THE PHARMACOLOGY AND PHYSIOLOGY OF ALCOHOL AND ALCOHOL USE DISORDERS

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Module I:
Introduction: The Pharmacology of Alcohol

What is alcohol?

The type of alcohol that is contained in beer, wine and spirits is called ethanol. However, the word "alcohol" also refers to several other substances. To understand the various types of alcohol, it is necessary to take a look at some very basic chemistry.

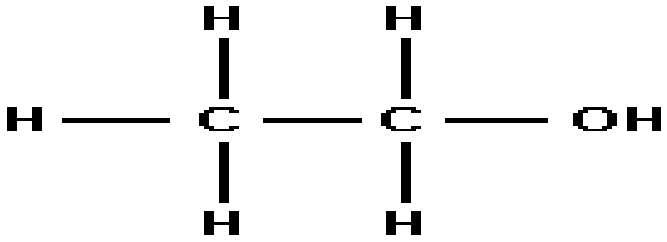
Everything we see, touch, smell and taste is made of elements: substances that cannot be decomposed into simpler substances by chemical reactions. Some important chemical elements are:

- Oxygen (O)
- Carbon (C)
- Phosphorus (P)
- Calcium (Ca)
- Potassium (K)
- Iron (Fe)
- Hydrogen (H)
- Nitrogen (N)
- Sulfur (S)
- Sodium (Na)
- Magnesium (Mg)

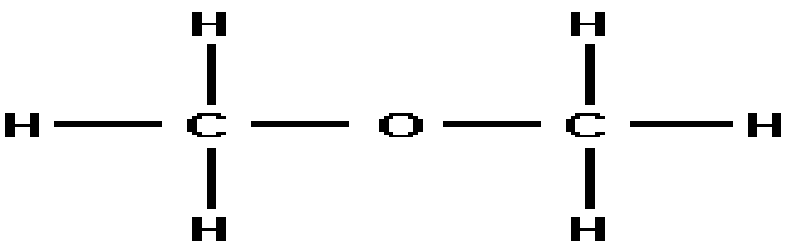
Elements are often combined together to make more complex substances. For example, water is made of up of two units of the element hydrogen and one unit of the element oxygen, so it is H_2O.

The diagram that is below shows two substances that are made up of exactly the same elements (six molecules/units of hydrogen [H], two molecules of carbon [C] and one molecule of oxygen [O]). However, these elements are arranged differently, specifically, they are in different places.

CHEMICAL ISOMERS: BOTH CHEMICALS ARE H_6C_2O, BUT THEY ARE NOT THE SAME CHEMICAL. One of them is ethanol/beverage alcohol and the other is dimethyl ether, a highly toxic substance.



ethanol



dimethyl ether

Types of Alcohol

There are many different types of alcohol, but we will discuss only three:

- Isopropyl ("rubbing alcohol")
- Methyl/methanol ("wood alcohol")
- Ethyl (beverage alcohol/ethylene/ethanol)

The first two types of alcohol are very toxic. During prohibition, wood alcohol was sometimes sold to people who were looking for ethanol. In other cases, people desperate for a drink of beverage alcohol tried drinking wood alcohol. Regardless of the source or reason, drinking as little as ¾ of an ounce (10 ml) of methanol can cause permanent blindness by destroying the optic nerve. Larger amounts can produce paralysis and death.

Where is alcohol[1] found?

As you already know, alcohol can be found in beer, wine, spirits (e.g., whiskey, vodka, rum) and other beverages. As a general rule, beer contains 6% alcohol, wine about 12% and spirits in the range of 40%, although there are exceptions to these guidelines. For example, some brands of rum can be up to 75.5 % alcohol. In spirits, the percentage of alcohol within the beverage is expressed in "proof". The proof of a particular type of beverage is calculated by doubling the percentage of alcohol within it. For example, if a type of whiskey is 42% alcohol, it is 84 proof.

Alcohol is also an ingredient in some over-the-counter (non-prescription) medicines and other products. The amount of alcohol in these medicines can be as low as 3% and as high as 20% (40 proof). This is considerably more than most wine, and is similar in alcohol content to "fortified wine" (e.g., brandy, cognac).

Alcohol Equivalents

Because various beverages vary in the percentage of alcohol that is in them, one ounce of beer is not equal to one ounce of wine, and one ounce of wine is not equivalent to one ounce of rum. Because of this variation, the idea of alcohol equivalents was developed. In general, 12 Oz. beer[2] (6% alcohol) = 4 oz wine (12% alcohol) =1.25 oz spirits (80 proof or 40% alcohol) =1 oz of 100 proof (50%) alcohol. This system makes it easier to compare the amount of alcohol that a particular person has consumed.

The Absorption of Alcohol

The absorption of alcohol begins immediately after a person begins to drink. Small amounts are absorbed by the mouth, which is one reason why some recovering alcoholics do not use alcohol-containing mouthwashes. Although the amount of alcohol that could reach the bloodstream is small, using this kind of mouthwash involves making a decision about how much alcohol can safely be consumed. Many people with alcohol use disorders agree that it is better to simply not allow any alcohol to enter the body.

[1] From this point forward, we will refer to ethyl alcohol simply as "alcohol"
[2] One average can or bottle

The majority of alcohol entered the bloodstream from the stomach, small intestine and colon (large intestine). The rate of absorption in the stomach depends on how quickly it empties itself (gastric emptying time). This factor is affected in large part by whether the alcohol is taken with food or soon after the person consumes food. In particular, the presence of food in the stomach delays the absorption of alcohol.

About 20-30% of alcohol enters the bloodstream through the stomach. The rest is taken in through the small intestine. Once again, the presence of food delays the absorption of alcohol.

So, it is a good idea to eat when drinking? In general, yes. This is because intoxication occurs more rapidly when the stomach and small intestine are empty, and also because the rapid absorption of alcohol increases the likelihood of nausea and vomiting.

The Metabolism of Alcohol

Metabolism is the method by which the body processes alcohol (and everything else one eats). Some of the alcohol is converted to other substances (such as fat, as in "beer belly"). Some is burned as energy (and converted to water and carbon dioxide). A small amount is excreted unchanged in the breath and urine. The liver metabolizes about 90% of alcohol. The lungs excrete about 5% during exhalation (breathing out). Alcohol excretion by the lungs forms the basis for breathalyzer testing. Another 5% is excreted into the urine.

The average person metabolizes about 1 standard drink (10 grams) per hour, while heavy drinkers have more active livers and may be able to metabolize up to 3 drinks per hour. People with liver diseases will metabolize less than 1 drink per hour. Another factor that affects of the metabolism is body weight. In general, the more a person weights, the more quickly alcohol can be metabolized. There are exceptions to this rule which we will address later

The metabolism of alcohol is carried out by chemicals called enzymes. Below is a diagram of how alcohol is fully metabolized. ------ = “broken down by” (and then the name of an enzyme), and →→→ = “changes into”

Alcohol ---------alcohol dehydrogenase (ADH) →→→ acetaldehyde----- acetaldehyde dehydrogenase (ALD-H) →→→ acetic acid (acetate) →→→ CO_2 & H_20 (carbon dioxide and water).

In short, alcohol is metabolized into acetaldehyde, which is metabolized into acetic acid, which then is converted into carbon dioxide and water.

Variations in Alcohol Metabolism

The most common variation in alcohol occurs among individuals of Asian descent. Approximately 50% of persons of Japanese ancestry have a variant (different) form of ALD-H that makes it harder for them to break down alcohol[3]. More specifically, this variant causes alcohol to be converted to acetaldehyde, but acetaldehyde is not easily metabolized into acetic acid. In these individuals, levels of acetaldehyde may be ten times higher than average. This is the basis for the “alcohol flush reaction”, which consists of all of some of the following symptoms:

[3] Other Asian individuals (e.g., those of Chinese ancestry) have this variant, but it is more predominant among Japanese).

1. Facial flushing
2. A widening of blood vessels (vasodilatation)
3. Rapid pulse rate (tachycardia)
4. Headache
5. Nausea
6. Vomiting
7. Fluid retention (edema)
8. Low blood pressure

It is not a coincidence that these same symptoms are present in individuals who take disulfiram (Antabuse) and then drink. (We will discuss Antabuse more thoroughly in a later portion of this course).

As you can imagine, the presence of the ALD-H variant decreases the desire to drink alcohol. This may be why liver disease is rare among persons who have this variant; they drink less and so are less prone to develop liver disease, a large proportion of which is due to excessive drinking.
In heavy alcohol drinkers, liver enzymes will show an increase, especially:

- SGOT (serum oxaloacetic tranaminase)
- SGPT (serum glutamic pyruvic tranaminase)

Blood alcohol level (BAL)/Blood alcohol concentration (BAC)

BAL and BAC are two different names for the same thing: A measure of the amount of alcohol in a person's system. This measure is usually expressed as a percentage, such as 0.10, signifying that 0.10% ($1/10^{th}$ of one percent) of the individual's blood volume is alcohol. Although the physical and psychological effect associated with a particular BAL can vary from person to person, typical levels and responses are shown below.

BAL	Behavior
0.05%	Relaxation, decrease in both inhibitions & alertness, possible personality change
0.08%	Legal level in Illinois & Most Other States for DUI
0.10	Slowed reaction time, impaired judgment, personality changes
0.15	Large, consistent changes in reaction time, increasing intoxication, mood/personality changes
0.20	Significant impairment of sensory and motor functions, marked intoxication
0.25	Severe motor and sensory disturbance, staggering gait, marked intoxication
0.30	Semi-stupor, marked decrease in awareness and breathing rate, blackouts
0.35	Surgical anesthesia, level of LD_1 (the amount of alcohol that would be a lethal dose for 1% of the general population), minimal level normally required to cause death
0.40	LD_{50}

LD_{50} signifies that on average fifty percent of drinkers with a blood alcohol level of 0.40 will die of alcohol poisoning.

There is another, less scientific description of BAL and behavior:

At less than 0.03%, the individual is dull and dignified

At 0.05%, he is dashing and debonair

At 0.10%, he may become dangerous and devilish

At 0.20%, he is likely to be dizzy and disturbing

At 0.25%, he may be disgusting and disheveled

At 0.30%, he is delirious and disoriented and surely drunk

At 0.35% he is dead drunk

At 0.40% the chances are he is dead

On average, 0.015% of a BAL is eliminated from the body every 60 minutes. Thus, it can take up to ten hours to eliminate that level of alcohol from the body.

Gender Differences and Alcohol Intoxication

In general, at the same level of alcohol consumption, women achieve higher a higher BAC than men. This is because:

1. A woman's body weight is usually less than a man's
2. Women tend to have less water in their bodies and a higher percent of body fat, so there is less tissue in which alcohol can dissolve
3. Women tend to metabolize alcohol less efficiently than men.
4. Eating habits (men tend to eat more before drinking and to eat [snacks] while drinking)

MICHELLE AND JUSTIN GO DRINKING

160 lb Justin 120 lb Michelle 3 oz 80 proof alcohol/hour

Begin drinking at 8:00 P.M.

After one hour:

- Justin is at 0.07
- Michelle is at 0.11

She may be experiencing mood swings and exhibits impaired reflexes, reaction time and judgment.

He is most likely less inhibited and impaired reasoning ability and depth perception. After two hours:

- Justin is at 0.13
- Michelle is at 0.20

She is markedly intoxicated with severely impaired judgment, coordination and awareness of her surroundings as well as slurred speech. At this point, she could pass out and/or enter into a "blackout" state, which will result in temporary amnesia.

He exhibits the same signs that Michelle did at 0.11, but with greater impairment. Additionally, he may demonstrate slurred speech and staggering.

What are the Primary Effects of Alcohol?

Alcohol:

1. Is a central nervous system (CNS) depressant, which means it is similar to sedative drugs in its action. As larger and larger amounts of this drug are ingested, it begins to increasingly slow the breathing/respiration rate. It is possible to suffer a fatal overdose on alcohol (e.g. respiratory arrest), but most people would pass out or vomit before a large enough amount entered their body. In moderate amounts, alcohol has minimal effects on a normal heart, but in larger doses or after a long period of heavy drinking, alcohol can stop the heart or damage it seriously. In addition, alcohol causes a dilation[4] of the blood vessels. When this occurs, the drinker feels a sense of warmth that can be misleading. Although the drinker may feel warm, the fact is that heat is being lost from the skin, and so the body's internal temperature can fall to a dangerous level, resulting in hypothermia.[5]
2. Causes ataxia[6], which is why inebriated people stagger when they walk. This lack of coordination is also the reason for one of the primary driving under the influence roadside tests administered by police: the "walk a straight line heel to toe" test. Another roadside test is the "horizontal nystagmus" test. The human eye generally focuses forward, toward the front (the "midline"). If a person moves her eyes sideways, up or down, the eyes naturally try to return to the midline. Nystagmus occurs when the eyes begin to drift sideways (less commonly up or down), then back to the midline on their own. Experienced police officers can gauge very accurately a person's BAL by measuring the angle at which nystagmus begins to occur[7]. This symptom usually occurs at BALs of 0.08 or higher.
3. Commonly produces a slowing of EEG (brain wave) patterns
4. Causes a decrease in antidiuretic hormones which normally act to retain water in the body. This leads to increased urination and possibly dehydration because of the loss of fluids from the body.
5. Produces hypoglycemia[8] for about three to four hours.
6. Irritates (to varying degrees) the lining of the stomach

Hangovers

Hangovers are considered by many to be a form of acute alcohol withdrawal. Typical symptoms include:

[4] An increase in size, specially the diameter
[5] A dangerous fall in the internal body temperature. (Whenever the term "hypo" precedes another word, it means under [hypodermic = under the skin] or low [hypoglycemia = low blood sugar, and hypotension=low blood pressure]).
[6] Lack of coordination
[7] More about alcohol intoxication and nystagmus can be found at http://www.horizontalgazenystagmus.com/alcoholgazenystagmusagn.html
[8] A decrease in glucose (blood sugar)

1. Upset stomach
2. Headache
3. Thirst
4. Fatigue
5. Anxiety/depression
6. Tachycardia (rapid pulse)

The severity of hangovers is determined by a number of factors:

1. The maximum BAL achieved, taking into account how much the person drank and also how quickly.
2. The amounts of congeners in the alcohol that was consumed

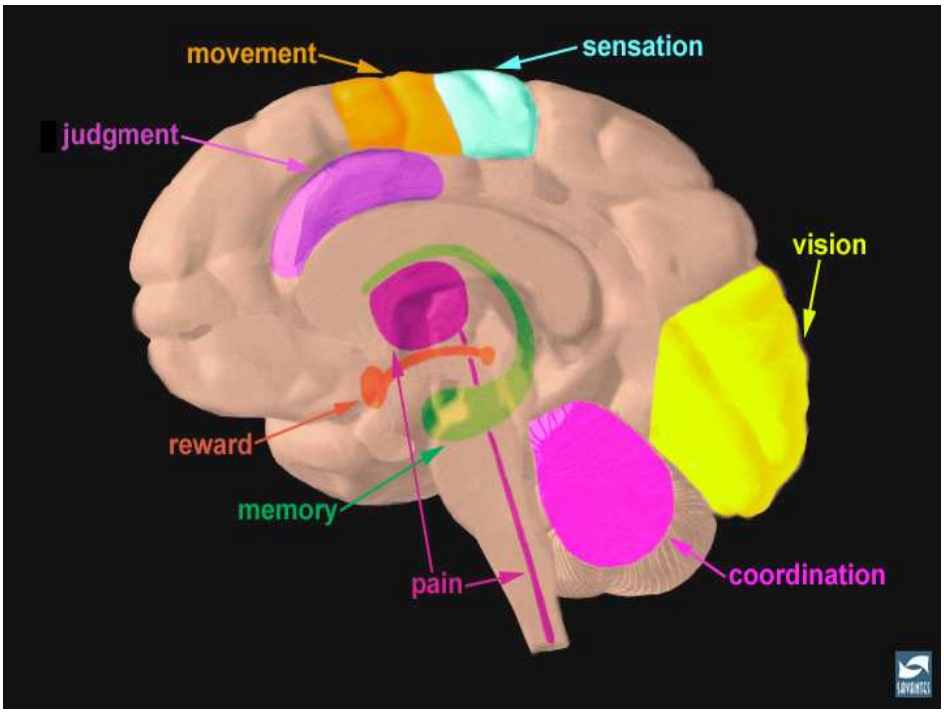
Congeners are toxic substances that are byproducts of fermentation in most alcoholic beverages. They give these beverages their characteristic look, taste and appearance. The approximate percentage of congeners in different types of alcohol is shown below:

- Bourbon, rye, rum (2%)
- Vodka, gin, grain alcohol (1%)
- Red wine (up to 1%)
- Wine (0.4%)
- Beer (0.1%)

One very important fact about congeners is that different ones are found in different types of alcohol. When more than one beverage is consumed, additional congeners enter the body, and it is believed that this mixture produces more serious hangovers. This is one reason why many say that one should not mix different types of alcohol together. If all of this is true (and we know some of it is), one of the worst drinks to consume is “Long Island Iced Tea”, which is a combination of vodka, tequila, rum, gin, triple sec, sweet and sour mix and Coca-Cola.

Alcohol and the Brain

Before we begin our discussion of alcohol and the brain, we need to take a look at how the brain is put together. The diagram below is a graphic of the human brain, split in two from the front to the back of the head, as if you were looking at one side (in this case, the left side) of the person. There are three basic sections that we need to look at.



In the picture above, the outer section of the brain is the cerebral cortex or cortex for short. This is the most advanced section of the brain. In particular, the "frontal cortex" (behind the forehead and at the top left in the drawing) is the section of the brain that controls, contains or produces the unique characteristics that make us humans. You'll notice that there is a purple area in the frontal cortex that is labeled "judgment". In addition, the frontal cortex is the site for logic, reasoning, impulse control, abstract thinking and other highly advanced functions.

Below (or inside, depending on your perspective) are a number of areas that we will simply call the "subcortical structures", because they are underneath the outer section of the brain. Two very important sections are labeled "reward" and "memory" in the picture above. Also in this part of the brain are sections that control very basic emotions (e.g., fear and rage), reproductive instincts, hunger and thirst.

The reward circuit (also called the reward pathway or reward center) is a collection of different part of the brain[9] that provides reinforcement (i.e., reward) for activities that are either critical to ones survival, or to the survival of ones values, name and species). Some of these activities are eating, sex and nurturing children. These functions are clearly high on the brain's priority list, and so as much time and energy go into them as necessary. The reward circuit is "switched on" by a neurotransmitter (brain chemical) called dopamine. You will hear more about it later on. This would also be a good place to mention that the brain contains naturally-occurring opioid chemicals called endorphins[10].

The most ancient part of the brain is the brain stem. In the picture on the following page, the section where "pain" appears is the brain stem. This is a very primitive part of the brain where alertness and control of breathing, heart rate, coughing and vomiting.

[9] For those who are interested, these include the ventral tegmentum and nucleus accumbens.
[10] Opioids include drugs such as heroin, hydrocodone (Vicodin) and oxycodone (OxyContin and Percodan), in addition to the naturally occurring endorphins.

Alcohol has a general sedating (inhibitory) effect on the entire human brain, beginning with the outer layer (the cerebral cortex) proceeding to the areas of the brain that lie underneath the cortex. Technically, it could be said that alcohol begins its effect with the cortex and then to the "subcortical" structures and brain stem.

As increasing amounts of alcohol are consumed, judgment, rational thinking, decision-making are affected, then coordination, balance, mood, and finally, vital/protective functions such as vomiting and respiration as the brain stem is affected.

The way that alcohol produces its desired effects (sedation, euphoria, disinhibition[11]) through a number of changes in the chemistry of the brain. First, as indicated above, alcohol has a generally depressing effect on the brain, beginning with the cortex. Thus, judgment, impulse control and decision making are among the first "victims" of alcohol consumption.

At least some of the desired effects of alcohol are caused when it increases the amount of a neurotransmitter called GABA[12]. At the same time, alcohol causes a release of one of the endorphins, beta-endorphin. When endorphins are released, they have an effect on mood similar to that of the opioids. Some of these effects include sedation and relief from anxiety. In turn, beta-endorphin stimulates the release of dopamine in the reward pathway. In short, the desired effects of alcohol are produced through an increase in GABA, beta-endorphin and dopamine.

In our next module, we will examine the range of medical problems associated with alcohol use disorders.

[11] Disinhibition refers to what many drinkers call "getting loose". Specifically, it refers to a state in which the drinker does or says things that are not characteristic of her. For example, shy people may become more outgoing, and those who are suppressing anger toward an authority figure may verbalize it (e.g. "telling off the boss).
[12] gamma amino butyric acid

Module II:
The Medical Effects of Alcohol

Alcohol consumption can produce damage or injury to a wide variety of organs and organ systems. In this section, we will confine our discussion to three specific systems:

- Gastrointestinal
- Circulatory/Cardiovascular
- Nervous

Gastrointestinal (GI) System

The GI system consists of all of the organs that are responsible for the:

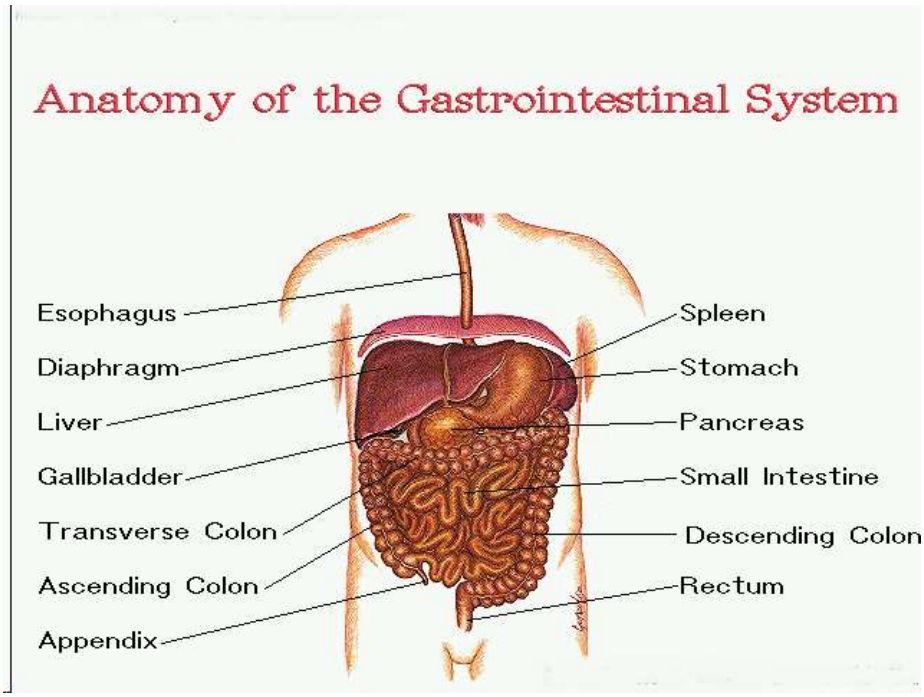
- Ingestion, digestion and absorption of food and some drugs
- Ingestion, absorption, and breakdown of some drugs
- Elimination of solid wastes.

With regard to alcohol, this is an important system because virtually all alcohol is introduced into the body through the mouth and stomach.

The GI system consists of these organs:

The gastrointestinal system:

- Mouth
- Esophagus
- Stomach
- Small intestine
- Large intestine (colon)
- Rectum
- Anus



The esophagus is the tube that leads from the mouth to the stomach. Alcohol consumption can affect the esophagus in several ways. For example, alcohol consumption can result in "heartburn" or gastric reflux disease (GRD). GRD can be caused by other factors, but overall, it is so common that most television viewers see at least one commercial a week promoting over-the-counter medicines that treat GRD. Chronic alcohol abuse leads to an increased incidence not only of heartburn but also of serious disorders of the esophagus up to and including cancer. Once alcohol passes through the esophagus and reaches the stomach, it begins to irritate the inner lining of the stomach and to increase levels of gastric acid and pepsin. Both of these are necessary for the proper digestion of food, but alcohol increases their levels beyond what is normally needed. Although throughout history, aperitifs (a type of small alcoholic beverage consumed before a meal) have often been considered healthy because they stimulate the release of gastric acid, alcohol is not necessary for proper digestion. In fact, if there is no food in the stomach, the effects of alcohol on this organ may lead to serious consequences, such as gastritis[13]. Symptoms of gastritis vary among individuals, but the most common symptoms include:

- Nausea or recurrent upset stomach
- Abdominal bloating
- Abdominal pain
- Vomiting
- Indigestion
- Burning or gnawing feeling in the stomach between meals or at night
- Hiccups

[13] For those of you who are interested, "itis" refers to an irritation or inflammation of the word that precedes it. For example, gastritis is an inflammation of the stomach, appendicitis is an inflammation of the appendix, and pancreatitis is an inflammation of the pancreas.

- Loss of appetite

In drinkers who fail to notice the association between alcohol consumption and gastritis, the condition becomes chronic. When this occurs, gastritis may lead to a peptic ulcer, a destruction of the tissue that lines the stomach. It may be helpful for some readers to think of a peptic ulcer as a sore or many sores inside the stomach. Peptic ulcers may lead to bleeding in the stomach and eventually anemia (a deficiency of red blood cells). The consumption of hot and spicy fried food along with alcohol can add to the erosion of the stomach lining.

About 20-30% of alcohol is absorbed through the stomach. The rest passes into the small intestine, where the majority of alcohol is taken into the blood stream. Alcohol can inflame the small intestine, but it is protected by chemicals that neutralize gastric acid and pepsin. The real danger associated with an inflamed small intestine is that the swelling can affect the pancreas, one of the accessory organs of the GI tract[14]. The pancreas is just behind the lower part of the stomach, and is responsible for secreting digestive enzymes into the small intestine. Its function is to produce digestive juices (pancreatic juices) and release them through a tube, the pancreatic duct, to the small intestine. The pancreas also controls the amount of sugar (glucose) in the blood, an issue that we will discuss later.

When the pancreatic bile duct is blocked, the gastric acid begins to digest the pancreas itself, producing a type of gastrointestinal cannibalism. If the drinker abstains from alcohol, the pancreatitis goes away by itself and in most cases, no permanent damage is done. If the drinker ignores the symptoms of pancreatitis (in some cases because he does not know that his alcohol use is the reason for those symptoms), the digestive enzymes may burst from the pancreas into the abdominal cavity, where they eat into blood vessels and produce bleeding. Finally, with repeated bouts of pancreatitis, a condition known as pancreatic insufficiency may develop.

The other job of the pancreas is to control the level of glucose (blood sugar). A special area on the underside of the pancreas has two different types of cells that either act to increase or decrease glucose as needed. If the pancreas is not functioning properly, the individual in question may develop either hyperglycemia (high blood sugar) or hypoglycemia (low blood sugar)[15]. If the pancreas is not functioning proper (in the case of pancreatic insufficiency), glucose levels may rise or fall dangerous.

Although many organs in the GI systems are affected by alcohol, none of is endangered as the liver. This is because the liver is the primary location for the metabolism (breakdown) of alcohol. There are dozens of ways in which the liver is affected, but three are the most important.

- Alcoholic fatty liver (hepatosis)
- Hepatitis
- Cirrhosis

At least nine out of ten chronic alcoholics will develop hepatosis. This term refers to a situation in which fat cells invade the normal structure of the liver. A problem (for the drinker) is that hepatosis has no obvious symptoms, but is detected by physical exam and blood laboratory studies, if and when the individual sees a doctor. If the person stops drinking, fatty liver will

[14] The GI system accessory organs aid in the intake, breakdown, absorption and excretion of alcohol

[15] The prefix "hyper" usually means "too much" or "above". Hyperthermia is high body temperature, and hypertension is high blood pressure. "Hypo" means "under" or "too little". A hypodermic needle is inserted under the skin, hypothermia is low body temperature and hypotension is abnormally low blood pressure.

disappear on its own in 4 to 6 weeks without formalized medical treatment. If, however, drinking continues, hepatosis may progress to the more serious condition of alcoholic hepatitis.

Hepatitis

Hepatitis" is a general word that refers to swelling or inflammation of the liver. Alcoholic hepatitis is caused by the toxic effects of alcohol on the liver after long-term use. This condition usually occurs after hepatosis but may also appear without any previous liver dysfunction.

Ten to thirty percent of all alcoholics will develop hepatitis if they continue to abuse alcohol. A person with alcoholic hepatitis feels generally ill, so there are symptoms that might bring the person to the attention of a doctor. Some of the symptoms of hepatitis include:

- Loss of appetite and weight,
- Low grade fever
- Abdominal pain
- Nausea and vomiting
- An enlarged, tender liver
- Abnormal laboratory tests of liver function

The treatment of alcoholic hepatitis involves abstinence from alcohol and following a healthy diet that provides adequate nutrition.

Cirrhosis

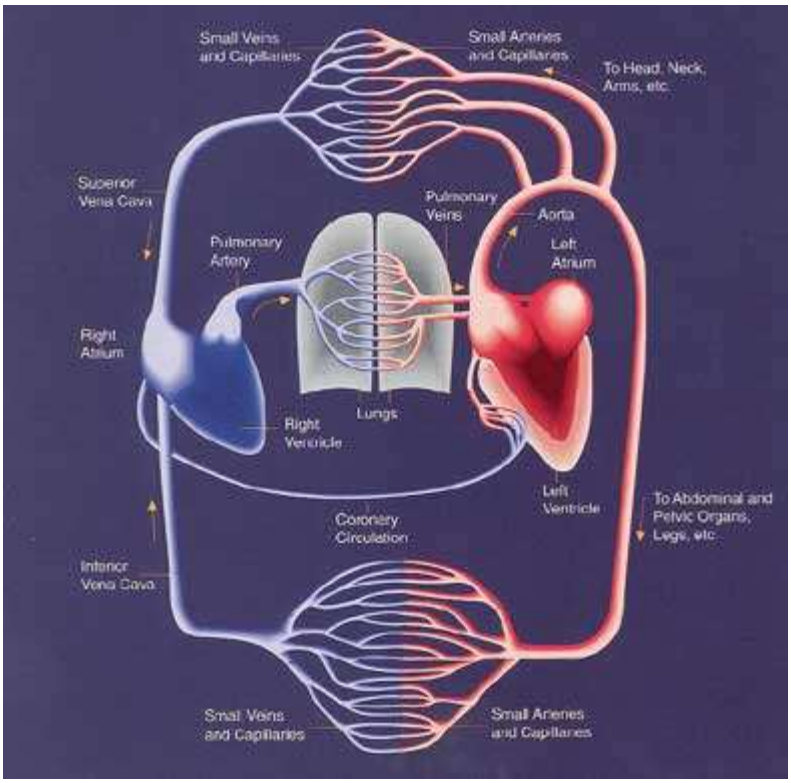
Normally, when liver cells are damaged, they regenerate (reproduce themselves as healthy cells). However, when the liver is subject to serious and persistent disorders such as hepatitis, these liver cells do not regenerate, but instead are replaced by scar tissue that can not carry out the normal functions of the liver. About 5-10% of all alcoholics develop this disorder, which usually develops after a long history of excessive alcohol intake. Cirrhosis he disease may follow alcoholic hepatitis or may occur without any previous symptoms.

This disorder is very serious. The liver performs over 100 separate functions, and when it is cirrhotic, it can lose the ability to:

- Synthesize protein
- Manufacture clotting factors
- Eliminate estrogen
- Store vitamins
- Assist in the regulation of blood sugar levels

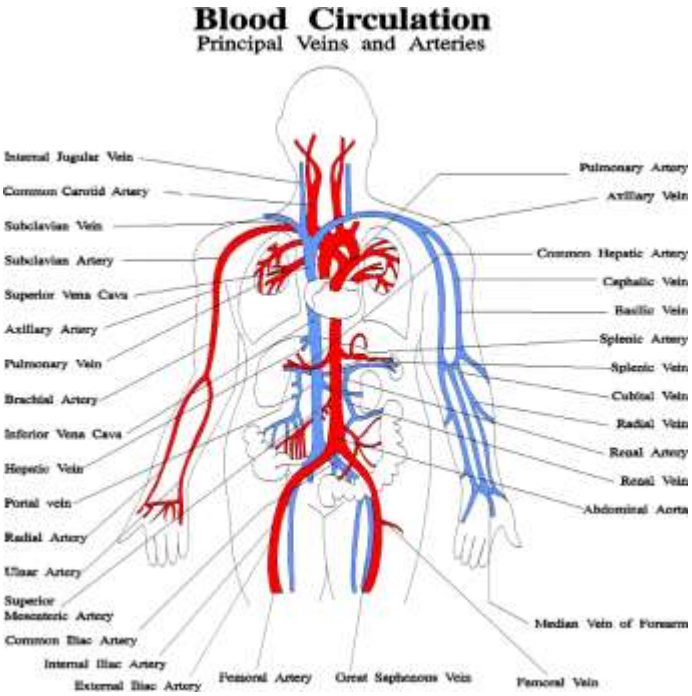
In addition, since most of it is metabolized in the liver, the individual can suffer diminished tolerance for alcohol as well as for other drugs that are metabolized in the liver.

Circulatory System (see graphic on next page)

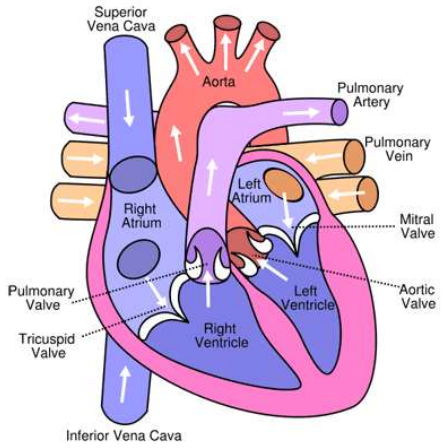


The cardiovascular system comprises the heart, with its four chambers; arteries, in which blood moves away from the heart; veins, in which blood returns to the heart; and a system of capillaries, which transport blood between small arteries and small veins. In this diagram, the heart has been split into two halves to illustrate better the functions of the right and left sides[16]

[16] This illustration below is from Vol. 19, No. 3, 1995 of the Journal *Alcohol Health & Research World*.



BLOOD VESSELS



THE HEART

The job of the circulatory system is to transport oxygen and nutrients (including glucose) through out the body and assist in the elimination of non-food waste products from the body. The components of the circulatory system are the:

- Heart
- Blood vessels (capillaries, veins, arteries)
- Blood

The blood itself is composed of platelets, white blood cells (WBC), and red blood cells (RBC). The function of each of these is beyond the scope of this course, but they all play major, although different, roles in maintaining life and general health.

In the first diagram above, the blood vessels are shown. Blue vessels are veins, which carry blood without oxygen[17] and red vessels, which carry blood that is "oxygenated".

The interaction of alcohol and the cardiovascular system is a complex one. Although there are exceptions to every rule, the scientific literature indicates that moderate consumption of alcohol (2 alcohol equivalents for day for men and one for women) can be beneficial for the heart and blood vessels. For example, moderate amounts of alcohol appear to:

- Raise the body's level of high density lipoproteins ("good" cholesterol).
- Decrease the risk of cerebrovascular accident/CVA (stroke)

However, someone with heart disease or at risk for it is generally advised by her physician to limit her alcohol intake, if not abstain completely.

Even an individual with no cardiovascular risk can damage his heart through regular consumption of larger amounts of alcohol (greater than two alcohol equivalents/day for men and one for women). This damage includes an increased risk of:

- High blood pressure
- Irregular heartbeat (Arrhythmia)
- Depression of bone marrow function

The latter is a serious problem because both red and white blood cells as well as platelets are formed in the bone marrow.

Perhaps the most damaging effect of alcohol on the cardiovascular system is the development of cardiomyopathy[18]. The myocardium is the heart muscle itself, and in fact, the term "cardiomyopathy" refers to any disease of the myocardium, whether it is caused by an infection, vitamin (thiamine deficiency), or some other cause. The type of heart muscle disease produced by alcohol is known as a dilated cardiomyopathy, because one or more heart chambers are abnormally enlarged with blood. Cardiomyopathy is often distinguished by the presence of:

- Palpitations[19]
- Labored breathing (without or without activity and/or when lying down)
- Irregular or rapid pulse
- Fatigue, weakness, faintness

In the diagram on the next page, a normal heart is shown in contrast to a heart with cardiomyopathy. You can see that the four chambers (RA, LA, RV, and LV) are dilated, or abnormally large.

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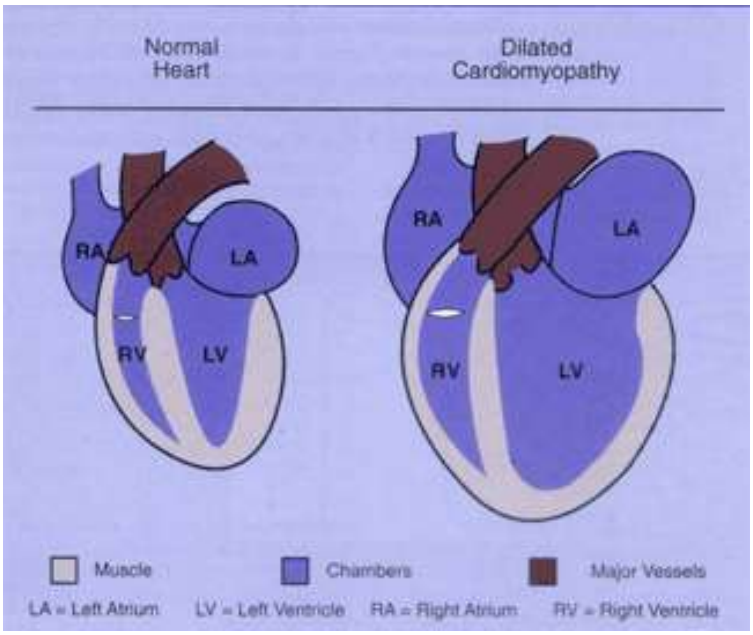
[17] To be precise, there is *one* vein that does carry oxygenated (containing oxygen) blood (the pulmonary vein) and *one* artery that does not carry oxygenated blood (the pulmonary artery).

[18] The suffix "pathy" usually refers to disease or dysfunction. Cardiomyopathy is a disorder of the myocardium, and neuropathy is a disorder of the nervous system.

[19] Unpleasant sensations of irregular and/or forceful beating of the heart.

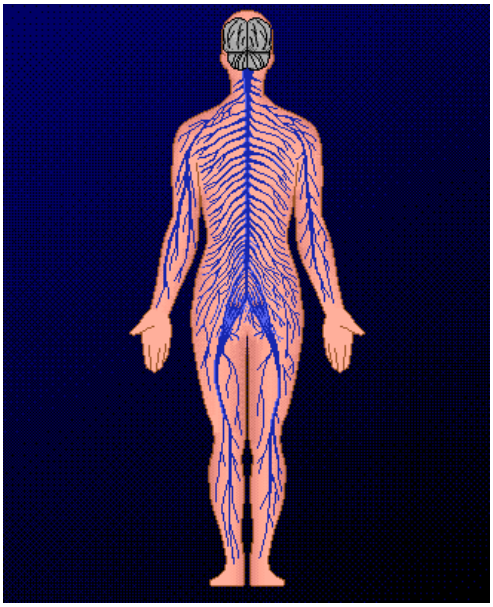


Normal heart **Heart in dilated cardiomyopathy**

When considering alcohol-related heart disease, the role of gender should also be taken into consideration. Women who consume only two or more drinks per day are at increased risk for atrial fibrillation, a condition involving atypical heart rhythm.

Nervous System

In Part I of this course, we discussed the physical properties of the brain. In addition to this organ, the human nervous system is composed of the spinal cord (combined with the brain, this is called the central nervous system) and the peripheral nervous system. Below is a diagram of the peripheral nervous system, which is composed of all of the nerves that branch out from the spinal cord to the arms, legs, hands, feet and trunk.



Peripheral Nervous System

The nervous system can be damaged either directly or indirectly through the effects of alcoholism. With the exception of alcohol withdrawal (which we will discuss in Part III of this course), the most commonly seen alcoholism-elated problems seen in hospitals has to do with liver dysfunction. When the liver becomes seriously impaired, it cannot breakdown toxic substances within the bloodstream, and eventually these substances reach the brain. Another problem often seen in hospitals is head trauma (often repeated) associated with alcohol consumption. Because an alcoholic may fall down regularly, the person is bound to hit his or her head at some point. The resulting concussion can produce either short- or long-term problems in the functioning of the brain that are commonly known as traumatic brain injuries.

Nutritional disorders can also cause damage to the nervous system. The most common if these is alcohol-related peripheral neuropathy, which is characterized by numbness, tingling, muscle weakness, depressed (slow) reflexes and a burning sensation in the hands and feet. Individuals with this disorder also may have a history of gait ataxia (lack of coordination when walking) and a history of frequent falls, which brings us back to the brain damage that concussions can produce. Peripheral neuropathy is produced in great part by vitamin B_1 (thiamine) deficiency.

Another serious disorder of the nervous system is the Wernicke Korsakoff syndrome. This is another disorder largely caused by a severe depletion of vitamins, with thiamine being the vitamin most often depleted. At one point, it was believed that there were two separate disorders, Wernicke's disease and the Korsakoff syndrome, but current medical opinion is that they are different manifestations of the same disorder.

Ataxia, mental confusion, disorientation and inattentiveness are common aspects of the Wernicke part of this syndrome. In addition, individuals with this disorder may have eye problems such as paralysis of eye movements (gaze paralysis), nystagmus (sideways, up and down or circular movements of the eyes) and a partial blindness in which only parts of the vision field can not be seen (retrobulbar neuropathy). The Korsakoff syndrome consists largely of antegrade amnesia, an inability to form new memories. Persons with this disorder may know who they are, where they are, and what is happening at a given moment, but they are unable to

recount what happened at a later time. For example, a doctor may introduce herself to a patient, but the next time he encounters her he not only does not remember her name, but reacts as if he has never seen her before. Even after repeated contacts, this patient would still be unable to recognize the doctor. As a result of antegrade amnesia, affected individuals may provide false information, not as a result of willfully lying, but rather an unconscious attempt to fill in gaps in their memory. This symptom is known as confabulation.

Nutritional Problems among Alcohol Dependent Individuals

As we have seen, poor nutrition is a major risk factor for developing alcohol-related health problems. Alcoholics often eat poorly, limiting their supply of essential nutrients and affecting both energy supply and structure maintenance. Furthermore, alcohol interferes with the nutritional process by affecting digestion, storage, utilization, and excretion of nutrients. For example, the liver is unable to make protein from amino acids or to manufacture a substance that can be converted into glucose in an emergency. Finally, individuals with gastritis, pancreatitis or other GI system problems may simply feel too ill to eat.

In our last module, we will examine the physical aspects of alcohol dependency treatment, ranging from the management of withdrawal symptoms to medications for the treatment of this disorder.

The Pharmacology and Physiology of Alcohol and Alcoholism
Module III: The Pharmacologic treatment of Alcohol Dependence

Note: Because this course covers only the pharmacology and physiology of alcohol and alcoholism, this module will be confined to a discussion of pharmacological approaches to alcohol dependency treatment.

Various medications are primary employed to treat alcohol use disorders, usually for one of two purposes. The first is to detoxify and stabilize alcohol dependent individuals, and the other is to prevent relapse among clients who are in treatment or who have completed the primary phase of treatment. It is important to note that the use of medication is rarely if ever the only means for achieving abstinence and preventing relapse, but rather an adjunct to "recovery check-ups", the use of community support (e.g., self-help groups and faith-based assistance), and other recovery management resources.

Among the medications used to treat alcohol dependency are:

1. Benzodiazepines
2. Disulfiram
3. Naltrexone
4. Acamprosate
5. Ondansetron
6. Topiramate (Topamax)

Treatment of acute alcohol withdrawal:

Alcohol withdrawal can be very serious; even life-threatening. It is often divided into three stages, with the most serious of these associated with heavier daily alcohol consumption.

Stage 1

- Anxiety
- Agitation
- Hypertension (high blood pressure)
- Eating Disturbances (e.g., anorexia)
- Quality of contact (awareness of examiner and people around him/her)
- Paroxysmal (sudden) sweats
- Tachycardia (elevated pulse)
- Sleep Disturbances (e.g., insomnia/poor quality of sleep)
- Clouding of sensorium/disorientation
- Hyperthermia (high internal body temperature)
- Hyperpyrexia overly brisk reflexes which may be a warning of impending seizures)
- Tremor ("the shakes")

Stage 2

This stage includes all of the signs of stage 1, but with increased severity. This distinguishing feature of this stage is the appearance of hallucinations, which are usually auditory, but may be

visual. These hallucinations are generally non- threatening, and the client usually has insight into their benign nature (i.e., s/he knows that they are a product of withdrawal). Seizures (convulsions) may appear at during this stage.

Stage 3

All of the symptoms of stage 1 and 2 are present, although with increased severity. However, the distinguishing feature of this stage is the appearance of delirium tremens ("DT's"). This is an acute, reversible organic psychosis that usually manifests itself within 72 hours after the last drink. The duration of DTs is two to six days. Hallucinations: may now include the olfactory (smell) and/or tactile (touch) senses. In addition, the hallucinations may be fused, so that, for example, visual and auditory hallucinations appear to be coming from the same source. In addition, the client often lacks insight into the benign nature of the hallucinations and believes that they are real rather than a product of alcohol withdrawal. In addition, these symptoms may appear:

- Disorientation (person, place, time)
- Misidentification common
- Emotional Lability (abrupt changes in mood)
- Anxiety and/or fear
- Depression
- Apathetic
- Anger
- Euphoria
- Agitation (May become more pronounced as the day turns into evening [he "sunset" effect]

Treatment of acute alcohol withdrawal

Medication is not always necessary in order for withdrawal to be facilitated. Some short-term programs (the "social setting" detoxification programs), help alcohol-dependent individuals through withdrawal with support and nourishment. However, when certain symptoms appear (e.g., tachycardia, severe tremor), physicians will use medications to ensure the physical safety of the patient.

Because of the cross-tolerance between alcohol and the sedative/hypnotics and benzodiazepines, any of these substances can be used to treatment alcohol withdrawal. Ideally, though, physicians will select the medication with the greatest margin of safety and the longest duration of action. Thus, substances in the benzodiazepine group (e.g., chlordiazepoxide/Librium or diazepam/Valium) are the drugs of choice. They possess a cross-tolerance[20] with alcohol, and do not share alcohol's high level of physical toxicity, and so are ideal detoxification resources. Benzodiazepines with a relatively long duration of action are usually preferred, since they create a greater degree of stability by minimizing the possibility of frequent shifts between withdrawal symptoms and sedation. Similarly, methadone (with a duration of 24 hours) is an ideal substitute for heroin (which has a duration of 4-6 hours) when detoxifying opiate dependent clients or assisting in their recovery with medication.

[20] The simultaneous development of tolerance between two classes of drugs

In treating alcohol use disorder, the lowest possible dose of a benzodiazepine is administered to the patient, and the dosage reduced over a period of time which ranges from 24 hours to ten days, with the longer detoxification periods required for patients with more severe symptoms.

Relapse Prevention

Once an alcohol dependent person is successfully detoxified treatment continues, but now the goal is to help the client maintain abstinence. This is accomplished through individual and /or group counseling in addition to the client's introduction to or development of community-based recovery resources. One important and proven resource is Alcoholics Anonymous, but in some cases, another support group or setting is better suited to the client. Medication is typically not used by itself to help the client maintain abstinence, but is rather an available adjunct.

Among the substances used to support relapse prevention are:

1. Disulfiram (Antabuse)
2. Naltrexone (Revia)
3. Acamprosate (Campral)
4. Ondansetron (Zofran)
5. Topiramate (Topamax)

Disulfiram (Antabuse)

In module I of this course, the metabolic pathway of alcohol was described. To review, this pathway it is

Alcohol →→→Acetaldehyde→→→Acetic acid→→→Water and carbon dioxide

As a review, acetaldehyde is a toxic substance that is normally converted very quickly into acetic acid. If too much acetaldehyde builds up in a person's system, the result can be a syndrome (collection of symptoms) that includes:

1. Facial flushing
2. A widening of blood vessels (vasodilatation)
3. Rapid pulse rate (tachycardia)
4. Headache
5. Nausea
6. Vomiting
7. Fluid retention (edema)
8. Hypotension (low blood pressure)

Disulfiram stops the breakdown of alcohol from acetaldehyde to acetic acid, thus increasing acetaldehyde levels. If the individual abstains from alcohol consumption, however, no effect occurs. The desire to avoid the symptoms listed above serves as deterrent to drinking. However, the effectiveness of disulfiram, and of most of the medications we will describe in this section, depends on patient compliance. In other words, the medication only works if the client takes it. No one can be forced to take medication for a substance dependency disorder, and so if the client wants to drink, s/he can "plan" a relapse.

Naltrexone (ReVia/Depade/Vivitrol)

It may seem odd that an opiate antagonist can be used as an adjunct to a relapse prevention plan. Clearly, if the drug in question was heroin, OxyContin or Vicodin, it would make sense to use naltrexone, but why would it be a successful deterrent to alcohol relapse? The answer is that the neuropharmacology of drug dependency is much more complex than it would appear on the surface. Not only does alcohol sedate the nervous system and increase dopamine levels in the reward pathway; it also interacts with the human body's endorphin system. By occupying and blocking the brain's internal opiate receptors, naltrexone takes away some of the pleasure produced by drinking.

Naltrexone is approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcoholism, *but only as an adjunct to counseling*. This makes sense, since no single pharmacological approach to substance dependency is particularly effective with the support of individual or group counseling. This is particularly true since, like disulfiram treatment, the effectiveness of naltrexone depends on patient compliance.

The recommended daily dose of naltrexone is 50 mg. Doses above that level may produce liver toxicity, especially in individuals whose livers may have already been damaged by heavy and/or long-term alcohol use. Thus, naltrexone is not recommended for people with active hepatitis and other liver diseases. In addition, the administration of this substance will precipitate opiate withdrawal in persons physically dependent on a drug within that group.

In addition to dosage forms designed for daily administration, naltrexone is also available as a once-a-month injection. This form of naltrexone reduces the problem of "missed doses", and can be an aid to patient compliance, since the individual only has to consent to administration every 30 days.

In clinical trials, naltrexone has been shown to be significantly more effective than placebo in reducing or stopping drinking. In one 12-week study of 70 alcoholic men, 23 percent of the ReVia-treated patients relapsed, compared with 54 percent of those receiving placebo. Of those who drank during the study, 50 percent of those on ReVia relapsed to heavy drinking, compared with 95 percent of those receiving placebo. Another study of 104 alcoholic men and women found that patients who took ReVia were about twice as successful in quitting drinking as patients who received placebo.

Acamprosate (Campral)

This medication is designed to suppress alcohol cravings by targeting specific brain chemicals that are thrown out of balance by drinking.

When alcohol is consumed, brain levels of the neurotransmitter GABA (gamma amino butyric acid) are elevated. Since GABA is an inhibitory (sedating) neurotransmitter, this increase in brain levels contributes (along with all the rest of the neurochemical changes produced by alcohol) to alcohol's sedating effects. In reaction to the release of GABA, another neurotransmitter, glutamate, is also released. As you can see, alcohol's effect on the human brain is anything but simple.

When alcohol consumption stops, glutamate levels remain high and can cause irritability, discomfort and a craving for alcohol. It has been said that, "GABA may be the reason people drink, but glutamate is the reason they can't stop ", which is to say that the pleasurable effects of

increased GABA levels make drinking reinforcing (rewarding), but the subsequent, unpleasant build up of glutamate makes individuals want to keep drinking)

The effectiveness of acamprosate can be reduced by the appearance of side effects such as:

- Dizziness
- Drowsiness
- Diarrhea
- Depression
- Suicidal ideation

Ondansetron (Zofran)

The effectiveness of ondansetron as an aid to relapse prevention is still being investigated. At this time, it is only approved by the FDA only for the treatment of nausea induced by cancer-related chemotherapy, and so its use to treat alcohol dependency is exploratory. .

Ondansetron is a serotonin antagonist[21], and may serve to decrease reduces the urge to drink by reducing depression, anxiety and hostility caused by an imbalance of serotonin. It appears to be most effective when administered to male-limited alcoholics[22].

Topiramate (Topamax)

Topiramate is approved for use as anticonvulsant. Some research has shown that it reduces craving for alcohol through its effects on dopamine and glutamate. Its usefulness can be limited by such side effects as:

- Occasional dizziness
- Tingling in the skin
- Psychomotor slowing (slowing of movements)
- Word-naming difficulties
- Weight loss

New Directions in the Pharmacological Treatment of Alcoholism

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is currently looking for medications that can:

- Induce sobriety in intoxicated patients
- Treat long-lasting withdrawal symptoms (post-acute withdrawal), which often lead to relapse
- Control alcohol craving
- Improve mental abilities of patients with alcohol-induced mental damage
- Decrease alcohol consumption by treating coexisting psychiatric disorders.

[21] A substance that blocks the ability of the neurotransmitter serotonin to attach to the brain
[22] Also known as Type 2 alcoholism, is characterized by an early-onset of heavy drinking, little environmental influence, inability to abstain from alcohol, and both guilt and fear about alcohol use

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