

Etiology and Treatment of Cocaine Addictive Disorder

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ABSTRACT

Addictive disorders are considered one of the main problems facing society today. In this article an elaboration will be made on the etiology, mechanisms of action and treatment of cocaine addictive disorder by unraveling its impacts on society and the human body. The drug cocaine will be used as a role model for explaining addictive disorders. After an introduction the reader will be guided towards medical aspects of addictive disorders, where history, toxicity, manifestations of toxicity and the mechanisms of action of cocaine are explained. The second part discusses the social aspects of the addiction to cocaine. The relation between cocaine and Anti-Social Personality Disorder are unraveled followed by issues such as priming, stress and relapse. Also the extent of the relationship between drug usage and addiction are explained, as well as the psychological and pharmaceutical treatment methods for addictive disorders widely applied today.

Key-words: Addictive Disorder; Cocaine; Overdose; Priming; Drugs

Drugs are a global problem haunting families, schools, neighborhoods, and countries as a whole. They are responsible for the collapse of families and overdose deaths, but they also affect the economy of countries, as drug dealers are involved in money laundering. Nowadays there is still a debate going on about the classification of drugs. Some countries, such as the Netherlands, make the distinction between soft and hard drugs (e.g. alcohol and marijuana vs cocaine). Most countries such as Germany, France and Brazil however, do not make this distinction, yet they hold strong negative opinions about drugs.

The problems related to all drugs are too broad to be discussed in the scope of this article. Therefore, it will be elaborated on the problems induced by a specific drug – cocaine –, which are of relevance on the user's life. As will be clear to the reader at the end of this paper, drug addiction cannot be overlooked. It is a very serious problem deteriorating people from the social norms into being outcasts in their own society. If the proper treatment is not provided, a drug addict who has total dependency on one particular drug will probably stop at nothing to obtain the drug. This can range from breaking simple laws, such as minor thefts, to eventually committing a murder. The mindset of the person elevates because of the craving for the drug, making him/her vulnerable to commit illegal or inappropriate acts to obtain it. Indeed, this is not the only problem to which drug addiction might lead to. Most drug addicts are socially inadequate and have problems with establishing positive social bonds. This can have a devastating effect on the drug dependent individual who will seek comfort with other drug addicts. At this point a vicious cycle is created as this individual does not get the help he/she needs. Instead of diminishing his/her addictive behavior, this behavior is encouraged by peers who are most often also addicts.

One drug that is used widely spread around the world is cocaine. Cocaine is only one type of illegal drug that can be injected in the body through many ways (e.g. smoking, sniffing and injecting). Cocaine gives the individual a big burst of energy called *euphoria*, what can be the reason why it is so popular amongst certain groups. It is commonly used by people who, for instance, have an extravagant night life, practice a job in the hectic sector of the stock market (stock market brokers), and individuals who feel the need for extra energy in general. These individuals feel stimulated to use that drug because they frequently feel a need for extra energy to maintain a good performance on tasks that require much mental or physical energy. The mechanisms by which cocaine effects the body will be discussed in detail in the medical section of this article, first however, emphasis will be made upon the history of cocaine.

The history of cocaine

The use of cocaine can be traced back to the South American Andean Indians, approximately 5000 years ago, who chew on the leaves of the *Erythroxylon Coca* plant for social, medical and religious reasons. As for the latter, these traditional Indian Cultures had many Gods, one of them being called *Mama Coca*. This Goddess of health and joy was considered to have the ability to bless humans. Before one could chew on the leaves of the *Erythroxylon Coca*, the individual had to make sure that *Mama Coca* was in a favorable mood. This could be achieved by sleeping with a woman prior to chewing coca leaves (Drugs, 2008).

After the colonization of the American continent, the *Erythroxylon Coca* soon became known throughout the rest of the world (Drugs, 2008). It was not earlier than 1855 when the active substance of *Erythroxylon Coca* was first isolated by Albert Niemann (1834-1861), who attained a pure sample of the active substance, and named it *cocaine* (Nationmaster, 2008). Soon after isolation, the cocaine alkaloid became a widely prescribed drug.

The first wide scale benefits of cocaine were noticed by Theodor Aschenbrandt, who administered cocaine to the Bavarian army in the XIX century. This general noticed that the substance he administered resulted in a wide variety of benefits during battle. He published his finding in the German Medical Journal, which resulted in an even more rapid awareness about the effects of cocaine (Drugs, 2008).

The father of American Surgery, William Halstead, who was an early user of cocaine, demonstrated the use of cocaine in nerve-block anesthesia in 1885.

The action mechanisms of cocaine

Nowadays cocaine is widely used by medical specialists as a local anesthetic in especially eye, nose and throat surgery. As for most other addictive drugs, cocaine induces its effects by influencing the central nervous system (CNS), independently if it enters the body by means of smoking, ingestion, injection or snorting it intranasally. Cocaine, or methyl3-benzoyloxy-8-methyl-8-azabicyclo [3.2.1] octaan-4-carboxylate (Fig. 1), is most often taken up by the body through the mucosa of the nose/mouth (IUPAC, 2008).

Figure 1: The chemical structure of cocaine (purified) (EMCDDA, 2009).

Cocaine induces addiction by activation of the pleasure pathway in the central nervous system where it inhibits several transporters in the synaptic cleft. These transporters fulfill an important function in the re-uptake of neurotransmitters by the pre-synaptic cleft. This pathway, called the Mesocorticolimbic Dopamine Pathway (MCLP), is the central place in the brain where drugs induce their effects (Butcher, Mineka & Hooley, 2007).

As for cocaine, it has been found that it affects three known high affinity targets in the transport of neurotransmitters namely the dopamine transporter (DAT), the serotonin transporter (SERT) and the norepinephrine transporter (NET) (Rang, Dale, Ritter & Flower, 2007). In normal situations these transporters bind to the specific neurotransmitter, which is released from the pre-synaptic vessel into the synaptic cleft making sure that re-uptake of the neurotransmitter occurs (Fig. 2).

Figure 2: The pharmacodynamics of cocaine (adapted from Silverthorn, 2007).

By inhibition of the transporter, for instance due to the presence of cocaine, the neurotransmitter will remain for a much longer period in the synaptic cleft, resulting in a prolonged binding with the receptor of the post-synaptic vessel. This, in turn, causes an induction of more action potentials, resulting in a stronger effect which brings the user to a state of "high". By inhibiting the function of the neurotransmitter re-uptake transporters, the function of monoamine oxidase (MAO) is also inhibited. MAO is an enzyme which degrades the neurotransmitter after re-uptake has occurred (Rang, Dale, Ritter & Flower, 2007).

By inhibiting the three mentioned transporters DAT, SERT and NET, complex neurochemical and behavioral effects are produced. The blockade of norepinephrine (noradrenaline) reuptake can result in tachycardia, and the inhibition of serotonin reuptake may induce hallucinations (Kumar & Clark, 2005).

Several studies have found that the dopaminergic system, especially the dopamine transporter, plays a major role in the addictive properties of cocaine addiction.

Studies of DAT-Knockout mice have found that the inhibition of dopamine transporters not only results in the addictive mechanism of cocaine, but that inhibition of DAT, SERT and NET together result in the rewarding mechanism of cocaine (Moore & Dalley, 2007). The brain rewarding pathways, consisting mainly of the ventral tegmental area (substantia nigra), the nucleus accumbens and the caudate nucleus, is characterized by high levels of dopamine and dopamine receptors (Fig. 3).

Figure 3: The brain reward pathways. The caudate nucleus can be found below the Corpus Callosum (adapted from The Lundbeck Institute, 2008).

The above mentioned mechanisms could explain the sensation of high speed and energy, as well as the craving for cocaine referred by users.

Manifestations of toxicity

The effects of cocaine can be best described as an experience of intense euphoria, which is the main reason why cocaine is considered as one of the most addictive of all drugs. Although there is no measurable physical dependence, there is certainly a psychological withdrawal which can be extremely difficult to treat. Abstinence of the drug causes extreme cravings in especially the first couple of months. These cravings can persist for years (Silverthorn, Garrison & Ober, 2007).

Cocaine toxicity can result in serious manifestations in which the most frequent are mentioned below. First of all, cocaine toxicity can result in serious cardiovascular effects, which are considered its most disturbing effects. The acute action on the cardiovascular system can induce hypertension, cardiac arrhythmia, myocardial infarct and cerebral hemorrhage due to the inability of re-uptake of neurotransmitters such as dopamine and norepinephrine in the brain (Kumar & Clark, 2005).

As for the central nervous system (CNS) other consequences can be extreme local fever (hyperpyrexia) with temperatures above 42 centigrade Celsius. Also the effects on the fetus are worth mentioning, as cocaine may cause a decrease in the blood flow towards the placenta. This in turn results in hypoxia and spontaneous abortion of the fetus. Chronic cocaine use in pregnant woman can also result in impairment in the neurological development of the fetus. (Kumar & Clark, 2005).

As for chronic cocaine use, the consequences can be the perforation of the nasal septum, a decrease in lung diffusing capacity and, in more serious cases, development of dilated cardiomyopathy (Rang, Dale, Ritter & Flower, 2007; Kumar & Clark, 2005; Stevens & Lowe, 2005).

The latter is characterized by cardiac dilation, which can progress over time, and the contractile (systolic) dysfunction of the heart. In most cases there is also a strong development of the heart cells (myocardocytes) which increase in size without an increase in dividing (hypertrophy) (Kumar & Clark, 2005; Kuar, 2007; Jochems & Joosten, 2006).

Cocaine overdose

The consequences of cocaine overdose on a physical level are considered severe. An overdose most often occurs when one has quit using cocaine for several months or years and then administers the same dose as before the abstinence period. Due to the fact that there is no tolerance anymore, the chances of overdose are high (Butcher et al., 2007, p. 412).

Tolerance can be defined as "the need for increased amounts of a substance to achieve the desired effects" (Butcher et al., 2007, p. 412). One develops tolerance when the body has increased the rate of metabolism. This defense mechanism results in a more fast elimination of the drug from the body. Although the user still assumes that the exact dose for the desired effect has not changed after the abstinence period, this dose will actually be much lower due to an absence, or partly absence, of the body's tolerance (Kumar & Clark, 2005).

Cocaine and Society

Because of its relatively cheap price and the strong feeling of euphoria, cocaine is considered a very popular drug amongst young adults. The use of crack (smokable cocaine) is considered a public health problem not only in the United States of America (US), but also in Australia, Brazil, Mexico, Canada and many countries in Europe. According to the most recent US National Survey on Drug Use and Health, more than 8.5 million people have used crack at least once in their lifetimes (Falck, Wang & Carlson, 2008).

Nowadays cocaine is most often prepared as a water-soluble powder which is officially known as *cocaine hydrochloride*. In the commercialization this substance is diluted with talcum powder, baking powder or lactose. In the streets, cocaine is also known as crack due to the crackling sounds which can be noticed when the drug is smoked. Injecting or sniffing the drug results in a more intense effect than smoking because much more cocaine reaches the bloodstream when it is injected or sniffed (Kumar & Clark, 2005).

Recently Fothergill Ensminger, Green, Robertson, and Juon (2009) published the results of their prospective study on adult cocaine use within the African-American population of Chicago ranging between age 6 to 42. They examined the pathways to adult cocaine use and obtained many interesting results. They found five variables to have a significant effect on cocaine abuse namely: first grade shy behavior, early adult church attendance, first grade aggression, adolescent substance abuse and early adult income. It was found that children who were aggressive in early childhood were more likely to use drugs as teenagers. The opposite proved to be true for individuals who showed shy behavior in their early years. Shy children were less likely to use drugs in their adolescence, probably due to the fact that shy children have reduced social interactions, fewer sources for obtaining drugs and are less influenced by peers who use drugs. Interestingly, individuals who went to church in their early childhood showed decreased chances of mid adult cocaine use. Furthermore, individuals with low incomes in early and/or mid adulthood, low school achievements, a certain ethnic background (e.g. African, Hispanic) and bad social (e.g. family) bonds also showed to have an increased risk in substance abuse (Fothergill et al., 2009).

Age statistics

Cocaine addiction is not constricted to one group of age. Although there are cases of individuals over age 50 that become addicted, the majority of people that try cocaine for the first time are between 12 and 49 years of age (Falck et al., 2008). This vast age range of users is what differentiates cocaine from other hard drugs, which are mostly associated with a smaller age range.

Currently, estimations are that there are about 2 to 6 million cocaine users in the US. Approximately 1.1% of the users are middle-school students and 2.3% are high-school students (Kumar & Clark, 2007). Cocaine is a very addictive substance but the level of severity addictiveness depends not only on its purity but also on the way in which it is administered to the body and the genetic predisposition of the individual to addiction. It is least addictive when it is smoked rather than when sniffed or injected through a needle. This is why most young users prefer to smoke it, being under the wrong assumption that it causes no addiction at all.

Anti-Social Personality Disorder (ASPD), and other health related issues

As for most drugs, cocaine is associated with many psychological disorders, one of them in particular is Anti-Social Personality Disorder (ASPD). Drug addiction or substance abuse share many symptoms with ASPD and this is why some doctors suggest that ASPD might actually lead to substance abuse such as cocaine. In addiction there is a strong relationship between ASPD and substance abuse in which the latter increases the chances of later development of ASPD. Robins (1998) has noted that this is due, in part, to the overlapping symptoms of the disorders and shared risk factors. Furthermore, Robins (1998) has argued that ASPD can actually cause addiction disorders.

Along with the connection between ASPD and cocaine dependence other health problems can be attributed to the use of cocaine. Typically, the environments in which individuals use drugs are considered unhealthy and can result in serious illnesses such as AIDS. Chronic drug dependent individuals tend to use the same needle to inject the drug for a group of people making the risk of blood transmitted diseases higher (Robins, 1998; Kumar & Clark, 2005).

Contrasting cocaine usage and addiction

Although much cocaine-related issues were already discussed in this paper, one can still ask him-/herself whether all drug users are also addicts. Falck (2008) tried to answer this question by conducting a longitudinal study over a course of 8 years with 172 cocaine-dependent individuals. These subjects were either crack addicts or crack users that never met the criteria of lifetime cocaine dependence in the DSM-IV-TR. Some constrains such as age, education, and homelessness, were inserted in order to attain a higher validity with respect to the outcomes of the experiment. The variables recorded in the study included the first time use, frequency of usage, and life time dependence. The main conclusion of that study was that it is possible to use crack for long periods (e.g.10 years) without meeting the DSM-IV-TR criteria

for lifetime cocaine dependence, although the majority of users develop addiction after long periods of chronic drug-use. It was also found that Caucasian-Americans have a higher chance of becoming cocaine-dependent than African-Americans.

It should be mentioned however that these results were not significantly valid to be generalized on a global scale due to the lack of international studies. "The findings also suggest that race/ethnicity and co-morbid psychiatric disorders are important indicators of who avoids and who succumbs to addiction. Interestingly, the groups did not differ in the mean age of crack initiation or the frequency of recent crack use, suggesting that duration and amount of use, while unquestionably being critically important factors in the development of cocaine addiction, are not its sole determinants" (Falck et al., 2008, p. 26-27).

Indeed, genetic susceptibility forms another very important factor in developing cocaine addiction. In fact, it accounts for approximately 40-60% of the risk of developing substance addiction such as cocaine. Yuferov, Levran, Proudnikov, Nielsen and Kreek (2010) published a review article in which they discussed various genes which play an important role in cocaine-, alcohol- and heroin addiction. They also elaborated on two important genes which show a strong relationship with cocaine addiction. Two single-nucleotide polymorphisms (SNPs) in the OPRK1 gene have been found to be associated with cocaine dependence. Various polymorphisms in a second gene, called PDYN, are known to increase the risk of alcohol- and cocaine dependence (Yuferov et al., 2010).

The treatment of cocaine addictive disorder

Although the treatment models that have been developed for cocaine addiction are not gender specific and have high drop-out rates, many studies have been conducted which support the effectiveness of drug treatment. One of the main problems in cocaine-addiction treatment is that many of these patients suffer from ASPD, which contributes to treatment resistance and promotes high drop-out rates.

The treatment of cocaine addictive disorder is performed, in most cases, on three levels: biological, psychological and socio-cultural. The biological treatment is also known as the medical- or pharmacological treatment and is considered as a first-line therapy. In this treatment medication, such as Desipramine and Naltrexone, are prescribed having the goal to reduce the cravings for the drug (Nunes-Dinis & Barth, 1993; Butcher & Clark, 2007).

Recently Katsidoni, Apazoglou and Panagis (2010) published an article in which they tested the stimulating- and inhibiting effect of serotonin 5-HT(2A) and 5-HT(2C) receptors, hereby mimicking the brain-rewarding effect of cocaine. It has been argued by many that especially the serotonin receptors, which are widely expressed in the MCLP, account for the behavioral effects of cocaine (Katsidoni et al., 2010). In this study, the nucleus accumbens and intra-ventral tegmental area of male Sprague-Dawley rats were stimulated by means of implanted electrodes, hereby mimicking the effect of cocaine. Various agonistic- and antagonistic drugs were administered by means of microinjection. It was found that especially the 5-HT(2C) receptors can modulate the effects of cocaine. With this research, Katsidoni and colleagues (2010) provided evidence that agonistic drugs for the 5-HT(2C) receptor could be a potential drug target for specifically treating the psychological addiction of cocaine and other drugs.

The psychological treatment of addictive disorders mainly targets the problems which originate from motivational, learning, and emotional dysfunctions. These problems may be symptoms of psychopathology or social learning. Social-learning models are used to treat, for instance, individuals who have deficits in social and cognitive learning skills. These deficits are the sources of chronic stress and promote increased use of the drug substance. With social-learning models one can think for instance of group therapy and cognitive-behavioral therapy (Nunes-Dinis & Barth, 1993). Other psychotherapeutic approaches, as psychodynamic psychotherapy and family system therapy, can also be part of the treatment.

A relatively new accepted treatment method within the field of Psychology is mindfulness training (MT). MT, originally derived from Buddhism, has been used as a treatment method for addictive disorders. Brewer et al. (2009) compared cognitive behavioral therapy (CBT) with MT in targeting stress reactivity in 36 individuals with cocaine addiction. They concluded that especially mindfulness training was effective in specifically targeting stress, which has proved to be an important provoking factor in many addictive disorders (Brewer et al., 2009).

As for treatment based on a socio-cultural perspective, it aims environmental restructuring, providing the patient with alternative living arrangements and promoting the interaction with reliable social groups such as family, church or Narcotics Anonymous (Nunes-Dinis & Barth, 1993).

Most programs, however, apply mixed-treatment models such as the bio-psycho-social integrative model in which biological, psychological and social factors are treated. Indeed, the choice of treatment is decided upon the patient's needs (Nunes-Dinis & Barth, 1993; Butcher et al., 2007).

Triggers of cocaine addiction relapse

Priming (Classical Conditioning)

Relapse is a very important concern in the treatment of addictive disorders. Spealman (2003) conducted a research in order to unravel the causes of relapse, through testing the casual relations between drug usage and certain related aspects such as priming, personality traits, and stress. In this research non-human primates (monkeys, squirrels and rats) were used as role-models for the human race. The research protocols were approved by the Harvard Medical School Institutional Animal Care and Use Committee (Spealman, 2003).

The first trigger of relapse discussed was re-exposure to the drug. Spealman (2003) hypothesized that a test subject was more vulnerable to relapse after s/he was re-exposed to cocaine. After many trials on animal subjects it was concluded that priming plays a very important role in relapse. Priming is very similar to classical conditioning and is basically the triggering of the craving for the drug after the individual is re-exposed to the drug or any stimuli associated to the drug through priming. The study by Spealman (2003) was first conducted on rats which were trained to inject themselves with a dosage of cocaine. The rats were primed with drug administration by means of an auditory stimulus (beep). After priming, a second situation was created in which there was an absence of auditory stimulus, but with presence of the drug. In this second situation, the rats seemed to return to their normal no drug seeking behavior by trying to apprehend self-injection.

However after the re-administration of the auditory stimuli, the rats yet again tried to inject themselves with the drug by stepping on a special platform.

In other similar studies (Spealman, 2003), a visual stimulus was used instead of an auditory. In these studies the same results as in the study using auditory stimulus, have been obtained. It was found that the drug seeking behavior seemed to increase when the rats were exposed to priming in which a bond link was established between drug administration and a visual or auditory stimulus.

Because the results found were not 100% correlated, it was stated that the differences in substance administration and dependence are attributed to personality traits. "The robust reinstatement of drug seeking induced by priming combined with restoration of the cocaine paired stimulus suggests a potentially important interaction between environmental and pharmacological triggers of relapse, possibly reflecting conditions analogous to those encountered by addicts in real-world situations" (Spealman, 2003, p. 61). From these results it became obvious that the re-exposure of animals to cocaine after absence of addiction can greatly increase the risk of relapse. In sum, if this model is applied to humans, cocaine ex-addicts should stay clear of not only cocaine but any other drug, as well as avoid triggers of relapse.

Stress

Stress and associated negative mood states have been repeatedly implicated as risk factors in drug addiction and relapse. "Although clinical observations suggest that exposure to stress can induce drug craving and relapse in human drug abusers, the mechanisms by which stress triggers renewed drug seeking remains largely unknown" (Spealman, 2003, p. 61). Similar procedures, such as the ones used to implicate priming in relapse, have been used to show the link between stress and relapse.

The same procedures as in the priming test of Spealman (2003) were followed: the rats were left at a place where they could administer the drug dosages to themselves. Electrical shocks, which served as a stress inducer, were introduced to the rats. These shocks were administered for a period of about 10-30 minutes on each tested rat. The relation between the stress induced by the shocks and the craving for the drug seems to be, although present, less significant than priming.

From the study of the relation between stress and relapse (Spealman, 2003) it was concluded that stress does have consequences on drug cravings but environmental factors play a more significant role at enhancing the drug seeking behavior in the subjects. When the rats were placed in an unfamiliar environment, even with the presence of the stressor, they did not significantly showed drug-seeking behavior. Other stressors as fox's urine (which the rats perceived as a predator/danger) were also investigated. The researchers also used food deprivation to elicit stress to the rats. Even with these different stressors, the rats reacted in the same manner, further proving that stress does not play a major part on relapse (Spealman, 2003).

It should be mentioned that the same studies that Spealman (2003) conducted on animals were also conducted on humans but at a smaller scale. The results obtained from the human testing were closely correlated with the ones obtained from the tests conducted on animals. This gave Spealman's experiments on animal's high accuracy when it came to generalizing their results to humans.

Conclusion

Issues of drug abuse in general, and cocaine dependence in particular, run deep in societies, destroying homes, deteriorating people's behavior and health, and ruining economies. Although at first when cocaine was discovered it seemed as if it was an almost harmless substance which has the power to elevate people's moods, it is now clear in to what extent the problems caused by cocaine can run.

Unpredictability, irrationality, and poor judgments are some of the immediate consequences that cocaine can have on users. At this stage, the user is often considered an outcast of society because s\he cannot behave conform to the norms of society.

Thousands of people around the world die of drug-overdose every year, in which a considerable amount is due to cocaine toxicity. As mentioned earlier, cocaine is not restricted to a specific age but has a rather wide spread range of age. Cocaine is therefore *colorblind* because it does not distinguish between skin color or ethnic subgroup, being used all around the world by different groups. As much as cocaine can cause mental disorders, some mental disorders (e.g. ASPD) can induce the person to seek avoidance from her/his depression and/or stressful life by administration of drugs.

Even after addiction treatment, the drug can take-over control of life once again by forcing the individual to retake the drug through what is called *relapse*. Many aspects take part in the relapse process in which priming seems to play a major role. An ex-drug user should stay clear from situations that might trigger the drug craving, such as parties or meetings in which drug use is promoted.

Many people have the wrong assumption that they can use cocaine without becoming addicted, but a wide variety of statistical studies show that the most likely outcome of using cocaine for long periods is addiction (Kumar & Clark, 2005; Falck, 2008; Gale, 2001). In sum, no drug-addict has ever assumed that s\he will become addicted, and a wise person should always keep in mind that a *penny* for prevention is better than a *million* for treatment.

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