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Toxicological effects of ecstasy: a review

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Abstract: Although ecstasy is wrongly classified as harmless, it can cause toxicity to the cardiovascular, hepatic, immune and nervous systems, and can even lead to death. Soon this review article seeks to identify and report the toxic effects of MDMA on the body, through studies published in the literature. Through PubMed and Scielo database articles, theses, monographs, book chapters referring to history, epidemiology, pharmacokinetics, pharmacodynamics and its main toxic events. Since, these need to be better elucidated, for the understanding of the damages caused by the substance. However, the data collected in this work point to the need to develop measures to combat consumption and the belief of its "innocuity".

Keywords: Abuse Drugs, Ecstasy, MDMA, Toxicology

I. INTRODUCTION

The discovery of ecstasy was made by the chemist Anton Köllisch, being synthesized in 1912 and its patent registered in 1914 by Merck's laboratory as an appetite suppressant, which was never commercialized due to its side effects. Soon after, in the mid 70's the drug started to be used for therapeutic purposes and quickly banned, due to its potential for abuse and illegality. In the 1980's, it was classified as an abusive drug for acting on the Central Nervous System (CNS) causing hallucinations and alterations in the autonomic nervous system, mood, sleep, appetite, thermoregulation [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. Currently, this psychoactive is illegally marketed in the form of pills, with concentrations ranging from 50 to 300mg, having a variety of colors, sizes and logos. In its composition there is the addition of several substances with the objective of mimicking its stimulating effects and cheapening the drug [3, 5, 8, 13].

Ecstasy is a sympathomimetic compound with indirect action, and because its structures are similar to endogenous catecholamines they act as synaptic and hallucinogenic stimulants. Thus, its actions result in increased release of neurotransmitters such as serotonin, dopamine and noradrenalin in synaptic clefts, and also as an inhibitor of monoamines oxidases [2, 3, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. The drug rapidly crosses the blood-brain barrier (BBB), causing the release and inhibition of serotonin, which are responsible for the psychomimetic effects. In addition, it produces effects on the dopaminergic system such as increased blood pressure, increased frequency and cardiac output, mydriasis, tremors and bronchodilation [3, 9, 15, 18, 20].

Ecstasy has a moderate potential to cause dependency and addiction [1, 11, 16]. However, depending on its dose, frequency of use, its purity, its association with other substances, physical and mental condition of the user, it can cause an increase in its degree of toxicity leading to irreversible changes in the liver, immune, nervous and cardiovascular systems [5, 6, 7, 10].

II. METHODS

This work is a bibliographic review, whose data were obtained through scientific articles, book chapters, monographs, dissertations, theses and epidemiological data. From which information on the pharmacokinetic and pharmacodynamic properties of ecstasy, complications due to the abusive use of this psychoactive, whether of order, neurological, hepatological, cardiovascular and immunological, were extracted. In addition, were included studies that presented the acute and chronic effects of the abusive use of this psychotropic with other drugs in order to justify the risks of its exacerbated ingestion.

The databases consulted were the Scientific Electronic Library Online (SciELO), US National Library of Medicine National Institutes of Health (PubMed), and academic Google search tools in Portuguese and English, with no limit being established on the year of publication.

Papers published in Portuguese and English were included, from which the titles and the abstract were observed, in order to evaluate if they had the necessary information for the construction of this article. As

exclusion criteria, all papers that did not contemplate the previous specifications and studies whose access to the full text was not possible were removed, in addition to texts that addressed the use of the drug for religious purposes. At the end, the texts selected and used for the construction of this article were 32 in total.

III. RESULTS AND DISCUSSION

3.1 History

MDMA (3,4-methylenedioximethamphetamine) also known as ecstasy or Molly, is a psychoactive that shares stimulant and hallucinogenic properties due to its similarity to endogenous catecholamines and the presence of methylenedioxy bonds in Rα and RN positions, similar to mescaline hallucinogen, in addition to groups -O-CH2-O- in R3 and R4 positions of its benzene ring [7, 8, 12, 16, 17]. Such properties make him a powerful agonist of the CNS. The chemist Anton Köllisch made its discovery in 1912 in Merck's laboratory in Germany and in 1914, it was patented as an appetite suppressant, however its marketing was not successful due to its side effects [1, 4, 5, 6, 7, 8, 10, 11, 12, 21].

In the mid 70's ecstasy had its therapy redirected thanks to its ability to induce feelings of confidence, empathy and introspection, but was quickly banned due to its adverse effects and potential for abuse [8, 10, 12, 15, 21]. In 1985, due to its media visibility, the consumption of ecstasy became very popular in the United States, where the first evidence of its abusive and neurotoxic potential emerged, making it illegal in the country. However, this was not enough to reduce its consumption, on the contrary, researches show that its search has increased and may be related to the ease in obtaining and consumption [1, 6, 8, 12, 14, 22].

3.2 Epidemiological

In 2013 studies, they estimated that 17 million people used ecstasy at least once in their lives, especially individuals aged 18-25 [17]. According to Word Drug of 2019[23], it is estimated that about 8.4 and 40 million people between the ages of 15 and 64 consumed ecstasy in 2016. The prevalence of ecstasy in continents such as Oceania, North America and Europe was higher. In Brazil, it is reported that the average consumption of this substance is between 0.2%, which corresponds to about 500,000 users. The consumption of ecstasy varies from 8th grade students to adults [17]. Guerreiro, et al. (2011) [4] reported that annual consumption in 2007 among young Americans from 8th to 12th grades varied between 1.5% and 4.5%. According to Xavier, et al. (2008) [12]about 6% of English students and of these, 13% university students, have already consumed MDMA in their lives.

According to the National Survey on Drug Use by the Brazilian Population, organized by Fiocruz, 0.7% of Brazilians reported the use of ecstasy at least once in their lives and 0.2% reported the use in the last 12 months, the majority being male [24]. Among users, there is a predominance of consumption among young university students totaling 7.5% and the evidence states that this number tends to grow each year due to the ease of substance by this audience [5, 6, 25].

According to the studies found, the use pattern of this substance is prevalent in high income young people, residents of urban centers, with good school education and/or practicing labor activities, who attend nightclubs and raves on weekends [4, 6, 7, 8, 11, 12, 14, 26]. The justification found for its popularity is due to the fact that it elicits effects of euphoria, well-being, agitation, disinhibition, sociability, empathy, excitement, besides being classified as a "safe drug with low toxicity and dependence" [6, 7 , 9, 10, 11, 12, 16, 18, 21, 27].

The consumption pattern of users is characterized by compulsive administrations of several pills at once or over long periods [7, 10]. It is often co-used with other drugs such as: alcohol, marijuana, opiates, cocaine, LSD, heroin, caffeine (energetic) and other stimulants, hallucinogens and depressants which contribute to the increase of their toxic effects [1, 2, 5, 7, 8, 10, 11, 13, 28, 29, 30].

It is usually consumed orally, although it can be used nasal, sublingual, anal, intravenous and subcutaneous in concentrations of 50 to 300 mg. As previously mentioned, it is marketed mainly in the form of pills with a variety of colors, sizes and logos, but also found in the form of capsule, tablets, powder, tablets and liquid [1, 3, 4, 5, 6, 7, 8, 11, 14, 16, 18]. In its composition there is the addition of several substances such as ketamine, benzylpiperazine, ephedrine, cocaine, diazepam, caffeine, dextromethorphan, ketamine, atropine, amphetamine, methamphetamine paracetamol, 3,4-methylenedioxyethylamphetamine (MDEA), 3,4-methylenedioxyamphetamine (MDA), par-methoxyamphetamine, and 4-bromo-2,5-dimethoxyphenethylamine in order to increase and/or mimic its stimulant effects and cheapen the drug [3, 4, 5, 6, 8, 9, 11, 12, 13].

3.3 Pharmacokinetics

The use of ecstasy is done primarily orally, producing its psychostimulant effects 20 to 60 minutes after its absorption, the peak plasma concentration can vary from 75 minutes to 2 hours after being ingested, remaining for a long period in the body, about 40 hours until it is completely eliminated [4, 5, 6, 7, 11, 12, 17, 22].

MDMA does not have a linear pharmacokinetics, since the amount of drug ingested is not directly proportional to the plasma levels found, and the second dose ingested may show plasma levels higher than expected [10, 11, 12, 15].

MDMA distribution is wide, easily crossing biological membranes and the blood-brain barrier. Its hepatic metabolization is performed by cytochrome P450, namely the isoforms CYP2B6, CYP2D6, CYP1A2 AND CYP3A4. A small percentage of MDMA is transformed into MDA, its active substance. For this, it goes through the process of N-desmetilization, whose reaction is performed mainly by CYP2D6 and, minority, by CYP1A2 and CYP2B6. The MDA and the rest of the MDMA are submitted to the process of O-desmetilization forming the 3,4-methylenedihydroxyamphetamine (HHA) and 3,4-dihydroxyamphetamine (HHMA), which will subsequently undergo the process of o-methylation by catechol-O-methyltransferase (COMT), forming the metabolites 4-hydroxy-3-methoxyamphetamine (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA). Approximately 65% of ecstasy is eliminated in urine without being metabolized, metabolites are also excreted by the renal pathway linked to glycuronic acid or sulfate [3, 4, 6, 10, 11, 12, 14, 25].

3.4 Pharmacodynamics

MDMA behaves as an indirect monoamine agonist in the CNS, by promoting the release and inhibition of noradrenaline (NA), adrenaline, dopamine (AD) and, mainly, serotonin (5-HT) which is related to the main clinical manifestations in the body [2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 18, 19, 20, 21, 25], and possibly associated with the induction of acetylcholine (ACh) release in several neuronal regions [4].

The increase in concentrations of neurotransmitters in cytoplasm are caused by several mechanisms that result in their stimulant and hallucinogenic effects. One of them is given by the deregulation of vesicular storage through the action of MDMA [6, 11, 15]. Furthermore, ecstasy acts by blocking serotonergic carriers (SERT) preventing 5-HT from returning to the interior of the presynaptic neuron resulting in increased release in the nerve terminals and the adrenal spinal cord. Ecstasy also increases the levels of extracellular monoamines through inhibition of monoamine oxidases (MAO) enzymes responsible for the enzymatic degradation of 5-HT and catecholamines [6, 8, 11, 12, 13, 15, 28].

There is a direct interaction between the serotonergic and dopaminergic systems, in which the stimulation of 5-HT receptors in gabaergic neurons leads to increased AD synthesis, mainly in striated regions and hippocampus [4, 7, 12, 15]. Ecstasy also promotes the increase in blood levels various hormones such as cortisol, dehydroepiandrosterone, antidiuretic (ADH) and adrenocorticotropic hormone (ACTH), prolactin [2, 7, 8, 12, 14, 25].

3.5 Toxicology

Ecstasy is considered harmless to most of its users because it has a moderate potential to cause dependency and addiction. However, there are several reports in the literature about adverse reactions and deaths associated with MDMA consumption [1, 6, 7, 11, 16, 17, 18, 20].According to systematic studies by Figurasin and Maguire (2019)[17], the mortality rate of ecstasy is 0 to 2% in admissions. Since this drug is manufactured illegally, there is no pharmaceutical control, so there is uncertainty about its composition, concentration, its degree of purity, that is, it is not known what the user is ingesting, and this ends up increasing its toxic potential. Moreover, most users make the association with other substances such as alcohol, opiates, cocaine, cannabis, heroin, among others, which may result in increased cumulative effects of the drug [1, 7, 8, 11, 12].

Experimental studies in several species, by different routes of administration, have observed that the lethal dose of ecstasy is variable [15, 19].An example of this is a case report of an individual who consumed 1 tablet of MDMA and died, and another who ingested 42 tablets and showed no symptoms. This fact denotes that toxicity is related to frequency of use, individual vulnerability and external environmental conditions [1, 7]. It is observed in the literature that the two most frequently reported causes of death are hyperthermia and hyponatremia and, although it is a severe picture of toxicity, deaths related to MDMA toxicity are considered rare.

It is noted that the toxicity of ecstasy is a result of high extracellular concentrations of the neurotransmitters NA, DA and 5-HT. With this, its use can trigger several pathological disorders classified as acute (in the first 24 hours), subacute (1 month of ingestion) and chronic (after several months), among which we can mention: hyperthermia, rhabdomyolysis, severe hyponatremia, disseminated intravascular coagulation, hepatotoxicity, nephrotoxicity, neurotoxicity and cardiovascular complications such as hypertension, tachycardia and cardiac arrhythmias [4, 10, 11, 12, 14, 20, 22, 25]. Some of the most significant toxic effects are reported in the following topics.

3.5.1 Effects on the Hepatic System

The hepatotoxicity of the drug is also reported in the literature when used chronically, as it also occurs in the cardiovascular system. In view of the possible complications caused in the gastrointestinal tract, studies

indicate that hepatotoxicity may be variable, from a mild alteration to fulminant liver failure, requiring transplantation [1, 22]. Generally, patients who have had contact with MDMA are icteric and weight impaired [3, 4, 6, 12, 17].In addition to the complications mentioned above, drug use can lead to the development of hepatic fibrosis in young people [7].

3.5.2 Effects on the Cardiovascular System

The effects on this system are characterized by the fact that the drug has a sympatomimetic action and this action associated with overdosage, can lead to a serious toxicity that manifests as cardiovascular, neurological, hepatic and electrolytic disorders. Such cardiovascular disorders include a significant increase in both heart rate and blood pressure, with cases of life-threatening cardiac arrhythmias, acute myocardial infarction, aortic dissection and intracranial hemorrhages being reported [6, 7, 8, 9, 11, 14, 17, 18, 21].

It should be noted that individuals who have any deviation from normality, such as cardiomyopathies, coronary disease and functional arrhythmias, are represented as a group at higher risk for the cardiotoxic effects caused by drug use [7, 8, 9, 12, 22]. Based on the reports of Voizeux, et al. (2019)[30], a 22 year old male patient with historical consumption of illicit substances (cannabis, cocaine and MDMA) was rescued presenting symptoms of hyperthermia, bilateral midriasis, general contracture and severe arrhythmia, indicating cardiac arrest caused by serotoninergic syndrome caused by abusive intake of MDMA. During hospitalization the patient presented besides the symptoms mentioned above, ventricular tachycardia and multiple organ failure. It is known that 5-HT is a neurotransmitter that acts in the regulation of emotions, muscle tone, temperature, heart rate and pain. The hyperactivation of central and peripheral serotonin receptors causes the appearance of signs and symptoms of this syndrome that can be fatal in the life of the patient [7, 8, 12, 20]. The cardiac intoxication by ecstasy, in its turn, occurs due to increased noradrenaline levels in the blood, resulting in the clinical picture of the patient in question.

According to Bastos (2011)[2], data collected at SACIT-Analysis of the Toxicological Information Center of Santa Catarina from January 2006 to July 2011, MDMA causes intraneural depletion of 5-HT leading to a serotonergic syndrome with the following manifestations: agitation (44%), psychomotor, tachycardia (39%), midriasis (21%) and hypertension (17%). It was also observed that 81% of the registered cases did not have the need of hospitalization, however considering the most serious, most of them were admitted to the Intensive Care Unit (ICU), where the patients needed to be submitted to orotracheal intubation and mechanical ventilation.

3.5.3 Effects on the Renal System

There are several reports in the literature about cases of kidney damage caused by the use of MDMA, but it is not yet clear about the mechanisms involved in this process. As for kidney damage secondary to ecstasy consumption, include acute or chronic renal failure, necrotizing renal vasculitis and acute injury of proximal tubules [6, 7, 8, 9, 12, 14, 22]. In addition, there is a case report about a possible direct toxic action of MDMA and its metabolites, which would have caused acute interstitial nephritis [7, 12, 15]. In general, amphetamines may induce nephrotoxicity manifesting as myoglobinuria, renal vascular necrosis, acute tubular necrosis, acute interstitial nephritis and acute or chronic renal failure, but this evidence is still implicit. Amphetamines and/or their metabolites are attributed to toxicity, rhabdomyolysis, renal vasoconstriction with renal ischemia and hypoxia, direct toxic effect or hyperthermia [12, 14]. Almeida and Silva (2000)[1] reported a case of urinary retention after ingestion of a large amount of MDMA (15 tablets in 36 hours), probably due to the agonistic alpha-adrenergic action of MDMA.

3.5.4 Effects on the Immune System

Several studies indicate that the drug can cause immunosuppression in its users both directly and indirectly by interfering with the immune system cells themselves, and through changes modulated by the central nervous system. Furthermore, the authors also state the importance of the immune system being a highly regulated organ system that presents a variability of potential targets for these modulations. It is known that there is significant presence of 5-HT receptors in the cells of the immune system, developing functions in the induction and production of immune response. Therefore, the mechanism of immunosuppression is directly linked to the interaction of ecstasy with serotonin transport, making the individual more susceptible to infections, allergic processes and autoimmune processes [10, 21].

According to Connor (2004)[21], through in vivo studies in animals and humans the administration of MDMA has harmful effects on both innate and adaptive immunity. Through the suppression in the synthesis of cytokines and antibodies, and in the increase of the production of Natural Killer cells and interleucine. However, more research is needed in order to obtain more information about these reports in order to actually prove such action [1, 7, 10]. Furthermore, as previously mentioned, MDMA is attributed to increased levels of hormones such as ACTH and cortisol, the latter having immunosuppressive properties and effects on other systems, including

the central nervous system [12].

Cortisol is the hormone responsible for body homeostasis, and in high concentrations can trigger several harmful effects to the body mainly on the immune system. Since it is related to the modulation of inflammatory responses, thus, in excess it can inhibit pro-inflammatory mediators among them the leucotrienes, thromboxanes and prostaglandins. They also cause lymphocytopenia, leaving the body more vulnerable to infections [31].

3.5.2 Effects on the Central Nervous System

Much is discussed about the neurotoxic potential of MDMA and some research suggests significant changes in different regions of the brain either in the cortex, thalamus or striated revealing its ability to cause neuronal degeneration through cell death by neuronal apoptosis [8, 14]. In neuroimaging studies with laboratory animals and in humans they identified that the administration of ecstasy seems to damage the structural and functional integrity of the 5-HT system [19]. Even immunocytochemical findings in rodents and primates recorded degeneration in neuronal terminals [4, 6, 7, 8, 12, 14, 15, 17, 18]. Other studies have reported a decrease in SERT - in 11 out of 14 brain regions - and changes in recipient density, which could result in ischemic lesions [8, 14, 19, 29]. Because of neurotoxicity, there is an increase in the activation of 5-HT2a receptors, causing intracellular oxidative stress, which will consequently cause neuronal death mediated by the enzyme caspase. This fact could explain the persistence of symptoms and cognitive changes, even after the suspension of drug use [4].

Kish (2002) [32]reported the case of a 26-year-old male patient, with moderate use of MDMA for 9 years, the presence of severe serotonergic depletions and their metabolites in his brain . However, although these studies consistently reveal that the use of MDMA can induce neuronal toxicity, they are definitely not conclusive as to the factor of influence, persistence, and mechanisms of these changes, which require more specific studies. On the other hand, Pimentel (2014)[8] and Carvalho (2004)[15]demonstrated that the toxicity capacity of ecstasy is directly related to hepatic metabolism, besides factors such as: route of administration, age, sex, species and dose ingested by occasion [3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 17, 21].

In summary, the main manifestations that can have relation to the damages in serotonergic neurotransmission are: short term memory deficit, mainly visual and verbal, cognitive difficulty, anxiety, depression, bruxism, psychosis and fatal effects such as subarachnoid and intracranial hemorrhage, thrombosis, stroke [3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 17, 21].

IV. CONCLUSION

Despite being a drug considered low toxicity by users, the abusive use of MDMA can trigger significant toxic effects, which can even be fatal, which opposes the concept of being a "harmless drug". It is worth noting that purity, dose, and co-administration with other drugs make their consumption more dangerous and increase the risk of mortality. It is also important to highlight the need for more studies on the harmful effects of the drug, as well as the dissemination of information on such negative effects and socio-educational campaigns to combat the use of ecstasy.

Abbreviations

CNS: Central Nervous System; BBB: Blood-Brain Barrier; MDMA: 3,4-methylenedioximethamphetamine; LSD: Lysergic acid diethylamide; MDEA: 4-methylenedioxyethylamphetamine; MDA: 3,4-methylenedioxyamphetamine; HHA: 3,4-methylenedihydroxyamphetamine; HHMA: 3,4-dihydroxyamphetamine; COMT: catechol-O-methyltransferase; HMMA: 4-hydroxy-3-methoxyamphetamine; HMA: 4-hydroxy-3-methoxyamphetamine; NA: Noradrenaline; AD: Dopamine; 5-HT: Serotonin; ACh: Acetylcholine; SERT: Serotonergic carriers; MAO: Monoamine oxidases; ADH: Antidiuretic; ACTH: Adrenocorticotropic Hormone; SACIT: Analysis of the Toxicological Information Center of Santa Catarina; ICU: Intensive Care Unit.

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