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 despite medical, social, interpersonal **Problems**

- **Tolerance**
- **Withdrawal**
- Use greater than **Intended**
- **Substantial** time spent to obtain or use substance
- Many efforts to **Cut down**
- Activities reduced
- Persistent use despite consequences

Mild: 2-3 symptoms  Moderate: 4-5 symptoms  Severe: ≥6 symptoms
Progression of Symptoms Over Time

- Preoccupation w/ obtaining drugs & using
- Persistent problems
- Persistent desire, cravings, inability to cut down
- Spiralling Distress

- Taken in larger amounts than intended
- Alternative activities
- Tolerance
- Withdrawal

Addiction

Koob & Le Moal, 1998
Brain Centers associated with addiction
Anatomy of the Brain

Activation of the reward pathway by addictive drugs

- PreFrontal Cortex
- VTA
- Nucleus Accumbens

- Alcohol
- Cocaine
- Heroin
- Nicotine

Acc
VTA
FCX
AMYG
VP
ABN
Raphé
LC
GLU
ENK
OPIOID
GABA
5HT
NE
HIPP
PAG
RETIC
To
dorsal
horn

Amphetamine
Cocaine
Opiates
Cannabinoids
Phencyclidine
Ketamine

Opiates
Ethanol
Barbiturates
Benzodiazepines
Nicotine
Cannabinoids

Reward Pathways
Activation of Reward Pathway

- **The nucleus accumbens (NA):** Action of amphetamines, cocaine, opiates, THC, phencyclidine, ketamine, and nicotine
- Opiates, alcohol, barbiturates and benzodiazepines 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

**FOOD**

Source: Di Chiara et al.

**SEX**

Source: Fiorino and Phillips.
Effects of Drugs on Dopamine Levels

**AMPHEMATINE**
- Time After Amphetamine
- % of Basal Release
- DA, DOPAC, HVA

**COCOAINE**
- Time After Cocaine
- % of Basal Release
- DA, DOPAC, HVA

**NICOTINE**
- Time After Nicotine
- Accumbens, Caudate

**ETHANOL**
- Time After Ethanol
- Dose (g/kg)
- 0.25, 0.5, 1, 2.5

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

Opioids Decrease D2 Receptors

Targets relevant to withdrawal/negative affect stage

- Corticotropin-releasing factor
- Norepinephrine
- Dynorphin
- Vasopressin
- Orexin (hypocretin)
- Substance P

- Neuropeptide Y
- Nociceptin (orphanin FQ)
- Endocannabinoids
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.
Behavior

Environmental exposure

Internal “drive” craving

Satiation

Environmental response

Reward reinforcement
Factors Associated with Addiction

**Host Factors**
- Genetic
- Co-morbid Psychiatric d/o
- Personality traits

**Agent Factors**
- Cost & availability
- Administration
- Reinforcing properties

**Environmental Factors**
- Family problems
- Occupation
- Peer groups
- Culture
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 less consistent in females
  - Adoption studies: Sons of alcoholics 4 times likely to be EtOHics whether raised by bio or non-EtOH adoptive parents (Schuckit 1972; Cloninger 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

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>44% (Tsuang et al., 1996)</td>
<td>81% (Kendler et al., 1999)</td>
</tr>
<tr>
<td></td>
<td>79% (Kendler et al., 2000)</td>
<td>79% (Kendler &amp; Prescott, 1998)</td>
</tr>
<tr>
<td>Heroin (opiates)</td>
<td>54% (Tsuang et al., 1996)</td>
<td>79% (Kendler et al., 1999)</td>
</tr>
<tr>
<td>Sedatives</td>
<td>87% (Kendler, et al., 2000)</td>
<td>79% (Kendler &amp; Prescott, 1998)</td>
</tr>
<tr>
<td>Marijuana</td>
<td>33% (Tsuang et al., 1996)</td>
<td>79% (Kendler &amp; Prescott, 1998)</td>
</tr>
<tr>
<td></td>
<td>58% (Kendler, et al., 2000)</td>
<td></td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>79% (Kendler, et al., 2000)</td>
<td>72% (Kendler et al., 1999)</td>
</tr>
<tr>
<td>Nicotine</td>
<td>53% (Carmelli et al., 1990)</td>
<td></td>
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</tbody>
</table>
Psychiatric Comorbidity

• Approx 50-60% of those with a substance disorder have a comorbid mental disorder including:
  – Antisocial personality disorder
  – Anxiety disorders
  – Depression

• Depression and alcoholism often co-occur
  – The depression generally improves with abstinence, though some dysphoria may remain.
  – Depression affects 13% of female alcoholics.

• Alcoholism is also more common in patients with schizophrenia and bipolar disorder.
### Psychiatric Comorbidity

**Brooner, 1997:**

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Lifetime</th>
<th>Current</th>
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</thead>
<tbody>
<tr>
<td>Any psychiatric comorbidity</td>
<td>47%</td>
<td>39%</td>
</tr>
<tr>
<td>Any Axis I disorder</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>Mood disorder</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>- major depression</td>
<td>16%</td>
<td>3%</td>
</tr>
<tr>
<td>- anxiety disorder</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Any personality disorder</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>- anti-social</td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>- avoidant</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>- borderline</td>
<td></td>
<td>5%</td>
</tr>
</tbody>
</table>
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 amounts, 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

- Non-Drug Users, Non-Drinkers, Low Risk Drinkers
- At-Risk Drug Users & Drinkers
- High Risk Drug Users & Drinkers
- Dependent Users
- Generalist (Medical care)
- Specialist

- Brief Intervention & Boosters
- Brief Treatment
- Referral
- 6-Mo. F/U
- Prevention/Education
- Continuum of Care

Screening, Prevention/Education, Brief Intervention & Boosters, Brief Treatment, Referral, 6-Mo. F/U
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
- Block euphoric effect of the drug
- Decrease and stop cravings and urges to use
- Prevention of relapse to compulsive use
- Improve functional status in all spheres of life
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)
• oxymorphine
• 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.

National Survey on Drug Use and Health (NSDUH)

![Graph: Specific I illicit Drug Dependence or Abuse in the Past Year 2013]

- Marijuana: 4,206
- Pain Relievers: 1,897
- Cocaine: 855
- Heroin: 517
- Stimulants: 469
- Tranquilizers: 423
- Hallucinogens: 277
- Inhalants: 132
- Sedatives: 99

Numbers in Thousands
Source Where Pain Relievers Were Obtained for Most Recent Nonmedical Use Among Past Year Users Aged 12 or Older: 2012-2013
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.
Function at Receptors: Full Opioid Agonists

Full agonist binding...

1. activates the mu receptor
2. is highly reinforcing
3. is the most abused opioid type
4. includes heroin, codeine, & others
Function at Receptors: Partial Opioid Agonists

- **Mu receptor**
  - Partial agonist binding ...
  - activates the receptor at lower levels
  - is relatively less reinforcing
  - is a less abused opioid type
  - includes buprenorphine
Function at Receptors: Opioid Antagonists

1. occupies without activating
2. is not reinforcing
3. blocks abused agonist opioid types
4. includes naloxone and naltrexone
Efficacy: Full Agonist (Methadone), Partial Agonist (Buprenorphine), Antagonist (Naloxone)
Signs and Symptoms of Opioid Withdrawal

- Dysphoric mood
- Nausea or vomiting
- Muscle aches/cramps
- Lacrimation
- Rhinorrhea
- Pupillary dilation
- Sweating, piloerection
- Diarrhea
- Yawning
- Fever
- Insomnia
Severity of Opioid-Withdrawal Symptoms after Abrupt Discontinuation of Equivalent Doses of Heroin, Buprenorphine, and Methadone
Precipitated Withdrawal

Full Agonist (e.g. heroin)

Partial Agonist (e.g. buprenorphine)

A Net Decrease in Receptor Activity if a Partial Agonist displaces Full Agonist
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
How to Avoid Overdose

- Only take medicine prescribed to you
- Don’t take more than instructed
- Call a doctor if your pain gets worse
- Never mix pain meds with alcohol
- Avoid sleeping pills when taking pain meds
- Dispose of unused medications
- Store your medicine in a secure place
- Learn how to use naloxone
- Teach your family + friends how to respond to an overdose

Are they breathing? → Call 911 for help

Signs of an overdose:
- Slow or shallow breathing
- Gasping for air when sleeping or weird snoring
- Pale or bluish skin
- Slow heartbeat, low blood pressure
- Won’t wake up or respond (rub knuckles on sternum)

Airway
Make sure nothing is inside the person’s mouth.

Prepare Naloxone
Are they any better? Can you get naloxone and prepare it quickly enough that they won’t go for too long without your breathing assistance?

1. Pull or pry off yellow caps
2. Pry off red cap
3. Grip clear plastic wings
4. Gently screw capsule of naloxone into barrel of tube
5. Insert white cone into nostril; give a short, vigorous push on end of capsule to spray naloxone into nose; one half of the capsule into each nostril
6. If no reaction in 3 minutes, give the second dose

Evaluate + support
- Continue rescue breathing
- Give another 2 sprays of naloxone in 3 minutes if no or minimal breathing or responsiveness
- Naloxone wears off in 30-90 minutes
- Comfort them; withdrawal can be unpleasant
- Get them medical care and help them not use more opiate right away
- Encourage survivors to seek treatment if they feel they have a problem

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
Methadone (MMT) Regulation

• Governmental regulation detailed and highly specific
  – Federal: Regulation comes from SAMHSA
  – State: Many have additional regulations (MD = COMAR)
  – Local: Some jurisdictions impose restrictions
    • NIMBY syndrome- Not in my Back Yard

• Accreditation of a treatment program is required
  – (e.g. Joint Commission, CARF, or with special permission, the state regulatory agency)
## Phases of Methadone Dosing

<table>
<thead>
<tr>
<th>PHASE</th>
<th>PURPOSE</th>
<th>RANGE IN MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Dose</td>
<td>Relieve opioid withdrawal</td>
<td>20-30 mg</td>
</tr>
<tr>
<td>Early Induction</td>
<td>Reach established tolerance level</td>
<td>+/- 5-10 mg every 3 days</td>
</tr>
<tr>
<td>Late Induction</td>
<td>Establish adequate dosing</td>
<td>+/- 5-10 mg every 5-10 days</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Maintain steady state, occupation of all opiate receptors</td>
<td>Usual range 60-120 mg/day</td>
</tr>
</tbody>
</table>
Methadone Induction Levels
Methadone Maintenance Levels
Methadone maintenance: moderate vs. high dose

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

Strain EC, et al. JAMA 1999
Effect of Counseling in MMT

Methadone vs. detox:
Treatment retention

Sees KL, JAMA 2000

MMT: methadone maintenance
M180: detox followed by psychosocial rx
Methadone vs Detox: Heroin use


MMT: methadone maintenance

M180: detox followed by psychosocial rx

Sees KL, JAMA 2000
Methadone

Full opioid agonist.

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

Cons:
• Use limited to federally 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 withdrawal 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
Drugs and practitioner must meet certain requirements
“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
“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
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
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)
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
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)
**ZUBSOLV VS SUBOXONE**

<table>
<thead>
<tr>
<th></th>
<th>ZUBSOLV</th>
<th>Suboxone tablet</th>
<th>Suboxone film</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5.7 mg/1.4 mg</strong></td>
<td></td>
<td>8 mg/2 mg</td>
<td>8 mg/2 mg</td>
</tr>
</tbody>
</table>

**ZUBSOLV**

Probuphine® is a subdermal implant of buprenorphine HCL embedded within a polymer matrix. It provides discrete, long-term delivery of a potential medical treatment for opioid addiction.

**Suboxone tablet**

Probuphine is designed to release sustained therapeutic drug levels in patients with Opioid addiction for up to six months.

**Suboxone film**

3a. When Opioids (such as oxycodone or heroin) attach to mu opioid receptors in the brain, dopamine is released, which results in pleasurable feelings or euphoria. However, in patients with Opioid addiction, once the Opioid exits the mu receptor, they begin to experience withdrawal symptoms and have drug “cravings.”

3b. Probuphine delivers buprenorphine continuously into the circulating blood. Buprenorphine, which is a partial mu opioid receptor agonist/antagonist, binds tightly to receptors in the brain, blocking other opioids from attaching to them. This could potentially reduce the potential for addictive behavior.
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.
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/oxycodeone/hydrocodeone)**
  - 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.
Buprenorphone 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.
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)
Treatment Retention: Buprenorphine vs LAAM vs Methadone

Rolley, EJ, NEJM 2000
Opioid-Positive Urines: Buprenorphine vs. LAAM vs. Methadone

B

Opioid-Positive Urine Specimens

Percentage Positive

Levomethadyl acetate
Buprenorphine
High-dose methadone
Low-dose methadone

Rolley, EJ, NEJM 2000
Retention in Treatment: Buprenorphine detox vs. maintenance

Approx. 75% of sample retained in maintenance
All participants who were medically withdrawn (control) dropped out of study by 60 days

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

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increase Effects of Opioid Substitute</strong></td>
<td>Alcohol, Antidepressants, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Anti-infectives, Ciprofloxacin, Erythromycin, Fluconazole, Ketoconazole, Benzodiazepines, Cimetidine</td>
<td>Alcohol, Antiretrovirals, Atazanavir, Indinavir, Nevirapine, Ritonavir, Saquinavir, Benzodiazepines, Fluvoxamine, Ketoconazole</td>
</tr>
<tr>
<td><strong>Decrease Effects of Opioid Substitute</strong></td>
<td>Anti-infectives, Fusidic acid, Rifampin, Antiretrovirals, Abacavir, Amprenavir, Efavirenz, Nevirapine, Ritonavir, Saquinavir, Barbiturates, Carbamazepine, Phenytoin</td>
<td>Carbamazepine, Phenobarbital, Phenytoin, Rifampin</td>
</tr>
</tbody>
</table>

Source: References 12, 16.
## Buprenorphine vs. Methadone

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better safety</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>More psychosocial support</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Higher patient satisfaction</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Lower drug costs</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Lower administrative costs</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Less risk of diversion</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Ease of accessibility</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>More effective</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Opioid agonists:  
Substituting one drug for another?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete abstinence?</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Reduce use of heroin?</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Reduce harm/mortality?</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Reduce criminal activity?</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Cost effective?</td>
<td>√</td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction?</td>
<td>√</td>
<td></td>
</tr>
</tbody>
</table>
Naltrexone

- Opioid antagonist. Not controlled substance, no federal regulations for prescribing
- 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 than oral naltrexone
- 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

Naltrexone Efficacy

Retention in treatment by study week and treatment group

Percentage of urine samples negative for various drugs of interest
Pharmacotherapy:
Alcohol

- **Drug antagonists**
- **Drug agonists**
  - Benzodiazepines
- **Neuromodulators**
  - Endorphin (naltrexone)
  - GABA (acamprosate, topiramate)
- **Aversive Agent**
  - Disulfiram
Pathophysiology of Alcohol Withdrawal

- Acute
- Chronic
- Sedation
- Tolerance

Central Nervous System Activity vs. Time

Drug-free

Last dose
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)

Inhibitory Substances  Excitatory Substances  Clinical Symptoms

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 Withdrawal—Early signs and symptoms (6-24 hrs after last drink)

- Anxiety
- Sleep disturbance
- Perceptual distortions (lights too bright, sounds too loud)
- Vivid Dreams
- Anorexia
- Nausea
- Headache
- Tachycardia
- Hypertension
- Diaphoresis
- Hyperthermia
- Hyperactive reflexes
- Tremor (6-8 cycles/sec)
Alcohol Withdrawal—Hallucinations and Seizures (12-24 hrs after last drink)

- Visual Hallucinations most common
  - Usually animal (dog or rodent in room)
- Auditory Hallucinations
  - Unformed sounds (clicks or buzzing)
  - Formed voices
    - Friends or relatives accusatory in nature
- Seizures
  - Generalized major motor seizures
  - Hx of past withdrawal seizures increases risk of seizures during future withdrawal episodes
AWS—Delirium Tremens (occurs 72-96 hours after last drink)

- Profound sympathetic hyperactivity (tachycardia, diaphoresis, hypertension)
- Global confusion and disorientation to place and time
- Frequent hallucinations with no insight
- Marked psychomotor activity and agitation
- Prognosis
  - Untreated mortality rate 15-20%
  - Treated mortality rate <1%
  - Causes of death: pneumonia, cardiovascular complications, trauma
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 $\rightarrow$ ADH $\rightarrow$ Acetaldehyde $\rightarrow$ ALDH $\rightarrow$ 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 (alcohol increases activity of endogenous opioids and opioid receptors leading to rewarding effect)
• 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.

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.18

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 Wilcoxon test: $^*P < 0.05$; $^†P < 0.01$.67

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%).

Reference:
Other non-FDA approved medications for alcohol dependence

- Odansetron
  - Selective 5-HT$_3$ receptor antagonist
  - Dosed at 4-16 mcg/kg
  - May be more effective in reducing drinking in early onset (<25 years of age) alcoholics than late-onset

- Baclofen
  - Selective GABA-B agonist
  - Dosed at 30-60 mg/day
  - RCT show mixed results in reducing drinking and abstinence

- Gabapentin
  - GABA agonist
  - Dosed 600-1800 mg/day (divided into 2x-3x/day)
  - Only 2 RCT: showed reduction in drinking days, heavy drinking and higher rate of abstinence
Pharmacotherapy:
Nicotine

• Drug antagonists

• Drug agonists
  – Nicotine replacement
  – Varenicline (partial agonist)

• Neuromodulators
  - Bupropion
  - 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.

Goniewicz ML. Tob Control 2013;doi:10.1136
Bupropion SR (Zyban, Wellbutrin)

- Bupropion SR (150-300 mg/day)
- Blocks dopamine and norepinephrine reuptake
- 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 cystine.
- 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 vs. Bupropion SR vs placebo

Jorenby, et. al., JAMA 2006
Varenicline:
12 weeks of treatment

Jorenby DE. JAMA 2006;296:56-63.
Varenicline: Extension to 24 weeks

Tonstad S. JAMA 2006;296:64-71.
Benefits of Integrating Pharmacotherapy and Psychosocial Treatments

• Treats broader range of symptoms
  – Medications can treat reward effects of use, cravings, withdrawal symptoms so that patient can focus on working on skills and behaviors to prevent relapse

• Offers broader range of patient-treatment matching
  – Medications can offer adjunctive treatment for those who have failed psychosocial treatment alone in the past

• Each form of treatment may offset the drawbacks of the other
  – Medications can be used to reinforce patient adherence to counseling and therapy
Integrating Pharmacotherapy into Addiction Treatment

• Broadway Center for Addictions at Johns Hopkins
  – Counselor
    • Initial screening and psychosocial intake
    • Develops treatment plan with patient
      – Individual counseling, groups, pharmacotherapy
    • Referral to medical/psychiatric care
    • Monitors adherence
  – Nursing
    • Monitors patient for intoxication, withdrawal symptoms
    • Dispenses methadone
    • Observe pt taking prescribed medication at dosing window
  – Physician/Nurse Practitioner
    • History and Physical
    • Prescribes and writes orders for medication
    • Monitors labs
  – Daily multidisciplinary treatment team meeting
Alcohol/Drug Use and Treatment Pathways

- Abstinence
  - Relapse
  - Cessation

- Substance use → Addictive Disorder

- Withdrawal Management
  - Setting
  - Medication
  - Speed

- Psychosocial Treatment
  - Residential (drug-free)
  - Outpatient (drug-free)
  - Psychological counselling
    - Support group

- Pharmacotherapy: Antabuse, Naltrexone, Acamprosate, Buprenorphine, Methadone

- Prevention/Harm Reduction
  - Education about overdose, naloxone
  - HIV/HCV risk reduction info