Medication-Assisted Treatment for Alcohol Dependence

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Seminar Objectives

- List barriers to taking pharmacotherapies and strategies to overcome these barriers.
- Describe how different addiction treatment modalities impact the disease process of alcohol dependence.
- Recognize the differences between the four FDA-approved pharmacotherapies for alcohol dependence.
- Select which combinations of addiction treatment that may be most beneficial for particular patients.
- Demonstrate skills learned during educational seminar when working with a pharmacotherapy prescriber.
- Translate information during educational seminar to patients, families and colleagues.
Section One: Pharmacotherapies and Myths
The purpose of today’s educational seminar is to provide addiction and other helping professionals with useful, unbiased information concerning pharmacotherapies so patients are afforded the best available resources and options for their treatment.

Let’s evaluate some of the good and not so good aspects of treating alcohol dependence with pharmacotherapies.
Medication Management Myths

Myth #1: Medications are not a part of treatment...

- There are four pharmacotherapies for alcohol dependence that are FDA-approved, and each medication should be used in conjunction with psycho-social-educational-spiritual therapy. Therefore, medications are a part of treatment, but only one part.

- The time is upon counselors to educate themselves to provide the best evidence-based practices available to patients.

- Medications have been used in the detoxification process for decades.
Medication Management Myths (cont.)

Myth #1: Medications are not a part of treatment...

- The National Institute on Alcohol Abuse and Alcoholism (NIAAA) recommends that counselors and prescribers consider using medications to help treat alcohol dependence.¹

- We are familiar with the use of medications in the treatment of many diseases, including alcohol dependence.

- Making the final decision about whether or not medications are a part of a patient’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...

- To reflect current terminology, “medications” are available by prescription and are used to treat an illness, disorder or disease; whereas, “drugs” are illicit psychoactive substances that are used to achieve a high.

- Medications are used to treat every disease or disorder, including alcohol dependence.
Myth #2: Medications are drugs, and you cannot be clean if you are taking anything...

- Millions of Americans use the patch, inhalers and/or bupropion (Zyban) to quit smoking, and this practice is widely encouraged by addiction professionals. These methods are pharmacotherapies and have gained broad social acceptance.

- Pharmacotherapies for alcohol dependence are not addictive.
**Myth #3:** Medications are a crutch...

- The single most accurate predictor of successful treatment outcome is the length of time in treatment. Pharmacotherapies can help patients remain in treatment longer, continue to stay committed to meeting their treatment goals and maintain long-term sobriety.

- Modern science has identified several changes that take place in an alcohol dependent’s brain. These changes do not instantaneously correct themselves after a patient stops drinking. In addition, the patient can think more clearly without so many physiological distractions taking away from counseling objectives.
Myth #3: Medications are a crutch...

- Pharmacotherapies are effective. Clinical data suggest that patients perform better in treatment when psycho-social-educational-spiritual therapy is combined with appropriate pharmacotherapies.⁴

- Not all “crutches” are detractors from sobriety goals, and not all “crutches” are bad. A patient needs some allowances to get them through each day in treatment, and any unhealthy “crutches” can be addressed therapeutically in treatment.
Medication Management Myths (cont.)

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Myth #4: Medications will get you high...

- None of the medications to treat alcohol dependence we are talking about today cause euphoria, even when they are combined with alcohol. In other words, they have no street value.

- In fact, naltrexone blocks the pleasurable effects from drinking alcohol, and disulfiram causes a severe physical reaction when combined with alcohol.

- Perhaps this statement stems from the history of over-prescribing and/or mismanagement of certain medications.
**Myth #5:** Alcoholics Anonymous (AA) says not to use medications...

- Contrary to popular belief, neither Alcoholics Anonymous (AA) literature nor either of its founding members spoke against using medications as a component of a recovery plan for alcohol dependence. This belief was held by leaders of specific chapters and spread erroneously to be AA doctrine.\(^5\)

- Even today, Alcoholics Anonymous does not endorse encouraging AA participants to not use prescribed medications or to discontinue taking prescribed medications for the treatment of alcohol dependence or related disorders.
*Myth #5: Alcoholics Anonymous (AA) says not to use medications...*

- *The Big Book* states, “God has abundantly supplied this world with fine doctors, psychologists, and practitioners of various kinds. Do not hesitate 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.”

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Medication Management Myths (cont.)

Myth #6: There are a lot of complications associated with using medications...

- When considering medication management for alcohol dependence, the risk of continued use of alcohol, the possible side effects and the benefits of the medication must be discussed.

- While it is true that some medications do have the potential to produce some uncomfortable side effects, these side effects do not occur with all patients or they occur with varying degrees of severity and lengths of time.

- It is beyond the counselors’ scope of practice to decide if the potential side effects from using medications are too cumbersome. This is an issue that should be discussed with the patient by the prescriber.
Medication Management Myths (cont.)

Myth #7: Using medications in addiction treatment is promoting the pharmaceutical companies...

- Pharmaceutical companies are going to continue to develop new medications regardless of how much they are used. Some may prove beneficial to your patients and some may not; however, every medication discussed in today’s seminar will be beneficial to someone, perhaps even just one particular patient. Your patients deserve the best available treatment options modern science can offer—this now includes pharmacotherapies.
**Myth #7:** Using medications in addiction treatment is promoting the pharmaceutical companies...

- Patients are now able to view and hear advertisements concerning new medications available for alcohol dependence via the Internet, television, print and radio. They can even request their own prescriptions from their doctor without consulting with their counselor. Counselors must remain abreast of pharmaceutical advancements so they can include pharmacotherapies into treatment planning and tailor a patient’s program, where appropriate.
Myth #7: Using medications in addiction treatment is promoting the pharmaceutical companies...

Today’s seminar is intended to educate addiction and other helping professionals about the benefits and limitations of all currently known and FDA-approved pharmacotherapies used to treat alcohol dependence, not just one particular medication, and open the door to additional resources available to treat alcohol dependence. Regardless of who created the treatment approach, patients deserve the best treatment practices available, and that includes pharmacotherapies.
How Does the Patient Feel about Taking Medications?

Addiction professionals are not alone in their feelings about using pharmacotherapies to help treat alcohol dependence.

- Many patients have questions about the safety, effectiveness and purpose of pharmacotherapies in addiction treatment.

- On the contrary, some patients feel strongly about including medications in their treatment plan.

Addiction professionals need to be prepared to appropriately address each situation, while explaining the possible benefits, as well as disadvantages, of using pharmacotherapies.
Not So Good Things about Using Medications to Treat Alcohol Dependence:

- Medications are not appropriate for everyone.
- Medications can produce side effects from use.
- Patients do not always take their medications as prescribed.
- Medications cost extra money.
Not So Good Things about Using Medications to Treat Alcohol Dependence:

- There is a stigma associated with using medications.
- Some patients do not feel comfortable taking pills or receiving an injection.
- Some medications increase the risk of overdose when combined with opiates.
Not So Good Things about Using Medications to Treat Alcohol Dependence:

- Sympathetic and educated prescribers are not easily available.

- Medications could decrease the emphasis on other forms of self-help.

- Medications could give patients a false sense of security.
Good Things about Using Medications to Treat Alcohol Dependence:

- Medications can help achieve complete abstinence from alcohol.
- Medications can help prevent relapse.
- Medications can reduce alcohol consumption.
- Medications help maintain recovery from alcohol.
Medication-Assisted Treatment

Good Things about Using Medications to Treat Alcohol Dependence:

- Medications can help patients stay in treatment longer.
- Medications can serve as a tool to initiate treatment.
- Medications support the therapeutic process.
- Medications can reduce absenteeism from work.
Medication-Assisted Treatment

Good Things about Using Medications to Treat Alcohol Dependence:

- Medications can increase self-confidence.
- Medications can reduce family conflict.
- Some medications are thought to alleviate cravings.
- Some medications block the effects of alcohol.
Medication-Assisted Treatment

Good Things about Using Medications to Treat Alcohol Dependence:

- Some medications are thought to decrease the desire to drink.
- Some medications provide incentives not to drink.
- Some medications reduce post acute withdrawal symptoms.
- Medications are another tool to enhance recovery.
Section Two: Understanding Alcohol Dependence
To understand how alcohol affects the brain, let us first review basic brain functioning.

Psychoactive chemicals mostly affect the central nervous system, which consists of the **brain** and **spinal cord**. The central nervous system is primarily responsible for:

- thinking, learning, and judgment
- emotions (happiness, paranoia, anger, anxiety, fear, love)
- voluntary movements (walking, running, reaching, sitting)
- sensory inputs (smelling, tasting, hearing, feeling)
To ensure the human body and person respond appropriately to the outside world, the brain manages itself by rapidly sending chemical signals or messages to billions of little neurons that are located everywhere in the human body.

- These messages are sent via neurotransmitters and instruct the neuron to do something.

- Neurons are commonly referred to as the building blocks of the entire nervous system, and each has its own shape, size, and function that are specific to the type of chemical signals (neurotransmitters) it can receive.
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.
However, 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 that are relevant to alcohol consumption and dependence:

- **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.)

Use the following illustrations to help you remember the primary function of each neurotransmitter as we discuss the effects they have on the brain when alcohol is consumed.

- **dopamine** – because it makes you happy
- **endogenous opioids** – because they make you euphoric and feel no pain
- **glutamate** – because it is the main excitatory neurotransmitter and speeds you up
- **GABA** – because it is the main inhibitory neurotransmitter and slows you down
Researchers have pinpointed the biological changes in the brain caused by excessive alcohol consumption.

- Changes in neuronal activities in many areas cause the brain to adapt to the presence of alcohol over time.

- These advances have afforded researchers the opportunity to address alcohol dependence from a biological perspective and develop pharmacotherapies to aid in treatment.

- Changes or adaptations in neuronal functioning occur regardless if one glass of wine is consumed or five beers by a first time drinker or alcoholic.
1. Alcohol is ingested.

2. Endorphins and enkaphalins (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.
Neuronal Activity in Alcohol Dependence

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.
Now, you might be thinking...

“What would happen if we were able to simply reduce the effects of dopamine and then perhaps drinking alcohol would not feel as good?”

Well, that is exactly what scientists have been working on for decades and fortunately, we have two medications that address this exact issue.
Which two medications work by blocking opioid receptors so the reward and reinforcing effects from dopamine are reduced?

- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
More Neuronal Activity in Alcohol Dependence

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 suppressed, and the increased GABA makes the body generally slow down.38

This imbalance is manifested by physical signs of alcohol intoxication. Which signs of alcohol intoxication do you normally witness with your patients?

- slurred speech
- incoordination
- impaired judgment
- drowsiness
- confusion

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The difference for alcohol dependents is that when alcohol is consumed repetitively, the brain is in a constant state of imbalance, and it will work to reinstate homeostasis. This is where alcohol dependence sets in and the brain adapts to the consistent presence of alcohol.

5. Since glutamate activity is reduced, 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? Stayed tuned...
Alcohol Dependence

To recap...

Increase in GABA and suppression of glutamate

alcohol use

upregulation of NMDA receptors (glutamate receptors) and tolerance

pleasurable effects and drive to repeat behavior

increase in endogenous opioid and dopamine activity
What Did You Learn?

Silvia is at a happy hour with a group of her colleagues from work. After two cocktails, she feels jubilant and engaging. She is laughing a lot and describes herself as having a “nice buzz.”

Which two neurotransmitters are involved in making Silvia feel like this?

- dopamine ✓
- GABA □
- glutamate □
- opioids ✓
What Did You Learn?

Michael is a 35-year-old male who has experienced blackouts and is unable to control his intake of alcohol. He has noticed that it takes increasingly more alcohol to achieve the same level of intoxicating effects that he enjoys.

Which two neurotransmitters are involved in making Michael feel like this?

- dopamine
- GABA
- glutamate
- opioids
Section Three: FDA-Approved Pharmacotherapies for Alcohol Dependence
Pharmacotherapy and Counselors

In recent decades, the treatment of addiction has entered into a new phase in which medication can play a vital role in helping someone recover.

However, over the years, some pharmacotherapies have been introduced as the next “great thing,” only to find out that there have been serious side effects, including cross addiction.

As we have learned more about brain chemistry and how addiction develops, more sophisticated pharmacological interventions have become available.
To be clear, neither the pharmaceutical companies nor NAADAC endorses ANY pharmacotherapy as a so-called “magic bullet” or quick fix to addiction.

Medications are just one tool of many counselors and patients have at their disposal to combat addiction.

It is highly unlikely that a patient will succeed in treatment with only medicinal interventions.

The Food and Drug Administration (FDA) is very clear that all pharmacotherapies for alcohol dependence should be administered in conjunction with psychosocial treatment and should not be used as a sole approach to addiction treatment.43
We are about to discuss the detailed aspects of each pharmacotherapy for alcohol dependence: who can take it, who cannot, special precautions, missed dose instructions, side effects, etc.

Depending on your professional licenses and credentials, many of the items discussed in the next section are beyond the scope of practice for most counselors, since most counselors do not have prescribing privileges.

The information in the next section should be used for information only and as a resource for educating the patient (and sometimes prescribers), when within the addiction professionals’ scope of practice.
Pharmacotherapy and Counselors (cont.)

- NAADAC feels it is important for addiction counselors to be as familiar with pharmacotherapies as possible.

- Often, counselors see the patient the most and are in the best position to recognize danger signs, abnormal side effects and to monitor compliance.

Addiction professionals should always direct a patient to his or her prescriber if any questions or concerns regarding prescribed medications arise.
There are currently four FDA-approved pharmacotherapies for alcohol dependence.

- Antabuse® (disulfiram) 1951
- ReVia®/Depade® (naltrexone) 1994
- Vivitrol® (naltrexone for extended-release injectable suspension) 2004
- Campral® (acamprosate) 2006
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

There is no difference between the starting, maintenance, and ending dosages.
**Additional Information for Acamprosate**

Risk of Overdose:
Risk of overdose is extremely remote, with the most severe side effect being diarrhea.

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.\(^{45}\)

Third-Party Payer Acceptance:
Does qualify for the Patient Assistance Program through Forest Laboratories, Inc. Covered by most major insurance carriers, Medicare, Medicaid, and the VA (if naltrexone is contraindicated).\(^{45}\)
How Does Acamprosate Work?

- **Mechanism of Action:**
  glutamate receptor modulator\(^47\)

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.\(^{48}\)

NOTE: The mechanism of action of acamprosate is not completely understood.
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? (cont.)

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.49

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? (cont.)

- 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\(^5\)
How Does Acamprosate Work? (cont.)

- Normal
  - Inhibition (GABA)
  - Excitation (Glutamate)

- Acute Alcohol Intake
  - Alcohol

- Tolerance
  - Alcohol
  - Adaptation

- Acute Withdrawal
  - Adaptation

- Post-Acute Withdrawal
  - Adaptation

- Normalcy Restored
  - (A)
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
Contraindications for Acamprosate

- Should not be administered to patients who have previously shown hypersensitivity to acamprosate calcium or any of its components.

- Should not be administered to patients who have severe renal (kidney) impairment, which is exhibited by a creatinine clearance of less than or equal to 30 mL/min.

- NOT contraindicated with patients who have mild to moderate renal (kidney) impairment, which is exhibited by a creatinine clearance of 30 to 50 mL/min. However, it is recommended that these patients take an adjusted dose of one 333 mg tablet three times a day.

- Since acamprosate is not metabolized by the liver, it is NOT contraindicated with patients who have mild to moderate hepatic (liver) impairment; therefore, no adjustment to dose is required.
There was a noted increase in adverse events of a suicidal nature (suicidal ideation, suicide attempts and/or completed suicides) during the clinical trials.

There was no difference in the rate of completed suicides.

As always, patients should be monitored closely for suicidal thoughts or attempts.

Utilize a standardized assessments like the Beck Scale for Suicide Ideation (BSSI) or the Hamilton Depression Inventory (HDI).
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)

The data from 3 of the studies is presented, with a discussion of the 4th study at the end of this section.
All three 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
Results: In all three studies, participants treated with acamprosate were able to maintain complete abstinence more frequently than those treated with placebo.\textsuperscript{54}
**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.\(^5^5\)
**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.\(^{56}\)
The fourth study of acamprosate differed significantly from the other three studies:\textsuperscript{58}

- did not undergo detoxification
- only reduced their drinking
- could test positive for marijuana
- 500mg tablet, twice a day

This study guided the FDA’s final determination that:

- patients must be abstinent from alcohol
- completed the detoxification process prior to initiating treatment
- two 333mg acamprosate three times a day\textsuperscript{60}
**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

(information from medication package insert)

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.
Additional Information for Disulfiram

(information from medication package insert)

- **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.

- **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.\(^6\)

- **Third-Party Payer Acceptance:**
  Covered by most major insurance carriers, Medicare, Medicaid, and the VA.\(^6\)
How Does Disulfiram Work?63

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? (cont.)

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 and neck
- Brief loss of consciousness
- Throbbing headache
- Lowered blood pressure
- Difficulty breathing
- Marked uneasiness
- Copious vomiting
- Nausea
- Flushing
- Sweating
- Thirst
- Weakness
- Chest pain

- Dizziness
- Palpitation
- Hyperventilation
- Rapid heartbeat
- Blurred vision
- Confusion
- Respiratory depression
- Cardiovascular collapse
- Myocardial infarction
- Acute congestive failure
- Unconsciousness
- Convulsions
- Death
The acute disulfiram-alcohol reaction usually lasts for 30 to 60 minutes, but can continue for several hours or for as long as there is alcohol in the blood.

In general, the reaction is proportional to the amount of alcohol consumed.

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
Contraindications for Disulfiram

Should not be administered to patients who experience psychosis or have recently received metronidazole or paraldehyde.

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 myocardial disease or coronary occlusion.

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 or have recently received metronidazole or paraldehyde.

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.
Special Precautions for Disulfiram\textsuperscript{64}

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.
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
Results: Participants treated with disulfiram did not maintain complete abstinence more frequently than those treated with placebo.66
**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.\(^{67}\)
**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.\(^6^7\)
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;

There is no difference between the starting, maintenance and endingdosages.
Additional Information for Naltrexone

Risk of Overdose:
Whereas overdose is possible, doses up to 800 mg daily did not produce any serious side effects. However, in the event of an overdose, appropriate medical treatment should be sought.

Addictive Properties:
Has not been found to be addictive, has a high abuse liability, develop tolerance, or produce withdrawal symptoms when the medication is ceased. There were no reports 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.68

Third-Party Payer Acceptance:
Covered by most major insurance carriers, Medicare, Medicaid, and the VA.68
How Does Naltrexone Work?\textsuperscript{71}

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.
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.
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 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
- dark urine
- nausea
- vomiting

(information from medication package insert)
Contraindications for Naltrexone

Information from medication package insert

- 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.
  - Naltrexone is NOT contraindicated for patients who have mild renal (kidney) impairment, but caution should be exercised when using naltrexone with this population. Patients with severe renal (kidney) impairment have not been evaluated for use of 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
**Results:** In some instances, participants treated with naltrexone were not able to maintain complete abstinence more frequently than those treated with placebo.\(^7^4\)

**Complete Abstinence - Volpicelli Study**

<table>
<thead>
<tr>
<th>Percentage of Participants Who Consumed No Alcohol During the Entire Study</th>
<th>naltrexone group</th>
<th>placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>54%</td>
<td>43%</td>
</tr>
</tbody>
</table>
Results: In some instances, participants treated with naltrexone were able to maintain complete abstinence more frequently than those treated with placebo.\textsuperscript{74}
**Results:** In both studies, participants treated with naltrexone had a greater reduction in relapse during the entire study than those treated with placebo.\textsuperscript{75}
Results: In both studies, participants treated with naltrexone had a greater reduction in relapse during the entire study than those treated with placebo.\(^7^5\)
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 experienced by 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

(information from medication package insert)
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.

(information from medication package insert)
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 with extended-release naltrexone is dramatically decreased in comparison to other medications due to the fact that it has to be administered by a health care professional, and it is not released to the individual.
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.\textsuperscript{76}

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? \(^{78}\)

- 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.
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
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

(information from medication package insert)
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.
Contraindications for Extended-Release Naltrexone

- 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.

- Should not be administered to patients with acute hepatitis or liver failure. Use in patients who have active liver disease should be carefully considered before administration.

- 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.
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.82

** not statistically significant
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. * statistically significant
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.84
**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.\textsuperscript{85}
# Medication Comparison

<table>
<thead>
<tr>
<th>Missed Dose Instructions</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Take missed dose if not almost time for the next dose; otherwise, skip missed dose and resume regular schedule</td>
<td></td>
<td></td>
<td>Take missed dose as soon as possible</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended Length of Treatment</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved by the FDA for use up to one year</td>
<td>FDA has not limited the amount of time</td>
<td>FDA alludes to 12 weeks, but many longer studies have been conducted</td>
<td>FDA has not limited the amount of time</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychosocial Counseling Requirements</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should be used in conjunction with a comprehensive bio-psycho-social-spiritual treatment program</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adolescents</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has not been FDA-approved for use with this population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elderly</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has not been FDA-approved for use with this population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Polysubstance Abusers</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has not been tested with this population</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Acamprosate</th>
<th>Disulfiram</th>
<th>Naltrexone – Oral</th>
<th>Naltrexone – Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category C designation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Section Four: Fitting Pharmacotherapies into Treatment
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

Regardless of the type of therapeutic interventions chosen, a treatment plan must be tailored to address the multiple needs of the individual, not just his or her alcohol dependence.

- sexual orientation
- gender differences
- homelessness
- family dynamics
- children/prenatal care
- legal issues
- learning, physical, developmental disabilities
- employment issues
- developmental needs
- co-occurring disorders
- cultural, racial, religious norms
Holistic Treatment (cont.)

Treatment is most successful when the services are comprehensive. Comprehensive and effective treatment should visually resemble the following diagram:¹²

From NIDA’s Principles of Drug Addiction Treatment
In addition to the patient’s knowledge of the benefits and disadvantages to addiction treatment with pharmacotherapies, 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, behavioral health issues and the patient’s ability (skill set) to self-medicate.

- **Role of the prescriber** – Does the patient have an existing relationship with a prescriber? Will the prescriber be engaged enough to determine the appropriateness of medication management? Can the patient be appropriately monitored during treatment?

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

- **Current level and type of substance abuse** – interactions with other substances and effectiveness with polysubstance dependence/abuse.

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

- **Current medications** – medication interactions (prescriber).

- **Ability to pay** – insurance coverage, out-of-pocket, Medicare/Medicaid, etc.
Section Five: Program Review
Review of Section Three

Scott does well during the day at work and rarely gives a thought to drinking. His walk to the subway takes him by several of his old drinking holes, and each night he fears that he will return to one of them.

Which pharmacotherapy do you feel is most appropriate for Scott?

- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
Maria had just completed a hospital-based detox from alcohol and was discharged to the local outpatient clinic for therapy. Maria has still had a great deal of urges, thinks a lot about drinking and finds herself around her old peers who use from time to time. She has been unsuccessful in the past in being compliant with prescribed daily medication for dealing with her addiction.

Which pharmacotherapy do you feel is most appropriate for Maria?

- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
Jamal’s past use of heroin and heavy use of alcohol has forced him into a residential treatment program with a court order. He has been detoxed and withdrawn from heroin. However, Jamal’s biggest fear is his use of alcohol and the quick fix it gives him will prompt his return once again to regular heroin use.

Which pharmacotherapy do you feel is most appropriate for Jamal?

- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
Michelle’s family has brought her to treatment after continued frustration over her binge style drinking that has now resulted in her third DUI arrest. Her husband and children are estranged, and she has lost her job due to her failure to report to work and complete assignments. Michelle’s inability to deal with her strong craving and urges to use is triggered by places she frequents and the friends she associates with.

Which pharmacotherapy do you feel is most appropriate for Michelle?

- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
Amir has been hospitalized most recently for severe renal (kidney) problems stemming from a long history of addiction. His physician has warned him that any continued use could be fatal or at a minimum will cause more severe damage, requiring the need for a transplant. He contends that his long history of dependency on alcohol and his strong cravings make it extremely difficult for him to maintain any long-term abstinence.

Which pharmacotherapy do you feel is most appropriate for Amir?
- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
Maggie has just completed her third medical detox in the past 18 months. Her concern is that when she returns to her work, she will once again be facing the constant urges to return to use that seems cyclical to her now more than ever. Maggie works as a waitress at a restaurant that is attached to a bar.

Which pharmacotherapy do you feel is most appropriate for Maggie?

- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
Russ lives alone with his cats and dogs. His circle of friends is small due to his limited income and ability to travel, eat out, or go to movies, etc. He frequently finds himself with some of his old drinking friends who always seem to have sufficient amounts of beer to share with him. He admits that he rarely thinks about drinking until he is around them and the alcohol is available.

Which pharmacotherapy do you feel is most appropriate for Russ?

- acamprosate
- disulfiram
- extended-release naltrexone
- naltrexone
Pharmacotherapy: Integrating New Tools into Practice

Medication Management for Addiction Professionals: Campral Series

New Innovations with Opioid Treatment: Buprenorphine

Blending Solutions: Integrating Motivational Interviewing with Pharmacotherapy

New Horizons: Integrating Motivational Styles, Strategies and Skills with Pharmacotherapy

Additional Resources: www.naadac.org/education
Thank You for Participating!

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