CLINICAL REPORT

INTEGRATED MASTER´S DEGREE IN DENTISTRY

Oral manifestations of drug abuse: a forensic perspective

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Abstract

Introduction: Ilicit drug abuse is a worldwide problem and has been reported over the years. Among the most abused drugs are cannabis, cocaine and methamphetamine. All of them are capable to induce a state of dependence and tolerance, underlying the route of administration and frequency of use. Due to their toxic power many body lesions and brain damages are reported.

Aims: This research article pretends to approach each drug mentioned above underlying the forensic scope and dissect some information regarding their chemical arrange, metabolism and toxicological mechanism in human body. Beyond that, the main sight is to dive in the oral environment and understand the toxic damage and harmfull manifestations, discussing some systemic signals and symptoms as well.

Material and methods: This review article is the result of an exhaustive research and exploration in "European Monitoring Centre for Drugs and Drug Addition" and Pubmed databases. Inclusion criteria comprise "10 years" and "Humans" reviews, cross-sectional studies, clinical trials and case reports. Some books concerning the molecules chemical action and forensic aspects were also consulted.

Key words: "ethanol AND oral cavity", "MDMA AND oral health", "oral heath in heroin addicted", "Cocaine abuse AND oral mucosa", "forensic toxicology AND drug abuse".

Development: There are some sort of drugs that work in similar ways. Both MDMA and cocaine induce the release and impair the reuptake of catecolamine-type neurotransmissors, allowing the user to feel euphoric and speedy. Their power of inducing user dependence is significant but not as high as heroin. Diacetylmorphine is a semi-synthetic drug produced from morphine known (extrated from *Papaver Somniferum*) for its analgesic properties. All of the ilicit substances approached have many hostile manifestations in human body. Both their oral and systemic effects will be specified throughout this review. Among many substances, alcohol plays a key role concerning mouth cancer development, which is the sixth most diagnosed worldwide according to World´s Health Organization. Its power to change cell membrane permeability creats a favorable environment for carcinogenic agents difusion into the cell. Actually, the synergism between alcoholism and tobacco smoke is proven to be the main risk factor for cancer evolution.

Conclusion: All health professionals, namely dentists, alongside with forensic toxicologists, are fundamental to diagnose and apply social and medical meseaures to stop drug dependence and tolerance among users. Information campaigns and special cares by dentists are essencial in this

phase. Nevertheless, general population should also be aware of these signals and symptons approached in order to play an active role too.

Introduction

The abused consumption of ilicit drugs has been a worldwide problem since olden times, for both users and society.[1, 9] Toxic substances envolve any type of product overconsumption regarding both dosis and frequency of administration. Even though there are certain drugs related to abusive intake as they lead to knotty states of dependence.[10]

Forensic toxicology has a wide scope by approaching fundamental analytical characteristics in juridical and health care areas, namely in intoxication related crimes. It provides means to identify and quantify toxic substances in clinical samples or *post-mortem* proves in exposed individuals. Plus, it has an extensive range as it purviews occupational, public health and constitutional areas, envolving live individuals and deadly victims. There are three central domains: post-mortem toxicology, behaviour toxicology and drug abuse control. *Post-mortem* toxicology is related to substances identification and quantification when there´s suspicion of drug associated crime. Behaviour toxicology pretends to study human performance and habits change due to continuous drug consumption. The control of drug administration is also an area comprehended in forensic toxicology. It is done when there´s signs of apparent contact with drugs, for exemple in work places as a prerequisite.[11]

Alcohol abuse is related to the development of a panoply of disorders and lesions in human body, such as vasculitis, palmar eythema and psoriasis.[2] Concerning the oral environment, the oxidative stress caused by its metabolism contributes highly to oral cancer growth, which is the sixth sort of cancer most diagnosed worldwide.[5, 12, 13] The metabolism of ethanol occurs mostly in the liver (only 2 to 10% is excreted by the lungs and kidneys) by the alcohol and aldehyde dehydrogenase enzymes, being converted in acetic aldehyde and in acetate later.[6] Should be told that the amount of ethanol administered and duration of habit are proven to have more responsability in the toxic action than the type of beverage.[5] Plus, the consumption of alcoholic drinks is associated with tobacco use, which is a synergist agent of the hostile activity and leads to worse case prognosis.[2]

Cocaine is the main opioid harvested from the leafs of *Erythroxylon coca*, a plant found in the region of Andes, South America.[14] It was first used as a local ester-type anesthesic in the XIX century, by Nieman.[15] The molecule is formed by benzoic acid and methylecgonine.[16] Although most percentage of its metabolism occurs in the blood stream by the plasmatic cholinesterases, the liver plays an important role too, which will be specified later on.[11] The molecule of cocaine works as a selective inibitor of catecolamines in the synaptic gap, such as dopamin, serotonin and

epinephrine. It bonds to pre-sinaptic receptors of these neurotransmissors, causing a continue and permanent stimulation of the post-synaptic neuron.[17] The user experiences feelings of euphoria, weel being, psichomotor hiperactivity and absence of tiredness, due to the stimulation of the rostro-caudal brain structure.[18] Its vasoconstriction action reduces the heat libertation, and since its use is associated with raves (with high concentration of people) and dance activities, cases of hyperthermia are reported.[19] As the metabolits are formed and excreted, takes place a "dysphoric crash", where the consumer experiences loss of energy and happiness, which contibutes to the dependence on the drug.[15]

Cocaine can be consumed as "powder-cocaine", crack cocaine or free base cocaine, depending on the process of transformation. *Erythroxylon coca* leafs and the cocaine paste ("pre-cocaine") can also be prepared for administration.[10, 15, 20] The toxic effects on the human body include, among others, the development of an oro-sinusal comunication, smooth muscle rhabdomyolysis and states of depression.[21]

In the eraly years of the XX century, MDMA (3,4-methylenedioxymethamphetamine) was first produced by Merck, a german pharmaceutical company.[22] In the 1970´s its ilegal production started in california, which lead to an increased recreative use of this sinthetic drug among hippies and youngsters at raves and night "techno" clubs.[22, 23] MDMA, MDA and MDEA are an amphethamine type stimulants, classified as ecstasy like drugs.[24] The methamphetamine palys its role in the central nervous system, blocking the reuptake of the catecolamine-type neurotransmissors, allowing the user to feel euphoric and speedy[25, 26]. "Meth mouth" is a term commonly used in literature reffering to rampant caries, over wear of teeth and jaw (leading to severe bruxism cases) among users.[27] Some cases will be approached in the present study.

Moreover, it´s important to understand the difference underlying the terms "opioid" and "opiace".[28] The first one refers to the substances that interact with opioid receptors, while "opiace" is restrict for those who come from the oppium poppy and its derivates.[29] Four different types of benzylisoquinoline alkaloids can be found in the milky fluid harvested from the green seed capsules of the *Papaver* (greek word for "poppy") *Somniferum* (latin word for sleep inducers): codeine, papaverine, noscapine and morphine.[29] Heroin is a semi-synthetic drug produced from morphine and represents a worldwide cause of high rates of morbility and mortality.[28] Synthesized in 1874, was first used by the Bayer industries as a cough supressant and abandoned later due to its strong power of dependence.[28]

There are three sorts of heroin sold on the streets. All of them are in salt or base form and are presented as a white powder, brownish powder or black tar.[28] Concerning users oral health, studies show that they have lower scores of oral hygine and higher prevalence of caries and periodontal disease. [30, 31]

Not that rarely, drugs are adultered and "cut" with other xenobiotics, as stretagy to incresse product´s weight and improve dealers profit. Moreover, most of the studied population is "poly-drug" user, which restricts all results accuracy.[17, 28]

The aim of this research is to explore subjects like the pathocytology, metabolism and action of each drug mentioned above in human body, after a continued abuse of the substance. The main purpose is to dive in their manifestations in oral cavity, approaching some sistemic symptoms and lesions too.

Alcohol

Ethanol consumption is a part of human culture since recorded history and it´s consider the most frequently abused psychotropic drug.[2, 8] Its misuse is related with multiple body lesions and lower health status. World Health Organization informs its increasing power to induct high rates of morbility and mortality, as it occupies the fiveth place between top substances responsable for disease development.[2] Moreover, alcoholism is associated with 50% of reported driving accidents, 50% of the murders and 25% of suicides.[6] It has a wide scope of social and familiar injury, such as domestic violence episodes, traffic accidents as well as poor performance at work.[2] The amount of alcohol consumed and the duration of habit are proven to be more harmful that the type of beverage itself.[5]

Ethanol is a water and lipidic soluble molecule and most of its metabolism takes place in the liver. Only 2 to 10% is excreted by lungs and in urine.[2, 6] The following figure pretends to demonstrate this process major part.

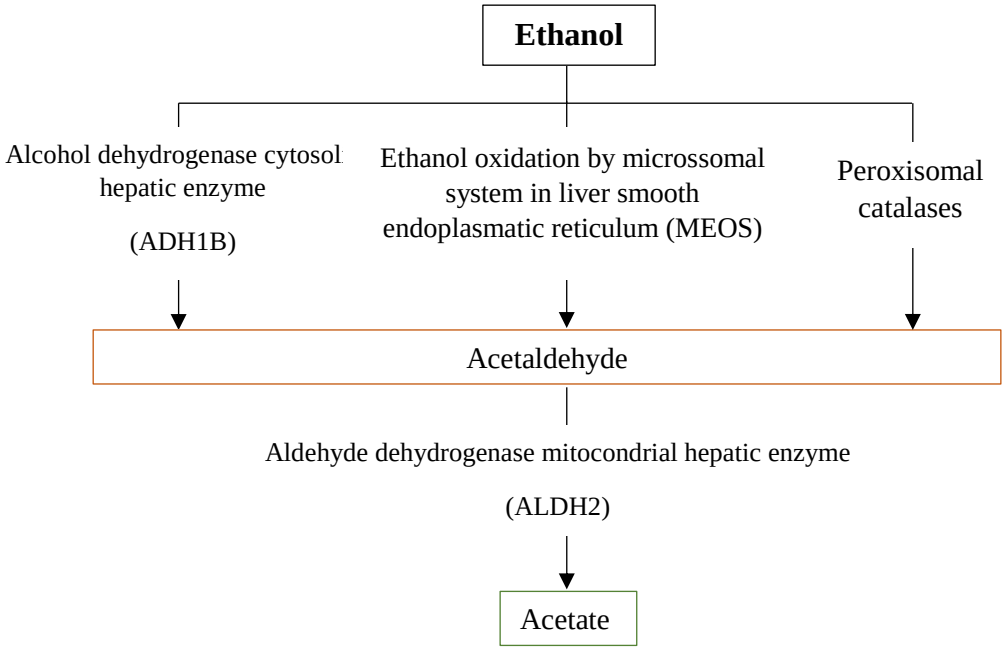

Figure 1: Ethanol metabolism.[2, 4-6]

There are three different pathways by which ethanol is metabolized in acetaldehyde. The peroxisomal catalases one is not relevant in human body, as so two main processes are considered: ADH1B (Alcohol dehydrogenase cytosolic hepatic enzyme) and MEOS (Microssomal system in liver smooth endoplasmatic reticulum).[6] Acetate is later transported to blood stream, where is

radly hydolised in carbon dioxide and water by extra hepatic tissues.[6] There´s a lot of information in literature concerning the existence of genetic polimorfism in ADH1B molecule that seems to influence alcoholic consumption habits, liver disease development and distinct reactions to ethanol intake.[2, 6] There is also a distinct genetic field regarding ALDH2 enzyme. When inactive provides a higher risk to develop mouth cancer.[5]

Moreover, hostile effects of alcohol consumption are also due to the increased production of free radicals and reduced antioxidant mechanisms, which leads to oxidative stress.[5]

Some authors explain that alcohol is not a carcinogen agent itself, but a "co-carcinogen".[12] This means that its most toxic metabolite, acetylaldehyde, is the main responsable to provide cancer cells growth.[2] Alcohol consume is associated with tobacco smoke, which results in a synergistic action, as ethanol molecules are capable of alter the carcinogen-activation pathway regarding compound founs in cigarette smoke.[12, 13]

As so, alcohol exposure causes damages in oral mucosa.[12, 32] It has the power to change cells membrane permeability resulting in morphologic and atrophic injuries that alter diffusion/reuptake padrons of toxic substances.[12]

Qihang Zeng et al. conclude that the pellicle formed by saliva in tooth enamel after acontacting with alcohol is weaker and less organized than the one in non exposed individuals.[33] They also found a decrease in saliva lubrificating properties, which signifficantly contributes to carious process development and consequent periodontal disease in the studied group.[33]

As mentioned, acetaldehyde molecule is the most toxic ethanol metabolite and the main responsable for carcinogenic mutations.[2, 5] Saliva seems to play an important role as it contains mutagenic concentrations of acetaldehyde during and after alcohol drinks ingestion.[2] Plus, cigarette smoke releases this substance, capable of alter oral microbioma.[2, 5, 12] Some studies approach the importance of fauna in inducing acetaldehyde production. *Candida albicans* and *Neisseria* species can segregate acetaldehyde due to their increased ADH1B enzyme and are often found in higher concentration in alcohol abusers.[5] This may explain the higher rates of oral cancer observed in this population. Moreover, acetaldehyde is proven to increase ethanol carcinogenic action.[12] Actually, synergism between alcohol and tobacco is pointed to be the major risk factor for oral cancer development, the sixth more common worldwide, with increasing case incidences over the years.[5, 12, 13]

Head and neck cancer are considered the most related with ethanol abuse according to World Health Organiation.[13] It appears with some of these signals: lump or sore in mouth and lips that does not heal, mouth bleeding, sore throat with no signs of improvement.[2] Ethanol abused consumption also powers the development of leukoplakia, erythroplakia and *lichen planus,* which increase the risk to undergo malignant transformation. Dentists must be aware of these changes and put into practice special cares and preventive measures.[2]

Black hairy tongue is a common, benign and asymptomatic manifestation among alcohol abusers. Normally does not affect the tips and sides of the tongue, having preference for dorsum and circumvallate papillae anterior region. It´s diagnosed when filiform papillae are hyperplasic and 3mm lenght, wich represents increased production oh keratin and decreased desquamation. Bad oral hygiene habits, ethanol abuse, tobacco smoke, radiation therapy are among the possible causes. It can be mistaken as acanthosis nigricans (lips are usually envolved too), hairy local leukoplakia (white lesions non removable by scraping) dark stains caused by food colouring. Secondary infection with candida albincans has been reported.[2, 34]

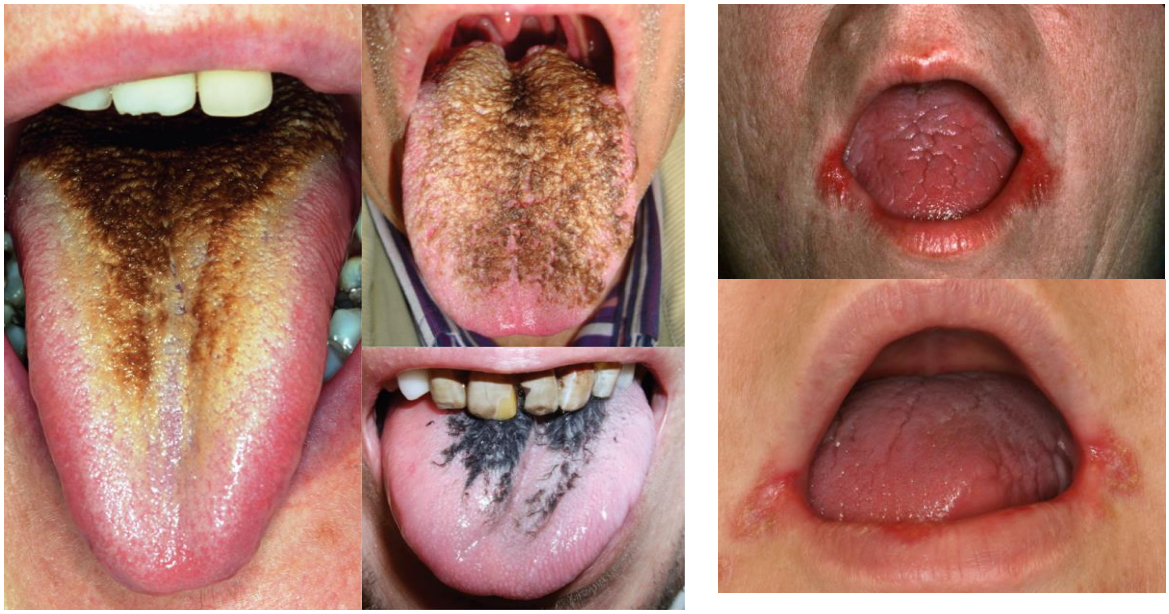

Figure 2: Black hairy tongue[2, 3] and angular cheilitis[8]. Adapted from Dinis-Oliveira, R.J., et al., *Clinical and forensic signs related to ethanol abuse: a mechanistic approach.* Toxicol Mech Methods, 2014. **24**(2): p. 81-110. and Dinis-Oliveira, R.J., et al., *Signs and Related Mechanisms of Ethanol Hepatotoxicity.* Curr Drug Abuse Rev, 2015. **8**(2): p. 86-103. , respectively, without author authorization.

Alcoholics normally have bad nutrition habits. They get their calories intake with ethanol and not with the propper vitamines. As so, oral musoca gets susceptable to get atrophied and more

vulnerable to toxic agent actions.[2] It seems to induce a rise of salivar glands volume due to fybrosis and lipidic inflitration, and a reduce in salivary flow (It is observed a decrease in PG2, PGF2, 6-keto-PGF1, prostaglandins that stimulate saliva secretion), which contributes to higher caries scores.[2] Sialosis is a non inflamatory and non neoplasic salivar glands tumefaction, mostly afecting the major ones. It is asymptomatic, bilateral, progressive and probably caused by ethanol induced interferences in autonomic inervation of sympathetic and parassympathetic nervous systems, given their active action in saliva secretion by salivary glands.[34] Mal nutrition states underlying alcohol intake, namely vitamine B2 deficiency, are in the origin of angular cheilitis, atrophic glossitis and seborrheic dermatitis-like facial eruption.[8, 34]

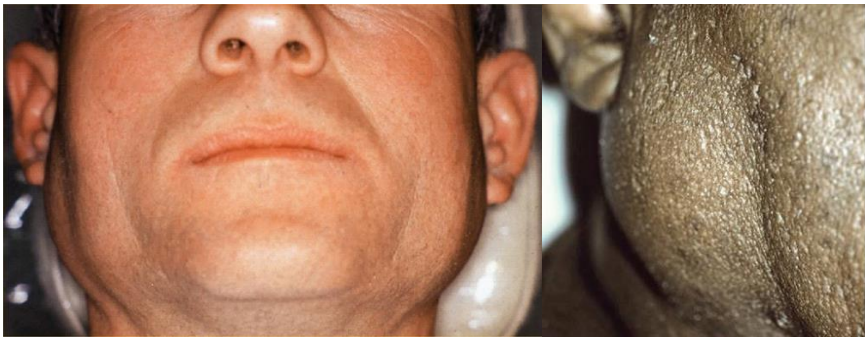

Figure 3: Sialosis[2]. Adapted from Dinis-Oliveira, R.J., et al., *Clinical and forensic signs related to ethanol abuse: a mechanistic approach.* Toxicol Mech Methods, 2014. **24**(2): p. 81-110., without author authorization.

Other manifestations related to ethanol abusive consumption include hypersensibility reactions, palmar and finger erythema, psoriasis and multilobulated sebaceous nodule protruding from the nasal tip, among others.[2, 8] Spider telangiectasias are vascular changes very often reported mostly on the face and upper chest, fading after death.[2] "Flushing" is classified as erythema episodes on the skin, getting worse with the quantity of alcohol consumed.[2] Asian people are more susctible to affected by flushing given ther ALDH2 enzyme deficiency.[2] Fetal alcohol syndrome comprehends congenital defects and neurodevelopment delays associated with ethanol abuse during pregnancy time. These changes influence the stomatognathic system, causing maxillary hypoplasia, oral clefts and long philtrum with small red region of upper lip.[2] Ricardo Jorge Dinis-Oliveira et al. concluded that ethanol exposure as the neurocortex is developing increases cell apoptosis and necrosis.[2]

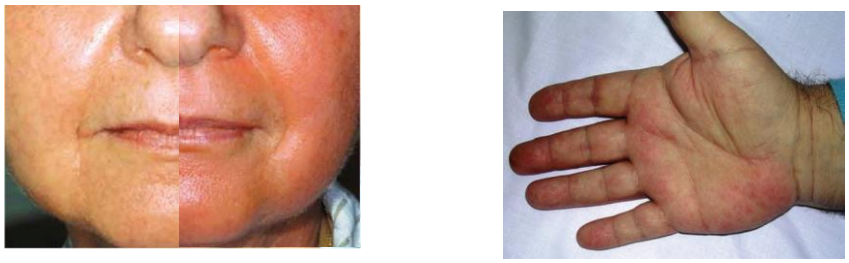

Figure 4: Facial "flushing" and palmar erythema[2, 7]. Adapted from Dinis-Oliveira, R.J., et al., *Clinical and forensic signs related to ethanol abuse: a mechanistic approach.* Toxicol Mech Methods, 2014. **24**(2): p. 81-110., without author authorization.

It is important to remind that are cases of these manifestations non ethanol related. Thus an effient diagnosis should be performed by health professionals, taking in account the ananmesis, clinical exams and xray images.[2, 8]

MDMA

MDMA (3,4- methylenedioxymethamphetamine) is a class of stimulant that belongs to ecstasy like type of drugs, as enlightened in the scheme that follows.[24]

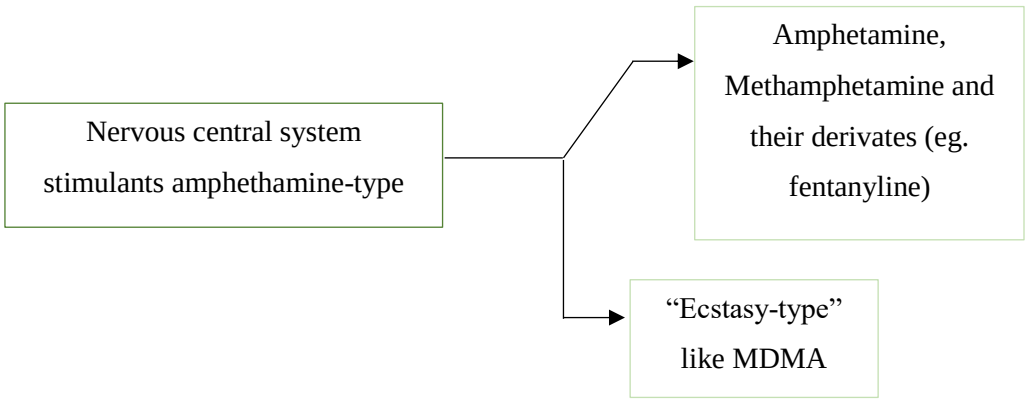

Figure 5: MDMA drug classification.

MA (methamphetamine) was first synthesized in Japan in 1893 and patented as MDMA by the german company Merck in 1914. During World War II the drug caught the eye of militarys who presumelly consumed it due to its strong awakness and increased vigillance effects.[22, 24, 25, 35]

Health professionals used to prescribe MDMA to pacients who suffer from ADHD disorder or as hunger supressant, being abondoned later as its toxic effects were proven. In fact, at comparable doses, MA has more powerful psychoactive results than amphetamine (commnly known as *speed*), which leads to its stronger power of dependence.[26, 36]

MDMA illegal prodution started in California, United States, throughout the 70´s, period in which was also used as treatment for cases of cocaine detoxification.[24] Many youngsters and hippies took the stimulant mostly in raves and night techno clubs, while the incidence rates of lesions related to its use was significantly rising.[22, 23] Ecstasy is another name that represents MDMA, but most of times is adulterated with other kind of xenobiotics, such as speed, ketamine and saliacylic acid, in order to increase dealers profit.[22, 23]

Regarding the psychoactive effects, MDMA has the power to increase the segregation of catecolamine-type neurotransmissors in synaptic gap: serotonin, and in lower rates, dopamine and noraepinephrine. Its strong activity relies also on its ability to inhibit the reuptake of these

substances by blending to the pre-synaptic neuron opioid receptors.[22, 24, 26] Thus, the prefrontal cortex and caudal nucleus in the brain, responsibles for emoticons and memory, are activated and modified.[24] This action leads to the short term outcomes: euphoria, hallucianations and increase of self-esteem, sexual desire, flow of words and sensory perception.[24-26, 36] Actually, this ilicit substance is known as "love drug" as it causes an extremelly urge to hug and feel someone´s touch.[22] Lack of hunger and need for sleep are also mentioned by users.[24] Related with its capability of mimic the sympathomimetic nervous system, other symptoms include vasoconstriction, tremors, tachycardia, mydriasis (dilated pupiles) and incresead body temperature.[22, 27] The fulminant hyperthermia is also associated with the scene where the drug is taken: places with high concentration of people on dance activities contribute to intensive sweating and water intake.[22] Since MDMA has an antidiuretic enhance (potentiates antidiuretic hormone secretion), kidney failure is likely to happen.[22] As so, some studies recommend to drink isotonic drinks instead of water under the drug stimulus in order to avoid hyponatraemia, a lack of balance in solut and minerals concentration in cells intersticial fluid (the cause seems to come from disturbs in sodim (Na^+) exchange).[1, 22]

The long term effects comprehend the development of tolerance and dependence, weight loss, depression, anxiety, hypertension, paranoia, mood swings, neurotoxicity and neurodegeneration.[24, 26, 36] MA use throughout pregnancy may cause a premature birth and hypothrophy, congenital abnormalities and delayed development of newborns´s brain and body structures.

The majority of the molecules taken are excreted by the liver, and lower percentage in urine, sweat, saliva and breast milk. Microssomatic enzymes and cytochrome P450 isoenzyme CYP2D6 produced in the liver are the main responsables for MDMA hydrolysis.[22] There are two cardinal inactive metabolites (nor-ephedrine and p-hydroxyl-nor-ephedrine) and one main active metabolite, amphetamine.[22, 24] As the product is metabolized and expelled, takes place a period of depletion, characterized by the reuptake of the mentioned monoamines in synaptic gap, as the homeostatic values of these are reestablished.[24] The administration of methamphetamine can be done by snorting (grinding the crystalline), smoking, inhaling and oral ingestion.[26] Moreover, injected methamphetamine has higher probability to induce lesions compared to smoked or inhaled.[36, 37]Vivek Shetty et al. concluded that "people who smoke or unhale MA have lower rates of dental disease than do those who inject MA".[36]

"Meth mouth" is an expression typically used in literature to describe some oral damages induced by use and abuse of methamphetamine type of drugs.[36, 38, 39] It includes a high incidence of rampant occlusal and interproximal caries, excessive tooth wear and grinding and jaw clenching that can go on hours after the end of mental stimulaton.[7, 22, 26] Plus, the toxic compounds contacting with oral mucosa also is a cause for cell injury, leading to tissue lesions and in worst cases, necrosis. It is proved that the duration of habit is the most influencer factor in post drug use manifestations.[24]

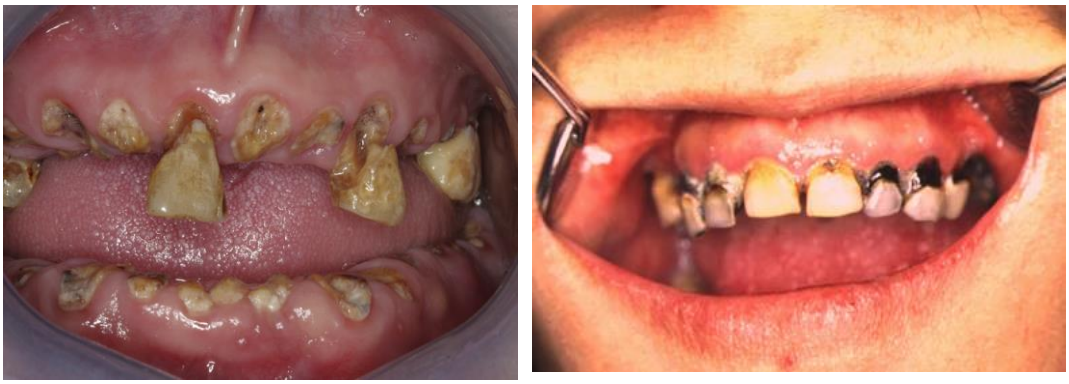

Figure 6: "Meth mouth"[1].Adapted from Colletti, G., et al., *Comprehensive surgical management of cocaine-induced midline destructive lesions.* J Oral Maxillofac Surg, 2014. **72**(7): p. 1395.e1-10 and De-Carolis, C., et al., *Methamphetamine abuse and "meth mouth" in Europe.* Med Oral Patol Oral Cir Bucal, 2015. **20**(2): p. e205-10 , respectively, without author authorization.

Salivary flow and saliva buffer capacity are also parameters assayed in regular methamphetamine users.[35] Authors showed that MA consumers have dry mouth (with cases of xerostomia reported, maybe due to the smitulation of inhibitory alfa-2 opioid receptors by MA) and decrease in saliva pH and quality, variables that play a key role in meth mouth development.[36] As the principal saliva functions are lost, teeth become much more vulnerable to be affected with caries and periodontal disease, ascribed to their fragile enamel structure and bacterial plaque and consequent tartarus accumulation in cervical teeth area.[35] Redfearn et al. refered individuals who report dry mouth during the use, which is capable of promoting tooth wear given the decrease in saliva buffer capacity and lubrification.[7]

Moreover, there´s a padron among junkies to prefer sweet foods, which creats a richer environment for acidiohilus bacterial growth, given the higher concentration of monosaccharides and ph decrease.[7] The acid drinks, like soda or beer, often chosen by users while on the drug are rich in

carbon, which is effervesvent and capable of dissolving enamel hydroxyapatite cristalline arrange.[7] The scenario gets worse due to the wrong eating patterns observed among the group.[26]

The “meth mouth” inducer agents are similar to the other drugs ones, but in MDMA the signs appear faster and are more severe. Tooth grinding, jaw clenching, TMJ pain and muscle trismus are the most frequently symptons described by users, comparing to other ilicit substances.[35] Some authors believe that reduction of saliva lubrification action and carbonated drinks consume have an influence in increasing tooth wear, as they cause an enamel surface energy rise.[7] The sympathomimetic action seems to have strong influence in stomatognathic system, stimulating facial muscles activity.[25] Curiously, Amrita Mukherjee et al. verified some taste modifications among methamphetamine users, depending on route of administration and frequency of consumption.[26]

Missing teeth index has also higher rates in methamphetamine consumers.[36, 38] The lower scores of oral hygiene verified are also caused by the wrong hygiene habits and fewer dentist appointments comparing to majority of population.[26]Plus, some authors also conclude that injected methamphetamine has more power to induce tooth loss comparing to smoked one.[26] Health professionals should pay attention to all symptoms and provide special care to this class of patients, as they often have economic difficulties.[25] Also to remind that most of them are probable to have brain damages and not be in their best mental state and order.

Heroin

Heroin or 3,6-diacetylmorphine is an opiace responsable for morbility and mortality high rates around the world since old times.[29, 31, 40] Most of the traffick originates from the Golden Triangle (Thailand, Myanmar and Lao People´s Democratic Republic) and it´s the drug with higher rates of addition treatment seek.[28]

Papaver Somniferum is the popular oppium poppy from where four types of benzylisoquinoline alkaloids are harvested: noscapine, morphine, codeine and papaverine. They all belong to a group of opiaces whose application goes back to medieval times given their analgesic properties (the very well known "milk of the poppy"). A milky fluid containing the opiaces flows from the green seed capsules cut and when dry the raw oppium is obtained. The percentage of each alkaloid depends on the region and plant growth conditions.[29]

Heroin is a semi-synthetic drud produced from morphine, capable of inducing a strong dependence, tolerance and withdrawal score effects. Its name was patented as cough supressant by Bayer pharmacolgical industries in 1898 and probably comes from the german word "heroisch", which means "extremely powerfull".[28, 29]

Diacetylmorphine molecule remains active for about 2 to 4 minutes and its metabolism occurs in the brain, liver and mostly in blood stream.[28, 29] The following figure pretends to simply this process understanding.

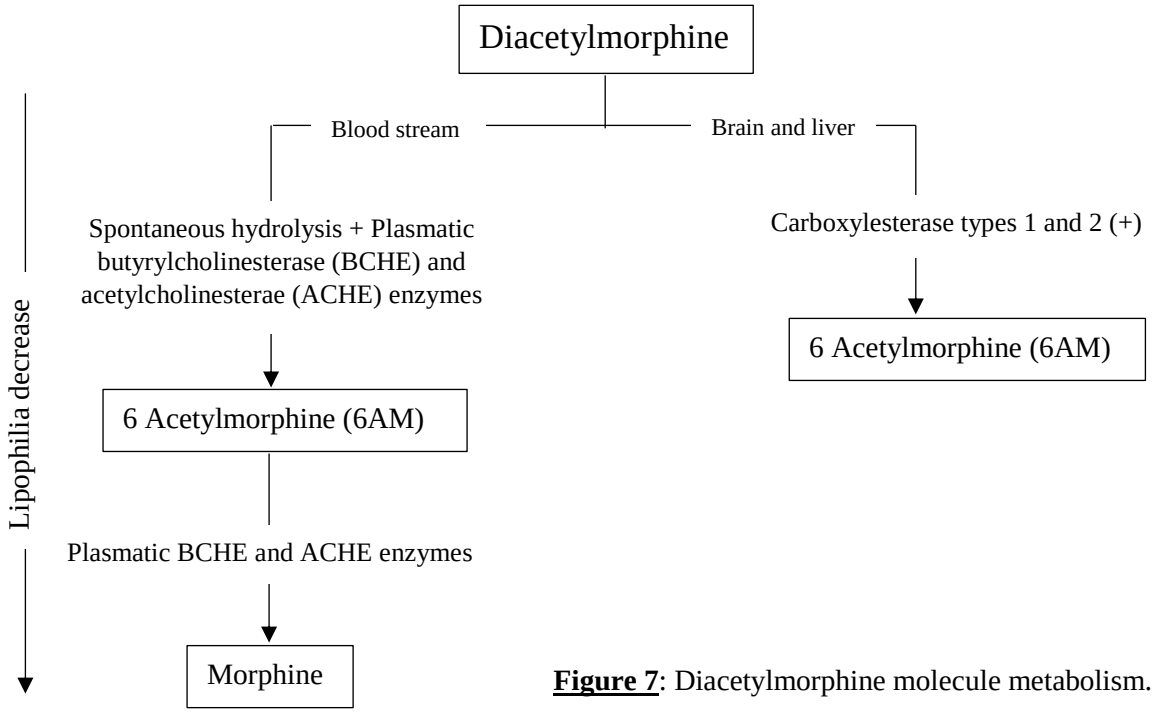

Figure 7: Diacetylmorphine molecule metabolism.

The spontaneous deacetylation occurs namely in the presence of ethanol, methanol and water.[29] Although present in both metabolic phases, BCHE enzyme has higher affinity to transform heroin in 6AM, while ACHE has stronger power to produce morphine from 6AM.[29] 6 acetylmorphine has a 30 minutes blood half-life, reason why is the biomarker most chosen by professionals. Thus the drug is often regarded as a "prodrug", acting more throughout its metabolites than itself.[28, 29]

Heroin out-turns are more powerfull than morphine ones. Diacetylmorphine has more facility to cross the hemoencephalic barrier due to the acetyl groups added, which are in charge of increasing molecule lipophilia and pharmacodynamics.[29]

There are three distinct types of heroin sold on the streets, all of them being in salt or base form.[28, 29] The next table pretends to aprise the preparation and administration methods.

White salt powder Pure heroin. Most synthesized in South East Asia. Water soluble.	Mainly intravenous (IV); Subcutaneous ("skin popping"); Snorting Not good for smoking as is decomposes when heaten up.
Brownish base powder Better stability with temperature rise and lower water solubility. Comes mostly from West Asia.	Smoke; Injection
Black tar Gummy or rock hard salt form substance original from South America (Mexico). It´s produced using the remaining heroin impurities underlying crude processing methods and cut substances, causes for its consistence and colour. Less expensive and more toxic type of diacetylmorphine.	Smoke; Injection

Table I: Heroin preparation and administration methods.

The injection of pure heroin can be done using a "cooker" (a spoon or bottle cup): users join water to the powder and the mixture is heaten up until dissolved. Sometimes addicted individuals pull blood into the hypodermic needle so that it can be mixed up with heroin, a process known as "booting". "Skin popping" is a kind of intradermal or subcutaneous injection not directly into the blood vassels. Usually this method is opted in case of accident, fewer vascular accesses or with the purpose to hide skin injection marks. Brownish powder smoking procedure is called "chasing the dragon": consumers keep a controlled flame underneath an aluminium or an other conductive material base, as the liquid prepared (powder + water) is kept moving. This way overheating and early drug transformation are impaired and the released smoke is inhaled using a straw. Injection administration is done creating a water soluble salt resultant from mixing something acid (such as citric or ascorbic acid, found respectively in lemons and vinegar) with the drug. The compound is heaten up and ready for injection.[28, 29]

The route of administration plays an important role in opioids transition. Usually individuals start with oral administration and move one to more effective methods, like snorting and intravenous injection, as the tolerance rises.[40] However, all of them are capable to damage individual cognitive properties.[41]

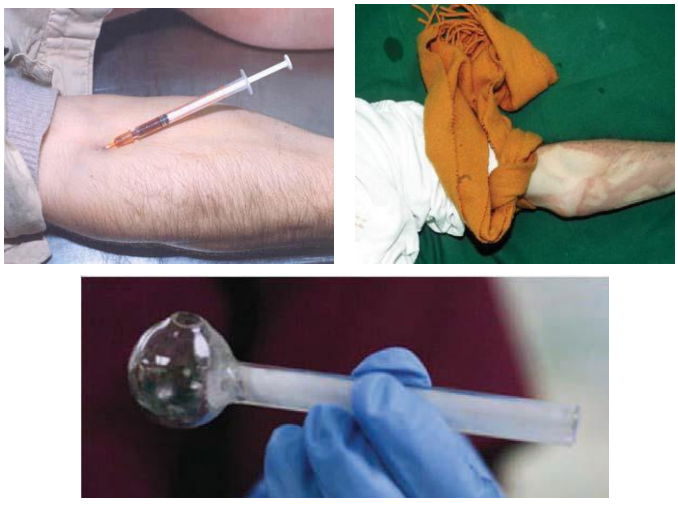

Figure 8: Needle injection, tourquinet and glass pipe. Adapted from Dinis-Oliveira, R.J., et al., *Clinical and forensic signs related to opioids abuse.* Curr Drug Abuse Rev, 2012. **5**(4): p. 273-90 and Dinis-Oliveira, R.J., et al., *Clinical and forensic signs related to cocaine abuse.* Curr Drug Abuse Rev, 2012. **5**(1): p. 64-83, respectively, without author authorization.

Skin and soft tissue lesions are the most common among injectable drug users who end up in hospital rooms.[3] Actually, heroin, morphine and codeine have the power to release histamine resulting in non immunologic cutaneous reactions, such as urticaria and erythroderma.[28] Abcesses are the most frequent type of damage reported. The main risk factors are "skin popping" as administration route, use of unsterilized needles and *speedball* consume (a mixture of cocaine and heroin).[3] Other dermatologic manifestations include track marks and hemorrhages with surrounding scaring of the skin (probably due to intima vein layer damage from needle insertion), "puffy-hand syndrome" (hand dorsum and fingers edema due to venous stasis or lymphatic drainage), fibromyosites (muscular fibrosis by conjugation of intramuscular injection and alcaline ph of the substance) and necrotizing fasciitis.[28, 42] Cases of dermatitis and anaphylactic reactions induced by heroin snorting are also usual.

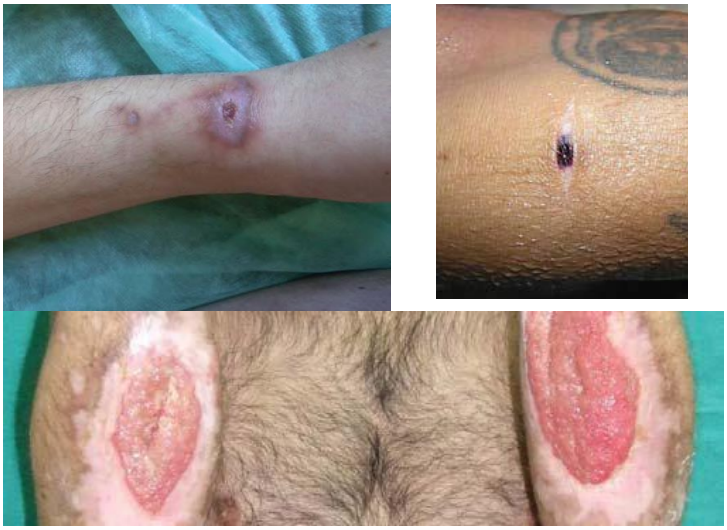

Figure 9: Tissue ulceration (adapted from Baranska-Rybak, W., et al., *Cutaneous manifestations of injectable drug use: hidden secrets.* Cutis, 2014. **93**(4): p. 185-7 and Dinis-Oliveira, R.J., et al., *Clinical and forensic signs related to opioids abuse.* Curr Drug Abuse Rev, 2012. **5**(4): p. 273-90 , without author authorization) and track injection marcks (adapted from Dinis-Oliveira, R.J., et al., *Clinical and forensic signs related to opioids abuse.* Curr Drug Abuse Rev, 2012. **5**(4): p. 273-90, without author authorization).

There´s not much information available in books and online databases concerning the oral effects of heroin abuse. Some authors describe dorsum tongue hyperpigmentation mostly in fungiform papillae, although not very common. Ricardo Jorge Dinis-Oliveira et al. mention the development of candidiasis among users of brownish heroin mixed with lemon juice.[28] Homologously to other drugs approached in the present review, heroin abusers have higher rates of caries, periodontal disease and tooth decay incidence. The bigger sugar intake results in oral ph decrease, while consumption of other xenobiotics contributs to lower salivary flow and xerostomia.[30] Both of

them provide the ideal environment for bacterial growth and occurence of carious processes, as saliva functions are lost and bacterial plaque is accumulated.[31] Despite that, majority of authors classify oral hygiene habits and behaviour as the main factors to lower oral health status.[30] Effectively, the conjugation between the drug toxic effects in oral mucosa and oral hygine habits has more power to induce cell injury than the substance action itself.[30] Persistent irregular eating patterns and few dentist appointments also stand among the causes of lower oral hygiene scores observed. Rokas Aukstakalnis et al. relate the decrease in immune system response and the rise of periodontitis and other opportunistic infections like candidiasis.[9] Hajar Shekarchizadeh et al. concludes that heroin consume is a great risk factor for oral diseases, specially in less educated and crystalline heroin addicted individuals.[30]

Cocaine

Cocaine or benzoylmethylecgonine is an opioid found in the leafs of *Erythroxylon coca*.[15] Actually, this specie produces fourteen types of alkaloids for its own protection against insects and predators and can be found in South America, in Andes region.[11, 17] The leafs are harvested and macerated with organic solvents, such as kerosene, generating cocaine paste (40 to 80% pure), which after reaction with hydrochloric acid transforms into cocaine hydrochloride. Powder cocaine is obtained after the solvent evaporation.[14, 16]

Nieman introduced cocaine in medicine and odontology as a local ester-type anesthesic agent, being able to reversibly stop the nervous conduction in the area in touch.[16] It is a bicyclic molecule composed by benzoic acid and methylecognine.[17] Its metabolism takes place mostly in the blood stream by cholinesterase-type enzymes and it´s represented in the following scheme.[11, 16, 17]

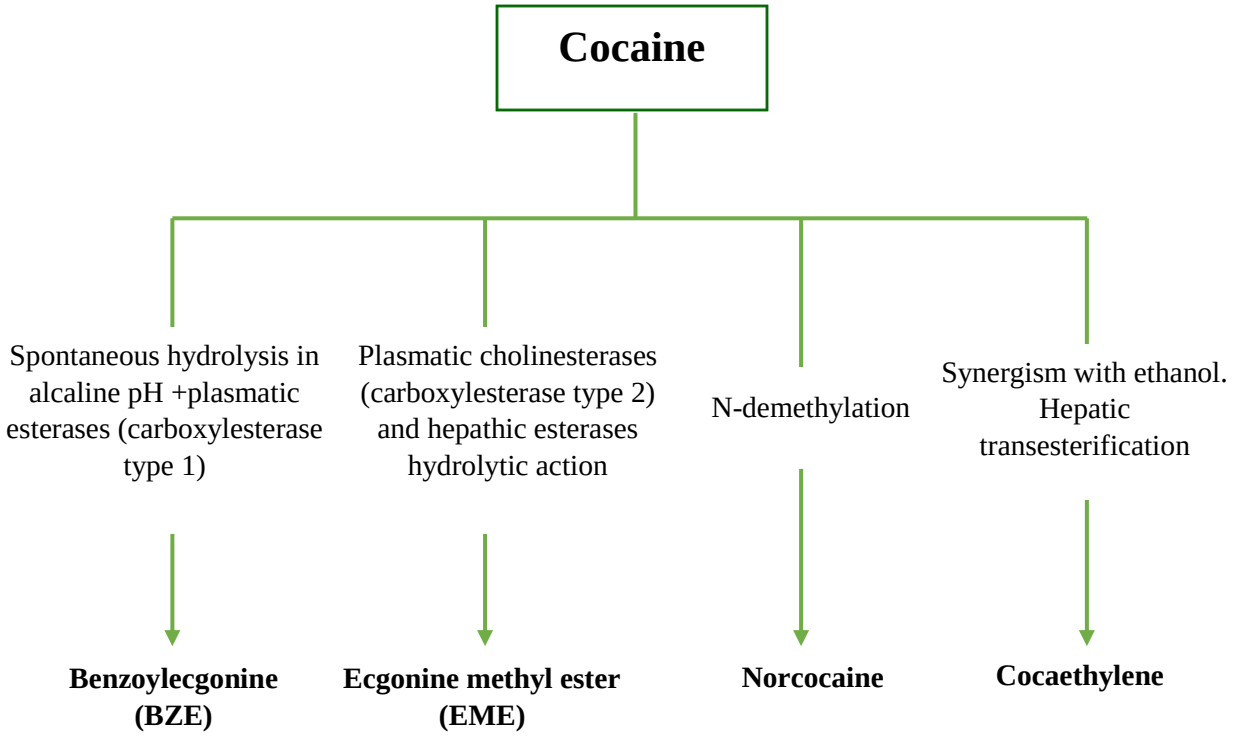

Figure 10: Benzoylmethylecgonine molecule metabolism.

Reaction between benzoylecgnonine (BZE) and ecgonine methyl ester (EME) originates ecgnonine. These are inative matabolites and can not act in central nervous system (CNS). Cocaethylene is the most toxic product, being synthesized when cocaine reacts with alcohol instead of water. In other hand, norcocaine is an active metabolite so that is able to exerce its function in CNS.[11]

Cocaine simulates sympathomimetic action of catecolamine neurotransmissors, like epinephrine, noradrenaline, dopamin and serotonin. As such, it´s capable of inducing vasoconstriction.[15] Furthermore, it blocks the reuptake of these molecules in the synaptic gap, causing a permanent stimulation and depolarization of the post-synaptic neuron. The consequent incentive given to the rostro-caudal brain structure allows the user to feel euphoria, well being sensation, psycho hyperactivity and abcense of tiredness.[16]

As a vasoconstrictor agent, cocaine has the ability of reducing the amount of heat liberated from the body. Plus, since its use is related to dance activities and places with high concentration of people there are some cases reporting hyperthermia.[11, 15, 16]

Cocaine can be prepared and administered in distinct ways and means as enlightened in the following table.[10, 15, 17, 18]

Powder cocaine Water soluble	Oral, sublingual, nasal, intravenous (IV), intramuscular (IM), subcutaneous, intravaginal; topic application in gums
Crack Not water soluble Cocaine hydrochloride is prepared in an alcaline solution (ex. sodium bicarbonate), under controlled temperature (around 90 to 97ºC). Crack is obtained after solute precipitation, whose fusion point is lower than powder cocaine.	Smoked with pipes (ex. glass pipes); Nasal and IV
Free base cocaine	Smoked like crack

Same chemical composition as crack. Distinct physical appearence and preparation mode. Crack deprotonation. Powder cocaine prepared in ammonia or sodium bicarbonate solution, occuring the non soluble agents precipitation and evaporation of solvent. Diethyl ether is used to separate the pure form of the drug from the cut substances. Rarely used (diethyl ether waste burns from ignition).	
***Erythroxylon coca* leafs**	Smoked (wrapped in cigarettes); Chewed, using lime ou ash (induces the release of cocaine to the saliva) Drank (infusion)
Cocaine paste	Smoked

Table II: Cocaine preparation and administration methods.

Not many articles are available concerning the histological damaged caused by the contact between cocaine and oral mucosa. However, some authors dedicated to study nuclear changes in cells exfoliated from there using *micronuclei* test as main biomarker.[18, 19, 43] Micronuclei (fig.7) appearence seems to indicate DNA breaks due to disturbs in mitotic spindle occured in methaphase when exposed to toxic agents. All conclusions appoint to a decrease in nuclear and cythoplasmatic area ratio and an increase in micronuclei incidence in these cells.[10, 19] Webber et al. talked about a possible association between the occurance of micronuclei and tumor cell proliferation and concludes that the clastogenic effetc has higher rates in the tongue and mouth floor. [43]

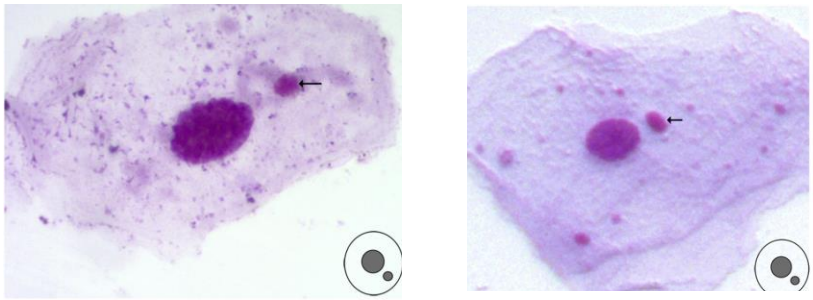

Figure 11: *Micronuclei* in cells exfolliated from oral mucosa. Adapted from Antoniazzi, R.P., et al., *Impact of crack cocaine use on the occurrence of oral lesions and micronuclei.* Int J Oral Maxillofac Surg, 2018. **47**(7): p. 888-895, without author authorization.

As so, cocaine abuse is responsable for ulceration and fistula development in oral mucosa.[10] Cocaine induced midline destructive lesion (CIMDL) is one of the most documented manifestation as result of snorting powder and crack cocaine.[39] In these cases, an oro-sinusal comunication in hard palate is observed around ulcerated tissue.[21] Plus, the vasoconstriction and toxic effects of the drug when in contact with nasal mucosa causes ischemia, hypoxia and consequent tissue necrosis, as verified in figure 8.[44-47] A collapse of the nose structure is notable.[45] The diagnosis should be done concerning the anamnesis, clinical exams, and confirmed by interpretation of hard palate and nose X ray.[15] An individualized removable prothesis can be precribed as palliative treatment. These allow the pacient to eat and breath without blending gastrointestinal and pulmonary systems.[46] It is very important to mention that any kind of treatment plan is condemned to failure if the user continues to consume the substance and not lines up with the health profissional indications.[46-48]

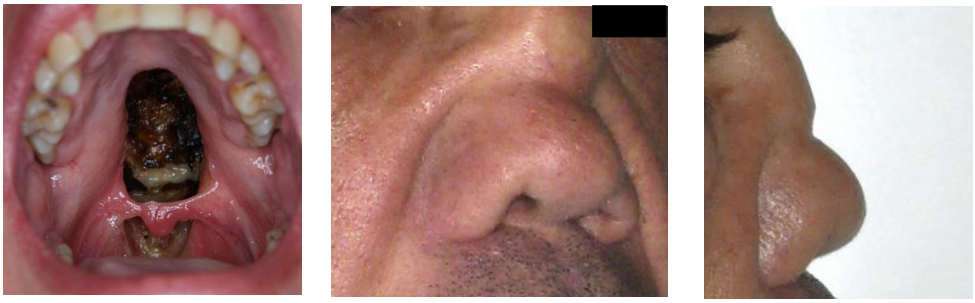

Figure 12: (1) CIMDL; (2;3) Loss of nasal structure induced by cocaine snorting. (1) adapted from Silvestre, F.J., et al., *Hard palate perforation in cocaine abusers: a systematic review.* Clin Oral Investig, 2010. **14**(6): p. 621-8, (2;3) adapted from Colletti, G., et al., *Comprehensive surgical management of cocaine-induced midline destructive lesions.* J Oral Maxillofac Surg, 2014. **72**(7): p. 1395.e1-10, both without author autorization.

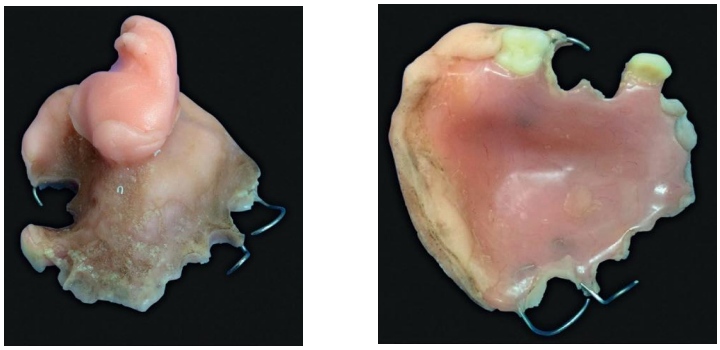

Figure 13: Exemple of removible prothesis specially made for palate perfomation in cocaine users by inhalation. Adapted from Blanco, G.F., et al., *Case for diagnosis. Palate perforation due to cocaine use.* An Bras Dermatol, 2017. **92**(6): p. 877-878, without author authorization.

Some studies assayed the salivary flow in cocaine users.[10, 49] All of them verified a decrese in saliva production comparing to non-users, with some cases of xerostomia reported. As known, saliva has an important role regarding its power of tooth enamel lubrification and softness of its surface, phosphate and calcium ions exhange in oral environment, among others. Therefore, in these conditions the tooth gets much more vulnerable to be infected with carious processes and resultant periodontal disease, which corroborates the conclusions found by the authors.[10, 43] Interesting to notice that Casarin et al. remarked a higher occurence of periodontitis in cocaine abusers, but with non-bacterial etiology.[50] The cause of lower oral health status noticed in users is multifactorial. Hygiene habits, type of diet and eating patterns, as well as visits to the dentists are parameters also evalluated.[10] Commonly drug users have preference for sweet foods and don´t go to the dentist very often, which also contributes to the higher rates of tooth and oral mucosa lesions.[14, 17, 19, 51]

Other body manifestations include smooth muscle rhabdomyolysis, spontaneous abortion and cocain induced necrosis and gangrene of extremities, among others.[15, 16, 51]

All health professionals should pay attention to these symptons and recognize patient abusive alcohol intake so that preventive measures can be put into practice.

Discussions and conclusions

Dentists, forensic toxicologists and health professionals overall have a special duty regarding drug abuse scene. The oral and body manifestations approached above are not pathogomonic signs for drug misuse. As so, symptoms observed among users must be studied and diagnosed taking into account anamnesis, extra and intra oral exams, histopathological samples and x-ray images.[15] Forensic toxicology area is fundamental to understand and identify possible exposure to xenobiotics, while *post-mortem* studies provide valuable information about substances that might be related to intoxication or crime scenes. Fathal overdose investigation, for exemple, is developed with three main stages: data and sample collection, toxicologic analysis and results interpretation[11]. Crime scene data collection is very important to clarify and even solve a juridical case, as most times non biological evidence is present. It includes objects for drug administration, such as glass pipes and needles, as weel as lemons or tourniquets used to increase venous accessibility.[28]

Many grug users who visit dentist office are concerned about their aesthetic appearance. Health professionals and namely dentists, who play an essential role in this scope, should use this as a motivating factor to abandon substances dependence.[36] These experts are trained to identify, observe and interpretate some of drug induced manifestations, having the responsability to report any changes that might seem caused by ilicit substances intake. They must be aware of mood changes, depressive mental states and violent reactions, which can also indicate drug consume. It is also required from them to pay attention to prescribed medication, as it may interact with drug molecules pharmacokinetics.

All patients demonstrating drug addition problems should be effectively accompained and, if needed, forwarded to rehabilitation centres where victims are targeted with contingy treatment, medication management and verification of drug use abandonment, always underlying current ethical rules. As so, is fundamental that professionals provide additional care and advice regarding oral hygiene, since it reflects itself in body homeostasis.[52] Health promotion can be done by campaigns or maybe school visits, and treatment centres should dispense oral status evaluation for patients.[30, 52] Methadone treatment is the most available one for heroin abusers, but its efficacy has been concerned since not all of it is sugar free and given its acidic ph (4,5 – 5,5). Some authors clarify and demonstrate HAT – assisted heroin treatment – as better method for heroin addicted individuals.[53, 54] Developed in Switzerland, is recently documented in literature and defends the medical prescription and intake of diacetylmorphine under the supervision of nurses. HAT was

proven to be more effective in reducing drug use among “ex-consumers” who already had been in oral methadone treatment. Authors remind that HAT should be an endless service in order to avoid patients breakdown and return to drug use.[53]

There are cases reported concerning children death after contact and accidental drug administration as they are left with no parents supervision reaching the toxic product.[55] Plus, drug users sons have higher probability to develop drug depende as they imitate and learn everything from their father and supposedly reliable figures.

It is very important to reach and understand what leads the patient to consume ilicit substances and work alongside him in order to combact ilicit substance high dependence.

To conclude, should be mentioned the need for more studies, literature reviews and clinical trials concerning forensic toxicology scope and namely the oral health status underlying drug use, so that preventive measures can be put into order to help those in need finding their own equilibrium.

List of abbreviations

ADH1B: Alcohol dehydrogenase cytosolic hepatic enzyme

MEOS: Ethanol oxidation by microssomal system in liver smooth endoplasmatic reticulum

ALDH2: Aldehyde dehydrogenase mitocondrial hepatic enzyme

PG2; PGF2; 6-keto-PGF1: different types of prostaglandins

MDMA: 3,4- methylenedioxymethamphetamine

MA: Methamphetamine

ADHD: Attention deficit hyperactivity disorder

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PARECER

Informo que o Trabalho de Monografia desenvolvido pela Estudante Ana Manuela Loureiro Verdura, com o título: *Oral manifestations of drug abuse: a forensic perspective*, está de acordo com as regras estipuladas na FMDUP, foi por mim conferido e encontra-se em condições de ser apresentado em provas públicas.

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Declaro que o presente trabalho, no âmbito da Monografia de Investigação/Relatório de Atividade Clínica, integrado no MIMD, da FMDUP, é da minha autoria e todas as fontes foram devidamente referenciadas.

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Ana Pamula L Verdura

(A investigadora)