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Chemical and pharmacological aspects of new psychoactive substances: focus on cathinones, piperazines and fentanyl-likes

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Abstract

Introduction: In the last twenty years we have seen a change in the drug abuse market. New ways of producing, selling, buying and consuming as well as the advent of some web sites have facilitated the emergence and spread of 'new psychoactive substances' (NSP). At the same time, the market for "traditional" drugs was implemented - too if not completely replaced - by a remarkable variety of new compounds with psychoactive properties.

Materials and methods: A computerized research was carried out for the articles to be inserted through use of international databases such as pubmed, scopus, researchgate, google scholar, by typing in keywords such as NPS together with the various classes of substances considered (cathinones, piperazines and fentanyl-likes compounds)

followed by some names of compounds belonging to the single categories, integrated with literature data. Also they are data from paper documents such as books and articles have been added.

Discussion and conclusions: Over a thousand new psychoactive substances (NPS) have been analyzed in recent years as the cause of acute intoxication among patients, often young, belonging to the emergency departments for especially acute psychiatric patients. Among the various NPS in this article, three of the most common classes have been analyzed, namely cathinones, piperazines and opioid derivatives of fentanyl.We focused on the chemical characteristics of the molecules and on the structure-activity relationship, or on their cellular toxicology on the central nervous system, explaining the mechanisms of action, bearing in mind that for these substances, the long-term toxicity mechanisms are still unknown. given that often patients come to observation only to stop episodes of acute intoxication and there are no specific treatments for their cessation, even if some (for example fentanyl) have properties of abuse and euphoria.

Introduction

The European Union legislation identifies as NSP any substance with psychoactive properties not yet classified or controlled by the UN conventions, regardless of when it was synthesized or how long it is used for other purposes, including lawful ones (UNODC, 2015). The EMCDDA defines NSP "any new narcotic or psychotropic substance, in pure form or in preparation, which is not controlled by drug conventions of the United Nations, but which may pose as serious a threat to human health as the substances that have already been listed by these conventions "(1). This definition also classifies NSP prescription drugs whose consumption occurs in a manner and / or in quantities such as to cause any psychoactive effect on humans. Many NSPs are actually compounds previously synthesized for research purposes, and only recently rediscovered as recreational drugs (eg. mephedrone). NSPs are also referred to as 'legal highs' to underline their legality status. NSPs are sold as 'research chemicals', 'bath salts', 'fertilizers', 'incense', etc. and packaged with the 'Product not for human consumption' label, to facilitate their marketing and 'legal' purchase(2). NSPs have been grouped into nine main groups: synthetic cannabinoids, synthetic cathinones, phenethylamines, tryptamines, piperazines, herbal highs, ketamines and PCP (phencyclidine) -like substances, aminoindanes and one group miscellaneous composed of the NSPs which for chemical / pharmacological characteristics do not fall into any of the categories listed above (eg. DMMA). In addition to the aforementioned categories, there are also the 'new stimulants' (eg. 4,4-dimethylaminorex / 4,4-DMAR; metiopropamine / MPA, etc.), the 'synthetic opioids / opiates' (eg. AH-7921, MT-45 etc.), the 'synthetic cocaine substitutes' (eg. RTI-111, RTI-121, RTI-126, etc.), the agonists of

the GABAA and GABAB receptor (eg. GHB, GBL, baclofen, phenibut, etc.), prescription drugs such as olanzapine and quetiapine(3). In this article we will focus on 3 classes of chemical substances, namely cathinones, piperazines and fentanyl derivatives, analyzing their chemical characteristics and correlating them with their pharmaco-toxicological effects.

Material and methods

A computerized research was carried out for the articles to be inserted through use of international databases such as pubmed, scopus, researchgate, google scholar, by typing in keywords such as NPS together with the various classes of substances considered (cathinones, piperazines and fentanyl-likes compounds) followed by some names of compounds belonging to the single categories, integrated with literature data. Also they are data from paper documents such as books and articles have been added. Among the various articles proposed we focused on those dealing with the chemical, drug and toxicological aspects, leaving out the strictly clinical part.

Results and discussion

Synthetics cathinones:

Synthetic cathinones are substances structurally similar to cathinone, a psychoactive molecule present in nature in the Khat plant. The natural analogue of synthetic cathinones is an active compound present in the leaves of the khat plant (Catha edulis), traditionally chewed by some populations of the Africa and the Arabian Peninsula for its psychostimulant properties(4). They are usually sold in the form of pills, capsules or powder. They are generally taken intranasally (snorted), oral ingestion by 'bombing' (ie. the powder is taken wrapped in a cigarette paper), dissolved in a drink or injected intravenously. The main desired clinical effects reported include a sense of euphoria, stimulation, increased energy, improved mood, hallucinogenic experiences and increased sexual arousal. The main side effects encountered include cardiac, psychiatric and neurological disorders, mainly a state of psychomotor agitation up to psychotic decompensation, hyperthermia, rhabdomyolysis, renal failure and seizures. Sympathomimetic effects include tachycardia, hypertension and psychoactive effects similar to amphetamine derivatives(3,5). According to the classification of Simmler et al. , cathinones can be divided according to their substrate of pharmacological action into:

- cathinones substrates of DAT, SERT and NERT with an MDMA-like pharmacological profile (eg benzedrone, butylone, ethylone, 4-MEC, etc.).

- cathinones substrates of monoamine transporters selective for DAT with an amphetamine and metamphetamino-like (e. g.cathinone, met-catinone, phlephedrone, nafirone, 1-nafirone...).

- cathinones not substrates of transporter inhibitors (eg MDPV, etc.).

Chemically cathinones are beta-keto-phenethylamines; being compounds structurally similar to amphetamines (such as MDMA and methamphetamine) and catecholamines act, albeit weakly, as central nervous system stimulants, inhibiting monoamine reuptake transporters and increasing the synaptic concentration of norepinephrine, dopamine and serotonin. Cathinone is an alkaloid (i.e. an organic compound containing nitrogen, mainly within a heterocyclic ring and mostly with the properties of a weak base) present in the leaves of a shrub cultivated in the Horn of Africa and in the region of the Arabian Peninsula and called khat, and similar in structure to the ephedrine and amphetamines, from which it differs from many in the presence of a ketone functional group.

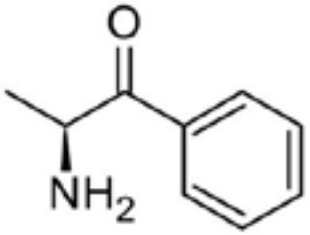

Figure 1: chemical structure of cathinone (IUPAC (S) -2-Amino-1-phenyl-1-propanone name)

Substituted cathinones are molecules characterized by a phenethylamine core with an alkyl group attached to the alpha carbon and a ketone group attached to the beta carbon, along with additional substitutions. As evident in Figure 2, the derivatives can be produced by substitutions in four positions of the cathinone molecule(6):
R 1 = hydrogen or any combination of one or more alkyl, alkoxy, alkylenedioxy, haloalkyl or halide substituents
R 2 = hydrogen or any alkyl group
R 3 = hydrogen, any alkyl group or incorporation into a cyclic structure
R 4 = hydrogen, any alkyl group or incorporation into a cyclic structure

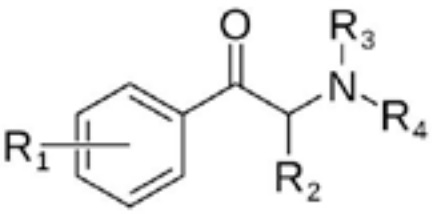

Figure 2: structure-activity relationship of the cathinone molecule: R indicates the positions where substituent groups of hydrogen atoms that modify the activity of the basic pharmacophore can be found

Several dozen cathinone molecules have been described; as an example, we will take one of them as an example. Mephedrone ((RS) -1- (4-methylphenyl) -2-methylaminopropan-1-one; 4-MMC) is a compound with a methyl substituent in position para to the aromatic ring of the corresponding metcatinone and whose chemical structure is shown in Figure 3. The hydrochloride appears as a white powder, white or yellowish crystals. The free base is a yellowish liquid at room temperature. It is sold in the salified form (hydrochloride), in the form of powder, more stable and soluble in water, a form that can be found on the illicit market as it is or contained in capsules or tablets(7,8). Purities often higher than 99% are reported. Mephedrone was initially marketed on the illegal market as a “safe and legal” substance, an alter-

native to the stimulant drugs already listed. Currently, however, it has also been placed under control by the authorities of several European countries, including Italy. The most immediate synthetic way for cathinones, sees the reaction between bromopropiophenone and methylamine, giving rise to a mixture racemic(9,10). The starting material for this synthetic route is commercially available or easily synthesized and requires laboratory equipment and chemical knowledge similar to those required for the synthesis of other stimulants such as amphetamines and MDMA. The main precursor for mephedrone synthesis, 4-methylpropiophenone, is commercially available on the Internet.

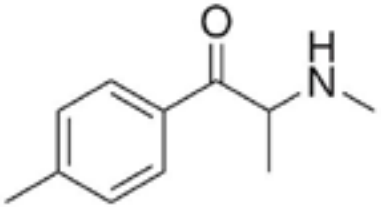

Figure 3: mephedrone structure

In a study (11) of administration of mephedrone, MDMA or amphetamine in rats, it was found that mephedrone and amphetamine produced a rapid increase in extracellular dopamine levels, respectively by 496% and 412%, while MDMA showed more limited effects (235%). The corresponding levels of serotonin increased by 941% in the case of mephedrone, by 911% in the case of MDMA but only by 165% following the intake of amphetamine.

Piperazines:

Piperazine is a hexatomic heterocyclic compound in which there are two nitrogen atoms in the 1,4 position (Figure 4). Piperazine is soluble in polar solvents such as water and ethylene glycol, while it is insoluble in solvents such as diethyl ether. It is a fairly strong base and has pKb = 4.19; it tends to rapidly absorb water and carbon dioxide present in the air(13). Although many piperazine derivatives are widespread in nature, it can be synthesized by reacting ammonia with 1,2-dichloroethane in alcohol, sodium and ethylene glycol with ethylenediamine hydrochloride or by reducing pyrazine with sodium in ethanol.

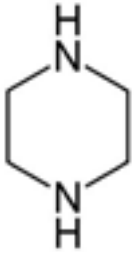

Figure 4: piperazine

The derivatives of piperazine represent a wide class of chemical compounds with important pharmacological activity. These include, for example, viagra and levitra, imatinib, cyclizine, trazodone, nefazodone and various drugs of abuse. Piperazine and some of its derivatives are also used as anthelmintics(14). As substances of abuse they are found in the form of capsules or tablets, more rarely in the form of powder, they are an alter-

native to ecstasy and have even exceeded the sale of the same. In fact, 40 mm of benzylpiperazine (BZP) have the effect of 120 mm of ecstasy, with a very low cost(15). In addition, they represent one of the main ingredients of drug cocktails Young people define this drug by several names: pep, euphoria, nemesis, Arlequin, Regenboogies, Duhovka, Rainbow or bliss. BZP is a central nervous system stimulant that generates an increase in pulse, blood pressure and pupillary dilation. It causes poor appetite, sweating, nausea, abdominal pain, migraines, tremors, loss of sleep, energy, confusion, irritability. The physiological and subjective effects reach their peak 1-2 hours after taking it orally. Symptoms caused by piperazines can persist for up to 24 hours. Taken in high doses they can produce hallucinations, convulsions and respiratory depression(16,17). The symptoms of ecstasy and benzylpiperazine overdose are similar, however piperazines are not part of the substances sought routinely with toxicological screening tests and are detectable only with special tests such as spectrophotometry and chromatography coupled to mass spectrometry, expensive and second level. Figure 5 shows piperazine derivatives. Among the derivatives we mention the Chlorophenylpiperazines(figure 6), molecules of synthetic origin of which there are three different types, depending on the position of the chlorine atom on the aromatic ring (ortho, meta and para isomers).

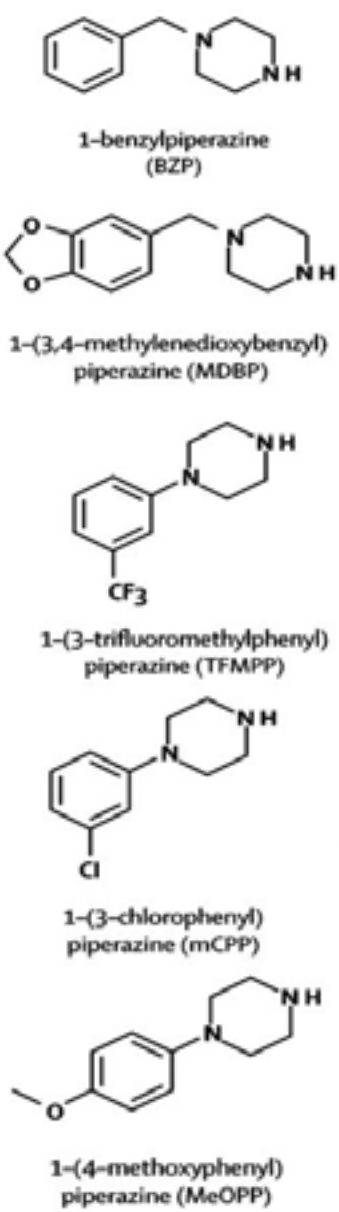

Figure 5: piperazine- derivates

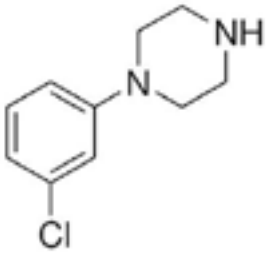

Figure 6: meta- Chlorophenylpiperazine

It is interesting to note that the acronym CPP is also used for the 4-chlorophenoxypropionic acid herbicide. The meta isomer (mCPP) is the best known as the active isomer. MCPP is known in the chemical industry as an intermediate in the synthesis of different drugs and can be found in biological samples as an active metabolite of the drugs themselves. mCPP has effects on the serotonergic system and its use can cause anxiety, mental confusion, tremors, panic attacks, fear of losing control, migraines, increased sensitivity to light and noise. MCPP is also the main metabolite of the antidepressant drug Trazodone. A case of overdose related to poly-drug use of psychotropic substances including mCPP has been reported in the literature(18). After ingesting 3 polychrome tablets, the patient developed anxiety, agitation, drowsiness, a sensation of sudden and intense heat, visual disturbances and tachycardia. Concentrations of mCPP were 320 ng / mL in plasma and 2300 ng / mL in urine. Plasma analyzes also revealed the presence of amphetamines (40 ng / mL), benzoylecgonine (47 ng / mL) and alcohol (0.7 g / L). The concentration of mCPP in plasma was approximately 6 times higher than the concentrations normally found in patients under treatment with trazodone (26-108 ng / mL, mean 56 ng / mL).

Fentanyl-likes compounds:

The common feature of most synthetic opioids of abuse is greater potency than heroin, that is taken from analgesia tests on animals, and therefore on humans they should not be taken literally as they could be underestimated, but they give a good idea of how dangerous the substance in question is (19). In fact, one could imagine that the greater potency is a relative problem, because if a substance is more potent it would be enough to use less in proportion. However, in the case of clandestine production and outlets, the purity and fineness are often uncertain and with the various dilution steps (cutting), what reaches the final consumer often has a real titre that varies from dose to dose(20). Fentanyl is a pharmaceutical product commonly used in anesthesia; the derivatives are potentially innumerable thanks to the fact that the basic skeleton of fentanyl has at least five positions in which it is possible to introduce chemical variants maintaining the desired action, ie the agonist action on MOR, mu opioid receptors (Figure 7). Most derivatives have not been formally studied and to date we have incomplete knowledge of them. The only ones for which there is satisfactory documentation are alfentanil, sufentanil, and remifentanil, used in humans, carfentanil, used in veterinary

medicine in large animals, and lofentanil studied but never commercialized. Of many others, such as acetylfentanil, acryloylphentanil, alfamethylfentanil, 3-methylfentanil, butyrylfentanil and its derivatives on C4 (methoxy and halogens), furanylfentanil, tetrahydrofuranilfentanil, cyclopentylfentanil, ocfentanil we know little more than what can be obtained from the circumstances of intoxication and deaths(20,21,22).

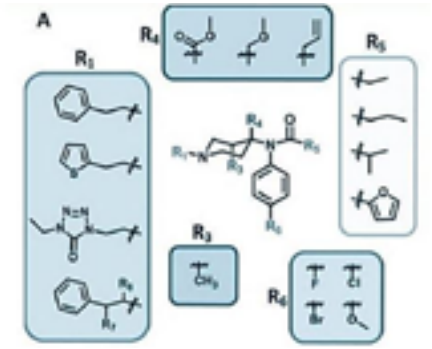

Figure 7: basic skeleton and substituent positions of fentanyl

For fentanyl, the lethal dose in humans, in the absence of support for cardiorespiratory functions, is around 2 mg; the analgesic concentrations in the blood are 1-2 ng / ml, the anesthetic concentrations of 10-20 ng / ml, as far as polyconsumption and therefore in the presence of other central nervous system depressants even concentrations of 7 ng / ml have been found to be lethal. The most important difference between fentanyl and heroin, and even more morphine, is pharmacokinetic in nature and is due to the fact that fentanyl is much more fat-soluble, distributing in lipids about 1000 times more than morphine(23). The fact that it is fat-soluble allows for easy entry but an equally easy exit from the central nervous system and for this reason its effects last less than heroin, which remains trapped within the blood brain barrier after being deacetylated in monoacetylmorphine and morphine. The final elimination, on the other hand, is slow, with a half-life of 3-7 hours, more prolonged than that of morphine (2-4 hours) and 99% dependent on the liver (cytochromes CYP 3A4, 3A5 and 3A7). Despite various negative aspects, there is a population of consumers who prefer the effects of fentanyl and actively seek out drug dealers who can supply them, preferably in the form of fentanyl-laced heroin, i.e. fentanyl-heroin blends, which associate the intense rush of the former with resistance of the effect of the second, with the ability of fentanyl to exceed the tolerance to street opioids or agonist therapy, in order to continue to "feel" the substance. The greater potency of fentanyl compared to heroin is directly due to the higher frequency of overdose. The fentanyl overdose is immediate, and the transition from unconsciousness to respiratory depression and death it is just as fast; with fentanyl, the transition from consciousness to respiratory failure can take seconds or a few minutes, without giving enough time for help to arrive(24).

Conclusions

The new psychoactive substances are constantly expanding and cause more and more frequent deaths from overdose and access to the emergency room and psychiatric environments due to the consequences of repeated acute poisoning. In the era of COVID there has been a marked increase in the use of these substances for two reasons: the easy availability of many substances via the internet with direct home delivery and the increase in stress, anxiety and depression pathologies that have driven many people to start using as self-treatment or to get such products high. In this article we wanted to talk about only some of the most used classes of substances, excluding cannabinoids, of which a lot has now been said, and the old classic drugs such as alcohol or stimulants. We focused on the chemical and pharmacological aspects without being excessively technical especially on the chemical part, knowing that much still needs to be done for the early identification of many of these substances for which there are only a few anecdotal cases in the literature and above all there are no antidotic therapies. or specific cessation.

Conflict of Interest Statement: the authors had no conflicts of interest to declare.

For the purposes of compliance with the provisions of art. 6-bis of Law no. 241/1990 and of the art. 7 of the Code of Conduct for public employees, issued with Presidential Decree no. 62/2013;
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not to find themselves in situations of incompatibility or in conditions of conflict of interest also potential.

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