the practitioner; this "X" number is assigned after 45 days if HHS does not act**
- **Both the physician's original DEA number and the new "X" number must be written on all buprenorphine prescriptions**

AMENDED CONTROLLED SUBSTANCES ACT

NARCOTIC DRUG:

- **Approved by the FDA for use in maintenance or detoxification treatment of opioid dependence**
- **Schedule III, IV, or V**
- **Drugs or combinations of drugs**
- **Buprenorphine is the only drug currently approved (Schedule III)**





Buprenorphine Induction: Goals

To find the dose of buprenorphine at which the patient:

- **Has no opioid withdrawal symptoms**
- **Discontinues or markedly reduces use of other opioids**
- **Experiences no cravings**
- **Has minimal or no side effects**

Buprenorphine Induction: Patient Education

- Sublingual tablets must be held under tongue for several minutes to dissolve.
- Instruct to:
  - Start with a moist mouth, but avoid acidic drinks (coffee or fruit juice)
  - Not talk.
  - Keep dissolving tablet under tongue.
  - Don't swallow until entire tablet is dissolved.

Buprenorphine Induction - Day 1

Instruct the patient to abstain from any opioid use, so that they are in mild withdrawal at time of first buprenorphine dose. Avoiding precipitated withdrawal is the key to successful induction

- 16 hours for short-acting opioids
- 24 hours for sustained-release opioid medications
- 36 hours for methadone

For methadone transfer:

- Stabilize on 30mg (1-2 weeks)
- Last day on methadone cut dose to 15mg
- Next day – no methadone
- Following day – bup induction

Buprenorphine Induction - Day 1

- Patients dependent on short-acting opioids (e.g.:heroin/oxycodone/hydrocodone)
  - Instruct patients to abstain from any opioid use for 16 to 24 hours prior to induction visit (so they are in mild-moderate withdrawal at induction visit)
  - Use opioid withdrawal scale (COWS > 8) to document and assess severity of withdrawal and to track the patient's response to first day's dose

Clinical Opiate Withdrawal Scale (COWS)

- Resting Pulse
- Sweating
- Restlessness
- Pupil Size
- Bone or Joint Aches
- Runny Nose or Tearing
- GI Upset
- Tremor
- Yawning
- Anxiety or Irritability
- Gooseflesh

Clinical Opiate Withdrawal Scale (COWS)

- ✓ Items are scored from 0 - 4 or 5.
- ✓ TOTAL SCORE:

5 - 12	Mild: aim for 8-10 minimum
13 - 24	Moderate
25 - 36	Moderately Severe
> 36	Severe

Buprenorphine Induction - Day 1

First dose: 2 to 4 mg SL buprenorphine/naloxone:

- Monitor in office for 1+ hours after first dose.
- Relief of opioid withdrawal symptoms should begin within 30-45 minutes after the first dose.
- Re-dose every 2-4 hours, if opioid withdrawal subsides then reappears.
- Aim for dose of 8 - 12 mg. in the first 24 hours

Buprenorphine Induction - Day 1

- If opioid withdrawal appears shortly after the first dose, it suggests that the buprenorphine may have precipitated a withdrawal syndrome.
- Greatest severity of buprenorphine-related precipitated withdrawal occurs in the first few hours (1-4) after a dose, with a decreasing (but still present) set of withdrawal symptoms over subsequent hours.

Buprenorphine Induction - Day 1

- If a patient has precipitated withdrawal consider:
  - Giving another dose of buprenorphine, attempting to provide enough agonist effect from buprenorphine to suppress the withdrawal,
  - OR
  - Stopping the induction, provide symptomatic treatments for the withdrawal symptoms, and have patient return the next day.
- Since the latter would risk losing the patient, the first option is often preferred.

Buprenorphine Induction - Day 2

- Have patient return to the office if possible.
- Assess opioid use and symptoms since first dose.
- Adjust dose accordingly:
  - Higher dose if there were withdrawal symptoms after leaving your office.
  - Lower dose if patient was over-medicated.
- Continue adjusting dose by 2 - 4 mg increments until an initial target dose of 12 - 16 mg is achieved for Day 2.

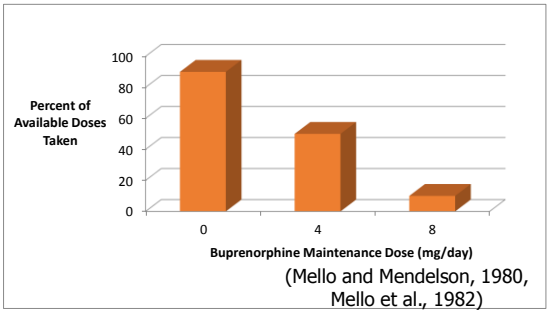
Buprenorphine Induction - Day 2 and Beyond

- If continued dose increases are requested after reaching 16 mg, wait for 5-7 days to reassess before any further dose increase
- Most patients can be stabilized between 12 mg and 16 mg
- The standard range is 8 mg to 24 mg
- The maximum recommended daily dose is 32 mg; doses in this range increase the risk of diversion

Buprenorphine Stabilization/Maintenance

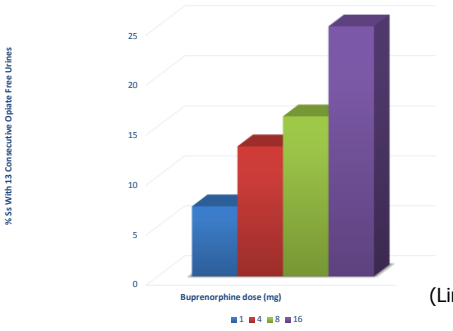
- Expect that the average daily dose will be somewhere between 8 and 24 mg of buprenorphine; most patients will not require more than 16 mg.
- Higher daily doses are more tolerable if taken sequentially or in divided doses rather than all at once.

Heroin Self-Administration During Buprenorphine Maintenance



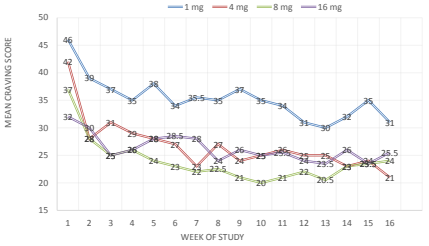
(Mello and Mendelson, 1980, Mello et al., 1982)

Different Doses of Buprenorphine: Opiate Use



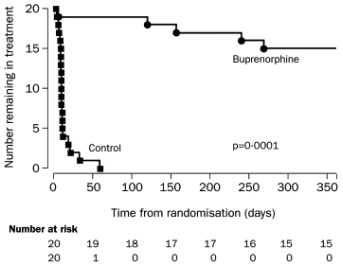
(Ling et al., 1998)

Mean Heroin Craving: 16 Week Completers



(Ling et al., 1998)

Retention in Treatment:
Buprenorphine detox vs. maintenance



Kakko, J, et al. Lancet 2003

Buprenorphine

Pros:

- Partial agonist (safer).
- Can be prescribed by office-based physicians.
- Patient satisfaction (office-based).
- Minimal drug-drug interactions

Cons:

- Expensive (~10$/day)
- Variations in practice

Drug-Drug Interactions Methadone vs Buprenorphine

Table 3

Potential Drug Interactions for Methadone and Buprenorphine

Interaction	Methadone	Buprenorphine
Increase Effects of Opioid Substitute	Alcohol Antidepressants • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline Anti-infectives • Ciprofloxacin • Erythromycin • Fluconazole • Ketoconazole Benzodiazepines Cimetidine	Alcohol Antiretrovirals • Atazanavir • Indinavir • Nevirapine • Ritonavir • Saquinavir Benzodiazepines Fluvoxamine Ketoconazole
Decrease Effects of Opioid Substitute	Anti-infectives • Fusidic acid • Rifampin Antiretrovirals • Abacavir • Amprenavir • Efavirenz • Nevirapine • Ritonavir • Saquinavir Barbiturates Carbamazepine Phenytoin	Carbamazepine Phenobarbital Phenytoin Rifampin

Source: References 12, 16.

Buprenorphine vs. Methadone

	Buprenorphine	Methadone
Better safety	--	--
More psychosocial support		√
Higher patient satisfaction	√	
Lower drug costs		√
Lower administrative costs	√	
Less risk of diversion		√
Ease of accessibility	√	
More effective	--	--

Opioid agonists:

Substituting one drug for another?

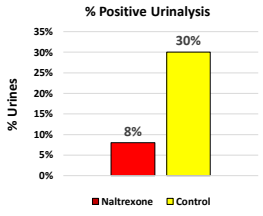
	YES	NO
Complete abstinence?		√
Reduce use of heroin?	√	
Reduce harm/mortality?	√	
Reduce criminal activity?	√	
Cost effective?	√	
Patient satisfaction?	√	

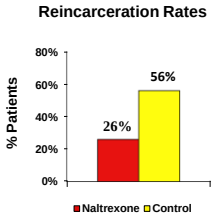
Naltrexone

- Opioid antagonist.
- Patient must be opioid free minimum of 7-10 days
- Patient acceptance is a barrier, but may be a good choice for highly-motivated.
- Limited evidence of efficacy; no comparisons with opioid agonists.
- Sustained-release injections 380 mg IM/monthly may be more effective.
- Side effects
  - Oral: gastrointestinal discomfort, elevated liver enzymes
  - XR injectable: elevated eosinophils, elevated liver enzymes, injection site reactions

Vivitrol (extended-release injectable naltrexone)

Naltrexone Efficacy

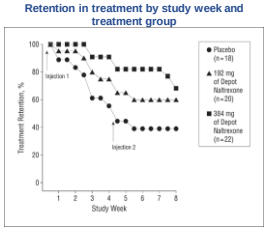


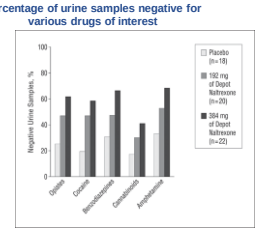


Cornish et al. (1997) J Subst Abuse Treat.

100

Naltrexone Efficacy





ARCHIVES OF GENERAL PSYCHIATRY

Comer, S. D. et al. (2006) Arch Gen Psychiatry

101

PCSS-O
Resource for Provider Support

The **Providers' Clinical Support System for Opioid Therapies,** funded by a SAMHSA grant, was created in response to the opioid overdose epidemic.

Through education and colleague support, this national coalition of healthcare organizations is charged with creating no cost programs on the safe and effective use of opioids for treatment of chronic pain and safe and effective treatment of opioid use disorder.

Target Audience

- The overarching goal of PCSS-O is to offer evidence-based CME trainings on the safe and effective prescribing of opioid medications in the treatment of pain and/or opioid addiction.
- Our focus is to reach providers and/or providers-in-training from diverse healthcare professions including physicians, nurses, dentists, physician assistants, pharmacists, and program administrators.

Training Modalities

PCSS-O offers training activities with CME at no cost to health professionals through the use of:

- **Live Webinars**
- **Archived Webinars**
- **Online Modules**

In addition, PCSS-O offers clinical resources:

- **Clinical Guidances:**
- **Listserv:** Provides an "Expert of the Month" to answer questions about content presented through PCSS-O project. To join email: pcss-o@aaap.org.

PCSS-O Colleague Support Program

- Offers general information to health professionals seeking guidance prescribing opioid medications.
- Comprised of a national network of trained providers with expertise in **addiction medicine/psychiatry and pain management.**
- Allows every colleague relationship to be unique and designed to the specific needs of both parties.
- Available at no cost.

For more information on requesting or becoming a mentor visit:
www.pcss-o.org/colleague-support

PCSS-O TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM For Opioid Therapies

PCSS-O is a collaborative effort led by American Academy of Addiction Psychiatry in partnership with: Addiction Technology Transfer Center, American Academy of Neurology, American Academy of Pain Medicine, American Academy of Pediatrics, American College of Physicians, American Dental Association, American Medical Association, American Osteopathic Academy of Addiction Medicine, American Psychiatric Association, American Society for Pain Management Nursing, International Nurses Society on Addictions, and Southeast Consortium for Substance Abuse Training.

For more information visit: www.pcss-o.org
Questions email: pcss-o@aaap.org

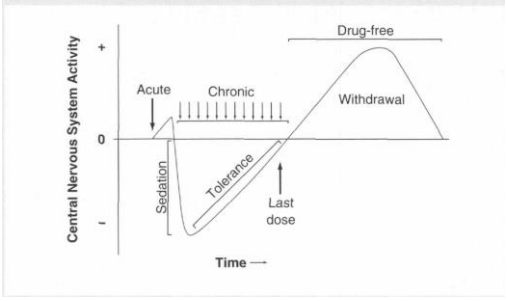
Twitter: @PCSSProjects

Funding for this initiative was made possible (in part) by Providers' Clinical Support System for Opioid Therapies (grant no. 1H79TI025595) from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Pharmacotherapy:
Alcohol

- Drug antagonists
- Drug agonists
  - Benzodiazepines
- Neuromodulators
  - Endorphin (naltrexone)
  - GABA (acamprosate, topiramate)
- Aversive Agent
  - Disulfiram

Pathophysiology of Alcohol Withdrawal



Pathophysiology of Alcohol Withdrawal (2)

- Disruption of homeostasis between GABA/glutamate neurotransmission
  - Chronic alcohol use causes diminished $GABA_A$ receptor response to GABA and downregulation of receptors
  - NMDA-type glutamate receptors are upregulated with chronic alcohol use
- Alcohol withdrawal is a state of diffuse cerebral disinhibition/hyperexcitation (diminished GABA inhibitory activity and increased glutamate excitatory activity)

Pathophysiology of Alcohol Withdrawal (3)

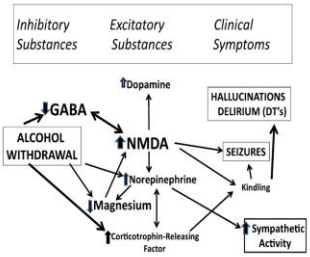


Fig. 4. Multifaceted pathogenesis of alcohol withdrawal syndrome. (*Data from* Glue P, Nutt D. Overexcitement and disinhibition: dynamic neurotransmitter interactions in alcohol withdrawal. Br J Psychiatry 1990;157:491–9.)

Alcohol Detoxification

- Etoh withdrawal symptoms: Treat with benzodiazepines
- Withdrawal seizures (generalized): Occur 24-48 hours after last drink. Rx: Benzos --long acting (diazepam, chlordiazepoxide) except in pts with liver problems (lorazepam, oxazepam)
- DTs: Occurs 72-96 hrs after last drink (unstable vital signs, visual hallucinations, disorientation)-- associated with high mortality so medical emergency
- Etoh induced amnestic d/o:
  - Wenicke-Korsakoff syndrome: Triad of encephalopathy, ataxia, opthalmoplegia. 80% progress to Korsakoff's psychosis (chronic amnestic d/o)
  - Rx Thiamine IM/IV, then PO
- Alcoholic Hallucinosis: auditory hallucinations occurring with clear sensorium (usually lasts up to 4 weeks)

Benzodiazepines

- Drugs of choice for treatment of alcohol withdrawal, but not used for long-term treatment of alcohol dependence.
- No evidence of benefit with long-term use.
- Substantial risk of abuse and deleterious effects.

Disulfiram (Antabuse)

- Dose: 250-500 mg daily.
- Alcohol –>ADH-> Acetaldehyde –> ALDH –> acetic acid
  - Inhibits ALDH. Causes accumulation of acetaldehyde. This causes tachcardia, palpitations, decreased BP, flushing, blurred vision, confusion.
- Randomized controlled trials have failed to demonstrate a benefit.
- May be beneficial for selected individuals, particularly if supervised.
- Side effects: disulfiram reaction, neuropathy.

Naltrexone

- Opioid antagonist, thought to reduce the reinforcing effects of alcohol.
- Usual Oral Dose: 50-100 mg daily.
- Extended-release injectable form (Vivitrol) 380 mg intramuscularly every 28 days
- Modestly improves short-term abstinence in conjunction with psychosocial treatment.
- Side effects: nausea (14%) & dizziness (12%)

Naltrexone for Alcohol Dependence

- Cochrane Review of NTX
  - decreased relapse to heavy drinking [RR = 0.64]
  - decreased return to any drinking [RR = 0.87]
  - NTX increased the time to first drink
  - NTX reduced craving
  - NTX was superior to acamprosate in reducing relapses, drinks and craving.

Srisurapanont & Jarusuraisin (2005) Cochrane Database Syst Rev. 2005 Jan 25;(1):CD001867

Extended-release injectable naltrexone decreased time to relapse

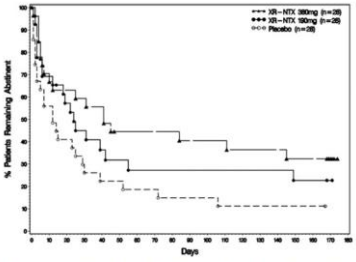


Figure 2. Kaplan–Meier analysis of time to first drink among patients abstinent (≥4 days) prior to treatment initiation: duration of initial abstinence was significantly greater for XR-NTX 380 mg compared with placebo (42 vs. 12 days; $P = 0.02$) and the percent of patients with sustained abstinence at the conclusion of the trial was also significantly greater for XR-NTX 380 mg compared with placebo (32% vs. 11%; $P = 0.02$), with the XR-NTX 190 mg group showing results that are intermediate for both parameters.[46]

Ann N Y Acad Sci. 2011 Jan

Fewer percentage drinking days on extended-release injectable naltrexone

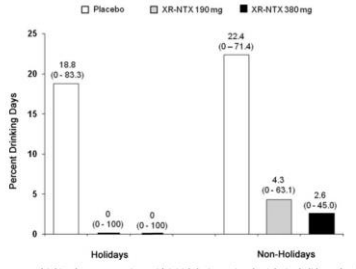


Figure 3. Median percent drinking days among patients with initial abstinence (≥4 days) during holiday and nonholiday periods for percent drinking days. Numbers in parentheses represent ranges for each category. Placebo, $N = 27$; XR-NTX 190 mg, $N = 26$; XR-NTX 380 mg, $N = 27$. Data analyzed by Wilcoxin test: $^*P < 0.05$; $\dagger P < 0.01$.[47]

Ann N Y Acad Sci. 2011 Jan

Acamprosate (Campral)

- Enhances function of GABA and blocks glutamate activity (reduces excitatory activity in brain that can lead to cravings and relapse)
- Usual Dose: 666 mg (2 pills) TID.
- Modestly improves abstinence (in some studies).
- Side effects: Diarrhea (17%).

Topiramate (Topamax)

not FDA approved for alcohol use disorders

- GABA enhancer, thought to reduce the rewarding effects of alcohol.
- In 2 RCTs, topiramate (300 mg/day) reduced alcohol use and increased abstinence over 12-14 weeks. In 1 study, low dose (75 mg/day) was also effective.
- Side effects: Parasthesias (50%), taste perversion (23%), anorexia (20%), difficulty with concentration (15%).

Pharmacotherapy:

Nicotine

- Drug antagonists
- Drug agonists
  - Nicotine replacement
  - Varenicline (partial agonist)
- Neuromodulators
  - Buproprion
  - Nortriptyline

Nicotine Replacement

- Nicotine replacement is safe and modestly effective.
- No form has been shown to be more effective.
- Higher doses or combinations may be more effective for heavy smokers.
- Smoking status in the second week is the best predictor of success.

(NNT~30)

Nicotine Replacement Products

- **Over the Counter**
  - Gum (polacrilex)
  - Patch (transdermal system)
  - Lozenge
    - Full Size
    - Mini
- **Prescription only**
  - Nasal spray
  - Oral inhaler

Nicotine Replacement: Safety

- In randomized controlled trials, there was no increase in mortality or severe adverse events.
- Trials of patients with stable cardiovascular disease likewise found no increase in risk.
- Less is known about the effect during acute cardiovascular syndromes.
- Nicotine patch combined with gum/lozenge/nasal spray more effective than using either form alone

Electronic cigarettes

Battery-powered devices that deliver nicotine vapor.

- In some studies, e cigs have been associated with modest reduction in smoking.
- Safety has not been established, but the vapor has lower levels of toxic substances.

Bullen C. Lancet 2013;382:1629-37.
Goniewicz ML. Tob Control 2013;doi:10.1136

Bupropion SR(Zyban, Wellbutrin)

- Bupropion SR (150-300 mg/day)
- Blocks dopamine and norepinephrine reuptae
- Use with nicotine replacement may be more effective.
- Longer-term use (up to a year) may reduce risk of relapse.

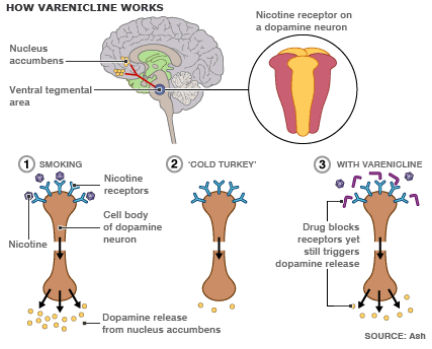
(NNT~20)

Varenicline

- An oral α4β2 nicotinic acetylcholine receptor partial agonist derived from cytisine.
- Partially activates receptor and also blocks effects of nicotine on the receptor
- Titrated up from 0.5 mg daily to 1 mg twice daily.
- Nausea, abnormal dreams and insomnia are the most common side effects. Some reports of severe psychiatric side effects and possible small increase in cardiovascular events.

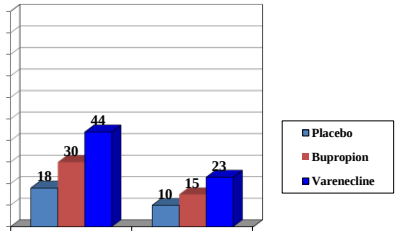
(NNT~10)

Varenicline: Mechanism of Action



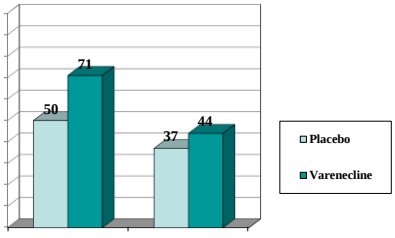
Varenicline:

12 weeks of treatment



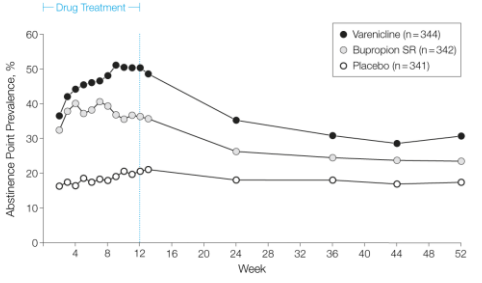
Jorenby DE. JAMA 2006;296:56-63.

Varenicline:
Extension to 24 weeks



Tonstad S. JAMA 2006;296:64-71.

Varenicline vs. Bupropion SR vs placebo



Jorenby, et. al., JAMA 2006