CLEANSING THE SELF

REVIEW OF SUBSTANCE ABUSE DISORDERS

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Cleansing The Self: A Review Of Substance Abuse Disorders

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Published by Jonah Sanders, 2022.

Introduction

As the editor of this compilation my sincere goal is to help educate the masses about the various substance issues that are presented. We must take a look at these issues principally because it not only affects us each individually but as a community, thus please read and take head.

- Jonah Sanders

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Substance use disorder

Substance use disorder (SUD) is the persistent use of drugs (including alcohol) despite substantial harm and adverse consequences. Substance use disorders are characterized byan array of mental/emotional, physical, and behavioral problems such as chronic guilt; an inability to reduce or stop consuming the substance(s) despite repeated attempts; driving while intoxicated; and physiological withdrawal symptoms. Drug classes that are involved inSUD include: alcohol; cannabis; phencyclidine and other hallucinogens, such as arylcyclohexylamines; inhalants; opioids; sedatives, hypnotics, or anxiolytics; stimulants; tobacco; and other or unknown substance.

In the Diagnostic and Statistical Manual of Mental Disorders 5th edition (2013), also knownas DSM-5, the DSM-IV diagnoses of substance abuse and substance dependence were merged into the category of substance use disorders. The severity of substance use disorders can vary widely; in the DSM-5 diagnosis of a SUD, the severity of an individual's SUD is qualified as mild, moderate, or severe on the basis of how many of the 11 diagnosticcriteria are met. The International Classification of Diseases 11th revision (ICD-11) divides substance use disorders into two categories: (1) harmful pattern of substance use; and (2) substance dependence.

In 2017, globally 271 million people (5.5% of adults) were estimated to have used one or more illicit drugs. Of these, 35 million had a substance use disorder. An additional 237 million men and 46 million women have alcohol use disorder as of 2016. In 2017, substanceuse disorders from illicit substances directly resulted in 585,000 deaths. Direct deaths from drug use, other than alcohol, have increased over 60 percent from 2000 to 2015. Alcohol useresulted in an additional 3 million deaths in 2016.

This section divides substance use disorder causes into categories consistent with the biopsychosocial model. However, it is important to bear in mind that these categories are used by scientists partly for convenience; the categories often overlap (for example, adolescents and adults whose parents had (or have) an alcohol use disorder display higher rates of alcohol problems, a phenomenon that can be due to genetic, observational learning,socioeconomic, and other causal factors); and these categories are not the only ways to classify substance use disorder etiology.

Similarly, most researchers in this and related areas (such as the etiology of psychopathology generally), emphasize that various causal factors interact and influenceeach other in complex and multifaceted ways.

Social determinants

Among older adults, being divorced, separated, or single; having more financial resources;lack of religious affiliation; bereavement; involuntary retirement; and homelessness are allassociated with alcohol problems, including alcohol use disorder.

Psychological determinants

Psychological causal factors include cognitive, affective, and developmental determinants, among others. For example, individuals who begin using alcohol or other drugs in their teensare more likely to have a substance use disorder as adults. Other common risk factors are being male, being under 25, having other mental health problems (with the latter two being related to symptomatic relapse, impaired clinical and psychosocial adjustment, reduced medication adherence, and lower response to treatment), and lack of familial support and supervision. (As mentioned above, some of these causal factors can also be categorized as social or biological). Other psychological risk factors include high impulsivity, sensation seeking, neuroticism and openness to experience in combination with low conscientiousness.

Biological determinants

Children born to parents with SUDs have roughly a two-fold increased risk in developing aSUD compared to children born to parents without any SUDs.

Diagnosis

Addiction and dependence glossary

addiction – a biopsychosocial disorder characterized by persistent use of drugs (includingalcohol) despite substantial harm and adverse consequences

addictive drug – psychoactive substances that with repeated use are associated with significantly higher rates of substance use disorders, due in large part to the drug's effect onbrain reward systems

dependence – an adaptive state associated with a withdrawal syndrome upon cessation of

repeated exposure to a stimulus (e.g., drug intake)

drug sensitization or reverse tolerance – the escalating effect of a drug resulting fromrepeated administration at a given dose

drug withdrawal – symptoms that occur upon cessation of repeated drug use

physical dependence – dependence that involves persistent physical–somatic withdrawalsymptoms (e.g., fatigue and delirium tremens)

psychological dependence – dependence that involves emotional–motivational withdrawalsymptoms (e.g., dysphoria and anhedonia)

reinforcing stimuli – stimuli that increase the probability of repeating behaviors paired withthem

rewarding stimuli – stimuli that the brain interprets as intrinsically positive and desirable oras something to approach

sensitization – an amplified response to a stimulus resulting from repeated exposure to it

substance use disorder – a condition in which the use of substances leads to clinically andfunctionally significant impairment or distress

tolerance – the diminishing effect of a drug resulting from repeated administration at a givendose

Individuals whose drug or alcohol use cause significant impairment or distress may have a substance use disorder (SUD). Diagnosis usually involves an in-depth examination, typicallyby psychiatrist, psychologist, or drug and alcohol counselor. The most commonly used guidelines are published in the Diagnostic and Statistical Manual of Mental Disorders
(DSM-5). There are 11 diagnostic criteria which can be broadly categorized into issuesarising from substance use related to loss of control, strain to one's interpersonal life, hazardous use, and pharmacologic effects.

DSM-5 guidelines for the diagnosis of a substance use disorder require that the individual have significant impairment or distress from their pattern of drug use, and at least two of thesymptoms listed below in a given year.

Using more of a substance than planned, or using a substance for a longer interval thandesired

'Inability to cut down despite desire to do so

Spending substantial amount of the day obtaining, using, or recovering from substance use

Cravings or intense urges to use

Repeated usage causes or contributes to an inability to meet important social, orprofessional obligations

Persistent usage despite user's knowledge that it is causing frequent problems at work,school, or home

Giving up or cutting back on important social, professional, or leisure activities because ofuse

Using in physically hazardous situations, or usage causing physical or mental harm

Persistent use despite the user's awareness that the substance is causing or at leastworsening a physical or mental problem

Tolerance: needing to use increasing amounts of a substance to obtain its desired effects

Withdrawal: characteristic group of physical effects or symptoms that emerge as amount ofsubstance in the body decreases

There are additional qualifiers and exceptions outlined in the DSM. For instance, if an individual is taking opiates as prescribed, they may experience physiologic effects of tolerance and withdrawal, but this would not cause an individual to meet criteria for a SUDwithout additional symptoms also being present. A physician trained to evaluate and treatsubstance use disorders will take these nuances into account during a diagnostic evaluation.

Severity

Substance use disorders can range widely in severity, and there are numerous methods to monitor and qualify the severity of an individual's SUD. The DSM-5 includes specifiers for severity of a SUD. Individuals who meet only 2 or 3 criteria are often deemed to have mild SUD. Substance users who meet 4 or 5 criteria may have their SUD described as moderate, and persons meeting 6 or more criteria as severe. In the DSM-5, the term drug addiction is synonymous with severe substance use disorder. The quantity of criteria met offer a rough gauge on the severity of illness, but licensed professionals will also take into account a moreholistic view when assessing severity which includes specific consequences and behavioralpatterns related to an individual's substance use. They will also typically follow frequency ofuse over time, and assess for substance-specific consequences, such as the occurrence of blackouts, or arrests for driving under the influence of alcohol, when evaluating someone foran alcohol use disorder. There are additional qualifiers for stages of remission that are based on the amount of time an individual with a diagnosis of a SUD has not met any of the 11 criteria except craving. Some medical systems refer to an Addiction Severity Index to assess the severity of problems related to substance use. The index assesses potential problems in seven categories: medical, employment/support, alcohol, other drug use, legal,

family/social, and psychiatric.

Screening tools

There are several different screening tools that have been validated for use with adolescents, such as the CRAFFT, and with adults, such as CAGE, AUDIT and DALI. Laboratory tests to detect alcohol and other drugs in urine and blood may be useful during the assessment process to confirm a diagnosis, to establish a baseline, and later, to monitorprogress. However, since these tests measure recent substance use rather than chronic useor dependence, they are not recommended as screening tools.

Management

Detoxification

Depending on the severity of use, and the given substance, early treatment of acute withdrawal may include medical detoxification. Of note, acute withdrawal from heavyalcohol use should be done under medical supervision to prevent a potentially deadlywithdrawal syndrome known as delirium tremens. See also Alcohol detoxification.

Therapy

Therapists often classify people with chemical dependencies as either interested or not interested in changing. About 11% of Americans with substance use disorder seek treatment, and 40–60% of those people relapse within a year. Treatments usually involveplanning for specific ways to avoid the addictive stimulus, and therapeutic interventions intended to help a client learn healthier ways to find satisfaction. Clinical leaders in recentyears have attempted to tailor intervention approaches to specific influences that affect addictive behavior, using therapeutic interviews in an effort to discover factors that led a person to embrace unhealthy, addictive sources of pleasure or relief from pain.

Treatments

From the applied behavior analysis literature and the behavioral psychology literature,

several evidence-based intervention programs have emerged, such as behavioral maritaltherapy, community reinforcement approach, cue exposure therapy, and contingency management strategies. In addition, the same author suggests that social skills training adjunctive to inpatient treatment of alcohol dependence is probably efficacious.

Medication

Medication-assisted treatment (MAT) refers to the combination of behavioral interventionsand medications to treat substance use disorders. Certain medications can be useful in treating severe substance use disorders. In the United States five medications are approvedto treat alcohol and opioid use disorders. There are no approved medications for cocaine, methamphetamine, or other substance use disorders as of 2002.

Medications, such as methadone and disulfiram, can be used as part of broader treatmentplans to help a patient function comfortably without illicit opioids or alcohol. Medications can be used in treatment to lessen withdrawal symptoms. Evidence has demonstrated theefficacy of MAT at reducing illicit drug use and overdose deaths, improving retention in treatment, and reducing HIV transmission.

Epidemiology

The disability-adjusted life year, a measure of overall disease burden (number of years lost due to ill-health, disability or early death), from drug use disorders per 100,000 inhabitants in2004.

Rates of substance use disorders vary by nation and by substance, but the overall prevalence is high. On a global level, men are affected at a much higher rate than women.Younger individuals are also more likely to be affected than older adults.

In 2020, 14.5% of Americans aged 12 or older had a SUD in the past year. Rates of alcohol use disorder in the past year were just over 5%. Approximately 3% of people aged 12 or olderhad an illicit drug use disorder. The highest rates of illicit drug use disorder were among those aged 18 to 25 years old, at roughly 7%.

There were over 72,000 deaths from drug overdose in the United States in 2017, which is athreefold increase from 2002. However the CDC calculates alcohol overdose deaths separately; thus, this 72,000 number does not include the 2,366 alcohol overdose deaths in

2017. Overdose fatalities from synthetic opioids, which typically involve fentanyl, have risen sharply in the past several years to contribute to nearly 30,000 deaths per year. Death rates from synthetic opioids like fentanyl have increased 22-fold in the period from 2002 to 2017. Heroin and other natural and semi-synthetic opioids combined to contribute to roughly 31,000 overdose fatalities. Cocaine contributed to roughly 15,000 overdose deaths, while methamphetamine and benzodiazepines each contributed to roughly 11,000 deaths. Of note,the mortality from each individual drug listed above cannot be summed because many of these deaths involved combinations of drugs, such as overdosing on a combination of cocaine and an opioid.

Deaths from alcohol consumption account for the loss of over 88,000 lives per year. Tobacco remains the leading cause of preventable death, responsible for greater than 480,000 deaths in the United States each year. These harms are significant financially withtotal costs of more than $420 billion annually and more than $120 billion in healthcare.

According to Statistics Canada (2018), approximately one in five Canadians aged 15 years and older experience a substance use disorder in their lifetime. In Ontario specifically, the disease burden of mental illness and addiction is 1.5 times higher than all cancers togetherand over 7 times that of all infectious diseases. Across the country, the ethnic group that isstatistically the most impacted by substance use disorders compared to the general population are the Indigenous peoples of Canada. In a 2019 Canadian study, it was found that Indigenous participants experienced greater substance-related problems than
non-Indigenous participants.

Statistics Canada's Canadian Community Health Survey (2012) shows that alcohol was themost common substance for which Canadians met the criteria for abuse or dependence.
Surveys on Indigenous people in British Columbia show that around 75% of residents on reserve feel alcohol use is a problem in their community and 25% report they have a problemwith alcohol use themselves. However, only 66% of First Nations adults living on reserve drink alcohol compared to 76% of the general population. Further, in an Ontario study on mental health and substance use among Indigenous people, 19% reported the use of cocaine and opiates, higher than the 13% of Canadians in the general population that reported using opioids.

Historical and ongoing colonial practices continue to impact the health of Indigenous Australians, with Indigenous populations being more susceptible to substance use and related harms. For example, alcohol and tobacco are the predominant substances used in Australia. Although tobacco smoking is declining in Australia, it remains disproportionately high in Indigenous Australians with 45% aged 18 and over being smokers, compared to 16%among non-Indigenous Australians in 2014–2015. As for alcohol, while proportionately more Indigenous people refrain from drinking than non-Indigenous people, Indigenous people who do consume alcohol are more likely to do so at high-risk levels. About 19% of Indigenous Australians qualified for risky alcohol consumption (defined as 11 or more standard drinks at least once a month), which is 2.8 times the rate that their non-Indigenous counterparts consumed the same level of alcohol.

However, while alcohol and tobacco usage are declining, use of other substances, such as cannabis and opiates, is increasing in Australia. Cannabis is the most widely used illicit drugin Australia, with cannabis usage being 1.9 times higher than non-Indigenous Australians.
Prescription opioids have seen the greatest increase in usage in Australia, although use is still lower that in the US. In 2016, Indigenous persons were 2.3 times more likely to misuse pharmaceutical drugs than non-Indigenous people.

Alcoholism

Alcoholism is, broadly, any drinking of alcohol that results in significant mental or physical health problems. Because there is disagreement on the definition of the word alcoholism, it is not a recognized diagnostic entity. Predominant diagnostic classifications are alcohol usedisorder (DSM-5) or alcohol dependence (ICD-11); these are defined in their respective sources.

Symptoms

Drinking large amounts of alcohol over a long period, difficulty cutting down, acquiring and drinking alcohol taking up a lot of time, usage resulting in problems, withdrawal occurring when stopping

Complications

Mental illness, delirium, Wernicke–Korsakoff syndrome, irregular heartbeat, cirrhosis of the liver, cancer, fetal alcohol spectrum disorder, suicide.

Treatment

Alcohol cessation typically with benzodiazepines, counselling, acamprosate, disulfiram,naltrexone.

Excessive alcohol use can damage all organ systems, but it particularly affects the brain, heart, liver, pancreas and immune system. Alcoholism can result in mental illness, delirium tremens, Wernicke–Korsakoff syndrome, irregular heartbeat, an impaired immune response,liver cirrhosis and increased cancer risk. Drinking during pregnancy can result in fetal alcohol spectrum disorders. Women are generally more sensitive than men to the harmful effects of alcohol, primarily due to their smaller body weight, lower capacity to metabolize alcohol, and higher proportion of body fat. In a small number of individuals, prolonged, severe alcohol misuse ultimately leads to cognitive impairment and frank dementia.

Environment and genetics are two factors in the risk of development of alcoholism, with

about half the risk attributed to each. Stress and associated disorders, including anxiety, arekey factors in the development of alcoholism as alcohol consumption can temporarily reduce dysphoria. Someone with a parent or sibling with an alcohol use disorder is three to four times more likely to develop an alcohol use disorder themselves, but only a minority of them do. Environmental factors include social, cultural and behavioral influences. High stress levels and anxiety, as well as alcohol's inexpensive cost and easy accessibility, increase the risk. People may continue to drink partly to prevent or improve symptoms of withdrawal. After a person stops drinking alcohol, they may experience a low level of withdrawal lasting for months. Medically, alcoholism is considered both a physical and mental illness. Questionnaires are usually used to detect possible alcoholism. Further information is then collected to confirm the diagnosis.

Prevention of alcoholism may be attempted by reducing the experience of stress and anxietyin individuals. It can be attempted by regulating and limiting the sale of alcohol (particularly to minors), taxing alcohol to increase its cost, and providing education and treatment.

Treatment of alcoholism may take several forms. Due to medical problems that can occur during withdrawal, alcohol cessation should be controlled carefully. One common method involves the use of benzodiazepine medications, such as diazepam. These can be taken while admitted to a health care institution or individually. The medications acamprosate, disulfiram or naltrexone may also be used to help prevent further drinking. Mental illness orother addictions may complicate treatment. Various forms of individual or group therapy orsupport groups are used to attempt to keep a person from returning to alcoholism. One support group is Alcoholics Anonymous.

The World Health Organization has estimated that as of 2016, there were 380 million peoplewith alcoholism worldwide (5.1% of the population over 15 years of age). As of 2015 in the United States, about 17 million (7%) of adults and 0.7 million (2.8%) of those age 12 to 17 years of age are affected. Alcoholism is most common among males and young adults.
Geographically, it is least common in Africa (1.1% of the population) and has the highest rates in Eastern Europe (11%). Alcoholism directly resulted in 139,000 deaths in 2013, up from 112,000 deaths in 1990. A total of 3.3 million deaths (5.9% of all deaths) are believed tobe due to alcohol. Alcoholism reduces a person's life expectancy by approximately ten years. Many terms, some slurs and others informal, have been used to refer to people affected by alcoholism; the expressions include tippler, drunkard, dipsomaniac and souse. In 1979, the World Health Organization discouraged the use of "alcoholism" due to its inexact meaning, preferring "alcohol dependence syndrome".

Signs and symptoms

The risk of alcohol dependence begins at low levels of drinking and increases directly withboth the volume of alcohol consumed and a pattern of drinking larger amounts on an occasion, to the point of intoxication, which is sometimes called "binge drinking".

Long-term misuse

Some of the possible long-term effects of ethanol an individual may develop. Additionally, inpregnant women, alcohol can cause fetal alcohol syndrome.

Alcoholism is characterised by an increased tolerance to alcohol – which means that an individual can consume more alcohol – and physical dependence on alcohol, which makesit hard for an individual to control their consumption. The physical dependency caused by alcohol can lead to an affected individual having a very strong urge to drink alcohol. These characteristics play a role in decreasing the ability to stop drinking of an individual with an alcohol use disorder. Alcoholism can have adverse effects on mental health, contributing topsychiatric disorders and increasing the risk of suicide. A depressed mood is a common symptom of heavy alcohol drinkers.

Warning signs

Warning signs of alcoholism include the consumption of increasing amounts of alcohol andfrequent intoxication, preoccupation with drinking to the exclusion of other activities, promises to quit drinking and failure to keep those promises, the inability to remember whatwas said or done while drinking (colloquially known as "blackouts"), personality changes associated with drinking, denial or the making of excuses for drinking, the refusal to admit excessive drinking, dysfunction or other problems at work or school, the loss of interest in personal appearance or hygiene, marital and economic problems, and the complaint of poorhealth, with loss of appetite, respiratory infections, or increased anxiety.

Physical

Short-term effects

Drinking enough to cause a blood alcohol concentration (BAC) of 0.03–0.12% typically causes an overall improvement in mood and possible euphoria (a "happy" feeling), increased self-confidence and sociability, decreased anxiety, a flushed, red appearance in

the face and impaired judgment and fine muscle coordination. A BAC of 0.09% to 0.25% causes lethargy, sedation, balance problems and blurred vision. A BAC of 0.18% to 0.30% causes profound confusion, impaired speech (e.g. slurred speech), staggering, dizziness and vomiting. A BAC from 0.25% to 0.40% causes stupor, unconsciousness, anterograde amnesia, vomiting (death may occur due to inhalation of vomit while unconscious) and respiratory depression (potentially life-threatening). A BAC from 0.35% to 0.80% causes a coma (unconsciousness), life-threatening respiratory depression and possibly fatal alcohol poisoning. With all alcoholic beverages, drinking while driving, operating an aircraft or heavymachinery increases the risk of an accident; many countries have penalties for drunk driving.

Long-term effects

Having more than one drink a day for women or two drinks for men increases the risk of heart disease, high blood pressure, atrial fibrillation, and stroke. Risk is greater with binge drinking, which may also result in violence or accidents. About 3.3 million deaths (5.9% of alldeaths) are believed to be due to alcohol each year. Alcoholism reduces a person's life expectancy by around ten years and alcohol use is the third leading cause of early death in the United States. Long-term alcohol misuse can cause a number of physical symptoms, including cirrhosis of the liver, pancreatitis, epilepsy, polyneuropathy, alcoholic dementia, heart disease, nutritional deficiencies, peptic ulcers and sexual dysfunction, and can eventually be fatal. Other physical effects include an increased risk of developing cardiovascular disease, malabsorption, alcoholic liver disease, and several cancers. Damage to the central nervous system and peripheral nervous system can occur from sustained alcohol consumption. A wide range of immunologic defects can result and theremay be a generalized skeletal fragility, in addition to a recognized tendency to accidental injury, resulting a propensity to bone fractures.

Women develop long-term complications of alcohol dependence more rapidly than do men. Additionally, women have a higher mortality rate from alcoholism than men. Examples of long-term complications include brain, heart, and liver damage and an increased risk of breast cancer. Additionally, heavy drinking over time has been found to have a negative effect on reproductive functioning in women. This results in reproductive dysfunction such as anovulation, decreased ovarian mass, problems or irregularity of the menstrual cycle, andearly menopause. Alcoholic ketoacidosis can occur in individuals who chronically misuse alcohol and have a recent history of binge drinking. The amount of alcohol that can be biologically processed and its effects differ between sexes. Equal dosages of alcohol consumed by men and women generally result in women having higher blood alcohol concentrations (BACs), since women generally have a lower weight and higher percentage of body fat and therefore a lower volume of distribution for alcohol than men.

Psychiatric

Long-term misuse of alcohol can cause a wide range of mental health problems. Severe cognitive problems are common; approximately 10 percent of all dementia cases are relatedto alcohol consumption, making it the second leading cause of dementia. Excessive alcoholuse causes damage to brain function, and psychological health can be increasingly affectedover time. Social skills are significantly impaired in people with alcoholism due to the neurotoxic effects of alcohol on the brain, especially the prefrontal cortex area of the brain. The social skills that are impaired by alcohol use disorder include impairments in perceivingfacial emotions, prosody, perception problems, and theory of mind deficits; the ability to understand humor is also impaired in people who misuse alcohol. Psychiatric disorders are common in people with alcohol use disorders, with as many as 25 percent also having severe psychiatric disturbances. The most prevalent psychiatric symptoms are anxiety and depression disorders. Psychiatric symptoms usually initially worsen during alcohol withdrawal, but typically improve or disappear with continued abstinence. Psychosis, confusion, and organic brain syndrome may be caused by alcohol misuse, which can lead toa misdiagnosis such as schizophrenia. Panic disorder can develop or worsen as a direct result of long-term alcohol misuse.

The co-occurrence of major depressive disorder and alcoholism is well documented. Amongthose with comorbid occurrences, a distinction is commonly made between depressive episodes that remit with alcohol abstinence ("substance-induced"), and depressive episodes that are primary and do not remit with abstinence ("independent" episodes).
Additional use of other drugs may increase the risk of depression. Psychiatric disordersdiffer depending on gender. Women who have alcohol-use disorders often have a co-occurring psychiatric diagnosis such as major depression, anxiety, panic disorder, bulimia, post-traumatic stress disorder (PTSD), or borderline personality disorder. Men withalcohol-use disorders more often have a co-occurring diagnosis of narcissistic or antisocialpersonality disorder, bipolar disorder, schizophrenia, impulse disorders or attention deficit/hyperactivity disorder (ADHD). Women with alcohol use disorder are more likely to experience physical or sexual assault, abuse, and domestic violence than women in the general population, which can lead to higher instances of psychiatric disorders and greater dependence on alcohol.

Social effects

Serious social problems arise from alcohol use disorder; these dilemmas are caused by thepathological changes in the brain and the intoxicating effects of alcohol. Alcohol misuse is associated with an increased risk of committing criminal offences, including child abuse, domestic violence, rape, burglary and assault. Alcoholism is associated with loss of employment, which can lead to financial problems. Drinking at inappropriate times and behavior caused by reduced judgment can lead to legal consequences, such as criminal charges for drunk driving or public disorder, or civil penalties for tortious behavior. An alcoholic's behavior and mental impairment while drunk can profoundly affect those surrounding him and lead to isolation from family and friends. This isolation can lead to marital conflict and divorce, or contribute to domestic violence. Alcoholism can also lead tochild neglect, with subsequent lasting damage to the emotional development of children ofpeople with alcohol use disorders. For this reason, children of people with alcohol use disorders can develop a number of emotional problems. For example, they can become afraid of their parents, because of their unstable mood behaviors. They may develop shameover their inadequacy to liberate their parents

from alcoholism and, as a result of this, may develop self-image problems, which can lead to depression.

Alcohol withdrawal

As with similar substances with a sedative-hypnotic mechanism, such as barbiturates and benzodiazepines, withdrawal from alcohol dependence can be fatal if it is not properly managed. Alcohol's primary effect is the increase in stimulation of the GABAA receptor, promoting central nervous system depression. With repeated heavy consumption of alcohol,these receptors are desensitized and reduced in number, resulting in tolerance and physicaldependence. When alcohol consumption is stopped too abruptly, the person's nervous system experiences uncontrolled synapse firing. This can result in symptoms that include anxiety, life-threatening seizures, delirium tremens, hallucinations, shakes and possible heart failure. Other neurotransmitter systems are also involved, especially dopamine, NMDAand glutamate.

Severe acute withdrawal symptoms such as delirium tremens and seizures rarely occur after 1-week post cessation of alcohol. The acute withdrawal phase can be defined as lasting between one and three weeks. In the period of 3–6 weeks following cessation, anxiety, depression, fatigue, and sleep disturbance are common. Similar post-acute withdrawal symptoms have also been observed in animal models of alcohol dependenceand withdrawal.

A kindling effect also occurs in people with alcohol use disorders whereby each subsequent withdrawal syndrome is more severe than the previous withdrawal episode; this is due to neuroadaptations which occur as a result of periods of abstinence followed by re-exposure to alcohol. Individuals who have had multiple withdrawal episodes are more likely to developseizures and experience more severe anxiety during withdrawal from alcohol than alcohol-dependent individuals without a history of past alcohol withdrawal episodes. The kindling effect leads to persistent functional changes in brain neural circuits as well as to gene expression. Kindling also results in the intensification of psychological symptoms of alcohol withdrawal. There are decision tools and questionnaires that help guide physicians in evaluating alcohol withdrawal. For example, the CIWA-Ar objectifies alcohol withdrawal symptoms in order to guide therapy decisions which allows for an efficient interview while at the same time retaining clinical usefulness, validity, and reliability, ensuring proper care forwithdrawal patients, who can be in danger of death.

Causes

A complex combination of genetic and environmental factors influences the risk of the development of alcoholism. Genes that influence the metabolism of alcohol also influence the risk of alcoholism, as can a family history of alcoholism. There is compelling evidence that alcohol use at an early age may influence the expression of genes which increase the risk of alcohol dependence. These genetic and epigenetic results are regarded as consistentwith large longitudinal population studies finding that the younger the age of drinking onset,the greater the prevalence of lifetime alcohol dependence.

Severe childhood trauma is also associated with a general increase in the risk of drug dependency. Lack of peer and family support is associated with an increased risk of alcoholism developing. Genetics and adolescence are associated with an increased sensitivity to the neurotoxic effects of chronic alcohol misuse. Cortical degeneration due tothe neurotoxic effects increases impulsive behaviour, which may contribute to the development, persistence and severity of alcohol use disorders. There is evidence that withabstinence, there is a reversal of at least some of the alcohol induced central nervous system damage. The use of cannabis was associated with later problems with alcohol use.Alcohol use was associated with an increased probability of later use of tobacco and illegaldrugs such as cannabis.

Availability

Alcohol is the most available, widely consumed, and widely misused recreational drug. Beeralone is the world's most widely consumed alcoholic beverage; it is the third-most popular drink overall, after water and tea. It is thought by some to be the oldest fermented beverage.

Gender difference

Based on combined data in the US from SAMHSA's 2004–2005 National Surveys on Drug Use & Health, the rate of past-year alcohol dependence or misuse among persons aged 12or older varied by level of alcohol use: 44.7% of past month heavy drinkers, 18.5% binge drinkers, 3.8% past month non-binge drinkers, and 1.3% of those who did not drink alcoholin the past month met the criteria for alcohol dependence or misuse in the past year. Maleshad higher rates than females for all measures of drinking in the past month: any alcohol use (57.5% vs. 45%), binge drinking (30.8% vs. 15.1%), and heavy alcohol use (10.5% vs.
3.3%), and males were twice as likely as females to have met the criteria for alcohol dependence or misuse in the past year (10.5% vs. 5.1%).

Genetic variation

There are genetic variations that affect the risk for alcoholism. Some of these variations aremore common in individuals with ancestry from certain areas, for example Africa, East Asia,the Middle East and Europe. The variants with strongest effect are in genes that encode themain enzymes of alcohol metabolism, ADH1B and ALDH2. These genetic factors influence the rate at which alcohol and its initial metabolic product, acetaldehyde, are metabolized.
They are found at different frequencies in people from different parts of the world. The alcohol dehydrogenase allele ADH1B2 causes a more rapid metabolism of alcohol to acetaldehyde, and reduces risk for alcoholism; it is most common in individuals from East Asia and the Middle East. The alcohol dehydrogenase allele ADH1B3 also causes a more rapid metabolism of alcohol. The allele ADH1B3 is only found in some individuals of African descent and certain Native American tribes. African Americans and Native Americans with this allele have a reduced risk of developing alcoholism. Native Americans, however, have a significantly higher rate of alcoholism than average; risk factors such as cultural environmental effects (e.g. trauma) have been proposed to explain the higher rates. The aldehyde dehydrogenase allele ALDH22 greatly reduces the rate at which acetaldehyde, the initial product of alcohol metabolism, is removed by conversion to acetate; it greatly

reducesthe risk for alcoholism.

A genome-wide association study (GWAS) of more than 100,000 human individuals identified variants of the gene KLB, which encodes the transmembrane protein β-Klotho, as highly associated with alcohol consumption. The protein β-Klotho is an essential element incell surface receptors for hormones involved in modulation of appetites for simple sugars and alcohol. Several large GWAS have found differences in the genetics of alcohol consumption and alcohol dependence, although the two are to some degree related.

DNA damage

Alcohol-induced DNA damage, when not properly repaired, may have a key role in the neurotoxicity induced by alcohol. Metabolic conversion of ethanol to acetaldehyde can occur in the brain and the neurotoxic effects of ethanol appear to be associated with acetaldehyde induced DNA damages including DNA adducts and crosslinks. In addition toacetaldehyde, alcohol metabolism produces potentially genotoxic reactive oxygen species,which have been demonstrated to cause oxidative DNA damage.

Diagnosis

Misuse, problem use, abuse, and heavy use of alcohol refer to improper use of alcohol, which may cause physical, social, or moral harm to the drinker. The Dietary Guidelines for Americans defines "moderate use" as no more than two alcoholic beverages a day for men and no more than one alcoholic beverage a day for women. The National Institute on AlcoholAbuse and Alcoholism (NIAAA) defines binge drinking as the amount of alcohol leading to a blood alcohol content (BAC) of 0.08, which, for most adults, would be reached by consumingfive drinks for men or four for women over a two-hour period. According to the NIAAA, men may be at risk for alcohol-related problems if their alcohol consumption exceeds 14 standard drinks per week or 4 drinks per day, and women may be at risk if they have more than 7 standard drinks per week or 3 drinks per day. It defines a standard drink as one
12-ounce bottle of beer, one 5-ounce glass of wine, or 1.5 ounces of distilled spirits. Despitethis risk, a 2014 report in the National Survey on Drug Use and Health found that only 10% ofeither "heavy drinkers" or "binge drinkers" defined according to the above criteria also met the criteria for alcohol dependence, while only 1.3% of non-binge drinkers met the criteria.
An inference drawn from this study is that evidence-based policy strategies and clinicalpreventive services may effectively reduce binge drinking without requiring addiction treatment in most cases.

The term alcoholism is commonly used amongst laypeople, but the word is poorly defined.Despite the imprecision inherent in the term, there have been attempts to define how the word alcoholism should be interpreted when encountered. In 1992, it was defined by the National Council on Alcoholism and Drug Dependence (NCADD) and ASAM as "a primary, chronic disease characterized by impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking." MeSH has had an entry for "alcoholism" since 1999, and references the 1992 definition.

The WHO calls alcoholism "a term of long-standing use and variable meaning", and use ofthe term was disfavored by a 1979 WHO expert committee.

In professional and research contexts, the term "alcoholism" is not currently favored, but rather alcohol abuse, alcohol dependence, or alcohol use disorder are used. Talbot (1989)observes that alcoholism in the classical disease model follows a progressive course: if aperson continues to drink, their condition will worsen. This will lead to harmful consequences in their life, physically, mentally, emotionally and socially. Johnson (1980) explores the emotional progression of the addict's response to alcohol. He looks at this infour phases. The first two are considered "normal" drinking and the last two are viewed as"typical" alcoholic drinking. Johnson's four phases consist of:Learning the mood swing. A person is introduced to alcohol (in some cultures this can happen at a relatively young age), and the person enjoys the happy feeling it produces. Atthis stage, there is no emotional cost.

Seeking the mood swing. A person will drink to regain that feeling of euphoria experienced inphase 1; the drinking will increase as more intoxication is required to achieve the same effect. Again at this stage, there are no significant consequences.

At the third stage there are physical and social consequences, i.e., hangovers, family problems, work problems, etc. A person will continue to drink excessively, disregarding theproblems.

The fourth stage can be detrimental, as Johnson cites it as a risk for premature death. As a person now drinks to feel normal, they block out the feelings of overwhelming guilt, remorse,anxiety, and shame they experience when sober.

DSM and ICD

In the United States, the Diagnostic and Statistical Manual of Mental Disorders (DSM) is themost common diagnostic guide for substance use disorders, whereas most countries use the International Classification of Diseases (ICD) for diagnostic (and other) purposes. The two manuals use similar but not identical nomenclature to classify alcohol problems.

Alcohol dependence - alcohol abuse combined with tolerance, withdrawal, and an uncontrollable drive to drink. The term "alcoholism" was split into "alcohol abuse" and "alcohol dependence" in 1980's DSM-III, and in 1987's DSM-III-R behavioral symptoms weremoved from "abuse" to "dependence". Some scholars suggested that DSM-5 merge alcohol abuse and alcohol dependence into a single new entry, named "alcohol-use disorder".

DSM-5 Alcohol use disorder "A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by [two or more symptoms out of a total of12], occurring within a 12-month period ....."

ICD-10 Alcohol harmful use, or Alcohol dependence syndrome

Definitions are similar to that of the DSM-IV. The World Health Organization uses theterm "alcohol dependence syndrome" rather than alcoholism. The concept of "harmful use" (as opposed to "abuse") was introduced in 1992's ICD-10 to minimize underreporting of damage in the absence of dependence. The term "alcoholism" was removed from ICD between ICD-8/ICDA-8 and ICD-9.

ICD-11 Episode of harmful use of alcohol, Harmful pattern of use of alcohol, or Alcoholdependence

Episode of harmful use of alcohol - "A single episode of use of alcohol that has caused damage to a person's physical or mental health or has resulted in behaviour leading to harmto the health of others ....."

Harmful pattern of use of alcohol - "A pattern of alcohol use that has caused damage to a person's physical or mental health or has resulted in behaviour leading to harm to the healthof others ....."

Alcohol dependence - "Alcohol dependence is a disorder of regulation of alcohol use arisingfrom repeated or continuous use of alcohol. The characteristic feature is a strong internal drive to use alcohol.....The features of dependence are usually evident over a period of at least 12 months but the diagnosis may be made if alcohol use is continuous (daily or almostdaily) for at least 1 month."

Social barriers

Attitudes and social stereotypes can create barriers to the detection and treatment of alcohol use disorder. This is more of a barrier for women than men.[why?] Fear of stigmatization may lead women to deny that they have a medical condition, to hide their drinking, and to drink alone. This pattern, in turn, leads family, physicians, and others to be less likely to suspect that a woman they know has alcohol use disorder. In contrast, reducedfear of stigma may lead men to admit that they are having a medical condition, to display their drinking publicly, and to drink in groups. This pattern, in turn, leads family, physicians, and others to be more likely to suspect that a man they know is someone with an alcohol use disorder.

Screening

Screening is recommended among those over the age of 18. Several tools may be used to detect a loss of control of alcohol use. These tools are mostly self-reports in questionnaire form. Another common theme is a score or tally that sums up the general severity of alcoholuse.

The CAGE questionnaire, named for its four questions, is one such example that may beused to screen patients quickly in a doctor's office.

Two "yes" responses indicate that the respondent should be investigated further.

The questionnaire asks the following questions:

Have you ever felt you needed to Cut down on your drinking?Have

people Annoyed you by criticizing your drinking?

Have you ever felt Guilty about drinking?

Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or

to get rid of a hangover?

The CAGE questionnaire has demonstrated a high effectiveness in detecting alcohol-relatedproblems; however, it has limitations in people with less severe alcohol-related problems, white women and college students.

Other tests are sometimes used for the detection of alcohol dependence, such as the Alcohol Dependence Data Questionnaire, which is a more sensitive diagnostic test than the CAGE questionnaire. It helps distinguish a diagnosis of alcohol dependence from one of heavy alcohol use. The Michigan Alcohol Screening Test (MAST) is a screening tool for alcoholism widely used by courts to determine the appropriate sentencing for people convicted of alcohol-related offenses, driving under the influence being the most common. The Alcohol Use Disorders Identification Test (AUDIT), a screening questionnaire developed by the World Health Organization, is unique in that it has been validated in six countries and is used internationally. Like the CAGE questionnaire, it uses a simple set of questions – a high score earning a deeper investigation. The Paddington Alcohol Test (PAT) was designedto screen for alcohol-related problems amongst those attending Accident and Emergency departments. It concords well with the AUDIT questionnaire but is administered in a fifth of the time.

Urine and blood tests

There are reliable tests for the actual use of alcohol, one common test being that of bloodalcohol content (BAC). These tests do not differentiate people with alcohol use disordersfrom people without; however, long-term heavy drinking does have a few recognizable effects on the body, including:

Macrocytosis (enlarged MCV)

Elevated GGT

Moderate elevation of AST and ALT and an AST: ALT ratio of 2:1

High carbohydrate deficient transferrin (CDT)

With regard to alcoholism, BAC is useful to judge alcohol tolerance, which in turn is a sign of alcoholism. Electrolyte and acid-base abnormalities including hypokalemia, hypomagnesemia, hyponatremia, hyperuricemia, metabolic acidosis, and respiratory alkalosis are common in people with alcohol use disorders.

However, none of these blood tests for biological markers is as sensitive as screeningquestionnaires.

Prevention

The World Health Organization, the European Union and other regional bodies, national governments and parliaments have formed alcohol policies in order to reduce the harm of alcoholism. Increasing the age at which licit drugs that are susceptible to misuse, such as alcohol, can be purchased, and banning or restricting alcohol beverage advertising are common methods to reduce alcohol use among adolescents and young adults in particular. Credible, evidence-based educational campaigns in the mass media about the consequences of alcohol misuse have been recommended. Guidelines for parents to preventalcohol misuse amongst adolescents, and for helping young people with mental health problems have also been suggested.

Management

Treatments are varied because there are multiple perspectives of alcoholism. Those who approach alcoholism as a medical condition or disease recommend differing treatments from, for instance, those who approach the condition as one of social choice. Most treatments focus on helping people discontinue their alcohol intake, followed up with life training and/or social support to help them resist a return to alcohol use. Since alcoholism involves multiple factors which encourage a person to continue drinking, they must all be addressed to successfully prevent a relapse. An example of this kind of treatment is detoxification followed by a combination of supportive therapy, attendance at self-help groups, and ongoing development of coping mechanisms. Much of the treatment community for alcoholism supports an abstinence-based zero tolerance approach; however,some prefer a harm-reduction approach.

Cessation of alcohol intake

Medical treatment for alcohol detoxification usually involves administration of a benzodiazepine, in order to ameliorate alcohol withdrawal syndrome's adverse impact. The addition of phenobarbital improves outcomes if benzodiazepine administration lacks the usually efficacy, and phenobarbital alone might be an effective treatment. Propofol also might enhance treatment for individuals showing limited therapeutic response to a benzodiazepine. Individuals who are only at risk of mild to moderate withdrawal symptoms can be treated as outpatients. Individuals at risk of a severe withdrawal syndrome as well asthose who have significant or acute comorbid conditions can be treated as inpatients. Directtreatment can be followed by a treatment program for alcohol dependence or alcohol use disorder to attempt to reduce the risk of relapse. Experiences following alcohol withdrawal, such as depressed mood and anxiety, can take weeks or months to abate while other symptoms persist longer due to persisting neuroadaptations.

Psychological

Various forms of group therapy or psychotherapy are often utilized to encourage and support abstinence from alcohol, or to reduce alcohol consumption to levels that are not associated with

adverse outcomes. Mutual-aid group-counseling is an approach used to facilitate relapse prevention.[8] Alcoholics Anonymous was one of the earliest organizationsformed to provide mutual peer support and it is still the largest. Others include LifeRing Secular Recovery, SMART Recovery, Women for Sobriety, and Secular Organizations for Sobriety.

Manualized Twelve Step Facilitation (TSF) interventions (i.e. therapy which encouragesactive, long-term Alcoholics Anonymous participation) for Alcohol Use Disorder lead to higher abstinence rates, compared to other clinical interventions and to wait-list controlgroups.

Moderate drinking

Rationing and moderation programs such as Moderation Management and DrinkWise do not mandate complete abstinence. While most people with alcohol use disorders are unable to limit their drinking in this way, some return to moderate drinking. A 2002 US study by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) showed that 17.7 percent of individuals diagnosed as alcohol dependent more than one year prior returned to low-risk drinking. This group, however, showed fewer initial symptoms of dependency.

A follow-up study, using the same subjects that were judged to be in remission in 2001–2002, examined the rates of return to problem drinking in 2004–2005. The study found abstinence from alcohol was the most stable form of remission for recovering alcoholics. There was also a 1973 study showing chronic alcoholics drinking moderately again, but a 1982 follow-up showed that 95% of subjects were not able to moderately drinkover the long term. Another study was a long-term (60 year) follow-up of two groups of alcoholic men which concluded that "return to controlled drinking rarely persisted for muchmore than a decade without relapse or evolution into abstinence." Internet based measuresappear to be useful at least in the short term.

Medications

In the United States there are four approved medications for alcoholism: acamprosate, twomethods of using naltrexone and disulfiram. Acamprosate may stabilise the brain chemistry that is altered due to alcohol dependence viaantagonising the actions of glutamate, a neurotransmitter which is hyperactive in the
post-withdrawal phase. By reducing excessive NMDA activity which occurs at the onset ofalcohol withdrawal, acamprosate can reduce or prevent alcohol withdrawal related neurotoxicity. Acamprosate reduces the risk of relapse amongst alcohol-dependent persons.

Naltrexone is a competitive antagonist for opioid receptors, effectively blocking the effects of endorphins and opioids. Naltrexone is used to decrease cravings for alcohol and encourage abstinence. Alcohol causes the body to release endorphins, which in turn release dopamine and activate the reward pathways; hence in the body Naltrexone reduces the pleasurable effects from consuming alcohol. Evidence supports a reduced risk of relapse among
alcohol-dependent persons and a decrease in excessive drinking. Nalmefene also appearseffective and works in a similar manner.

Disulfiram prevents the elimination of acetaldehyde, a chemical the body produces when breaking down ethanol. Acetaldehyde itself is the cause of many hangover symptoms fromalcohol use. The

overall effect is discomfort when alcohol is ingested: an extremely fast-acting and long-lasting, uncomfortable hangover.

Several other drugs are also used and many are under investigation.

Benzodiazepines, while useful in the management of acute alcohol withdrawal, if used long-term can cause a worse outcome in alcoholism. Alcoholics on chronic benzodiazepines have a lower rate of achieving abstinence from alcohol than those nottaking benzodiazepines. This class of drugs is commonly prescribed to alcoholics for insomnia or anxiety management. Initiating prescriptions of benzodiazepines or sedative-hypnotics in individuals in recovery has a high rate of relapse with one author reporting more than a quarter of people relapsed after being prescribed sedative-hypnotics.Those who are long-term users of benzodiazepines should not be withdrawn rapidly, as severe anxiety and panic may develop, which are known risk factors for alcohol use disorderrelapse. Taper regimes of 6–12 months have been found to be the most successful, with reduced intensity of withdrawal.

Calcium carbimide works in the same way as disulfiram; it has an advantage in that the occasional adverse effects of disulfiram, hepatotoxicity and drowsiness, do not occur withcalcium carbimide.

Ondansetron and topiramate are supported by tentative evidence in people with certain genetics. Evidence for ondansetron is more in those who have just begun having problemswith alcohol. Topiramate is a derivative of the naturally occurring sugar monosaccharide D-fructose. Review articles characterize topiramate as showing "encouraging", "promising", "efficacious", and "insufficient" evidence in the treatment of alcohol use disorders.

Evidence does not support the use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), antipsychotics, or gabapentin.

Research

Topiramate, a derivative of the naturally occurring sugar monosaccharide D-fructose, hasbeen found effective in helping alcoholics quit or cut back on the amount they drink.
Evidence suggests that topiramate antagonizes excitatory glutamate receptors, inhibits dopamine release, and enhances inhibitory gamma-aminobutyric acid function. A 2008 review of the effectiveness of topiramate concluded that the results of published trials arepromising, however as of 2008, data was insufficient to support using topiramate in conjunction with brief weekly compliance counseling as a first-line agent for alcohol dependence. A 2010 review found that topiramate may be superior to existing alcohol pharmacotherapeutic options. Topiramate effectively reduces craving and alcohol withdrawal severity as well as improving quality-of-life-ratings.

Baclofen, a GABAB receptor agonist, is under study for the treatment of alcoholism. According to a 2017 Cochrane Systematic Review, there is insufficient evidence to determinethe effectiveness or safety for the use of baclofen for withdrawal symptoms in alcoholism.

Dual addictions and dependences

Alcoholics may also require treatment for other psychotropic drug addictions and drug dependences.

The most common dual dependence syndrome with alcohol dependence is benzodiazepine dependence, with studies showing 10–20 percent of alcohol-dependent individuals had problems of dependence and/or misuse problems of benzodiazepine drugssuch as diazepam or clonazepam. These drugs are, like alcohol, depressants.
Benzodiazepines may be used legally, if they are prescribed by doctors for anxiety problemsor other mood disorders, or they may be purchased as illegal drugs. Benzodiazepine use increases cravings for alcohol and the volume of alcohol consumed by problem drinkers.
Benzodiazepine dependency requires careful reduction in dosage to avoid benzodiazepinewithdrawal syndrome and other health consequences. Dependence on other
sedative-hypnotics such as zolpidem and zopiclone as well as opiates and illegal drugs is common in alcoholics. Alcohol itself is a sedative-hypnotic and is cross-tolerant with othersedative-hypnotics such as barbiturates, benzodiazepines and nonbenzodiazepines.
Dependence upon and withdrawal from sedative-hypnotics can be medically severe and, aswith alcohol withdrawal, there is a risk of psychosis or seizures if not properly managed.

Epidemiology

The World Health Organization estimates that as of 2016 there are 380 million people with alcoholism worldwide (5.1% of the population over 15 years of age). Substance use disorders are a major public health problem facing many countries. "The most common substance of abuse/dependence in patients presenting for treatment is alcohol." In the United Kingdom, the number of 'dependent drinkers' was calculated as over 2.8 million in 2001. About 12% of American adults have had an alcohol dependence problem at some timein their life. In the United States and Western Europe, 10 to 20 percent of men and 5 to 10 percent of women at some point in their lives will meet criteria for alcoholism. Estonia had the highest death rate from alcohol in Europe in 2015 at 8.8 per 100,000 population. In the United States, 30% of people admitted to hospital have a problem related to alcohol.

Within the medical and scientific communities, there is a broad consensus regarding alcoholism as a disease state. For example, the American Medical Association considers alcohol a drug and states that "drug addiction is a chronic, relapsing brain disease characterized by compulsive drug seeking and use despite often devastating consequences.It results from a complex interplay of biological vulnerability, environmental exposure, and developmental factors (e.g., stage of brain maturity)."
Alcoholism has a higher prevalence among men, though, in recent decades, the proportion of female alcoholics has increased.
Current evidence indicates that in both men and women, alcoholism is 50–60 percent genetically determined, leaving 40–50 percent for environmental influences. Most alcoholicsdevelop alcoholism during adolescence or young adulthood.

Prognosis

Alcoholism often reduces a person's life expectancy by around ten years. The most commoncause of death in alcoholics is from cardiovascular complications. There is a high rate of suicide in chronic alcoholics, which increases the longer a person drinks. Approximately 3–15 percent of alcoholics commit suicide, and research has found that over 50 percent of all suicides are associated with alcohol

or drug dependence. This is believed to be due to alcohol causing physiological distortion of brain chemistry, as well as social isolation.
Suicide is also very common in adolescent alcohol abusers, with 25 percent of suicides in adolescents being related to alcohol abuse. Among those with alcohol dependence after oneyear, some met the criteria for low-risk drinking, even though only 25.5 percent of the group received any treatment, with the breakdown as follows: 25 percent were found to be still dependent, 27.3 percent were in partial remission (some symptoms persist), 11.8 percent asymptomatic drinkers (consumption increases chances of relapse) and 35.9 percent were fully recovered – made up of 17.7 percent low-risk drinkers plus 18.2 percent abstainers. In contrast, however, the results of a long-term (60-year) follow-up of two groups of alcoholic men indicated that "return to controlled drinking rarely persisted for much more than a

decade without relapse or evolution into abstinence." There was also "return-to-controlleddrinking, as reported in short-term studies, is often a mirage."

History

Historically the name "dipsomania" was coined by German physician C.W. Hufeland in 1819 before it was superseded by "alcoholism". That term now has a more specific meaning. The term "alcoholism" was first used in 1849 by the Swedish physician Magnus Huss to describethe systematic adverse effects of alcohol. Alcohol has a long history of use and misuse throughout recorded history. Biblical, Egyptian and Babylonian sources record the history of abuse and dependence on alcohol. In some ancient cultures alcohol was worshiped and in others, its misuse was condemned. Excessive alcohol misuse and drunkenness were recognized as causing social problems even thousands of years ago. However, the defining of habitual drunkenness as it was then known as and its adverse consequences were not well established medically until the 18th century. In 1647 a Greek monk named Agapios wasthe first to document that chronic alcohol misuse was associated with toxicity to the nervous system and body which resulted in a range of medical disorders such as seizures, paralysis, and internal bleeding. In the 1910s and 1920s, the effects of alcohol misuse and chronic drunkenness boosted membership of the temperance movement and led to the prohibition of alcohol in many Western countries, nationwide bans on the production, importation, transportation, and sale of alcoholic beverages that generally remained in placeuntil the late 1920s or early 1930s; these policies resulted in the decline of death rates from cirrhosis and alcoholism. In 2005, alcohol dependence and misuse was estimated to cost the US economy approximately 220 billion dollars per year, more than cancer and obesity.

Society and culture

The various health problems associated with long-term alcohol consumption are generally perceived as detrimental to society, for example, money due to lost labor-hours, medical costs due to injuries due to drunkenness and organ damage from long-term use, and secondary treatment costs, such as the costs of rehabilitation facilities and detoxification centers. Alcohol use is a major contributing factor for head injuries, motor vehicle injuries (27%), interpersonal violence (18%), suicides (18%), and epilepsy (13%). Beyond the financialcosts that alcohol consumption imposes, there are also significant social costs to both the alcoholic and their family and friends. For instance, alcohol consumption by a pregnant woman can lead to an incurable and damaging condition known as fetal

alcohol syndrome, which often results in cognitive deficits, mental health problems, an inability to live independently and an increased risk of criminal behaviour, all of which can cause emotional stress for parents and caregivers. Estimates of the economic costs of alcohol misuse, collected by the World Health Organization, vary from one to six percent of a country's GDP.One Australian estimate pegged alcohol's social costs at 24% of all drug misuse costs; a similar Canadian study concluded alcohol's share was 41%. One study quantified the cost tothe UK of all forms of alcohol misuse in 2001 as £18.5–20 billion. All economic costs in the United States in 2006 have been estimated at $223.5 billion.

The idea of hitting rock bottom refers to an experience of stress that is attributed to alcohol misuse. There is no single definition for this idea, and people may identify their own lowest points in terms of lost jobs, lost relationships, health problems, legal problems, or other consequences of alcohol misuse. The concept is promoted by 12-step recovery groups andresearchers using the transtheoretical model of motivation for behavior change. The first use of this slang phrase in the formal medical literature appeared in a 1965 review in the British Medical Journal, which said that some men refused treatment until they "hit rock bottom", but that treatment was generally more successful for "the alcohol addict who has friends and family to support him" than for impoverished and homeless addicts.

Stereotypes of alcoholics are often found in fiction and popular culture. The "town drunk" is a stock character in Western popular culture. Stereotypes of drunkenness may be based on racism or xenophobia, as in the fictional depiction of the Irish as heavy drinkers. Studies by social psychologists Stivers and Greeley attempt to document the perceived prevalence of high alcohol consumption amongst the Irish in America. Alcohol consumption is relatively similar between many European cultures, the United States, and Australia. In Asian countriesthat have a high gross domestic product, there is heightened drinking compared to other Asian countries, but it is nowhere near as high as it is in other countries like the United States. It is also inversely seen, with countries that have very low gross domestic product showing high alcohol consumption. In a study done on Korean immigrants in Canada, they reported alcohol was even an integral part of their meal, and is the only time solo drinking should occur. They also believe alcohol is necessary at any social event as it helps conversations start.

Peyote, a psychoactive agent, has even shown promise in treating alcoholism. Alcohol hadactually replaced peyote as Native Americans' psychoactive agent of choice in rituals when peyote was outlawed.

Cannabis

Cannabis, also known as marijuana among other names, is a psychoactive drug from the Cannabis plant. Native to Central and South Asia, the cannabis plant has been used as a drug for both recreational and entheogenic purposes and in various traditional medicines forcenturies.

Tetrahydrocannabinol (THC) is the main psychoactive component of cannabis, which is one of the 483 known compounds in the plant, including at least 65 other cannabinoids, including cannabidiol (CBD). Cannabis can be used by smoking, vaporizing, within food, or as an extract.

Cannabis has various mental and physical effects, which include euphoria, altered states of mind and sense of time, difficulty concentrating, impaired short-term memory, impaired body movement (balance and fine psychomotor control), relaxation, and an increase in appetite. Onset of effects is felt within minutes when smoked, but may take up to 90 minuteswhen eaten. The effects last for two to six hours, depending on the amount used. At high doses, mental effects can include anxiety, delusions (including ideas of reference), hallucinations, panic, paranoia, and psychosis. There is a strong relation between cannabis use and the risk of psychosis, though the direction of causality is debated. Physical effects include increased heart rate, difficulty breathing, nausea, and behavioral problems in children whose mothers used cannabis during pregnancy; short-term side effects may also include dry mouth and red eyes. Long-term adverse effects may include addiction, decreased mental ability in those who started regular use as adolescents, chronic coughing,susceptibility to respiratory infections, and cannabinoid hyperemesis syndrome.

Cannabis is mostly used recreationally or as a medicinal drug, although it may also be used for spiritual purposes. In 2013, between 128 and 232 million people used cannabis (2.7% to 4.9% of the global population between the ages of 15 and 65). It is the most commonly used illegal drug in the world, though it is legal in some jurisdictions, with the highest use among adults (as of 2018) in Zambia, the United States, Canada, and Nigeria.

While cannabis plants have been grown since at least the 3rd millennium BCE, evidence suggests that it was being smoked for psychoactive effects at least 2,500 years ago in the Pamir Mountains. Since the early 20th century, cannabis has been subject to legal restrictions. The possession, use, and cultivation of cannabis is illegal in most countries. In2013, Uruguay became the first country to legalize recreational use of cannabis. Other countries to do so are Canada, Georgia, Malta, Mexico, and South Africa, plus 19 states, twoterritories, and the District of Columbia in the United States (though the drug remains federally illegal).

Medical cannabis, or medical marijuana, refers to the use of cannabis to treat disease or improve symptoms; however, there is no single agreed-upon definition (e.g., cannabinoids derived from cannabis and synthetic cannabinoids are also used). The rigorous scientific study of cannabis as a medicine has been hampered by production restrictions and by the fact that it is classified as an illegal drug by many governments. There is limited evidence suggesting cannabis can be used to reduce nausea and vomiting during chemotherapy, to improve appetite in people with HIV/AIDS, or to treat chronic pain and muscle spasms. Its use for other medical applications is insufficient for drawing conclusions about safety or efficacy. There is evidence supporting the use of cannabis or its derivatives in the treatmentof chemotherapy-induced nausea and vomiting, neuropathic pain, and multiple sclerosis.
Lower levels of evidence support its use for AIDS wasting syndrome, epilepsy, rheumatoidarthritis, and glaucoma.

So far, the medical use of cannabis is legal only in a limited number of territories, including Canada,

Belgium, Australia, the Netherlands, New Zealand, Spain, and many U.S. states. Thisusage generally requires a prescription, and distribution is usually done within a framework defined by local laws.

According to DEA Chief Administrative Law Judge, Francis Young, "cannabis is one of the safest therapeutically active substances known to man." Being under the effects of cannabisis usually referred to as being "high" or "stoned." Cannabis consumption has both psychoactive and physiological effects. The "stoned" experience can vary widely, based (among other things) on the user's prior experience with cannabis, and the type of cannabis consumed. When smoking cannabis, a euphoriant effect can occur within minutes of smoking. Aside from a subjective change in perception and mood, the most common
short-term physical and neurological effects include increased heart rate, increased appetite, impairment of short-term and working memory, and psychomotor coordination.

Additional desired effects from consuming cannabis include relaxation, a general alteration of conscious perception, increased awareness of sensation, increased libido and distortionsin the perception of time and space. At higher doses, effects can include altered body image,auditory and/or visual illusions, pseudohallucinations and ataxia from selective impairmentof polysynaptic reflexes. In some cases, cannabis can lead to dissociative states such as depersonalization and derealization.

Cannabis has held sacred status in several religions and has served as an entheogen – a chemical substance used in religious, shamanic, or spiritual contexts – in the Indian subcontinent since the Vedic period. The earliest known reports regarding the sacred statusof cannabis in the Indian subcontinent come from the Atharva Veda, estimated to have been composed sometime around 1400 BCE. The Hindu god Shiva is described as a cannabisuser, known as the "Lord of bhang.

In modern culture, the spiritual use of cannabis has been spread by the disciples of theRastafari movement who use cannabis as a sacrament and as an aid to meditation.

Cannabis is consumed in many different ways, all of which involve heating to decarboxylateTHCA in the plant into THC. Common available forms are:

Smoking, which typically involves burning and inhaling vaporized cannabinoids ("smoke")from small pipes, bongs (portable versions of hookahs with a water chamber),
paper-wrapped joints or tobacco-leaf-wrapped blunts, and other items.

Vaporizer, which heats any form of cannabis to 165–190 °C (329–374 °F), causing the active ingredients to evaporate into vapor without burning the plant material (the boiling point of THC is 157 °C (315 °F) at atmospheric pressure).

Cannabis tea, which contains relatively small concentrations of THC because THC is an oil (lipophilic) and is only slightly water-soluble (with a solubility of 2.8 mg per liter). Cannabistea is made by first adding a saturated fat to hot water (e.g. cream or any milk except skim)with a small amount of cannabis.

Edibles, where cannabis is added as an ingredient to one of a variety of foods, includingbutter and baked goods. In India it is commonly made into a beverage, bhang.

Tincture of cannabis, sometimes known as green dragon, is an alcoholic cannabisconcentrate.

Capsules, typically containing cannabis oil, and other dietary supplement products, forwhich some 220 were approved in Canada in 2018.

Adverse effects

Short-term

Acute negative effects may include anxiety and panic, impaired attention and memory, an increased risk of psychotic symptoms, the inability to think clearly, and an increased risk ofaccidents. Cannabis impairs a person's driving ability, and THC was the illicit drug most frequently found in the blood of drivers who have been involved in vehicle crashes. Those with THC in their system are from three to seven times more likely to be the cause of the accident than those who had not used either cannabis or alcohol, although its role is not necessarily causal because THC stays in the bloodstream for days to weeks after intoxication.

Some immediate undesired side effects include a decrease in short-term memory, dry mouth, impaired motor skills, reddening of the eyes, dizziness, feeling tired and vomiting. Some users may experience an episode of acute psychosis, which usually abates after six hours, but in rare instances, heavy users may find the symptoms continuing for many days.

Legalization has increased the rates at which children are exposed to cannabis, particularlyfrom edibles. While the toxicity and lethality of THC in children is not known, they are at riskfor encephalopathy, hypotension, respiratory depression severe enough to require ventilation, somnolence and coma.

Fatality

Cannabis is suspected of being a potential, and under-reported, contributory factor or directcause in cases of sudden death, due to the strain it can place on the cardiovascular system. Multiple deaths have been attributed to cannabinoid hyperemesis syndrome.

A 16-month survey of Oregon and Alaska emergency departments found a report of thedeath of an adult who had been admitted for acute cannabis toxicity.

Long-term

Addiction experts in psychiatry, chemistry, pharmacology, forensic science, epidemiology,and the police and legal services engaged in delphic analysis regarding 20 popular recreational drugs.

Cannabis was ranked 11th in dependence, 17th in physical harm, and 10th in social harm.

Psychological effects

A 2015 meta-analysis found that, although a longer period of abstinence was associated with smaller magnitudes of impairment, both retrospective and prospective memory wereimpaired in cannabis users. The authors concluded that some, but not all, of the deficits associated with cannabis use were reversible. A 2012 meta-analysis found that deficits inmost domains of cognition persisted beyond the acute period of intoxication, but was notevident in studies where subjects were abstinent for more than 25 days. Few high quality studies have been performed on the long-term effects of cannabis on cognition, and the results were generally inconsistent. Furthermore, effect sizes of significant findings were generally small. One review concluded that, although most cognitive faculties were unimpaired by cannabis use, residual deficits occurred in executive functions. Impairmentsin executive functioning are most consistently found in older populations, which may reflectheavier cannabis exposure, or developmental effects associated with adolescent cannabis use. One review found three prospective cohort studies that examined the relationship between self reported cannabis use and intelligence quotient (IQ). The study following the largest number of heavy cannabis users reported that IQ declined between ages 7–13 and age 38. Poorer school performance and increased incidence of leaving school early were both associated with cannabis use, although a causal relationship was not established. Cannabis users demonstrated increased activity in task-related brain regions, consistentwith reduced processing efficiency.

A reduced quality of life is associated with heavy cannabis use, although the relationship is inconsistent and weaker than for tobacco and other substances. The direction of cause and effect, however, is unclear.

The long-term effects of cannabis are not clear. There are concerns surrounding memoryand cognition problems, risk of addiction, and the risk of schizophrenia in young people.

Although global abnormalities in white matter and grey matter are not associated with heavy cannabis use, reduced hippocampal volume is consistently found. Amygdala abnormalities are sometimes reported, although findings are inconsistent.

Cannabis use is associated with increased recruitment of task-related areas, such as the dorsolateral prefrontal cortex, which is thought to reflect compensatory activity due to reduced processing efficiency. Cannabis use is also associated with downregulation of CB1receptors. The magnitude of down regulation is associated with cumulative cannabis exposure, and is reversed after one month of abstinence. There is limited evidence that chronic cannabis use can reduce levels of glutamate metabolites in the human brain.

Cannabis dependence

About 9% of those who experiment with marijuana eventually become dependent accordingto DSM-IV (1994) criteria. A 2013 review estimates daily use is associated with a 10–20% rate of dependence. The highest risk of cannabis dependence is found in those with a history of poor academic achievement, deviant behavior in childhood and adolescence, rebelliousness, poor parental relationships, or a parental history of drug and alcohol problems. Of daily users, about 50% experience withdrawal upon cessation of use (i.e. are dependent), characterized by sleep problems, irritability, dysphoria, and craving. Cannabis withdrawal is less severe than withdrawal from alcohol.

According to DSM-V criteria, 9% of those who are exposed to cannabis develop cannabis use disorder, compared to 20% for cocaine, 23% for alcohol and 68% for nicotine. Cannabisuse disorder in the DSM-V involves a combination of DSM-IV criteria for cannabis abuse and dependence, plus the addition of craving, without the criterion related to legal troubles.

Psychiatric

At an epidemiological level, a dose–response relationship exists between cannabis use andincreased risk of psychosis and earlier onset of psychosis. Although the epidemiological association is robust, evidence to prove a causal relationship is lacking. But a biological causal pathway is plausible, especially if there is a genetic predisposition to mental illness, in which case cannabis may be a trigger.

Cannabis may also increase the risk of depression, but insufficient research has been performed to draw a conclusion. Cannabis use is associated with increased risk of anxietydisorders, although causality has not been established.

A February 2019 review found that cannabis use during adolescence was associated with an increased risk of developing depression and suicidal behavior later in life, while findingno effect on anxiety.

Reviews in 2019 found that research was insufficient to determine the safety and efficacy ofusing cannabis to treat schizophrenia, psychosis, or other mental disorders.

Physical

Heavy, long-term exposure to marijuana may have physical, mental, behavioral and socialhealth consequences. It may be "associated with diseases of the liver (particularly with co-existing hepatitis C), lungs, heart, and vasculature". A 2014 review found that while cannabis use may be less harmful than alcohol use, the recommendation to substitute it for problematic drinking was premature without further study. Various surveys conducted between 2015 and 2019 found that many users of cannabis substitute it for prescription drugs (including opioids), alcohol, and tobacco; most of those who used it in place of alcohol or tobacco either reduced

or stopped their intake of the latter substances.

Cannabinoid hyperemesis syndrome (CHS) is a severe condition seen in some chronic cannabis users where they have repeated bouts of uncontrollable vomiting for 24–48 hours.Four cases of death have been reported as a result of CHS.

A limited number of studies have examined the effects of cannabis smoking on the respiratory system. Chronic heavy marijuana smoking is associated with coughing, production of sputum, wheezing, and other symptoms of chronic bronchitis. The availableevidence does not support a causal relationship between cannabis use and chronic obstructive pulmonary disease. Short-term use of cannabis is associated with bronchodilation. Other side effects of cannabis use include cannabinoid hyperemesis syndrome (CHS), a condition which involves recurrent nausea, cramping abdominal pain, and vomiting.

Cannabis smoke contains thousands of organic and inorganic chemical compounds. This tar is chemically similar to that found in tobacco smoke, and over fifty known carcinogens have been identified in cannabis smoke, including; nitrosamines, reactive aldehydes, and polycylic hydrocarbons, including benz[a]pyrene. Cannabis smoke is also inhaled more deeply than tobacco smoke. As of 2015, there is no consensus regarding whether cannabis smoking is associated with an increased risk of cancer. Light and moderate use of cannabisis not believed to increase risk of lung or upper airway cancer. Evidence for causing these cancers is mixed concerning heavy, long-term use. In general there are far lower risks of pulmonary complications for regular cannabis smokers when compared with those of tobacco. A 2015 review found an association between cannabis use and the development oftesticular germ cell tumors (TGCTs), particularly non-seminoma TGCTs. Another 2015
meta-analysis found no association between lifetime cannabis use and risk of head or neck cancer. Combustion products are not present when using a vaporizer, consuming THC in pill form, or consuming cannabis foods.

There is concern that cannabis may contribute to cardiovascular disease, but as of 2018, evidence of this relationship was unclear. Research in these events is complicated becausecannabis is often used in conjunction with tobacco, and drugs such as alcohol and cocainethat are known to have cardiovascular risk factors. Smoking cannabis has also been shownto increase the risk of myocardial infarction by 4.8 times for the 60 minutes after consumption.

There is preliminary evidence that cannabis interferes with the anticoagulant properties of prescription drugs used for treating blood clots. As of 2019, the mechanisms for the anti-inflammatory and possible pain relieving effects of cannabis were not defined, and there were no governmental regulatory approvals or clinical practices for use of cannabis asa drug.

Emergency Department Visits

Emergency room (ER) admissions associated with cannabis use rose significantly from 2012 to 2016; adolescents from age 12-17 had the highest risk. At one Colorado medical center following legalization, approximately two percent of ER admissions were classified ascannabis users. The

symptoms of one quarter of these users were partially attributed to cannabis (a total of 2567 out of 449,031 patients); other drugs were sometimes involved. Ofthese cannabis admissions, one quarter were for acute psychiatric effects, primarily suicidalideation, depression, and anxiety. An additional third of the cases were for gastrointestinal issues including Cannabinoid hyperemesis syndrome.

According to the United States Department of Health and Human Services, there were 455,000 emergency room visits associated with cannabis use in 2011. These statistics include visits in which the patient was treated for a condition induced by or related to recentcannabis use. The drug use must be "implicated" in the emergency department visit, but does not need to be the direct cause of the visit. Most of the illicit drug emergency room visits involved multiple drugs. In 129,000 cases, cannabis was the only implicated drug.

Reproductive health

There is sufficient evidence of reproductive health harms from cannabis that its use whentrying to conceive, during pregnancy, and while breastfeeding, is not advisable.

It has been recommended that cannabis use be stopped before and during pregnancy as it can result in negative outcomes for both the mother and baby. However, maternal use of marijuana during pregnancy does not appear to be associated with low birth weight or earlydelivery after controlling for tobacco use and other confounding factors.

Pharmacology

The high lipid-solubility of cannabinoids results in their persisting in the body for long periods of time. Even after a single administration of THC, detectable levels of THC can befound in the body for weeks or longer (depending on the amount administered and the sensitivity of the assessment method). Investigators have suggested that this is an important factor in marijuana's effects, perhaps because cannabinoids may accumulate inthe body, particularly in the lipid membranes of neurons.

Researchers confirmed that THC exerts its most prominent effects via its actions on two types of cannabinoid receptors, the CB1 receptor and the CB2 receptor, both of which are Gprotein-coupled receptors. The CB1 receptor is found primarily in the brain as well as in some peripheral tissues, and the CB2 receptor is found primarily in peripheral tissues, but is

also expressed in neuroglial cells. THC appears to alter mood and cognition through itsagonist actions on the CB1 receptors, which inhibit a secondary messenger system (adenylate cyclase) in a dose-dependent manner.

Via CB1 receptor activation, THC indirectly increases dopamine release and produces psychotropic effects. CBD also acts as an allosteric modulator of the μ- and δ-opioid receptors. THC also potentiates the effects of the glycine receptors. It is unknown if or howthese actions contribute to the effects of cannabis.

Chemistry

The main psychoactive component of cannabis is THC, which is formed via decarboxylationof THCA from the application of heat. Raw leaf is not psychoactive because the cannabinoids are in the form of carboxylic acids.

Cannabinoids

THC and its major (inactive) metabolite, THC-COOH, can be measured in blood, urine, hair, oral fluid or sweat using chromatographic techniques as part of a drug use testing program or a forensic investigation of a traffic or other criminal offense. The concentrations obtainedfrom such analyses can often be helpful in distinguishing active use from passive exposure, elapsed time since use, and extent or duration of use. These tests cannot, however, distinguish authorized cannabis smoking for medical purposes from unauthorized recreational smoking. Commercial cannabinoid immunoassays, often employed as the initial screening method when testing physiological specimens for marijuana presence, havedifferent degrees of cross-reactivity with THC and its metabolites. Urine contains predominantly THC-COOH, while hair, oral fluid and sweat contain primarily THC. Blood may contain both substances, with the relative amounts dependent on the recency and extent of usage.

The Duquenois–Levine test is commonly used as a screening test in the field, but it cannot definitively confirm the presence of cannabis, as a large range of substances have been shown to give false positives. Researchers at John Jay College of Criminal Justice reportedthat dietary zinc supplements can mask the presence of THC and other drugs in urine.
However, a 2013 study conducted by researchers at the University of Utah School of Medicine refute the possibility of self-administered zinc producing false-negative urine drugtests.

Types of cannabis

CBD is a 5-HT1A receptor agonist, which is under laboratory research to determine if it hasan anxiolytic effect. It is often claimed that sativa strains provide a more stimulating psychoactive high while indica strains are more sedating with a body high. However, this isdisputed by researchers.

A 2015 review found that the use of high CBD-to-THC strains of cannabis showed significantly fewer positive symptoms, such as delusions and hallucinations, better cognitive function and both lower risk for developing psychosis, as well as a later age ofonset of the illness, compared to cannabis with low CBD-to-THC ratios.

Psychoactive ingredients

According to the United Nations Office on Drugs and Crime (UNODC), "the amount of THC present in a cannabis sample is generally used as a measure of cannabis potency." The three main forms of cannabis products are the flower/fruit, resin (hashish), and oil (hash oil).The UNODC states that cannabis often contains 5% THC content, resin "can contain up to 20% THC content", and that "Cannabis oil may contain more than 60% THC content."

A 2012 review found that the THC content in marijuana had increased worldwide from 1970to 2009. It is unclear, however, whether the increase in THC content has caused people to consume more THC or if users adjust based on the potency of the cannabis. It is likely thatthe higher THC content allows people to ingest less tar. At the same time, CBD levels in seized samples have lowered, in part because of the desire to produce higher THC levels and because more illegal growers cultivate indoors using artificial lights. This helps avoid detection but reduces the CBD production of the plant.

Australia's National Cannabis Prevention and Information Centre (NCPIC) states that thebuds (infructescences) of the female cannabis plant contain the highest concentration ofTHC, followed by the leaves. The stalks and seeds have "much lower THC levels". The UNstates that the leaves can contain ten times less THC than the buds, and the stalks one hundred times less THC.

After revisions to cannabis scheduling in the UK, the government moved cannabis back from

a class C to a class B drug. A purported reason was the appearance of high potency cannabis. They believe skunk accounts for between 70 and 80% of samples seized by police(despite the fact that skunk can sometimes be incorrectly mistaken for all types of herbal cannabis). Extracts such as hashish and hash oil typically contain more THC than high potency cannabis infructescences.

Laced cannabis and synthetic cannabinoids

Hemp buds (or low-potency cannabis buds) laced with synthetic cannabinoids started to besold as cannabis street drug in 2020.

The short term effects of cannabis can be altered if it has been laced with opioid drugs suchas heroin or fentanyl. The added drugs are meant to enhance the psychoactive properties, add to its weight, and increase profitability, despite the increased danger of overdose.

Legal status of cannabis possession for non-medical use

Since the beginning of the 20th century, most countries have enacted laws against the cultivation, possession or transfer of cannabis. These laws have had an adverse effect on cannabis cultivation for non-recreational purposes, but there are many regions where handling of cannabis is legal or licensed. Many jurisdictions have lessened the penalties forpossession of small quantities of cannabis so that it is punished by confiscation and sometimes a fine, rather than imprisonment, focusing more on those who traffic the drug onthe black market.

In some areas where cannabis use had been historically tolerated, new restrictions were instituted, such as the closing of cannabis coffee shops near the borders of the Netherlands,and closing of coffee shops near secondary schools in the Netherlands. In Copenhagen, Denmark in 2014, mayor Frank Jensen discussed possibilities for the city to legalize cannabis production and commerce.

Some jurisdictions use free voluntary treatment programs and/or mandatory treatment programs for frequent known users. Simple possession can carry long prison terms in somecountries, particularly in East Asia, where the sale of cannabis may lead to a sentence of lifein prison or even execution. Political parties, non-profit organizations, and causes based onthe legalization of medical cannabis and/or legalizing the plant entirely (with some restrictions) have emerged in such countries as China and Thailand.

In December 2012, the U.S. state of Washington became the first state to officially legalize cannabis in a state law (Washington Initiative 502) (but still illegal by federal law), with the state of Colorado following close behind (Colorado Amendment 64). On 1 January 2013, thefirst marijuana "club" for private marijuana smoking (no buying or selling, however) was allowed for the first time in Colorado. The California Supreme Court decided in May 2013 that local governments can ban medical marijuana dispensaries despite a state law in California that permits the use of cannabis for medical purposes. At least 180 cities acrossCalifornia have enacted bans in recent years.

In December 2013, Uruguay became the first country to legalize growing, sale and use of cannabis.

After a long delay in implementing the retail component of the law, in 2017 sixteenpharmacies were authorized to sell cannabis commercially. On 19 June 2018, the Canadian Senate passed a bill and the Prime Minister announced the effective legalization date as 17 October 2018. Canada is the second country to legalize the drug.

In November 2015, Uttarakhand became the first state of India to legalize the cultivation ofhemp for industrial purposes. Usage within the Hindu and Buddhist cultures of the Indian subcontinent is common, with many street vendors in India openly selling products infusedwith cannabis, and traditional medical practitioners in Sri Lanka selling products infused with cannabis for recreational purposes and well as for religious celebrations. Indian laws criminalizing cannabis date back to the colonial period. India and Sri Lanka have allowed cannabis to be taken in the context of traditional culture for recreational/celebratory purposes and also for medicinal purposes.

On 17 October 2015, Australian health minister Sussan Ley presented a new law that willallow the cultivation of cannabis for scientific research and medical trials on patients.

On 17 October 2018, Canada legalized cannabis for recreational adult use making it the second country in the world to do so after Uruguay and the first G7 nation. The Canadian Licensed Producer system aims to become the Gold Standard in the world for safe and secure cannabis production, including provisions for a robust craft cannabis industry wheremany expect opportunities for experimenting with different strains. Laws around use vary from province to province including age limits, retail structure, and growing at home.

As the drug has increasingly been seen as a health issue instead of criminal behavior, marijuana has also been legalized or decriminalized in: Czech Republic, Colombia, Ecuador, Portugal, South Africa and Canada. Medical marijuana was legalized in Mexico in mid-2017;legislators plan to legalize its recreational use by late 2019.

On 28 June 2021, Clarence Thomas, one of the U.S. Supreme Court's most conservative justices, possibly opened the door to federal legalization of cannabis in the United States when he wrote "A prohibition on interstate use or cultivation of marijuana may no longer be

necessary or proper to support the federal government's piecemeal approach."

Legality by country

Currently, Uruguay and Canada are the only countries that have fully legalized the cultivation, consumption and bartering of recreational cannabis nationwide. In the United States, 19 states, 2 territories, and the District of Columbia have legalized the recreational use of cannabis – though the drug remains illegal at the federal level. Laws vary from stateto state when it comes to the commercial sale. Court rulings in Georgia and South Africa have led to the legalization of cannabis consumption, but not legal sales. A policy of limitedenforcement has also been adopted in many countries, in particular Spain and the Netherlands where the sale of cannabis is tolerated at licensed establishments. Contrary topopular belief, cannabis is not legal in the Netherlands but it has been decriminalized sincethe 1970s. In 2021, Malta was the first European Union member to legalize the use of canabis for recreational purposes. Lebanon has recently become the first Arab country to legalize the plantation of cannabis for medical use.

Penalties for illegal recreational use ranges from confiscation or small fines to jail time and even death. In some countries citizens can be punished if they have used the drug in anothercountry, including Singapore and South Korea.

United States Regulation and Prohibition of Cannabis

The Marihuana Tax Act of 1937 was one of the first measures to cannabis nationwide. This act was overturned in 1969 in Leary v. United States, and was repealed and replaced with the Controlled Substances Act by Congress the next year. Under the CSA cannabis was assigned a Schedule I classification, deemed to have a high potential for abuse and no accepted medical use – thereby prohibiting even medical use of the drug. The classificationhas remained since the CSA was first signed into law, despite multiple efforts to reschedule.In direct response, the Libertarian Party (United States) was one of the first major parties toendorse cannabis legalization in their first platform in 1972 which stated, "We favor the repeal of all laws creating "crimes without victims" now incorporated in Federal, state and local laws—such as laws on voluntary sexual relations, drug use, gambling, and attempted suicide." As cannabis prohibition continued into the 21st Century, the U.S. Marijuana Party was formed in 2002 as a single-issue party to end the war on drugs and to legalize cannabis. States have also begun to engage in the process of Nullification (U.S. Constitution) to override federal laws pertaining to cannabis. California started the trend bylegalizing medicinal cannabis in 1996. Now, cannabis has been fully legalized for recreational use in 19 states with most states having some sort of state nullification of federal cannabis laws.

Usage

In 2013, between 128 and 232 million people used cannabis (2.7% to 4.9% of the global population between the ages of 15 and 65). Cannabis is by far the most widely used illicitsubstance.

United States

Between 1973 and 1978, eleven states decriminalized marijuana. In 2001, Nevada reducedmarijuana possession to a misdemeanor and since 2012, several other states have decriminalized and even legalized marijuana.

In 2018, almost half of the people in the United States had tried marijuana, 16% had used itin the past year, and 11% had used it in the past month. In 2014, daily marijuana use amongst US college students had reached its highest level since records began in 1980, rising from 3.5% in 2007 to 5.9% in 2014 and had surpassed daily cigarette use.

In the US, men are over twice as likely to use marijuana as women, and 18–29-year-olds aresix times more likely to use as over-65-year-olds. In 2015, a record 44% of the US population has tried marijuana in their lifetime, an increase from 38% in 2013 and 33% in 1985.

Marijuana use in the United States is three times above the global average, but in line with other Western democracies. Forty-four percent of American 12th graders have tried the drugat least once, and the typical age of first-use is 16, similar to the typical age of first-use for alcohol but lower than the first-use age for other illicit drugs.

Cannabis as a gateway drug

The gateway hypothesis states that cannabis use increases the probability of trying "harder"drugs. The hypothesis has been hotly debated as it is regarded by some as the primary rationale for the United States prohibition on cannabis use. A Pew Research Center poll found that political opposition to marijuana use was significantly associated with concerns about the health effects and whether legalization would increase marijuana use by children.

Some studies state that while there is no proof for the gateway hypothesis, young cannabisusers should still be considered as a risk group for intervention programs. Other findings indicate that hard drug users are likely to be poly-drug users, and that interventions must address the use of multiple drugs instead of a single hard drug. Almost two-thirds of the poly drug users in the 2009–2010 Scottish Crime and Justice Survey used cannabis.

The gateway effect may appear due to social factors involved in using any illegal drug. Because of the illegal status of cannabis, its consumers are likely to find themselves in situations allowing them to acquaint with individuals using or selling other illegal drugs. Studies have shown that alcohol and

tobacco may additionally be regarded as gateway drugs; however, a more parsimonious explanation could be that cannabis is simply more readily available (and at an earlier age) than illegal hard drugs. In turn, alcohol and tobaccoare typically easier to obtain at an earlier age than is cannabis (though the reverse may be true in some areas), thus leading to the "gateway sequence" in those individuals, since theyare most likely to experiment with any drug offered.

A related alternative to the gateway hypothesis is the common liability to addiction (CLA) theory. It states that some individuals are, for various reasons, willing to try multiple recreational substances. The "gateway" drugs are merely those that are (usually) available at an earlier age than the harder drugs. Researchers have noted in an extensive review that itis dangerous to present the sequence of events described in gateway "theory" in causative terms as this hinders both research and intervention.

In 2020, the National Institute on Drug Abuse released a study backing allegations that marijuana is a gateway to harder drugs, though not for the majority of marijuana users. The National Institute on Drug Abuse determined that marijuana use is "likely to precede use of other licit and illicit substances" and that "adults who reported marijuana use during the firstwave of the survey were more likely than adults who did not use marijuana to develop an alcohol use disorder within 3 years; people who used marijuana and already had an alcohol use disorder at the outset were at greater risk of their alcohol use disorder worsening.
Marijuana use is also linked to other substance use disorders including nicotine addiction." It also reported that "These findings are consistent with the idea of marijuana as a "gatewaydrug." However, the majority of people who use marijuana do not go on to use other, "harder"substances. Also, cross-sensitization is not unique to marijuana. Alcohol and nicotine also prime the brain for a heightened response to other drugs and are, like marijuana, also typically used before a person progresses to other, more harmful substances."

Phencyclidine or phenylcyclohexyl piperidine (PCP), also known as angel dust among othernames, is a dissociative hallucinogenic drug used for its mind-altering effects. PCP may cause hallucinations, distorted perceptions of sounds, and violent behavior. As a recreational drug, it is typically smoked, but may be taken by mouth, snorted, or injected. It may also be mixed with cannabis or tobacco.

Adverse effects may include seizures, coma, addiction, and an increased risk of suicide. Flashbacks may occur despite stopping usage. Chemically, PCP is a member of the arylcyclohexylamine class, and pharmacologically, it is a dissociative anesthetic. PCP worksprimarily as an NMDA receptor antagonist.

PCP is most commonly used in the United States. While usage peaked in the US in the 1970s, between 2005 and 2011 an increase in visits to emergency departments as a resultof the drug occurred. As of 2017 in the United States, about 1% of people in grade 12 reported using PCP in the prior year while 2.9% of those over the age of 25 reported using itat some point in their lives.

Effects

Behavioral effects can vary by dosage. Low doses produce a numbness in the extremities and intoxication, characterized by staggering, unsteady gait, slurred speech, bloodshot eyes,and loss of balance. Moderate doses (5–10 mg intranasal, or 0.01–0.02 mg/kg intramuscular or intravenous) will produce analgesia and anesthesia. High doses may lead to convulsions. The drug is often illegally produced under poorly controlled conditions; this means that users may be unaware of the actual dose they are taking.

Psychological effects include severe changes in body image, loss of ego boundaries, paranoia, and depersonalization. Psychosis, agitation and dysphoria, hallucinations, blurredvision, euphoria, and suicidal impulses are also reported, as well as occasional aggressive behavior. Like many other drugs, PCP has been known to alter mood states in an unpredictable fashion, causing some individuals to become detached, and others to becomeanimated. PCP may induce feelings of strength, power, and invulnerability as well as a numbing effect on the mind.

Studies by the Drug Abuse Warning Network in the 1970s show that media reports of PCP-induced violence are greatly exaggerated and that incidents of violence are unusualand often limited to individuals with reputations for aggression regardless of drug use.
Although uncommon, events of PCP-intoxicated individuals acting in an unpredictable fashion, possibly driven by their delusions or hallucinations, have been publicized. Other commonly cited types of incidents include inflicting property damage and self-mutilation ofvarious types, such as pulling one's own teeth. These effects were not noted in its medicinaluse in the 1950s and 1960s, however, and reports of physical violence on PCP have often been shown to be unfounded.

Recreational doses of the drug also occasionally appear to induce a psychotic state, withemotional and cognitive impairment that resembles a schizophrenic episode. Users generally report feeling detached from reality.

Symptoms are summarized by the mnemonic device RED DANES: rage, erythema (rednessof skin), dilated pupils, delusions, amnesia, nystagmus (oscillation of the eyeball when moving laterally), excitation, and skin dryness.

Addiction

PCP is self-administered and induces ΔFosB expression in the D1-type medium spiny neurons of the nucleus accumbens, and accordingly, excessive PCP use is known to causeaddiction. PCP's rewarding and reinforcing effects are at least partly mediated by blockingthe NMDA receptors in the glutamatergic inputs to D1-type medium spiny neurons in the nucleus accumbens.PCP has been shown to produce conditioned place aversion and conditioned place preference in animal studies.

Schizophrenia

A 2019 review found that the transition rate from a diagnosis of hallucinogen-induced psychosis (which included PCP) to that of schizophrenia was 26%. This was lower than cannabis-induced psychosis (34%) but higher than amphetamine (22%), opioid (12%), alcohol (10%) and sedative (9%) induced psychoses. In comparison, the transition rate toschizophrenia for "brief, atypical and not otherwise specified" psychosis was found to be36%.

Methods of administration

PCP comes in both powder and liquid forms (PCP base is dissolved most often in ether), buttypically it is sprayed onto leafy material such as cannabis, mint, oregano, tobacco, parsley,or ginger leaves, then smoked.

PCP can be ingested through smoking. "Fry" or "sherm" are street terms for marijuana ortobacco cigarettes that are dipped in PCP and then dried.

PCP hydrochloride can be insufflated (snorted), depending upon the purity.

The free base is quite hydrophobic and may be absorbed through skin and mucusmembranes (often inadvertently).

Management of intoxication

Management of PCP intoxication mostly consists of supportive care – controlling breathing, circulation, and body temperature – and, in the early stages, treating psychiatric symptoms. Benzodiazepines, such as lorazepam, are the drugs of choice to control agitation and seizures (when present). Typical antipsychotics such as phenothiazines and haloperidol have been used to control psychotic symptoms, but may produce many undesirable side effects – such as dystonia – and their use is therefore no longer preferred; phenothiazines are particularly risky, as they may lower the seizure threshold, worsen hyperthermia, and boost the anticholinergic effects of PCP. If an

antipsychotic is given, intramuscular haloperidol has been recommended.

Forced acid diuresis (with ammonium chloride or, more safely, ascorbic acid) may increase clearance of PCP from the body, and was somewhat controversially recommended in the past as a decontamination measure. However, it is now known that only around 10% of a dose of PCP is removed by the kidneys, which would make increased urinary clearance of little consequence; furthermore, urinary acidification is dangerous, as it may induce acidosisand worsen rhabdomyolysis (muscle breakdown), a not-unusual manifestation of PCP toxicity.

Pharmacology

PCP is well known for its primary action on the NMDA receptor, an ionotropic glutamate receptor, in rats and in rat brain homogenate. As such, PCP is an NMDA receptor antagonist.The role of NMDAR antagonism in the effect of PCP, ketamine, and related dissociative agents was first published in the early 1980s by David Lodge and colleagues. Other NMDA receptor antagonists include ketamine, tiletamine, dextromethorphan, nitrous oxide, and dizocilpine (MK-801).

Research also indicates that PCP inhibits nicotinic acetylcholine receptors (nAChRs) amongother mechanisms. Analogues of PCP exhibit varying potency at nACh receptors and NMDA receptors. Findings demonstrate that presynaptic nAChRs and NMDA receptor interactions influence postsynaptic maturation of glutamatergic synapses and consequently impact synaptic development and plasticity in the brain. These effects can lead to inhibition of excitatory glutamate activity in certain brain regions such as the hippocampus and cerebellum thus potentially leading to memory loss as one of the effects of prolonged use. Acute effects on the cerebellum manifest as changes in blood pressure, breathing rate, pulserate, and loss of muscular coordination during intoxication.

PCP, like ketamine, also acts as a potent dopamine D2High receptor partial agonist in rat brain homogenate and has affinity for the human cloned D2High receptor. This activity maybe associated with some of the other more psychotic features of PCP intoxication, which isevidenced by the successful use of D2 receptor antagonists (such as haloperidol) in the treatment of PCP psychosis.

In addition to its well explored interactions with NMDA receptors, PCP has also been shown to inhibit dopamine reuptake, and thereby leads to increased extracellular levels of dopamine and hence increased dopaminergic neurotransmission. However, PCP has little affinity for the human monoamine transporters, including the dopamine transporter (DAT). Instead, its inhibition of monoamine reuptake may be mediated by interactions with allosteric sites on the monoamine transporters. PCP is notably a high-affinity ligand of the PCP site 2 (Ki = 154 nM), a not-well-characterized site associated with monoamine reuptakeinhibition.

Studies on rats indicate that PCP interacts indirectly with opioid receptors (endorphin and enkephalin) to produce analgesia.

A binding study assessed PCP at 56 sites including neurotransmitter receptors and transporters and found that PCP had Ki values of >10,000 nM at all sites except the dizocilpine (MK-801) site of the NMDA receptor (Ki = 59 nM), the σ2 receptor (PC12) (Ki =136 nM), and the serotonin transporter (Ki = 2,234 nM).[38] The study notably found Ki values of >10,000 nM for the D2 receptor, the opioid receptors, the σ1 receptor, and the dopamine and norepinephrine transporters. These results suggest that PCP is a highly selective ligand of the NMDAR and σ2 receptor. However, PCP may also interact with allosteric sites on the monoamine transporters to produce inhibition of monoamine reuptake.

Mechanism of action

Phencyclidine is an NMDA receptor antagonist that blocks the activity of the NMDA receptorto cause anaesthesia and analgesia without causing cardiorespiratory depression. NMDA isan excitatory receptor in the brain, when activated normally the receptor acts as an ion channel and there is an influx of positive ions through the channel to cause nerve cell depolarisation. Phencyclidine enters the ion channel and binds, reversibly and
non-competitively, inside the channel pore to block the entry of positive ions to the cell,thereby inhibiting cell depolarisation.

Neurotoxicity

Some studies found that, like other NMDA receptor antagonists, PCP can cause a kind of brain damage called Olney's lesions in rats. Studies conducted on rats showed that high doses of the NMDA receptor antagonist dizocilpine caused reversible vacuoles to form in certain regions of the rats' brains. All studies of Olney's lesions have only been performed onnon-human animals and may not apply to humans. One unpublished study by Frank Sharp reportedly showed no damage by the NDMA antagonist ketamine, a structurally similar drug,far beyond recreational doses, but due to the study never having been published, its validity is controversial.

PCP has also been shown to cause schizophrenia-like changes in N-acetylaspartate and Nacetylaspartylglutamate levels in the rat brain, which are detectable both in living rats andupon necropsy examination of brain tissue. It also induces symptoms in humans that mimicschizophrenia. PCP not only produced symptoms similar to schizophrenia, it also yielded electroencephalogram changes in the thalamocortical pathway (increased delta decreased alpha) and in the hippocampus (increase theta bursts) that were similar to those in schizophrenia. PCP-induced augmentation of dopamine release may link the NMDA and dopamine hypotheses of schizophrenia.

Pharmacokinetics

PCP is metabolized into PCHP, PPC and PCAA. The drug is metabolized 90% by oxidative hydroxylation in the liver during the first pass. Metabolites are glucuronidated and excretedin the urine. Nine percent of ingested PCP is excreted in its unchanged form.

When smoked, some of the compound is broken down by heat into 1-phenylcyclohexene(PC) and piperidine.

The time taken before the effects of PCP manifest is dependent on the route of administration. The onset of action for inhalation occurs in 2–5 minutes, whereas the effectsmay take 15 to 60 minutes when ingested orally.

Frequency of use

PCP began to emerge as a recreational drug in major cities in the United States in 1960s. In1978, People magazine and Mike Wallace of 60 Minutes called PCP the country's "number one" drug problem. Although recreational use of the drug had always been relatively low, it began declining significantly in the 1980s. In surveys, the number of high school students admitting to trying PCP at least once fell from 13% in 1979 to less than 3% in 1990.

Arylcyclohexylamine

Arylcyclohexylamines, also known as arylcyclohexamines or arylcyclohexanamines, are achemical class of pharmaceutical, designer, and experimental drugs.

Phencyclidine (PCP) is believed to be the first arylcyclohexylamine with recognized anesthetic properties, but several arylcyclohexylamines were described before PCP in thescientific literature, beginning with PCA (1-phenylcyclohexan-1-amine) the synthesis of which was first published in 1907. PCE was reported in 1953 and PCMo (4-(1-phenyl-cyclohexyl)-morpholine see chart below for figure) in 1954, with PCMo described as a potent sedative. Arylcyclohexylamine anesthetics were intensively investigated at Parke-Davis, beginning with the 1956 synthesis of phencyclidine and later the related compound ketamine. The 1970s saw the debut of these compounds, especiallyPCP and its analogues, as illicitly used recreational drugs due to their dissociative hallucinogenic and euphoriant effects. Since that time, the class has been expanded by scientific research into stimulant, analgesic, and neuroprotective agents, and also by clandestine chemists in search of novel recreational drugs.

Structure

An arylcyclohexylamine is composed of a cyclohexylamine unit with an aryl moiety attachment. The aryl group is positioned geminal to the amine. In the simplest cases, the aryl moiety is typically a phenyl ring, sometimes with additional substitution. The amine isusually not primary; secondary amines such as methylamino or ethylamino, or tertiary cycloalkylamines such as piperidino and pyrrolidino, are the most commonly encounteredN-substituents.

Pharmacology

Arylcyclohexylamines varyingly possess NMDA receptor antagonistic, dopamine reuptake inhibitory, and μ-opioid receptor agonistic properties. Additionally, σ receptor agonistic, nACh receptor antagonistic, and D2 receptor agonistic actions have been reported for someof these agents. Antagonism of the NMDA receptor confers anesthetic, anticonvulsant, neuroprotective, and dissociative effects; blockade of the dopamine transporter mediates stimulant and euphoriant effects as well as psychosis in high amounts; and activation of theμ-opioid receptor causes analgesic and euphoriant effects. Stimulation of the σ and D2 receptors may also contribute to hallucinogenic and psychotomimetic effects.

These are versatile agents with a wide range of possible pharmacological activities depending on the extent and range to which chemical modifications are implemented. The

various choice of substitutions that are made allows for "fine-tuning" of the pharmacologicalprofile that results. As examples, BTCP is a selective dopamine reuptake inhibitor, PCP is primarily an NMDA antagonist, and BDPC is a potent μ-opioid agonist, while PRE-084 is a selective sigma receptor agonist. Thus, radically different pharmacology is possible throughdifferent structural combinations.

Notes on numbering

PCP itself is composed of three six-membered rings, which can each be substituted by avariety of groups. These are traditionally numbered in the older research as first the cyclohexyl ring, then the phenyl, and finally the piperidine ring, with the different rings represented by prime notation (') next to the number. For instance, 4-methyl-PCP,
4'-methyl-PCP and 4''-methyl-PCP are all known compounds, with similar activity but quitedifferent potencies.

However, since the widespread sale of these compounds as grey-market designer drugs, nearly all such compounds that have come to prominence either have a bare cyclohexyl ringor a 2-ketocyclohexyl ring, while the piperidine is replaced by a variety of alkyl or cycloalkyl amines and most substitution has taken place on the phenyl ring. Consequently it is common for widely used phenyl substituted analogues such as 3'-MeO-PCP and
3'-MeO-PCE to be referred to as 3-MeO-PCP and 3-MeO-PCE without the prime, eventhough this is technically incorrect and could lead to confusion.

Inhalant

Inhalants are a broad range of household and industrial chemicals whose volatile vapors or pressurized gases can be concentrated and breathed in via the nose or mouth to produce intoxication, in a manner not intended by the manufacturer. They are inhaled at room temperature through volatilization (in the case of gasoline or acetone) or from a pressurizedcontainer (e.g., nitrous oxide or butane), and do not include drugs that are sniffed after burning or heating. For example, amyl nitrite (poppers), nitrous oxide and toluene – a solventwidely used in contact cement, permanent markers, and certain types of glue – are considered inhalants, but smoking tobacco, cannabis, and crack are not, even though these drugs are inhaled as smoke or vapor.

Complications

Pneumonia, cardiac arrest, poisoning, suffocation, coma, pulmonary aspiration, heart attack,hypoxia, methemoglobinemia

While a few inhalants are prescribed by medical professionals and used for medical purposes, as in the case of inhaled anesthetics and nitrous oxide (an anxiolytic and pain relief agent prescribed by dentists), this article focuses on inhalant use of household and industrial propellants, glues, fuels, and other products in a manner not intended by the manufacturer, to produce intoxication or other psychoactive effects. These products are used as recreational drugs for their intoxicating effect. According to a 1995 report by the National Institute on Drug Abuse, the most serious inhalant use occurs among homeless children and teenagers who "... live on the streets completely without family ties." Inhalantsare the only substance used more by younger teenagers than by older teenagers. Inhalant users inhale vapor or aerosol propellant gases using plastic bags held over the mouth or by breathing from a solvent-soaked rag or an open container. The practices are known colloquially as "sniffing", "huffing" or "bagging".

The effects of inhalants range from an alcohol-like intoxication and intense euphoria to vivid hallucinations, depending on the substance and the dose. Some inhalant users are injured due to the harmful effects of the solvents or gases or due to other chemicals used in the products that they are inhaling. As with any recreational drug, users can be injured due to dangerous behavior while they are intoxicated, such as driving under the influence. In some cases, users have died from hypoxia (lack of oxygen), pneumonia, heart failure or arrest, or aspiration of vomit. Brain damage is typically seen with chronic long-term use of solvents as opposed to short-term exposure.

Even though many inhalants are legal, there have been legal actions taken in some jurisdictions to limit access by minors. While solvent glue is normally a legal product, aScottish court has ruled that supplying glue to children is illegal if the store knows the children intend to inhale the glue. In the US, thirty-eight of 50 states have enacted laws

making various inhalants unavailable to those under the age of 18 or making inhalant useillegal.

Inhalants can be classified by the intended function. Most inhalant drugs that are used non-medically are ingredients in household or industrial chemical products that are not intended to be concentrated and inhaled. A small number of recreational inhalant drugs are pharmaceutical products that are used illicitly.

Product category

Another way to categorize inhalants is by their product category. There are three mainproduct categories: solvents; gases; and medical drugs which are used illicitly.

Solvents

A range of petroleum-based products that can be used as inhalants.

A wide range of volatile solvents intended for household or industrial use are inhaled as recreational drugs. This includes petroleum products (gasoline and kerosene), toluene (usedin paint thinner, permanent markers, contact cement and model glue), and acetone (used in nail polish remover). These solvents vaporize at room temperature. Ethanol (the alcohol which is normally drunk) is sometimes inhaled, but this cannot be done at room temperature. The ethanol must be converted from liquid into gaseous state (vapor) or aerosol (mist), in some cases using a nebulizer, a machine that agitates the liquid into an aerosol. The sale of nebulizers for inhaling ethanol was banned in some US states due to safety concerns.

Gases

Computer-cleaning dusters are dangerous to inhale because the gases expand and coolrapidly upon being sprayed.

A number of gases intended for household or industrial use are inhaled as recreational drugs. This includes chlorofluorocarbons used in aerosols and propellants (e.g., aerosol hairspray, aerosol deodorant). A gas used as a propellant in whipped cream aerosol containers, nitrous oxide, is used as a recreational drug. Pressurized canisters of propane and butane gas, both of which are intended for use as fuels, are used as inhalants.

Medical anesthetics

Several medical anesthetics are used as recreational drugs, including diethyl ether (a drugthat is no longer used medically, due to its high flammability and the development of saferalternatives) and nitrous oxide, which is widely used in the 2010s by dentists as an anti-anxiety drug during dental procedures. Diethyl ether has a long history of use as a recreational drug. The effects of ether intoxication are similar to those of alcohol intoxication, but more potent. Also, due to NMDA antagonism, the user may experience all the psychedelic effects present in classical dissociatives such as ketamine in forms of thought loops and the feeling of the mind being disconnected from one's body. Nitrous oxideis a dental anesthetic that is used as a recreational drug, either by users who have access tomedical-grade gas canisters (e.g., dental hygienists or dentists) or by using the gas contained in whipped cream aerosol containers. Nitrous oxide inhalation can cause pain relief, depersonalisation, derealisation, dizziness, euphoria, and some sound distortion.

Classification by effect

Common household products such as nail polish contain solvents that can be concentratedand inhaled, in a manner not intended by the manufacturer, to produce intoxication. Misuseof products in this fashion can be harmful or fatal.

It is also possible to classify inhalants by the effect they have on the body. Some solvents act as depressants, causing users to feel relaxed or drowsy while others act as stimulants.Many inhalants act primarily as asphyxiant gases, with their primary effect due to oxygen deprivation. Nitrous oxide can be categorized as a dissociative drug, as it can cause visualand auditory hallucinations. Other agents may have more direct effects at receptors, as inhalants exhibit a variety of mechanisms of action. The mechanisms of action of many non-medical inhalants have not been well elucidated. Anesthetic gases used for surgery, such as nitrous oxide or enflurane, are believed to induce anesthesia primarily by acting asNMDA receptor antagonists, open-channel blockers that bind to the inside of the calcium channels on the outer surface of the neuron, and provide high levels of NMDA receptor blockade for a short period of time.

This makes inhaled anesthetic gases different from other NMDA antagonists, such as ketamine, which bind to a regulatory site on the NMDA-sensitive calcium transporter complex and provide slightly lower levels of NMDA blockade, but for a longer and much more predictable duration. This makes a deeper level of anesthesia achievable more easilyusing anesthetic gases but can also make them more dangerous than other drugs used forthis purpose.

Administration and effects

Inhalant users inhale vapors or aerosol propellant gases using plastic bags held over the mouth or by breathing from an open container of solvents, such as gasoline or paint thinner.Nitrous oxide gases from whipped cream aerosol cans, aerosol hairspray or non-stick fryingspray are sprayed into plastic bags. Some nitrous oxide users spray the gas into balloons.
When inhaling non-stick cooking spray or other aerosol products, some users may filter the aerosolized particles out with a rag. Some gases, such as propane and butane gases, are inhaled directly from the canister. Once these solvents or gases are inhaled, the extensive capillary surface of the lungs rapidly absorb the solvent or gas, and blood levels peak rapidly. The intoxication effects occur so quickly that the effects of inhalation can resemblethe intensity of effects produced by intravenous injection of other psychoactive drugs.

Ethanol is also inhaled, either by vaporizing it by pouring it over dry ice in a narrow containerand inhaling with a straw or by pouring alcohol in a corked bottle with a pipe, and then usinga bicycle pump to make a spray. Alcohol can be vaporized using a simple container and open-flame heater. Medical devices such as asthma nebulizers and inhalers were also reported as means of application. The practice gained popularity in 2004, with the marketingof the device dubbed AWOL (Alcohol without liquid), a play on the military term AWOL (Absent Without Leave). AWOL, created by British businessman Dominic Simler, was first introduced in Asia and Europe, and then in the United States in August 2004. AWOL was used by nightclubs, at gatherings and parties, and it garnered attraction as a novelty, as people 'enjoyed passing it around in a group'. AWOL uses a nebulizer, a machine that agitates the liquid into an aerosol. AWOL's official website states that "AWOL and AWOL 1 are powered by Electrical Air Compressors while AWOL 2 and AWOL 3 are powered by electrical oxygen generators", which refer to a couple of mechanisms used by the nebulizer drug delivery device for inhalation. Although the AWOL machine is marketed as having no downsides, such as the lack of calories or hangovers, Amanda Shaffer of Slate describes these claims as "dubious at best". Although inhaled alcohol does reduce the caloric content,the savings are minimal. After expressed safety and health concerns, sale or use of AWOL machines was banned in a number of American states.

The effects of solvent intoxication can vary widely depending on the dose and what type of solvent or gas is inhaled. A person who has inhaled a small amount of rubber cement or paint thinner vapor may be impaired in a manner resembling alcohol inebriation. A person who has inhaled a larger quantity of solvents or gases, or a stronger chemical, may experience stronger effects such as distortion in perceptions of time and space, hallucinations, and emotional disturbances. The effects of inhalant use are also modified bythe combined use of inhalants and alcohol or other drugs.

In the short term, many users experience headaches, nausea and vomiting, slurred speech,loss of motor coordination, and wheezing. A characteristic "glue sniffer's rash" around the nose and mouth is sometimes seen after prolonged use. An odor of paint or solvents on

clothes, skin, and breath is sometimes a sign of inhalant abuse, and paint or solventresidues can sometimes emerge in sweat.

According to NIH, even a single session of inhalant use "can disrupt heart rhythms and lower oxygen levels", which can lead to death. "Regular abuse can result in serious harm tothe brain, heart, kidneys, and liver."

Dangers and health problems

Addiction experts in psychiatry, chemistry, pharmacology, forensic science, epidemiology, and the police and legal services engaged in delphic analysis regarding 20 popular recreational drugs. Inhaled solvents were ranked 13th in dependence, 13th in physical harm,and 8th in social harm.

Statistics on deaths caused by heavy inhalant use are difficult to determine. It may be severely under-reported because death is often attributed to a discrete event such as a stroke or a heart attack, even if the event happened because of inhalant use. Inhalant use was mentioned on 144 death certificates in Texas during the period 1988–1998 and was reported in 39 deaths in Virginia between 1987 and 1996 from acute voluntary exposure toused inhalants.

General risks

Regardless of which inhalant is used, inhaling vapors or gases can lead to injury or death.One major risk is hypoxia (lack of oxygen), which can occur due to inhaling fumes from a plastic bag, or from using proper inhalation mask equipment (e.g., a medical mask for nitrous oxide) but not adding oxygen or room air. Another danger is freezing the throat.
When a gas that was stored under high pressure is released, it cools abruptly and can causefrostbite if it is inhaled directly from the container. This can occur, for example, with inhalingnitrous oxide. When nitrous oxide is used as an automotive power adder, its cooling effect isused to make the fuel-air charge denser. In a person, this effect is potentially lethal. Many inhalants are volatile organic chemicals and can catch fire or explode, especially when combined with smoking. As with many other drugs, users may also injure themselves due toloss of coordination or impaired judgment, especially if they attempt to operate machinery.

Solvents have many potential risks in common, including pneumonia, cardiac failure or arrest, and aspiration of vomit. The inhaling of some solvents can cause hearing loss, limbspasms, and damage to the central nervous system and brain. Serious but potentially reversible effects include liver and kidney damage and blood-oxygen depletion. Death frominhalants is generally caused by a very high concentration of fumes. Deliberately inhaling solvents from an attached paper or plastic bag or in a closed area greatly increases the chances of suffocation. Brain damage is typically seen with chronic long-term use as

opposed to short-term exposure. Parkinsonism

Female inhalant users who are pregnant may have adverse effects on the fetus, and the baby may be smaller when it is born and may need additional health care (similar to thoseseen with alcohol – fetal alcohol syndrome). There is some evidence of birth defects and disabilities in babies born to women who sniffed solvents such as gasoline.

In the short term, death from solvent use occurs most commonly from aspiration of vomit while unconscious or from a combination of respiratory depression and hypoxia, the secondcause being especially a risk with heavier-than-air vapors such as butane or gasoline vapor.Deaths typically occur from complications related to excessive sedation and vomiting.
Actual overdose from the drug does occur, however, and inhaled solvent use is statistically more likely to result in life-threatening respiratory depression than intravenous use of opioids such as heroin. Most deaths from solvent use could be prevented if individuals wereresuscitated quickly when they stopped breathing and their airway cleared if they vomited. However, most inhalant use takes place when people inhale solvents by themselves or in groups of people who are intoxicated. Certain solvents are more hazardous than others, such as gasoline.

In contrast, a few inhalants like amyl nitrate and diethyl ether have medical applications andare not toxic in the same sense as solvents, though they can still be dangerous when used recreationally. Nitrous oxide is thought to be particularly non-toxic, though heavy long-termuse can lead to a variety of serious health problems linked to destruction of vitamin B12 andfolic acid.

Risks of specific agents

The hypoxic effect of inhalants can cause damage to many organ systems (particularly thebrain, which has a very low tolerance for oxygen deprivation), but there can also be additional toxicity resulting from either the physical properties of the compound itself or additional ingredients present in a product. Organochlorine solvents are particularly hazardous; many of these are now restricted in developed countries due to their environmental impact.

Methylene chloride, after being metabolized, can cause carbon monoxide poisoning. Gasoline sniffing

can cause lead poisoning, in locations where leaded gas is not banned.

Ingestion of alkyl nitrites can cause methemoglobinemia, and by inhalation it has not beenruled out.

Carbon tetrachloride can cause significant damage to multiple systems, but its associationwith liver damage is so strong that it is used in animal models to induce liver injury.

Use of butane, propane, nitrous oxide and other inhalants can create a risk of freezing burnsfrom contact with the extremely cold liquid . The risk of such contact is greatly increased by

the impaired judgement and motor coordination brought on by inhalant intoxication.Benzene use can cause bone marrow depression. It is also a known carcinogen.

Toluene can damage myelin.

Toxicity may also result from the pharmacological properties of the drug; excess NMDA antagonism can completely block calcium influx into neurons and provoke cell death through apoptosis, although this is more likely to be a long-term result of chronic solventuse than a consequence of short-term use.

Sudden sniffing death syndrome

Inhaling butane gas can cause drowsiness, unconsciousness, asphyxia, and cardiac arrhythmia. Butane is the most commonly misused volatile solvent in the UK and caused 52% of solvent-related deaths in 2000. When butane is sprayed directly into the throat, thejet of fluid can cool rapidly to −20 °C by adiabatic expansion, causing prolonged laryngospasm.

Some inhalants can also indirectly cause sudden death by cardiac arrest, in a syndrome known as "sudden sniffing death". The anaesthetic gases present in the inhalants appear tosensitize the user to adrenaline and, in this state, a sudden surge of adrenaline (e.g., from afrightening hallucination or run-in with aggressors), may cause fatal cardiac arrhythmia.

Furthermore, the inhalation of any gas that is capable of displacing oxygen in the lungs (especially gases heavier than oxygen) carries the risk of hypoxia as a result of the very mechanism by which breathing is triggered. Since reflexive breathing is prompted by elevated carbon dioxide levels (rather than diminished blood oxygen levels), breathing a concentrated, relatively inert gas (such as computer-duster tetrafluoroethane or nitrous oxide) that removes carbon dioxide from the blood without replacing it with oxygen will produce no outward signs of suffocation even when the brain is experiencing hypoxia. Oncefull symptoms of hypoxia appear, it may be too late to breathe without assistance, especiallyif the gas is heavy enough to lodge in the lungs for extended periods. Even completely inert gases, such as argon, can have this effect if oxygen is largely excluded.

Legal aspects

Even though solvent glue is normally a legal product, there is a case where a court has ruledthat supplying glue to children is illegal. Khaliq v HM Advocate was a Scottish criminal casedecided by the High Court of Justiciary on appeal, in which it was decided that it was an offense at common law to supply glue-sniffing materials that were otherwise legal in the knowledge that they would be used recreationally by children. Two shopkeepers in Glasgowwere arrested and charged with supplying to children "glue-sniffing kits" consisting of a quantity of petroleum-based glue in a plastic bag. They argued there was nothing illegal about the items that they had supplied. On appeal, the High Court took the view that, even though glue and plastic bags might be perfectly legal, everyday items, the two shopkeepersknew perfectly well that the children were going to use the articles as inhalants and the charge on the indictment should stand. When the case came to trial at Glasgow High Court the two were sentenced to three years' imprisonment.

"Thirty-eight of 50 [US] states have enacted laws making various inhalants unavailable tothose

under the age of 18. Other states prohibit the sale of these items to anyone withoutrecognition of purpose for the purchase. Some states mandate laws against using these products for purposes of getting high, while some states have laws about possessing certain inhalants. Nearly every state imposes fines and jail terms for violation of their specific laws."

"Connecticut law bans the unauthorized manufacture or compounding, possession, control, sale, delivery, or administration of any "restricted substance". It defines restricted substances as... specific volatile substances if they are sold, compounded, possessed or controlled, or delivered or administered to another person for breathing, inhaling, sniffing, or drinking to induce a stimulant, depressant, or hallucinogenic effect. Violators can be fined upto $100." As well, 24 states "ban the use, possession, or sale or other distribution of inhalants... like glue and solvents."

"Louisiana prohibits the sale, transfer, or possession of model glue and inhalable toluene substances to minors. In Ohio, it is illegal to inhale certain compounds for intoxication—a common, general prohibition other states have enacted. Some states draw their prohibitionsmore narrowly... In Massachusetts, retailers must ask minors for identification before sellingthem glue or cement that contains a solvent that can release toxic vapors."

Propellant gases

"New Jersey... prohibits selling or offering to sell minors products containingchlorofluorocarbon that is used in refrigerant."

The sale of alkyl nitrite-based poppers was banned in Canada in 2013. Although not considered a narcotic and not illegal to possess or use, they are considered a drug. Sales that are not authorized can now be punished with fines and prison. Since 2007, reformulatedpoppers containing isopropyl nitrite are sold in Europe because only isobutyl nitrite is prohibited. In France, the sale of products containing butyl nitrite, pentyl nitrite, or isomers thereof, has been prohibited since 1990 on grounds of danger to consumers. In 2007, the government extended this prohibition to all alkyl nitrites that were not authorized for sale asdrugs. After litigation by sex shop owners, this extension was quashed by the Council of State on the grounds that the government had failed to justify such a blanket prohibition: according to the court, the risks cited, concerning rare accidents often following abnormal usage, rather justified compulsory warnings on the packaging.

In the United Kingdom, poppers are widely available and frequently (legally) sold in gay

clubs/bars, sex shops, drug paraphernalia head shops, over the Internet and on markets. Itis illegal under Medicines Act 1968 to sell them advertised for human consumption, and tobypass this, they are usually sold as odorizers. In the U.S., originally marketed as a prescription drug in 1937, amyl nitrite remained so until 1960, when the Food and Drug Administration removed the prescription requirement due to its safety record. This requirement was reinstated in 1969, after observation of an increase in recreational use.
Other alkyl nitrites were outlawed in the U.S. by Congress through the Anti-Drug Abuse Actof 1988. The law includes an exception for commercial purposes. The term commercial purpose is defined to mean any use other than for the production of consumer products containing volatile alkyl nitrites meant for inhaling or otherwise introducing volatile alkyl nitrites into the human body for euphoric or physical effects. The law came into effect in 1990. Visits to retail outlets selling these products reveal that some manufacturers have since reformulated their products to abide by the regulations, through the use of the legal cyclohexyl nitrite as the primary ingredient in their products, which are sold as video head cleaners, polish removers, or room odorants.

Nitrous oxide

Nitrous oxide "whippets" are small aerosol containers designed for charging whipped cream dispensers.

In the United States, possession of nitrous oxide is legal under federal law and is not subjectto DEA purview. It is, however, regulated by the Food and Drug Administration under the Food Drug and Cosmetics Act; prosecution is possible under its "misbranding" clauses, prohibiting the sale or distribution of nitrous oxide for the purpose of human consumption as a recreational drug. Many states have laws regulating the possession, sale, and distribution of nitrous oxide. Such laws usually ban distribution to minors or limit the amount of nitrous oxide that may be sold without a special license. For example, in the stateof California, possession for recreational use is prohibited and qualifies as a misdemeanor. In New Zealand, the Ministry of Health has warned that nitrous oxide is a prescription medicine, and its sale or possession without a prescription is an offense under the Medicines Act. This statement would seemingly prohibit all non-medicinal uses of the chemical, though it is implied that only recreational use will be legally targeted. In India, for general anesthesia purposes, nitrous oxide is available as Nitrous Oxide IP. India's gas cylinder rules (1985) permit the transfer of gas from one cylinder to another for breathing purposes. Because India's Food & Drug Authority (FDA-India) rules state that transferring a drug from one container to another (refilling) is equivalent to manufacturing, anyone found doing so must possess a drug manufacturing license.

Patterns of non-medical use

Inhalant drugs are often used by children, teenagers, incarcerated or institutionalized people,and impoverished people, because these solvents and gases are ingredients in hundreds of legally available, inexpensive products, such as deodorant sprays, hair spray, contact cement and aerosol air fresheners. However, most users tend to be "... adolescents (betweenthe ages of 12 and 17)." In some countries, chronic, heavy inhalant use is concentrated in marginalized, impoverished communities. Young people who become used to heavy amounts of inhalants chronically are also more likely to be those who are isolated from theirfamilies and community. The article "Epidemiology of Inhalant Abuse: An International Perspective" notes that "[t]he most serious form of obsession with inhalant use probably occurs in countries other than the United States where young children live on the streets completely without family ties. These groups almost always use inhalants at very high levels (Leal et al. 1978). This isolation can make it harder to keep in touch with the sniffer and encourage him or her to stop sniffing."

The article also states that "... high [inhalant use] rates among barrio Hispanics almost undoubtedly are related to the poverty, lack of opportunity, and social dysfunction that occurin barrios" and states that the "... same general tendency appears for Native-American youth" because "... Indian reservations are among the most disadvantaged environments in the United States; there are high rates of unemployment, little opportunity, and high rates ofalcoholism and other health problems." There are a wide range of social problems associated with inhalant use, such as feelings of distress, anxiety and grief for the community; violence and damage to property; violent crime; stresses on the juvenile justice system; and stresses on youth agencies and support services.

Opioid use disorder

Opioid use disorder (OUD) is a substance use disorder relating to the use of an opioid. Anysuch disorder causes significant impairment or distress. Signs of the disorder include a strong desire to use opioids, increased tolerance to opioids, difficulty fulfilling obligations,trouble reducing use, and withdrawal symptoms with discontinuation. Opioid withdrawal symptoms may include nausea, muscle aches, diarrhea, trouble sleeping, agitation, and a low mood. Addiction and dependence are components of a substance use disorder.
Complications may include opioid overdose, suicide, HIV/AIDS, hepatitis C, and problems atschool, work, or home.

Opioids include substances such as heroin, morphine, fentanyl, codeine, dihydrocodeine, oxycodone, and hydrocodone. In the United States, a majority of heroin users begin by usingprescription opioids that may also be bought illegally. Risk factors for misuse include a history of substance use, substance use among family and friends, mental illness, low socioeconomic status, and race. Diagnosis may be based on criteria by the American Psychiatric Association in the DSM-5. If more than two of eleven criteria are present during a year, the diagnosis is said to be present.

Individuals with an opioid use disorder are often treated with opioid replacement therapy using methadone or buprenorphine. Being on such treatment reduces the risk of death. Additionally, individuals may benefit from cognitive behavioral therapy, other forms of support from mental health professionals such as individual or group therapy, twelve-step programs, and other peer support programs. The medication naltrexone may also be usefulto prevent relapse. Naloxone is useful for treating an opioid overdose and giving those at risk naloxone to take home is beneficial.

In 2013, opioid use disorders affected about 0.4% of people. As of 2016, about 27 million people are affected. Long term opioid use occurs in about 4% of people following their use for trauma or surgery-related pain. Onset is often in young adulthood. Males are affected more often than females. It resulted in 122,000 deaths worldwide in 2015, up from 18,000 deaths in 1990. In the United States during 2020 alone, there were more than 65,000 deathsdue to opioid overdose, of which more than 15,000 were the result of heroin use.

Addiction and dependence are components of a substance use disorder and addiction represents the more severe form. Opioid dependence can occur as physical dependence,psychological dependence, or both.

Withdrawal

Opioid withdrawal can occur with a sudden decrease in, or the cessation of, opioids after prolonged use. Onset of withdrawal depends on which opioid was used last. With heroin thistypically occurs five hours after use, while with methadone it might not occur until two days later. The length of time that major symptoms occur also depends on the opioid used. For

heroin withdrawal, symptoms are typically greatest at two to four days, and can last for up totwo weeks. Less significant symptoms may remain for an even longer period, in which case the withdrawal is known as post-acute-withdrawal syndrome.

Agitation

Anxiety

Muscle pains

Increased tearing

Trouble sleeping

Runny nose

Sweating Yawning

Goose bumps

Dilated pupils

Diarrhea

Fast heart rate

High blood pressure

Abdominal cramps

Shakiness

Cravings

Sneezing

Treatment of withdrawal may include methadone and buprenorphine. Medications fornausea or diarrhea may also be used.

Opioid intoxication

Signs and symptoms of opioid intoxication include:

Decreased perception of pain
Euphoria

Confusion

Desire to sleep

Nausea

Constipation

Miosis

Bradycardia

Hypotension

Hypokinesis (slowed movement)Head

nodding

Slurred speech

Hypothermia

Opioid overdose

Signs and symptoms of opioid overdose include, but are not limited to:

Pin-point pupils may occur. Patient presenting with dilated pupils may still be experiencingan opioid overdose.

Decreased heart rate Decreased

body temperatureDecreased

breathing

Altered level of consciousness. People may be unresponsive or unconscious.Pulmonary edema

(fluid accumulation in the lungs)

Shock

Death

Cause

Opioid use disorder can develop as a result of self-medication. Scoring systems have beenderived to assess the likelihood of opiate addiction in chronic pain patients. Prescription opioids are the source of nearly half of misused opioids and the majority of these are initiated for trauma or surgery pain management. Further to this, healthcare practitioners

have long been aware that despite the effective use of opioids for managing pain, the empirical evidence that supports the use of opioids long term is minimal. In addition to this,many studies that involved patients with chronic pain have failed to show any sustained improvement in their pain or ability to function with long term opioid use.

According to position papers on the treatment of opioid dependence published by the UnitedNations Office on Drugs and Crime and the World Health Organization, care providers should not treat opioid use disorder as the result of a weak moral character or will but as a medical condition. Some evidence suggests the possibility that opioid use disorders occur due to genetic or other chemical mechanisms which may be difficult to identify or change, such as dysregulation of brain circuitry involving reward and volition. However, the exact mechanisms involved are unclear, leading to debate regarding the influence of biology and free will.

Dependence

Drug dependence is an adaptive state associated with a withdrawal syndrome upon cessation of repeated exposure to a stimulus (e.g., drug intake). Dependence is a component of a substance use disorder. Opioid dependence can manifest as physicaldependence, psychological dependence, or both.

Increased brain-derived neurotrophic factor (BDNF) signaling in the ventral tegmental area (VTA) has been shown to mediate opioid-induced withdrawal symptoms via downregulationof insulin receptor substrate 2 (IRS2), protein kinase B (AKT), and mechanistic target of rapamycin complex 2 (mTORC2). As a result of downregulated signaling through these proteins, opiates cause VTA neuronal hyperexcitability and shrinkage (specifically, the size of the neuronal soma is reduced). It has been shown that when an opiate-naive person begins using opiates in concentrations that induce euphoria, BDNF signaling increases in the VTA.

Upregulation of the cyclic adenosine monophosphate (cAMP) signal transduction pathway by cAMP response element binding protein (CREB), a gene transcription factor, in the nucleus accumbens is a common mechanism of psychological dependence among severalclasses of drugs of abuse. Upregulation of the same pathway in the locus coeruleus is also a mechanism responsible for certain aspects of opioid-induced physical dependence.

Opioid receptors

A genetic basis for the efficacy of opioids in the treatment of pain has been demonstrated forseveral specific variations; however, the evidence for clinical differences in opioid effects is ambiguous. The pharmacogenomics of the opioid receptors and their endogenous ligands have been the subject of intensive activity in association studies. These studies test broadlyfor a number of phenotypes, including opioid dependence, cocaine dependence, alcohol dependence, methamphetamine dependence/psychosis, response to naltrexone treatment, personality traits, and others. Major and minor variants have been reported for every receptor and ligand coding gene in both coding sequences, as well as regulatory regions.

Newer approaches shift away from analysis of specific genes and regions, and are based onan unbiased screen of genes across the entire genome, which have no apparent relationshipto the phenotype in question. These GWAS studies yield a number of implicated genes, although many of them code for seemingly unrelated proteins in processes such as cell adhesion, transcriptional regulation, cell structure determination, and RNA, DNA, and proteinhandling/modifying.

118A>G variant

While over 100 variants have been identified for the opioid mu-receptor, the most studied mu-receptor variant is the non-synonymous 118A>G variant, which results in functional changes to the receptor, including lower binding site availability, reduced mRNA levels, altered signal transduction, and increased affinity for beta-endorphin. In theory, all of thesefunctional changes would reduce the impact of exogenous opioids, requiring a higher doseto achieve the same therapeutic effect. This points to a potential for greater addictive capacity in these individuals who require higher dosages to achieve pain control. However,evidence linking the 118A>G variant to opioid dependence is mixed, with associations shown in a number of study groups, but negative results in other groups. One explanation for the mixed results is the possibility of other variants

which are in linkage disequilibrium with the 118A>G variant and thus contribute to different haplotype patterns that more specifically associated with opioid dependence.

Non-opioid receptor genes

The preproenkephalin gene, PENK, encodes for the endogenous opiates that modulate pain perception, and are implicated in reward and addiction. (CA) repeats in the 3' flanking sequence of the PENK gene was associated with greater likelihood of opiate dependence inrepeated studies. Variability in the MCR2 gene, encoding melanocortin receptor type 2 has been associated with both protective effects and increased susceptibility to heroin addiction. The CYP2B6 gene of the cytochrome P450 family also mediates breakdown of opioids and thus may play a role in dependence and overdose.

Diagnosis

The DSM-5 guidelines for the diagnosis of opioid use disorder require that the individual hasa significant impairment or distress related to opioid uses. To make the diagnosis two or more of eleven criteria must be present in a given year:

More opioids are taken than intended

The individual is unable to decrease the number of opioids used

Large amounts of time are spent trying to obtain opioids, use opioids, or recover from takingthem

The individual has cravings for opioids

Difficulty fulfilling professional duties at work or school

Continued use of opioids leading to social and interpersonal consequencesDecreased social or

recreational activities

Using opioids despite being in physically dangerous settings

Continued use despite opioids worsening physical or psychological health (i.e. depression, constipation)

Tolerance

Withdrawal

The severity can be classified as mild, moderate, or severe based on the number of criteriapresent.

Prevention

The CDC gives specific recommendations for prescribers regarding initiation of opioids, clinically appropriate use of opioids, and assessing possible risks associated with opioid therapy. Large retail pharmacy chains in the US are implementing protocols, guidelines, andinitiatives to take back unused opioids, providing naloxone kits, and being vigilant for suspicious prescriptions. Insurance programs can help limit opioid use by setting quantity limits on prescriptions or requiring prior authorizations for certain medications.

Opioid related deaths

Naloxone is used for the emergency treatment of an overdose. It can be given by many routes (e.g., intramuscular, intravenous, subcutaneous, intranasal, and inhalation) and acts quickly by displacing opioids from opioid receptors and preventing activation of these receptors by opioids. Naloxone kits are recommended for laypersons who may witness an opioid overdose, for individuals with large prescriptions for opioids, those in substance use treatment programs, or who have been recently released from incarceration. Since this is a life-saving medication, many areas of the United States have implemented standing orders for law enforcement to carry and give naloxone as needed. In addition, naloxone could be used to challenge a person's opioid abstinence status prior to starting a medication such asnaltrexone, which is used in the management of opioid addiction.

Good Samaritan laws typically protect bystanders that administer naloxone. In the United States, at least 40 states have Good Samaritan laws to encourage bystanders to take actionwithout fear of prosecution. As of 2019, 48 states allow for a pharmacist to have the authority to distribute naloxone without an individual prescription.

Homicide, suicide, accidents and liver disease are also opioid related causes of death for those with OUD. Many of these opioid related causes of death are unnoticed due to the oftenlimited information provided on death certificates.

Management

Opioid use disorders typically require long-term treatment and care with the goal of reducing risks for the individual, reducing criminal behaviour, and improving the long-term physical and psychological condition of the person. Some strategies aim to reduce drug useand lead to abstinence from opioids, while others attempt to stabilize on prescribed methadone or buprenorphine with continued replacement therapy indefinitely. No single treatment works for everyone, so several strategies have been developed including therapy and drugs.

As of 2013 in the US, there was a significant increase of prescription opioid abuse comparedto illegal opiates like heroin. This development has also implications for the prevention, treatment and therapy of opioid dependence. Though treatment reduces mortality rates, theperiod during the first four weeks after treatment begins and the four weeks after treatment ceases are the times that carry the highest risk for drug-related deaths. These periods of increased vulnerability are significant because many of those in treatment leave programs during these critical periods.

Medications

Opioid replacement therapy (ORT) involves replacing an opioid, such as heroin, with a longeracting but less euphoric opioid. Commonly used drugs for ORT are methadone or buprenorphine which are taken under medical supervision. As of 2018, buprenorphine/naloxone is preferentially recommended, as the addition of the opioid antagonist naloxone is believed to reduce the risk of

abuse via injection or insufflation without causing impairment.

The driving principle behind ORT is the program's capacity to facilitate a resumption of stability in the user's life, while the patient experiences reduced symptoms of drug withdrawal and less intense drug cravings; a strong euphoric effect is not experienced as a result of the treatment drug. In some countries (not the US, or Australia), regulations enforcea limited time for people on ORT programs that conclude when a stable economic and psychosocial situation is achieved. (People with HIV/AIDS or hepatitis C are usually excluded from this requirement.) In practice, 40–65% of patients maintain abstinence from additional opioids while receiving opioid replacement therapy and 70–95% can reduce their use significantly. Along with this is a concurrent elimination or reduction in medical (improper diluents, non-sterile injecting equipment), psychosocial (mental health, relationships), and legal (arrest and imprisonment) issues that can arise from the use of illegal opioids. Clonidine or lofexidine can help treat the symptoms of withdrawal.

Participation in methadone and buprenorphine treatment reduces the risk of mortality due to overdose. The starting of methadone and the time immediately after leaving treatment with both drugs are periods of particularly increased mortality risk, which should be dealt with byboth public health and clinical strategies. ORT has proven to be the most effective treatmentfor improving the health and living condition of people experiencing illegal opiate use or dependence, including mortality reduction and overall societal costs, such as the economic loss from drug-related crime and healthcare expenditure. ORT is endorsed by the World Health Organization, United Nations Office on Drugs and Crime and UNAIDS as being effective at reducing injection, lowering risk for HIV/AIDS, and promoting adherence to antiretroviral therapy.

Buprenorphine and methadone work by reducing opioid cravings, easing withdrawal symptoms, and blocking the euphoric effects of opioids via cross-tolerance, and in the caseof buprenorphine, a high-affinity partial agonist, also due to opioid receptor saturation. It is this property of buprenorphine that can induce acute withdrawal when administered beforeother opioids have left the body. Naltrexone, a μ-opioid receptor antagonist, also blocks theeuphoric effects of opioids by occupying the opioid receptor, but it does not activate it, so itdoes not produce sedation, analgesia, or euphoria, and thus it has no potential for abuse or diversion.

In the United States, since March 2020 as a result of the COVID-19 pandemic, buprenorphinemay be dispensed via telemedicine.

The ultimate aim of methadone maintenance is for the individual to return to a more normallife. They could be eligible for drug dependency care, career counseling, and educational assistance once they start taking methadone under medical supervision. They can self-referto social service providers as they continue to feel better and want to get back on their feet. Methadone may even be able to assist these individuals in avoiding relapse. Methadone is along-acting drug, which means it sticks to the same opioid receptors in the brain as opium and prescription painkillers. As a result, patients who are taking methadone as part of an overdose treatment procedure will not feel opioid cravings or the severe withdrawal effects that come with it. This will encourage people in rehab to concentrate more on medication, laying a solid foundation for healing, rather than constantly fighting cravings and relapse impulses. Methadone is a long-acting drug that can last up to 56 hours

in the body. This means it fits better as a preventive drug so it doesn't require regular dosing during the day. Methadone users in detox also find more luck in therapy because they don't have to deal with constant opioid cravings or the severity of acute withdrawal symptoms. Advantages of methadone include:

Reduction in infectious disease due to the cessation of opiate misuse, especially injectiondrug abuse

Reduction in illegal crime due to the cessation in illicit drug usageOverall

increase in quality of life

Improved social functioning

More attendance in alcohol therapy since withdrawal symptoms aren't a diversion

Methadone replacement therapy will also help people achieve stabilization early on in their rehabilitation. People should devote 100% of their time to recovery, helping them to solve the underlying problems that lead to their opiate addiction. They will get a career and start to find a better balance in their lives. It also enables parents to continue raising their children ina safe home environment.

When their conditions improve and they want to refrain from taking methadone, they mustbe properly weaned off the medication, which must be done under medical observation.

Although other medication-assisted therapies for opiate addiction, such as buprenorphine, are available, methadone is often seen as the most promising alternative for people who are heavily addicted to opiates. Methadone has a number of serious side effects, including:

Slowed breathing

Sexual dysfunction

Nausea

Vomiting

Restlessness

Itchy eyes

Dosages can be adjusted after 1–2 days, or another medication may be recommended for your situation if you experience side effects. Lung and breathing complications are possiblelong-term side effects of methadone use. Methadone, as an opiate, has the potential to be addictive. Any opponents believe that replacement drugs only substitute one addiction withanother, and that methadone can be manipulated and exploited in some cases. Long-term usage has the ability to cause brain changes. Methadone causes changes in thought, cognitive performance, and memory by influencing nerve cells in the brain. An initial review is performed during alcohol therapy. The person will be evaluated and interviewed during this evaluation, and then the treatment team will then devise the optimal treatment plan forthat individual.

Buprenorphine

Buprenorphine is a partial opioid receptor agonist. Unlike methadone and other full opioidreceptor agonists, buprenorphine is less likely to cause respiratory depression due to its ceiling effect. Treatment with buprenorphine may be associated with reduced mortality.
Buprenorphine under the tongue is often used to manage opioid dependence. Preparationswere approved for this use in the United States in 2002. Some formulations of buprenorphine incorporate the opiate antagonist naloxone during the production of the pillform to prevent people from crushing the tablets and injecting them, instead of using the sublingual (under the tongue) route of administration.

Other opioids

Evidence of effects of heroin maintenance compared to methadone are unclear as of 2010. ACochrane review found some evidence in opioid users who had not improved with other treatments. In Switzerland, Germany, the Netherlands, and the United Kingdom, long-term injecting drug users who do not benefit from methadone and other medication options may be treated with injectable heroin that is administered under the supervision of medical staff.Other countries where it is available include Spain, Denmark, Belgium, Canada, and Luxembourg.

Dihydrocodeine in both extended-release and immediate-release form are also sometimes used for maintenance treatment as an alternative to methadone or buprenorphine in some European countries. Dihydrocodeine is an opioid agonist. It may be used as a second line treatment. A 2020 systematic review found low quality evidence that dihydrocodeine may beno more effective than other routinely used medication interventions in reducing illicit opiateuse.

An extended-release morphine confers a possible reduction of opioid use and with fewer depressive symptoms but overall more adverse effects when compared to other forms of long-acting opioids. Retention in treatment was not found to be significantly different. It isused in Switzerland and more recently in Canada.

Naltrexone

Naltrexone is an opioid receptor antagonist used for the treatment of opioid addiction. Naltrexone is not as widely used as buprenorphine or methadone for OUD due to low rates ofpatient acceptance, non-adherence due to daily dosing, and difficulty achieving abstinence from opioids before beginning treatment. Additionally, dosing naltrexone after recent opioid use could lead to precipitated withdrawal. Conversely, naltrexone antagonism at the opioid receptor can be overcome with higher doses of opioids. Naltrexone monthly IM injections received FDA approval in 2010, for the treatment of opioid dependence in abstinent opioid users.

Behavioral therapy

Cognitive behavioral therapy (CBT), a form of psychosocial intervention that is used to improve

mental health, may not be as effective as other forms of treatment. CBT primarilyfocuses on an individual's coping strategies to help change their cognition, behaviors andemotions about the problem. This intervention has demonstrated success in many psychiatric conditions (e.g., depression) and substance use disorders (e.g., tobacco).
However, the use of CBT alone in opioid dependence has declined due to the lack of efficacy,and many are relying on medication therapy or medication therapy with CBT, since both were found to be more efficacious than CBT alone. A form of CBT therapy known as motivational interviewing (MI) is often used opioid use disorder. MI leverages a person intrinsic motivation to recover through education, formulation of relapse prevention strategies, reward for adherence to treatment guidelines, and positive thinking to keep motivation high—which are based on a person's socioeconomic status, gender, race, ethnicity, sexual orientation, and their readiness to recover.

Twelve-step programs

While medical treatment may help with the initial symptoms of opioid withdrawal, once thefirst stages of withdrawal are through, a method for long-term preventative care is attendance at 12-step groups such as Narcotics Anonymous. Narcotics Anonymous is a global service that provides multilingual recovery information and public meetings free of charge. Some evidence supports the use of these programs in adolescents as well.

The 12-step program is an adapted form of the Alcoholics Anonymous program. The program strives to help create behavioural change by fostering peer-support and self-help programs. The model helps assert the gravity of addiction by enforcing the idea that addictsmust surrender to the fact that they are addicted and be able to recognize the problem. It also helps maintain self-control and restraint to help promote one's capabilities.

Digital care programs

Digital care program have increased in number since the Coronavirus pandemic mandated the increased usage of remote healthcare options. These programs offer treatment and continuing care remotely, via smartphone and desktop applications. This often includes remote substance testing, access to peer support meetings, recovery coaching or therapy, and self-guided learning modules. Examples of digital care programs for opioid use disorderinclude: Chess, Pear Therapeutics, DynamiCare Health, Kaden Health and WeConnect.

Epidemiology

Globally, the number of people with opioid dependence increased from 10.4 million in 1990 to 15.5 million in 2010. In 2016, the numbers rose to 27 million people who experienced thisdisorder. Opioid use disorders resulted in 122,000 deaths worldwide in 2015, up from 18,000deaths in 1990. Deaths from all causes rose from 47.5 million in 1990 to 55.8 million in 2013.

Overdose deaths involving opioids, United States. Deaths per 100,000 population by year.

The current epidemic of opioid abuse is the most lethal drug epidemic in American history. In 2008, there were four times as many deaths due to overdose than there were in 1999. In 2017, in the US, "the age-adjusted drug poisoning death rate involving opioid analgesics increased from 1.4 to 5.4

deaths per 100,000 population between 1999 and 2010, decreased
to 5.1 in 2012 and 2013, then increased to 5.9 in 2014, and to 7.0 in 2015. The age-adjusteddrug poisoning death rate involving heroin doubled from 0.7 to 1.4 deaths per 100,000 resident population between 1999 and 2011 and then continued to increase to 4.1 in 2015."

In 2017, the U.S. Department of Health and Human Services (HHS) announced a public health emergency due to an increase in the misuse of opioids. The administration introduced a strategic framework called the Five-Point Opioid Strategy, which includes providing access recovery services, increasing the availability of reversing agents for overdose, funding opioid misuse and pain research, changing treatments of people managing pain, and updating public health reports related to combating opioid drug misuse.

The US epidemic in the 2000s is related to a number of factors. Rates of opioid use and dependency vary by age, sex, race, and socioeconomic status. With respect to race the discrepancy in deaths is thought to be due to an interplay between physician prescribing and lack of access to healthcare and certain prescription drugs. Men are at higher risk for opioid use and dependency than women, and men also account for more opioid overdoses than women, although this gap is closing. Women are more likely to be prescribed pain relievers, be given higher doses, use them for longer durations, and may become dependentupon them faster.

Deaths due to opioid use also tend to skew at older ages than deaths from use of other illicitdrugs. This does not reflect opioid use as a whole, which includes individuals in younger agedemographics. Overdoses from opioids are highest among individuals who are between the ages of 40 and 50, in contrast to heroin overdoses, which are highest among individuals whoare between the ages of 20 and 30. 21- to 35-year-olds represent 77% of individuals who enter treatment for opioid use disorder, however, the average age of first-time use of prescription painkillers was 21.2 years of age in 2013. Among the middle class means of acquiring funds have included Elder financial abuse through a vulnerability of financial transactions of selling items and international dealers noticing a lack of enforcement in theirtransaction scams throughout the Caribbean.

In 2018, the Massachusetts Supreme Judicial Court found that a probationer with opioid usedisorder could be detained for a parole violation after she tested positive for fentanyl.

In October 2021, New York Governor Kathy Hochul signed legislation to combat the opioidcrisis. This included establishing a program for the use of medication-assisted substanceuse disorder treatment for incarcerated individuals in state and local correctional facilities,decriminalizing the possession and sale of hypodermic needles and syringes, establishingan online directory for distributors of opioid antagonists, and expanding the number of eligible crimes committed by individuals with a substance use disorder that may be considered for diversion to a substance use treatment program. Until these laws were signed, incarcerated New Yorkers did not reliably have access to medication-assisted treatment and syringe possession was still a class A misdemeanor despite New York authorizing and funding syringe exchange and access programs. This legislation acknowledges the ways New York State laws have contributed to opioid deaths: in 2020 more than 5112 people died from overdoses in New York State, with 2192 deaths in New York City.

Sedative

A sedative or tranquilliser is a substance that induces sedation by reducing irritability or excitement.

They are CNS depressants and interact with brain activity causing its deceleration. Various kinds of sedatives can be distinguished, but the majority of them affectthe neurotransmitter gamma-aminobutyric acid (GABA). In spite of the fact that each sedative acts in its own way, most produce relaxing effects by increasing GABA activity.

This group is related to hypnotics. The term sedative describes drugs that serve to calm orrelieve anxiety, whereas the term hypnotic describes drugs whose main purpose is to initiate, sustain, or lengthen sleep. Because these two functions frequently overlap, and because drugs in this class generally produce dose-dependent effects (ranging from anxiolysis to loss of consciousness) they are often referred to collectively as
sedative-hypnotic drugs.

Sedatives can be used to produce an overly-calming effect (alcohol being the most commonsedating drug). In the event of an overdose or if combined with another sedative, many of these drugs can cause deep unconsciousness and even death.

Advances in pharmacology have permitted more specific targeting of receptors, and greater selectivity of agents, which necessitates greater precision when describing these agents and their effects:

Anxiolytic refers specifically to the effect upon anxiety. (However, some benzodiazepinescan be all three: sedatives, hypnotics, and anxiolytics).

Tranquilizer can refer to anxiolytics or antipsychotics. Soporific and

sleeping pill are near-synonyms for hypnotics.

The term "chemical cosh"

The term "chemical cosh" (a club) is sometimes used popularly for a strong sedative,particularly for:

widespread dispensation of antipsychotic drugs in residential care to make people withdementia easier to manage. use of methylphenidate to calm children with attention deficit hyperactivity disorder, thoughparadoxically this drug is known to be a stimulant.

Types of sedatives

Barbiturates

Amobarbital

Benzylbutylbarbiturate

Butalbital Pentobarbital

Phenobarbital

Secobarbital

Sodium thiopental

Benzodiazepines

Alprazolam

Chlordiazepoxide

Clobazam

Clonazepam

Clorazepate

Diazepam

Estazolam Etizolam

Flunitrazepam

Lorazepam

Midazolam

Nitrazepam

Oxazepam

Temazepam

Triazolam Nonbenzodiazepine

hypnoticsEszopiclone

Zaleplon

Zolpidem

Zopiclone

Orexin antagonists

Lemborexant

Suvorexant

First generation Antihistamines

Brompheniramine

Captodiame

Chlorpheniramine

Cyproheptadine

Dimenhydrinate

Diphenhydramine

Doxylamine

Hydroxyzine

Promethazine General

anaestheticsChloral

hydrate Chlorobutanol

Chloroform

Cyclopropane

Desflurane

Diethyl ether

Enflurane

Esketamine

Ethyl chloride

Etomidate

Isoflurane

Halothane

Ketamine

Methoxyflurane

Nitrous oxide

Propofol

Sevoflurane

Xenon

Herbal sedatives

Cannabis Chamomile

Duboisia hopwoodii

Kava (Piper methysticum)

Lemon balm

Nepeta

Passiflora spp.(passiflora incarnata)

Physochlaina - notably P. infundibularis

Prostanthera striatiflora

Valerian

Methaqualone and analogues

Afloqualone

Cloroqualone

Diproqualone

Etaqualone

Mebroqualone

Mecloqualone

Methaqualone

Methylmethaqualone

Nitromethaqualone Skeletal

Muscle RelaxantsBaclofen

Carisoprodol

Chlorzoxazone

Clonidine

Cyclobenzaprine

Gabapentin

Meprobamate

Metaxalone

Methocarbamol

Orphenadrine

Phenibut

Pregabalin

Tizanidine

Opioids Alfentanil

Carfentanil

Codeine

Diamorphine

Fentanyl

Hydrocodone

Hydromorphone

Meperidine

Methadone

Morphine

Opium

Oxycodone

Oxymorphone

Propoxyphene

Remifentanil

Sufentanil

Tapentadol

Tramadol

Certain Neurosteroids

Allopregnanolone

Ganaxolone

Hydroxydione

Antidepressants

Amoxapine

Clomipramine

Desipramine

Doxepin

Imipramine

Mirtazapine

Nefazodone

Nortriptyline

Trazodone

Trimipramine

Antipsychotics

Asenapine

Clozapine

Fluphenazine

Haloperidol

Loxapine

Olanzapine

Prochlorperazine

Quetiapine

Thiothixene

Trifluoperazine

Orally active alcohols

2-methyl-2-butanol (2M2B)

Ethanol

Gamma-Hydroxybutyric acid

Others

Bromide salts (like potassium bromide)

Dexmedetomidine

Dextromethorphan

Glutethimide

Thalidomide

Therapeutic use

Doctors often administer sedatives to patients in order to dull the patient's anxiety related topainful or anxiety-provoking procedures. Although sedatives do not relieve pain in themselves, they can be a useful adjunct to analgesics in preparing patients for surgery, andare commonly given to patients before they are anaesthetized, or before other highly uncomfortable and invasive procedures like cardiac catheterization, colonoscopy or MRI.

Risks

Sedative dependence

Some sedatives can cause psychological and physical dependence when taken regularly over a period of time, even at therapeutic doses. Dependent users may get withdrawal symptoms ranging from restlessness and insomnia to convulsions and death. When usersbecome psychologically dependent, they feel as if they need the drug to function, althoughphysical dependence does not necessarily occur, particularly with a short course of use. Inboth types of dependences, finding and using the sedative becomes the focus in life. Both physical and psychological dependence can be treated with therapy.

Misuse

Many sedatives can be misused, but barbiturates and benzodiazepines are responsible for most of the problems with sedative use due to their widespread recreational or non-medicaluse. People who have difficulty dealing with stress, anxiety or sleeplessness may overuse orbecome dependent on sedatives. Some heroin users may take them either to supplement their drug or to substitute for it. Stimulant users may take sedatives to calm excessive jitteriness. Others take sedatives recreationally to relax and forget their worries. Barbiturate overdose is a factor in nearly one-third of all reported drug-related deaths. These include suicides and accidental drug poisonings. Accidental deaths sometimes occur when a drowsy, confused user repeats doses, or when sedatives are taken with alcohol.

A study from the United States found that in 2011, sedatives and hypnotics were a leading source of adverse drug events (ADEs) seen in the hospital setting: Approximately 2.8% of allADEs present on admission and 4.4% of ADEs that originated during a hospital stay were caused by a sedative or hypnotic drug. A second study noted that a total of 70,982 sedativeexposures were reported to U.S. poison control centers in 1998, of which 2310 (3.2%) resulted in major toxicity and 89 (0.1%) resulted in death. About half of all the people admitted to emergency rooms in the U.S. as a result of nonmedical use of sedatives have alegitimate prescription for the drug, but have taken an excessive dose or combined it with alcohol or other drugs.

There are also serious paradoxical reactions that may occur in conjunction with the use of sedatives that lead to unexpected results in some individuals. Malcolm Lader at the Instituteof Psychiatry in London estimates the incidence of these adverse reactions at about 5%, even in short-term use of the drugs. The paradoxical reactions may consist of depression, with or without suicidal tendencies, phobias, aggressiveness, violent behavior and symptoms sometimes misdiagnosed as psychosis.

Dangers of combining sedatives and alcohol

Sedatives and alcohol are sometimes combined recreationally or carelessly. Since alcohol isa strong depressant that slows brain function and depresses respiration, the two substances compound each other's actions and this combination can prove fatal.

Worsening of psychiatric symptoms

The long-term use of benzodiazepines may have a similar effect on the brain as alcohol, andare also implicated in depression, anxiety, posttraumatic stress disorder (PTSD), mania, psychosis, sleep disorders, sexual dysfunction, delirium, and neurocognitive disorders (including benzodiazepine-induced persisting dementia which persists even after the medications are stopped). As with alcohol, the effects of benzodiazepine on neurochemistry,such as decreased levels of serotonin and norepinephrine, are believed to be responsible fortheir effects on mood and anxiety. Additionally, benzodiazepines can indirectly cause or worsen other psychiatric symptoms (e.g., mood, anxiety, psychosis, irritability) by worseningsleep (i.e., benzodiazepine-induced sleep disorder). Like alcohol, benzodiazepines are commonly used to treat insomnia in the short-term (both prescribed and self-medicated), but worsen sleep in the long-term. While benzodiazepines can put people to sleep but, whileasleep, the drugs disrupt sleep architecture: decreasing sleep time, delaying time to REM sleep, and decreasing deep slow-wave sleep (the most restorative part of sleep for both energy and mood).

Dementia

Sedatives and hypnotics should be avoided in people with dementia, according to the medication appropriateness tool for co-morbid health conditions in dementia criteria. Theuse of these medications can further impede cognitive function for people with dementia,who are also more sensitive to side effects of medications.

Amnesia

Sedatives can sometimes leave the patient with long-term or short-term amnesia. Lorazepam is one such pharmacological agent that can cause anterograde amnesia. Intensive care unit patients who receive higher doses over longer periods, typically via IV drip, are more likely to experience such side effects. Additionally, the prolonged use of tranquilizers increases the risk of obsessive and compulsive disorder, where the person becomes unaware whether he has performed a scheduled activity or not, he may also repetitively perform tasks and still re-performs the same task trying to make-up for continuous doubts. Remembering names that were earlier known becomes an issue suchthat the memory loss becomes apparent.

Disinhibition and crime

Sedatives — most commonly alcohol but also GHB, Flunitrazepam (Rohypnol), and to a lesser extent, temazepam (Restoril), and midazolam (Versed) — have been reported for theiruse as date rape drugs (also called a Mickey) and being administered to unsuspecting patrons in bars or guests at parties to reduce the intended victims' defenses. These drugs are also used for robbing people.

Statistical overviews suggest that the use of sedative-spiked drinks for robbing people isactually much more common than their use for rape. Cases of criminals taking rohypnol themselves before they commit crimes have also been reported , as the loss of inhibitionsfrom the drug may increase their confidence to commit the offence, and the amnesia produced by the drug makes it difficult for police to interrogate them if they are caught.

Hypnotic

Hypnotic (from Greek Hypnos, sleep), or soporific drugs, commonly known as sleeping pills,are a class of psychoactive drugs whose primary function is to induce sleep (or surgical anesthesia) and to treat insomnia (sleeplessness).

This group of drugs is related to sedatives. Whereas the term sedative describes drugs that serve to calm or relieve anxiety, the term hypnotic generally describes drugs whose main purpose is to initiate, sustain, or lengthen sleep. Because these two functions frequently overlap, and because drugs in this class generally produce dose-dependent effects (rangingfrom anxiolysis to loss of consciousness), they are often referred to collectively as sedative-hypnotic drugs.

Hypnotic drugs are regularly prescribed for insomnia and other sleep disorders, with over 95% of insomnia patients being prescribed hypnotics in some countries. Many hypnotic drugs are habit-forming and—due to many factors known to disturb the human sleep pattern—a physician may instead recommend changes in the environment before and duringsleep, better sleep hygiene, the

avoidance of caffeine and alcohol or other stimulating substances, or behavioral interventions such as cognitive behavioral therapy for insomnia (CBT-I), before prescribing medication for sleep. When prescribed, hypnotic medication should be used for the shortest period of time necessary.

Among individuals with sleep disorders, 13.7% are taking or prescribed nonbenzodiazepines,while 10.8% are taking benzodiazepines, as of 2010, in the USA. Early classes of drugs, suchas barbiturates, have fallen out of use in most practices but are still prescribed for some patients. In children, prescribing hypnotics is not yet acceptable—unless used to treat night terrors or sleepwalking. Elderly people are more sensitive to potential side effects of daytimefatigue and cognitive impairments, and a meta-analysis found that the risks generally outweigh any marginal benefits of hypnotics in the elderly. A review of the literature regarding benzodiazepine hypnotics and Z-drugs concluded that these drugs can have adverse effects, such as dependence and accidents, and that optimal treatment uses the lowest effective dose for the shortest therapeutic time period, with gradual discontinuation in order to improve health without worsening of sleep.

Falling outside the above-mentioned categories, the neurohormone melatonin and itsanalogues (such as ramelteon) serve a hypnotic function.

Hypnotica was a class of somniferous drugs and substances tested in medicine of the1890s and later. These include Urethan, Acetal, Methylal, Sulfonal, paraldehyde,
Amylenhydrate, Hypnon, Chloralurethan and Ohloralamid or Chloralimid.

Research about using medications to treat insomnia evolved throughout the last half of the 20th century. Treatment for insomnia in psychiatry dates back to 1869, when chloral hydratewas first used as a soporific. Barbiturates emerged as the first class of drugs in the early 1900s, after which chemical substitution allowed derivative compounds. Although they werethe best drug family at the time (with less toxicity and fewer side effects), they were dangerous in overdose and tended to cause physical and psychological dependence.

During the 1970s, quinazolinones and benzodiazepines were introduced as safer alternatives to replace barbiturates; by the late 1970s, benzodiazepines emerged as thesafer drug.

Benzodiazepines are not without their drawbacks; substance dependence is possible, anddeaths from overdoses sometimes occur, especially in combination with alcohol and/or other depressants. Questions have been raised as to whether they disturb sleep architecture.

Nonbenzodiazepines are the most recent development (1990s–present). Although it is clearthat they are less toxic than barbiturates, their predecessors, comparative efficacy over benzodiazepines have not been established. Such efficacy is hard to determine without longitudinal studies. However, some psychiatrists recommend these drugs, citing research suggesting they are equally potent with less potential for abuse.

Other sleep remedies that may be considered "sedative-hypnotics" exist; psychiatrists will sometimes prescribe medicines off-label if they have sedating effects. Examples of these include mirtazapine (an antidepressant), clonidine (an older antihypertensive drug), quetiapine (an antipsychotic), and the over-the-counter allergy and antiemetic medicationsdoxylamine and

diphenhydramine. Off-label sleep remedies are particularly useful when first-line treatment is unsuccessful or deemed unsafe (as in patients with a history of substance abuse).

Types

Barbiturate

Barbiturates are drugs that act as central nervous system depressants, and can therefore produce a wide spectrum of effects, from mild sedation to total anesthesia. They are also effective as anxiolytics, hypnotics, and anticonvulsalgesic effects; however, these effects are somewhat weak, preventing barbiturates from being used in surgery in the absence of otheranalgesics. They have dependence liability, both physical and psychological. Barbiturates have now largely been replaced by benzodiazepines in routine medical practice – such as inthe treatment of anxiety and insomnia – mainly because benzodiazepines are significantly less dangerous in overdose. However, barbiturates are still used in general anesthesia, for epilepsy, and for assisted suicide. Barbiturates are derivatives of barbituric acid.

The principal mechanism of action of barbiturates is believed to be positive allostericmodulation of GABAA receptors.

Quinazolinones

Quinazolinones are also a class of drugs which function as hypnotic/sedatives that containa 4-quinazolinone core. Their use has also been proposed in the treatment of cancer.

Examples of quinazolinones include cloroqualone, diproqualone, etaqualone (Aolan, Athinazone, Ethinazone), mebroqualone, Afloqualone (Arofuto), mecloqualone (Nubarene,Casfen), and methaqualone (Quaalude).

Benzodiazepines

Benzodiazepines can be useful for short-term treatment of insomnia. Their use beyond 2 to4 weeks is not recommended due to the risk of dependence. It is preferred that benzodiazepines be taken intermittently—and at the lowest effective dose. They improve sleep-related problems by shortening the time spent in bed before falling asleep, prolongingthe sleep time, and, in general, reducing wakefulness. Like alcohol, benzodiazepines are commonly used to treat insomnia in the

short-term (both prescribed and self-medicated), but worsen sleep in the long-term. While benzodiazepines can put people to sleep (i.e., inhibit NREM stage 1 and 2 sleep), while asleep, the drugs disrupt sleep architecture by decreasing sleep time, delaying time to REM sleep, and decreasing deep slow-wave sleep (the most restorative part of sleep for both energy and mood).

Other drawbacks of hypnotics, including benzodiazepines, are possible tolerance to their effects, rebound insomnia, and reduced slow-wave sleep and a withdrawal period typified byrebound insomnia and a prolonged period of anxiety and agitation. The list of benzodiazepines approved for the treatment of insomnia is fairly similar among most countries, but which benzodiazepines are officially designated as first-line hypnotics prescribed for the treatment of insomnia can vary distinctly between countries.
Longer-acting benzodiazepines such as nitrazepam and diazepam have residual effects that may persist into the next day and are, in general, not recommended.

It is not clear as to whether the new nonbenzodiazepine hypnotics (Z-drugs) are better thanthe short-acting benzodiazepines. The efficacy of these two groups of medications is similar. According to the US Agency for Healthcare Research and Quality, indirect comparison indicates that side-effects from benzodiazepines may be about twice as frequent as from nonbenzodiazepines. Some experts suggest using nonbenzodiazepines preferentially as a first-line long-term treatment of insomnia. However, the UK National Institute for Health and Clinical Excellence (NICE) did not find any convincing evidence in favor of Z-drugs. A NICE review pointed out that short-acting Z-drugs were inappropriately compared in clinical trials with long-acting benzodiazepines. There have been no trials comparing short-acting Z-drugs with appropriate doses of short-acting benzodiazepines. Based on this, NICE recommended choosing the hypnotic based on cost and the patient's preference.

Older adults should not use benzodiazepines to treat insomnia—unless other treatments have failed to be effective. When benzodiazepines are used, patients, their caretakers, and their physician should discuss the increased risk of harms, including evidence which showstwice the incidence of traffic collisions among driving patients, as well as falls and hip fracture for all older patients.

Nonbenzodiazepine

Nonbenzodiazepines are a class of psychoactive drugs that are very "benzodiazepine-like"in nature. Nonbenzodiazepine pharmacodynamics are almost entirely the same as benzodiazepine drugs, and therefore entail similar benefits, side-effects and risks.
Nonbenzodiazepines, however, have dissimilar or entirely different chemical structures, andtherefore are unrelated to benzodiazepines on a molecular level.

Examples include zopiclone (Imovane, Zimovane), eszopiclone (Lunesta), zaleplon (Sonata),and zolpidem (Ambien, Stilnox, Stilnoct).

Research on nonbenzodiazepines is new and conflicting. A review by a team of researchers suggests the use of these drugs for people that have trouble falling asleep (but not staying asleep), as next-day impairments were minimal. The team noted that the safety of these drugs had been established, but called for more research into their long-term effectiveness in treating insomnia. Other evidence suggests that tolerance to nonbenzodiazepines may beslower to develop than with benzodiazepines. A different team was more skeptical, finding little benefit over benzodiazepines.

Melatonin

Melatonin, the hormone produced in the pineal gland in the brain and secreted in dim lightand darkness, among its other functions, promotes sleep in diurnal mammals.

Antihistamines

In common use, the term antihistamine refers only to compounds that inhibit action at theH1 receptor (and not H2, etc.).

Clinically, H1 antagonists are used to treat certain allergies. Sedation is a common side-effect, and some H1 antagonists, such as diphenhydramine (Benadryl) and doxylamine,are also used to treat insomnia.

Second-generation antihistamines cross the blood–brain barrier to a much lower degreethan the first ones. This results in their primarily affecting peripheral histamine receptors, and therefore having a much lower sedative effect. High doses can still induce the centralnervous system effect of drowsiness.

Antidepressants

Examples include:

Serotonin antagonists and reuptake inhibitorsTrazodone

Tricyclic antidepressants

Amitriptyline

Doxepin

Trimipramine

Tetracyclic antidepressants

Mianserin

Mirtazapine

Antipsychotics

Examples of antipsychotics with sedation as a side effect that are occasionally used forinsomnia:

First-generation

Chlorpromazine

Second-generation

Clozapine

Olanzapine

Quetiapine

Risperidone

Zotepine

Miscellaneous drugs

Alpha-adrenergic agonist

Clonidine

Guanfacine

Cannabinoids

Cannabidiol

Tetrahydrocannabinol

Orexin receptor antagonist

Suvorexant

Lemborexant

Gabapentinoids

Gabapentin

Pregabalin

Phenibut

Risks

The use of sedative medications in older people generally should be avoided. These medications are associated with poorer health outcomes, including cognitive decline.

Therefore, sedatives and hypnotics should be avoided in people with dementia, according tothe clinical guidelines known as the Medication Appropriateness Tool for Comorbid Health Conditions in Dementia (MATCH-D). The use of these medications can further impede cognitive function for people with dementia, who are also more sensitive to side effects of medications.

Anxiolytic

An anxiolytic (/ ˌ æŋksiəˈlɪtɪk, ˌ æŋksioʊ-/; also antipanic or antianxiety agent) is a medication or other intervention that reduces anxiety. This effect is in contrast to anxiogenicagents which increase anxiety. Anxiolytic medications are used for the treatment of anxiety disorders and their related psychological and physical symptoms.

Barbiturates

Barbiturates are powerful anxiolytics but the risk of abuse and addiction is high. Many experts consider these drugs obsolete for treating anxiety but valuable for the short-termtreatment of severe insomnia, though only after benzodiazepines or non-benzodiazepineshave failed.

Benzodiazepines

Benzodiazepines are prescribed to quell panic attacks. Benzodiazepines are also prescribedin tandem with an antidepressant for the latent period of efficacy associated with many ADsfor anxiety disorder. There is risk of benzodiazepine withdrawal and rebound syndrome if BZDs are rapidly discontinued. Tolerance and dependence may occur. The risk of abuse in this class of medication is smaller than in that of barbiturates. Cognitive and behavioral adverse effects are possible.

Benzodiazepines include: alprazolam (Xanax), bromazepam, chlordiazepoxide (Librium), clonazepam (Klonopin), diazepam (Valium), lorazepam (Ativan), oxazepam, temazepam, andTriazolam.

Antidepressants

Antidepressant medications can reduce anxiety. The SSRIs paroxetine and escitalopram andSNRIs venlafaxine and duloxetine are USFDA approved to treat generalized anxiety disorder.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are a class of medications used in the treatment of

depression, anxiety disorders, OCD and some personality disorders. SSRIs canincrease anxiety initially due to negative feedback through the serotonergic autoreceptors, for this reason a concurrent benzodiazepine can be used until the anxiolytic effect of the

SSRI occurs.

Serotonin–norepinephrine reuptake inhibitors

Serotonin–norepinephrine reuptake inhibitor (SNRIs) include venlafaxine and duloxetine drugs. Venlafaxine, in extended release form, and duloxetine, are indicated for the treatmentof GAD. SNRIs are as effective as SSRIs in the treatment of anxiety disorders.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have anxiolytic effects; however, side effects are often moretroubling or severe and overdose is dangerous. They are considered effective, but have generally been replaced by antidepressants that cause fewer adverse effects. Examples include imipramine, doxepin, amitriptyline, nortriptyline and desipramine.

Tetracyclic antidepressant

Mirtazapine has demonstrated anxiolytic effect comparable to SSRIs while rarely causing or exacerbating anxiety. Mirtazapine's anxiety reduction tends to occur significantly faster thanSSRIs.

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are first-generation antidepressants effective for anxiety treatment but their dietary restrictions, adverse effect profile and availability of newermedications have limited their use. MAOIs include phenelzine, isocarboxazid and tranylcypromine. Pyrazidol is a reversible MAOI that lacks dietary restriction.

Sympatholytics

Sympatholytics are a group of anti-hypertensives which inhibit activity of the sympathetic nervous system. Beta blockers reduce anxiety by decreasing heart rate and preventing shaking. Beta blockers include propranolol, oxprenolol, and metoprolol. The Alpha-1 agonistprazosin could be effective for PTSD. The Alpha-2 agonists clonidine and guanfacine have demonstrated both anxiolytic and anxiogenic effects.

Buspirone

Buspirone (Buspar) is a 5-HT1A receptor agonist used to treated generalized anxiety disorder. If an individual has taken a benzodiazepine, buspirone will be less effective.

Pregabalin

Pregabalin (Lyrica) produces anxiolytic effect after one week of use comparable to lorazepam, alprazolam, and venlafaxine with more consistent psychic and somatic anxietyreduction. Unlike BZDs, it does not disrupt sleep architecture nor does it cause cognitive orpsychomotor impairment.

Hydroxyzine

Hydroxyzine (Atarax) is an antihistamine originally approved for clinical use by the FDA in 1956. Hydroxyzine has a calming effect which helps ameliorate anxiety. Hydroxyzine efficacy is comparable to benzodiazepines in the treatment of generalized anxiety disorder.

Phenibut

Phenibut (Anvifen, Fenibut, Noofen) is an anxiolytic used in Russia. Phenibut is a GABAB receptor agonist, as well as an antagonist at α2δ subunit-containing voltage-dependent calcium channels (VDCCs), similarly to gabapentinoids like gabapentin and pregabalin. Themedication is not approved by the FDA for use in the United States, but is sold online as a supplement.

Mebicar

Mebicar is an anxiolytic produced in Latvia and used in Eastern Europe. Mebicar has an effect on the structure of limbic-reticular activity, particularly on the hypothalamus, as wellas on all 4 basic neuromediator systems – γ aminobutyric acid (GABA), choline, serotonin and adrenergic activity. Mebicar decreases noradrenaline, increases serotonin, and exertsno effect on dopamine.

Fabomotizole

Fabomotizole (Afobazole) is an anxiolytic drug launched in Russia in the early 2000s. Its mechanism of action is poorly-defined, with GABAergic, NGF and BDNF release promoting,MT1 receptor agonism, MT3 receptor antagonism, and sigma agonism thought to have some involvement.

Bromantane

Bromantane is a stimulant drug with anxiolytic properties developed in Russia during the late 1980s. Bromantane acts mainly by facilitating the biosynthesis of dopamine, through indirect genomic upregulation of relevant enzymes (tyrosine hydroxylase (TH) and aromaticL-amino acid decarboxylase (AAAD)).

Emoxypine

Emoxypine is an antioxidant that is also a purported anxiolytic. Its chemical structureresembles that of pyridoxine, a form of vitamin B6.

Menthyl isovalerate

Menthyl isovalerate is a flavoring food additive marketed as a sedative and anxiolytic drug inRussia under the name Validol.

Racetams

Some racetam based drugs such as aniracetam can have an antianxiety effect.

Etifoxine

Etifoxine has similar anxiolytic effects as benzodiazepine drugs, but does not produce the same levels of sedation and ataxia. Further, etifoxine does not affect memory and vigilance,and does not induce rebound anxiety, drug dependence, or withdrawal symptoms.

Alcohol

Alcohol is sometimes used as an anxiolytic by self-medication. fMRI can measure theanxiolytic effects of alcohol in the human brain.

Alternatives to medication

Cognitive behavioral therapy (CBT) is an effective treatment for panic disorder, social anxiety disorder, generalized anxiety disorder, and obsessive-compulsive disorder, while exposure therapy is the recommended treatment for anxiety related phobias. Healthcare providers canguide those with anxiety disorder by referring them to self-help resources. Sometimes medication is combined with psychotherapy but research has not found a benefit of combined pharmacotherapy and psychotherapy versus monotherapy.

If CBT is found ineffective, both the Canadian and American medical associations thensuggest the use of medication.

Stimulant

Stimulants (also often referred to as psychostimulants or colloquially as uppers) is an overarching term that covers many drugs including those that increase activity of the central nervous system and the body, drugs that are pleasurable and invigorating, or drugsthat have sympathomimetic effects. Stimulants are widely used throughout the world as prescription medicines as well as without a prescription (either legally or illicitly) as performance-enhancing or recreational drugs. Among narcotics, stimulants produce a noticeable crash or comedown at the end of their effects. The most frequently prescribed stimulants as of 2013 were lisdexamfetamine, methylphenidate (Ritalin), and amphetamine(Adderall). It was estimated in 2015 that the percentage of the world population that had used cocaine during a year was 0.4%. For the category "amphetamines and prescription stimulants" (with "amphetamines" including amphetamine and methamphetamine) the value was 0.7%, and for MDMA 0.4%.

Stimulants in therapeutic doses, such as those given to patients with ADHD, increases ability to focus, vigor, sociability, libido and may elevate mood. However, in higher doses stimulants may actually decrease the ability to focus, a principle of the Yerkes-Dodson Law.In higher doses stimulants may also produce euphoria, vigor, and decrease need for sleep. Many, but not all, stimulants have ergogenic effects. Drugs such as ephedrine, pseudoephedrine, amphetamine and methylphenidate have well documented ergogenic effects, while cocaine has the opposite effect. Neurocognitive enhancing effects of stimulants, specifically modafinil, amphetamine and methylphenidate have been documented in healthy adolescents, and is a commonly cited reason among illicit drug users for use, particularly among college students in the context of studying.

In some cases psychiatric phenomenon may emerge such as stimulant psychosis, paranoia,and suicidal ideation. Acute toxicity has been reportedly associated with a homicide, paranoia, aggressive behavior, motor dysfunction, and punding. The violent and aggressive behavior associated with acute stimulant toxicity may partially be driven by paranoia. Most drugs classified as stimulants are sympathomimetics, that is they stimulate the sympatheticbranch of the autonomic nervous system. This leads to effects such as mydriasis, increasedheart rate, blood pressure, respiratory rate and body temperature. When these changes become pathological, they are called arrhythmia, hypertension, and hyperthermia, and may lead to rhabdomyolysis, stroke, cardiac arrest, or seizures. However, given the complexity ofthe mechanisms that underlie these potentially fatal outcomes of acute stimulant toxicity, it is impossible to determine what dose may be lethal.

Chronic

Assessment of the effects of stimulants is relevant given the large population currently taking stimulants. A systematic review of cardiovascular effects of prescription stimulants found no association in children, but found a correlation between prescription stimulant useand ischemic heart attacks. A review over a four-year period found that there were few negative effects of stimulant treatment, but stressed the need for longer-term studies. A review of a year long period of prescription stimulant use in those with ADHD found that cardiovascular side effects were limited to transient increases in blood pressure only.
Initiation of stimulant treatment in those with ADHD in early childhood appears to carry benefits into adulthood with regard to social and cognitive functioning, and appears to berelatively safe.

Abuse of prescription stimulants (not following physician instruction) or of illicit stimulants carries many negative health risks. Abuse of cocaine, depending upon route of administration, increases risk of cardiorespiratory disease, stroke, and sepsis. Some effects are dependent upon the route of administration, with intravenous use associated with the transmission of many disease such as Hepatitis C, HIV/AIDS and potential medical emergencies such as infection, thrombosis or pseudoaneurysm, while inhalation may be associated with increased lower respiratory tract infection, lung cancer, and pathological restricting of lung tissue. Cocaine may also increase risk for autoimmune disease and damage nasal cartilage. Abuse of methamphetamine produces similar effects as well as marked degeneration of dopaminergic neurons, resulting in an increased risk for Parkinson'sdisease.

Medical uses

Stimulants have been used in medicine for many conditions including obesity, sleep disorders, mood

disorders, impulse control disorders, asthma, nasal congestion and, in caseof cocaine, as local anesthetics. Drugs used to treat obesity are called anorectics and generally include drugs that follow the general definition of a stimulant, but other drugs suchas cannabinoid receptor antagonists also belong to this group. Eugeroics are used in management of sleep disorders characterized by excessive daytime sleepiness, such as narcolepsy, and include stimulants such as modafinil. Stimulants are used in impulse control disorders such as ADHD and off-label in mood disorders such as major depressive disorder to increase energy, focus and elevate mood. Stimulants such as epinephrine, theophylline and salbutamol orally have been used to treat asthma, but inhaled adrenergic drugs are now preferred due to less systemic side effects. Pseudoephedrine is used to relieve nasal or sinus congestion caused by the common cold, sinusitis, hay fever and other respiratory allergies; it is also used to relieve ear congestion caused by ear inflammation or infection.

Cocaine analogues

Hundreds of cocaine analogues have been created, all of them usually maintaining a benzyloxy connected to the 3 carbon of a tropane. Various modifications include substitutions on the benzene ring, as well as additions or substitutions in place of the normal carboxylate on the tropane 2 carbon. Various compound with similar structure activity relationships to cocaine that aren't technically analogues have been developed aswell.

Mechanisms of action

Most stimulants exert their activating effects by enhancing catecholamine neurotransmission. Catecholamine neurotransmitters are employed in regulatory pathwaysimplicated in attention, arousal, motivation, task salience and reward anticipation. Classicalstimulants either block the reuptake or stimulate the efflux of these catecholamines, resulting in increased activity of their circuits. Some stimulants, specifically those with empathogenic and hallucinogenic effects, also affect serotonergic transmission. Some stimulants, such as some amphetamine derivatives and, notably, yohimbine, can decrease negative feedback by antagonizing regulatory autoreceptors. Adrenergic agonists, such as,in part, ephedrine, act by directly binding to and activating adrenergic receptors, producing sympathomimetic effects.

There are also more indirect mechanisms a drug can elicit activating effects. Caffeine is an adenosine receptor antagonist, and only indirectly increases catecholamine transmission inthe brain. Pitolisant is an H3-receptor inverse agonist. As H3 receptors mainly act as autoreceptors, pitolisant decreases negative feedback to histaminergic neurons, enhancinghistaminergic transmission.

Notable stimulants

Amphetamine

Amphetamine is a potent central nervous system (CNS) stimulant of the phenethylamine class that is approved for the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.

Amphetamine is also used off-label as a performance and cognitive enhancer, and recreationally as an aphrodisiac and euphoriant. Although it is a prescriptionmedication in many countries, unauthorized possession and distribution of amphetamine is

often tightly controlled due to the significant health risks associated with uncontrolled or heavy use. As a consequence, amphetamine is illegally manufactured in clandestine labs tobe trafficked and sold to users. Based upon drug and drug precursor seizures worldwide, illicit amphetamine production and trafficking is much less prevalent than that of methamphetamine.

The first pharmaceutical amphetamine was Benzedrine, a brand of inhalers used to treat avariety of conditions. Because the dextrorotary isomer has greater stimulant properties, Benzedrine was gradually discontinued in favor of formulations containing all or mostly dextroamphetamine. Presently, it is typically prescribed as mixed amphetamine salts, dextroamphetamine, and lisdexamfetamine.

Amphetamine is a norepinephrine-dopamine releasing agent (NDRA). It enters neurons through dopamine and norepinephrine transporters and facilitates neurotransmitter efflux byactivating TAAR1 and inhibiting VMAT2. At therapeutic doses, this causes emotional and cognitive effects such as euphoria, change in libido, increased arousal, and improved cognitive control. Likewise, it induces physical effects such as decreased reaction time, fatigue resistance, and increased muscle strength. In contrast, supratherapeutic doses of amphetamine are likely to impair cognitive function and induce rapid muscle breakdown.
Very high doses can result in psychosis (e.g., delusions and paranoia), which very rarely occurs at therapeutic doses even during long-term use. As recreational doses are generallymuch larger than prescribed therapeutic doses, recreational use carries a far greater risk ofserious side effects, such as dependence, which only rarely arises with therapeutic amphetamine use.

Caffeine

Caffeine is a stimulant compound belonging to the xanthine class of chemicals naturally found in coffee, tea, and (to a lesser degree) cocoa or chocolate. It is included in many soft drinks, as well as a larger amount in energy drinks. Caffeine is the world's most widely used psychoactive drug and by far the most common stimulant. In North America, 90% of adults consume caffeine daily. A few jurisdictions restrict its sale and use. Caffeine is also includedin some medications, usually for the purpose of enhancing the effect of the primary ingredient, or reducing one of its side-effects (especially drowsiness). Tablets containing standardized doses of caffeine are also widely available.

Caffeine's mechanism of action differs from many stimulants, as it produces stimulant effects by inhibiting adenosine receptors. Adenosine receptors are thought to be a large driver of drowsiness and sleep, and their action increases with extended wakefulness. Caffeine has been found to increase striatal dopamine in animal models, as well as inhibitthe inhibitory effect of adenosine receptors on dopamine receptors, however the implications for humans are unknown. Unlike most stimulants, caffeine has no addictive potential. Caffeine does not appear to be a reinforcing stimulus, and some degree of aversion may actually occur, which people preferring placebo over caffeine in a study on drug abuse liability published in an NIDA research monograph. In large telephone surveys only 11% reported dependence symptoms. However, when people were tested in labs, onlyhalf of those who

claim dependence actually experienced it, casting doubt on caffeine's ability to produce dependence and putting societal pressures in the spotlight.

Coffee consumption is associated with a lower overall risk of cancer. This is primarily due toa decrease in the risks of hepatocellular and endometrial cancer, but it may also have a modest effect on colorectal cancer. There does not appear to be a significant protective effect against other types of cancers, and heavy coffee consumption may increase the risk of bladder cancer. A protective effect of caffeine against Alzheimer's disease is possible, butthe evidence is inconclusive. Moderate coffee consumption may decrease the risk of cardiovascular disease, and it may somewhat reduce the risk of type 2 diabetes. Drinking
1-3 cups of coffee per day does not affect the risk of hypertension compared to drinking little or no coffee. However those who drink 2–4 cups per day may be at a slightly increasedrisk. Caffeine increases intraocular pressure in those with glaucoma but does not appear toaffect normal individuals. It may protect people from liver cirrhosis. There is no evidence that coffee stunts a child's growth. Caffeine may increase the effectiveness of some medications including ones used to treat headaches. Caffeine may lessen the severity of acute mountain sickness if taken a few hours prior to attaining a high altitude.

Ephedrine

Ephedrine is a sympathomimetic amine similar in molecular structure to the well-knowndrugs phenylpropanolamine and methamphetamine, as well as to the important neurotransmitter epinephrine (adrenaline). Ephedrine is commonly used as a stimulant, appetite suppressant, concentration aid, and decongestant, and to treat hypotension associated with anaesthesia.

In chemical terms, it is an alkaloid with a phenethylamine skeleton found in various plants inthe genus Ephedra (family Ephedraceae). It works mainly by increasing the activity of norepinephrine (noradrenaline) on adrenergic receptors. It is most usually marketed as the hydrochloride or sulfate salt.

The herb má huáng (Ephedra sinica), used in traditional Chinese medicine (TCM), contains ephedrine and pseudoephedrine as its principal active constituents. The same may be trueof other herbal products containing extracts from other Ephedra species.

MDMA

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy, or molly) is a euphoriant, empathogen, and stimulant of the amphetamine class. Briefly used by some psychotherapists as an adjunct to therapy, the drug became popular recreationally and the DEA listed MDMA as a Schedule I controlled substance, prohibiting most medical studies and applications. MDMA is known for its entactogenic properties. The stimulant effects of MDMA include hypertension, anorexia (appetite loss), euphoria, social disinhibition, insomnia (enhanced wakefulness/inability to sleep), improved energy, increased arousal, and increased perspiration, among others. Relative to catecholaminergic transmission, MDMA enhances serotonergic transmission significantly more, when compared to classical stimulants like amphetamine. MDMA does not appear to be significantly addictive or dependence forming.

Due to the relative safety of MDMA, some researchers such as David Nutt have criticized the scheduling level, writing a satirical article finding MDMA to be 28 times less dangerous than horseriding, a condition he termed "equasy" or "Equine Addiction Syndrome".

MDPV

Methylenedioxypyrovalerone (MDPV) is a psychoactive drug with stimulant properties thatacts as a norepinephrine-dopamine reuptake inhibitor (NDRI). It was first developed in the1960s by a team at Boehringer Ingelheim. MDPV remained an obscure stimulant until around 2004, when it was reported to be sold as a designer drug. Products labeled as bathsalts containing MDPV were previously sold as recreational drugs in gas stations and convenience stores in the United States, similar to the marketing for Spice and K2 as incense.

Incidents of psychological and physical harm have been attributed to MDPV use.

Mephedrone

Mephedrone is a synthetic stimulant drug of the amphetamine and cathinone classes. Slangnames include drone and MCAT. It is reported to be manufactured in China and is chemicallysimilar to the cathinone compounds found in the khat plant of eastern Africa. It comes in theform of tablets or a powder, which users can swallow, snort, or inject, producing similar effects to MDMA, amphetamines, and cocaine.

Mephedrone was first synthesized in 1929, but did not become widely known until it was

rediscovered in 2003. By 2007, mephedrone was reported to be available for sale on the Internet; by 2008 law enforcement agencies had become aware of the compound; and, by 2010, it had been reported in most of Europe, becoming particularly prevalent in the United Kingdom. Mephedrone was first made illegal in Israel in 2008, followed by Sweden later that year. In 2010, it was made illegal in many European countries, and, in December 2010, the EUruled it illegal. In Australia, New Zealand, and the US, it is considered an analog of other illegal drugs and can be controlled by laws similar to the Federal Analog Act. In September 2011, the USA temporarily classified mephedrone as illegal, in effect from October 2011.

Methamphetamine

Methamphetamine (contracted from N-methyl-alpha-methylphenethylamine) is a potent psychostimulant of the phenethylamine and amphetamine classes that is used to treat attention deficit hyperactivity disorder (ADHD) and obesity. Methamphetamine exists as twoenantiomers, dextrorotary and levorotary. Dextromethamphetamine is a stronger CNS stimulant than levomethamphetamine; however, both are addictive and produce the same toxicity symptoms at high doses. Although rarely prescribed due to the potential risks, methamphetamine hydrochloride is approved by the United States Food and Drug Administration (USFDA) under the trade name Desoxyn. Recreationally, methamphetamine is used to increase sexual desire, lift the mood, and increase energy, allowing some users toengage in sexual activity continuously for several days straight.

Methamphetamine may be sold illicitly, either as pure dextromethamphetamine or in an equal parts mixture of the right- and left-handed molecules (i.e., 50% levomethamphetamineand 50% dextromethamphetamine). Both dextromethamphetamine and racemic methamphetamine are schedule II controlled substances in the United States. Also, the production, distribution, sale, and possession of methamphetamine is restricted or illegal in many other countries due to its placement in schedule II of the United Nations Convention on Psychotropic Substances treaty. In contrast, levomethamphetamine is an
over-the-counter drug in the United States.

In low doses, methamphetamine can cause an elevated mood and increase alertness, concentration, and energy in fatigued individuals. At higher doses, it can induce psychosis, rhabdomyolysis, and cerebral hemorrhage. Methamphetamine is known to have a high potential for abuse and addiction. Recreational use of methamphetamine may result in psychosis or lead to post-withdrawal syndrome, a withdrawal syndrome that can persist formonths beyond the typical withdrawal period. Unlike amphetamine and cocaine, methamphetamine is neurotoxic to humans, damaging both dopamine and serotonin neurons in the central nervous system (CNS). Unlike the long-term use of amphetamine in prescription doses, which may improve certain brain regions in individuals with ADHD, thereis evidence that methamphetamine causes brain damage from long-term use in humans; this damage includes adverse changes in brain structure and function, such as reductions ingray matter volume in several brain regions and adverse changes in markers of metabolic

integrity. However, recreational amphetamine doses may also be neurotoxic.

Methylphenidate

Methylphenidate is a stimulant drug that is often used in the treatment of ADHD and narcolepsy and occasionally to treat obesity in combination with diet restraints and exercise. Its effects at therapeutic doses include increased focus, increased alertness, decreased appetite, decreased need for sleep and decreased impulsivity. Methylphenidate isnot usually used recreationally, but when it is used, its effects are very similar to those of amphetamines.

Methylphenidate acts as a norepinephrine-dopamine reuptake inhibitor, by blocking the norepinephrine transporter (NET) and the dopamine transporter (DAT). Methylphenidate hasa higher affinity for the dopamine transporter than for the norepinephrine transporter, and soits effects are mainly due to elevated dopamine levels caused by the inhibited reuptake of dopamine, however increased norepinephrine levels also contribute to various of the effectscaused by the drug.

Methylphenidate is sold under a number of brand names including Ritalin. Other versionsinclude the long lasting tablet Concerta and the long lasting transdermal patch Daytrana.

Cocaine

Cocaine is an SNDRI. Cocaine is made from the leaves of the coca shrub, which grows in the mountain regions of South American countries such as Bolivia, Colombia, and Peru, regionsin which it was cultivated and used for centuries mainly by the Aymara people. In Europe, North America, and some parts of Asia, the most common form of cocaine is a white crystalline powder. Cocaine is a stimulant but is not normally prescribed therapeutically for its stimulant properties, although it sees clinical use as a local anesthetic, in particular in ophthalmology. Most cocaine use is recreational and its abuse potential is high (higher thanamphetamine), and so its sale and possession are strictly controlled in most jurisdictions.
Other tropane derivative drugs related to cocaine are also known such as troparil andlometopane but have not been widely sold or used recreationally.

Nicotine

Nicotine is the active chemical constituent in tobacco, which is available in many forms, including cigarettes, cigars, chewing tobacco, and smoking cessation aids such as nicotine patches, nicotine gum, and electronic cigarettes. Nicotine is used widely throughout the world for its stimulating and relaxing effects. Nicotine exerts its effects through the agonismof nicotinic acetylcholine receptor, resulting in multiple downstream effects such as increase in activity of dopaminergic neurons in the midbrain reward system, and acetaldehyde one ofthe tobacco constituent decreased the expression of monoamine oxidase in the brain.
Nicotine is addictive and dependence forming. Tobacco, the most common source of nicotine, has an overall harm to user and self score 3 percent below cocaine, and 13 percentabove amphetamines, ranking 6th most harmful of the 20 drugs assessed, as determined bya multi-criteria decision analysis.

Phenylpropanolamine

Phenylpropanolamine (PPA; Accutrim; β-hydroxyamphetamine), also known as the stereoisomers norephedrine and norpseudoephedrine, is a psychoactive drug of thephenethylamine and amphetamine chemical classes that is used as a stimulant, decongestant, and anorectic agent. It is commonly used in prescription and
over-the-counter cough and cold preparations. In veterinary medicine, it is used to controlurinary incontinence in dogs under trade names Propalin and Proin.

In the United States, PPA is no longer sold without a prescription due to a proposed increased risk of stroke in younger women. In a few countries in Europe, however, it is still available either by prescription or sometimes over-the-counter. In Canada, it was withdrawnfrom the market on 31 May 2001. In India, human use of PPA and its formulations were banned on 10 February 2011.

Propylhexedrine

Propylhexedrine (Hexahydromethamphetamine, Obesin) is a stimulant medication, sold over-the-counter in the United States as the cold medication Benzedrex. The drug has alsobeen used as an appetite suppressant in Europe. Propylhexedrine is not an amphetamine, though it is structurally similar; it is instead a cycloalkylamine, and thus has stimulant effects that are less potent than similarly structured amphetamines, such as methamphetamine.

The abuse potential of propylhexedrine is fairly limited, due its limited routes of administration: in the United States, Benzedrex is only available as an inhalant, mixed withlavender oil and menthol. These ingredients cause unpleasant tastes, and abusers of the drug have reported unpleasant "menthol burps". Injection of the drug has been found to cause transient diplopia and brain stem dysfunction.

Pseudoephedrine

Pseudoephedrine is a sympathomimetic drug of the phenethylamine and amphetaminechemical classes. It may be used as a nasal/sinus decongestant, as a stimulant, or as a

wakefulness-promoting agent.

The salts pseudoephedrine hydrochloride and pseudoephedrine sulfate are found in manyover-the-counter preparations, either as a single ingredient or (more commonly) in combination with antihistamines, guaifenesin, dextromethorphan, and/or paracetamol (acetaminophen) or another NSAID (such as aspirin or ibuprofen). It is also used as a precursor chemical in the illegal production of methamphetamine.

Catha edulis (Khat)

Khat is a flowering plant native to the Horn of Africa and the Arabian Peninsula.

Khat contains a monoamine alkaloid called cathinone, a "keto-amphetamine", that is said tocause excitement, loss of appetite, and euphoria. In 1980, the World Health Organization (WHO) classified it as a drug of abuse that can produce mild to moderate psychological dependence (less than tobacco or alcohol), although the WHO does not consider khat to beseriously addictive. It is banned in some countries, such as the United States, Canada, and Germany, while its production, sale, and consumption are legal in other nations, including Djibouti, Ethiopia, Somalia, and Yemen.

Modafinil

Modafinil, sold under the brand name Provigil among others, is a CNS stimulant used totreat sleepiness due to narcolepsy, shift work sleep disorder, or obstructive sleep apnea.While it has seen off-label use as a purported cognitive enhancer, the research on its effectiveness for this use is not conclusive.

Recreational use and issues of abuse

Stimulants enhance the activity of the central and peripheral nervous systems. Common effects may include increased alertness, awareness, wakefulness, endurance, productivity, and motivation, arousal, locomotion, heart rate, and blood pressure, and a diminished desire for food and sleep. Use of stimulants may cause the body to reduce significantly its production of natural body chemicals that fulfill similar functions. Until the body reestablishes its normal state, once the effect of the ingested stimulant has worn off the usermay feel depressed, lethargic, confused, and miserable. This is referred to as a "crash", and may provoke reuse of the stimulant.

Abuse of central nervous system (CNS) stimulants is common. Addiction to some CNS stimulants can quickly lead to medical, psychiatric, and psychosocial deterioration. Drugtolerance, dependence, and sensitization as well as a withdrawal syndrome can occur.Stimulants may be screened for in animal discrimination and self-administration modelswhich have high sensitivity albeit low specificity. Research on a progressive ratio
Self-administration protocol has found amphetamine, methylphenidate, modafinil, cocaine,and nicotine to all have a higher break point than placebo that scales with dose indicating reinforcing effects.

Treatment for misuse

Psychosocial treatments, such as contingency management, have demonstrated improvedeffectiveness when added to treatment as usual consisting of counselling and/or case-management. This is demonstrated with a decrease in dropout rates and alengthening of periods of abstinence.

Testing

The presence of stimulants in the body may be tested by a variety of procedures. Serum andurine are the common sources of testing material although saliva is sometimes used.
Commonly used tests include chromatography, immunologic assay, and mass spectrometry.

Tobacco smoking

Tobacco smoking is the practice of burning tobacco and ingesting the smoke that is produced. The smoke may be inhaled, as is done with cigarettes, or simply released from themouth, as is generally done with pipes and cigars. The practice is believed to have begun asearly as 5000–3000 BC in Mesoamerica and South America. Tobacco was introduced to Eurasia in the late 17th century by European colonists, where it followed common trade routes. The practice encountered criticism from its first import into the Western world onwards but embedded itself in certain strata of a number of societies before becoming widespread upon the introduction of automated cigarette-rolling apparatus.

Smoking is the most common method of consuming tobacco, and tobacco is the most common substance smoked. The agricultural product is often mixed with additives and thencombusted. The resulting smoke is then inhaled and the active substances absorbed through the alveoli in the lungs or the oral mucosa. Many substances in cigarette smoke trigger chemical reactions in nerve endings, which heighten heart rate, alertness and reaction time, among other things. Dopamine and endorphins are released, which are often associated with pleasure.

German scientists identified a link between smoking and lung cancer in the late 1920s, leading to the first anti-smoking campaign in modern history, albeit one truncated by the collapse of Nazi Germany at the end of World War II. In 1950, British researchers demonstrated a clear relationship between smoking and cancer. Evidence continued to mount in the 1980s, which prompted political action against the practice. Rates of consumption since 1965 in the developed world have either peaked or declined. However, they continue to climb in the developing world. As of 2008 to 2010, tobacco is used by about49% of men and 11% of women aged 15 or older in fourteen low-income and middle-incomecountries (Bangladesh, Brazil, China, Egypt, India, Mexico, Philippines, Russia, Thailand, Turkey, Ukraine, Uruguay and Vietnam), with about 80% of this usage in the form of smoking.The gender gap tends to be less pronounced in lower age groups.

Many smokers begin during adolescence or early adulthood. During the early stages, a combination of perceived pleasure acting as positive reinforcement and desire to respond tosocial peer pressure may offset the unpleasant symptoms of initial use, which typically include nausea and coughing.

After an individual has smoked for some years, the avoidanceof withdrawal symptoms and negative reinforcement become the key motivations to continue.

A 2009 study of first smoking experiences of seventh-grade students found out that the most common factor leading students to smoke is cigarette advertisements. Smoking byparents, siblings and friends also encourages students to smoke.

Popularization

In 1612, six years after the settlement of Jamestown, Virginia, John Rolfe was credited as the first settler to successfully raise tobacco as a cash crop. The demand quickly grew as tobacco, referred to as "brown gold", revived the Virginia joint stock company from its failed gold expeditions. In order to meet demands from the Old World, tobacco was grown in succession, quickly depleting the soil. This became a motivator to settle west into the unknown continent, and likewise an expansion of tobacco production. Indentured servitude became the primary labor force up until Bacon's Rebellion, from which the focus turned to slavery. This trend abated following the American Revolution as slavery became regarded asunprofitable. However, the practice was revived in 1794 with the invention of the cotton gin.

Frenchman Jean Nicot (from whose name the word nicotine is derived) introduced tobacco to France in 1560, and tobacco then spread to England. The first report of a smoking Englishman is of a sailor in Bristol in 1556, seen "emitting smoke from his nostrils". Like tea,coffee and opium, tobacco was just one of many intoxicants that was originally used as a form of medicine. Tobacco was introduced around 1600 by French merchants in what todayis modern-day Gambia and Senegal. At the same time, caravans from Morocco brought tobacco to the areas around Timbuktu, and the Portuguese brought the commodity (and theplant) to southern Africa, establishing the popularity of tobacco throughout all of Africa by the 1650s.

Soon after its introduction to the Old World, tobacco came under frequent criticism from state and religious leaders. James VI and I, King of Scotland and England, produced the treatise A Counterblaste to Tobacco in 1604, and also introduced excise duty on the product.Murad IV, sultan of the Ottoman Empire 1623–40 was among the first to attempt a smoking ban by claiming it was a threat to public morals and health. The Chongzhen Emperor of China issued an edict banning smoking two years before his death and the overthrow of the Ming dynasty. Later, the Manchu rulers of the Qing dynasty, would proclaim smoking "a more heinous crime than that even of neglecting archery". In Edo period Japan, some of the earliest tobacco plantations were scorned by the shogunate as being a threat to the military economy by letting valuable farmland go to waste for the use of a recreational drug instead of being used to plant food crops.

Religious leaders have often been prominent among those who considered smoking immoral or outright blasphemous. In 1634, the Patriarch of Moscow forbade the sale of tobacco, and sentenced men and women who flouted the ban to have their nostrils slit andtheir backs flayed. Pope Urban VIII likewise condemned smoking on holy places in a papalbull of 1624. Despite some concerted efforts, restrictions and bans were largely ignored.
When James I of England, a staunch anti-smoker and the author of A Counterblaste to Tobacco, tried to curb the new trend by enforcing a 4000% tax increase on tobacco in 1604 it

was unsuccessful, as suggested by the presence of around 7,000 tobacco outlets in Londonby the early 17th century. From this point on for some centuries, several administrations withdrew from efforts at discouragement and instead turned tobacco trade and cultivation into sometimes lucrative

government monopolies.

By the mid-17th century most major civilizations had been introduced to tobacco smoking and in many cases had already assimilated it into the native culture, despite some continuedattempts upon the parts of rulers to eliminate the practice with penalties or fines. Tobacco, both product and plant, followed the major trade routes to major ports and markets, and then on into the hinterlands. The English language term smoking appears to have entered currency in the late 18th century, before which less abbreviated descriptions of the practice such as drinking smoke were also in use.

Growth in the US remained stable until the American Civil War in 1860s, when the primary agricultural workforce shifted from slavery to sharecropping. This, along with a change in demand, accompanied the industrialization of cigarette production as craftsman James Bonsack created a machine in 1881 to partially automate their manufacture.

Social attitudes and public health

In Germany, anti-smoking groups, often associated with anti-liquor groups, first published advocacy against the consumption of tobacco in the journal Der Tabakgegner (The TobaccoOpponent) in 1912 and 1932. In 1929, Fritz Lickint of Dresden, Germany, published a paper containing formal statistical evidence of a lung cancer–tobacco link. During the Great Depression Adolf Hitler condemned his earlier smoking habit as a waste of money, and laterwith stronger assertions. This movement was further strengthened with Nazi reproductive policy as women who smoked were viewed as unsuitable to be wives and mothers in a German family. In the 20th century, smoking was common. There were social events like thesmoke night which promoted the habit.

The anti-tobacco movement in Nazi Germany did not reach across enemy lines during theSecond World War, as anti-smoking groups quickly lost popular support. By the end of theSecond World War, American cigarette manufacturers quickly reentered the German black market. Illegal smuggling of tobacco became prevalent, and leaders of the Nazi
anti-smoking campaign were silenced. As part of the Marshall Plan, the United States shipped free tobacco to Germany; with 24,000 tons in 1948 and 69,000 tons in 1949. Per capita yearly cigarette consumption in post-war Germany steadily rose from 460 in 1950 to1,523 in 1963. By the end of the 20th century, anti-smoking campaigns in Germany were unable to exceed the effectiveness of the Nazi-era climax in the years 1939–41 and Germantobacco health research was described by Robert N. Proctor as "muted".

In 1950, Richard Doll published research in the British Medical Journal showing a close linkbetween smoking and lung cancer. Beginning in December 1952, the magazine Reader's Digest published "Cancer by the Carton", a series of articles that linked smoking with lung cancer.

In 1954, the British Doctors Study, a prospective study of some 40 thousand doctors for about 2.5 years, confirmed the suggestion, based on which the government issued advicethat smoking and lung cancer rates were related. In January 1964, the United States Surgeon General's Report on Smoking and Health likewise began suggesting the relationship between smoking and cancer.

As scientific evidence mounted in the 1980s, tobacco companies claimed contributory negligence as the adverse health effects were previously unknown or lacked substantial credibility. Health authorities sided with these claims up until 1998, from which they reversed their position. The Tobacco Master Settlement Agreement, originally between the four largest US tobacco companies and the Attorneys General of 46 states, restricted certaintypes of tobacco advertisement and required payments for health compensation; which lateramounted to the largest civil settlement in United States history.

From 1965 to 2006, rates of smoking in the United States declined from 42% to 20.8%. The majority of those who quit were professional, affluent men. Although the per-capita number of smokers decreased, the average number of cigarettes consumed per person per day increased from 22 in 1954 to 30 in 1978. This paradoxical event suggests that those who quit smoked less, while those who continued to smoke moved to smoke more light cigarettes. The trend has been paralleled by many industrialized nations as rates have eitherleveled-off or declined. In the developing world, however, tobacco consumption continues torise at 3.4% in 2002. In Africa, smoking is in most areas considered to be modern, and manyof the strong adverse opinions that prevail in the West receive much less attention. Today Russia leads as the top consumer of tobacco followed by Indonesia, Laos, Ukraine, Belarus, Greece, Jordan, and China.

As a result of public pressure and the FDA, Walmart and Sam's club announced that they were raising the minimum age to purchase tobacco products, including all e-cigarettes, to21 starting 1 July 2019.

Psychology

Most smokers begin smoking during adolescence or early adulthood. Some studies also show that smoking can also be linked to various mental health complications. Smoking haselements of risk-taking and rebellion, which often appeal to young people. The presence of peers that smoke and media featuring high-status models smoking may also encourage smoking. Because teenagers are influenced more by their peers than by adults, attempts byparents, schools, and health professionals at preventing people from trying cigarettes are often unsuccessful.

Children of smoking parents are more likely to smoke than children with non-smoking parents. Children of parents who smoke are less likely to quit smoking. One study found thatparental smoking cessation was associated with less adolescent smoking, except when theother parent currently smoked. A current study tested the relation of adolescent smoking to rules regulating where adults are allowed to smoke in the home. Results showed that restrictive home smoking policies were associated with lower likelihood of trying smoking for both middle and high school students.

Behavioural research generally indicates that teenagers begin their smoking habits due to peer pressure, and cultural influence portrayed by friends. However, one study found that direct pressure to smoke cigarettes played a less significant part in adolescent smoking, with adolescents also reporting low levels of both normative and direct pressure to smoke cigarettes. Mere exposure to tobacco retailers may motivate smoking behaviour in adults. Asimilar study suggested that

individuals may play a more active role in starting to smoke than has previously been thought and that social processes other than peer pressure also need to be taken into account. Another study's results indicated that peer pressure was significantly associated with smoking behavior across all age and gender cohorts, but that intrapersonal factors were significantly more important to the smoking behavior of 12- to 13-year-old girls than same-age boys. Within the 14- to 15-year-old age group, one peer pressure variable emerged as a significantly more important predictor of girls' than boys' smoking. It is debated whether peer pressure or self-selection is a greater cause of adolescent smoking.

Psychologist Hans Eysenck (who later was questioned for nonplausible results and unsafe publications) developed a personality profile for the typical smoker. Extraversion is the traitthat is most associated with smoking, and smokers tend to be sociable, impulsive, risk taking, and excitement seeking individuals.

Persistence

The reasons given by some smokers for this activity have been categorized as addictive smoking, pleasure from smoking, tension reduction/relaxation, social smoking, stimulation, habit/automatism, and handling. There are gender differences in how much each of these reasons contribute, with females more likely than males to cite tension reduction/relaxation,stimulation and social smoking.

Some smokers argue that the depressant effect of smoking allows them to calm their nerves, often allowing for increased concentration. However, according to the Imperial College London, "Nicotine seems to provide both a stimulant and a depressant effect, and itis likely that the effect it has at any time is determined by the mood of the user, the environment and the circumstances of use. Studies have suggested that low doses have a depressant effect, while higher doses have stimulant effect."

Patterns

A number of studies have established that cigarette sales and smoking follow distinct time-related patterns. For example, cigarette sales in the United States of America have been shown to follow a strongly seasonal pattern, with the high months being the months ofsummer, and the low months being the winter months.

Similarly, smoking has been shown to follow distinct circadian patterns during the wakingday—with the high point usually occurring shortly after waking in the morning, and shortly before going to sleep at night.

Health effects of tobacco

Tobacco smoking is the leading cause of preventable death and a global public health concern. There are 1.1 billion tobacco users in the world. One person dies every six secondsfrom a tobacco related disease.

Tobacco use leads most commonly to diseases affecting the heart and lungs, with smokingbeing a major risk factor for heart attacks, strokes, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), emphysema, and various types and subtypes ofcancers

(particularly lung cancer, cancers of the oropharynx, larynx, and mouth, esophagealand pancreatic cancer). Cigarette smoking increases the risk of Crohn's disease as well as the severity of the course of the disease. It is also the number one cause of bladder cancer. Cigarette smoking has also been associated with sarcopenia, the age-related loss of musclemass and strength. The smoke from tobacco elicits carcinogenic effects on the tissues of the body that are exposed to the smoke. Regular cigar smoking is known to carry serious health risks, including increased risk of developing various types and subtypes of cancers, respiratory diseases, cardiovascular diseases, cerebrovascular diseases, periodontal

diseases and teeth loss, and malignant diseases.

Tobacco smoke is a complex mixture of over 7,000 toxic chemicals, 98 of which are associated with an increased risk of cardiovascular disease and 69 of which are known to be carcinogenic. The most important chemicals causing cancer are those that produce DNAdamage, since such damage appears to be the primary underlying cause of cancer.
Cunningham et al. combined the microgram weight of the compound in the smoke of one cigarette with the known genotoxic effect per microgram to identify the most carcinogenic compounds in cigarette smoke: acrolein, formaldehyde, acrylonitrile, 1,3-butadiene, acetaldehyde, ethylene oxide, and isoprene. In addition to the aforementioned toxic chemicals, flavored tobacco contains flavorings which upon heating release toxic chemicalsand carcinogens such as carbon monoxide (CO), polycyclic aromatic hydrocarbons (PAHs), furans, phenols, aldehydes (such as acrolein), and acids, in addition to nitrogenous carcinogens, alcohols, and heavy metals, all of which are dangerous to human health. A comparison of 13 common hookah flavors found that melon flavors are the most dangerous,with their smoke containing four classes of hazards in high concentrations.

The World Health Organization estimates that tobacco caused 5.4 million deaths in 2004 and 100 million deaths over the course of the 20th century. Similarly, the United States Centers for Disease Control and Prevention describes tobacco use as "the single most important preventable risk to human health in developed countries and an important causeof premature death worldwide." Although 70% of smokers state their intention to quit only 3–5% are actually successful in doing so.

The probabilities of death from lung cancer before age 75 in the United Kingdom are 0.2% formen who never smoked (0.4% for women), 5.5% for male former smokers (2.6% in women), 15.9% for current male smokers (9.5% for women) and 24.4% for male "heavy smokers" defined as smoking more than 5 cigarettes per day (18.5% for women). Tobacco smoke can combine with other carcinogens present within the environment in order to produce elevateddegrees of lung cancer.

The risk of lung cancer decreases almost from the first day someone quits smoking. Healthycells that have escaped mutations grow and replace the damaged ones in the lungs. In the research dated December 2019, 40% of cells in former smokers looked like those of people who had never smoked. Rates of smoking have generally leveled-off or declined in the developed world. Smoking rates in the United States have dropped by half from 1965 to 2006, falling from 42% to 20.8%in adults. In the developing world, tobacco consumption is rising by 3.4% per year.

Smoking alters the transcriptome of the lung parenchyma; the expression levels of a panelof seven genes (KMO, CD1A, SPINK5, TREM2, CYBB, DNASE2B, FGG) are increased in the lung tissue of smokers.

Passive smoking is the inhalation of tobacco smoke by individuals who are not actively smoking. This smoke is known as second-hand smoke (SHS) or environmental tobacco smoke (ETS) when the burning end is present, and third-hand smoke after the burning endhas been extinguished. Because of its negative implications, exposure to SHS has played acentral role in the regulation of tobacco products. Six hundred thousand deaths were attributed to SHS in 2004. It also has been known to produce skin conditions such as freckles and dryness.

In 2015, a meta-analysis found that smokers were at greater risk of developing psychotic disorder. Tobacco has also been described an anaphrodisiac due to its propensity for causing erectile dysfunction. There is a correlation between tobacco smoking and a reducedrisk of Parkinson's disease.