Alcohol, nicotine, caffeine, and mental disorders

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Alcohol, nicotine, and caffeine are the most widely consumed psychotropic drugs worldwide. They are largely consumed by normal individuals, but their use is even more frequent in psychiatric patients. Thus, patients with schizophrenia tend to abuse all three substances. The interrelationships between depression and alcohol are complex. These drugs can all create dependence, as understood in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). *Alcohol abuse is clearly deleterious to the brain, provoking acute and chronic mental disorders, ranging from intoxication with impairment of cognition, to delirium tremens, hallucinosis, and dementia. In contrast, the main health consequences of nicotine, notably cancer and cardiovascular diseases, lie outside the realm of psychiatry. However, the issues of nicotine dependence and motivation to smoke or quit are of concern to psychiatrists.*

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Alcohol, nicotine, and caffeine share several common features. Being palatable for their mild psychotropic properties, they are the most widely consumed drugs worldwide. As licit psychoactive drugs, they are used mostly by "normal" people, in contrast to illicit "hard drugs," which are traditionally viewed as the province of the deviant. Known to mankind for several centuries, alcohol, nicotine, and caffeine have become an important part of culture, serving as a vehicle for social interaction, shaping the urban landscape with dedicated places—from the Ottoman coffeehouse to the German Brauhaus and the Parisian café—stimulating the opening of international trade routes and bringing substantial tax revenues to governments. Abnormal patterns of substance use have been described since antiquity. Aristotle recorded the effects of alcohol withdrawal and warned that drinking could be injurious during pregnancy[1]; the Roman physician Celsus held that dependence on intoxicating drink was a disease.[2] Today, alcohol and nicotine are public health problems because of their association with physical ailments such as cirrhosis, cancer, and cardiovascular disease. Of these three substances, only alcohol causes clear neuropsychiatric sequelae. Frequent heavy drinking, especially when associated with malnutrition, has been shown to lead to central nervous system (CNS) deterioration. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*,[3] the current nomenclature of the American Psychiatric Association, has specific diagnostic categories for alcohol-, nicotine-, and caffeine-related disorders. According to *DSM-IV*'s definition, all three substances can induce dependence. Conversely, patients presenting with various mental disorders may be more prone than the general population to use or abuse these three common substances. Thus, patients with bipolar depression are more likely to abuse alcohol at certain times in the course of their illness. Patients with schizophrenia have high rates of consumption of all three substances, which they use to relieve dysphoria.[4]

Alcohol

The consumption of alcoholic beverages, in the form of beer or wine, is mentioned in the records of the earliest known civilizations. Physicians' prescriptions of beer were found on Sumerian clay tablets (c 2100 BC). Egyptian doctors in their medical papyri (c 1500 BC) included beer or wine in about 15% of their prescriptions.[5] Alcohol—an inebriating substance—is consumed because it relieves the mind from anxiety and inhibitions. In the 19th century medical literature, alcohol was recognized as a major cause of mental morbidity, and the phenomenology of acute and chronic alcoholism was already well known. Ball,[6] a renowned professor of psychiatry in Paris, wrote in 1880 that "of all the poisons that, to a variable degree, exert a deleterious influence on the constitution, alcohol is without doubt the substance whose effects have been most thoroughly described and meticulously investigated."

Alcohol and the *DSM-IV* classification

DSM-IV offers two categories of *alcohol use disorders*: *alcohol abuse* and *alcohol dependence*. Abuse is a maladaptive pattern of drinking, resulting in adverse consequences (neglect of children or work, marital problems) or dangerous behavior (driving while drunk). Dependence is indicated by loss of control and continued drinking despite alcohol-related problems, and by evidence of tolerance or symptoms of withdrawal. Typically, the dependent subject wants to stop drinking but cannot, and morning drinking is characteristic. The disorders induced by alcohol are well known, and will not be detailed here. *DSM-IV* lists withdrawal delirium (delirium tremens), psychotic disorders with delusions or hallucinations, persisting dementia, and persisting amnestic disorder. Recognizing the frequent association between alcohol and depression, *DSM-IV* also includes the category *alcohol-induced mood disorder* to diagnose mood disorders developing during, or within a month, of alcohol intoxication or withdrawal.

Depression and alcohol

The interrelationship between depression and alcohol is complex, but highly important in clinical practice. About 100 years ago, the readers of a booklet written by Bode, a German physician,[7] could learn that depression and alcohol abuse are often linked. The author thought that regular drinking could be a consequence of the "depression" caused by an unfavorable climate, stating for instance that alcoholism had been observed in Italians moving to the fog and rain of London, or in German colonial officers posted in tropical countries. In a more modern vein, Bode also added that alcohol abuse could be one of the first symptoms of "melancholia," the usual term at the time for today's major depression. He wrote that the melancholic patient "turned to the bottle" to alleviate feelings of anxiety, guilt, sorrow, sadness, and mental vacuity. This statement would still be considered pertinent today. Intuitively, the association between depression and alcohol seems to have good face value. However, this association is much more complex than meets the eye. Interestingly, a U-shaped relationship of depression and alcohol consumption has been observed in large population samples. It was found that lower-level drinkers had lower depression scores than both nondrinkers and heavy drinkers.[8] The fact that moderate alcohol users are merrier than teetotalers is illustrated by Sir John's comment in Shakespeare's play, *Henry IV, Part 2* (act 4): "A man cannot make him laugh; but that's no marvel; he drinks no wine."

The causal element in the association between depression and alcoholism is debatable. Is depression secondary to alcoholism, or vice versa? Or, are both possible? In the case of alcohol-induced mood disturbances, alcoholism is clearly primary, and depression secondary. Mood disturbances are characteristic of heavy drinkers, particularly during withdrawal. When not drinking, alcoholics often report depression, irritability, suspiciousness, lethargy, apprehension, anxiety, and poor concentration. About a quarter of recently detoxified alcoholics have a depressive syndrome. *Alcohol-induced depression* usually remits in less than 1 month without specific treatment. The clinical course of depression when it coexists with alcoholism is generally benign and self-limited, with most patients becoming euthymic within 2 to 3 weeks of abstention without antidepressant treatment. In some depressed alcoholics, however, a more chronic depression persists, and may predict a worse outcome for the alcoholism. In that case, antidepressants should definitely be used, since they may lower the relapse rate.

The reverse of alcohol-induced depression, namely *depression-induced alcoholism*, can also be observed. Drinking may be secondary to depression, when alcohol is used as self-medication by the patient. The alcoholic may drink to relieve his mind from sorrow, fear, and despondency, or to combat loneliness or the blues. Since alcohol absorption may have a transient arousing or

mood-lifting effect, this strategy has some short-term benefit, but it is doomed in the long run. In fact, as described in the paragraph above, the paradox is that chronic use of alcohol is more likely to make the subject more withdrawn, more depressed, or more anxious. However, it should be remembered that, although depression can lead to alcoholism, most cases of alcoholism are not explained by primary depression, contrary to popular belief.

A primary mood disorder should be particularly suspected in certain circumstances, notably in females and in the cases of early-onset drinking. Also, the possibility of bipolar disorder should be kept in mind.

Women may be more at risk than men to develop this form of secondary alcoholism. The hypothesis that depressive symptoms predicted subsequent alcohol problems for females, whereas alcohol problems predicted subsequent depressive symptoms for males, was tested in a random sample of 1306 adults from Erie County, New York, assessed in 1986, 1989, and 1993.[9] Measures of alcohol problems in the previous year included an alcohol abuse/dependence diagnosis and a heavy alcohol use index. The Center for Epidemiologic Studies Depression Scale was used to assess depressive symptoms over 1 month. For females, depressive symptoms predicted subsequent alcohol problems over 3 years (odds ratio 3.04; 95% confidence interval [CI] 1.35-6.80; $P<0.01$) and 4 years (odds ratio 2.42; 95% CI 1.14-5.12; $P<0.05$), but not for 7 years. Similarly, another study showed that the risk of heavy drinking was 2.6 times greater in women with a history of depressive disorder than in women with no history of depressive disorder.[10]

Early-onset drinking may often be secondary to a primary psychiatric disorder. This notion is supported by a study[11] that found that 81% of 339 alcoholics had associated mental disorders. Alcoholics with onset of heavy drinking before 20 years of age had significantly more antisocial personality traits, drug abuse, bipolar disorder, panic disorder, suicide attempts, and paternal alcoholism than alcoholics with onset after age 20 years. Alcoholics with onset before and after 20 years of age also differed significantly from each other for cerebrospinal fluid concentrations of somatostatin.

Bipolar disorder

It is too often ignored that episodic drinking may be a symptom of bipolar illness. In a recent study,[12] the independent familial aggregation of bipolar disorder and alcoholism, and the finding that the onset of bipolar disorder tended to precede that of alcoholism, were compatible with a self-medication hypothesis as the explanation for the frequent cooccurrence of these disorders; in contrast, the independent familial aggregation and the tendency toward an earlier onset of alcoholism than that of nonbipolar depression suggest that unipolar mood disorders are frequently secondary to alcoholism. Other authors[13] evaluating the prevalence of substance abuse and dependence among subjects with bipolar I disorder versus bipolar II disorder found that alcohol was the most commonly abused drug among both bipolar I and bipolar II subjects; bipolar I subjects appear to have higher rates of substance abuse and dependence than bipolar II subjects.

Genetics of alcoholism

An association between alcohol and depression can be inferred from the findings of numerous familial, epidemiological, and molecular genetics studies. Adoption and twin studies had concluded, a few decades ago, that genetics exerts a small but definite effect on the development of alcoholism.[14] An important caveat is the difficulty of discerning whether the biological mother's contribution is genetic or environmental (eg, drinking during the critical periods of gestation and nursing). Also, clinical and epidemiological studies have consistently revealed an association between alcohol use disorders and both bipolar and nonbipolar mood disorders. However, the evidence regarding the nature of this association is unclear. Winokur[15] advanced the "depressive spectrum" hypothesis, on the basis of his findings that persons developing unipolar depression prior to age 40 had more alcoholism and antisocial personality in their male relatives. However, subsequent researchers who investigated the relatives of patients with unipolar or bipolar depression were unable to replicate a genetic association between mood disorders and drinking. There is a consensus that genetic factors play a role in the vulnerability to mood disorder, and it is likely that hereditary factors influence the appearance of alcoholism too. However, both class of disorders are probably influenced by distinct genetic factors. Data on family studies or genetic studies generally suggest that alcoholism and depression are two independent illnesses, albeit both quite common.

Individual differences in the pharmacokinetics and pharmacodynamics of alcohol were known long before the advent of molecular genetics. Men metabolize a signifi-

cant fraction of alcohol in the stomach prior to absorption, in contrast to women who have less active stomach enzymes. Alcohol is absorbed into the bloodstream through the stomach (20%) and intestine (80%). In women, alcohol absorption through the stomach is higher premenstrually and during ovulation.[16] Up to 90% of alcohol consumed is metabolized in the liver. The rapidly developing tolerance to some of the effects of alcohol is partly attributable to enzyme induction in the liver. The ability to metabolize acetaldehyde, a compound produced by the catabolic breakdown of alcohol, is impaired in some Japanese or Chinese individuals, resulting in flushing and discomfort after moderate amounts of alcohol.

Molecular genetics made it possible to identify polymorphisms in genes that intervene in the pharmacokinetics of alcohol (eg, the enzymes aldehyde dehydrogenase and alcohol dehydrogenase).[17] Recent research findings have shown the genetic association or linkage of alcoholism to genes that also play a role in other psychiatric disorders and in the response to drug treatment. Examples include the association of alcoholism with the γ-aminobutyric acid receptor $GABA_A$[18] (GABA is the major inhibitory neurotransmitter of the CNS); the linkage of suicidality, severe suicide attempts, and alcoholism to the tryptophan hydroxylase gene[19] (the rate-limiting enzyme in the synthesis of serotonin [5-hydroxytryptamine, 5-HT]); the linkage of antisocial alcoholism to the autoreceptor $5\text{-}HT_{1B}$ gene[20]; and the linkage of severe and antisocial alcoholism to the dopamine D_2 and D_4 receptor genes.[21]

Alcoholism and drug treatment

Alcohol interferes with the central metabolism of the neurotransmitters—especially indolamines—involved in the pathophysiology and drug treatment of mood disorders. Several lines of research support an important role for brain 5-HT pathways in the control of alcohol drinking behavior. It is known that drinking increases the rate of 5-HT turnover and decreases the platelet uptake of 5-HT.[22] Serotonergic compounds reduce ethanol self-administration in conditioned rats.[23] Results are consistent with activation of $5\text{-}HT_{1A}$ and $5\text{-}HT_{1B}$ receptor subtypes in mediation of the conditioned or secondary reinforcing properties of ethanol. The observation that alcohol modifies neurotransmitter function is part of the rationale for the psychopharmacological treatment of alcoholism.

It was shown that men and women who are diagnosed with major depression at the time that they are admitted for inpatient treatment of alcohol dependence have shorter times to first drink and alcohol relapse.[24] This suggests that it is of paramount importance to diagnose and treat comorbid depression in alcoholic patients who are seen for treatment. Antidepressants have shown efficacy in the treatment of alcoholism with comorbid depression, and sometimes even in the absence of comorbid depression. In particular, antidepressants have been helpful in the reduction of craving and relapse rates during detoxification.

When antidepressant treatment should be started is debatable. Antidepressant treatment should certainly be initiated if depression persists after 2 to 4 weeks of alcohol withdrawal. However, certain authors recommend using antidepressant drugs much earlier, in order to diminish alcohol consumption, craving, and the risk of relapse. It should be kept in mind that the adverse effects of the drug may be potentiated by alcohol intake if treatment is started early, when the patient is still drinking or when detoxification is not complete. Also, the patient's medical condition may necessitate lower antidepressant doses. Particular attention should be paid to anticholinergic and cardiovascular adverse effects. The use of tricyclic compounds may be limited by the occurrence of hepatic and myocardial abnormalities in alcoholic patients. Also, the pharmacokinetics of the drug may be changed in the alcoholic. For instance, imipramine clearance is increased in the alcoholic, its half-life is shortened, and much lower plasma levels will be observed.[25]

The choice of medication is likely to be determined by the availability of various classes of drugs, which differs between countries. Serotonergic drugs have been extensively studied in depressive alcoholics and they have proven effective in maintaining abstinence. They may, therefore, be a useful adjuvant in the therapy of alcoholism. Selective serotonin reuptake inhibitors (SSRIs) seem to have short-term effects in alcohol dependence, and are probably more effective in men and in the presence of comorbid depression.[26] Citalopram[27] was shown to decrease alcohol consumption in nondepressed subjects with alcohol dependence. Fluoxetine[28] at antidepressant doses was able to prevent relapses in weaned alcoholics. Trazodone,[29] a relatively selective inhibitor of 5-HT reuptake, was able at low doses to significantly decrease craving for alcohol in detoxified alcohol-dependent subjects. Tianeptine,[30] a compound that increases 5-HT reuptake, was shown to be particularly suitable in depressed patients after withdrawal from alcohol abuse or dependence, because of its relative lack of sedative,

anticholinergic, and cardiovascular effect. Viloxazine,[31] an inhibitor of norepinephrine reuptake, was shown to be superior to placebo on the reduction of alcohol consumption. Besides antidepressants, some studies investigated the effect of mood-regulating agents. Overall, little benefit was found with lithium, whereas valproate seemed more promising.

Recently, acamprosate has been introduced as a clinical treatment to reduce relapse in recovering alcoholics in Europe, while naltrexone has been approved for a similar use by the US Food and Drug Administration. Acamprosate exerts agonist-like effects at GABA receptors and antagonist effects at the *N*-methyl-D-aspartate (NMDA) receptor; its ability to modulate the expression of NMDA receptor subunits in specific brain regions may be of relevance for its anticraving properties.[32] Naltrexone is hypothesized to reduce ethanol consumption by blocking central opioid receptors, which in turn modulate the positive reinforcing properties of ethanol.[33]

Nicotine

Tobacco is native to America, where it may have been cultivated by man as early as 5000 to 3000 BC.[34] Columbus came into contact with Indians smoking tobacco when he landed in Cuba, on his very first trip to America. The rest of the story of how the plant quickly conquered the world is well known. Like caffeine, nicotine may be regarded as a stimulant. Nicotine is not directly associated with psychiatric disorders, apart from the observation that psychiatric patients smoke more than the general population. Nicotine's toxicity concerns mostly the cardiovascular system and cancer. The neurotoxic and neuroprotective properties of nicotine had not been thoroughly investigated until recently. A study in rats[35] has shown that nicotine produces selective degeneration in the medial habenula, a region with a dense concentration of nicotinic cholinergic receptors. A significant public health concern is the risk to pregnant women. Prenatal exposure to tobacco probably inflicts damage to the developing brain, as suggested by a recent study showing upregulation of nicotinic cholinergic receptors in the brains of monkeys exposed to tobacco in gestation and the early neonatal period.[36] Nicotine has a neuroprotective action in neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. It protects neurons against the neurotoxicity caused by β-amyloid, the major component of senile plaques.[37]

Psychological, sociological, and biological factors associated with nicotine use

The onset of smoking typically occurs in the teenage years. Some American studies found that the median age of initiation is 16 to 17 years.[38] According to recent French epidemiological data, the mean age of smoking onset is as early as 14 years.[39] People choose to smoke because they appreciate the psychoactive, stimulant effect of nicotine. Smokers report that smoking helps them concentrate, reason, and perform—observations consistent with studies demonstrating that nicotine improves attention, learning, reaction time, and problem solving. For example, studies suggest that nicotine increases the speed of sensory information processing in smokers.[40] Smokers also report that smoking helps them relax, particularly in stressful situations, and improves their mood. They report pleasure and reduced anger, tension, depression, and stress. One explanation for the use of nicotine is that smokers rely on these positive reinforcements to cope with their environment. This hypothesis is borne out by the fact that individuals with psychiatric or psychological problems characterized by negative affect and difficulty coping are more likely to be smokers than individuals who are more emotionally stable.[41] The psychological and societal factors that influence experimentation with tobacco will also influence the propensity to experiment with other substances and, generally, different patterns of behavior. As expected, there is an association among the use of various psychoactive substances in adolescents. For instance, the National Household Survey conducted by the National Institute on Drug Abuse in 1985 found that, among 12- to 17-year-olds, the proportion using alcohol and marijuana was 74.2% and 47.3%, respectively, among current smokers, as compared with only 23.5% and 5.8%, respectively, among nonsmokers. Similarly, a recent Canadian study of 13 549 students showed that adolescents who used alcohol or cannabis or who smoked cigarettes were also more likely to use stimulants (amphetamines, diet pills) for recreational purposes.[42] One important factor in smoking initiation is the example provided by parents and peers. Smoking is more frequent among adolescents whose parents smoke or whose boyfriend or girlfriend smokes.[43] Societal tolerance, the absence of a clear set of rules, and the permissive attitude of some parents toward smoking also bear, without a doubt, some responsibility for initiation of smoking in the young.

A variety of psychological, sociological, and biological factors have a role in the progression from smoking experimentation to regular smoking. While many young people are exposed to the pleasurable effects of nicotine, only a minority go on to become regular smokers. According to a recent Sofres poll,[44] approximately 22% of the French population aged 15 or more continues smoking despite their knowledge of the actual or potential adverse consequences. Admittedly, possessing the theoretical knowledge that a substance is dangerous in the long term does not automatically entail that one feels emotionally, personally, and directly concerned. Psychological factors have been described by various authors, including psychoanalysts.[45] They include a difficulty solving intrapsychic conflicts and resorting to acts, substances, or food to alleviate feelings of boredom, emptiness, or anxiety that cannot be elaborated psychologically. Individuals who rely on cigarette smoking to cope with their environment generally consider it an efficient strategy because of its rapidity of action (nicotine reaches the brain within seconds) and availability (purchasing cigarettes requires relatively moderate cost and effort). The psychological factors that lead to smoking are often the same factors that lead to the use of other substances. Thus, cigarette smoking is often associated with the use of other substances, and the quantity of alcohol and nicotine consumed tends to follow parallel curves (moderate drinkers tending to be moderate smokers, and heavy drinkers tending to be heavy smokers).[46] Statistically, cigarette smoking and nicotine dependence are more prevalent in persons with a history of child abuse and neglect, in children whose parents have problems with alcohol and other drugs, in single teenage mothers and their children, in children and adolescents in foster care, in school dropouts, unemployed youths,[47] adolescents who are incarcerated and those in vocational schools,[48] and in persons with a history of incarceration. By high-school graduation, 28% of adolescents smoke cigarettes, but their peers who have dropped out of high school have rates approaching 70%.[49] In adults, smoking is more frequent among divorcees and single parents. Vulnerability factors may be undesirable states from which relief is sought. Resorting or not to smoking—or to other substances—in order to deal with life stressors or boredom is largely determined by an individual's repertoire of coping mechanisms. Delinquent behavior and experimentation with liquor, beer, and marijuana are also associated with teenage smoking. Smoking is also strongly linked to a variety of lifestyle indicators: it is associated with alcohol and caffeine consumption.[50]

Whether genetic factors explain some of the variation in cigarette smoking is not yet clear. Twin studies have produced variable estimates of the heritability of smoking behavior, ranging from 33% to 84% in American and Australian samples.[51,52] Interindividual differences have been shown in nicotine intake per cigarette and cotinine (the metabolite of nicotine) half-life.[53] CYP2A6, a genetically variable liver enzyme, is largely responsible for metabolizing nicotine to cotinine.[54] One study found that subjects carrying one or two inactive CYP2A6 alleles have impaired nicotine metabolism and are underrepresented in tobacco-dependent populations.[55] Different frequencies of the inactive CYP2A6 alleles have been reported in various populations.[56] However, a recent study, based on a more exact genotyping method, found no relation between genetic characteristics of nicotine metabolism and cigarette consumption.[57] Dopamine pathways are thought to mediate the pleasurable effects of nicotine in the brain. Studies suggest a relationship between genetic polymorphisms of the dopamine D_2 receptor gene and the dopamine transporter gene and smoking, indicating that these genes may belong to a multifactorial set of risk factors associated with smoking.[58,59] More studies will be required before these genetic issues are settled.

Nicotine dependence

"Tobacco dependence" was included for the first time in the nomenclature of mental disorders with the publication of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition *(DSM-III)* in 1980.[60] The diagnosis of tobacco dependence or addiction did not exist in second edition, *DSM-II* (the previous classification in 1968).[61] The definitions of dependence are based on consensus and have been repeatedly modified during the last decades. Prevalence rates of tobacco dependence are greatly influenced by the definitions chosen. Thus, *DSM-III* criteria were so overinclusive that a study[62] of 1006 middle-aged, male smokers showed that 90% were tobacco dependent according to *DSM-III*. Using *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition–Revised *(DSM-III-R)*[63] criteria, Stanton studied the 12-month prevalence rate of dependence of 967 daily cigarette-smoking 18-years-olds and found 19.3% to be dependent.[64] In *DSM-IV*,[3] this diagnostic category is called "nicotine" dependence instead of "tobacco" dependence. A similar historical evolution was observed with *ICD*, the World Health Organization's Classification of Diseases.

ICD-10, published in 1992,[65] contains a category for tobacco dependence, whereas the previous edition, *ICD-9*,[66] devised in the mid-1970s, had no such specific category and offered only a category for nicotine abuse.

Smoking withdrawal and cessation

Motivation and education are key factors. Clinical practice shows that smoking cessation can only be successful when an individual has made up his or her mind, is motivated, and has devised a personal strategy for how and when to stop. The subjective difficulty and the degree of discomfort entailed in the process vary markedly among individuals, from minimal in some to substantial in others. This is greatly influenced by an individual's psychological motivation. As part of the smoking cessation process, the smoker will have to overcome the discomfort due to dependence and will also have to reverse established habits reinforced by sociocultural factors. Individuals have to give up the immediate and short-lived gratification provided by cigarettes, and they have to change their lifestyle and routine. The practice of smoking is in large part a habit, a learned behavior with elements of conditioning, which is elicited by many stimuli (colors, smells, tastes, aromas, locations, times of the day such as the cigarette in the morning or after dinner, persons, familiar surroundings). Lighting up a cigarette is largely a conditioned ritual that has to be extinguished. The changes produced by withdrawal are physiological (eg, decreased heart rate), behavioral, and subjective (increased craving, ie, a strong subjective drive to use the substance, anxiety, irritability, etc). The prevalence of signs and symptoms at 2 days postcessation in individuals who quit smoking without assistance (self-quitters) is as follows[67]: anxiety 49%; craving 37%; decreased heart rate 61%; depression 31%; difficulty concentrating 43%; hunger 53%; irritability 38%; nocturnal awakening 39%; restlessness 46%. Most symptoms begin 6 to 12 hours following smoking cessation, peak in 1 to 3 days, and last on average 3 to 4 weeks.[68] Craving and hunger are generally the only remaining symptoms 4 weeks after cessation. The apparent degree of dependence and severity of withdrawal symptoms are not well correlated with ultimate success in smoking cessation.

Decline in the prevalence of smoking

A decline in the prevalence of smoking has been witnessed since the 1950s. According to a Sofres poll,[43] exsmokers are more numerous than current smokers in the French population (27% and 22% of the population, respectively). During the late 1950s, almost 80% of men in Western European countries were tobacco smokers. A prevalence of 42% was reported in the USA in 1965. Thanks in large part to educational efforts, smoking prevalence has declined to approximately 20% to 25% in many Western countries. A striking feature of the decline in cigarette smoking over the last past two decades in these countries has been the emergence of a marked socioeconomic gradient. In Britain, in 1990, only 16% of professional men and women were cigarette smokers, while 48% of men and 36% of women in unskilled manual occupations continued to smoke.[69] This distinction cannot be explained by biological differences between the two groups[70]; rather, it seems likely that while many people across all socioeconomic strata are potential smokers, education and prevention efforts can reduce smoking frequency. A similar trend has emerged in the USA, where smoking has declined very significantly among persons with substantial formal education. When compared with figures from 1974, 1976, and 1977, cigarette smoking prevalence had declined by 1990 to 1991 from 18.8% to 3.3% among physicians (average annual decline of 1.15 percentage points); from 31.7% to 18.3% among registered nurses (average annual decline of 0.88 percentage points); and from 37.1% to 27.2% among licensed practical nurses (average annual decline of 0.62 percentage points).[71]

NRT and drug treatment

Even though various treatment programs are available, most smokers quit by using their own, personally devised method, and most quit without any pharmacological or professional assistance. Nonetheless, pharmacotherapy such as nicotine replacement therapy (NRT) can be used to assist smokers who find it difficult to quit on their own. NRT is available in the form of nicotine gum or transdermal patches. NRT facilitates the initial period of cessation by reducing the severity of withdrawal symptoms such as craving and affective discomfort. Studies have demonstrated that (i) pharmacological treatment is efficacious—NRT doubles the success rate in some cases at 6 months of follow-up[72]; (ii) behavioral treatment is itself more efficacious than NRT; and (iii) success rates are almost always higher when NRT and behavioral treatment are combined.[73] In general, adding NRT to a behavioral intervention doubles the cessation rate. However,

clinical practice shows that a strong personal commitment and motivation to quit are the essential preconditions to successful abstinence and, without these, pharmacological aids will not have a significant impact on cessation success. NRT should not be considered if motivation, the mainstay of smoking cessation, is not clearly present. One important limitation of NRT is that the urge to smoke, or craving, is not solely determined by nicotine deprivation.[74] As discussed earlier, the urge to use tobacco is also elicited by many environmental stimuli.

Bupropion, which was originally introduced as an antidepressant, tends to double the abstinence rate. For instance, in a double-blind, placebo-controlled study,[75] the abstinence rates at 12 months were 15.6% in the placebo group, as compared with 16.4% in the nicotine-patch group, 30.3% in the sustained-release bupropion group, and 35.5% in the group given bupropion and the nicotine patch. It has been hypothesized that bupropion, a weak inhibitor of synaptic reuptake of dopamine, may maintain stimulation of pleasure response areas in the absence of nicotine by enhancing dopamine activity in the nucleus accumbens.

Caffeine

Tea and coffee are major sources of caffeine. Caffeine is also found in maté, in small concentrations in cocoa, and in caffeinated soft drinks. Coffee originates from Ethiopia. It was in widespread use throughout the Islamic world by the end of the 15th century. A couple of centuries later, Europeans started cultivating the plants in their colonies. The history of tea is considerably older, since it was already being planted and processed in China around the 3rd century AD. It is estimated that an average cup of coffee contains 100 mg caffeine, whereas a cup of tea or a 0.3 L glass of cola beverage contains about 40% of that amount.

Caffeine use

Approximately 80% of the inhabitants of affluent countries drink coffee or tea daily. Caffeine is appreciated because it is a stimulant; it induces alertness, elevates mood, and facilitates ideation. Subjectively, caffeine increases feelings of well-being, motivation for work, and desire to socialize. Blockade of A_1 and A_{2A} adenosine receptors appears to be the most likely mechanism of action for caffeine in brain.[76]

Patients with schizophrenia have high caffeine intakes.[77] In nonhumans, caffeine enhances dopamine function by blocking the A_{2a} adenosine receptor. Thus, caffeine might be expected to worsen positive symptoms and improve negative symptoms.

Caffeine consumption seems to be influenced by genetic factors, to the same degree as alcohol and nicotine. A study in 486 monozygotic and 335 dizygotic female twin pairs showed that the resemblance for total caffeine consumption, heavy caffeine use, caffeine intoxication, caffeine tolerance, and caffeine withdrawal was substantially greater in monozygotic than in dizygotic twins,[78] and the heritability of caffeine consumption was estimated at 35% to 77%.

Caffeine dependence

DSM-IV has diagnostic categories for caffeine intoxication, and caffeine-induced anxiety and sleep disorder.[3] The existence of caffeine dependence is debated. *DSM-IV* criteria for substance dependence, as applied to caffeine, are often met in the general population. For instance, about one quarter of 21 adolescents who consumed caffeine daily met these criteria in a study in New England.[79] A study of the generic *DSM-IV* criteria for dependence in 162 caffeine users found that the "strong desire or unsuccessful attempt to stop use" criterion was endorsed by 56% of interviewees.[80] *DSM-IV-TR*,[81] the recently published text revision of *DSM-IV*, proposes research criteria for caffeine withdrawal.

Caffeine withdrawal

One of the reasons for proposing caffeine as a model of dependence-inducing drug is the fact that it induces withdrawal symptoms, although they are limited. Like nicotine, caffeine use is reinforced by the taste and smell of coffee, the hedonic psychoactive effect of mental stimulation, and the desire to avoid the discomfort of withdrawal. The severity of withdrawal symptoms increases with the caffeine maintenance dose. Even short periods of caffeine deprivation, equivalent to skipping a regular morning coffee, can produce deficit in sustained attention.[82] Withdrawal symptoms are rapidly relieved by caffeine intake. Signs and symptoms of withdrawal, in decreasing order of frequency, include headache, drowsiness, impaired concentration, work difficulty, depression, anxiety, irritability, nausea or vomiting, and muscle aches and stiffness.[83] The withdrawal syndrome usually shows an onset 18 to 24 h after cessation; its intensity peaks between 20 to

48 h after abstinence; its duration ranges from 2 days to a week. Tolerance to the sleep-disturbing effects of caffeine has been demonstrated. However, there is little evidence for upward dose adjustment, possibly because of the unpleasant effects of higher doses.
Since caffeine is not associated with significant health hazards or incapacitation, its potential to induce dependence does not pose a serious problem for the individual or society.

Overlapping addictions

No psychoactive drug has been studied in so many individuals as have alcohol, nicotine, and caffeine. The experience that we have with these compounds is tantamount to an open trial conducted over a couple of millennia in billions of subjects! This review of mankind's most consumed drugs could also have encompassed betel and khat, which are both widely consumed in Africa and Asia for their mild stimulant properties. In the near future, we are likely to gain more experience with cannabis, the use of which is tending to be decriminalized. Since these drugs are so much appreciated, it may be assumed that they procure beneficial and pleasant effects. The benefits obtained in terms of creativity, anxiety reduction, social disinhibition, and pleasure have been extensively described in poetry and literature, rather that in medical treatises.
There exists a tendency for some normally functioning adults to have multiple addictions. This led many authors to discuss theories of addictive personality. A study[84] of overlapping addictions to common substances (alcohol, caffeine, chocolate, or cigarettes) and activities (exercise, gambling, Internet use, television, or video games) in college men and women found moderate to large correlations, both within and between substances and activities. Several gender differences in addictive tendencies were also revealed: men scored higher than women on addiction to alcohol, cigarettes, gambling, television, and Internet use, but women scored higher on caffeine and chocolate. Animal studies have shown that rewards obtained from various drugs, as well as food, playing, and sex, stimulate a midbrain reward circuit, involving dopamine and structures such as the nucleus accumbens. The issue of addiction is more complex in humans, who have the conscious capacity to evaluate, in the prefrontal cortex, whether pleasurable activities are appropriate and acted upon, or should be deferred or resisted. This fascinating duality of the human, oscillating between biological urges and conscious choice, has always been a fundamental question in our history, as exemplified by the fact that our attitude toward intoxicants and games is discussed in religious texts. ❑

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Alcohol, nicotina, cafeína y trastornos mentales

El alcohol, la nicotina y la cafeína son las sustancias psicotrópicas utilizadas más ampliamente en todo el mundo. Ellas son consumidas en gran cantidad por sujetos normales y su utilización es mucho más frecuente en los pacientes psiquiátricos. De hecho los pacientes esquizofrénicos tienden a abusar de estas tres sustancias. Las interrelaciones entre depresión y alcohol son complejas. Todas estas sustancias pueden crear dependencia, de la manera en que está definida en el Manual Diagnóstico y Estadístico de los Trastornos Mentales, 4ª edición (DSM-IV). *El abuso de alcohol es claramente deletéreo para el cerebro, provocando trastornos mentales agudos y crónicos, que van desde la intoxicación con deterioro cognitivo hasta el delirium tremens, la alucinosis y la demencia. En cambio, las principales consecuencias para la salud de la nicotina, especialmente el cáncer y las enfermedades cardiovasculares, están fuera del dominio de la psiquiatría. Sin embargo, el tema de la dependencia de la nicotina y la motivación para fumar o para dejar de hacerlo le conciernen a los psiquiatras.*

Alcool, nicotine, caféine et troubles mentaux

Alcool, nicotine et caféine sont les substances psychotropes les plus largement utilisées à travers le monde. Si elles sont largement consommées par les individus normaux, leur utilisation est encore plus fréquente chez les patients psychiatriques. Ainsi, les schizophrènes ont tendance à abuser de ces trois substances. Par ailleurs, les relations mutuelles entre dépression et alcool sont complexes. Ces substances peuvent être à l'origine d'une dépendance, ainsi qu'elle est définie dans le Manuel Diagnostique et Statistique des Troubles Mentaux, 4e édition (DSM-IV). *L'abus d'alcool est clairement délétère pour le cerveau, provoquant des troubles mentaux aigus et chroniques allant de l'intoxication avec déficit de la cognition, au delirium tremens, à l'hallucinose et à la démence. En revanche, les principales conséquences de la nicotine en termes de santé, notamment cancer et maladies cardio-vasculaires, sont hors du domaine de la psychiatrie. Il n'en reste pas moins que le problème de la dépendance à la nicotine et la motivation pour fumer ou s'arrêter font partie des préoccupations des psychiatres.*

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