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Cocaine: consumption and consequences

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Original article

BACKGROUND

The group that make up the Addictions Committee* has analyzed the primary addiction problems in Mexico with the aim of identifying fields for inter-institutional collaboration and making public policy proposals. This group has published a document on the abuse of alcoholic beverages, and another on cannabis consumption.

INTRODUCTION

Cocaine derives from the scientific name of the Erythroxylon coca plant. Its appearance is that of a fine, white, crystalline powder. The German chemist Friedrich Gaedcke isolated it from the leaves of the plant in 1885. However, it was Albert Niemann who has the credit for isolating it in the form we know, in 1859. Europeans used it a short while beforehand, when John Pemberton (1831-1887) invented French Wine Coca, a precursor of Coca-Cola, in 1886. In 1863, Angelo Mariani (1838-1914) invented the famous Vin Mariani. This drink was made with coca leaves and Bordeaux wine. Mariani was a chemist and he made pills, elixirs, and infusions of cocaine. All of these products were commercialized with various therapeutic indications, particularly to improve mood and reduce tiredness. Pope Leo XIII was a keen drinker of Vin Mariani, and even appeared on its label.[1]

Dr. Pemberton invented Coca-Cola as an imitation of Vin Mariani. Pemberton was, in fact, a morphine addict, and sought refuge in cocaine,[1] and at that time, even Freud considered that it could reduce, control, and even cure dependency on opiates and their derivatives.[2] Modern Coca-Cola has not contained cocaine since 1909.[3]

Due to cocaine being a powerful stimulant, it was noticed that daily consumption caused alterations in sleep and loss of appetite. If the person did not take it, they could become desperate, and an association began to be made between consumption and adverse effects. In the United States, these behaviors attracted attention, which became a concern, and finally, its use was prohibited altogether. In 1920, legislators were obligated to include cocaine in the list of prohibited drugs through the approval of the Dangerous Drugs Act, but unfortunately, cocaine consumption was already established in the population and incorporated into the culture.[1]

It was not considered a problem in Mexico until the 1980s, due to low prevalence, and its consumers generally belonged to privileged economic classes; writers, intellectuals, and artists. Consumption began to increase after the 1970s, and particularly in the 1990s, and the way in which cocaine was used, both by smoking and in its new form, *crack*, began to be studied. Studies were also conducted on usage patterns, profiles of new users, and differences by sex.[4] Its use became a problem around the 2000s which coincided with a change in the international routes carrying the drug to the US, which changed from the Caribbean to the Central America/Mexico corridor.[5]

NEUROBIOLOGY OF THE EFFECTS OF COCAINE ON THE BRAIN

Cocaine is classified in Group I of the Single Convention on Narcotic Drugs 1961, amended by the 1972 Protocol, and it

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also appears on the list of preparations of Exempt Narcotics of some provisions included in List II of the 1961 Convention on the condition that it has no more than 0.1% of cocaine calculated in base cocaine.[6]

Crack is obtained by combining cocaine with ammonia or bicarbonate of soda and an aqueous solution. It comes in small rock form which is highly addictive, and it is taken by smoking. It also comes in free base form, which is generally consumed more in the Andean region and in other South American countries. This substance is a result of an extraction from coca leaves with kerosene and sulphuric acid and not with cocaine itself. Like *crack*, free base is a highly dangerous drug due to its low cost and rapid absorption, farmacokinetically it is eliminated in five minutes. Drugs with greater addictive capacity are those that are absorbed quickly. Kerosene produces various toxic effects, one of the most potent and damaging of which is myelin destruction. Sulphuric acid also produces a wide variety of toxic effects including pulmonary emphysema and lung cancer.[7]

The drugs are taken orally 100-200 mg, nasally 5x30 mg, snorting (inhaling) cocaine 60-250mg, free base 60-250mg, and *crack*, which has no clear dosage. Cocaine rapidly metabolizes (90 mins) to benzoylecgonine and ecgonine methyl ester (EME) which are inactive. It has been noted that a maximum of 10% of unchanged cocaine is eliminated through urine.[7]

Users generally take cocaine for its stimulating effect and a sense of self-confidence, and it is classified by some as an "ego-drug". The user may become talkative, have rapid thoughts and over time can become irritable and aggressive. But the effect wears off quickly, after 30 or a maximum of 90 minutes and the user may experience the sensation of loss of self-confidence, fear, and anxiety, which leads them to seek another dose. If the subject drinks alcohol at the same time, a compound called cocaethylene is formed, which has a longer average life (150 mins) but ultimately has the same unpleasant effects.[3]

The neurobiological mechanisms of cocaine consumption include facilitating the bioavailability of dopamine in the motivation-reward system. Cocaine interferes with the serotonin transporter SERT, the dopamine transporter DAT, the norepinephrine transporter NET, in that order of potency.[7]

These transporters are proteins which are expressed in the terminals of these neurotransmitters and are responsible for transporting returning serotonin, dopamine, and norepinephrine inside their respective synaptic terminals.[8] In other words, the reuptake of neurotransmitters is one of the mechanisms that use neurons to terminate the action of said neurotransmitters. Therefore if reuptake of dopamine does not occur, it stays in the synaptic space, increasing the time that the dopamine receptors are activated. The ventral tegmental area (VTA) is the region of the brain that synthesizes and releases dopamine. Its target sites are the nucleus *accumbens*, the amygdala, and the prefrontal cortex, among others.[9] Therefore, the increase of dopamine due to interference with the DAT increases dopamine in these target sites. Due to it being noted that dopamine is coupled with its D1 and D2 receptors in the nucleus *accumbens*, it has been determined that it is its action on the D2 which facilitates the installation of dependency. However, with chronic administration, D2 expression is reduced, due to which it is not believed that it participates in maintaining an addiction. This has been observed using the technique of Positron Emission Tomography (PET), although it is not known if D2 expression is reduced as a consequence of cocaine use or because the patients were already expressing it because they had become addicted. However, there are studies on volunteers (not addicted to cocaine) who were given methylphenidate. Those in whom lower D2 expression had been detected using PET reported feeling pleasant effects of this drug, but this was not the case with those who had a high expression of D2, who reported displeasure.

In studies on rats, those that were overexpressing D2 drank less alcohol than control rats. However, as they drank, even though it was a small amount, D2 expression was reduced, and therefore the rats drank more alcohol. Furthermore, it has been observed that the dominant males in a troop of monkeys have higher D2 than their subordinates. When allowed to self-administer cocaine, the subordinate ingests more than the dominant. In some monkeys that have self-administered cocaine for weeks or months and then been left abstinent for three weeks or up to a year, D2 recovers its basal expression.[10]

In other words, dopamine and its receptors, particularly D2, as well as the dopamine transporter, are important sites for the installation and maintenance of cocaine consumption. In relapse, the very important function of glutamate has been widely studied and demonstrated. Glutamatergic AMPA receptor agonists applied to the nucleus *accumbens*, the ventral tegmental area, and the prefrontal cortex prevent relapse in the self-administration of cocaine.[11] Along the same vein, the administration of agonists in these cerebral regions facilitates relapse.

Within the executive systems are the prefrontal cortex, the internal globus pallidus (GPi) and the habenula. The third right frontal gyrus has been critically involved in the inhibition of conduct expression. This cortex activates the subthalamic nucleus and this in turn increases the activity of the internal globus pallidus, and with that, the thalamus is inhibited and the expression of the conduct is reduced.[12] The habenula activates the inhibitory neurons of the tegmental rostromedial nucleus and this inhibits the VTA.[13] The failure in either of these systems facilitates impulsivity and cocaine consumption in the subject.

EPIDEMIOLOGY OF COCAINE CONSUMPTION IN THE MEXICAN POPULATION

The last National Survey on Addictions[14] shows that in a period of nine years (2002-2011) illegal drug consumption at some point in a lifetime in the population of people aged 12-65 increased from 0.8% to 1.8%. Cocaine consumption has shown variations in the population's preference at the end of the eighties and at the beginning of the nineties it had a greater presence in the national market, and later it was coupled with the consumption level of other substances, increasing again in the beginning of the noughties. While the consumption of other drugs doubled between 1988 and 2008, cocaine consumption went up by seven times, from 0.33 to 2.60 in the population aged 12-65.[15,16]

Currently cocaine (including *crack*), followed by marijuana, is one of the substances most preferred by the population and its consumption at some point during a lifetime increased between 2002 and 2011 from 0.3% to 0.5%. This order of preference is the same for men as it is for women with a ratio of 2:1 respectively. Among the group of women, cocaine and *crack* consumption is higher among the youngest age group of 12-25 year olds. It can be noted that the current generations have greater accessibility to drugs, greater consumption, and a greater probability of progressing from abuse to dependency than previous generations.[16]

In relation to other drugs, it was document that those who consume tobacco and alcohol before the age of 18 have an increased likelihood of using other drugs; in the case of cocaine, 7.6% of users experimented with tobacco early and 3.8% did so with alcohol.

Cocaine consumption by regions of the country indicates that consumption is slightly higher in the south, (0.6%) than in the central region (0.2%).[16]

In the last report on Mexico City, the Drugs Information Reporting System[17] showed statistics from 45 healthcare and law enforcement institutions which captured data from 1,261 cases. Of this figure, 429 (34%) were cocaine users, 35.4% were men and 27.5% were women. Some 34% had used cocaine "at some time in their life", and 24% had taken it "within the last month". Some 8.2% of the men advised using cocaine as the first substance they used, and 0.7% of users of this substance started before the age of 11. The most affected group were users between the ages of 15 and 19 years of age, at 45.9%.

The Student Survey in Mexico City[18] indicated that from 2006 through 2009, there was an increase in the prevalence of consumption, from 17.8% to 21.5%; this consumption is higher in men than in women (7.9% *vs*. 6.1%), and higher in degree students (28.5%) than high school students (16.1%). Cocaine takes third place in students' preference (3.5%), after marijuana and inhalants. However, through these measurements, taken every three years, it has been observed that cocaine consumption remains stable with respect to 2006. One important figure is that 75% of students consider cocaine consumption to be dangerous, which would probably have an influence as a protective mechanism.

Another source of information is obtained from drug users who have sought treatment in Juvenile Integration Centers,[19] which have observed an increase during the nineties, and use –at some time in their life– went from 12.2% in 1990 to 71.4% in 2000. Until 2007, cocaine use –at some time in their life– remained relatively stable, but in the last three years, there has been another downward trend, situating it at levels close to or even below 50% in terms of –at some time in their life– (48.7% in the second half of 2010) (Fig. 1). Consumption of both cocaine as well as free base and *crack* each present decreasing tendencies, with figures at the start of 2010 of 39.6% and 24.8% respectively.

High percentages of cocaine consumption are reported in treatment centers in practically all of Mexico, whereas *crack* is usually reported with a higher frequency by substance users treated in the northeast, central, and southern regions of the country (Fig. 2).

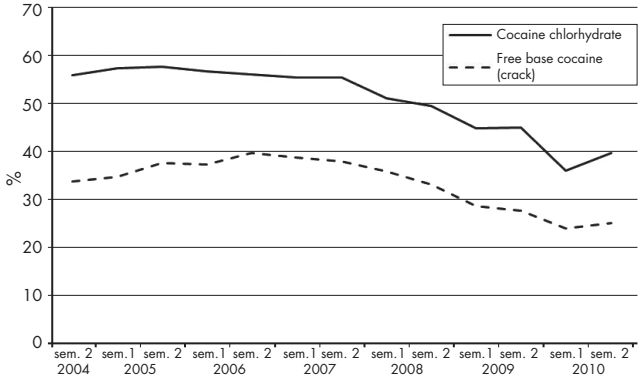

Figure 1. Use of cocaine and *crack* at some time in the lives of drug users who sought treatment from the JIC from the second half of 2004 through the second half of 2010.

Figure 2. JIC units in which the treatment population reported *crack* use at some time in their lives above the national median (24.8%) Second half of 2010.

Drugs with the greatest impact are those for which greater problems in use are reported and which motivate seeking treatment in JICs. The comparison of cases that indicated cocaine or *crack* as the drug with greatest impact casts light on some significant differences. Firstly, there is a significantly higher proportion of men than women (89.3% *vs*. 10.7% respectively) in users of *crack* as the highest impact drug than there is in cocaine (84.1% *vs*. 15.9% respectively). Furthermore, these users have a greater percentage of unemployed people (32.3% *vs*. 22.8%) and a lower percentage of active students (6.9% *vs*. 15.1%).

In the same way, those who indicate *crack* as their greatest impact drug also refer to having used a larger number of illicit drugs at some time in their life than those who reported cocaine as their highest impact drug (3.37 on average [SD: 1.8] *vs*. 2.76 [SD: 1.9]. They also have a higher rate of tobacco consumption (90.6% *vs*. 85.9% of cocaine users), inhalants (36.7% *vs*. 18.6%), Rohypnol (7.1% *vs*. 4.1%), and hallucinogenic substances (8.0% *vs*. 4.7%). Those who indicated cocaine as their drug of greatest impact have a higher percentage of use of stimulants (22.9% *vs*. 14.4%) and in particular, methamphetamines (11.7% *vs*. 5.6%) at some time in their lives. Finally, users of *crack* as the greatest impact drug have a much higher frequency of illicit drug use within the previous month, and 42.7% *vs*. 29.2% refer to having used them daily.[20]

RISK FACTORS OF COCAINE CONSUMPTION

According to the investigation, experimental cocaine consumption is associated with factors common to the use of substances in general, such as those with high accessibility, low risk perception, peer pressure, low behavioral control, and low school attendance. However, studies developed in the JIC have found that cocaine users maintain a negative view of their families (perceiving them as aggressive and untrustworthy), interpersonal relationships (friends also perceived as untrustworthy) and of themselves (perceived as aggressive and unsatisfied among other aspects).[21] As part of the group of major stimulant consumers, cocaine users show signs of impulse control disorders, low self-esteem and depression (primarily with feelings of failure, disappointment, punishment, guilt, and self-criticism). They also report being exposed to particularly violent family relationships, with a history of physical, emotional, and sometimes sexual violence; factors which are also associated with criminal activity and violent behavior reported by the users themselves.[19,22] Finally, they report their basic safety needs (calmness, emotional security, and trust, among others) not being met.

COCAINE AND ITS EFFECTS ON HEALTH

Further to the effects cocaine produces on the nervous system, effects have also been observed in the rest of the body. Within the most immediate are vasoconstriction, pupil dilation (mydriasis), hyperthermia, tachycardia, and hypertension. The effects derived from euphoria, primarily during the first 30 minutes, are hyper-stimulation, feeling less tired, and a state of higher mental alertness. Other effects that primarily present themselves in the medium to long term are arrhythmia, myocardial infarction, thoracic pain, shortness of breath, cerebral vascular events, convulsions, headaches, nausea, abdominal pain, anorexia, and malnutrition.

There are also specific effects depending on the method of administration. Nasal administration can cause nosebleeds, anosmia, septum perforation, dysphonia, and dysfunction in swallowing. Oral administration can cause intestinal ischemia, and injection can cause allergies, HIV, hepatitis, and other infections.

The effects can depend on individual sensitivity and dosage, as has been described before. This is related to the method of administration and the purity of the product, which is impure in in at least 40% of cases, frequently contaminated with talc, cornstarch, or sugar. It is also contaminated with procaine (an anesthetic) or amphetamines.[23]

One factor that can promote the biological effect of cocaine is the free fraction in blood. Some 90% binds itself to albumin in such a way that when the albumin reduces, the consequences of the same dose can be greater. At the root of anorexia and frequent dietary transgressions that can be experienced in cocaine consumption, hypoalbuminemia can be one of the effects that also aggravates others.

There is a vicious circle in terms of effects on both acute and chronic health in cocaine consumption, probably to a greater level than that of other drugs. Hyper-stimulation and a sensation of greater energy can raise the tolerance threshold to other cardiovascular, respiratory, and pain symptoms, which can be fatal if not dealt with.[3]

COCAINE AND PREGNANCY

Through increased cocaine use in the general population due to its increasing availability[24] and the reflection of this in the consumption trends in women of reproductive age, it is estimated that the number of pregnant women who consume cocaine has also increased.[25]

Assessing the exact prevalence of cocaine consumption during pregnancy is complex due to the variability of populations and methodologies used. However, some studies carried out around the world establish a rate between 1.8% and 18%,[26-28] and the dangerous nature of cocaine exposure expands during pregnancy to affect maternal, fetal, and neonatal wellbeing.

Based on the principles of the teratological-neurobehavioral model, numerous studies have described the impact that prenatal exposure to cocaine has on the health, Central Nervous System, behavior, and development of a child,[29] associated with genetic makeup, the environment (perinatal and postnatal), dosage, and development stage at the time of exposure.

It is important to mention that the physiological changes associated with pregnancy affect the absorption, distribution, metabolism, and elimination[30] of cocaine, increasing its harmful effects on the mother, the fetus, and the newborn.

The activity of plasma cholinesterase, which metabolizes cocaine to ecgonine and benzoylecgonine, is reduced in pregnant women, diminishing the speed at which cocaine is metabolized into inactive compounds, thereby maximizing the harmful effects of cocaine in the mother and the fetus.[24] Pregnant women metabolize cocaine to active norcaine at a much higher level; in this way, mother and baby are exposed to this high concentration of the active metabolite of cocaine.[31,32]

Due to the lipophilic properties of cocaine, it rapidly passes through the placenta by simple diffusion, exposing the fetus to a higher concentration of cocaine.[33]

The systematic response to cocaine involves cardiovascular effects (vasoconstriction, hypertension, and tachycardia), which favor the contraction of umbilical arteries, placental insufficiency, and intrauterine growth restriction (IUGR).[34]

Its hypertensive nature and the increase in uterine contractibility due to the increase in levels of norepinephrine predisposes placental abruption;[35,36] an increase in plasmatic levels of oxytocin shown in animal models suggests and explains the work of birth and premature birth,[37,38] and furthermore that cocaine consumption in the first trimester increases the risk of spontaneous miscarriage.[39]

Congenital deformities occur in between 7% and 17% of newborns exposed to cocaine (also bear in mind the concurrent consumption of alcohol in 60%-90% of consumers). As it is lipophilic and has a relatively low molecular weight, it is possible for it to pass through the placenta and the blood brain barrier, giving rise to fetal tachycardia, reduced heartbeat variability, lack of acceleration, and hypertension (abnormal cardiotocographic trace). Withdrawal syndrome is present in 10%-40% of newborns exposed to cocaine.[40,41]

Due to its effect on the monoaminergic neurotransmission systems (dopamine, norepinephrine, epinephrine, and serotonin) neurological development is affected,[42-44] altering the long term circuits for learning, attention, inhibition,[45] and language.[46] Alterations have also been reported in growth (height, weight, brain size).[47]

These complications are found in related to dosage, consumption time and gestational stage; as well as occasionally reflecting the impact of multiple exposures which combine cocaine consumption with other substances (alcohol, tobacco, cannabis, and heroin) to act in synergy and aggravate the adverse effects on the mother, fetus, and newborn.

Other features have been described within the context of substance abuse in pregnant women, which involve high levels of stress, absence of prenatal care, risk behaviors, and exposure to violence; in intravenous cocaine users, there is a greater prevalence of sexually transmitted diseases (HIV and hepatitis C).

PSYCHIATRIC COMORBIDITY IN COCAINE USERS

Dual Diagnosis (the coexistence of psychopathology and psychoactive substance consumption) is made on a neurobiological basis. Dysfunction of noradrenergic, serotonergic, and dopaminergic systems have been described, which are normally involved in behavioral inhibition localized in the septohippocampal area and the amygdala.[48] These changes reduce the capacity for impulse control and perception of reward phenomena, increasing vulnerability to developing disorders due to cocaine use.[49] It has been possible to demonstrate a dopaminergic deficit in Major Depressive Disorder, and when self-medicating with cocaine administration, the subject shows increased concentrations of dopamine in the striatum, as well as sensitivity to direct or indirect dopaminergic agonists, secondary to an increase in the function of the nucleus *accumbens*. Corticotrophin Release Factor (CRF) is a hypothalamic peptide distributed in limbic areas and in brainstem nuclei which, on releasing corticotropin, regulates the response to different stress situations involved in Depressive and Anxiety Disorders.

On the other hand, during withdrawal syndrome for psychoactive substances there is an increase in the neurotransmission of CRF, a fact that seems to indicate the existence of a common neurobiological alteration in depression and substance dependence. Furthermore, in depressed patients, it has been possible to detect a reduction in cerebrospinal fluid in concentrations of NPY (Neuropeptide Y), there being opposite rates between this neuropeptide and CRF.[50] During abstinence from cocaine, decreased neurotransmission measured by NPY occurs. Furthermore, vulnerable people who consume cocaine can develop a psychotic disorder secondary to their use due to a phenomenon of progressive sensitization which, in the majority of cases, clinically manifests itself as transitory psychotic episodes. This sensitization can be attributed to an imbalance between the D3 dopaminergic receptors and the D1 and D2 receptors, and a greater affinity of cocaine for the D3 receptor has been observed, which is responsible for the development of a faster tolerance phenomenon.[51] Personality disorders most frequently associated with cocaine use are Antisocial Disorder and Limit Disorder. As such, while various authors propose that aggression, hyper-activity, and impulsivity are

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characteristic traits of people who develop dependency on cocaine, others respond that the behavioral effect secondary to compulsive substance consumption can cause diagnoses of antisocial and limit disorder to increase by 19.2% and 11.2% respectively. Regardless of one theory or another, one recent study, carried out on a sample of 3,360 pairs of male twins included in a specific register of Vietnam war veterans (the Vietnam Era Twin Registry) confirms the close relationship that exists, genetically speaking, between antisocial personality disorder and cocaine dependency.[52]

Various studies have confirmed the elevated prevalence of a history of attention deficit hyperactivity disorder (ADHD) in subjects with cocaine dependency and/or abuse. Conversely, the prevalence of disorders due to cocaine use in subjects with a diagnosis of attention deficit disorder is also very high. Dopaminergic hypofunction has been described in patients with ADHD, in whom it has been possible to demonstrate a reduction in extracellular dopamine, as well as an increase in the density of dopamine transporters and uncontrolled neuronal discharges.[53]

VIOLENCE AND ITS RELATION WITH SUBSTANCE CONSUMPTION

Some studies have found that drug abuse is a factor in committing crimes such as homicide and robbery; evidence suggests that higher incidences of criminality are associated with higher drug abuse. But at the same time, it is known that not all those who abuse drugs become violent or commit criminal acts.[54]

It should be emphasized that violence is present in societies not only due to drug use and trafficking; cultural and environmental factors are also involved, but this phenomenon has a global and a microsocial impact. The illegal drugs trade in general destabilizes the economy of countries as well as that of civil society, as a result of increased crime, corruption of the legal and political system, drug abuse, and the loss of social cohesion.

The increase of criminal acts has a specific cost in use of medical, funerary, security, and treatment services, especially if society has been exposed for prolonged periods of time.

Another phenomenon related with crime is its attraction for young people to get involved in drug trafficking due to potential earnings, which can lead them to drop out of school. Crime and violence, related to drug abuse, has an impact at different levels of society which ranges from international problems related to trafficking and organized criminal activities, to crimes committed against individuals who abuse drugs and the innocent people caught in the crossfire, to crimes which occur due to the necessities of users and dependent people in order to obtain money or resources to buy drugs.[54,55]

Explaining the relationship between drugs and crime is complicated; it requires an integrated vision that is centered on the individual (physical and psychological aspects, including psychiatric and pharmacological factors), as well as social and cultural view (distribution of property, socio-economic differences) which have an impact when combined.

In the case of cocaine, it has been found that abuse is associated with an increase in the likelihood of committing a violent crime, and with *crack* specifically, the psychopharmacological effect and its relation to an increase in carrying weapons has been documented.[56]

It has also been documented that there is a greater risk in victimization of people who take drugs, doing so makes them temporarily or permanently vulnerable due to being incapable of interpreting and responding to dangerous situations.

CONCLUSIONS

The information presented indicates that cocaine is not a new drug; it is a dangerous drug that compromises individual and social health. In Mexico, it was not considered a problem until almost the 1980s. In the following decade, with the closure of Caribbean routes to take the drug out of the Andean region and towards the United States and Europe, cocaine found a path through the Central America/Mexico corridor, its consumption extended to Mexico, and between 1988 and 2011 there was an almost eightfold increase in the number of people who had experimented with it.

Cocaine use showed a marked increase in drug users who sought treatment in Juvenile Integration Centers during the nineties, going from just over one in ten people to seven out of ten people in 2000. This remained stable until 2007, when there was a period of decrease with less than five users out of every ten people who sought help. This tendency included *crack* and was also observed in the population treated in non-governmental centers and among students in Mexico City where there have been three and a half decades of periodic measurements taken.

This data shows that as the perception of danger around the drug has varied over time, so too has its consumption, with periods of growth and decline, on which epidemiological studies have been based. These trends, which are the product of variations in external markets, internal factors, and public policies, should be considered when evaluating prevention programs and anticipating the demand for treatment.

Cocaine is still considered as a dangerous drug, a factor which favors prevention programs, as it does not require resource investment in order to raise awareness of the danger of the drug in the same way that alcohol does, thereby freeing up resources for other aspects of the problem.

The fact that it is not very widely used in the form of

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injection means that there is a lower risk of spreading infectious diseases; however, this should still be monitored carefully due to the risk of other illnesses such as HIV and hepatitis C from this form of administration.

A quarter of users who consume cocaine smoke it in the form of *crack* or "rock", and these users are usually people who are unemployed or those who use a larger proportion of drugs than those who use cocaine in its powder form. This necessitates timely identification and treatment programs for this underserved population. The association between this form of use and violence in the three forms described in the document (pharmacological effects, robbery to obtain money, and participation in drug-dealing to obtain drugs) is important, and therefore treatment programs should include actions for social development and opportunities for emotional and social development for these groups, along with crime prevention.

Epidemiological monitoring systems should be attuned to reporting free base consumption, which is highly dangerous due to its low price and rapid absorption, leading dependent people to repeated use and rapid deterioration with the aim of feeding their habit.

Cocaine remains a drug which is mostly consumed by men, but among women that have used cocaine, a large proportion prefer the smoked form. This observation, together with the risks of consumption during pregnancy, indicates the need for identifying and treating pregnant women and those at risk of unwanted pregnancy. The lifestyle of users, with frequent exposure to violence, puts them at particular risk of unwanted pregnancy and the baby's exposure to the drug during pregnancy and after birth.

The fact that a third of cocaine users start before the age of 18 and have smoked or drunk during early adolescence increases the probability of experimenting with cocaine. This indicates pathways to prevention with integrated programs that prevent the use of tobacco, delay the start of alcohol consumption, and reduce adolescents' exposure to cocaine at the same time as giving them skills to develop away from the use of drugs, with social development programs that care for the needs of the most deprived groups who take this drug in its most dangerous forms. The observation that use extends beyond adolescence necessitates longer term programs that are adapted to the needs of people who go through other cycles of life.

Its association with the different forms of violence described in the document, mean that emphasis must be placed on differentiating these phenomena. In spite of having violent behavior or being a victim of crime or aggression in common with one another, they have a different etiology and as such, the programs aimed at its control and reduction should also be different.

The document explains the mechanisms by which the drug produces pleasure, which is what causes users to seek the drug, but it also describes the process of dependency, especially with short-term variations, reasons which underlie the frequent relapses in the populations with severe dependency in treatment and of the harm caused to multiple organs and to the life of society.

The multiple effects on users' health described in this work indicate the need for treatment not only to integrate care for the problems derived from the consumption of alcohol, tobacco, and other drugs, but that it should also follow a comprehensive model that allows for the care of the physical, mental, and social health of users.

The study of addicts in treatment has allowed for a knowledge of its comorbidity, especially with depression, behavioral disorders, and family and social problems that can arise. This includes criminal behavior.

The knowledge gained in this investigation has allowed advances to be made in the pharmacological and psychotherapeutic options. The most useful models have been those which are based on the knowledge of addiction and its development. The knowledge gained can also allow *ad hoc* treatments to be designed for the physical, mental, and emotional health needs of each person with dependency, thereby facilitating adherence to treatment. The challenge is to pass this knowledge to the community and to those responsible for prevention and treatment programs. There is much more to be said by research in terms of the development of medications and better models of intervention.

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