Editorial

A review on 2 C-B and "pink cocaine"

A propósito del 2 C-B y de la "cocaína rosa"

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Received: 04/03/2024 · Accepted: 25/03/2024

Cómo citar este artículo/citation: Climent Díaz, B. (2024). A review on 2 C-B and "pink cocaine". *Revista Española de Drogodependencias*, *49*(1), 10-14.

New psychoactive substances (NPS) have become a global phenomenon and their use is related to significant health problems. NPS include different groups of substances with clearly differentiated characteristics (by chemical structure, effects, legal status, etc.) (ONU, 2023). The characteristics of NPS are variable, as are their action mechanism and their effects on the central nervous system (CNS). Those effects depend on the chemical structure of each substance and their impact on specific points in the CNS. Mainly, the effects can be psychostimulant, entactogenic, hallucinogenic or sedative (EMCDDA, 2023).

From the perspective of health services, we must address both the prevention of NPS consumption and improve the existing knowledge about them in view of correct diagnosis and treatment of intoxication caused by their use.

In many cases products purchased online or on the drug market do not contain the desired substance. The most common issues include the concomitant presence of other substances, the possible presence of adulterant substances and impurities or even the absence of the desired substance itself, since on many occasions those

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substances are replaced by others. Other substances are often added to enhance or compensate certain effects, a fact that most consumers are unaware of. Furthermore, the doses of the substances contained in drug samples are completely arbitrary. These are two essential aspects in the consumption of new psychoactive drugs.

Consumers are exposed to the toxic effects of unidentified substances that are often mixed and taken in variable, uncontrolled doses, which can determine the probability of unpredictable intoxication.

Understanding the properties and characteristics of these compounds along with their toxicity is essential for the treatment of affected patients.

Among the NPSs are the compounds of the "2C" series. They are ring-substituted phenethylamines and the terminology "2Cs" refers to an acronym created by Alexander Shulgin to describe the presence of two carbons between the amino group and the benzene ring in the chemical structure (Shulgin & Shulgin, 1991).

4-Bromo-2,5-dimethoxyphenylethylamine (2C-B), also known as "tucibi", "tusi", "pink panther" or "nexus", among other names, was synthesized in 1974 by Shulgin, constituting the first compound of the "2Cs" family3. Other compounds of the series were synthesized later, such as 2C-E, 2C-T-2, 2C-T-7, 2C-I, etc. (Shulgin & Shulgin, 1991).

Although this group of compounds has been on the market for new psychoactive drugs as psychostimulants for many years, they have currently gained notoriety due to consumption trends and **a fatal intoxication** case that supposedly took place after consumption.

In this case the most current problem is that the product distributed and consumed as "tusibi", "tusi", or "pink cocaine", is often a mixture of substances that usually may not contain 2C-B or another of the compounds in this group. The term "pink cocaine" generates confusion as the substance is not related to cocaine (although cocaine could also be part of the mixture), which may lead to wrong assumptions by consumers about the expected effects.

Identifications of samples containing ketamine, 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine, cocaine, caffeine, drugs and other NPS that may include even synthetic opiates have been described (Energy Control; González et al., 2013). Ketamine is one of the main substances found in these mixtures. The presence of different unidentified substances and at variable uncontrolled doses in these mixtures can also represent additive toxicity, both stimulant and depressant, carries a high potential risk of acute toxic effects.

2C and "pink cocaine" are generally available in the form of a tablets, capsules, powder (usually but not always pink) or liquid, depending on whether they are ingested orally or inhaled. The latter option implies the fastest and most intense effects.

Limited information is available on the mechanisms of action and toxicity of the 2C family. In the case of 2C-B, it acts as a serotonergic agonist at 5HT2a, 5HT2b, 5HT2c and alpha1 adrenergic receptors. According to Shulgin & Shulgin (1991), doses of 2C-B would range between 12

and 24 mg and its maximum effects would be reached within 30 to 75 minutes, with a duration between 4 and 8 hours. 2C-B is metabolized by monoamine oxidases A and B and to a lesser extent by cytochrome P450. Any medication or substance with monoamine oxidase inhibitory properties consumed concomitantly with 2C-B can cause an overdose.

As with most NPS, toxicokinetics and toxicodynamics vary due to different conditioning factors (genetic, drug interactions, polydrug use, etc.) among users. Besides, it must be considered the fact that some users may be more susceptible to toxicity.

The reported effects of 2C and particularly 2C-B are a combination of hallucinogenic and stimulant effects (Nugteren-van Lonkhuyzen et al., 2020). At low doses, 2Cs generally have stimulating effects and increased visual, auditory, and tactile sensations. In moderate doses, they can cause hallucinations. At higher doses, users may experience unpleasant hallucinations and sympathomimetic manifestations such as tachycardia, hypertension, and hyperthermia. There is a wide variability of effects across the different members of the 2 C family. 2C-B has specific effects on emotional processing and mood states that allow its classification as an entactogenic substance with a psychedelic-hallucinogenic effect (González et al., 2015).

Patients affected by 2C intoxication are likely to present sympathomimetic syndrome, serotonin syndrome, hallucinogenic conditions, or some combination thereof (González et al., 2013). Signs and symptoms may include hallucinations, delirium, nausea, vomiting, agitation, tachycardia and cardiac arrhythmias, hypertension, respiratory depression, tremors, and seizures. A description of cerebral edema in the hours following the consumption of 2 C-B has been observed (Spoelder et al., 2019). The intensity of the toxic effects varies, with the different substances of the 2C family (Dean et al., 2013). For example, the effects of 2C-E are stronger than those of 2 C-B and 2 C-I.

In the case of "pink cocaine" consumption, clinical manifestations will vary depending on the composition of the mixture of substances contained in the sample (Energy Control; González et al., 2013).

Based on the data analyzed by prevention support organizations, the presence of ketamine is predominant and can produce sedative effects (since ketamine is an anesthetic) and dissociative effects, all in relation to the dose consumed (Palamar, 2023). The presence of other NPS such as MDMA or different amphetamines will produce entactogenic, psychostimulant or hallucinogenic effects depending on the substance with the characteristic toxicity of each of them. Caffeine in high doses will produce the typical stimulant effects, but with the probability of characteristic toxic effects such as high blood pressure, tachycardia and arrhythmias, anxiety, insomnia, etc. Those caffeine doses may have an increased effect if "pink cocaine" is consumed with energy drinks with a high caffeine content. It is important to bear in mind the possibility of additional cardiovascular and neurological toxic effects due to the concomitant consumption of substances with sympathomimetic effects, as it would happen with "pink cocaine" (MDMA, amphetamines, caffeine, etc.).

The diagnosis of poisoning by 2C compounds and in particular by these mixtures such as "pink cocaine" or "tucibi" does not differ from that of other NPS and is based on a complete anamnesis, physical examination and complementary tests to rule out complications, and identify the consumption of other drugs and concomitant organic pathologies.

Since the information obtained from the history is usually scarce and even contradictory, special attention must be paid to the signs and symptoms presented by the patient. This information will allow an approach to the patient's condition through the toxindromes (Hoffman, 2015).

Given the presence of different substances in "pink cocaine" and the high percentage of multiple drugs linked to the consumption of NPS (it is usually accompanied by the consumption of alcohol, cannabis, cocaine, or other drugs), the clinical symptoms may undergo modifications that distance them from the toxidromes expected with 2C (sympathomimetic, serotonergic and hallucinogenic), and a sedative toxidrome 0may also appear.

The etiological diagnosis of intoxication by substances of the 2C family, "pink cocaine" and the NPS group is a clinical challenge, which requires frequent updates on available information, characteristics/patterns, and consumption with continued variability. Emergency services usually rely on the information provided by patients or their companions. Given the difficulty in providing diagnostic support from healthcare laboratories to identify these substances, the diagnostic approach will be carried out under clinical suspicion, and based on the interpretation of the symptoms through the toxidromes 0in order to establish an appropriate treatment. A pending issue in our healthcare system is the lack of etiological diagnosis in suspected NSP intoxication, in addition to the limited clinical training on them.

The management of intoxication by compounds of family 2 C and in particular "pink cocaine" or "tusibi" does not generally differ from that of other NPS, and is based on symptoms (Hoffman, 2015). There are no antidotes (except for opiates) and the pillars of treatment are basic care aspects such as airway protection, maintenance of breathing and circulation. Treatment may vary depending on the clinical manifestations in each case: sedation with benzodiazepines, neuroleptics and/or anesthetics are used in cases of psychomotor agitation, as in sympathomimetic clinics. In case of hyperthermia, cooling by physical means is recommended. In the case of seizures treatment includes benzodiazepines and/or antiepileptics.

The protocolization of health care for intoxication by drug abuse (both regular and NSP), and the possibility of carrying out subsequent analytical studies in reference laboratories, will allow improved treatment and collection of epidemiological and clinical data on this phenomenon.

Finally, the real challenge for healthcare professionals, educators, public administrators, legislators, security forces, etc., implies the prevention of consumption, which must be at the center of all actions carried out in response to drug abuse.

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