What is MAT and Why Is Everyone Talking About It?

Thomas E. Freese\textsuperscript{1,2} 
Tom Litwicki\textsuperscript{1,2}

\textsuperscript{1} Pacific Southwest Addiction Technology Transfer Center 
\textsuperscript{2} UCLA Integrated Substance Abuse Programs 
\textsuperscript{3} Center for Applied Behavioral Health Policy 

www.psattc.org 
www.uclaisap.org

Goals of the Training

• As a result of participating in this training, participants will be able to:
  – Understand the scope of the problem with alcohol and prescription and other opiate abuse
  – Describe the way that alcohol and opioids impact brain functioning
  – List 3 medical treatments for alcohol addiction
  – List 3 medical treatments for opioid addiction

Gallery Walk: Attitudes and Beliefs

• The goal for clients in treatment is…

• Using medications in addiction treatment is good because…

• Using medications in addiction treatment is not so good because…

• I do addiction treatment because…
Alcohol

**Drinking Guidelines**

- **Per week**
  - Men: > 14 drinks
  - Women: > 7 drinks
  - Elders (65+): > 7 drinks

- **Per occasion**
  - > 4 drinks
  - > 3 drinks
  - > 1 drink

**So, What’s a Drink?**

**Alcohol Use among Secondary Students: National Findings, 2008**

- Any Alcohol Use: 28.8%
- Drunk: 10.2%
- Use of Flavored Alcoholic Beverages: 27.6%

**SOURCE:** NIDA, Monitoring the Future Survey, 2008 National Findings.
Binge Drinking: “Not Just for Kids”

- More than one in five men ages 50-64 report binge drinking within the past month.
- Nearly one in ten older women reported recent binge drinking.
- Among those over age 65, 14% of men and 3% of women reported binge drinking.
- Also, 19% of older men and 13% of older women consumed enough alcohol on a daily basis to be classified as heavy drinkers by the American Geriatric Society.

SOURCE: Join Together Online, August 18, 2009; SAMHSA, NSDUH, 2005-06.

Any Past Month Alcohol Use, by Age Group, National Findings

Past Month Binge Drinking, by Age Group, National Findings

SOURCE: SAMHSA, NSDUH, 2007 Results.
Past Month Heavy Alcohol Use, by Age Group, National Findings

SOURCE: SAMHSA, NSDUH, 2007 Results.

Treatment Admissions for Alcohol Abuse: National Findings

- Alcohol as a primary substance accounted for 40% of all admissions in 2007 (down from 50% in 1997).
- 45% of primary alcohol admissions reported secondary drug abuse, as well.
- About three-quarters of admissions for abuse of alcohol alone and for abuse of alcohol with secondary drug abuse were male.
- For alcohol-only admissions, the average age at admission was 39 years, compared with 35 years among admissions for primary alcohol with secondary drug abuse.

Trends in Treatment Admissions for Primary Alcohol Abuse: 1997-2007

- Alcohol as a primary substance accounted for 40.5% of all admissions in 2007 (down from 50% in 1997).
- 45% of primary alcohol admissions reported secondary drug abuse, as well.
- About three-quarters of admissions for abuse of alcohol alone and for abuse of alcohol with secondary drug abuse were male.
- For alcohol-only admissions, the average age at admission was 39 years, compared with 35 years among admissions for primary alcohol with secondary drug abuse.
Alcohol Use in California by Race/Ethnicity

- Primary alcohol abuse was reported by:
  - 23.1% of American Indians/Alaska Natives
  - 19.1% of Whites
  - 16.8% of Hispanics/Latinos
  - 16.6% of African Americans
  - 14.4% of Asian/Pacific Islanders


Basic Brain Functioning

Generally speaking, when a neurotransmitter is released from the pre-synaptic neuron and reaches the post-synaptic neuron, it binds to its receptors and activates the neuron.

Binding works on a “lock and key” mechanism, meaning not all neurotransmitters can bind to all receptors, much like not all keys fit into all locks.

Only the circle neurotransmitters will bind to the receptors, whereas, the square neurotransmitters will not.
**Neurotransmitters**
For our purposes, there are four main neurotransmitters relevant to alcohol:

- **dopamine** – regulates motivation and pleasure; most addictive psychoactive chemicals increase dopamine, as do eating, gambling and sex.
- **endogenous opioids** – produces euphoria and is a naturally occurring pain reducer.
- **glutamate** – major excitatory neurotransmitter that usually causes the neuron to do something; can produce anxiety, insomnia, hyperactivity, etc.
- **GABA** – short for gamma-amino butyric acid, major inhibitory neurotransmitter that usually causes the neuron to not do something; can produce relaxation, sedation, slurred speech, etc.

**Neurotransmitters (cont.)**
neurotransmitter effects when alcohol is consumed.

- Dopamine makes you happy.
- Endogenous opioids make you euphoric and feel no pain.
- Glutamate speeds you up.
- GABA – the main inhibitory neurotransmitter… it slows you down.

**Alcohol Neuronal Activity**
1. Alcohol is ingested.
2. The brain’s natural endogenous opioids are first released from the arcuate nucleus, which activates the areas of the brain known as the ventral tegmental area and the nucleus accumbens.
Alcohol Neuronal Activity

3. In response to this increased endogenous opioid activity, dopamine is released.
4. Since dopamine is a main reward neurotransmitter, increases in the nucleus accumbens makes the drinker feel good.
5. The brain remembers those good feelings caused by the dopamine and alcohol.
6. The brain desires to repeat the behavior again to get the same good feelings.

Another Neuronal Activity
(at the same time…)

1. Alcohol is ingested.
2. GABA, a major inhibitory neurotransmitter, is increased and creates an imbalance in the brain.
3. The brain is constantly trying to maintain a balance of inhibitory and excitatory signals so homeostasis can be achieved, and this increase in GABA caused by alcohol creates an imbalance.
4. The excitatory signals of glutamate are overridden by the increase in GABA, and the body generally slows down.

Another Neuronal Activity

5. Since the glutamate excitatory signals are overridden by the GABA inhibitory signals, glutamate is not able to activate the NMDA (glutamate) receptors as it usually does.
6. So, the brain increases the amount of NMDA receptors available for glutamate, in hopes that more opportunities for activation will yield more activity. This process is called upregulation.
7. As the brain desired, this method of upregulation works and the imbalance is corrected.

8. However, more alcohol is required to feel the same level of intoxication (tolerance).

So now the brain has fully adapted to constant presence of alcohol. What do you think will happen once alcohol is taken away?

**Another Neuronal Activity**

- Normal
  - Excitation = Inhibition
  - Alcohol: Inactivation

- Acute Alcohol Intoxication
  - Alcohol: Excitation

- Tolerance
  - Alcohol: Inactivation

Alcohol Dependence

- To recap...
  - Alcohol use
  - Decrease in dopamine and increase in GABA
  - Upregulation of GABA receptors and NMDA receptors
  - Increase in negative feedback and decrease in positive feedback
  - Excitatory neurotransmission
  - Increased activity in endogenous opioids and dopamine

Alcohol Dependence Chart:

- Alcohol: Decrease in dopamine and increase in GABA
- Decrease in dopamine and increase in GABA
- Increase in endogenous opioids and dopamine
- Excitatory neurotransmission
- Increased activity in endogenous opioids and dopamine
An Open Conversation about Medication-Assisted Treatment

• Using medication in addiction treatment is a good idea because...
• Using medication in addiction treatment is a not-so-good idea because...
• I do addiction treatment because...

Medication-Assisted Treatment Myths

Myth #1: Medications are not a part of treatment.
- The pharmacotherapies that are FDA-approved for treatment of addiction should be used in conjunction with psycho-social-educational-spiritual therapy. Therefore, medications can be used as a part of treatment, but only one part.
- Medications are used in the treatment of many diseases, including addiction.
- Making the final decision about whether or not medications are a part of a client's treatment is out of the counselor's scope of practice.

Myth #2: Medications are drugs, and you cannot be clean if you are taking anything.
The field needs to change terminology to reflect current trends. “Drugs” are illicit psychoactive substances that are used to achieve a “high.” “Medications” are available by prescription and are used to treat an illness, disorder or disease.
- Millions of Americans use medications (e.g., Zyban, nicotine patches) to quit smoking, and this practice is widely encouraged by addiction professionals.
- Physical dependence and addiction are not the same thing.
- The goal of addiction treatment is to assist a client in stopping his or her compulsive use of drugs or alcohol and love a normal, functional life.
**Medication-Assisted Treatment Myths**

**Myth #2**  Medications are drugs, and you cannot be clean if you are taking anything.

If appropriately administered, medication-assisted treatment for addiction will not produce euphoric effects.

Pharmacotherapies are effective. Clinical data suggest that clients perform better in treatment when psycho-social-educational-spiritual therapy is combined with appropriate pharmacotherapies.

**Medication-Assisted Treatment Myths**

**Myth #3**  Alcoholics Anonymous (AA) and Narcotics Anonymous (NA) does not support the use of medications.

Neither Alcoholics Anonymous (AA)/Narcotics Anonymous (NA) literature nor its founding members spoke or wrote against using medications.

Even today, AA/NA does not endorse encouraging AA/NA participants to not use prescribed medications or to discontinue taking prescribed medications for the treatment of addiction.

- The Big Book states, “God has abundantly supplied this world with fine doctors, psychologists, and practitioners of various kinds. Do not hesitated to take your health problems to such persons. Most of them give freely of themselves, that their fellows may enjoy sound minds and bodies. Try to remember that though God has wrought miracles among us, we should never belittle a good doctor or psychiatrist. Their services are often indispensable in treating a newcomer and in following his case afterward.” *(Chapter 9, Emphasis added)*
Treatment Planning

- Addiction professionals must evaluate the appropriateness of including pharmacotherapies into a patient’s individualized treatment plan.

- There are many factors that contribute to a patient’s individualized treatment plan, and sometimes medications are not appropriate for all patients or situations.

Treatment Planning (cont).

- **Information gained during the assessment** – physical history, treatment history, ability to manage medications.

- **Role of the prescriber** – Does the patient have an existing relationship with a prescriber? Can the patient be appropriately monitored during treatment? Are their other medications that will interact?

- **Fits with the patient** – effectiveness and treatment goals.

- **Current level and type of substance abuse** – interactions with other substances.

- **Treatment compliance** – previous experience with other pharmacotherapies and psychosocial therapy.

- **Ability to pay** – insurance coverage, out-of-pocket, Medicare/Medicaid, etc.

Stages of Change Model

The Stages of Change Model identifies five independent stages of behavior and thinking that patients experience when making changes.

By identifying which stage of change a patient is currently in, addiction professionals can better determine treatment options are most appropriate.
### Stages of Change Model (cont.)

<table>
<thead>
<tr>
<th>Stages</th>
<th>Patient's Feeling/Doing</th>
<th>What Can the Counselor Do?</th>
<th>Are Medications Appropriate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precontemplation</td>
<td>not ready to change - the patient has little or no thought or interest in changing behavior</td>
<td>raise ambivalence – increase the patient's perception of risks and problems with current behavior</td>
<td>if the patient does not believe that they have a problem with alcohol then they probably will not be open to taking medication; however, knowing there are medications that could help may create an interest in treatment and offer hope</td>
</tr>
<tr>
<td>Contemplation</td>
<td>thinking about change - the risks and benefits of change are assessed by the patient</td>
<td>tip the decisional balance – evoke reasons for change and risks of not changing; strengthen the patient's self-efficacy for behavior change</td>
<td>could promote the consideration of possible severity and support the notion that change is possible; patients can view medications as another tool to help them achieve their goals</td>
</tr>
<tr>
<td>Determination</td>
<td>getting ready to make change - the patient gets ready to change and tests the waters by creating a plan of action</td>
<td>help the patient to determine the best course of action to take in seeking change; develop a plan</td>
<td>can be a part of a patient's treatment plan; schedule and regimen may promote the patient's commitment to the plan and set a timeframe for initiating the plan</td>
</tr>
<tr>
<td>Action</td>
<td>making the change – the patient makes steps to change</td>
<td>help the patient implement the plan; use skills; problem-solve; support self-efficacy</td>
<td>positive effects from medication can reinforce initial success of treatment; can reduce cravings and post-acute withdrawal symptoms</td>
</tr>
<tr>
<td>Maintenance</td>
<td>sustaining the change – the patient continues the action plan until change has been integrated into the patient's lifestyle</td>
<td>help the patient identify and use strategies to prevent relapse; resolve associated problems</td>
<td>can prevent relapse; can support stabilization and resolution of other problems during psychosocial therapy sessions; can reduce cravings and post-acute withdrawal symptoms</td>
</tr>
<tr>
<td>Relapse</td>
<td>slipping back into previous behavior – the patient goes back to the behavior and must reenter the cycle of change</td>
<td>help the patient recycle through the stages of contemplation, preparation, and action; without becoming stuck or demoralized because of relapse and identify the triggers leading to relapse</td>
<td>can support the patient's commitment to change; can reduce cravings and post-acute withdrawal symptoms</td>
</tr>
</tbody>
</table>

### Behavioral Interventions

Without question, medication interventions have been extremely effective and beneficial to the patient in early, as well as long-term, recovery.

However, it is imperative that pharmacotherapies are paired with some form of evidence-based behavioral therapeutic intervention.
Behavioral Interventions (cont.)

Psychosocial therapy interventions that have been thoroughly researched and have shown good efficacy include:

- Cognitive Behavioral Therapy (CBT)
- Motivational Enhancement Therapy (MET)
- Person-Centered Therapy (PCT)

The Addiction Technology Transfer Centers (ATTC) have developed helpful resources for evidence-based practices: www.nattc.org/resPubs/bpat/index.html.

Fitting Pharmacotherapies into Treatment

Etiology of Alcohol Dependence

Alcohol dependence is involuntary and is affected by many factors:

- Environment
- Physiology
- Genetics
- Social Influences
- Personality
- Conditioning
- Abuse
- Initial Use
- Self Regulated Use
- Dependence
- Coping/Expectancies
- Spiritual Values
- Reinforcement

All of these factors can have arrows to initial experience and then to any or all of the three patterns of use. Most could have arrows that demonstrate linear or reciprocal causality as well.
Four Legs of Addiction
Think of this concept as a chair, with each leg representing a component of a patient's treatment plan.

Psychological Biological
Spiritual Social

All four legs are required to “support” the patient, and if one leg is missing, the chair will be unstable and unable to accomplish its goal.

Holistic Treatment
The treatment plan must also address the multiple needs of the individual:
- sexual orientation
- gender differences
- homelessness
- family dynamics
- children/prenatal care
- legal issues
- disabilities
- employment issues
- developmental needs
- co-occurring disorders
- cultural, racial, religious norms

Pharmacotherapies for Alcohol Addiction
History of Pharmacotherapies for Alcohol Dependence

- **1784** – Diseases, including alcohol dependence, are viewed by most physicians as an imbalance of the body’s four humors: blood, phlegm, black bile, and yellow bile. As a solution to alcohol dependence, physicians regularly exercised bleeding the patient, inducing perspiration, vomiting and fright, ingesting mercury-laden calomel (which is poisonous) and blistering the skin.¹³

- **1835** – Robert MacNish describes alcohol dependence as “a condition passed by predisposition from parents to their children.”¹⁴

- **1849** – Swedish physician Magnus Huss first introduced the term alcoholism, which was defined as “a state of chronic alcohol intoxication that was characterized by severe physical pathology and disruption of social functioning.”¹⁵ Huss recommends the use of fusel oil and opium to treat alcohol dependence.

- **1879** – Chloral hydrate is used to treat alcohol dependence.

- **1880s** – Paraldehyde is used to treat alcohol dependence.

- **Late 1800s** – Withdrawals experienced as a result of alcohol dependence during the detoxification process are alleviated by the administration of whiskey, beer, sherry, chloral hydrate, strychnine, atropine, coca, marijuana, hyoscyamus, belladonna, quinine, iron, placebos, soapsuds enemas and other purgatives.

- **1889** – J.R. Black advocates substituting alcohol dependence for morphine dependence.

- **1907** – Involuntary and voluntary sterilization laws for alcohol dependents begin being passed in most states.

- **1936** – The first prefrontal lobotomy is performed on an alcohol dependent patient, where a sharp instrument is inserted into the prefrontal lobes of the brain to destroy the nerve fibers that lead to the thalamus.

- **1938** – Electroconvulsive therapy, otherwise known as ECT or shock therapy, is invented to induce seizures without the use of medication.

- **1938** – The serum from self-inflicted blisters on the abdomen injected into the patient’s arm is used to treat alcohol dependence.
**History of Pharmacotherapies for Alcohol Dependence**

- **1939** – Amphetamines are used to treat alcohol dependence, alleviate a hangover and decrease the overt signs of intoxication.
- **1947** – Dr. Roger Williams describes that alcohol dependence is caused by "a genetically transmitted biochemical defect," manifested by "an increased need for vitamins and other nutritional elements not available in other diets."  
- **1949** – Lithium is used to treat alcohol dependence.
- **1950s** – The inhalation of carbon dioxide to induce coma is used to treat alcohol dependence.
- **1951** – Disulfiram is approved by the FDA as a treatment for alcohol dependence.
- **1953** – LSD is used to treat alcohol dependence.

- **1953** – LSD is used to treat alcohol dependence.
- **1960s** – Benzodiazepines are used during detoxification of alcohol dependents.
- **1954** – Naltrexone is approved by the FDA as a treatment for alcohol dependence.
- **2004** – Acamprosate is approved by the FDA as a treatment for alcohol dependence.
- **2006** – Naltrexone for extended-release injectable suspension is approved by the FDA as a treatment for alcohol dependence.
- **2007 and beyond** – ???

**Disulfiram**
Disulfiram General Facts

- Generic Name: disulfiram
- Marketed As: Antabuse®
- Purpose: Discourages drinking by making the patient physically sick when alcohol is consumed
- Indication: An aid in the management of selected chronic alcohol patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage.
- Year of FDA-Approval: 1951

Disulfiram Administration

- Amount: one 250mg tablet
- Method: mouth
- Frequency: once a day

Can be crushed, diluted or mixed with food.

- Abstinence Requirements: must be taken at least 12 hours after last consumption of alcohol
- The starting dose is a maximum of 500mg once a day for one to two weeks.

Disulfiram Administration (cont.)

- Missed Dose Instructions: Take missed dose if not almost time for the next dose; otherwise, skip missed dose and resume regular schedule.
- Risk of Overdose: Overdose is possible with disulfiram, and the local Poison Control Center should be contacted if a patient is exhibiting signs of overdose.
- Recommended Length of Treatment: The FDA has not limited the amount of time a patient can be prescribed disulfiram. Patients can be administered disulfiram for months or even years with effective results.
- Psychosocial Counseling Requirements: Should be used in conjunction with a comprehensive psychosocial treatment program.
Appropriate Populations for Disulfiram

- **Age Range:** 18 to 65 years old
- **Adolescents:** Has not been tested or FDA-approved for use with this population.
- **Elderly:** Has not been tested or FDA-approved for use with this population, however, if disulfiram is prescribed to an elderly patient, it is recommended that a low dose be administered due to the higher frequency of hepatic, renal, and cardiac problems in this population.
- **Pregnancy:** Has not been adequately tested on pregnant or nursing women; Pregnancy Category C designation, meaning that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Polysubstance Abusers:** Has not been adequately tested with this population.

Additional Disulfiram Information

- **Addictive Properties:** Has not been found to be addictive, have a high abuse liability, or produce withdrawal symptoms when the medication is ceased. There were no reports of misuse, such as injection, smoking or prescription deviation during the clinical trials.61
- **Cost:** $57.59 per month, which is around $1.92 a day.62
- **Third-Party Payer Acceptance:** Covered by most major insurance carriers, Medicare, Medicaid, and the VA.61

How Does Disulfiram Work?

Disulfiram works by blocking the oxidation of alcohol during the acetaldehyde stage. When alcohol is ingested:

1. alcohol is broken down in the liver by the enzyme alcohol dehydrogenase to acetaldehyde;
2. then, acetaldehyde is converted by the enzyme acetaldehyde dehydrogenase to acetic acid.

Disulfiram works by blocking the enzyme acetaldehyde dehydrogenase. This causes acetaldehyde to accumulate in the blood at 5 to 10 times higher than what would normally occur with alcohol alone.
How Does Disulfiram Work?

Since acetaldehyde is poisonous, a buildup of it produces a highly unpleasant series of symptoms, which is commonly referred to as the "disulfiram-alcohol reaction."

- throbbing in head/neck
- brief loss of consciousness
- throbbing headache
- lowered blood pressure
- difficulty breathing
- marred unsexiness
- copious vomiting
- nausea
- flushing
- sweating
- thirst
- weakness
- chest pain
- dizziness
- palpitation
- hyperventilation
- rapid heartbeat
- blurred vision
- confusion
- respiratory depression
- cardiovascular collapse
- myocardial infarction
- congestive heart failure
- unconsciousness
- convulsions
- death

How Does Disulfiram Work?

- The disulfiram-alcohol reaction usually lasts for 30 to 60 minutes, but can continue for several hours.
- In general, the reaction is proportional to the amount of alcohol consumed.
- As long as there is alcohol in the blood, the disulfiram-alcohol reaction will continue.
- Symptoms are usually fully developed when the patient’s blood alcohol concentration is 50 mg per 100 mL, but mild reactions can occur in sensitive patients with levels as low as five to ten mg per 100 mL.
- Further, the disulfiram-alcohol reaction can be triggered when alcohol is consumed one or even two weeks after the last dose of disulfiram was taken.

Side Effects of Disulfiram

- Common side-effects:
  - skin rash
  - acneform eruption
  - headache
  - mild drowsiness
  - mild fatigue
  - impotence
  - metallic or garlic-like aftertaste

- Consult a physician:
  - extreme fatigue
  - weakness
  - loss of appetite
  - nausea
  - vomiting
  - general sense of uneasiness
  - yellowness of the skin or eyes (liver disease)
  - dark urine (liver disease)

Serious side effects = eye pain, peripheral neuritis, polyneuritis, peripheral neuropathy, hepatitis, hepatic failure
Disulfiram Contraindications

- Should never be administered to a patient when he or she has consumed alcohol recently or is currently intoxicated from alcohol.
- Should never be administered to a patient that has consumed alcohol-containing preparations such as cough syrup, tonics, etc.
- Should not be administered to patients who have severe heart disease.
- Should not be administered to patients who have previously exhibited hypersensitivity to disulfiram or to other thiuram derivatives used in pesticides and rubber vulcanization.
- Should not be administered to patients who experience psychosis.
- Although not contraindicated, should be used with extreme caution in patients with diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, chronic and acute nephritis or hepatic cirrhosis or impairment.

Drug Interactions for Disulfiram

- Disulfiram appears to decrease the rate at which certain medications are metabolized and therefore, may increase the blood levels and the possibility of toxicity of medications given simultaneously.
- The following medications have been identified to interact with disulfiram:
  - phenytoin
  - oral anticoagulants
  - isoniazid
  - nitrite
- Of course, disulfiram negatively interacts with alcohol and any substances containing alcohol.
- Disulfiram is safe to use with naltrexone, acamprosate, and barbiturates, with no adjustment to dose necessary.

Precautions for Disulfiram

- The patient should be fully informed of the disulfiram-alcohol reaction and strongly cautioned against drinking alcohol.
- It is recommended that patients taking disulfiram carry an identification card outlining the disulfiram-alcohol reaction, what emergency professionals should know about this medication in the event of an emergency and the patient’s physician contact information. Cards can be obtained from Odyssey Pharmaceuticals upon request.
- Disulfiram should never be administered to a patient without his or her knowledge.
- Patients taking disulfiram should not be exposed to ethylene dibromide or its vapors, paint fumes, paint thinner, varnish or shellac.
- Patients taking disulfiram should exercise extreme caution when applying aftershave, mouthwash, lotions, colognes and rubbing alcohol.
Because disulfiram was FDA-approved in 1951, all originally submitted clinical data is outdated and potentially obsolete. To present reasonably comparable clinical data from populations reflective of modern day patients, data from two recent alternative clinical trials are presented instead.

- Fuller et al. (1 year)
- Chick et al. (6 months)

Testing the effectiveness of disulfiram is considerably more difficult than testing other pharmacotherapies because disulfiram does not produce a psychoactive effect simply from taking it.

Scientific Research about Disulfiram (cont.)

- Both studies we are about to discuss were:
  - partially-blind
  - randomized
  - placebo-controlled

- All participants in the studies were required to:
  - be alcohol dependent
  - participate in psychosocial therapy

Scientific Research about Disulfiram (cont.)

- Results: Participants treated with disulfiram did not maintain complete abstinence more frequently than those treated with placebo.

<table>
<thead>
<tr>
<th>250mg of disulfiram</th>
<th>1mg of disulfiram</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients Who Consumed No Alcohol During the Entire Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.0%</td>
<td>22.5%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

** not statistically significant
Scientific Research about Disulfiram (cont.)

- **Results:** In both studies, participants treated with disulfiram had a greater reduction in the number of drinking days during the entire study than those treated with placebo.

<table>
<thead>
<tr>
<th>Study</th>
<th>Average Total Drinking Days During the Entire Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuller et al.</td>
<td>39.8</td>
</tr>
<tr>
<td>Chick et al.</td>
<td>50.7</td>
</tr>
</tbody>
</table>

* statistically significant

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Chick et al.</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>67.8%</td>
</tr>
<tr>
<td>End of study</td>
<td>13.3%</td>
</tr>
</tbody>
</table>

Reduction in Drinking Days - Chick et al. Study*

<table>
<thead>
<tr>
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<td></td>
</tr>
</tbody>
</table>
| Treatment Planning for Richard

- 25-year-old white male, drinking since age 14
- ten credits short of finishing college
- currently employed
- not married and no children
- has mild anxiety, but not within past 30 days
- taking Prozac and Xanax
- past history of depression
- recent DUI
- drinks alone at home most nights
- No treatment history
- independently seeking help
- influenced by peer group of drinkers
- committed to controlling use of alcohol
**Acamprosate General Facts**

Generic Name:  
- acamprosate calcium

Marketed As:  
- Campral®

Purpose:  
- Encourages sobriety by reducing post-acute withdrawal symptoms from alcohol dependence

Indication:  
- For the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.

Year of FDA-Approval: 2004

**Acamprosate Administration**

Amount: two 333mg tablets  
Method: mouth  
Frequency: three times a day

- Cannot be crushed, halved or diluted, but can be mixed with food.

Abstinence requirements: patient must be finished with medical detoxification and abstinent from alcohol at treatment initiation.
**Appropriate Populations for Acamprosate**

**Age Range:** 18 to 65 years old

**Adolescents:** Has not been tested or FDA-approved.

**Elderly:** Has not been tested or FDA-approved; acamprosate plasma concentrations are likely to be higher in this population compared to younger adults due to reduced kidney function.

**Pregnancy:** Has not been adequately tested on pregnant or nursing women; Pregnancy Category C designation, used only if the potential benefit justifies the potential risk to the fetus.

**Polysubstance Abusers:** Has not been adequately tested with this population.

**Addictive Properties:**

- Has not been found to be addictive and no reports of misuse

**Cost:**

- $135.90 per month, which is around $4.53 a day.46

**Third-Party Payer Acceptance:**

- Patient Assistance Program through Forest Laboratories, Inc.
- Covered by most major insurance carriers,
- Covered by Medicare, Medicaid, and the VA (if naltrexone is contraindicated).

**How Does Acamprosate Work?**

**Mechanism of Action:**

glutamate receptor modulator

**Remember that repetitive consumption of alcohol causes:**

- the brain to suppress glutamate activity, which causes an increase in NMDA receptors, counteracting alcohol’s depressive effects.

*NOTE: The mechanism of action of acamprosate is not completely understood.*
How Does Acamprosate Work?

- When alcohol is not present in a dependent’s body:
  1. Glutamate behaves normally.
  2. But there are more NMDA receptors due to upregulation, so there is more glutamate activity than normal.
  3. Since glutamate is the main excitatory neurotransmitter, the normal balance between inhibitory and excitatory is altered, resulting in:
     - alcohol withdrawal

How Does Acamprosate Work?

- During alcohol withdrawal, the depressant effects of alcohol are no longer present to counteract the effect of the increased glutamate activity, which is complicated by decreased GABA function.
- Symptoms such as...
  - hallucinations
  - tremors/seizures
  - insomnia
  - dysphoria
  - mood disturbances
  - anxiety

...can become a powerful motive for people to resume their drinking.

How Does Acamprosate Work?

- reduces glutamate activity by “monitoring” the amount of glutamate that can react at the NMDA receptors
- limits the amount of glutamate released by the neuron^50
How Does Acamprosate Work?

Side Effects of Acamprosate

The following side effects occurred in 3% or more of patients during the clinical trials:
- accidental injury
- anxiety
- depression
- diarrhea
- dizziness
- dry mouth
- gas
- insomnia
- itching
- loss of appetite
- nausea
- pain
- sweating
- skin sensations
- weakness

Drug Interactions for Acamprosate

Acamprosate has no known drug interactions.

No adjustment of dose is required when acamprosate is taken in conjunction with:
- alcohol
- antidepressants
- anxiolytics
- disulfiram
- hypnotics
- naltrexone (oral)
- non-opioid analgesics
- sedatives
Research about Acamprosate

There were four studies of acamprosate submitted to the FDA for approval consideration.

- Pelc et al. (13 weeks)
- Sass et al. (48 weeks)
- Paille et al. (52 weeks)
- Mason et al. (26 weeks)

Research about Acamprosate

The studies we are about to discuss were:

- double-blind
- randomized
- placebo-controlled

All participants in the studies were required to:

- be alcohol dependent
- participate in psychosocial therapy
- be abstinent from alcohol for several days prior to treatment initiation

Research about Acamprosate

Results: In all three studies, participants treated with acamprosate were able to maintain complete abstinence more frequently than those treated with placebo.
Research about Acamprosate

• **Results:** In all three studies, participants treated with acamprosate had a greater reduction in the number of drinking days during the entire study than those treated with placebo.

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>Percentage of Days Abstinent (Acamprosate)</th>
<th>Percentage of Days Abstinent (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-Week</td>
<td>85%</td>
<td>67%</td>
</tr>
<tr>
<td>48-Week</td>
<td>74%</td>
<td>29%</td>
</tr>
<tr>
<td>52-Week</td>
<td>67%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Research about Acamprosate

• **Results:** In all three studies, participants treated with acamprosate were able to regain complete abstinence after one relapse more frequently than those treated with placebo.

<table>
<thead>
<tr>
<th>Study Duration</th>
<th>Percentage of Participants Who Regained Complete Abstinence for the Reminder of the Study after First Relapse (Acamprosate)</th>
<th>Percentage of Participants Who Regained Complete Abstinence for the Reminder of the Study after First Relapse (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-Week</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>48-Week</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>52-Week</td>
<td>0%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Naltrexone
Naltrexone General Facts

**Generic Name:**
- naltrexone hydrochloride

**Marketed As:**
- ReVia® and Depade®

**Purpose:**
- To discourage drinking by decreasing the pleasurable effects experienced by consuming alcohol.

**Indication:**
- In the treatment of alcohol dependence and for the blockade of the effects of exogenous administered opioids.

**Year of FDA-Approval:** 1994

Naltrexone Administration

**Amount:** one 50mg tablet

**Method:** mouth

**Frequency:** once a day

- Can be crushed, diluted or mixed with food.

**Abstinence requirements:** must be taken at least 7-10 days after last consumption of opioids; abstinence from alcohol is not required;

Appropriate Populations

**Age Range:**
- 18 to 65 years old

**Adolescents:**
- Has not been tested or FDA-approved.

**Elderly:**
- Has not been tested or FDA-approved.

**Pregnancy:**
- Has not been adequately tested on pregnant or nursing women; Pregnancy Category C designation, used only if the potential benefit justifies the potential risk to the fetus.

**Polysubstance Abusers:**
- Has not been adequately tested with this population.
**Additional Information**

**Addictive Properties:**
- Has not been found to be addictive or produce withdrawal symptoms when the medication is ceased.
- Administering naltrexone will invoke opioid withdrawal symptoms in patients who are physically dependent on opioids.

**Cost:**
- $110.68 per month, which is around $3.69 a day.69

**Third-Party Payer Acceptance:**
- Covered by most major insurance carriers, Medicare, Medicaid, and the VA.68

---

**How Does Naltrexone Work?**

**Remember:**
1. Endogenous opioids are first released from the arcuate nucleus, which activates the areas of the brain known as the ventral tegmental area and the nucleus accumbens.
2. In response to this increased endogenous opioid activity, dopamine is released.
3. Since dopamine is a main reward neurotransmitter, increases in the nucleus accumbens makes the drinker feel good.
4. The brain remembers those good feelings caused by the dopamine and alcohol.
5. The brain desires to repeat the behavior again to get the same good feelings.

**How Does Naltrexone Work?**

- Naltrexone is an opioid receptor antagonist and blocks opioid receptors.

  By blocking opioid receptors, the “reward” and acute reinforcing effects from dopamine are diminished, and alcohol consumption is reduced.
How Does Naltrexone Work?

When naltrexone is present, endogenous opioids are released, but they are NOT able to bind to opioid receptors. Therefore,

- the ventral tegmental area and nucleus accumbens are NOT activated;
- dopamine is NOT released; and
- the drinker does NOT feel the same level of reinforcing effects and “reward” from consuming alcohol.

Side Effects of Naltrexone

The following side effects occurred in 2% or more of patients during the clinical trials:

- nausea
- anxiety
- vomiting
- fatigue
- headache
- insomnia
- nervousness
- dizziness
- drowsiness

Naltrexone Contraindications

- Should not be administered to patients with opioid physical dependence or undergoing acute opiate withdrawal.
- Should not be administered to patients receiving opioid analgesics. This can be ensured by administering the naloxone challenge test and/or a urine screen.
- Should not be administered to patients who have previously shown hypersensitivity to naltrexone or any other components of the medication.
- Should not be administered to patients with acute hepatitis or liver failure. Naltrexone is NOT contraindicated for patients who have mild to moderate hepatic (liver) impairment, but caution should be exercised when using naltrexone with this population.
Research about Naltrexone

There were two studies of naltrexone submitted to the FDA for approval consideration.

- Volpicelli et al. (12 weeks)
- O’Malley et al. (12 weeks)

Both studies were:
- double-blind
- randomized
- placebo-controlled

All participants in the studies were required to:
- be alcohol dependent
- participate in psychosocial therapy

Research for Naltrexone

Results: In some instances, participants treated with naltrexone were not able to maintain complete abstinence more frequently than those treated with placebo.

Complete Abstinence - Volpicelli Study:

<table>
<thead>
<tr>
<th>naltrexone group</th>
<th>placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>54%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Research for Naltrexone

Results: In some instances, participants treated with naltrexone were able to maintain complete abstinence more frequently than those treated with placebo.

Complete Abstinence - O’Malley et al. Study:

<table>
<thead>
<tr>
<th>Supportive therapy*</th>
<th>Coping skills therapy**</th>
</tr>
</thead>
<tbody>
<tr>
<td>naltrexone</td>
<td>61%</td>
</tr>
<tr>
<td>placebo</td>
<td>43%</td>
</tr>
</tbody>
</table>

Type of Therapy Administered:
- *supportive therapy
- **coping skills therapy
Research for Naltrexone

• **Results:** In both studies, participants treated with naltrexone had a greater reduction in relapse during the entire study than those treated with placebo.

![Reduction in Relapse - Volpicelli et al. Study](chart)

- **Reduction in Relapse - Volpicelli et al. Study**
- *statistically significant*

<table>
<thead>
<tr>
<th>naltrexone group</th>
<th>placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>23%</td>
<td>54%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage of Participants Who Relapsed During the Study</th>
<th>naltrexone group</th>
<th>placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>30%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

Research for Naltrexone

• **Results:** In both studies, participants treated with naltrexone had a greater reduction in relapse during the entire study than those treated with placebo.

![Reduction in Relapse - O'Malley et al. Study](chart)

- **Reduction in Relapse - O'Malley et al. Study**
- *statistically significant*

<table>
<thead>
<tr>
<th>Type of Therapy Administered</th>
<th>naltrexone</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive therapy*</td>
<td>43%</td>
<td>89%</td>
</tr>
<tr>
<td>Coping skills therapy*</td>
<td>89%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Scott

- 40-year-old black male with a GED
- Drinks four to five times per week
- Two failed marriages due to drinking and fighting
- Drinking on days when he does not plan on doing so
- Has mild liver impairment, high cholesterol and overweight
- Currently employed but may lose job due to missed work
- Recent DUI
- In an on-and-off relationship, which he says is positive
- Hangs with a group of drinking buddies (lots of peer pressure)
- Has previously been suicidal while drunk before
- Says drinking is out of control and causes problems in his life
- I able to maintain sobriety for a week at a time
- Open to treatment so he won’t does lose his job or girlfriend
- Open to treatment
Extended-Release Naltrexone

Extended-Release Naltrexone General Facts
- **Generic Name:** naltrexone for extended-release injectable suspension
- **Marketed As:** Vivitrol®
- **Purpose:** To discourage drinking by decreasing the pleasurable effects from consuming alcohol.
- **Indication:** For the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment.
- **Year of FDA-Approval:** 2006

Extended-Release Naltrexone Administration
- **Amount:** one 380mg injection
- **Method:** deep muscle in the buttock
- **Frequency:** every 4 weeks
- Must be administered by a healthcare professional and should alternate buttocks each month.
- Abstinence requirements: must be taken at least 7-10 days after last consumption of opioids; must not be actively drinking at time of administration.
- Should not be administered intravenously.
Extended-Release Naltrexone Administration

- **Missed Dose Instructions:**
  Take missed dose as soon as possible.

- **Risk of Overdose:**
  Doses up to 784 mg did not produce any serious side effects. The risk of overdose beyond this dosage is unknown. However, the risk of overdose is decreased due to the fact that it has to be administered only by a health care professional.

- **Recommended Length of Treatment:**
  The FDA has not limited the amount of time a patient can be prescribed extended-release naltrexone.

- **Psychosocial Counseling Requirements:**
  Should be used in conjunction with a comprehensive psychosocial treatment program.

Appropriate Populations for Extended-Release Naltrexone

- **Age Range:** 18 to 65 years old
- **Adolescents:** Has not been tested or FDA-approved for use with this population.
- **Elderly:** Has not been tested or FDA-approved for use with this population.
- **Pregnancy:** Has not been adequately tested on pregnant women; Pregnancy Category C designation, meaning that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. For nursing mothers, a decision should be made whether to discontinue nursing or discontinue the medication, taking into account the importance of the medication to the mother.
- **Polysubstance Abusers:** Has not been adequately tested with this population.

Additional Information for Extended-Release Naltrexone

- **Addictive Properties:** Has not been found to be addictive, have a high abuse liability, develop tolerance, or produce withdrawal symptoms when the medication is ceased. There were no reports of misuse, such as injection, smoking or prescription deviation during the clinical trials. However, administering naltrexone will invoke opioid withdrawal symptoms in patients who are physically dependent on opioids.
- **Cost:** $866.46 per month, which is around $28.88 per day (injectors fee not included).
- **Third-Party Payer Acceptance:** Approximately 90% of patients thus far have received insurance coverage with no restrictions. In addition, extended-release naltrexone now has a J code for payors.
How Does Extended-Release Naltrexone Work?

- Since extended-release naltrexone is a different version of oral naltrexone, it is not surprising that extended-release naltrexone works in the brain exactly like oral naltrexone.

- The only difference is that one injection of extended-release naltrexone blocks opioid receptors for one entire month compared to approximately 28 doses of oral naltrexone to receive the same longevity.

- **NOTE:** Patients should be advised that because extended-release naltrexone is an intramuscular injection and not an implanted device, it is not possible to remove it from the body once extended-release naltrexone has been injected.

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How Does Extended-Release Naltrexone Work? (cont.)

Extended-release naltrexone is an opioid receptor antagonist and blocks opioid receptors. By blocking opioid receptors, the "reward" and acute reinforcing effects from dopamine are diminished, and alcohol consumption is reduced.

---

How Does Extended-Release Naltrexone Work? (cont.)

When extended-release naltrexone is present, endogenous opioids are released, but they are NOT able to bind to opioid receptors. Therefore,

- the ventral tegmental area and nucleus accumbens are NOT activated;
- dopamine is NOT released; and
- the drinker does NOT feel the same level of reinforcing effects and "reward" from consuming alcohol.
How Does Extended-Release Naltrexone Work? (cont.)

How often do you feel your patients take their prescribed medication when it is not administered by a treatment provider?

- 100% of the time
- 99% to 75% of the time
- 74% to 50% of the time
- 49% to 50% of the time
- 24% to 0% of the time

Which FDA-approved pharmacotherapy for alcohol dependence do you think has the highest compliance rates for taking the medication as prescribed?

- acamprosate
- disulfiram
- naltrexone
- extended-release naltrexone

Side Effects of Extended-Release Naltrexone

The following side effects occurred in 5% or more of patients during the clinical trials:

- abdominal pain
- anxiety
- back pain/stiffness
- depression
- diarrhea
- dizziness
- drowsiness
- dry mouth
- headache
- injection site tenderness, pain, swelling, itching, and/or discoloration
- joint stiffness
- loss of appetite
- muscle cramps
- nausea (33%)
- pharyngitis
- rash
- sleep disorder
- upper respiratory tract infection
- vomiting

Side Effects of Extended-Release Naltrexone (cont.)

- Worsening injection site reactions that do not improve within one month should be brought to the attention of the patient’s physician.

- The patient’s physician should be contacted if he or she experiences difficulty breathing, coughing, or wheezing.

Extended-release naltrexone does not appear to cause liver damage at recommended dosages, but it does have the capacity to cause damage to liver cells when given in excessive doses. Discontinue use and seek medical attention if the following symptoms of liver impairment occur:

- extreme fatigue
- weakness
- abdominal pain
- general sense of uneasiness
- yellowness of the skin or eyes
- white bowel movements
- loss of appetite
- dark urine
- nausea
- vomiting
**Contraindications for Extended-Release Naltrexone**

- Should not be administered to patients with opioid physical dependence or undergoing acute opiate withdrawal.

- Should not be administered to patients receiving opioid analgesics. This can be ensured by administering the naloxone challenge test and/or a urine screen.

- Should not be administered to patients who have previously shown hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent.

**Extended-release naltrexone is NOT contraindicated for patients who have mild renal (kidney) impairment, which is exhibited by a creatinine clearance of 50 to 80 mL/min; therefore, no adjustment to dose is necessary. Patients with moderate to severe renal impairment have not been evaluated for use of extended-release naltrexone so caution should be exercised with this population.**

**Extended-release naltrexone is NOT contraindicated for patients who have mild to moderate hepatic (liver) impairment; therefore, no adjustment to dose is necessary. Patients with severe hepatic impairment have not been evaluated for use of extended-release naltrexone so caution should be exercised with this population.**

**Drug Interactions for Extended-Release Naltrexone**

The following medication interactions have been identified for oral naltrexone and may possibly be applied to the injectable formulation:

- Extended-release naltrexone counteracts the effects of opioid-containing medicines, such as cough and cold remedies, antidiarrheal preparations and opioid analgesics.

- Patients should be warned of the potentially serious consequences of taking opioids (heroin, oxycontin, etc.) while taking extended-release naltrexone because large amounts of opioids are required to achieve the desired intoxicating effect; this drastically increases the patient's risk of overdose, leading to serious injury, coma or death. Additionally, patients should be warned that they may be more sensitive to lower doses of opioids after treatment with extended-release naltrexone is ceased.

- The safety of patients taking extended-release naltrexone and antidepressants simultaneously during the clinical trials did not decrease when compared to patients not taking antidepressants.
Special Precautions for Extended-Release Naltrexone

- During clinical trials, there was a noted increase in adverse events of a suicidal nature in patients taking extended-release naltrexone relative to patients administered placebo. Counselors should continue to closely monitor and record all suicidal events for patients with alcohol dependence, including those taking extended-release naltrexone.

- It is recommended that patients administered extended-release naltrexone carry an identification card alerting emergency professionals of the specific treatment needs of the patient.

- In the event of an emergency where pain management is required, regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics or general anesthesia is suggested. However, if opioid analgesia is required, it should be noted that the patient may necessitate greater than usual amounts to achieve the desired effect, and the resulting respiratory depression may be deeper and more prolonged.

- It is recommended that patients administered extended-release naltrexone carry an identification card alerting emergency professionals of the specific treatment needs of the patient.

Special Precautions for Extended-Release Naltrexone (cont.)

- If a patient develops pneumonia that does not respond to antibiotics, progressive dyspnea (difficulty breathing) or hypoxemia (not enough oxygen in the blood), the diagnosis of eosinophilic pneumonia should be considered.

- Since extended-release naltrexone is an intramuscular injection, caution should be exercised with patients suffering from thrombocytopenia (decreased number of platelets in the blood) or any coagulation (clotting) disorder.

Scientific Research about Extended-Release Naltrexone

- There has only been one major clinical trial for extended-release naltrexone, and it was submitted to the FDA for approval consideration Garbutt et al. (6 months)

  The study was:
  - double-blind  
  - randomized  
  - placebo-controlled

  All participants in the studies were required to:
  - be alcohol dependent
  - participate in psychosocial therapy
• **Results**: Participants treated with extended-release naltrexone did not maintain complete abstinence more frequently than those treated with placebo.

- **Complete Abstinence**

<table>
<thead>
<tr>
<th>Percentage of Participants Who Consumed No Alcohol During the Entire Study</th>
<th>extended-release naltrexone</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

---

• **Results**: Participants treated with extended-release naltrexone had a greater reduction in the number of heavy drinking days during the entire study than those treated with placebo.

- **Reduction in Heavy Drinking Days**

<table>
<thead>
<tr>
<th>Median Heavy Drinking Days Per Month</th>
<th>baseline</th>
<th>placebo</th>
<th>extended-release naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>6.0</td>
<td>2.1</td>
<td></td>
</tr>
</tbody>
</table>

---

• **Results**: Participants treated with extended-release naltrexone who had a seven-day abstinence period prior to treatment initiation were not able to maintain statistically significant complete abstinence more frequently than those treated with placebo.

- **Complete Abstinence with 7-Day Lead-In**

<table>
<thead>
<tr>
<th>Percentage of Participants Who Consumed No Alcohol During the Entire Study</th>
<th>extended-release naltrexone</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>65%</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

---
• Results: Participants treated with extended-release naltrexone who had a seven-day abstinence period prior to treatment initiation had a greater reduction in the number of heavy drinking days during the entire study than those treated with placebo.

<table>
<thead>
<tr>
<th>Reduction in Heavy Drinking Days with 7-Day Lead-In*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Heavy Drinking Days Per Month</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Extended-release naltrexone</td>
</tr>
</tbody>
</table>

• 56-year-old white female
• Mother of three adult children
• Married, but in couple’s therapy
• Successful attorney, as is husband
• History of alcohol abuse since college
• Never experimented with any other drugs
• Has attended outpatient treatment several times
• No known psychiatric disorders
• Currently drinks five drinks four to five times a week
• Often drives intoxicated, but no DUI to date
• Does not like taking medication
• Recently diagnosed with gastritis
• Not sleeping well, losing weight
• Recent emergency room visit for a drunken fall
• Unable to control drinking
• Drinking unexpectedly
• Husband and children are concerned
• Feels psychosocial therapy is good for her
• Appears to be motivated this time to maintain sobriety

Prescription (Rx) Drug Misuse: What’s the Problem?
What is Misuse?

- Misuse = "Non-medical use" or any use that is outside of a medically prescribed regimen

- Examples can include:
  - Taking for psychoactive "high" effects
  - Taking in extreme doses
  - Mixing pills
  - Using with alcohol or other illicit substances
  - Obtaining from non-medical sources

Commonly Misused Rx Drugs

Classified in 3 classes

- Opiates: pain-killers
  - Ex) Vicodin, Oxycontin, Tylenol, Codeine

- CNS Depressants (Sedatives/Tranquilizers): treat anxiety and sleep disorders
  - Ex) Xanax, Ativan, Valium, Soma

- Stimulants: ADHD, weight loss
  - Ex) Adderall, Ritalin, Concerta, Dexedrine, Fastin

Media Attention

- Newsweek
- Ritalin: Are We Overprescribing Our Kids?
- The OxyContin Underground
SPLENDID FOR Wind, Colic, Distressing in the Bowels, Diarrhoea, Cholera and Teething Troubles.
Rx Drug Misuse in the U.S.

6.4 million aged 12+ used a Rx drug (non-medically) in the past year

- 227,000 Tranquilizers
- 1,100,000 Stimulants
- 1,800,000 Sedatives
- 4,700,000 Painkillers

Sources: NSDUH, 2006

Number of New Non-medical Users of Therapeutics

<table>
<thead>
<tr>
<th>Year</th>
<th>Pain Relievers</th>
<th>Stimulants</th>
<th>Sedatives</th>
<th>Tranquilizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1970</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1975</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1980</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>1985</td>
<td>0</td>
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<tr>
<td>1990</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1995</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Percentage of population with past month use of pharmaceuticals

- Pain Relievers: 2.0, 2.9, 1.4, 1.8, 2.1, 2.1
- Stimulants: 0.8, 0.8, 0.7, 0.7, 0.7, 0.7
- Sedatives: 0.1, 0.1, 0.1, 0.1, 0.1, 0.1
- Tranquilizers: 0.5, 0.5, 0.5, 0.5, 0.5, 0.5

Sources: National Survey on Drug Use and Health, 2002-2007
Rates of Prescription Narcotic Abuse

Nonmedical use of prescription narcotics:
- 2006: 33.5 million (13.6%) over age 12
- 1.64 million prescription narcotic users meet diagnostic criteria for opioid abuse or dependence (second only to marijuana [4.17 million])
- Hydocodone (Vicodin) is most widely prescribed drug in US.

Los Angeles

- Sales sharply increased for oxycodone (84%) and hydrocodone (47%) between 2001 and 2005.
- Codeine, hydrocodone, and morphine were distributed in the largest amounts when compared with the grams of other opiates distributed.

Fatal Drug Poisoning

- Between 1999 and 2002, the number of opioid analgesic poisonings on death certificates rose 91.2%.
- During this time period, poisoning from opioid analgesics surpassed both cocaine and heroin poisoning as the most frequent type of drug poisoning found on death certificates in the U.S.*
- In Florida 2007, 3 times more deaths from prescription drugs than from all illicit drugs combined.**

Prescription Drug Use Among Teens

Continuing Brain Development

Early in development, synapses are rapidly created and then pruned back. Children’s brains have twice as many synapses as the brains of adults.

Brain Development Ages 5-20 years

- MRI scans of healthy children and teens compressing 15 years of brain development (ages 5–20)
- Red indicates more gray matter, blue less gray matter.
- Neural connections are pruned back-to-front.
- The prefrontal cortex (“executive” functions), is last to mature.

Information taken from NIDA’s Science of Addiction

Source: Paul Thompson, Ph.D., UCLA Laboratory of Neuroimaging
The interaction between the developing nervous system and drugs of abuse leads to:

- Difficulty in decision making
- Difficulty understanding the consequences of behavior
- Increased vulnerability to memory and attention problems

This can lead to:

- Increased experimentation
- Opioid (and other substance) addiction

Young Brains Are Different from Older Brains

- Alcohol and drugs affect the brains of adolescents and young adults differently than they do adult brains
  - Adolescent rats are more sensitive to the memory and learning problems than adults*
  - Conversely, they are less susceptible to intoxication (motor impairment and sedation) from alcohol*
- These factors may lead to higher rates of dependence in these groups

*Hiller-Sturmhöfel, and Swartzwelder (NIAAA Publication 213)

Prescription Drug Abuse among U.S. High School Seniors

- More than 12% of high school seniors said they had used opioid-based prescription drugs for non-medical purposes at least once in their lifetime.
- Eight percent did so within the past year.
- Reasons for use included: to relax, relieve tension, get high, experiment, relieve pain, or have a good time with their friends.
- Those who used the drugs for reasons other than pain relief were more likely to use other addictive drugs and have signs of addictive disorders.

New Landscape of Drug Abuse among Teens

- **Marijuana**: 1.6 million
- **Prescription Medicine**: 1.5 million
- **Cough Medicine**: 2.4 million
- **Crack/Cocaine**: 2.4 million
- **Ecstasy**: 1.0 million
- **Meth**: 1.0 million
- **LSD**: 1.3 million
- **Heroin**: 1.1 million
- **Ketamine**: 1 million
- **GHB**: 1 million

---

**Generation Rx**

- Rx/OTC med abuse has penetrated teen culture
- 18% of teens have abused Vicodin
- 20% tried Ritalin or Adderall without Rx
- 9% abused OTC cough syrup to get high. High percentages of these also use other substances.
- Equal or greater abuse of OTC/Rx than cocaine, Ecstasy, LSD, ketamine, heroin, GHB, ice
- Believe that Rx Meds safer (50%), less addictive (33%)
- Ease of access: medicine cabinets
- “Drugs are fun” vs “Drugs help kids when they are having a hard time”

April 21, 2005. Partnership for a Drug Free America. 17th annual study of teen drug abuse. N= 7,300, error margin +/- 1.5%

---

**Source of Prescription Medicines Misused in the Past Year Among Youth (Ages 12-17), 2005-2006**

- **Physician**: 30%
- **From Friend/Relative**: 20%
- **Purchased**: 10%
- **Other**
Summary of 2007 CSS Results

- Prescription pain killers 2nd to marijuana in 11th grade and 3rd in 9th grade, just after inhalants.
- All non-marijuana drugs exceeded by recreational use of cold/cough medicine ("to get high"), and equal to marijuana in 9th.
- Previous levels of substance use underestimated by under-assessing "medicinal" drugs.
- Prevalence rates for unchanged questions stable.
- No meaningful declines on any measure with exception of methamphetamines in 11th.
- Some increases in indicators of heavy/risky use in 11th.


Lifetime Prevalence

<table>
<thead>
<tr>
<th>Street Drugs</th>
<th>Grade 9 (%)</th>
<th>Grade 11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Inhalants</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Methamphetamines</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>LSD/psychedelics</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

Prescription/Medicinal Drugs*

<table>
<thead>
<tr>
<th></th>
<th>Grade 9 (%)</th>
<th>Grade 11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painkillers</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sedatives/tranquilizers</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Diet pills</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Ritalin/Adderal</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>OTC Cold/Cough Medicines</td>
<td>26</td>
<td>25</td>
</tr>
</tbody>
</table>

Aggregated Lifetime Categories of Drug Use

<table>
<thead>
<tr>
<th>Category</th>
<th>Grade 9 (%)</th>
<th>Grade 11 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>47</td>
<td>66</td>
</tr>
<tr>
<td>Marijuana</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>Prescription Drugs</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>OTC Cold/Cough Medicines</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Prescription/OTC</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Any Drug Except Marijuana</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>Total Drugs</td>
<td>31</td>
<td>46</td>
</tr>
<tr>
<td>Total AOD Use</td>
<td>52</td>
<td>69</td>
</tr>
</tbody>
</table>

Prevalence of Drinking and Driving among California-based 11th Graders

![Graph showing prevalence of drinking and driving](image)


Prescription Drug Use Among Older Adults

Prevalence of Alcohol Use/Misuse among Older Adults

- Depends on definition of at-risk or problem drinking:
  - 1-15% of older adults are at-risk or problem drinkers
- Differs with sampling approach
- Alcohol use problems are the most common substance issues for older adults. Confounded by prescription, herbal, and over-the-counter medications

Source: P. Lenahan, SARC, September 2007 presentation on Drug Use and Older Adults.
**RX Drug Abuse in Older Adults**

- Older Adults account for 13% of US population but use 1/3 of all medications prescribed.
- 7.2 million (21.7%) receive at least 1 Rx annually.
- Older adults use Rx drugs 3 times more than the general population.
- On average, older persons take 4.5 medications per day.
- Nationally, 2.8 million (8.4%) of older adults abuse Rx drugs in the last year while in California, 612,000 (3.7%).


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**Extent of the Problem: Medical Exposure**

- General US population
  - Women = 20.0%
  - Men = 12.5%
- Among elders aged 65 and older, 21.7%, or 7.22M, receive at least 1 abusable Rx annually
  - Women = 24.6%
  - Men = 17.7%

SOURCE: Simoni-Wastila et al., Sub Use and Misuse, 2004; Simoni-Wastila et al., 2004.

---

**Medical Exposure to AbusablesRx Drugs by Gender and Age**

- [Bar chart showing medical exposure by gender and age group](chart).

SOURCE: Simoni-Wastila et al., 2004.
Types of Drugs Used by Past Month Illicit Drug Users: Age 50+, 2002-2003 Annual Averages

- Other: 14%
- Prescription Drugs Only: 33%
- Only Marijuana: 47%
- Only Marijuana & Prescription Drugs: 4%

1.4 Million Illicit Drug Users (1.8%)

Primary Drug of Abuse at Admission: Sonoma County, FY 2006-FY 2008

- Alcohol: 44.2%
- Cocaine/Crack: 23.7%
- Heroin: 13.1%
- Methamphetamine: 8.9%
- Marijuana: 8.9%
- OxyContin: 2.8%
- Methadone: 2.1%
- Tranquilizers: 0.8%
- Sedative/Hypnotics: 0.9%
- Other: 0.8%

Number of Admissions

Primary Drug of Abuse at Admission by Gender: Sonoma County, FY 2006-FY 2008

- Alcohol
  - Men: 63%
  - Women: 62%
- OxyContin
  - Men: 62%
  - Women: 38%
- Non-Rx Methadone
  - Men: 59%
  - Women: 37%
- Other Opiates/Synthetics
  - Men: 73%
  - Women: 78%
- Tranquilizers
  - Men: 41%
  - Women: 51%
- Sedative/Hypnotics
  - Men: 32%
  - Women: 49%

SOURCE: Sonoma County, SWITS System, queries received 8/17/09.
Primary Drug of Abuse at Admission by Age: Sonoma County, FY 2006-FY 2008

Source: Sonoma County, SWITS System, queries received 8/17/09.

Side Effects can be Lethal if…
- Combining Rx & OTC medications.
- Taking Rx and OTC meds with alcohol.
- Using Rx and OTC with other illicit drugs.
- Interactions: Rx & OTC meds with other physical medications (i.e., HIV or Hepatitis)

Efforts in California
- Establishment of statewide Rx Drug Task force charged with:
  - Monitoring trends and strategies at the state and local levels.
  - Developing prevention strategies for Rx & OTC drug abuse.
  - Developing intervention strategies for Rx & OTC drug abuse in treatment settings.
Prescription Drug Abuse: What are we talking about?

Overview

• Three classes of commonly abused Rx drugs (opioids, sedatives, stimulants)
  – What are they?
  – How do they act in the brain and body?
  – What are their effects?
  – Neurobiology
What are opioids?

- Opiate: derivative of opium poppy
  - Morphine
  - Codeine
- Opioid: any compound that binds to opiate receptors
  - Semisynthetic (including heroin)
  - Synthetic
  - Oral, transdermal and intravenous formulations
- Narcotic: legal designation

Effects of Opioids

- Sedation
- Pupil constriction
- Slurred speech
- Impaired attention/memory
- Constipation, urinary retention
- Nausea
- Confusion, delirium
- Seizures
- Slowed heart rate
- Respiratory depression

Opioid Receptors

- Receptor types
  - mu, delta, kappa
- Receptors located throughout body
  - Pain relief: central and peripheral nervous system
  - Reward and reinforcement: deep brain structures
  - Side effects: constipation, sedation, itch, mental status changes
- Receptor interactions
  - Full agonists
  - Partial agonists
  - Antagonists
Endogenous Opioids

- Produced naturally in body
- Act on opioid receptors
- Examples: endorphins, enkephalins, dynorphins, endomorphins
- Produce euphoria and pain relief; naturally increased when one feels pain or experiences pleasure

Pain: the Fifth Vital Sign

- JACHO Guidelines 2000:
  - Mandated pain assessment and treatment
  - Nurse and physician education required
- When opioids prescribed properly for pain, addiction rare in patients without underlying risk factors
  - Vulnerabilities same as for other addictions: genetic, peer and social influences, trauma and abuse history
Pain Control and Addiction

- “Pseudoaddiction”:  
  - Presence of drug-seeking behavior in context of inadequate pain control  
  - Behavior stops with adequate pain relief  
  - Description of a clinical interaction (not a true diagnosis)
- Physical dependence  
  - with continued use, withdrawal syndrome produced by rapid dose reduction; occurs via neuroadaptation  
  - Not synonymous with addiction

Opioid Withdrawal

- Dysphoric mood  
- Nausea or vomiting  
- Diarrhea  
- Tearing or runny nose  
- Dilated pupils  
- Muscle aches  
- Goosebumps  
- Sweating  
- Yawning  
- Fever  
- Insomnia
Morphine

- Routes: oral, intramuscular, intravenous, rectal
- Sustained release preparations:
  - MS Contin
  - Oramorph
  - Kadian
  - Avinza

Codeine

- Opiate (naturally occurring in poppy)
- Low potency
- Pain relief via 10% conversion to morphine
- Most commonly prescribed opioid in the world
- Probably the most widely used analgesic
  - (Excluding aspirin)

Semisynthetic Opioids

- Hydrocodone with Tylenol:
  - Norco
  - Lortab
  - Vicodin
  - Lorcet
- Hydrocodone with ibuprofen: Vicoprofen
- Hydromorphone: Dilaudid
- Oxycodone with Tylenol: Percocet
- Oxycodone with aspirin: Percodan
- OxyContin
**OxyContin**

- Used to treat pain associated with arthritis, lower back injuries, and cancer
- Most commonly in tablet form: 10mg, 20mg, 40mg, 60mg, and 80mg tablets
- Dosed every 12 hours, half-life 4.5 hours
- Abuse: may be chewed, crushed, snorted or injected
  - Eliminates time-release coating
  - Enhances euphoria, "rush"
  - Increases risk for serious medical consequences

**Synthetic Opioids**

- Methadone
- Demerol (meperidine)
- Fentanyl
- Suboxone/Subutex (buprenorphine)
- Tramadol
  - Complex mechanism of action
  - Nonscheduled, less abuse potential
Opiates and Reward

- Opiates bind to opiate receptors in the nucleus accumbens: increased dopamine release

Dextromethorphan

- Over-the-counter cough suppressant
- Structurally related to morphine
- Mechanism: NMDA antagonist
- Dissociative psychedelic properties in excess doses (like ketamine, PCP)
**Sedative-Hypnotics**

- Used to treat anxiety and sleep disorders
- Mechanism: enhances GABA
  - acts to slow normal brain function
- Barbiturates
  - Phenobarbital
  - Pentobarbital
  - Fioricet (butalbital/acetaminophen/caffeine)

**Sedative-Hypnotics Cont’d**

- Benzodiazepines
  - Librium (chlordiazepoxide HCL)
  - Valium (diazepam)
  - Restoril (temazepam)
  - Klonopin (clonazepam)
  - Ativan (lorazepam)
  - Xanax (alprazolam)
- Non-benzo hypnotics
  - Ambien (zolpidem)
  - Sonata (zaleplon)
  - Lunesta (eszopiclone)
- Soma
- Cross-tolerance with alcohol (GABA related)

**Sedative-Hypnotic Effects**

- Sedation
- Slurred speech
- Incoordination
- Unsteady gait
- Impaired attention or memory
- Stupor or coma
- Overdose risk increased with opioids or in combination with other sedatives, including alcohol
Sedating Drugs and Overdose

Other Sedative-Hypnotic Risks
- No significant adverse medical consequences of long-term use
- Amnesia
  - Difficulty with recent memory
- Tolerance, physiological dependence, addiction
  - Addiction risk factors same as for other drugs of abuse

Sedative-Hypnotic Withdrawal
- Increased pulse, blood pressure, or sweating
- Hand tremor
- Nausea or vomiting
- Transient hallucinations or illusions
- Agitation
- Anxiety
- Seizures
Protracted Withdrawal

• Abstinence syndrome
  – Anxiety
  – Muscle twitching
  – Low mood
  – Sweating
  – Headache
  – Derealization
• Rebound insomnia
  – Especially with short-acting benzodiazepines

Sedative-Hypnotic Neurobiology

Source: www.ccforum.com
**Prescription Stimulants**

- Stimulants (i.e., amphetamines) are often prescribed to treat individuals diagnosed with attention-deficit hyperactivity disorder (ADHD).
- Substantial amounts of pharmaceutical amphetamines are diverted from medical use to non-prescription use.
- Amphetamines increase wakefulness and alertness and have been used by:
  - The military, by pilots, truck drivers, and other workers to keep functioning past their normal limits

**Short-Term Effects**

- Euphoria
- Increased energy/productivity
- Increased concentration
- Decreased appetite
- Increased libido
- Decreased sleep

**Ritalin**

- When used to treat ADHD, patients may report increased attention, decreased impulsivity, and decreased hyperactivity.
- Milder stimulant that works by affecting the levels of chemicals (neurotransmitters) in the nervous system.
- May also be used in the treatment of depression in certain cases
- Long-acting form: Concerta
Adderall

- Adderall is used to treat attention deficit hyperactivity disorder (ADHD).
- Adderall is a combination of stimulants (amphetamine and dextroamphetamine).
- It increases the ability to pay attention, focus, and control behavior problems.
- This drug may also be used to treat certain sleeping disorders (narcolepsy).

Medical Risks

- Norepinephrine release causes constriction of blood vessels, elevated blood pressure and rapid heart rate
- Increased activity levels
- Dangerously high body temperatures
- Increased risk of seizures
- Potentially fatal arrhythmias, heart attack, or stroke

Psychiatric Symptoms

- Psychiatric symptoms associated with use of larger doses of amphetamines include depression, anxiety, psychosis, and suicidal ideation
- Symptoms may depend on differences in sensitivity, frequency and quantity of use, and method of administration
- Abstinence syndrome may occur (dysphoria, anhedonia, irritability, insomnia/hypersomnia, anxiety, low energy)
A Brief History of Opioid Treatment

- Neolithic era (9000 B.C.E. to 3000 B.C.E.): Opium cultivated for food, anesthesia, and ritual purposes
- 15th Century: Recreational use of opium reported, but use was limited by its rarity and expense
- 1874: Heroin was first synthesized

A Brief History of Opioid Treatment

- 1964: Methadone is approved.
- 1974: Narcotic Treatment Act limits methadone treatment to specifically licensed Opioid Treatment Programs (OTPs).
- 1984: Naltrexone is approved, but has continued to be rarely used (approved in 1994 for alcohol addiction).
- 1993: LAAM is approved (for non-pregnant patients only), but is underutilized.

A Brief History of Opioid Treatment, Continued

- 2002: Tablet formulations of buprenorphine (Subutex®) and buprenorphine/naloxone (Suboxone®) were approved by the Food and Drug Administration (FDA).
- 2004: Sale and distribution of ORLAAM® is discontinued.
Medications to Treat Addiction

- Addiction is a chronic, relapsing brain disease characterized by compulsive use despite harmful consequences
- Medications as part of comprehensive treatment plan
- Treatment approaches:
  - Medications (Bio)
  - Therapy, lifestyle changes (Psycho-Social)
- Thorough evaluation and diagnosis essential

Pharmacotherapy in Substance Use Disorders

- Treatment of withdrawal ("detox")
- Treatment of psychiatric symptoms or co-occurring disorders
- Reduction of cravings and urges
- Substitution therapy

Opioid Detoxification

- Medications used to alleviate withdrawal symptoms:
  - Opioid agonists (methadone, buprenorphine)
  - Clonidine
  - Other supportive medications
    - anti-diarrheals, anti-nausea agents, ibuprofen, muscle relaxants, anti-anxiety medications
Opioid Replacement Goals

- Reduce symptoms & signs of withdrawal
- Reduce or eliminate craving
- Block effects of illicit opioids
- Restore normal physiology
- Promote psychosocial rehabilitation and non-drug lifestyle

Naltrexone General Facts

- **Generic Name:** naltrexone hydrochloride
- **Marketed As:** ReVia® and Depade®
- **Purpose:** To discourage opioid use by reducing or eliminating the euphoric effects experienced by consuming exogenous administered opioids.
- **Indication:** In the treatment of alcohol dependence and for the blockade of the effects of exogenous administered opioids.
- **Year of FDA-Approval:** 1984

Methadone General Facts

- **Generic Name:** methadone hydrochloride
- **Marketed As:** Methadose® and Dolophine® (among others)
- **Purpose:** To discourage illicit opioid use due to cravings or the desire to alleviate opioid withdrawal symptoms.
- **Indication:** For the treatment of moderate to severe pain not responsive to non-narcotic analgesics; for detoxification treatment of opioid addiction; for maintenance treatment of opioid addiction, in conjunction with appropriate social and medical services.
- **Year of FDA-Approval:** 1964
**Methadone General Facts**  
*(Information from medication package insert)*

- **Amount:** maintenance dose of 80 to 120mg
- **Method:** mouth
- **Frequency:** once a day
- The effect of consuming food with methadone has not been evaluated and therefore, is not recommended.
- **Abstinence requirements:** must be abstinent from opioids long enough to experience mild to moderate opioid withdrawal symptoms.
- **Initial dose will vary depending upon the client’s usage pattern, but should not exceed 40mg.**

*Risk of Overdose:* Just like with any opioid, overdose is possible. In the event of an overdose, appropriate medical treatment should be sought.

---

**Pregnancy:**

Methadone is the preferred method of treatment for medication-assisted treatment for opioid dependence in pregnant women. An expert review of published data on experiences with methadone use during pregnancy concludes that it is unlikely to pose a substantial risk. But, there is insufficient data to state that there is no risk.

Methadone has not been adequately tested on pregnant women. Therefore, methadone has a Pregnancy Category C designation, meaning that it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised when using methadone with this population.

---

**Detoxification:** relatively contraindicated unless done in hospital with monitoring.

Babies born to mothers who have been taking opioids regularly prior to delivery may be physically dependent and may experience opioid withdrawal symptoms. It is known that methadone is excreted through breast milk, and a decision should be made whether to discontinue nursing or to discontinue the medication, taking into account the importance of the medication to the mother and continued illicit opioid use.
Methadone General Facts

Addictive Properties:
Chronic administration produces physical dependence. Since methadone is an opioid, it does have a high abuse liability and does produce withdrawal symptoms when the medication is ceased too abruptly or tapered down too quickly.

Third-Party Payer Acceptance:
Covered by most major insurance carriers, Medicare, Medicaid and the VA.

Understanding DATA 2000


- Expands treatment options to include both the general health care system and opioid treatment programs.
  - Expands number of available treatment slots
  - Allows opioid treatment in office settings
  - Sets physician qualifications for prescribing the medication
DATA 2000: Physician Qualifications

Physicians must:
• Be licensed to practice by his/her state
• Have the capacity to refer patients for psychosocial treatment
• Originally limited to 30 patients later expanded to allow for 100 patients after the first year of experience
• Be qualified to provide buprenorphine and receive a license waiver

DATA 2000: Physician Qualifications

A physician must meet one or more of the following qualifications:
– Board certified in Addiction Psychiatry
– Certified in Addiction Medicine by ASAM or AOA
– Served as Investigator in buprenorphine clinical trials
– Completed 8 hours of training by ASAM, AAAP, AMA, AOA, APA (or other organizations that may be designated by Health and Human Services)
– Training or experience as determined by state medical licensing board
– Other criteria established through regulation by Health and Human Services

Development of Subutex®/Suboxone®

• U.S. FDA approved Subutex® and Suboxone® sublingual tablets for opioid addiction treatment on October 8, 2002.
• Product launched in U.S. in March 2003
• Interim rule changes to federal regulation (42 CFR Part 8) on May 22, 2003 enabled Opioid Treatment Programs (specialist clinics) to offer buprenorphine.
Only physicians can prescribe the medication.

However, the entire treatment system should be engaged.

Effective treatment generally requires many facets. Treatment providers are important in helping the patients to:

- Manage physical withdrawal symptoms
- Understand the behavioral and cognitive changes resulting from drug use
- Achieve long-term changes and prevent relapse
- Establish ongoing communication between physician and community provider to ensure coordinated care
- Engage in a flexible treatment plan to help them achieve recovery

Development of Tablet Formulations of Buprenorphine

- Buprenorphine is marketed for opioid treatment under the trade names of Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone)
- Over 25 years of research
- Over 5,000 patients exposed during clinical trials
- Proven safe and effective for the treatment of opioid addiction
Buprenorphine: A Science-Based Treatment

Clinical trials have established the effectiveness of buprenorphine for the treatment of heroin addiction. Effectiveness of buprenorphine has been compared to:

- Placebo (Johnson et al. 1995; Ling et al. 1998; Kakko et al. 2003)
- Methadone (Johnson et al. 1992; Strain et al. 1994a, 1994b; Ling et al. 1996; Schottenfield et al. 1997; Fischer et al. 1999)
- Methadone and LAAM (Johnson et al. 2000)

Buprenorphine Research Outcomes

- Buprenorphine is as effective as moderate doses of methadone.
- Buprenorphine is as effective as moderate doses of LAAM.
- Buprenorphine's partial agonist effects make it mildly reinforcing, encouraging medication compliance.
- After a year of buprenorphine plus counseling, 75% of patients retained in treatment compared to 0% in a placebo-plus-counseling condition.

Buprenorphine as a Treatment for Opioid Addiction

- A synthetic opioid
- Described as a mixed opioid agonist-antagonist (or partial agonist)
- Available for use by certified physicians outside traditionally licensed opioid treatment programs
The Role of Buprenorphine in Opioid Treatment

- Partial Opioid Agonist
  - Produces a ceiling effect at higher doses
  - Has effects of typical opioid agonists—these effects are dose dependent up to a limit
  - Binds strongly to opiate receptor and is long-acting
- Safe and effective therapy for opioid maintenance and detoxification

Partial vs. Full Opioid Agonist

<table>
<thead>
<tr>
<th>Opiate Effect</th>
<th>Dose of Opiate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Agonist (e.g., methadone)</td>
<td>death</td>
</tr>
<tr>
<td>Partial Agonist (e.g. buprenorphine)</td>
<td>Antagonist (e.g. Naloxone)</td>
</tr>
</tbody>
</table>

Advantages of Buprenorphine in the Treatment of Opioid Addiction

1. Patient can participate fully in treatment activities and other activities of daily living easing their transition into the treatment environment
2. Limited potential for overdose
3. Minimal subjective effects (e.g., sedation) following a dose
4. Available for use in an office setting
5. Lower level of physical dependence
Advantages of Buprenorphine/Naloxone in the Treatment of Opioid Addiction

- Combination tablet is being marketed for U.S. use
- Discourages IV use
- Diminishes diversion
- Allows for take-home dosing

Disadvantages of Buprenorphine in the Treatment of Opioid Addiction

1. Greater medication cost
2. Lower level of physical dependence (i.e., patients can discontinue treatment)
3. Not detectable in most urine toxicology screenings

Why was Buprenorphine/Naloxone Combination Developed?

- Developed in response to increased reports of buprenorphine abuse outside of the U.S.
- The combination tablet is specifically designed to decrease buprenorphine abuse by injection, especially by out of treatment opioid users.
What is the Ratio of Buprenorphine to Naloxone in the Combination Tablet?

- Each tablet contains buprenorphine and naloxone in a 4:1 ratio
  - Each 8 mg tablet contains 2 mg of naloxone
  - Each 2 mg tablet contains 0.5 mg of naloxone
- Ratio was deemed optimal in clinical studies
  - Preserves buprenorphine’s therapeutic effects when taken as intended sublingually
  - Sufficient dysphoric effects occur if injected by some physically dependent persons to discourage abuse.

Why Combining Buprenorphine and Naloxone Sublingually Works

- Buprenorphine and naloxone have different sublingual (SL) to injection potency profiles that are optimal for use in a combination product.

<table>
<thead>
<tr>
<th>SL Bioavailability</th>
<th>Injection to Sublingual Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine 40-60%</td>
<td>Buprenorphine ≈ 2:1</td>
</tr>
<tr>
<td>Naloxone 10% or less</td>
<td>Naloxone ≈ 15:1</td>
</tr>
</tbody>
</table>

SOURCE: Amass et al., 2004.

Buprenorphine/Naloxone: What You Need to know

- Basic pharmacology, pharmacokinetics, and efficacy is the same as buprenorphine alone.
- Partial opioid agonist; ceiling effect at higher doses
- Blocks effects of other agonists
- Binds strongly to opioid receptor, long acting
The Use of Buprenorphine in the Treatment of Opioid Addiction

Induction
Maintenance
Tapering Off/Medically-Assisted Withdrawal

Induction

Induction Phase

Working to establish the appropriate dose of medication for patient to discontinue use of opiates with minimal withdrawal symptoms, side-effects, and craving
Direct Buprenorphine Induction from Short-Acting Opioids

- Ask patient to abstain from short-acting opioid (e.g., heroin) for at least 6 hrs. and be in mild withdrawal before administering buprenorphine/naloxone.
- When transferring from a short-acting opioid, be sure the patient provides a methadone-negative urine screen before 1st buprenorphine dose.


Direct Buprenorphine Induction from Long-Acting Opioids

- Controlled trials are needed to determine optimal procedures for inducting these patients.
- Data is also needed to determine whether the buprenorphine only or the buprenorphine/naloxone tablet is optimal when inducting these patients.


Direct Buprenorphine Induction from Long-Acting Opioids

- Clinical experience has suggest that induction procedures with patients receiving long-acting opioids (e.g. methadone-maintenance patients) are basically the same as those used with patients taking short-acting opioids, except:
  - The time interval between the last dose of medication and the first dose of buprenorphine must be increased.
  - At least 24 hrs should elapse before starting buprenorphine and longer time periods may be needed (up to 48 hrs).
  - Urine drug screening should indicate no other illicit opiate use at the time of induction.
Stabilization and Maintenance

Stabilization Phase

*Patient experiences no withdrawal symptoms, side-effects, or craving*

Maintenance Phase

Goals of Maintenance Phase:
1. Help the person stop and stay away from illicit drug use and problematic use of alcohol
2. Continue to monitor cravings to prevent relapse
3. Address psychosocial and family issues
**Maintenance Phase**

Psychosocial and family issues to be addressed:
- a) Psychiatric comorbidity
- b) Family and support issues
- c) Time management
- d) Employment/financial issues
- e) Pro-social activities
- f) Legal issues
- g) Secondary drug/alcohol use

**Buprenorphine Maintenance: Summary**

- Take-home dosing is safe and preferred by patients, but patient adherence will vary and this can impact treatment outcomes.
- 3x/week dosing with buprenorphine/naloxone is safe and effective as well (Amass, et al., 2001).
- **Counseling needs to be integrated into any buprenorphine treatment plan.**

**Medically-Assisted Withdrawal**

(a.k.a. Dose Tapering)
Buprenorphine Withdrawal

- Working to provide a smooth transition from a physically-dependent to non-dependent state, with medical supervision
- Medically supervised withdrawal (detoxification) is accompanied with and followed by psychosocial treatment, and sometimes medication treatment (i.e., naltrexone) to minimize risk of relapse.

Medically-Assisted Withdrawal (Detoxification)

- Outpatient and inpatient withdrawal are both possible
- How is it done?
  - Switch to longer-acting opioid (e.g., buprenorphine)
    - Taper off over a period of time (a few days to weeks depending upon the program)
    - Use other medications to treat withdrawal symptoms
  - Use clonidine and other non-narcotic medications to manage symptoms during withdrawal

The Two Buprenorphine-Naloxone Protocols

NIDA-CTN 0001:
Buprenorphine-Naloxone vs. Clonidine for Short-Term Inpatient Opiate Detoxification

NIDA-CTN 0002:
Buprenorphine-Naloxone vs. Clonidine for Short-Term Outpatient Opiate Detoxification

Initiated in 8 Regional Nodes and 12 Community Treatment Programs
NIDA CTN 001/002 Buprenorphine-Naloxone Detoxification Protocols

Two, open-label, randomized clinical trials
Compared Buprenorphine-Naloxone (BUP/NX) and Clonidine for Short-Term (2 weeks) opioid Detoxification in Residential or Outpatient Settings

Study Schema

1. Obtain Informed Consent
2. Perform Screening/Baseline Assessments
   Randomize (2:1) and Enroll
   - N=240 Buprenorphine/Naloxone 13 days detoxification
   - N=120 Clonidine 13 days detoxification
   Follow-up at 1 month
   Follow-up at 3 months
   Follow-up at 6 months

Primary Efficacy Endpoint

It is hypothesized that BUP/NX detoxification, compared to clonidine, will be associated with a better treatment response.

A treatment responder = anyone who completes the 13-day detoxification and whose last urine specimen is negative for opioids.
So, what did we find?

### Demographics 0001 (Inpatient)

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Bup/Nx</th>
<th>Clonidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td><strong>Race No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Black</td>
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</tr>
<tr>
<td>Hispanic</td>
<td>12</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><strong>Age in Years: Mean</strong></td>
<td>35.6</td>
<td>37.4</td>
<td>-</td>
</tr>
<tr>
<td>(Range 21-61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Employed (%)</strong></td>
<td></td>
<td></td>
<td>66</td>
</tr>
<tr>
<td><strong>Mean Education in Years (SD)</strong></td>
<td>-</td>
<td>-</td>
<td>12.8 (1.7)</td>
</tr>
<tr>
<td><strong>Mean Years of Heroin Use (SD)</strong></td>
<td>-</td>
<td>-</td>
<td>6.6 (8.1)</td>
</tr>
</tbody>
</table>

### Present and Opioid Negative 0001 (Inpatient)

- Day 3-4
- Day 7-8
- Day 10-11
- Day 13-14

Graph showing the distribution of patients on clonidine and Bup/Nx across different days.
### Demographics 0002 (Outpatient)

<table>
<thead>
<tr>
<th></th>
<th>Bup/Nx</th>
<th>Clonidine</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Race No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Black</td>
<td>36</td>
<td>28</td>
<td>37</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age in Years: Mean (Range 21-61)</td>
<td>38.3</td>
<td>40.0</td>
<td>-</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mean Education in Years (SD)</td>
<td>-</td>
<td>-</td>
<td>12.4 (2.1)</td>
</tr>
<tr>
<td>Mean Years of Heroin Use (SD)</td>
<td>-</td>
<td>-</td>
<td>9.4 (9.6)</td>
</tr>
</tbody>
</table>

### Present and Opioid Negative 0002 (Outpatient)

![Graph showing comparison of Clonidine and Bup/Nx over days 3-4, 7-8, 10-11, and 13-14]

### Lessons from Additional Analyses: Predictors of Treatment Success

- Medication was the best predictor of treatment outcome for opiate detoxification regardless of treatment setting.
- Inpatient treatment was a strong predictor of treatment success.
- Those with greater reduction in opioid withdrawal severity from baseline to day 3 were more likely to have positive treatment outcome.
- Those who did the best with clonidine had low severity withdrawal symptoms at baseline.

Lessons from a Study of Longer and Shorter Taper Schedules

- Differences in being drug free at end of taper did not differ for 7 or 28 day groups (after 4 week stabilization)
- A relatively quick taper may be advantageous and did not result in relapse to drug use at greater rates than longer tapers
- Patients stabilized physiologically on a range of buprenorphine doses can be tapered successfully over 7 days
- There was no advantage to prolonging the tapering schedule for weeks.


Additional Research

- More research is needed to answer questions such as:
  - To what degree do these patients return to opioid use following taper.
  - What counseling is best coupled with this taper?
  - What difference would it make if the treatment were provided in a physician’s office rather than in a substance abuse treatment program or clinic where other ancillary services are available?

Extended vs. Short-term Buprenorphine-Naloxone for Treatment of Opioid-Addicted Young Adults

The CTN Clinical Trial

G. Woody, MD
Principal Investigator
Delaware Valley Node

Woody, et al., 2008
**The Context of the Study**

Usual treatment for opioid-addicted young adults:
- Short-term withdrawal
- Individual or group counseling in residential or outpatient settings
- Duration is several weeks or months

Study Objective:
- Compare 2 strategies for using buprenorphine
  - Short-term withdrawal
  - Continuing treatment for 12 weeks

**Study Locations**

- Mercy Recovery
  - Westbrook, ME
- Brandywine Counseling
  - Newark, DE
- Ayudante
  - Española, NM
- Mountain Manor Treatment Ctr
  - Baltimore, MD
- Duke Addictions Program
  - Durham, NC
- UNM Addiction & Substance Abuse Programs, Albuquerque, NM

**Inclusion Criteria**
- Age 14-21
- DSM-IV criteria for Opioid Dependence
- Provided Informed consent
- Assent + Parental consent if under 18
- Successfully complete study quiz

**Exclusion Criteria**
- Medical/psychiatric making participation unsafe
- Receiving psych meds (except SSRIs)
- Abuse of alcohol/sedatives
- Sedative OD in past 6 months
- Using benzodiazepines more than 15 of the previous 28 days
- Unable to give UA negative for benzo/methadone
- Being incarcerated or likely to leave area
- Pregnant or breastfeeding
- Unable/unwilling to use birth control
Counseling
- 1 individual and 1 group session per week minimum
- More frequent sessions provided, as needed
- Counseling methods drawn from NIDA manuals:
  - CBT interventions,
  - Referral to treatment
  - Referral to age-appropriate self-help groups

Study Design
- Screening (N=236)
- Randomization (N=154)
- Detox (n=80)
  - Withdrew (n=62)
  - Completed Tx (n=16)
  - Included in Primary Analysis (n=78)**
- 12-Week (n=74)
  - Withdrew (n=22)
  - Completed Tx (n=52)
  - Included in Primary Analysis (n=74)

Medication Dosages
- Medication administered on site 5-7 days per week
- On-site doses were directly observed by study personnel
- Take home doses given when clinic was closed
Medication Dosages

Day 1:
- 2 mg administered and observed for 1.5 – 2 hours
- A second dose of 2-6 mg administered as appropriate

Day 2:
- Received dose from day 1 unless adjustment needed and observed for 1.5 – 2 hours
- Additional 2-6 mg could be administered as needed

Day 3:
- Received dose from day 2 unless adjustment needed and observed for 1.5 – 2 hours
- Additional 2-6 mg could be administered as needed

Detox Group
- Maximum dose = 14 mg
- Taper began immediately and ended by day 14

12-week group
- Maximum dose = 24 mg
- Taper began at week 9 and ended by week 12

Medication was stopped if three (3) consecutive missed doses
- For detox group, **not restarted**
- For 12-week group, restarted if returned within 7 days
  - When restarted, administered half of last dose
  - Observed for 1.5 – 2 hours
  - If well tolerated, received remaining portion of medication dose

Patients encouraged to continue counseling if medication stopped
**Study Design**

- Screening (N=236)
- Randomization (N=154)

- Detox (n=80)
  - Withdrew (n=62)
  - Completed Tx (n=16)
- Included in Primary Analysis (n=78)*
  - *2 excluded (never entered tx)
- 12-Week (n=74)
  - Withdrew (n=22)
  - Completed Tx (n=52)
- Included in Primary Analysis (n=74)

---

**Participant Demographics**

- Detox
- Column 1
- White
- Black
- Hispanic

---

**The Results—Opioid Positive Urine Tests**

- Baseline
- Study Time
- Month
- % Opioid-Positive Urine Test Results

- Detox
- 12-Week: <sup>Superscript</sup>binoporphine, <sup>Superscript</sup>naloxone
What About Other Indicators?

<table>
<thead>
<tr>
<th>Retention in Trial*</th>
<th>Detox</th>
<th>12-Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td># Counseling Sessions Attended (Mean)**</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>Additional Addiction Tx (after Trial)</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>Alcohol Use During Trial</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>Alcohol Use After Trial</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>Marijuana Use During Trial*</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>Marijuana Use After Trial</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>Cocaine Use During Trial*</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>Cocaine Use After Trial*</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>IDU During Trial*</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
<tr>
<td>IDU After Trial</td>
<td>Detox</td>
<td>12-Wk</td>
</tr>
</tbody>
</table>

* p<.01, **p<.05 (trend)

Baseline Hepatitis C Rates

- Additionally, 4 of 83 patients (5%) converted from negative to positive during the trial.
- Indicates benefits of medication use over extended periods as part of standard treatment.

Implications of the Study
High Prevalence among Young Adults

- Heroin use stable
- Non-medical use of prescription opioids increasing
- Willingness for experimentation among young adults
- Long-term prognosis among addicted young adults is unknown. Outcomes with addicted adults are poor
- High rates school drop out, legal problems, psychiatric problems, HIV-risk behaviors

High Prevalence among Young Adults

- Low rates of admission for young adults to treatment programs for primary opioid addiction
- Methadone is not available in all areas
  - limited number of programs,
  - not an option if under 16
  - For those between 16 and 18 years, standard care requires 2 failed behavioral treatments and legal guardian consent

Lessons Learned

- Longer treatment seems to be better than a quick detox for these opioid addicted young adults
- When compared to those in the detox group, patients in 12-week condition showed:
  - Fewer opioid positive urines
  - Greater retention in active treatment phase
  - Lowered use of marijuana and cocaine use and injection drug use
  - Effect only during active treatment with buprenorphine
Lessons Learned

- Return to opioid use in both groups after this fairly brief medical treatment is concerning given
  - Young age
  - Short duration of opioid use
- Adult trials have consistently shown better outcomes with longer treatment
- Young adults will likely need long-term opioid agonist treatment
- Hepatitis C rates and conversion of 4 participants make need for treatment even more urgent

Woody, et al., 2008; Feillin, 2008

Lessons Learned

- Once DSM-IV Criteria met for opioid dependence are met, course of addiction similar to adults
- Frequent relapse after withdrawal in this sample could encourage caution when tapering young adult patients.
- While tapering, these patients need:
  - Drug abuse counseling
  - Close monitoring for relapse
- When tapering is clinically indicated, consider using Naltrexone following withdrawal.

Woody, et al., 2008; Feillin, 2008

Methamphetamine
Medications considered for treatment of methamphetamine dependence

**Negative Results**
- Imipramine
- Desipramine
- Tyrosine
- Ondansetron
- Fluoxetine

**Under Consideration**
- Gabapentin
- Modafinil
- Topirimate
- Disulfiram
- Lobeline
- Aripiprazole

**Promising Evidence**
- Bupropion; Methylphenidate SR

---

**Promising Pharmacotherapies?**

- Newton, T. et al (Biological Psychiatry, Dec, 2005) **Bupropion reduces craving and reinforcing effects of methamphetamine in a laboratory self-administration study.**
- Elkashef, A. et al (recently completed; reported at the ACNP methamphetamine satellite meeting in Kona, Hawaii) **Bupropion reduces meth use in an outpatient trial, with particularly strong effect with less severe users.**
- Tiihonen, J. et al (recently completed; reported at the ACNP methamphetamine satellite meeting in Kona, Hawaii) **Methylphenidate SR** (sustained release) has shown promise in a recent Finnish study with very heavy amphetamine injectors.

---

**Behavioral Treatments**

The FDA labeling on these medications is clear:

The medications should be used in combination with behavior treatments for addiction

Good treatment is holistic, integrated and multifaceted, taking into account the physical, behavioral and spiritual wellbeing of the individual.

Medications can help us take care of the physical...

…we need to do the rest
For more information, contact:

Thomas E. Freese, PhD
tfreese@mednet.ucla.edu

Beth Rutkowski, MPH
brutkowski@mednet.ucla.edu

www.psattc.org
www.uclaisap.org