The Treatment of Addiction and Withdrawal Associated with Tobacco and Alcohol

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LEARNING OBJECTIVES

After completing this continuing education program, the pharmacist should be able to:

1. Explain the addictive nature of ethanol and nicotine.
2. List the acute and chronic effects of consuming ethanol.
3. Describe the treatment of ethanol overdose, withdrawal, and addiction.
4. List the acute and chronic effects of smoking tobacco.
5. Describe the treatment of nicotine addiction.

ABSTRACT: Alcohol and tobacco are the 2 most abused substances in the United States. More deaths and long-term health care effects result from the abuse of these substances than all other illicit substances combined. Each year, in the United States alone, more than 100,000 people die as a result of alcohol use and over 430,000 as a result of tobacco-related use. A major danger of these 2 drugs is that they are legal, making them widely available and, therefore, acceptable to many individuals. Both are considered "gateway substances," meaning they can lead to abuse of illegal substances such as marijuana and cocaine. Alcohol has significant acute effects especially on the central nervous system, but most of the more devastating effects occur following chronic consumption. The treatment of ethanol intoxication is usually just supportive. The treatment of withdrawal requires substitution of the depressant effects of alcohol with long-acting sedative/hypnotic drugs like the benzodiazepines. Treatment of addiction to alcohol requires long-term psychosocial therapy and, in most instances, pharmacotherapy. Only 2 drugs are currently marketed for the treatment of alcohol abuse: disulfiram and naltrexone. Nicotine is one of the most psychologically addictive substances known. Although not without acute toxicity, the greatest impact of its effects are because of addiction to nicotine leading to significant increased risk of chronic disease. A very important component of the treatment

nicotine addiction is pharmacotherapy. There are 5 drugs that are considered first-line medications (bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch) and 2 drugs that are second-line medications (clonidine and nortriptyline). These have all been shown to increase long-term smoking abstinence rates.

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THE TREATMENT OF ADDICTION AND WITHDRAWAL ASSOCIATED WITH TOBACCO AND ALCOHOL

INTRODUCTION

Substance abuse is one of the most economically and socially costly problems facing this country today. In 1998, an estimated 5 million people met the criteria for addiction to illegal drugs.[1] This figure does not include individuals addicted to legal drugs of abuse such as alcohol and tobacco. In 1997 alone, there were almost 16,000 drug-induced deaths; these deaths were associated mostly with illicit drug overdose.[2] When drug-related deaths attributable to IV drugs users transmitting infectious disease are added, the total increases to over 52,000.[3] When deaths associated with legal drug use are considered, the number of deaths rises dramatically. Each year, in the United States alone, more than 100,000 people die as a result of alcohol[4], and over 430,000 as a result of tobacco-related use.[5]

It is important to distinguish between misuse and abuse. Misuse would include not following the directions for a drug or using the medication for the wrong indication or wrong patient. This definition may vary widely within medically or socially acceptable norms. The question then becomes, when does misuse become abuse? While this can be a gray area, abuse usually manifests when the use of the substance becomes a problem. Problems can be physical, psychologic, or social in nature.[6]

The reasons for substance abuse are many, and vary from individual to individual. Peer pressure is a major reason for substance abuse[4] and is particularly influential in young drug abusers who are high school- or college-aged. The number one reason stated by high school students for using substances of abuse is peer pressure.[4,7] Other influences on this age group include a positive portrayal in the media and on television and rebellion against laws, penalties, and authority. Other possible reasons for substance abuse in the general population include an individual's desire to reduce psychologic or physical pain, anxiety, and depression. The abuser may not be able to overcome these afflictions on his/her own, and so abuses the substance as a way of self-medicating. Other reasons include pleasure-seeking behavior and the need to

experiment.[8] Possible symptoms of drug abuse are changes in class attendance or work performance, alteration of personal appearance, mood swings or changing associations (associating with individuals who are abusing the same drug), withdrawal from responsibility, withdrawal from family contacts, unusual patterns of behavior, and a defensive attitude concerning drug use.[9]

The abuse of any substance should not be confused with addiction. Thousands of people abuse or "recreationally use" substances every year and do not become dependent on them. The definition of addiction is complex and highly debated. One accepted view is to consider it comprised of the following 3 key elements.[6] The first element is compulsive abuse or compulsive substance seeking. The abuser experiences an irresistible impulse to find and use the drug. Therefore, compulsion serves as the bridge between abuse and addiction. The second element is the lack of control of substance use. The abuser may not feel that he or she has the ability or power to stop. The final and most important element is continued use despite negative consequences. These consequences may be health-related problems that manifest either acutely (i.e., overdose) or chronically (i.e., liver failure). Physical, psychologic, or psychiatric problems may be a direct or indirect result of the substance in question. Other consequences include alienation from family members or the inability to properly perform on the job. The abuse begins to interfere with daily life.

Other components of addiction include psychologic dependence, physical dependence, and development of tolerance toward the drugs' effect.[6] A psychologically dependent individual exhibits a craving or a "need" for the substance s/he abuses. Stimulants such as nicotine, amphetamines, cocaine, and caffeine induce very psychologically addictive types of effects. Physical dependence is primarily characterized by withdrawal. While the abuser may still crave the substance, the main reason for use is to avoid the devastating symptoms of withdrawal, particularly after long-term abuse. S/he begins to need it just to feel normal. This type of addiction can be much more dangerous, and often can result in death in chronic abusers. Depressants like alcohol, barbiturates and opioids are associated with inducing physical dependence. Generally, psychologic dependence precedes physical dependence, but the vast majority of addicted individuals demonstrate both types, each operating to different extents. Tolerance is the need for more of the drugs to produce the same effect experienced at a lower dose.

Alcohol and tobacco are the 2 most abused substances in the United States. More deaths and long-term health care complications result from the abuse of these substances than all other illicit substances combined.[6] Currently, there are over 60 million users of tobacco including both cigarette and smokeless forms.[6] It is believed that about 30% of cancer deaths and 90% of chronic obstructive pulmonary disease (COPD) in this country are because of smoking.[10] Alcohol-induced health problems are sited in over 25% of all hospital admissions.[11] Alcohol abuse has been linked to a number of socially and economically devastating situations including family violence and fatal automobile accidents. It is estimated that alcohol is responsible for adding a $170 billion burden on the United States economy.[4] These statistics indicate only the monetary cost of alcohol and tobacco abuse; the social and personal costs are even greater.

A major danger of these 2 drugs is because they are legal, making them widely available and acceptable to many people. Both are considered "gateway substances," meaning they can lead to use of illegal substances such as marijuana and crack (free base cocaine).[12] Research has shown that people who smoke cigarettes are 7 times more likely to abuse other drugs.[1] In addition, there is a strong correlation between the use of alcohol and nicotine. People who abuse 1 are more likely to abuse the other.[13] Because of their legality, the general population may view the addiction potential of alcohol and tobacco as limited. Despite negative advertising and trends making it less socially acceptable, the percentage of high school students using alcohol and tobacco rose in the 1990s.[3] Also, with the exception of alcohol-related accidents and alcohol poisoning, the devastating physical effects of alcohol and tobacco take years to develop. This is compared with other drug abuse–related morbidity and mortality (i.e., cocaine or heroin overdose) that usually occur more quickly, leading to the perception that these drugs are much more dangerous.

The following will detail the physiologic, psychologic, and addictive effects of both alcohol and nicotine and describe pharmacologic therapy used in the treatment of their abuse.

ALCOHOL

The use of alcohol dates back to 7,000 BC with the recipe for beer invented in 5000 BC.[14] Since its introduction, our country has had a love-hate relationship with alcohol. Temperance movements leading to the 18th Amendment (Prohibition) showed that our society recognized the problems that arose from alcohol abuse. In the United States today, approximately 70% of the adult population occasionally consumes some type of alcoholic beverage.[4] Approximately 10% are unable to limit their intake, and consume 50% of the alcohol purchased.[15] Currently, there are over 11 million heavy drinkers (consumption of 5 or more drinks on the same day on at least 5 days per month), and 40% of emergency room admissions are related to alcohol abuse.[1]

The diagnostic criteria for alcoholism are based on the same parameters used for addiction. The use is compulsive, out of control, and results in negative consequences that do not deter the individual from continuing to abuse. In addition, alcoholics tend to exhibit strong denial.[6] This may be because alcohol consumption is legal, and the abuser feels that s/he can "stop at any time." However, alcoholism fits all the criteria of a disease; it is progressive and potentially fatal. A disease is defined as "any deviation from or interruption of the normal structure or function of any part, organ, or system of the body that is manifested by a characteristic set of symptoms and signs and whose etiology, pathology, and prognosis may be known or unknown."[16] By this definition, alcoholism (addiction to alcohol) is a disease and not a self-induced state. This view may aid the health care professional in the proper treatment and care of addicted individuals.

Effects of Alcohol on the Body

The percentage of ethanol in various alcoholic beverages varies extensively. One "drink" contains about 14 grams of alcohol, and this amount can be found in ½ ounce of absolute alcohol, 12 oz of beer, 5 oz of wine, or 1½ oz of 80-proof liquor.[4] Consumption of this 1 drink will cause an increase in blood alcohol level of about 25 mg/dl in a healthy 70-kg male.[17] That same healthy male can metabolize about 7-10 g per hour[10]; therefore, drinking even 1 drink an hour can lead to an intoxicated state. After consumption, absorption is fast, and peak blood

levels of ethanol are reached in approximately 30 minutes.[10] However, food can delay this absorption because it slows gastric emptying time (GET). Carbon dioxide or heating the alcoholic beverage increases GET and therefore increases absorption.[6] This may be why anecdotal accounts of champagne, beer, or hot sake consumption state that individuals feel the effects of alcohol from these beverages more quickly.

Approximately 90% of the alcohol in blood is eliminated by oxidation in the liver; the remainder is excreted by the lungs (forming the basis for breathalyzer tests), and a minimal amount in urine and sweat.[18] Three enzyme systems in the liver perform this metabolism. Alcohol dehydrogenase (AD) plays the most important role. It metabolizes alcohol to acetaldehyde, its major metabolite, in the hepatocyte. This metabolite is then broken down further by AD into carbon dioxide (CO_2) and water. Ethanol has a unique pharmacokinetic profile in that the rate of its metabolism is zero order and is therefore independent of both time and the concentration of ethanol in the blood.[10,18] The heavy elimination load and subsequent exposure to the highly toxic acetaldehyde, which the liver faces in chronic alcoholics, is responsible for its deterioration and subsequent failure.[9]

The observation that females become intoxicated more quickly than males is owing to ethanol's pharmacokinetic profile. Generally, women weigh less than men; therefore, one would expect their blood alcohol concentration (BAC) to rise more quickly. Nevertheless, this does not account for faster intoxication of a female whose total body weight is equivalent to a male counterpart. Blood levels in females rise more quickly because females have a lower gastric content of AD and they therefore absorb approximately 30% more ethanol than males.[10] Additionally, they have a lower percentage of body water because of their increased fat content compared with a male of the same weight. Therefore, plasma levels of the ethanol (which is hydrophilic) remain higher in females. These differences lead to greater physical damage to the female body over the long term. The death rate for female alcoholics is more than 50% higher than male alcoholics.[19]

The excessive ingestion of alcohol has many effects on different organ systems. The most marked effects occur on the central nervous system (CNS). Alcohol affects many different ion channels in the CNS; it has been shown to increase the action of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at the $GABA_a$ receptor[10] and inhibit the functioning of excitatory N-methyl-D-aspartate (NMDA) receptors.[20] Essentially, this increase in inhibition in the CNS leads to the depressant effects seen with excessive acute alcohol intake.

Alcohol has also been shown to interact with both nicotinic receptors,[21] 5-HT_3 receptors,[22] and affect the activity of various kinases and signaling enzyme systems in the CNS.[10] Alcohol causes the release of dopamine in the nucleus accumbens of the brain (the pleasure center)[4] and causes the release of endogenous opioids.[10] This combination is responsible for the euphoric effects experienced by the drinker. The psychologic effects of euphoria, disinhibition, increased social interaction, and increased self-confidence are dose dependent and vary significantly from individual to individual.[9]

Above a certain dose, however, severe motor incoordination, dysphoria, vomiting, coma, and even death (0.4 mg%-0.5 mg%) can result.[9] In most states, the level designating legal

intoxication is between 0.08 mg% and 0.10 mg%.[8] Besides death from the toxic effects of acute ingestion, the individual often vomits while in an alcohol-induced stupor or coma, which may result in aspiration and subsequent respiratory failure. Table 1 (Adapted from Reference 9) shows the relationship to the effect of alcohol and blood alcohol concentration.

Table 1

Acute Effects of Alcohol on the Drinker

BAC (%)*	EFFECT
0.02-0.03	Slight euphoria, loss of shyness
0.04-0.06	Relaxation, euphoria, feeling of well-being, lowering of caution and inhibitions
0.07-0.09	Slight impairment of balance, speech, vision, reaction time Caution, reason, and memory impaired, judgment and self-control reduced
0.1-0.125	Euphoria, significant impairment of motor coordination Impairment of speech, balance, vision, reaction time, and hearing
0.13-0.15	Euphoria reduced, dysphoria beginning to appear, gross motor impairment and lack of physical control Blurred vision and major loss of balance
0.16-0.20	Dysphoria, nausea, drinker may appear as a "sloppy drunk"
0.25	Total mental confusion, needs assistance walking Dysphoria with nausea and vomiting
>0.40	Coma, severe respiratory depression, and possible death

*BAC (%) can be converted to mg/dl by multiplying the number by 100 (e.g., BAC (%) of 0.1 = 100 mg/dl)

The intoxicating effects of alcohol are most significant as blood level is rapidly rising.[4] For instance, a person with a BAC of 0.02 mg% whose blood level is currently rising may "feel" the effects more than when his or her BAC is 0.04 mg% and decreasing. A "hangover" is produced from excessive use of alcohol that results in dizziness, nausea, dry mouth, thirst, headache, and inability to concentrate. These are frequently seen hours after the last drink is ingested. The most important factor contributing to the development of a hangover is the blood level of ethanol. Other factors include decreased blood sugar, the production of acetaldehyde (a toxic metabolite of alcohol), decreased REM sleep, the presence of low molecular weight alcohols, and dehydration secondary to the inhibition of vasopressin in the kidney.[23] Ethanol, through the formation of acetaldehyde, is known to cause depression of myocardial contractility with the potential to induce arrythmias.[10] Additionally, alcohol causes vasodilation from both a central effect and by directly relaxing smooth muscle; broken blood vessels in noses of chronic alcoholics is evidence of this effect.[4,10] During acute ingestion of alcohol, and even though the individual may feel warm because of increased cutaneous blood flow, excess heat loss resulting from vasodilation has the potential to induce a potentially lethal hypothermic state (especially in a cold environment).[24]

While both ethanol and acetaldehyde are acutely toxic to the body, many of the more devastating effects of alcohol occur following chronic consumption. In addition to the direct effects, chronic alcoholics can experience nutritional and vitamin deficiencies secondary to malabsorption or poor eating habits.[4] Alternatively, overindulgence in alcohol consumption in addition to a well balanced diet can result in obesity.[8] There is an increased risk of both morbidity and mortality including but not limited to liver disease, hypertension, arrhythmias, cancer, neurologic problems, accidents, and suicide.[4] One study showed that individuals who frequently consume more then 5 drinks per episode are twice as likely to die from an injury than individuals who drink less then this amount.[18]

The liver is a prime target organ for the chronic toxicity associated with alcohol consumption largely from exposure to acetaldehyde. Approximately 15%-30% of heavy drinkers will develop liver disease.[10] The primary effects are fatty infiltration of the liver, hepatitis, and cirrhosis, which is attributable to direct toxicity.[25] In the United States, ethanol abuse is the leading cause of cirrhosis and liver transplantation. The risk of developing liver complications is related to the average daily intake, duration of abuse, and presence of concurrent hepatitis infection. The disease can have an insidious onset, and often the individual may not exhibit any overt nutritional abnormalities.[10]

The gastrointestinal tract is also highly susceptible to the effects of alcohol. Alcohol increases gastric acid and pancreatic secretions.[10] This weakens the mucosal barrier, which is why patients with peptic ulcer disease are advised not to drink. Although alcohol is thought not to cause peptic ulcers it appears to exacerbate existing ones.[26] There is an increased risk of gastritis and possible reversible injury to the small intestine. Diarrhea, weight loss, and vitamin deficiency (especially water-soluble vitamins) resulting from malabsorption are common.[27] The use of vitamin supplementation usually does not protect against toxicity.[10] Additionally, chronic alcohol abuse is the leading cause of both acute and chronic pancreatitis the United States.[28]

Brain atrophy and decrease in cognitive functioning may be present in chronic alcoholics.[29] Neurologic deficits can also be manifest, the most frequent being a generalized symmetric peripheral nerve injury.[10] It begins with distal paresthesias in hands and feet followed by degenerative changes in the CNS resulting in ataxia and dementia. Chronic consumption of ethanol is a leading cause of dementia in the United States.[30] Wernike-Korsakoff's Syndrome, although an uncommon occurrence, is a potentially dangerous situation. It presents as paralysis of the external eye muscles, ataxia, confusion, and can eventually lead to coma and death.[10] The disease is related to a deficiency in thiamine, but rarely presents in patients without a history of concurrent alcohol abuse.[4]

Long-term cardiovascular effects can be irreversible.[10] Ventricular hypertrophy and fibrosis result from high consumption with chronic use. As mentioned previously, acetaldehyde buildup results in atrial and ventricular arrhythmias (this is also a serious threat in acute withdrawal). Ventricular tachycardia may lead to an increased risk of sudden death in alcoholics.[31] Reversible hypertension may result by an unknown mechanism.[32] There is evidence, however, that HDL is increased and coronary artery disease is reduced in individuals who consume moderate amounts of alcohol on a regular basis.[33,34]

Chronic ingestion of ethanol also has deleterious effects on both sexual functioning and the pulmonary system. Initially, the consumption of alcohol may increase sexual performance by causing disinhibition that leads to increases in libido. Continued abuse leads to sexual dysfunction in males.[4] Alcoholics have a higher rate of infections especially those associated with the lungs.[10] The mechanism appears to be by directly impairing the immune system.[10]

Fetal Alcohol Syndrome (FAS), while not a chronic effect on the woman, has devastating and long-term effects on the child. The prevalence in the general population is 0.5 to 1/1000 live births.[35] The disease is a constellation of birth defects including retarded body growth, microcephaly, poor coordination, underdevelopment of midfacial region (flattened face), heart defects, and mental retardation. High consumption of alcohol is required for serious effects to occur, but the threshold level for less severe neurologic deficits is not known.[10] Alcohol rapidly crosses the placenta but the fetal liver has no AD activity. The drug then directly inhibits embryonic cellular proliferation. Despite negative advertising and extensive education programs, almost 20% of pregnant women drink alcohol during their pregnancy.[36]

Alcohol Addiction and Diagnosis

There are varying levels of alcohol abuse. Social/Recreational use may or may not be considered by some to be abuse. Habituation, an established pattern of use with no major negative consequences, is the next step up from social use.[6] Abuse would comprise continued use despite negative consequences. Addiction is a compulsion to abuse, and may include both physical and psychologic components. As stated above, depressants like alcohol are extremely physically addictive, and most of the withdrawal symptoms are related to this. However, there still remains a significant psychologic component. Mild cases of physical withdrawal are characterized by irritability, anxiety, and insomnia.[10] In general, the withdrawal symptoms are the opposite of the drug's effects and typically begin 8 to 12 hours after the last drink.[4] More severe cases include convulsions, toxic psychosis, and delirium tremens. Delirium tremens occurs only in a small percentage of alcohol withdrawal cases, but can be very severe. Only 5% of patients experiencing withdrawal from ethanol demonstrate delirium tremens, but 10% to 20% of those that do, will die.[6]

The diagnosis of alcoholism is difficult, particularly when the degree is not blatant or severe. *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)[37] gives the most accurate method for diagnosis, but the following screening questions may aid the practitioner and patient in this determination. The predictive value for alcoholism is related to the number positively answered on the CAGE questionnaire.[38] (1=62%, 2=82%, 3=99%, 4=100% diagnosis of alcohol abuse).

C - Have you ever felt the need to <u>cut down</u> on your drinking?
A - Have you ever been <u>annoyed</u> by criticism of your drinking?
G - Have you ever felt <u>guilty</u> about your drinking?
E - Do you ever have an <u>eye opener</u> in the morning?

Treatment for Overdose

As stated previously, the average lethal does of ethanol ranges from 400-500 mg/dl (or 0.4 mg%-0.5 mg%). The goals of treatment of acute alcohol intoxication are to prevent severe respiratory depression and aspiration of vomitus.[10] If the patient is provided cardiovascular and respiratory

support, recovery is likely.[10] Supportive care includes treatment of metabolic alterations and fluid replacement. The replacement of glucose may be required for hypoglycemia and ketosis. Thiamine (100 mg IM or IV) should always be given before glucose in alcoholics to prevent development of Wernicke-Korsakoff's syndrome. Dehydration and vomiting may necessitate electrolyte replacement (monitoring potassium is especially important if the patient is vomiting excessively).[10]

Treatment for Withdrawal

The management of chronic alcoholism requires not only control of withdrawal, but also long-term psychosocial therapy to prevent relapse.[10] The immediate goal for treating a chronic alcoholic is to manage potential withdrawal symptoms of seizure, delirium, and possible arrhythmia.[39] Electrolyte abnormalities, especially potassium, magnesium, and phosphate, should be monitored during this period. As stated above, thiamine should always be given as replacement therapy.

The mildest form of withdrawal begins about 6-8 hours after the last drink, and the effects (tremor, anxiety, and insomnia) will most likely stop within 1-2 days.[10] The severity is usually related to the degree and duration of alcohol abuse. More severe cases may include the symptoms above, along with visual hallucinations, total disorientation, and abnormalities in vital signs. The prognosis for an individual going through withdrawal is related to the severity and any underlying complications such as liver disease or cardiovascular abnormalities.

Severe detoxification requires substitution of the depressant effects of alcohol with long-acting sedative/hypnotic drugs like the benzodiazepines (BZ). The ideal treatment includes a gradual tapering of the BZ over several weeks to "wean" the patient off the depressant effects.[10] Tapering of alcohol itself has been used to obtain this same effect; however, this approach may not be best for the patient psychologically, since it exposes them directly to the drug of addiction. Even though acute withdrawal treatment lasts only a few weeks, it may take several months for the patient's CNS activity (especially sleep patterns) to return to normal.

The BZ of choice should be long acting, have active metabolite(s) that are eliminated slowly, and be economical.[40] This will serve to decrease the severity of withdrawal symptoms and allow for adequate tapering. Chlordiazepoxide and diazepam are the most commonly used, but some clinicians also use clorazepate. If the patient has concurrent liver disease, a long acting product may be harmful because of increased concentration of nonmetabolized drug. Therefore, a short-acting BZ such as oxazepam is indicated. There is a trade-off, however, because oxazepam may increase the risk of seizures, which is already a problem in alcohol withdrawal.[40]

Three treatment regimes for withdrawal have been proposed (summarized in table 2).[40]

Table 2

Fixed-Schedule Therapy

Drugs

Chlordiazepoxide 50-100 mg PO q6h for 1 day followed by
Chlordiazepoxide 25-50 mg PO q6h for 2 days

Advantages

Prevents delirium tremens and seizures. May be useful in patients with a history of seizures, acute illness, or pregnancy.

Front-Loading Therapy

Drugs

Diazepam 20 mg q2h until resolution of withdrawal symptoms occurs; usually need ~ 60 mg

Advantages

High doses given to treat early signs and symptoms of withdrawal may decrease seizures. Intensive monitoring and medication administration are limited to short period.

Symptom-Triggered Therapy

Drugs

Same as above, but medication is given only when the patient exhibits withdrawal symptoms.

Advantages

Drug-induced adverse effects less likely because of decreased medication administration.

Treatment of seizures associated with alcohol withdrawal does not require pharmacotherapy unless the seizures progress to status epilepticus because they generally end before any drug can be administered.[40]

Treatment of Alcoholism

Once stabilization and management of acute withdrawal are over, the patient should be referred to a psychosocial treatment program. Individual therapy or support groups such as Alcoholics Anonymous may aid the patient in breaking habits and the psychologic addiction to the drug. Even with this support, approximately 50% relapse within 1 year.[10] Concurrent treatment of other coexisting mental disorders such as depression and anxiety may decrease the likelihood of relapse.[10]

Only 2 drugs are currently marketed as long-term pharmacotherapy for alcohol abuse. Disulfiram (Antabuse®) is only indicated for this purpose. It inhibits the enzyme aldehyde dehydrogenase, which breaks down acetaldehyde, a toxic metabolite of alcohol producing a noxious reaction in the body when the patient ingests alcohol.[4] The buildup of acetaldehyde produces symptoms of flushing, throbbing headache, nausea, vomiting, sweating, hypotension, confusion, tachycardia, palpitations, and blurred vision. This extreme discomfort usually lasts 30 minutes to several hours, and is meant as a deterrent for taking the first drink.

One of the therapeutic benefits of disulfiram is that the reaction can occur up to 2 weeks after the last dose (though it is usually 7-10 days) because of the slow rate of reestablishment of aldehyde dehydrogenase.[41] However, it inhibits the metabolism of other drugs such as phenytoin, warfarin, and isoniazid, so care should be taken when prescribing and counseling patients on its use.[4] There are some potential problems with the use of disulfiram as a deterrent for alcohol abuse. The noxious reaction that patients experience may contribute to compliance issues, and necessitates that disulfiram should be only used in conjunction with close supervision or behavioral therapy. The reaction can oftentimes be intense, creating problems in patients with concurrent disease states such as cardiovascular, pulmonary, or renal failure.[9]

The patient should wait at least 24 hours after the last drink before starting therapy.[40] Avoid the use in patients who have seizures, vascular disease, diabetes mellitus, are over the age of 60, or are pregnant or plan to become pregnant.

During the first 2 weeks of treatment with disulfiram, the maximal daily dose should not exceed 500 mg; during the maintenance phase, the dose range is 125 mg to 500 mg daily. Patients may remain in the maintenance phase of disulfiram dosing for months to years. Disulfiram (if possible) should be administered in the AM when the urge to drink is usually at its lowest ebb.[4]

Disulfiram has been used for many years, but recently its use has decreased because of compliance and adverse effect issues.[4] Current studies have shown that the effectiveness of disulfiram for increasing abstinence rates is minimal at best.[42]

Naltrexone, traditionally indicated for opioid overdose, is also used for treatment of chronic alcohol addiction. Studies show that along with psychotherapy, the drug decreases both relapse rates and the craving for alcohol.[43] In patients that did relapse, they reported feeling better able to control themselves.[44,45] It is thought to work by blocking the ethanol-induced activation of dopaminergic pathways that are important to reward.[4] In this manner, it may alter the brain's response to ethanol, resulting in decreased craving for the drug or blunting the high associated with its use.

Naltrexone is given after detoxification at doses of 50 mg HS for a few months.[4] Naltrexone exhibits adverse side effects at normal doses that are usually mild, and may include nausea (the most common adverse effect—occurring in ~10%), dizziness, or headache.[9] However, at higher doses elevation in liver enzymes have been seen,[46] and, therefore, it should not be used in patients with acute hepatitis or liver failure.[4] Patients should not be given naltrexone if they are currently opioid dependent because it can precipitate severe withdrawal. It is also important to avoid concurrent therapy with disulfiram since both have a potential for hepatotoxicity.[10]

Other potential future drugs for alcoholism currently in clinical trials include nalmefene[10] (an opioid antagonist), acamprosate[47] (a modulator of NMDA receptors), and ondansetron[48] (a 5-HT_3 receptor antagonist).

NICOTINE

When the explorers of the New World returned to Europe in the 1600s, they brought back a leafy plant that native people had known about for centuries: tobacco.[6] Worldwide use of this plant spread, and its active ingredient nicotine would eventually become one of the most abused substances in the world. In the U.S., 1964 marked the first Surgeon General's report linking smoking to disease.[6] Increased rates of cardiovascular diseases, non-malignant respiratory disease (emphysema, asthma), and lung and other cancers have all been linked to the use of tobacco.[49] About 20% of all deaths and 30% of all cancer deaths in the U.S. are directly related to smoking.[10] A 2-pack a day smoker will live 8 years less than a nonsmoker.[6] Despite these warnings, over 60 million Americans smoke regularly, while over 150 million have used tobacco at some time in their life.[1] This number does not include the approximately 7 million who currently use smokeless forms of tobacco.[1]

In addition to the well-known rolled cigarette form of tobacco, which accounts for about 90% of use today,[6] several smokeless forms exist that can be nearly as deadly. In fact, up until the end of World War II, smokeless forms remained the preferred method of abuse.[50] Moist snuff, also called "dip," is finely chopped tobacco placed in the mouth next to the gums. The nicotine is then slowly absorbed through small capillaries. Loose-leaf or "chew" is larger sections of leaf that are stuffed into the mouth and chewed. These forms result in a much greater chance of developing cheek and gum cancer than are seen in nonusers.[51] Cigars, rolled tobacco forms that are smoked but not meant for inhalation, also have potential to cause mouth and throat cancers.[52] The use of cigars has drastically increased over the last decade.[53]

Second-hand smoke or environmental tobacco smoke is responsible for 40,000 deaths that are attributable to heart disease[54], 3000 deaths from lung cancer,[55] and for increasing the number of asthma attacks and severity in up to 1 million asthmatic children.[55]

Effects of Nicotine on the Body

One cigarette contains 6-11 mg of nicotine, but delivers only 1-3 mg to the body.[56] The nicotine can reach the brain via smoking in about 5-8 seconds. Smokeless forms take longer (about 5-8 minutes) but deliver between 3.5-4.5 mg total.[6] While a fatal dose can occur if over 70 mg were injected directly into the bloodstream, cases of overdose are rare.[6] If taken orally, the individual will vomit before overdose can take effect, and IV is not a route of nicotine abuse.

Nicotine's pharmacologic actions are complex and are a summation of both excitatory and inhibitory effects on many effector systems in the human body.[4] The stimulation occurs from both a direct action on autonomic ganglia and secondarily to interaction with nicotinic receptors on the adrenal glands causing the release of catecholamines.[4] Nicotine's inhibitory effects are the result of it remaining on nicotinic receptors and thereby causing blockade of transmission. The effect on nicotine on the sympathetic branch of the autonomic nervous system is strong and produces palpitations and tachycardia that are often experienced with initial use.

Acute systemic effects of nicotine usually include CNS stimulation, respiratory stimulation, skeletal muscle relaxation, peripheral vasoconstriction, and increased blood pressure, heart rate,

cardiac output, oxygen consumption, and vomiting.[4,57] Nicotine produces vomiting from both a direct irritating effect and a central effect on the emetic chemoreceptor trigger zone.[4]

The chronic use of cigarettes may have serious adverse health effects. The long-term effects on the cardiovascular and respiratory systems are the most pronounced and deadly. Smoking is a major risk factor for the development of atherosclerosis. It is believed that carbon monoxide in cigarette smoke increases the LDL cholesterol levels resulting in greater atherosclerotic plaque buildup.[6]

Nicotine is a potent vasoconstrictor, so people who smoke have a much greater chance of developing hypertension and increasing the potential for a stroke. This vasoconstriction and atherosclerosis can eventually lead to a myocardial infarct.[6]

By far, the most devastating effects of smoking on the body are seen in the respiratory system. The risk of developing non-malignant respiratory diseases such as emphysema, asthma, chronic bronchitis, and COPD is greatly increased in smokers.[49] The risk of developing lung cancer is increased in smokers by 12-20 times over nonsmokers.[49] It has been estimated that smoking causes 87 % of all lung cancers.[48] Inhaled smoke contains over 4000 different chemicals of which 40 are suspected or known carcinogens.[54] One of the most potent groups of carcinogens found in cigarette smoke are the polycyclic aromatic hydrocarbons (PAHs).[58] In addition to carcinogenicity resulting from direct contact with the lungs, many other forms of cancer are also directly caused by smoking including mouth, larynx, pharynx, esophageal, bladder, pancreatic, liver, cervical, and kidney.[49] Smoking increases the activity and abundance of arylhydrocarbon hydroxylase, an enzyme that metabolizes PAHs into active carcinogens.[5]

Cancer resulting from tobacco use is dose related, meaning as number of packs per day and number of years of smoking increases, so does the probability that the smoker will develop some form of cancer. Low tar cigarettes do not decrease the risk of cancer, primarily because the individual will smoke more often and inhale more deeply to get the same effect.[60] Smokeless forms of tobacco, while they do not affect the lungs, create circulatory problems secondary to vasoconstriction, leukoplakia (white spots on gums that are precancerous) and cancers of the mouth, pharynx, and esophagus.[61]

Smoking in pregnancy is also of great concern because nicotine and carbon monoxide easily cross the placenta. Children born to mothers who smoke have an average lower birth weight. This relationship is dose related. The more the woman smokes, the greater the reduction in weight.[62] There is a higher risk of the baby being stillborn and an increased risk of Sudden Infant Death Syndrome (SIDS).[63] There is also evidence of an increased risk of Attention-Deficit/Hyperactivity Disorder (ADHD) in offspring of mothers who smoke.[64]

Nicotine Addiction

Nicotine, like all stimulants, can cause significant psychologic dependence. The reward center of the brain is stimulated through an increased concentration of dopamine at the nucleus accumbens.[4] Additionally, at least some of the euphoric effects of nicotine are because of the release of endorphins.[4]

Nicotine is probably the most psychologically addictive substance known to man. Although 80% of smokers believe smoking causes cancer they continue to smoke.[65] In addition to the pleasurable effects experienced from a cigarette, there are several reasons given for continued use. There is a ritualistic aspect to smoking that health care workers should be aware of. People make associations between smoking and other activities, and often "always" smoke at certain times such as in their car, after a meal, while they are drinking alcohol, or first thing in the morning with their coffee. These behaviors, while not directly related to the addicting properties of nicotine, are habitual in nature, and can be difficult for the smoker to break.[6] Other aspects such as perceptions about maturity and sexual attractiveness, and a desire to be rebellious, may influence younger users.

Nicotine can be a mood elevator or depressor**,** depending on the current state of the user. The desire to manipulate mood can be a strong influence on the use of nicotine.[6] Addiction to nicotine may be related to the desire to obtain a familiar physical and mental mood. This is called state dependence, which means that individuals desire to obtain a familiar state regardless if is pleasurable or not.[6]

The craving for tobacco occurs most notably because the patient is going through acute withdrawal. There is significant tolerance to the subjective effects of nicotine demonstrated by smokers stating that the first cigarette of the day feels the best.[4] However, the calm experienced by smokers who haven't had a cigarette in a while is probably related to the prevention or lessening of withdrawal than nicotine itself acting as a true sedative.[6]

Continued use of nicotine is probably a combination of the desire to obtain the rewarding effects of nicotine and the desire not to experience withdrawal symptoms.[4] The nicotine withdrawal syndrome includes irritability, anxiety, depressed mood, difficulty in concentrating, restlessness, decreased heart rate, increased appetite, weight gain, and craving for nicotine. This usually begins within 24 hours of cessation of smoking.[4] After 2 weeks without nicotine, all of these symptoms will usually be gone except craving (which, as stated above, may never truly cease) and increased appetite.[6]

One theory of the molecular basis for nicotine withdrawal is that long-term use of nicotine will be followed by up-regulation of nicotinic receptors.[66] When the smoker tries to quit or has not had a cigarette in some time, the activity of acetylcholine on these receptors is amplified creating a state of agitation, restlessness, and discontent. The individual is driven to reach for another cigarette to reduce stress and create a sense of well-being.

Other evidence for nicotine withdrawal has shown that there is a significant decrease in the brain's reward function with abrupt cessation of smoking, and this may then lead to the craving associated with tobacco withdrawal.[67]

Nicotine craving in patients who were chronic smokers may actually never completely go away, even years after quitting. Issues related to weight loss and craving cessation are the most significant reasons that people continue to smoke.[6] Nicotine decreases appetite and suppresses metabolism. Smokers weigh around 6 pounds less than nonsmokers.[68]

Treatment of Smoking

The benefits from cessation of smoking are numerous and are summarized in table 3.[6,69,70] Simply stated: people who stop smoking live longer than people who continue to smoke.[71]

Table 3

Within	Benefit
36 hours	Blood carbon monoxide levels return to normal
48 hours	Senses of smell & taste begin to return
1 week	Risk of heart attack decreases and breathing improves
8-12 weeks	Circulation improves, constricted blood vessels begin to relax
1-9 months	Fatigue, coughing, sinus congestion, and shortness of breath improve
5 years	Heart disease death rate returns to normal
10 years	Lung cancer death risk *almost* back to normal

While the health risks are substantial, many patients are reluctant to quit because of the habitual nature of the addiction and the withdrawal symptoms they experience when trying to quit. Guidelines for the treatment of nicotine addiction were released in 1996[72] and updated in 2000.[73] There are various aspects to a successful smoking cessation program and they include the following: skills building, social support, and pharmacotherapy. Skills that should be developed include teaching patients mechanisms to resist cues that induce them to smoke. Social support includes encouragement and positive feedback from friends, family, and health care workers. Pharmacotherapy should be with one of the 5 first-line drugs (bupropion SR, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patch) or the 2 second-line drugs (clonidine and nortriptyline) that have all been proven to increase long-term smoking abstinence rates.[73]

All patients should be urged to stop smoking every time they encounter a health care professional. Patients who want to quit should be provided information and counseling to help them succeed with smoking cessation. Patients unwilling to quit should be provided with a motivational intervention. It has been shown that even minimal interaction can increase the likelihood that the patient will stop smoking, the longer the intervention the greater the likelihood that they will stop.[73] Pharmacotherapy with behavioral modification is considered the treatment of choice.[4]

Nicotine Replacement Therapy

Nicotine Replacement Therapy (NRT) is the replacement of the nicotine in a benign manner (i.e., not smoke inhalation), which is then tapered over several weeks. The smoker has to "want" to quit for treatment to be effective. Treatment with NRT shows success rates double that of cessation attempts without it.[74] This method decreases intensity of withdrawal symptoms while significantly decreasing exposure to carcinogens. Nicotine replacement is available as a patch, gum, spray, or nasal inhaler.

The patch produces a more consistent steady state blood level than the gum and appears to be associated with better patient compliance.[4] But the success rate on the patch alone is only 20%

for 12 months.[4] Combinations of the patch and gum have not been associated with increased efficacy or patient compliance.[75,76] NRT is contraindicated in patients with cardiovascular disease including irregular heartbeat, hypertension, currently smoking, and a history of myocardial infarction (MI) and active peptic ulcer disease.[9] The gum form is contraindicated in patients with active temporomandibular joint disease (TMJ).[9] Although not strictly contraindicated, use in pregnancy should be only when the benefit obviously outweighs the risk toward the fetus.[4]

Patients should be made aware that along with NRT they should be working on their coping skills and determining alternatives that they can rely on instead of smoking.[77] NRT can only decrease the craving for nicotine, so the patient can then focus on lifestyle changes, which is the key to long-term success.

Nicotine patches are most effective over an 8-week period; use beyond this duration has not been associated with greater percent success rates.[74] Gum should be continued for 1 to 3 months on a fixed schedule and not on a when needed basis.[72] Up to 20% of patients who have stopped smoking will continue to use the gum for more than 1 year.[78]

It is recommended that the maximal dose of the patch should be used for smokers who smoke 10 or more cigarettes per day. Although many use a step-down approach, decreasing the dosage every 2 weeks, no evidence exists that this method is superior to only using the maximal dose for 6 weeks.[74]

The 2-mg dose of the gum is considered the optimum dose, but the 4-mg dose should be considered for heavy smokers (>20 cigarettes per day).[72] Generally, patients cut down gum use on their own gradually because of the unpleasant taste of the gum. This type of gum is not to be chewed continuously; patients should use the "chew and park" technique. Chewing should occur for a few seconds depending on how much nicotine release is desired. The patient should then park the gum between the cheek and gum for a period of time to allow absorption of the drug. Food or beverage should not be consumed for 15 minutes before or during use of the gum.[79]

Most forms of NRT have minimal dose-related adverse effects, which may include nausea and dizziness. If the patient experiences these to any great extent, a dose reduction is merited. About 50% of patch users reported skin irritation during the course of therapy, but it was usually mild, and less than 5% needed to discontinue therapy owing to skin problems.[72] The irritation can be alleviated by using over-the-counter (OTC) hydrocortisone cream, switching the brand of patch, or switching to another form of NRT.[9] Rotation of patch sites (do not use a site more than once a week) will help to prevent local irritation.

Bupropion SR (Zyban® sustained-release product), an antidepressant agent, has been shown to have efficacy in reducing problems associated with nicotine withdrawal.[9] In some patients, bupropion has been shown to decrease patients' craving for cigarettes[4] and reduce relapse rates.[4] In fact, the use of bupropion has actually been shown to have greater success rates than NRT.[80] A combination of the 2 has demonstrated the greatest success rate at 51%.[80] The mechanism of action is unknown, but it may be related to blocking dopamine reuptake.[73] The usual dosage of bupropion SR is 150 mg qd for 3 days, then 150 mg BID for 7-12 weeks with or without NRT.

The most common adverse effects are insomnia and dry mouth.[80] Patients should be directed to stop smoking during the second week of therapy.[81]

Clonidine has been shown to be effective in increasing abstinence rates in smokers.[73] The FDA has not approved it owing to its significant adverse effect profile (dry mouth, drowsiness, dizziness, sedation, and constipation); it is considered a second-line drug.[73]

Nortriptyline is used only when other first-line drugs are contraindicated or in patients when the first-line drugs have proven ineffective. It has been shown to be effective in increasing abstinence rates in smokers.[73] The most common adverse effects include sedation, dry mouth, blurred vision, urinary retention, light-headedness, and hand tremors.

Despite these measures, failure rates for smoking cessation therapy run about 80%.[4] Only about 15% of all long-term smokers are able to quit permanently. Fluoxetine may have some effectiveness in treating depression that may occur when someone stops smoking.[82] The following is a list of Internet resources that may aid both the practitioner and patient in their mission to quit smoking:

American Cancer Society—www.cancer.org
Center for Disease Control—www.cdc.gov/tobacco
National Institute on Drug Abuse—www.nida.nih.gov
Nicotine Anonymous—www.nicotine-anonymous.org
National Heart, Lung, and Blood Institute—www.nhlbi.nih.gov
Free Resource to help you Quit—www.quitnet.org

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