6

EMERGING DRUGS

CLINICAL COMMITTEE REPORTS

pnsd

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD, POLÍTICA SOCIAL E IGUALDAD

realities

myths

effects

types

risks

use

abuse

addiction

emerging drugs

GOVERNMENT OF SPAIN

MINISTRY OF HEALTH, SOCIAL POLICY AND EQUALITY

GENERAL SECRETARIAT FOR SOCIAL POLICY AND CONSUMER PROTECTION

GOVERNMENT DELEGATION FOR THE NATIONAL PLAN ON DRUGS

ACKNOWLEDGEMENTS

The Clinical Committee of the Government Delegation for the National Plan on Drugs would like to acknowledge the contribution and documentary and technical support of the following people:

Noelia Llorens Aleixandre
Mercedes Rubio Ferreiro
Francisco Ràbago Lucerga

MINISTRY
OF HEALTH, SOCIAL POLICY
AND EQUALITY

Published and distributed by:

ONLINE NIPO: 860-11-054-9
PAPER NIPO: 860-11-054-9
ISBN: 978-84-920522-8-8
Legal deposit: M-38788-2011

Layout: ADVANTIA COMUNICACIÓN GRÁFICA, S.A.

Printed by: ADVANTIA COMUNICACIÓN GRÁFICA, S.A.

Website: http://www.pnsd.mspsi.es

Clinical Committee of the Government Delegation for the National Plan on Drugs

Chair

Mrs. Nuria Espí de Navas
Government Delegate for the National Plan on Drugs

Members

Mr. Manuel Sanchís Fortea
Mrs. Julia González Alonso
Mrs. Elena Álvarez Martín
Mr. Carlos Álvarez Vara
Mr. Julio Bobes García
Mrs. Begoña Brime Beteta
Mr. Exuperio Díez Tejedor
Mrs. Magí Farré Albaladejo
Mr. Juan Flores Cid
Mr. Aurelio Luna Maldonado
Mrs. Amparo Sánchez Máñez
Mrs. Rosario Sendino Gómez
Mrs. Marta Torrens Melich

Preface

This sixth report by the Clinical Committee of the Government Delegation for the National Plan on Drugs analyses the wide range of effects of the so-called "emerging drugs". This term would include other expressions such as "synthetic drugs", "designer drugs" or "recreational drugs", which are very commonly used but whose meaning may not be sufficiently clear and accurate. Emerging drugs are illegaly synthetized substances intended to cause, by means of some variations in the chemical structure, similar or even higher effects than classical drugs as well as to avoid the normative control that the latter are subject to. These drugs appear, reappear or emerge in the market and the mass media (which explains the term used in this monograph) in a recurrent manner.

Since the analysis and review of drugs policies of the last few years, and more specifically in Spain since the National Plan on Drugs came into effect in 1985, the social perception of the issue of drug use and drug addiction has changed dramatically. The world of drug abuse and psychoactive substances with recreational purposes is constantly changing. Therefore it is vital for all those professionals involved in their clinical-therapeutic treatment and prevention to know the current trends of use, the types of substances used or the new use and toxicity patterns.

Their use and abuse are linked to a festive atmosphere, mostly on weekends, among teenagers and young people, who are familiar with their stimulating effects that help relate to others, but who, most of the times, ignore their harmful effects to their health. All this is frequently exacerbated by the use of alcohol and the common fraud regarding the composition of these "pills", which are adulterated with all kind of psychoactive or solvent products.

There is an increasingly high number of these substances. The European Union informed of the emegence of around 40 new substances in 2010, including plants and fungus, vitamines, minerals, legal drugs or their copies and unauthorized chemical substances with various ways of marketing and use (pills, plant extracts, fresh or dry fungus, soaps, vegetable fertilizers, infusions, inhaling products, etc.).

Moreover, their spreading has been significantly increased by the Internet, which contains a huge amount of information about their procurement, synthesis, identificacion, use, effects and marketing of this type of substances. It is pseudo-scientific information not verified or contrasted

frequently used to justify the promotion of the use of these substances on many websites. This is why the new trends of use and development may escape from the control and follow-up mechanisms of the State. The virtual and global nature of the Internet, the difficulty in applying legal restrictive measures and their relative anonymity and rapidity foster their trade and distribution.

The Clinical Committee of the Government Delegation for the National Plan on Drugs provides professionals with a practical monography condensing the current knowledge on emerging drugs and their effects on people's health and welfare. This volume contains updated information on the current situation of the use of this type of substances in our country and reviews some legal and social aspects related to it. Its accessible language and clear presentation make the reading and understanding easier to all those interested in this subject.

I would like to express my gratitude to all the members of the Clinical Committee for the work done and encourage them to keep on this task.

Leire Pajín Iraola
Minister of Health, Social Policy and Equality

Contents

I. Introduction

There has been a fundamental debate about the title "emerging drugs" instead of more common expressions such as "synthetic drugs", "designer drugs" or "recreational drugs.[1]" The term "emerging" has been finally chosen because somehow it includes the other three when qualifying the noun "drugs" and it does not prejudge "when" they have been emerging or their condition (natural, produced in a laboratory from a principle present in nature or totally synthetic). They appear, reappear or emerge from an underlying imperceptible position, before becoming extremely popular in the mass media. Apart from some exceptions, they emerge through the years in a recurrent manner. Methamphetamine, for example, has been "new" in Europe more than three times during the last ten years.

Most designer drugs[2] (term that implicitly refers to a personal creative author that sets the trend) were "emerging" synthesis between 1910 and 1940. The European chemical-pharmaceutical industry managed to master the molecular synthesis during the passage from the 19th century to 20th century on the basis of the work on the anilines, raw material of modern industrial colorants and sulfonamides.

Therefore, "emerging" does not always mean "new". It may sometimes be just a re-discovery of what is already known and it is not always a synthesis voluntarily pursued. LSD-25 was a casual finding by Professor Hoffman when he was investigating the products derived from the rye ergot fungus (*Claviceps purpurea*) and their application to fight against migraines for the laboratories Sandoz in Basel (Switzerland). "Venus-CB2" by Alexander Shulgin was new and synthetized *ad-hoc* in 1974[3]. The rest are well-known modifications of ephedrine, ephedrone (or methcathinone), synthetic opioids or meperidine.

They are also "emerging" because sometimes they suddenly appear outside their permanent and traditional context of production and use, although they are not new at all. Many of them derive from sacred plants such as the *psylocibe* fungus, the *teonanacatl* of several Mesoamerican pre-Columbian cultures, the *ayahuasca* of the shamans in the Amazon basin, the *peyote or peyotl* of the huicholes and other arawak tribes of the Great Prairies, the *salvia divinorum*, *tabernante iboga* of the priestly initiated of the Gulf of Guinea, *betel* of India, *khat* of the Golden Horn and Aden (Yemen), etc.

It is worth looking over the ancient traditions of ritual or cultural consumption. During the last twenty years, the "ectopic" use of some of these substances has been justified as the legitimate religious use among "converted" people that practise a religion and its rites very far away from their places of origin. As an example we can refer to the users of *peyote* in the United States and of *ayahuasca* in the shamanic groups of the Santo Daime Church in Madrid. Nevertheless, in these cases the regulations on limiting the use, sale and distribution of prohibited substances by the UN Conventions of 1961 and 1971 have been implemented.

A heterogeneous group of substances known as *spice*[4] have also been regarded as "emerging". Sometimes, they are presented with a generic name specified by a postmodern pop sonorous qualifying adjective. Other times they are presented in a more serious way, pretending to be a guaranteed, reliable product even with a registered patent. Far from reality. On many occasions, their claimed contents are not analytically detected whereas undeclared substances are found in thieir composition, mainly synthetic cannabinoids, not subject to prior investigation and whose effects are mostly ignored. They are not forbidden and do not prove positive in the diagnosis tests of cannabinoids in biological fluids. Their successful emergency and spreading are due to the Internet. They are announced and offered as natural substances, as if they were innocuous. However, the hemlock is natural too, like tsunamis or volcano eruptions, which are not innocuous at all.

The spreading of the distribution and use of spice drugs has raised the alarm in modern communities[5], such as the European Union, which has already developed a very effective early warning system in order to investigate, monitor, control or fight against their sale by illegal means, for example, the use of the Internet to sell drugs only available on prescription and at chemist's shops.

Furthermore, it is not the first time that innovation and unexpected emergence have worried developed societies[6]. In the 70s-80s there were some active groups that violated the regulations restricting psychotropics. Ephedrines were even sold by mail, cash on delivery, with a "recipe" to produce other molecules from them just by using a fairly-equipped kitchen. These were called "pan-drugs" or "kitchen drugs". The use of microwaves in the 80s enabled to improve the methods used although

today these techniques are obsolete except for the ketamine or the Gamma hydroxybutyrate (GHB).

We are deeply involved in a dialectical relation between, on the one hand, the producers-sellers, who have technical teams expert on biochemical synthesis, which enables them to obtain new substances for people looking forward to new experiences with not totally illegal drugs; and on the other hand, those people responsible for Public Health and the implementation of regulations that limit the distribution of substances potentially dangerous to health[7].

II. General concepts

2.1. Definitions

Emerging drugs

Substances that appear in the drug market at a given moment as an innovation. They can be previously known or be new drugs, and in general terms, they are not included in the lists of psychotropic or narcotic substances, therefore they are not illegal.

Legal highs

Products that include one or several substances, from mixed herbs to drugs produced in a laboratory, with the same effects as illegal drugs such as marihuana, ecstasy, cathinone, LSD or cocaine, but that do not use any psychoactive ingredients or prohibited substances (Figure 1). These products can be used in different ways (smoking, swallowing, etc.).

Figure 1. ***Legal highs.***

www.smh.com.au/technology/technology-news/legal-highs-the--lowdown-on-a-law-enforcers-nightmare-20100721-10kae.html (Picture by Craig Sillitoe)

In some European countries, particulary in the United Kingdom, the products included in this new category are legally sold in shops on the

street, in music festivals or on the Internet. They can be found as air fresheners, incense or bath salts, although their purpose is very different.

The most characteristic products of this category are the spice drugs that contain synthetic cannabinoids and, in 2009-2010, mephedrone, which was sold in the EU until it was controlled at the end of 2010. Many of them are included in the group of research chemicals.

Research chemicals (RCs)

They are also called "new synthetic substances". They are synthetic psychoactive substances, not internationally controlled, sold by suppliers that operate mainly on the Internet. This does not mean that they are new substances. Some of them are and others were synthetized many years ago.

On many ocassions they are presented in plastic bags with a tag showing their name and weight and with sentences such as "Not for human consumption" and "For technical use only / For laboratory use only". Again the prototype was mephedrone, as already mentioned in the section about legal highs.

The main characteristic of this category of products is that there is little scientific knowledge on them. There are hardly any pharmacological and toxicological studies, therefore the consequences of their social consumption are ignored.

Pharming parties

It is a term conceived by the media to refer to meetings or parties where the attendants exchange prescribed drugs and take them at random in order to get intoxicated.

Club drugs - Recreational drugs

Generic term used to refer to psychoactive drugs, generally illegal, used by people in organized festivals (rave parties), electronic music discotheques (dance clubs) and recreational drugs subculture. The most commonly

used substances are: Ecstasy (MDMA) and other amphetamine derivatives, *Rohypnol* or *Rohipnol* (flunitrazepam), GHB, ketamine, LSD and other hallucinogenic substances.

Designer drugs

This term is used to describe substances synthetized or produced to cause the same subjective effects as illicit drugs. They are usually produced in a clandestine laboratory by modifying, to different degrees, the molecular structures of the existing medicines. Less commonly, they are medicines with a chemical structure completely different from that of illegal recreational drugs but with similar subjective effects. Sometimes synthetized substances have proven higher power (alpha-methylfentanyl) and toxicity than the original products or contain very toxic contaminants (MPTP in MPPP or manganese in methcathinone).

It is worth highlighting that some substances, new or already known, legal or illegal, may fall under one or more of the definitions above.

2.2. Classification

There is a wide range of substances that can be included in the group of the so-called "emerging drugs" and they can be legal highs, research chemicals, recreational drugs or designer drugs. Table 1 below shows a classification suggested by the authors of this monography to serve as a guide for further analysis of the main groups considered in this classification.

Table 1. Classification of emerging drugs.

PHENYLETHYLAMINES AND AMPHETAMINE DERIVATIVES	Psychostimulating effects	Amphetamines	- Amphetamine (d,l-amphetamine)* - Dextroamphetamine (d-amphetamine)* - Methamphetamine (d,l-methamphetamine) - Dextromethamphetamine (d-amphetamine) - Levomethamphetamine (l-methamphetamine)* - Methylphenidate* - Ephedrine (*ephedra*)* - Anoretics (phentermine and other derivatives)*
		Cathinones	- Cathinone (*khat*) - Methcathinone (ephedrone) - Methylmethcathinone (mephedrone) - Ethylone (see entactogens) - Methylone (see entactogens) - Butylone (see entactogens)
	Entactogenic effects Methylenedioxyamphetamine	- 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy", "Adam") - 3,4-methylenedioxyamphetamine (MDA, "love pill"), - 3,4-methylenedioxyethylamphetamine (MDEA or MDE, "Eve") - N-methyl-1-(3,4-methylenedioxyphenyl)-2 butamine (MBDB) - 3,4-methylenedioxymethcathinone (methylone, "explosion") - 3,4-methylenedioxyethylcathinone (ethylone) - β-keto-N-methylbenzodioxolylpropylamine (bk-MBDB, butylone)	
	Hallucinogenic effects Methoxyamphetamines	- 4-bromo-2,5-dimethoxyamphetamine (DOB) - 4-methyl-2,5-dimethoxyamphetamine (DOM, serenity-tranquility-peace or STP) - 2,4,5-trimethoxyamphetamine (TMA-2) - paramethoxyamphetamine (PMA) - 4-bromo-2,5-dimethoxyphenylamphetamine (2CB-MFT) - 2,5-dimethoxy-4-bromo-phenethylamine (2-CB, nexus) - 2,5-dimethoxy-4-iodophenethylamine (2-C-I) - 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2) - 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7) - 8-bromo-2,3,6,7-benzo-dihydrodifuran- ethylamine (2-CB-Fly) - Bromo-benzodifuranyl-isopropylamine (bromo-*dragon-fly*)	

	Others	- Pyrovalerone - Naphyrone (naphtylpyrovalerone, NRG-1) - Alpha-pyrrolidinopentiophenone (α-PVP) - Methylenedioxypyrovalerone (MDPV)
Tryptamines	- N,N-dimethyltryptamine (DMT) - 5-methoxy-dimethyltryptamine (5-MeO-DMT) - Bufotenine (cebilcin, 5-hydroxy-dimethyltryptamine, 5-HO-DMT or 5-OH-DMT) - 4-hydroxy-N-methyl-N-isopropyltryptamine (4-HO-MiPT) - Diisopropyl-4-acetoxytryptamine (4-acetoxy-DiPT, ipracetin) - O-Acetylpsilocin (4-acetoxy-N,N-dimethyltryptamine, 4-AcO-DMT, 4-acetoxy-DMT) - 4-hydroxy-N-methyl-N-ethyltryptamine (4-HO-MET) - 5-methoxy-alpha-methyltryptamine (5-MeO-AMT) - 5-methoxy-di-isopropyltryptamine (5-MeO-DiPT, Foxy, Foxy Methoxy) - 5-methoxy-methylisopropyltryptamine (5-MeO-MiPT) - α-methyltryptamine (AMT) - N,N-diisopropyl-tryptamine (DiPT) - N,N-dipropyltryptamine (DPT) - 4-Acetoxy-N,N-diethyltryptamine (4-acetoxy-DET, ethacetin, ethylacybin, 4-AcO-DET)	
1-aryl-piperazines derivatives	Benzylpiperazines	- 1-benzylpiperazine (BZP) - 1-(3,4-methylenedioxybenzyl)piperazine (MDBP)
	Phenylpiperazines	- 1-(3-chlorophenyl)piperazine (mCPP) - 1-(3-trifluoromethylphenyl)piperazine (TFMPP) - 1-(4-methoxyphenyl)piperazine (MeOPP)
pyrrolidinophenones derivatives	- α-pyrrolidinopropiophenone (PPP) - 4-methoxy-α-pyrrolidinopropiophenone (MOPPP) - 3,4-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP) - 4-methyl-α-pyrrolidinopropiophenone (MPPP) - 4-methyl-α-pyrrolidino-hexanophenone (MPHP) - 4-methyl-α-pyrrolidinobutyrophenone (MPBP) - α-pyrrolidinovalerophenone (PVP)	

OPIOIDS DERIVATIVES	Fentanyl analogs	- α-methylfentanyl (China White) - Parafluorofentanyl - 3-methylfentanyl
	Phetidine analogs	- MPPP (contaminated with an impurity called MPTP that can cause permanent symptoms of Parkinson's disease)
	Others	- Dextromethorphan*
ARYLCYCLOHEXYLAMINES	Phencyclidine derivatives (PCP)	- Ketamine* - 3-methoxy-phencyclidine (3-MeO-PCP) - 4-methoxy-phencyclidine (4-MeO-PCP) - Eticyclidine (PCE, CI-400, N-ethyl-1-phenylcyclohexylamine) - 2-(3-methoxyphenyl-2-(ethylamino)cyclohexanone) (methoxetamine) - Rolicyclidine (PCPy; 1-(1-phenylcyclohexyl)pyrrolidine) - Tenocyclidine (TCP; 1-(1-(2-thienyl)cyclohexyl)piperidine) - 2-(3-methoxyphenyl-2-(ethylamino)cyclohexane) (3-MeO-PCE)
METHAQUALONE DERIVATIVES	- Methylmethaqualone - Mebroqualone	
SYNTHETIC CANNABINOID DERIVATIVES (SPICE DRUGS)	- AM-694 - CP 47,497 - Cannabicyclohexanol - CP 55,940 - HU-210 - JWH-018 - JWH-073 - JWH-200 - JWH-250 - THC-O-acetate	
GHB AND DERIVATIVES	- Gammahydroxybutyrate (GHB, liquid ecstasy, gammahydroxybutyric acid, hydroxybutyrate, sodium oxybate)* - Gamma-butyrolactone (GBL) - 1,4-butanediol (BD) - Gammahydroxyvaleric acid	

Source: Drawn up by the Clinical Committee of the Government Delegation for the National Plan on Drugs.
* These substances are marketed in some countries although they are subject to different types of regulatory restrictions.

2.3. Ways of presentation. Ways of use. Ways of administration

The ways of presentation and use of this group of substances, the ways of administration used in each case and the combined use with other drugs (polydrug use) are described in the sections corresponding to each subgroup of substances considered in this report.

Nevertheless, it must be taken into account that the little scientific information on some substances included under this denomination (and even on some complete groups of substances) is an obstacle in preventing the abuse of emerging drugs. Most of the available research focuses on aspects regarding their chemical production and, only ocassionally tackle the effects of these substances on animal tissues and cells. The evidence of their effects on human beings comes mainly from the self-consumption experiences told by users themselves in writing or on video in some particular Internet forums or on websites such as youtube or in books[8,9].

2.4. Early Warning System (EWS)

The Early Warning System is an information exchange mechanism devised by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol in collaboration with the EU Member States at the end of 1997[10]. At present, over 110 substances have already been identified and notified to the EMCDDA and Europol by the Member States.

In 2009 the presence of twenty-four new psychotropic substances was notified to the EMCDDA and Europol through the EU Early Warning System. Nine of them were synthetic cannabinoids from, at least, four different chemical groups. At that time, this figure was, not only the highest number of substances ever notified in a single year, but also, twice the number of substances notified in 2008 (thirteen new substances). All the new substances were synthetic and three of them had medicinal effects[5].

In 2010, besides the notification of the 7 new substances belonging to the "traditional" chemical categories of psychoactive compounds (5

phenethylamines, 1 tryptamine 1 piperazine), 15 synthetic cathinones and 11 new synthetic cannabinoids were identified[11], in addition to a plant-based substance, a synthetic cocaine derivative and a ketamine derivative.

The European Union Council Decision 2005/387/JHA, of 10th May 2005, on the information exchange, risk-assessment and control of new psychoactive substances replaces the Joint Action of 16th June 1997 concerning the information exchange, risk assessment and the control of new synthetic drugs.

Decision 2005/387/JHA keeps the three consecutive stages of the Joint Action:

- An Early Warning System to exchange information on new psychotropic substances quickly.

- An assessment, by a scientific committee, on the risks to health and society linked to consumption, production and trafficking of a new psychotropic substance.

- A procedure to apply new control measures to the new psychotropic substance.

This legal tool applies to any new synthetic or narcotic drug notified to the EMCDDA and Europol, and sets the procedure, schedule and deadlines for each stage. The REITOX network, made up of the National Focal Points (EU Member States) and the EMCDDA, and the EMCDDA's Scientific Committee play a vital role in this procedure.

When a new psychoactive substance is first detected, the EU Member States send detailed information on its production, trafficking and consumption (including additional information on its potential medical use) to the European Police Office (Europol) in The Hague as well as to the EMCDDA in Lisbon, through the Europol National Units and the REITOX National Focal Points, taking into account the respective fields of action of these bodies.

Europol and the EMCDDA gather the relevant information and communicate it immediately to each other and send it to the Europol

National Units and the REITOX network representatives in the Member States, to the European Commission and to the European Medicines Agency (EMA) in London.

If Europol and the EMCDDA consider that the information notified by the Member States on some new substance is worth further analysis, this information is presented in a joint report by Europol and the EMCDDA and sent to the EU Council, the European Commission and the EMA.

Although the European Union Council Decision 2005/387/JHA of 10th May 2005 on the information exchange, risk-assessment and control of new psychoactive substances has turned out to be a very useful tool to tackle new substances in the EU, its use has had to face a number of limitations, particularly regarding the impossibility of tackling several substances at the same time, the excessive length of the process of assessment and decision and the lack of parlamentary options other than penal options. Consequently, the Commission is planning to modify the Decision in the second half of 2011 and for this purpose, it will request the participation of the Parliament, the Council and the Member States.

Joint report

Including:

- A chemical and physical description of the new substance and the name by which it is known.
- Frequency, circumstances and/or amount of the new substance.
- Means and methods of production of the new substance and involvement of the organized crime in the production and trafficking of this substance.
- Health and social risks linked to the new psychoactive substance, including the users' profile.
- Whether the new substance is currently under analysis or it has already been assessed by the EU system.

- Whether it is necessary to implement control measures (at the national level) for the new psychoactive substances in the different Member States.

- Chemical precursors, ways and purpose of the expected use of the new substance and any other new use.

The EMA sends information to Europol and the EMCDDA on whether the new psychoative substance has got an authorization to be marketed in the EU or in any of its Member States, it is waiting to receive this authorization or it had got this authorization but it was suspended at any time in the past.

The EMCDDA, together with Europol, published some guidelines: "Early warning system on new psychoactive substances – operating guidelines" (www.emcdda.europa.eu/html.cfm/index52448EN.html) in order to help the Member States implement the Early Warning System and give transparency to the whole process. These guidelines have been drawn up again in order to include the purposes and deadlines set by Council Decision 2005/387/JHA, replacing the former EMCDDA guidelines of 2002.

Risk assessment report

On the basis of the joint report by the EMCDDA and Europol, the EU Council, at the request of most of its members, can ask for a risk assessment report, including both social and health risks caused by the production, use or trafficking of a new psychoactive substance, as well as the involvement of the organized crime and potential consequences of the implementation of control measures on the new substance assessed.

In order to draw up this report, the EMCDDA calls a special meeting of its Scientific Committee. This Scientific Committee can request the additional participation of five experts (from the Member States) on scientific fields with no representation (or inadequately represented) in the Scientific Committee and whose contribution is needed to carry out an appropriate assessment of potential risks. The European Commission, Europol and the EMA take part in this meeting too.

Risk assessment takes into account all the aspects that, according to the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, guarantee the international control on a particular substance. The "Risk assessment of new psychoactive substances – operating guidelines" (www.emcdda.europa.eu/html.cfm/index100978EN.html), published by the EMCDDA in August 1999, are subject to continuous review and amendment, in line with the new objectives, experience and current knowledge on the subject.

Aftewards, a risk assessment report is drawn up including a scientific analysis and a law-implementation analysis and containing all the opinions given by the members of the Scientific Committee. This report is sent to the European Commission and to the EU Council.

So far, and under the terms of the Joint Action on new synthetic drugs of 1997, 11 risk assessment reports have been carried out regarding the following substances: MBDB, 4-MTA, GHB, ketamine, PMMA, 2C-I, 2C-T2, 2C-T-7, TMA-2, BZP and mephedrone. The last risk assessment report, drawn up in July 2010, was on mephedrone and resulted in the Decision of the EU Council of 2nd December 2010 (2010/759/EU) whereby control measures are implemented on 4-methylmethcathinone (mephedrone) (OJEU 8/12/2010).

Control measures

Once the risk assessment report has been drawn up, the EU Council can decide, by qualified majority or at the request of the European Commission, whether to implement or not control measures on the new psychoactive substance.

If the European Commission does not consider it to be necessary to implement control measures on the new substance, it must send a report to the EU Council explaining its point of view. In these cases, one or more Member States can present their initiatives to the EU Council.

If the EU Council decides to implement control measures to a new psychoactive substance, the Member States must take the necessary actions, in accordance with the national legislation, so that, within one year after the EU Council Decision is adopted, control measures and

penal punishment are implemented to the new psychotropic substance according to the Convention on Psychotropic Substances of 1971 or the Single Convention on Narcotic Drugs of 1961.

Until the end of 2010, control measures have been implemented to the following substances according to the procedure explained above:

- **4-MTA**. Council Decision 1999/615/JHA of **13th September 1999**.

- **PMMA**. Council Decision 2002/188/JHA of **28th February 2002**.

- **2C-I, 2C-T-2, 2c-T-7 and TMA-2**. Council Decision 2003/847/JHA of **27th November 2003**.

- **BZP**. Council Decision 2008/206/JHA of **3rd March 2008**.

- **Mephedrone**. Council Decision 2010/759/EU of **2nd December 2010.** Until then mephedrone was illegal in fifteen European countries only (Austria, Belgium, Denmark, Estonia, France, Germany, Ireland, Italy, Latvia, Luxembourg, Malta, Poland, Romania, Sweden and the United Kingdom) and it was legal in 12 countries, Spain included.

  The scientific assessment, carried out by the EMCDDA, on the risks associated to the consumption of mephedrone has proven that this substance can cause serious health problems and addiction. Moreover, it has no therapeutic value or any other legal use. The member countries have one year (from 2nd December 2010) to take the necessary measures, in accordance with their national laws, to implement control measures on this substance.

Lastly, in 2000 the EMCDDA Scientific Committee assessed the risks associated to the use of GHB (www.emcdda.europa.eu/html.cfm/index33345EN.html). As a result of this assessment, the GHB was added to the Schedule IV of the Convention on Psychotropic Substances of 1971.

European Legal Drug Database (ELDD)

The ELDD includes a review of the different legal classifications of substances as well as a complete list of the substances controlled by the EU Member States and Norway.

This database contains:

- Legal texts in their original formats to enable researchers and analysts to look up the original data sources directly.

- Profile of each EU Member State, whose data have been gathered and sent by the REITOX National Focal Points and the texts of the national laws and regulations.

- Detailed legal reports and publications on several relevant aspects regarding the legal situation of drugs in the EU, as well as legislation regulating this subject in the different Member States.

- Short thematic documents providing an overview on the legal position of the EU Member States regarding illegal drugs.

- News and documents enabling users to keep updated on new events related to this subject.

III. Current situation

3.1. International situation: prevalence of use, trafficking and seizures

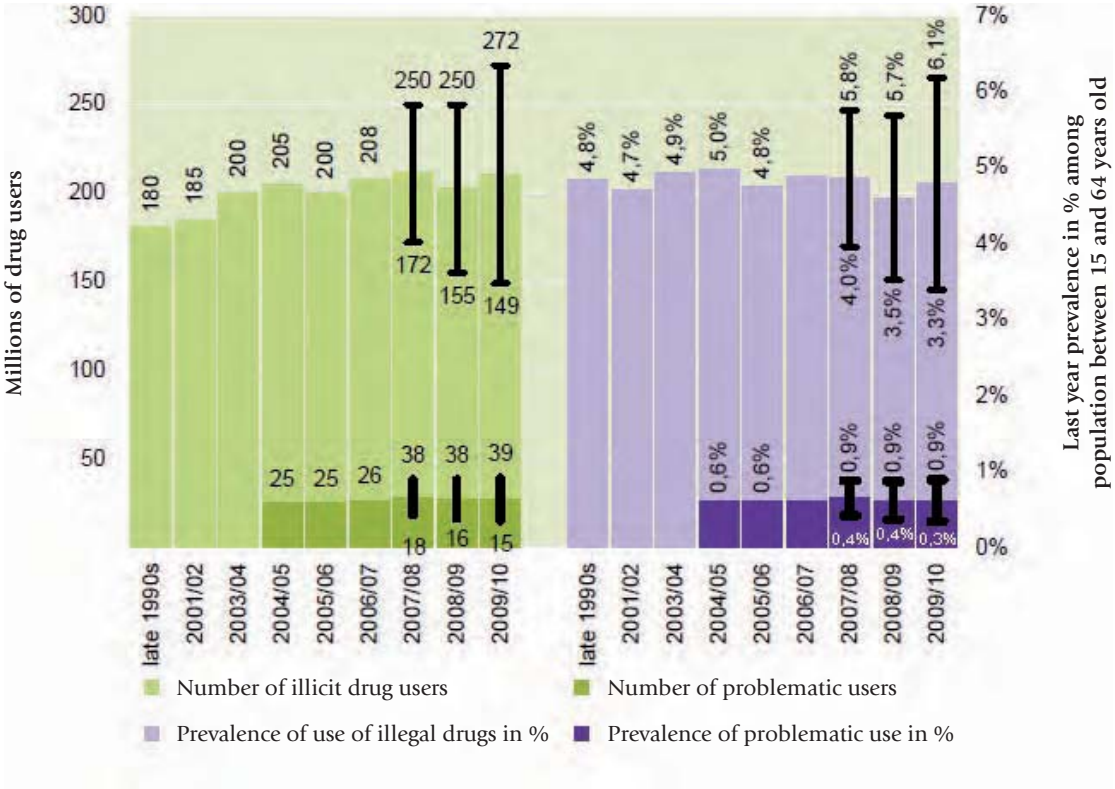
3.1.1. Situation around the world

The *World Drug Report 2011* of the United Nations Office on Drugs and Crime (UNODC)[12] estimates that in 2009 between 149 and 272 million people between 15 and 64 years old around the world (3.3% to 6.1% in this group of population) used illegal drugs during the last year and half of them did it during the last month (Figure 2). Between 15 and 39 millions can be considered to be problematic users (they use illicit drugs regularly and can be considered to be drug addicts or they inject themselves with drugs); this figure remains stable.

Cannabis continues to be the most used illegal substance around the world. In 2009 between 125 and 203 million people between 15 and 64 years old (2.8%-4.5% in this group of population) had used cannabis during the last year. In terms of yearly prevalence, cannabis is followed by amphetamine-type stimulants (mainly metamphetamine, amphetamine and ecstasy) with prevalence between 0.3% and 1.3%, opioids (including opium, heroin and opioids on prescription) with 0.5%-0.8% and cocaine used by 0.3%-0.5% of the world population in this group of age (Figure 3).

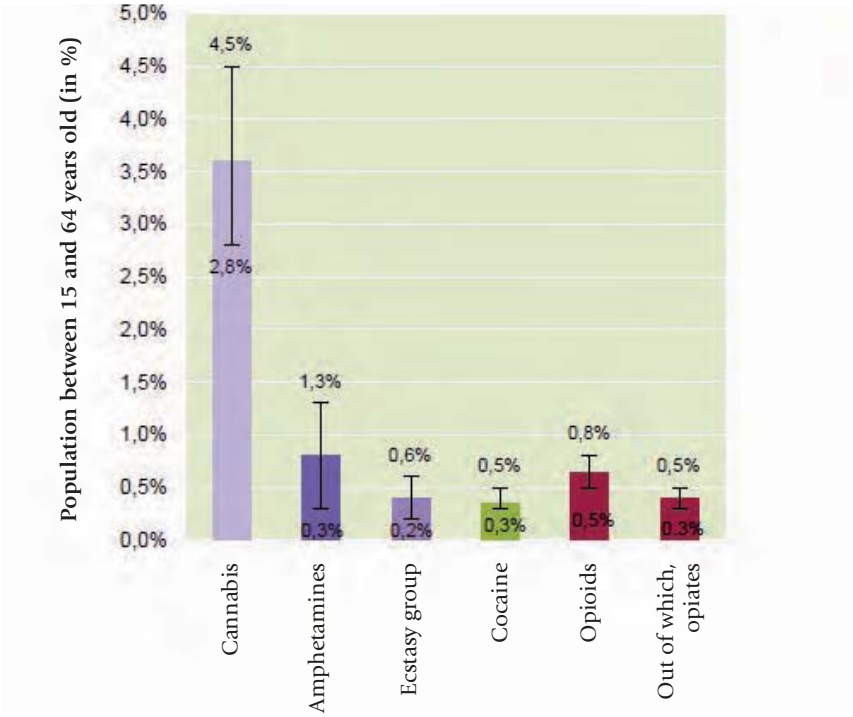
The total number of users of illicit drugs has increased since the end of the 90s but, at present, most of the experts agree that the use of drugs, such as cannabis, amphetamines, ecstasy, cocaine and opioids, heroin included, has stabilized in 2009, unlike the increasing trend of the new psychoactive substances.

Figure 2. Yearly prevalence and number of users of illegal drugs around the world, between 1990 and 2010. Worldwide data in population between 15 and 64 years old.



Source: *World Drug Report 2011* of the United Nations Office on Drugs and Crime (UNODC)[12].

Figure 3. Yearly prevalence of worldwide drug use, according to the type of illegal drug in 2009 - 2010. Worldwide data in population between 15 and 64 years old.



Source: *World Drug Report 2011* of the United Nations Office on Drugs and Crime (UNODC)[12].

Regarding its production, the cannabis herb (marihuana) keeps a stable trend and it has spread all over the world, mainly in America and Africa, whereas the production of cannabis resin (hashish) is still concentrated in Morocco and Afghanistan. The area used to cultivate cocaine and its potential production decreased in 2010. There has been a slight increase in the number of hectares used to cultivate poppy, but the world production of opium decreased in 2010 because of a disease in the Afghan poppies. The total production of amphetamine-type stimulants all over the world has spread and metamphetamine is the most produced one at present.

Trafficking flows vary according to the type of drug. The most seized type, the cannabis herb, is usually locally produced, therefore its international trafficking is limited. Cocaine and heroin are usually trafficked within a region or between different regions, and many of them are consumed far away from the countries of cultivation and

production. Most of the amphetamine-type stimulants are produced in the region where they are used, but precursors are trafficked from one region to the other.

The number of seizures has increased in the last decade, doubling in terms of cocaine, heroin and cannabis and over tripling in terms of amphetamine-type stimulants.

Concern about the "new drugs"

The *World Drug Report 2010* of the United Nations Office on Drugs and Crime (UNODC)[12] warned about the use of new drugs and the emergence of new markets. These substances imply new challenges since they appear and develop faster than the necessary regulations and the relevant authorities have very little time to adjust to the new reality. Moreover, a dynamic marketing and short trafficking itineraries make it easier for producers to market the new products and operate new markets.

World Drug Report 2011 of the United Nations Office on Drugs and Crime (UNODC)[12] focuses on the emergence, during the last few years, of new synthetic compounds in the illicit drugs market whose consumption is increasingly higher. Many of these substances are marketed as legal highs (i.e. substances whose use and marketing is not forbidden or controlled), offered as legal substitutes of classical drugs, with similar effects, not subject to international regulations, although they undergo different types of controls depending on the country.

A number of factors account for the fact that these substances are increasingly supplying the illicit drugs market: (a) the possibility of using chemical products and precursors not subject to regulation. (b) the substances themselves also escape from the international control. (c) the substances that they replace are less available (d) user satisfaction (e) they are easily accessible on the Internet and specialized establishments.

Below you will find some data on the "new drugs", although the information available is limited.

Amphetamine-type stimulants (ATS)

They can be divided into two main categories: amphetamines (amphetamine and metamphetamine mainly) and ecstasy (MDMA and similar stimulants).

The worldwide use prevalence during the last year among population between 15 and 64 years old stands between 0.3% and 1.3% (14 and 57 millions) for amphetamines and between 0.2% and 0.6% (11 and 28 millions) for ecstasy.

The most used type of substance varies depending on the region and within the same region. Amphetamines prevail in Africa, America and Asia whereas ecstasy prevails in Europe and Oceania and in North America there is no big difference between both groups. In eastern and southeastern Asia the ATS markets spread last year and some experts consider that metamphetamine is one of the three most used illicit drugs in several countries of Asia, such as China, Japan or Indonesia.

The worldwide use of ATS remained stable in 2009. According to the experts, the use of substances belonging to the group of amphetamines remained stable or increased and the use of substances belonging to the group of ecstasy remained stable (although it decreased in Asia).

Metamphetamine is the most produced ATS all over the world. The production of amphetamine and ecstasy is smaller since it entails a more specialized process. Southern Asia has become one of the main regions in obtaining ephedrine and pseudoephedrine for the illicit production of metamphetamine. India is one of the main producers of precursors in the world and attempts to produce these stimulants have also been reported in Sri Lanka. Bangladesh has an increasingly important chemical industry.

Around 10,600 ATS-related laboratories were dismantled in 2009. Most of them were used to produce metamphetamine and were located in the United States.

ATS seizures increased considerably all over the world in 2009 and slightly exceeded the level reached in 2007. This increase was mainly due to metamphetamine seizures, which increased by over 40%, up to 31

tons. Amphetamine seizures increased by around 10%, up to 33 tons, and ecstasy seizures decreased slightly (5.4 tons) when comparing to the already low levels of 2008. Amphetamine, metamphetamine and ecstasy have been regularly seized in southern Asia during the last five years.

Africa is a cause for concern regarding ATS trafficking. Metamphetamine trafficking from Africa was first reported at the end of 2008. Western Africa, in particular, is becoming increasingly important as a new point of origin of metamphetamine for the illicit markets of eastern Asia. "Couriers" often cross Europe, western Asia or eastern Africa to reach those markets.

Mephedrone

Mephedrone has recently emerged in the market and it is used as non-illegal substitute for amphetamines or cocaine. Its use is increasingly frequent in Europe, North America and Australia.

It emerged in the illegal market in 2007 and it started being controlled in the European Union in December 2010. It is still marketed in the illegal market both in Europe and in other developed countries, mainly the United States and Australia.

Piperazines

Its stimulating effects make some of its derivatives, such as BZP or TFMPP, be sold as ecstasy in order to mitigate the shortage of MDMA.

Ketamine

It is not subject to international control and it is often sold as an alternative to ecstasy. This substance is very popular in eastern and southern Asia. Most of it is produced and seized in this region. Seizures have tripled during the period 2005-2009.

Spice

The cannabis market has diversified by introducing synthetic cannabinoids, with similar effects to cannabis. They have been detected in smoked herb mixtures since 2008. They are usually plant-based preparations to which one or more synthetic cannabinoids are added. Due to the fact that they do not contain internationally regulated products, they are sold in the market as legal alternatives to cannabis. As a reaction to this, some countries have implemented control measures on *spice* and other similar products in order to try to curb their spread.

3.1.2. Situation in Europe

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in their *2010 Annual report on the state of the drugs problem in Europe*[13], cannabis is still the most used drug in Europe, where 23 million people (6.8%) between 15 and 64 years old have used it during the last year. They account for 18% of the total number of cannabis users around the world.

Cannabis is followed by cocaine with a prevalence of use of 4 million during the last year (1.3% of the population in this group of age). Ecstasy and amphetamines have been used by 2.5 million (0.8%) and 2 million (0.6%) people respectively, taking into account the use among the European population between 15 and 64 years old during last year. Regarding the use of heroin, there are an estimated number of 1.2-1.5 million problematic heroin users in Europe.

Although it is difficult to set trends at the European level, due to the differences among countries, the cannabis use seems to have stabilized or even decreased. The figures of cocaine use vary a lot depending on the country, with higher figures in western and southern European countries. The use of heroin has been traditionally associated to health and social problems since the 70s and it is still today the main cause of drug-use-related morbility/mortality. In some countries its use may have increased as compared to the decreasing trend prevailing so far. With regard to amphetamines and ecstasy, after a remarkable increase in the 90s, their use has stabilized or even decreased, although this general trend does not apply to some countries where their use has recently increased.

Drug production in Europe is mainly related to cannabis, amphetamines and ecstasy. The cultivation of cannabis in closed areas is stepping up its production. The worldwide production of amphetamine is still concentrated in Europe (80% of laboratories), mainly in the Netherlands, Poland and Belgium. The Netherlands and Belgium are also the main producers of ecstasy in Europe. The production of metamphetamine concentrates in the Czech Republic. Domestic production of opium has been detected in Russia and Ukraine.

Regarding drug trafficking, most of the seizures in Europe involve cannabis coming from Morocco. Cocaine is usually marketed by sea, although seizures by air are more frequent. In 2009 around 40% of worldwide heroin seizures took place in Europe.

Concern about "new drugs"

The EMCDDA in their *2010 Annual report on the state of the drugs problem in Europe*[13], shows the importance of the "new drugs".

The world of new psychoactive substances is dynamic and changing and may have significant consequences in terms of public health, although they usually emerge in limited social groups or particular places.

The availability of objective and updated information entails a big challenge from a practical and methodological point of view, but it is vital to be able to implement appropriate policies and to give the necessary answers.

Many non-regulated synthetic compounds have emerged in Europe in the last few years. New plant-based products have also emerged during the period 2008-2010. These products are smoked and contain synthetic cannabinoids. The use of synthetic cathinones has also increased.

Notification of new substances

As already explained in the previous chapter, the EU Early Warning System-EWS[10] was set up in 1997. Besides several European countries, the European Commission, the EMCDDA, Europol and the European Medicines Agency collaborate with it.

Over 110 substances have been notified since it was set up. The substances notified to the EU Early Warning System can be checked in detail in the annual reports published jointly by the EMCDDA and Europol[14].

Below you will find the description of some of the data available on some of these substances at the European level. Please note that the information is very limited, sometimes referring to some specific studies only.

Amphetamine-type stimulants (ATS)

As already discussed, the ATS can be divided into two major groups: amphetamines and ecstasy.

An estimated number of 12 million Europeans between 15 and 64 years old have used amphetamines sometime (3.7% in this group of population) and 2 million (0.6%) did it last year. 11 million Europeans in this group of age (3.3%) have used ecstasy sometime in their lives and 2.5 millions (0.8%) did it last year.

The analysis of the trend of use of amphetamines and ecstasy in Europe shows some stabilization or even a decrease all over the world, although there have been some recent increases in some countries. The use of metamphetamine, which has increased in some places around the globe, remains low in Europe, although its use has spread from Slovakia and the Czech Republic to some countries in northern Europe (Latvia, Norway, Sweden and, to a lesser extent, Finland).

In general terms, in most western and southern European countries the problematic use of amphetamines only accounts for a small part of the drugs problem[15]. Despite this, it is necessary to take into consideration that, in some countries, such as the Czech Republic, the use of amphetamine or metamphetamine, generally parenterally, accounts for a significant percentage of the total number of problematic drugs users.

According to the International Narcotics Control Board more than one third of the amphetamine seized at the global level was seized in western and central Europe. This proves the vital role of this region as producer and user of amphetamines[16]. In Europe the number of metamphetamine

seizures has been gradually increasing since 2003, reaching the highest number in 2007, followed by a slight decrease in 2008. The number of ecstasy seizures has slightly decreased, after the stabilization seen from 2003 to 2006.

Cathinones

The Early Warning System (EWS)[10] has detected a significant increase in the use of synthetic cathinones in the last few years.

Mephedrone first emerged in Europe in 2007 and its popularity increased among young users, which led to a specific demand of this substance. Moreover, it could be easily procured on the Internet, where it was sold as a legal alternative to cocaine or ecstasy. Great amounts of mephedrone were seized in Germany, the Netherlands, Sweden and the United Kingdom in 2009.

In 2009 the British magazine Mixmag[17], specialized in disco music, carried out an Internet survey to 2,295 people that used to go to night clubs in the United Kingdom. Among the results, we can highlight the fact that mephedrone was the forth most used drug (after cannabis, ecstasy and cocaine) and the most used "legal" psychotropic substance. Lifetime, last year and last month prevalences of use stood at 41.7%, 37.3% and 33.6% respectively[13].

The use of khat[18] in the European Union concentrates among the immigrants coming from the Horn of Africa. Although sometimes it is possible to obtain the plant through the Internet trafficking of psychotropic plants, which is expanding, the spread and use outside these communities of immigrants is extremely limited.

Research has been carried out on the use of khat in Denmark, Germany, Spain, Italy, Sweden, the United Kingdom and Norway; and its use among the Somali and Yemeni communities in the United Kingdom has been throughly analysed. Research carried out in Europe does not provide with a solid basis to determine the prevalence rates, but provides with some overview on the use patterns. Generally speaking, studies show relatively high use levels (34-67%), and up to 10% of usual users, most of whom meet some of the addiction criteria.

The lack of knowledge of real use prevalence of this substance is still significant and we do not know much about its social or health consequences. There is some evidence of the existence of "khat tourism": for example, Somali people coming from Scandinavia and tourists coming from the Middle East that use khat in London. The data provided by research also show an increasing generational gap regarding use patterns. Most of usual users of khat got the habit before arriving in Europe. The use of khat is less spread among second-generation immigrants.

Piperazines

Obtaining and interpreting data on piperazine seizures is complicated because there are different piperazine mixtures, alone or combined with other drugs, such as amphetamine and MDMA. Besides, laboratories do not always have the necessary resources to identify all the components, particularly if they are non-regulated substances.

The availability of BZP seems to have decreased after the EU Council decided to implement control measures all over the EU in 2008. Nevertheless, some Member States keep on informing of BZP seizures. In 2009, mCPP was still the most available "new synthetic drug" in the ecstasy illegal market, both alone and combined with MDMA.

In Europe, the Early Warning System (EWS)[10] reveals that the proportion of ecstasy pills with mCPP (or piperazines in general) increased significantly in the first semester of 2009, probably exceeding the number of ecstasy pills containing MDMA.

The Drugs Information and Follow-up System of the Netherlands, which receives samples sent by users for their analysis, observed that the number of these samples doubled as compared to previous years, probably due to the increasing concern of users about the negative effects of piperazines.

These changes show an increasingly complex ecstasy market that may be affected by the fluctuating availability of the chemical precursor of MDMA, PMK (piperonyl methyl ketone).

Ketamine

Its prevalence of use is low among the general population, but high prevalence is observed in certain groups, contexts or geographical areas (particularly in India and China).

Among people going to night clubs, the prevalence of use in the last month stands at 0.6%, according to 363 surveyed people in the Czech Republic in 2008, and at 32.4% according to the Mixmag survey carried out among 2,295 people in the United Kingdom in 2009[17].

GHB (Gamma hydroxybutyrate) / GBL (Gamma Butyrolactone)

Just like with ketamine, the prevalence of use of GHB is low among the general population, but its use is frequent in some particular contexts.

The results of the Mixmag survey show a prevalence of use of 1.7% for GHB and 1.6% for GBL[17] in the last month. Another survey carried out at night clubs in Amsterdam in 2003 and 2008 (646 people surveyed) showed a slight increase in the prevalence of use of GHB in the last month, which had increased from 4.2% to 4.7%. A survey carried out among 363 people going to night clubs in the Czech Republic in 2008 showed a prevalence of use of GHB of 0.3% in the last month.

In London a survey carried out among people going to night clubs that had needed medical assistance inside the clubs concluded that up to two thirds of the cases were related to the use of GHB/ GBL.

A survey regularly carried out among 15-16 year-old school students in Frankfurt concluded that the number of students that had been offered GHB had increased from 1% in 2002 to 5% in 2008.

Spice and synthetic cannabinoids

Monitoring these products is complicated. On the one hand, there is a wide variaty of new cannabinoids that are added to products produced from herbs and their chemical composition is not totally known. On the

other hand, no significant seizures of spice-type products have been notified and no reports on related criminal activities have been published.

Spice started to be sold through the Internet and in specialized shops as a herb mixture to be smoked. In 2008 some forensic chemists identified some synthetic additives that were psychoactive substances among its components. During 2009 the "*spice* phenomenon" kept on getting significant attention, the names and brand diversified and the psychoactive compounds added were also modified as a reaction to the new control measures. In 2009 the Early Warning System (EWS)[10] identified nine new synthetic cannabinoids.

A survey was carried out among 1,463 students between 15 and 18 years old in Frankfurt. The results showed that around 6% of them had used *spice* sometime in their lives and 3% had used it in the last month. These figures may be influenced by the attention paid to spice by the media when the survey was carried out, since only 1% of the students surveyed admitted to have used it five or more times. Almost two thirds of those who had used s*pice* some time in their lives admitted to have used cannabis in the last month.

Sale of new substances on the Internet

Internet is revolutionizing markets and individual and group relationships in many fields and obviously it also has an impact on drugs, and particularly on new substances.

Although new substances can be purchased in specialized shops (smartshops, headshops, etc.), a usual way of buying them is through online shops. According to the Mixmag survey, 92% buy drugs on websites, 95% through friends, 78% in shops, 67% in festivals and 51% through dealers[13].

The Early Warning System (EWS)[10] monitors the sale of new psychoactive substances through the Internet since 2006. The data gathered through the years, although they are not directly comparable since some methodological changes have been introduced in order to improve quality and coverage, provide some interesting information.

An Internet survey on "legal" psychotropic substances was carried out in 2009. The United Kingdom, followed by Germany and the Netherlands, were the countries with the highest number of online shops.

Another survey on online shops (wholesale and retail) was carried out in 2010. It focused on shops accessible to any European Internet user interested in buying legal psychotropic substances, hallucinogenic fungus or GHB/GLB. For each website found the survey obtained information on products for sale, product description, prices, availability in stock, delivery countries, components, medical warnings and users' opinions.

Below you will find some of the main results:

Regarding the location of the online shops, some countries happened to have at least twenty shops (38 in the Netherlands and 20 in the United Kingdom and Germany), some others had at least five shops (Poland, France and Hungary) and finally some countries with fewer shops (Spain, the Czech Republic, Portugal, Slovakia, Italy and Sweden).

Regarding the type of products, 64 shops sold hallucinogenic fungus, together with material for their cultivation, which makes think that their sale may be increasing since in 2006 there were only 39 shops selling them.

The number of online shops selling spice seems to have decreased since 55 shops were identified in 2009 and only 21 in 2010, although the survey coverage was wider. Fifteen of these admitted to sell spice and the location of eight of them was found out (three in the United States and one in Spain, Poland, Portugal, Romania and the United Kingdom). The other six shops selling spice said that they had run out of stock and they may be using that brand name to attract customers.

According to the research, 77 websites were selling mephedrone. Most of them sold this substance only and were located in the United Kingdom. After the classification of mephedrone and other synthetic cathinones as drugs subject to regulation in the United Kingdom since April 2010, most of these websites have ceased to exist.

The research did not find any online shop registered in the EU selling GHB, but GBL was found in four websites, although none of them offered GBL as a drug or suggested that it could be used for psychoactive purposes.

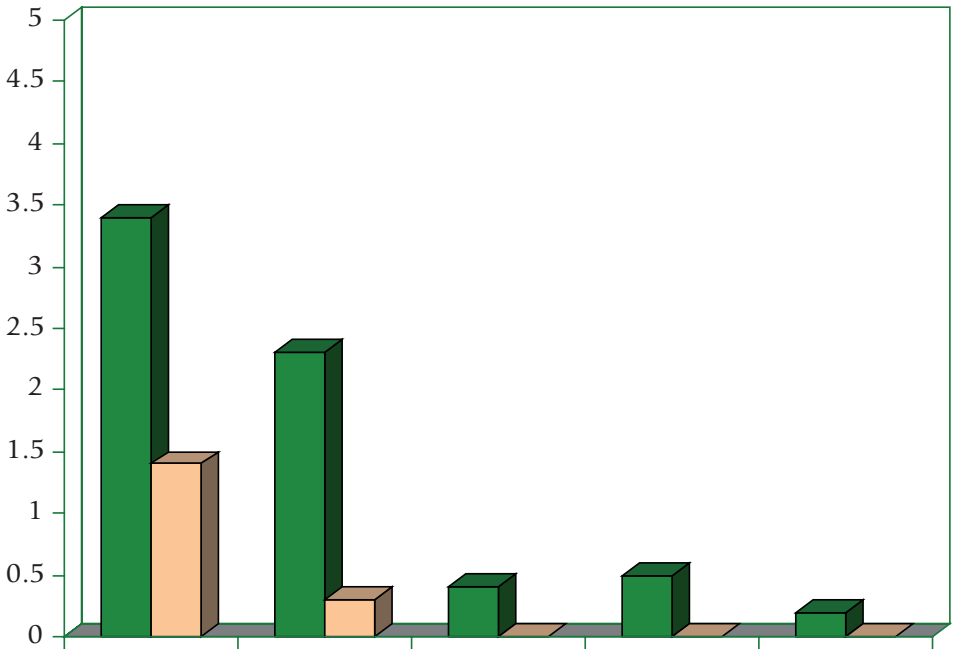
3.2. Current situation in Spain: prevalence of use, trafficking and seizures

Use of ecstasy

In 2009, 4.9% of people between 15 and 64 years old had tried ecstasy sometime, 0.8% had used it in the last year and 0.4% in the last month.

The prevalence of use during the last year was higher among men (1.4%) than among women (0.3%), and among people between 15 and 34 years old (1.8%) than among older people (0.2%). The highest prevalence of use is found in men between 15 and 24 years old (Figure 4)[19].

Figure 4. Prevalence of use of ecstasy during the last 12 months among Spanish population between 15 and 64 years old, according to sex and age (%). Spain 2009.



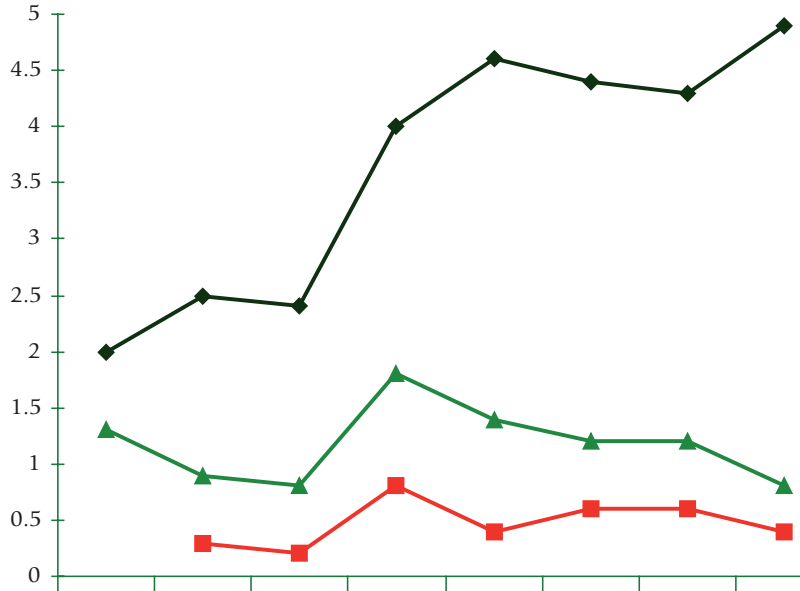
	15-24	25-34	35-44	45-54	55-64
Male	3.4	2.3	0.4	0.5	0.2
Female	1.4	0.3	0	0	0

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. EDADES (household survey on alcohol and drugs in Spain) 2009.

Its use is very sporadic. Actually, the survey EDADES 2009 does not show any daily users. The average age of onset was 20.5 years old, higher than the average age of onset of substances such as tobacco, alcohol, cannabis, hallucinogens or amphetamines[19].

Regarding trends of use, last year and last 30 days use stabilized since 2003, although the level of experimentation with this substance has increased (Figure 5).

Figure 5. Trend of the prevalence of use of ecstasy among Spanish population between 15 and 64 years old (%). Spain, 1995-2009.

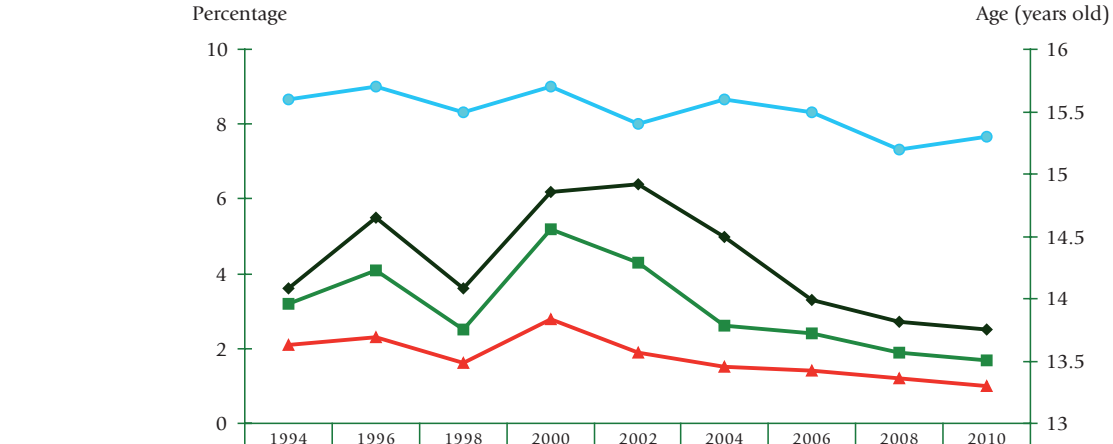


	1995	1997	1999	2001	2003	2005	2007	2009
Lifetime	2	2.5	2.4	4	4.6	4.4	4.3	4.9
Last year	1.3	0.9	0.8	1.8	1.4	1.2	1.2	0.8
Last 30 days		0.3	0.2	0.8	0.4	0.6	0.6	0.4

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. EDADES 1995-2009.

With regard to students between 14 and 18 years old, in 2010 2.5% had used these substances sometime in their lives, 1.7% during the last year and 1.0% during the last month (Figure 6). Just like the rest of illegal drugs, the proportion of users was much higher among men than among women. The percentage of boys that had used ecstasy during the last 30 days stood at 1.3% as compared to 0.6% among girls.

Figure 6. Prevalence of use of ecstasy (percentage) and average age of onset among secondary-school students between 14 and 18 years old. Spain, 1994-2010.



	1994	1996	1998	2000	2002	2004	2006	2008	2010
Lifetime	3.6	5.5	3.6	6.2	6.4	5.0	3.3	2.7	2.5
Last year	3.2	4.1	2.5	5.2	4.3	2.6	2.4	1.9	1.7
Last 30 days	2.1	2.3	1.6	2.8	1.9	1.5	1.4	1.2	1
Age of onset	15.6	15.7	15.5	15.7	15.4	15.6	15.5	15.2	15.3

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. ESTUDES (school survey on drugs) 1994-2010.

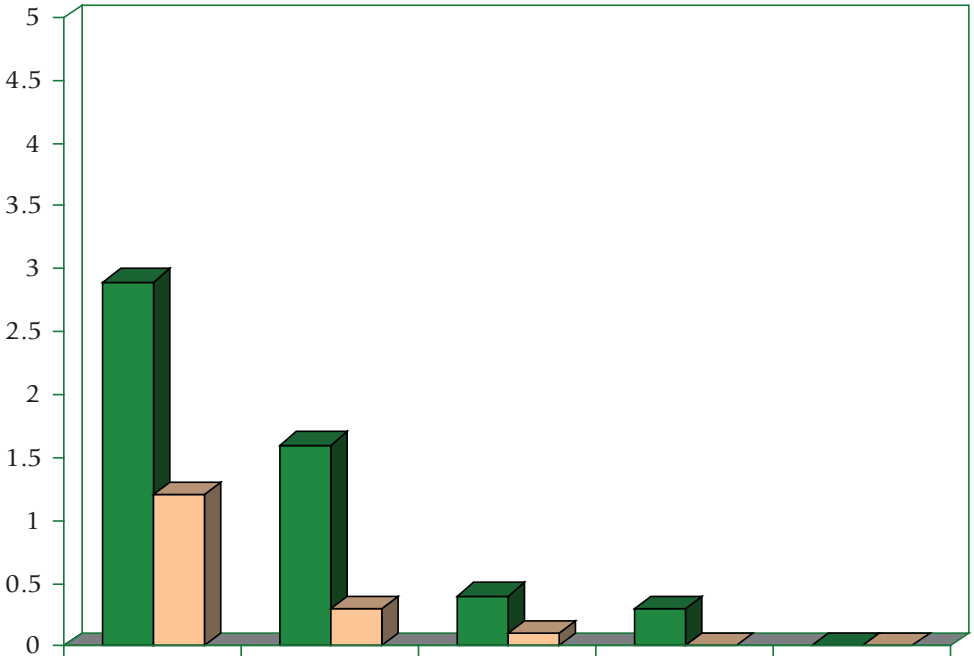
The use increases with age, the highest increase being between 16 and 17 years old. The average age of onset stood at 15.3 years old, with no significant variations as compared to previous years (Figure 6).

In 2010, the prevalence of use of this substance continued the decreasing trend that began in 2000.

Use of amphetamines

In 2009 3.7% of people between 15 and 64 years old had tried amphetamines sometime, 0.6% had used amphetamines during the last year and 0.3% during the last month. Like in previous cases, the use was far more spread among men than among women and in the group between 15 and 34 years old than between 35 and 64 years old (Figure 7)[19].

Figure 7. Prevalence of use of amphetamines during the last 12 months among Spanish population between 15 and 64 years old, according to sex and age (%). Spain 2009.



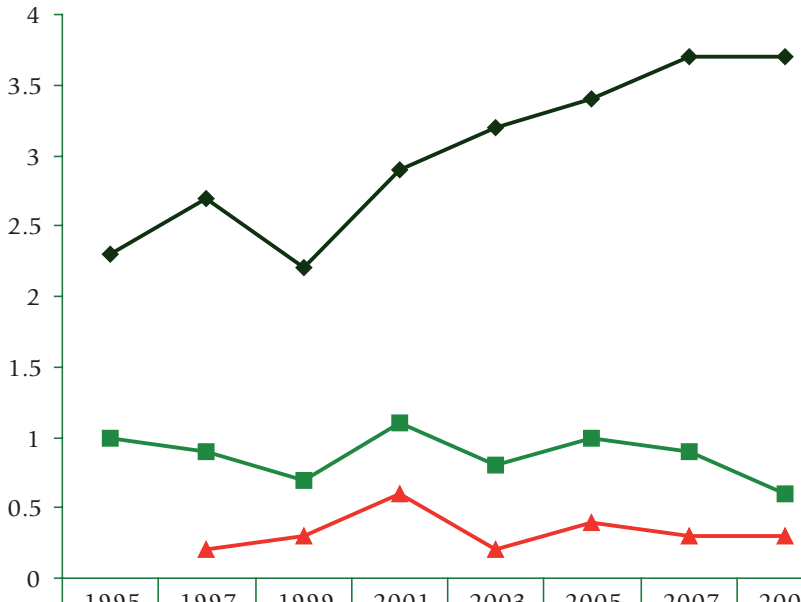
	15-24	25-34	35-44	45-54	55-64
Male	2.9	1.6	0.4	0.3	0
Female	1.2	0.3	0.1	0	0

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. EDADES 2009.

The average age of onset stood at 20.1 years old.

In general terms, usual and recent uses of amphetamines show a relative stabilization since 2005, although, just like with ecstasy, there has been an increase in terms of experimental use (Figure 8)[19].

Figure 8. Trend of the prevalence of use of amphetamines among Spanish population between 15 and 64 years old (%). Spain 1995-2009.



	1995	1997	1999	2001	2003	2005	2007	2009
Lifetime	2.3	2.7	2.2	2.9	3.2	3.4	3.7	3.7
Last year	1	0.9	0.7	1.1	0.8	1	0.9	0.6
Last 30 days		0.2	0.3	0.6	0.2	0.4	0.3	0.3

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. EDADES 2009.

Regarding students between 14 and 18 years old, the spread of the use of amphetamines was similar to that of ecstasy in 2010. 2.6% of the students between 14 and 18 years old had used them sometime in their lives, 1.6% during the last year and 0.9% during the last month. Again their use was higher among men, increased with age and, just like with ecstasy, was sporadic. The higher increase in terms of prevalence of use was between 17 and 18 years old (Table 2).

Table 2. Prevalence of use of speed and amphetamines during the last 12 months among Secondary-school students between 14 and 18 years old (%), according to sex and age. Spain 1994-2010.

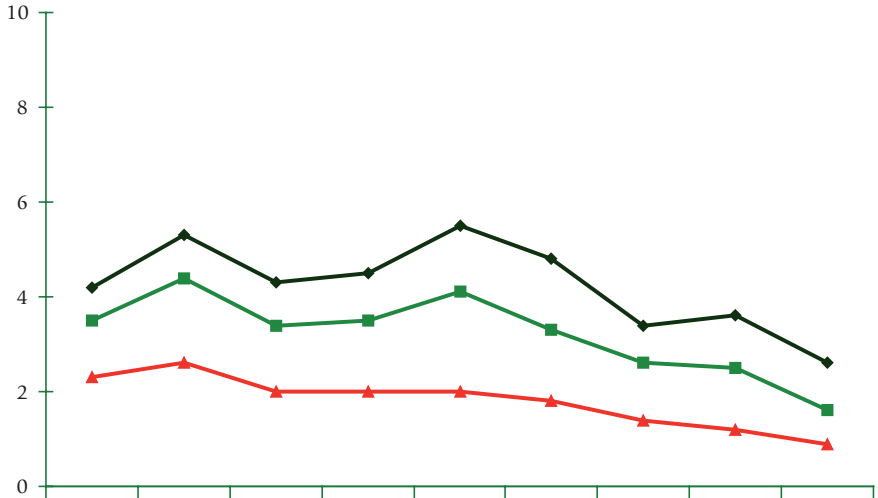
	1994	1996	1998	2000	2002	2004	2006	2008	2010
TOTAL	3.5	4.4	3.4	3.5	4.1	3.3	2.6	2.5	1.6
SEX									
Male	4.4	5.5	4.5	4.6	4.8	4.3	3.3	3.2	2.2
Female	2.5	3.4	2.5	2.4	3.4	2.3	2.0	1.8	1.0
AGE									
14 years old	1.2	1.1	1.7	1.2	1.1	0.5	0.5	0.8	0.6
15 years old	2.2	2.7	2.3	2.4	2.7	1.7	1.7	1.5	1.0
16 years old	4.1	4.6	3.2	3.3	4.0	3.1	2.7	2.6	1.6
17 years old	4.7	6.2	4.7	4.8	5.9	5.8	3.7	4.0	2.4
18 years old	6.6	9.7	7.0	7.6	8.8	7.9	6.8	5.5	3.8

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. ESTUDES (school survey on drugs) 1994-2010.

The age of onset stood at 15.5 years old, being similar for both men and women and remaining relatively stable in the last few years.

Lifetime, last year and last month prevalences of use of amphetamines have showed a decrease in Spain, 2010 registering the lowest figures since 1994 (Figure 9).

Figure 9. Trend of the prevalence of use of amphetamines among Secondary-school students between 14 and 18 years old (%). Spain, 1994-2010.



	1994	1996	1998	2000	2002	2004	2006	2008	2010
Lifetime	4.2	5.3	4.3	4.5	5.5	4.8	3.4	3.6	2.6
Last year	3.5	4.4	3.4	3.5	4.1	3.3	2.6	2.5	1.6
Last 30 days	2.3	2.6	2	2	2	1.8	1.4	1.2	0.9

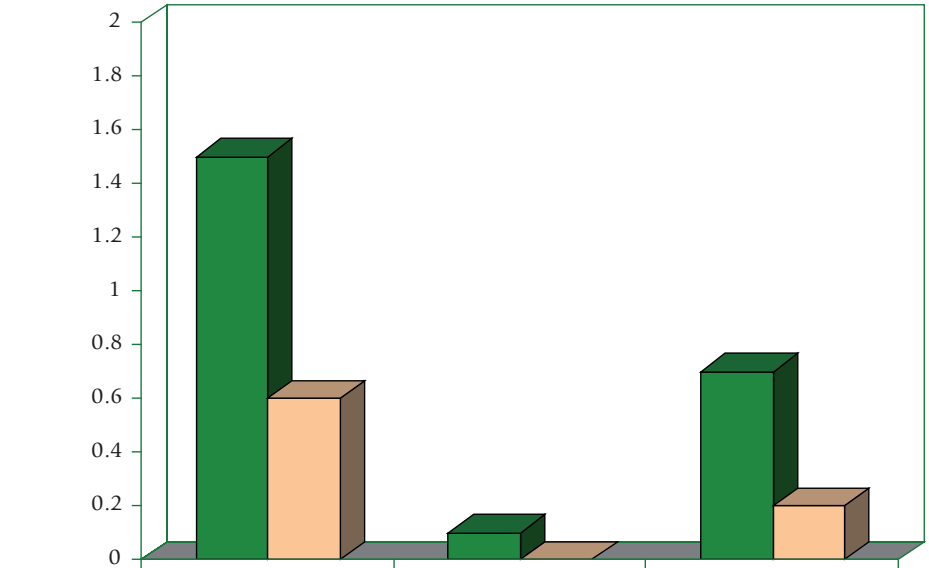
Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. ESTUDES 1994-2010.

Use of hallucinogens

This category includes several types of substances. The following fall under this category: hallucinogens strictly speaking, such as LSD, "acid" and magic mushrooms, and dissociative drugs such as ketamine (special-K, ketolar, imalgene, etc.). Therefore, individual prevalences breakdown by each specific type is not feasible.

In 2009 3.7% of the population between 15 and 64 years old had tried hallucinogens sometime in their lives, 0.5% had used them during the last year and 0.2% during the last month. Just like in previous cases, the prevalence of use during the last 12 months was higher among men (0.7%) than among women (0.2%) and in the group between 15 and 34 years old (1.1%) than in the group between 35 and 64 years old (0.1%). For example, Figure 10 shows that men between 15 and 34 years old account for the highest proportion of hallucinogens users[19].

Figure 10. Prevalence of use of hallucinogens during the last 12 months according to age and sex (%). Spain, 2009. 1994-2010.



	15-34 years old	35-64 years old	15-64 years old
Male	1.5	0.1	0.7
Female	0.6	0	0.2

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. EDADES 2009.

Average age of onset stood at 19.7 years old. The trend of use has remained relatively stable during the last few years (prevalence of use during the last 12 months: 0.6% in 1999 and 0.6% in 2007).

In 2010 3.5% of Secondary-school students had used them sometime in their lives, 2.1% in the last year and 1.0% in the last 30 days. The use was much more spread among boys, with figures doubling those of girls. Just like for the rest of substances, the prevalence of use increased with age. The trend of use is clearly decreasing since 2004.

Emerging drugs module in ESTUDES 2010

The introduction of a specific module about this type of substances for the first time in the National Survey on the Use of Drugs among Secondary-school Students between 14 and 18 years old in Spain (2010) has enabled to get an understanding of the prevalence of use of these

substances as well as the perception of risk and availability that this group of population associates to their use.

The nine substances included in this specific module of emerging drugs are the following: ketamine, spice, piperazines, mephedrone, nexus (2CB), methamphetamine, magic mushroooms, research chemicals and legal highs.

Prevalence of use

3.5% of students between 14 and 18 years old admitted to have used one or more of the drugs mentioned above (included in the group of emerging drugs) sometime in their lives. 2.5% used them sometime during the year before being surveyed and 1.3% in the last month.

Taking into account that we are talking about young people between 14 and 18 years old whose record of use of psychoactive substances should be limited in time, the different time references (sometime, last year, last month) may coincide; therefore, the data included here will refer to the indicator "sometime", unless specified otherwise.

According to sex, 4.7% of boys and 2.4% of girls used these drugs. The data, broken down according to age, showed the highest prevalence of use at 18 years old (6.5% of 18-year-old students used one or more of these substances sometime in their lives), against 5.4% at 17 years old, 3.4% at 16, 2.6% at 15 and 1.6% at 14. These figures are consistent with the usual (in this group of age) higher prevalence of use of almost all drugs as age increases.

As to the continued use of this group of substances, 7 out of 10 students between 14 and 18 years old that admitted to have used some of the emerging drugs sometime in their lives had also used them during the last year (continuity last year/sometime in their lives of 0.72%) and, half of them had also done it during the last month (continuity last month/last year of 0.53%). Generally speaking, one third (continuity last month/sometime in their lives of 0.38%) of students between 14 and 18 years old that had tried one or more of the substances analysed has continued using them, although, as mentioned earlier, it is necessary to take into account that both the age of those surveyed and the relatively recent emergence of these substances in the market favour the

overlapping of the time intervals used in the indicators and has an impact on the values obtained in terms of continuity in the use.

Table 3. Prevalence of use of emerging drugs among secondary-school students during the last year (%). Preliminary data. ESTUDES 2010.

Emerging drugs	Lifetime	Last year	Last month
Ketamine	1.1	0.8	0.4
Spice	1.1	0.8	0.5
Piperazines	0.4	0.3	0.2
Mephedrone	0.4	0.3	0.2
Nexus	0.5	0.3	0.2
Metamphetamine	0.8	0.6	0.4
Magic mushrooms	2.1	1.6	0.7
Research chemicals	0.4	0.3	0.2
Legal highs	0.7	0.6	0.5

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. ESTUDES 2010.

The prevalence of use in the last month shows very low figures, which confirms its sporadic and experimetal character among the students of this group of age.

As shown in Table 3, magic mushrooms, spice and ketamine are the most used substances in all time references. According to sex, there are significant differences ($p<0,001$) in the use of all substances, with higher prevalence among boys, for all substances and time references.

Risk perception

The data referring to the perception of risk associated to the use of each of the substances considered show, as expected, that those surveyed always associate higher risk to usual consumption (once a week or more often) than to sporadic consumption (once a month or less often) for any of the substances considered. Moreover, the figures of ESTUDES 2010 reveal something particularly interesting: between 40 and 50% of those

surveyed admit not to be able to associate a certain level of risk to the use of the substances they are asked about. This shows that they may not know the substance or that they know it but ignore its effects and consequences. This information is key in order to conceive and guide preventive interventions.

Among those able to ascribe a certain level of risk to their use, 85% of those surveyed consider that the usual consumption of any of the new substances may cause quite a lot or a lot of health problems. 70% thinks the same regarding sporadic consumption.

The analysis of the perception of risk depending on whether the person surveyed admits to be a user or not clearly shows that the perception of risk associated to the use of any substance is always lower among users ($p<0,05$). Generally speaking, the people using a certain substance consider its use less dangerous, regardless of whether the consumption is usual or sporadic. Among users ascribing a certain level of risk to their use, 75% consider that usual consumption causes quite a lot or a lot of problems (against 85% among the total group of surveyed people, regardless of whether they are users or not) and only 55% think the same regarding sporadic consumption (against 70% among the total group of surveyed people, regardless of whether they are users or not).

However, it is surprising that a high percentage of users ignore the health problems that the substance they are using may cause. For example, almost one fifth (19.5%) of those having used ketamine are not able to ascribe a certain level of risk to its sporadic use. Around one forth (23.9%) of spice users, more than one third of piperazine users (35.3%), 30.3% of mephedrone users, 28.7% of nexus users, 23.2% of metamphetamine users, 22.6% of magic mushroom users, 28.8% of users of research chemicals and 31.3% of users of legal highs are in a similar situation. There is almost no difference in the perception of risk associated to usual consumption among users.

Perceived availability

As to the difficulty perceived by students between 14 and 18 years old in buying the different substances included in this module (perceived availability), over 50% of those surveyed are not able to establish how easy or difficult it is to get these substances, as expected taking into

account their age and the recent emergence of these substances in the market.

Those that gave their opinion on the greater or smaller availability of these substances stated that nexus, mephedrone and piperazines were the most difficult drugs to get. 69.5% of young people say that it would be difficult or almost impossible for them to get nexus, 69.1% say that it would be difficult or almost impossible to get mephedrone and 68.5% say that it would be difficult or almost impossible to get piperazines. The most accessible substances for this group of age are magic mushrooms (50.3% of those surveyed say that it would be easy or very easy for them to get this substance), followed by ketamine and spice (40.2% of students consider that it would not be very difficult to get ketamine and 39.8% consider that it would not be difficult to get spice).

For all the substances considered, getting them is considered to be easier among users than non users, with significant differences ($p<0,001$).

Among those that use each of the substances considered, piperazines are the most difficult to get according to users (24.5% of piperazine users say that it is difficult for them to get this substance). Magic mushrooms are the easiest substance to get according both to users and non users.

Polydrug use among users of emerging drugs

The data obtained from the survey ESTUDES 2010 enable to get some information on users of emerging drugs regarding the use of other licit and illicit drugs. In general terms, the use of illegal drugs is considerably higher among users of emerging drugs as compared to those that did not use them. 91% of users of emerging drugs used illegal drugs against 41.7% of non users of emerging drugs ($p<0,001$).

Likewise, the prevalence of binge drinking was higher among users of emerging drugs (86.9% of those who used emerging drugs during the last month did binge drinking during the same period, against 66.1% among those that did not use any emerging drug ($p<0,001$)); higher prevalence of getting drunk (92.2% of those who used emerging drugs sometime in their lives got also drunk sometime in their lives, against 57.4% among those who did not use any emerging drug) and higher prevalence of use of alcohol (96.4% of those who used emerging drugs

sometime in their lives had drunk alcohol at least once, as compared to 74.3% of those who had never used emerging drugs).

90.2% of those who had used emerging drugs during the last year drinks alcohol regularly (sometime during the last month), 19.4% used ecstasy during the same period (last year) and 23% may be considered to be a usual user (sometime during the last month) of cocaine (powder). However, only 3.8% of young people between 14 and 18 years old having used new substances sometime in their lives have not used any other illegal substance or alcohol.

Regarding the use of some emerging drugs not subject to legal control (Spice, legal highs, etc.) in order to imitate or replace the effects of illegal drugs, in Spain for example, 70.4% of those having used spice sometime in their lives had also used cannabis during the last month. This figure makes sense since synthetic cannabinoids containing spice cause similar effects to cannabis and their purchase and use are still legal. A survey carried out to 1463 students from 15 to 18 years old in Germany showed a very similar percentage (around 65%) of spice users that also used cannabis regularly (last month).

Therefore, taken into consideration that

- The prevalence of use of the different emerging drugs considered in this module is not extremely high
- The vast majority of those having used one or more of these emerging drugs also use other licit and illicit drugs and that
- Around half of those surveyed do not seem to have much information on this group of substances

We could conclude that in 2011 and in this group of age (between 14 and 18 years old), emerging drugs are not a vital problem in the field of drug abuse in Spain. They are used sporadically and together with more classical drugs more widespread in our country (alcohol, cannabis, cocaine, ecstasy, etc.).

The information obtained from other sources such as websites, forums, chat rooms, etc. shows that these emerging drugs may be more widespread in a group of older drug users with a longer use record that

are looking forward to having new experiences and avoiding the legal controls of classical illegal drugs.

Although information on the prevalence of emerging drugs at the international level has only been available recently (except for the data mentioned here from the survey ESTUDES 2010 in Spain and some studies with a smaller sample, in high-risk groups and contexts already mentioned in this chapter), the European Commission has recently presented the results of a survey on drugs and young people ("Youth attitudes on drugs"), as a continuation to other three similar surveys carried out in 2002, 2004 and 2008[20]. This last edition (2011) has included some questions relating to experiences and attitudes of young people regarding the so-called "new substances".

The sample was made up of 12,000 young people from 15 to 24 years old, coming from the 27 EU Member States. According to the survey, less than 5% of those surveyed admitted to have used "new substances" sometime in their lives. Nevertheless, this figure was higher (around 10-15%) in the United Kingdom, Poland, Latvia and Ireland. However, the figures obtained must be carefully assessed since the category "new substances" includes a wide range of substances depending on the Member State considered, which has a significant impact on the comparability of the data obtained in the different countries.

As to the ways of accessing these substances, around half of the young people surveyed (54%) admitted to have started using them through friends, one third were offered these substances in parties or clubs, 30% purchased them in specialized establishments and only 7% bought them through the Internet.

Admitted to treatment because of use of amphetamines, ecstasy and other stimulants other than cocaine

The indicator "admissions to treatment" is a register gathering individualized data on admissions to outpatient treatment because of abuse or addiction to psychoactive substances all over Spain. It was set up in 1987[21]. This register is part of a wider information subsystem developed in the framework of the National Plan on Drugs in collaboration with the Regional Plans on Drugs that also includes the

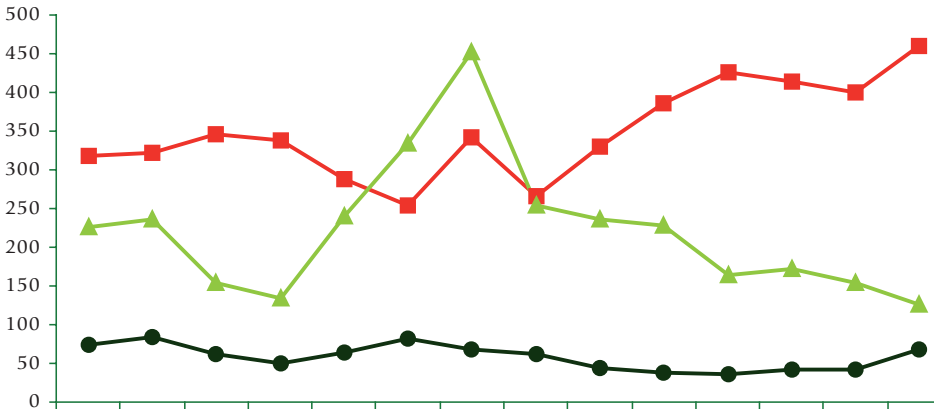
indicator "hospital emergencies related to drugs" and the indicator "mortality because of severe reaction to drugs". This information subsystem was conceived to monitor the development and characteristics of the problematic use of psychoactive drugs.

In 2009, 52,549 admissions to treatment because of abuse or addiction to psychoactive substances were registered in Spain (alcohol and tobacco excluded).

Stimulants other than cocaine (amphetamines, ecstasy and other) accounted for only 1.6% of first admissions in 2009, and for 1.2% of the total number of admissions. If these figures are compared with those obtained for cocaine, heroin and cannabis, we can see that in Spain the impact of these drugs on the specific treatment services is minimal.

Time trend analysis showed a slight increase in the number of amphetamine-related treatments and a decrease in the number of ecstasy-related treatments in 2009. (Figure 11).

Figure 11. Trend of the number of people admitted to treatment because of abuse or addiction to amphetamines, ecstasy and hallucinogens. Spain, 1996-2009.



	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Amphetamines	319	323	347	339	288	255	342	266	330	386	426	415	400	461
Ecstasy	226	237	154	135	240	335	452	254	236	229	165	172	155	127
Hallucinogens	74	85	62	50	64	83	68	63	44	39	37	43	43	69

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. Treatment Indicator 1996-2009.

Mortality because of severe reaction after using psychoactive substances

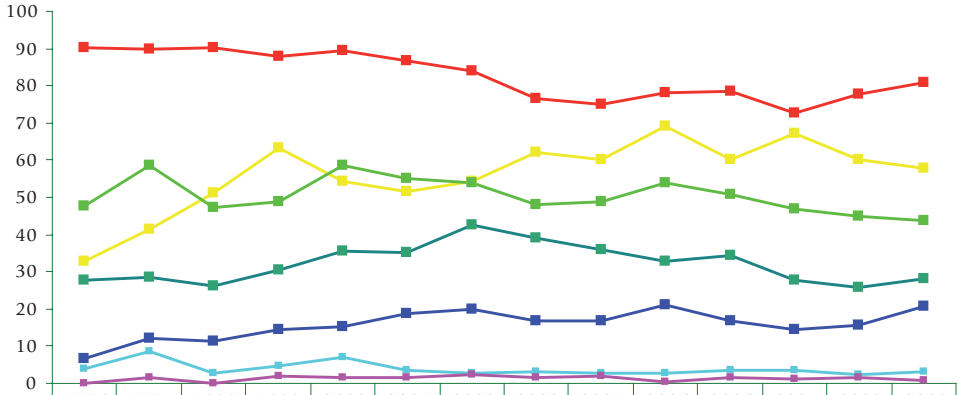
Since 1983, the indicator "mortality" gathers information on those deaths, with judicial intervention, mainly and directly caused by a severe adverse reaction to the non medical and intentional use of psychoactive substances, excluding tobacco and alcohol (only registered when used together with another psychoactive substance, as long as this substance is not benzodiazepine or antidepressant)[22].

Figure 12 shows the trend in the proportion of deaths due to a severe reaction after using psychoactive substances in Spain from 1996 to 2009. The information corresponds to the percentage of deceased people whose toxicological analysis showed each of the substances or metabolites considered. The addition of percentages for each of the years studied is higher than 100 due to the simultaneous identification of several substances or their metabolites in the same toxicological analysis. Polydrug use is the most usual pattern among the deceased because of a severe reaction to psychoactive substances.

In 2009, opioids continue to be the substance identified in the highest number of deceased people (81% of the samples), although cocaine is getting closer (57.8%), with the second position. Although the information obtained in 2009 does not entail any change in the decreasing general trend seen during the last few years regarding opioids, and as compared to 2007, there has been a slight increase (8%) in the presence of this group of substances in toxicological analysis and a 9.2% decrease regarding cocaine; therefore we should keep an eye on these trends over the next few years.

On the third position we find hypnosedatives (43.6%), among which we can highlight benzodiazepines (42.2%), followed by alcohol, cannabis and amphetamines. All of them show a stable trend in the last few years.

Figure 12. Trend of the proportion of deaths due to a severe reaction after using psychoactive substances depending on the type of substance detected in the toxicological analysis. Spain 1996-2009 (%).



	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Opioids	90.4	89.8	90.1	88	89.4	86.8	83.8	76.7	74.9	78.20	78.7	72.8	77.7	81
Cocaine	32.7	41.4	51.2	63.3	54.4	51.7	54.2	62.2	60.1	69.20	60	67	60.2	57.8
Hypnosedatives	47.7	58.6	47.4	48.8	58.5	55.2	54	48	48.7	54.10	50.7	46.9	45.1	43.6
Amphetamines	4	8.6	2.8	4.5	6.9	3.4	2.9	3.1	2.6	2.60	3.6	3.6	2.2	3
Cannabis	6.5	12.2	11.3	14.3	15.2	18.7	20	16.7	16.7	20.90	16.8	14.6	15.6	20.6
MDMA	0.1	1.5	0	1.8	1.6	1.5	2.5	1.6	1.9	0.40	1.7	1.1	1.4	0.9
Alcohol	27.7	28.6	26.2	30.5	35.5	35.3	42.5	39	35.8	33.00	34.3	27.8	25.9	28.1

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. Mortality Indicator 1996-2009.

Hospital emergencies related to the non-therapeutic use of psychoactive drugs

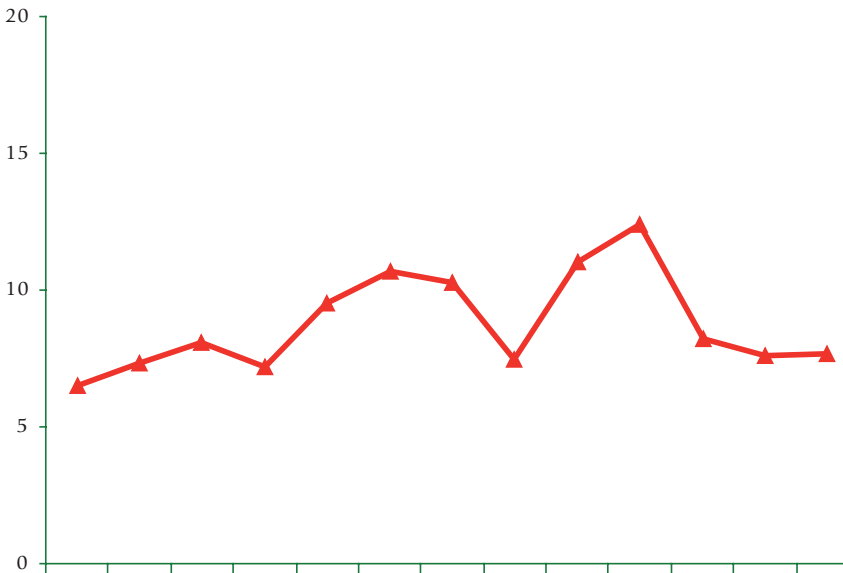
This indicator gathers information on hospital emergencies related to the non-medical or non-therapeutic use of psychoactive substances in Spain since 1987 (excluding tobacco and alcohol). It also gathers information on the number of references to the different psychoactive substances on the clinical record of those patients going to the hospital because of this reason (non-medical or non-therapeutic use of psychoactive substances) although no causal reason between the substance mentioned and the diagnosis is finally established[23].

In 2009, the percentage of times on which ecstasy was mentioned (3.2%) on the clinical records of those people that went to a hospital emergency service for a drug-use-related reason decreased as compared to 2008 (5%), although it remains higher than some years ago (1.6% in 1996).

References to amphetamines have remained stable, at around 5%, during the period 2004-2009. The number of references to hallucinogens had shown a decreasing trend until 2005, which saw an increase, and it had stood at around 2% since then, with an increase in 2009, standing at 3.2%.

If amphetamines, ecstasy and hallucinogens are considered altogether, their references at emergency services reached a peak in 2006 and, although the trend has not been very stable, as you can see in Figure 13, there has been a significant decrease during the period 2006-2009.

Figure 13. Trend of the number of references to ecstasy, amphetamines or hallucinogens in hospital emergencies due to a severe reaction to psychoactive drugs (%). Spain, 1996-2009.



	1996	1997	1998	1999	2000	2001	2002	2004	2005	2006	2007	2008	2009
Ecstasy, amphetamines or hallucinogens	6.5	7.3	8.1	7.2	9.5	10.7	10.3	7.5	11	12.4	8.2	7.6	7.7

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. Emergencies Indicator 1996-2009.

Regarding the group of emergencies directly related to drugs, in 2009 most of the patients were still men (78.4%). The highest proportion of women was found in emergencies with references to the use of hypnosedatives (24.2%), amphetamines (21.3%) and volatile substances (21.2%).

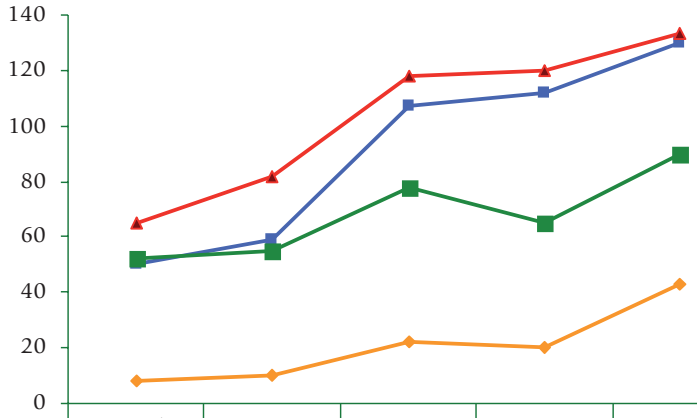
For the time being, the information system of the Spanish Drug Observatory has not registered any emergency or death related to the so-called emerging drugs, except for ketamine, which is analysed below.

Problems related to the use of ketamine

If we compare the number of people admitted to treatment because of the use of ketamine, as a main or secondary drug, with the number of people admitted to treatment due to the use of any other drug (for example, 461 people admitted because of the use of amphetamines in 2009), it is clear that, although nowadays ketamine is considered to be an emerging drug that must be closely monitored, it is a psychoactive substance whose use in Spain is limited at present and causes less related problems than many other drugs.

Figure 14 shows an increase in the number of people admitted to treatment because of use of ketamine in 2007 against 2006, further stabilization in 2008 and a slight increase again in 2009. Regarding the indicator, "emergencies related to or in which the use of ketamine is mentioned" between 2005 and 2007 there has been an increase in the number of references to ketamine in emergencies related to non-therapeutic use of pyschoactive substances and also in the number of emergencies in which there is a direct relationship between these and the use of ketamine. During the period 2007-2008, the number of references to this substance stabilized and the number of emergencies clearly related to the use of ketamine decreased. Both have slightly increased in 2009.

Figure 14. Admission to Treatment because of use of ketamine. Emergencies in which ketamine was mentioned or in which there was a direct relationship to the use of this substance. Trend (Number of cases). Spain, 2005-2009.



	2005	2006	2007	2008	2009
Admission to treatment (main drug)	8	10	22	20	43
Admission to treatment (secondary drug)	50	59	107	112	130
Emergencies (mentioned)	65	82	118	120	133
Emergencies (direct relationship)	52	55	78	65	90

Source: Government Delegation for the National Plan on Drugs. Spanish Drug Observatory. Admission to Treatment Indicator 2005-2009. Emergencies Indicator 2005-2009.

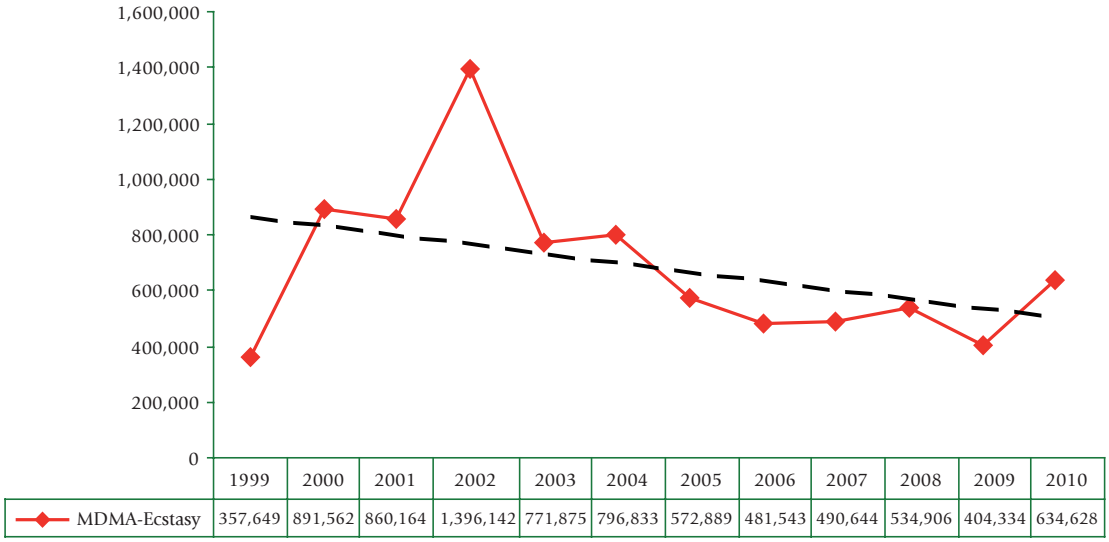
Seizures in Spain

Altogether, the number of seizures of non-cocaine psycho-stimulants (amphetamines and MDMA) increased by 98% in 2010 as compared to 2009.

MDMA-Ecstasy

The number of seizures of MDMA-ecstasy in Spain shows a decreasing general trend, except for 2002, when around one million and a half pills were seized (Figure 15). In 2010, there was a 57% increase in the number of units/pills of MDMA-ecstasy seized as compared to 2009 (or at least of what is supposed to be sold as ecstasy in the market, although further toxicological analysis may confirm the presence of substances other than MDMA).

Figure 15. Seizures of MDMA-Ecstasy (units) in Spain. 1999-2010.



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
MDMA-Ecstasy	357,649	891,562	860,164	1,396,142	771,875	796,833	572,889	481,543	490,644	534,906	404,334	634,628

Source: Home Office. Intelligence Centre against Organised Crime. 1999-2010.

In 2009 some toxicological reports warned about the presence of substances other than MDMA (mainly 2CB and piperazines) in around 50% of the pills seized and classified as ecstasy, which is consistent with the data published by the UNODC on the analysis of drugs seized at the international level. Nevertheless, in 2010 there has been a significant decrease in the proportion of pills sold as ecstasy that only contain substances other than MDMA.

The Netherlands and Belgium continue to be the main countries of origin of the ecstasy seized in Spain, although some data suggest that some of the ecstasy used may come from Eastern Europe and even Asia.

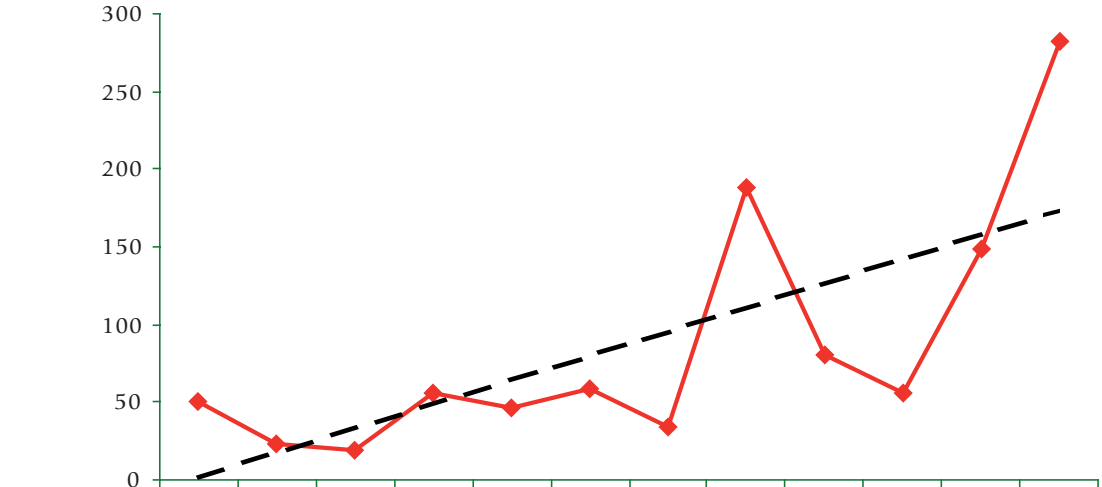
The trafficking of ecstasy to Spain is usually carried out by criminal organizations (most of them British, Dutch and Belgian) whose main means of transport are cars, caravans and campers. They also use airline passengers. The airports with the highest volume of this type of drugs are Barcelona, Madrid, Palma de Mallorca and the Canary Islands.[24]

The price of this substance has followed a sustained decreasing trend since it was first monitored, in the mid 90s. This is in line with the trend seen in the EU. Nevertheless, in 2007 the price of ecstasy pills increased slightly although it decreased again in 2008 and 2009 until reaching €10.17/unit.

Amphetamines

The amount of amphetamine (both in pills and in powder-sulphate of amphetamine) seized in Spain in 2010 has significantly increased as compared to previous years, reaching the highest figures since 2007 in terms of pills (239.6% increase during the period 2009-2010) and a peak, during the last decade, in terms of amphetamine sulphate in powder (90.6% increase during the period 2009-2010) (Figures 16 and 17).

Figure 16. Amount of amphetamine sulphate (powder) seized (kg) in Spain. 1999-2010.

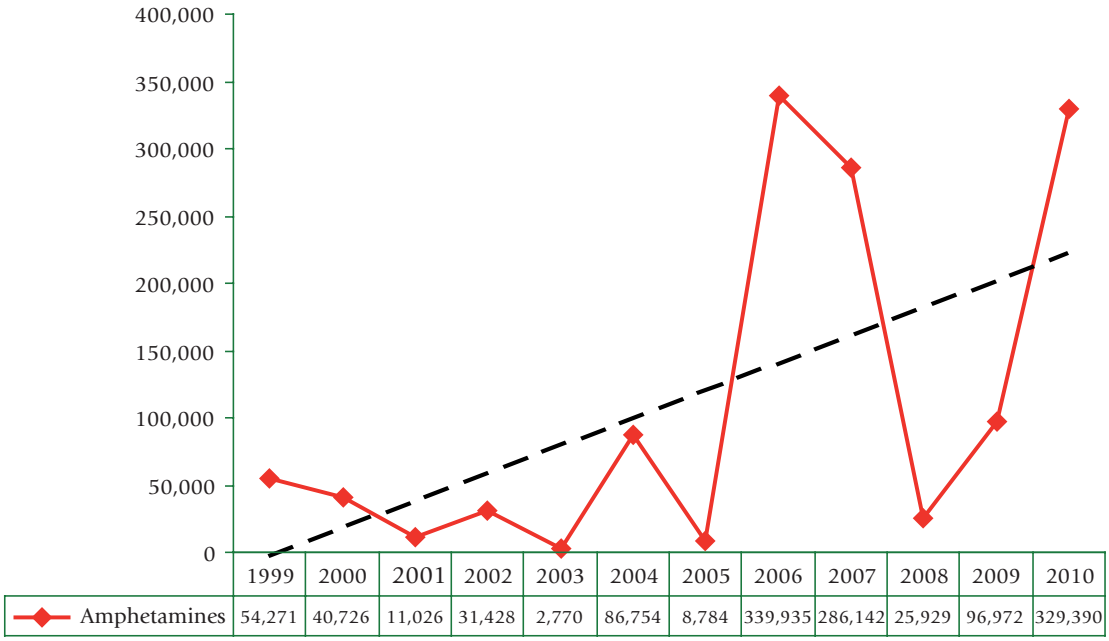


	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Speed	50	23	19	56	47	59	34	188	81	56	148	282

Source: Home Office. Intelligence Centre against Organised Crime. 1999-2010.

In the EU there has also been a recent increase in the number of amphetamine seizures as well as in the number of clandestine laboratories for the production of amphetamines and methamphetamines. The retail price of amphetamines has remained stable or has decreased during the period 2003-2008 in all those EU countries that have provided information to the EMCDDA[15]. In Spain the price of the dose of amphetamine sulphate stands at around €9 and has remained relatively stable since then.

Figure 17. Amount of amphetamines (units) seized in Spain. 1999-2010.



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Amphetamines	54,271	40,726	11,026	31,428	2,770	86,754	8,784	339,935	286,142	25,929	96,972	329,390

Source: Home Office, Intelligence Centre against Organised Crime. 1999-2010.

Unlike other crop-dependant drugs (for example, heroin or cannabis), whose places of production and use are not usually near, amphetaminic stimulants have a more "regional" character since they are mostly used in the same geographical area in which they are produced.

This has a clear impact on the means of transport used from the place of origin to the final destination for their use. The laboratories in which the different drugs are synthetized are usually located in the outskirts of the cities and from there the drug is carried by car to the place of the first sale, both wholesale and retail. The most frequent way is to hide the drug in false bottoms in cars. Other less frequent means of transport are the train and the coach.[24]

Furthermore, the Spanish law enforcement agencies seized different amounts of the so-called "new substances" due to their recent emergence or re-emergence in the illicit drugs market. In 2010 over 3 l of GHB, around 3 kg of ketamine in powder and 2 l of liquid ketamine, 500 g of 2CB as part of the composition of over 2,500 pills, over 51 kg of substances belonging to the group of piperazines (mCPP,

CPP, TFMPP and BZP) and around 257 g of mephedrone were registered.

During the first six months of 2011, almost 4 litres of ketamine, 1l of GHB, 41,600 units of methaqualone and almost 500,000 units of mephedrone (coinciding with the first six months of EU control) were registered. Moreover, around 250,000 tablets containing ayahuasca, among other substances, were also registered.

Nevertheless, it must be taken into account that registrations and seizures are not simultaneous since the first require the analysis and confirmation of the laboratories of reference for the analysis of the substances seized. Consequently, there is some delay in the final notification to the institutions responsible for the detection and mapping of the new patterns of use and the new ways of illicit traficking of psychoactive substances.

IV. Amphetamines

4.1. Composition

Amphetamines are a heterogeneous group of substances initially developed by the pharmaceutical industry from ephedrine, a natural product contained in the ephedra (or *ma-huang*). The ephedrine was marketed as a bronchodilator since there was not any more selective substance at that time. The amphetamine emerged later and was marketed as a nasal vasodilator for local application.

The name of this group of substances comes from the contraction of the term describing the chemical structure of the amphetamine (Alpha-Methyl-PHenyl-ETHyl-AMINE). Many substances derived from amphetamines emerged in the pharmaceutical market between the 60s and 70s; they were used as anoretics in the treament of obesity (fenproporex, mefenorex, clobenzorex, amfepramone, phentermine or fenfluramine).

Spain was one of the European countries with a higher prevalence of use of amphetaminic derivatives for several years. Their use was frequent among students, during the examination period, in order to be able to study longer, improve their performance and reduce tiredness. However, these products were gradually withdrawn from the market as a result of the emergence of some cases of abuse and addiction related to their use, pulmonary hypertension (amphetamine and anoretics), brain haemorrhages (phenylpropanolamine) or heart valvular damages (fenfluramine and dexfenfluramine). At present, there are very few derivatives being still marketed: in Spain only the ephedrine, for oral use and injectable, used as a brochodilator and vasopressor for hypotension, and the methylphenidate are available in the market (to treat the attention deficit and hyperactivity disorder [ADHD]). In the United States both the amphetamine (in different ways) and the methylphenidate are marketed for the treatment of ADHD and narcolepsy.[25]

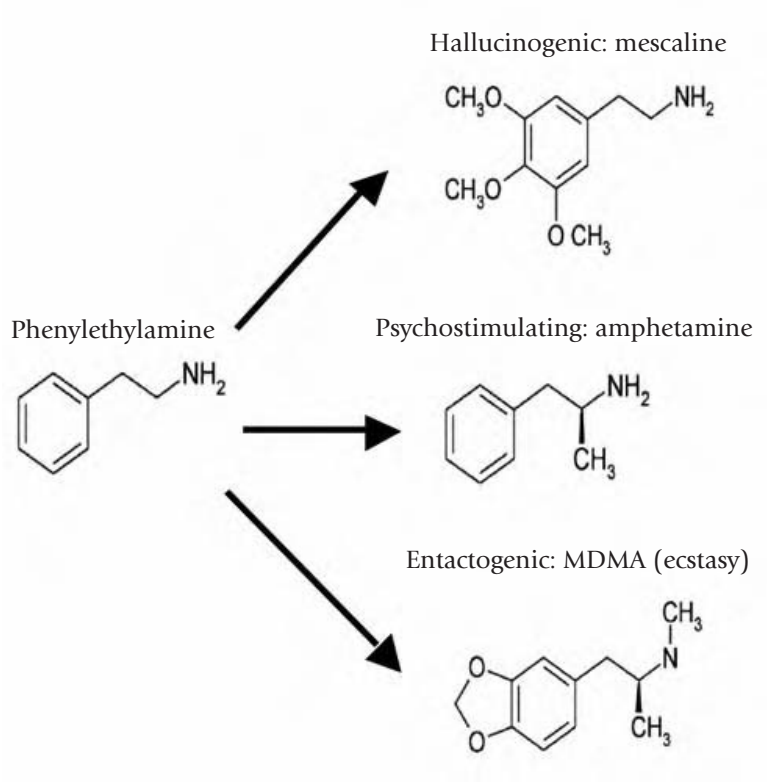
In a broader sense, the group of amphetamines includes products with psychostimulating (classical amphetamines), entactogenic (similar to MDMA) and even hallucinogenic (similar to mescaline) effects. The fact that they cause one effect or the other depends on each substance, their action on the different types of neurotransmitters, the dose administered

and, finally, the particularities and idiosyncrasy of each user. Nevertheless, it must be taken into account that some products that cause psychostimulating effects in low or medium doses may cause intense perceptive changes and/or hallucinations if taken in higher doses. However other products cause clearly hallucinogenic effects even in very low doses[26,27].

Many amphetamines present a chiral centre that leads to enantiomeric forms (generally S or R; dextro [d] or levo [l]). Both enantiomers can have different actions. Regarding the amphetamine, the dextro-amphetamine form has an impact on the central nervous system mainly and therefore it may be abused of. The levo-amphetamine acts on the peripheral nervous system mainly and presents a low potential of abuse. Likewise, regarding methamphetamines, the dextro-methamphetamine is illegal as a result of its potential of abuse, whereas the levo-methamphetamine is available in the United States, with no need for medical prescription, as a nasal vasoconstrictor for local application.

Most of the substances within the group of amphetamines derive from phenylethylamine, although this is not always the case. Figure 18 shows the typical chemical structures of the three types of amphetamines described above (depending on the main effects caused).

Figure 18. Chemical structure of phenylethylamine and prototype derivatives of psychostimulating, entactogenic and hallucinogenic effects.



Source: Clinical Committee of the Government Delegation for the National Plan on Drugs.

There is not a single agreed classification for this wide group of substances included under the term "amphetamines". Table 4 shows the proposal made by the authors of this monography.

Table 4. Classification of amphetamines.

PHENYLETHYLAMINES AND AMPHETAMINE DERIVATIVES	Pyschostimulating effects	Amphetamines	- Dextroamphetamine - d,l-amphetamine - Methamphetamine - Methylphenidate - Ephedrine (*ephedra*) - Anorectics (phentermine and other derivatives)
		Cathinones	- Cathinone (*khat*) - Methcathinone (ephedrone) - Methylmethcathinone (mephedrone) - Ethylone (see entactogens) - Methylone (see entactogens) - Butylone (see entactogens)
	Entactogenic effects Methylenedioxy-amphetamine	- 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy", "Adam") - 3,4-methylenedioxyamphetamine (MDA, "love pill"), - 3,4-methylenedioxyethylamphetamine (MDEA or MDE, "Eve") - N-methyl-1-(3,4-methylenedioxyphenyl)-2 butamine (MBDB) - 3,4-methylenedioxymethcathinone (methylone, "explosion") - 3,4-methylenedioxyethylcathinone (ethylone) - β-keto-N-methylbenzodioxolylpropylamine (bk-MBDB, Butylone)	
	Hallucinogenic effects Methoxy-amphetamines	- 4-bromo-2,5-dimethoxyamphetamine (DOB) - 4-methyl-2,5-dimethoxyamphetamine (DOM, serenity-tranquility-peace or STP) - 2,4,5-trimethoxyamphetamine (TMA-2) - paramethoxyamphetamine (PMA) - 4-bromo-2,5-dimethoxyphenylamphetamine (2CB-MFT) - 2,5-dimethoxy-4-bromo-phenethylamine (2-CB, nexus) - 2,5-dimethoxy-4-iodophenethylamine (2-C-I) - 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2) - 2,5-dimethoxy-4-(n)-propylthiophenethylamine (2C-T-7) - 8-bromo-2,3,6,7-benzo-dihydrodifuran-ethylamine (2-CB-Fly) - Bromo-benzodifuranyl-isopropylamine (Bromo-dragon-Fly)	
	Others	- Pyrovalerone - Naphyrone (naphtylpyrovalerone, NRG-1) - Alpha-pyrrolidinopentiophenone (α-PVP) - Methylenedioxypyrovalerone (MDPV)	

Source: Clinical Committee of the Government Delegation for the National Plan on Drugs.

4.2. Nomenclature

Amphetamines can be included in different groups of substances. Some of them are included within the psychostimulants, others within entactogens and finally, others within hallucinogens. They are the main group within the so-called "designer drugs" (synthetic drugs), produced in such a way that they can escape from legal restrictions. They are also included within the so-called recreational drugs or club drugs, and finally some of the amphetaminic derivatives (mephedrone or naphyrone-NRG-1) are clear examples of the type of products or substances to which we refer when talking about "emerging drugs" (legal highs, research chemicals) and the use of the Internet to get them. The market of this type of substances is always changing and has a great capacity of adaptation to the prohibitions and legal gaps in the different countries or areas all around the world.[28,29]

4.3. Ways of administration and use

In general terms the most usual way of administration of this group of substances is orally in form of tablets (pills), capsules or wrapped in rolling paper (*bomblets*). If they are in powder, they can be sniffed. The MDMA is sometimes presented in form of crystalline powder taken orally and that is called "crystal" (Figure 19).

Methamphetamine is taken orally, intranasally (sniffed, *speed*), by smoking (when presented in form of small pieces of glass called *ice* or *crystal meth*, similar to *crack)* and also intravenously (sometimes together with heroin or other opiods).

Figure 19. *Crystal or ice* (methamphetamine)

Some of the psychostimulating amphetamines are used by sportspeople, professional drivers or pilots in order to increase their performance, particularly to reduce fatigue or sleepiness. Nowadays most amphetaminic derivatives are included in the lists of substances forbidden in competitive sports. Moreover, they used to be taken during the examination period to study and reduce fatigue and sleepiness. The abuse of methylphenidate (used for therapeutic purposes in TDAH) has been recently described, both as drug of abuse and substance used to improve the intellectual performance.

It is generally consumed in group, its use is social during the weekend, at parties or celebrations (*raves*) and discotheques and it is linked to some particular music styles, DJs, repetitive rhythms and very loud music. The places where these substances are taken are usually very hot and crowded with people dancing for hours. These circumstances may reinforce the increase of body temperature caused by the drug itself and lead to a heat stroke or hyperthermia. Research carried out with animals have proven that amphetamines are toxic in lower doses if animals are very close to each other or crowded together in the same cage, as compared to situations in which they are alone or in small groups. This effect is known as aggregation toxicity.

The consumption of several or consecutive doses in the same party is frequent. The average number of pills per session varies from 1.7 to 2.5 (from ½ pill to over 20). The dose interval also varies (1-4 hours). Several doses, repeated in a short period of time, and the simultaneous consumption of other psychoactive substances increase the risk of undesirable risks and overdose.

Furthermore, in recent years it has been found out that pills that are said to contain MDMA, contain this in a lower proportion, being mixed with other substances, mainly amphetaminic derivatives. In their 2010 Report, the International Narcotics Control Board (INCB) highlights the fact that the pills sold as ecstasy may contain a considerable amount of psychoactive substances such as BZP, mCPP and 1-(3 trifluoromethylphenyl) piperazine. In the EU, 50% of the pills sold as ecstasy in 2008 contained mCPP, as compared to 10% in 2006[16]. The average content of MDMA per pill is around 60-70 mg (from 0 to 50-100mg).

4.4. Pharmacology

Drug action

This group of substances has a very complex mechanism of action. Amphetaminic derivatives stimulate the release of neuronal neurotransmitters, mainly dopamine (DA), noradrenaline (NE) and serotonin (5-HT), increasing their concentration in the synaptic space, favouring the combination with their receptors and thus their stimulation.

This releasing effect is caused in two ways. On the one hand, by reversing the direction of the flow of the membrane carrier in charge of re-uptaking noradrenaline (DAT), serotonin (SERT) and dopamine (DAT); on the other hand, through the action of these derivatives on the vesicular carrier (VMAT-2) that facilitates the exit of neurotransmitters from the synaptic vesicles to the neuronal cytoplasm. Both ways increase the availability of neurotransmitters in the synaptic space, which favours their combination to their receptors and the emergence of different effects.

Besides the above-mentioned mechanism, amphetaminic derivatives inhibit the re-uptaking of 5-HT, DA and NA and are specific agonists of receptors 5HT2, alpha adrenergic-2 and muscarinic-1. They also have inhibiting effects on monoaminooxidase and some of these substances reduce the activity of the enzyme tryptophan-hydroxylase, which is vital to produce 5HT (the MDMA for example) or tyrosine-hydroxylase, which is vital to produce NA and DA (methamphetamine for example). Few hours after their consumption, the MDMA, methamphetamine and other amphetaminic derivatives cause, by different ways, "exhaustion" and shortage of serotonin and dopamine for around 24 hours, from which the consumer usually recovers within 2-3 days. This is the reason why a lot of users have a feeling of depression, lack of energy, apathy or slump after using these substances during the weekend, from which they usually recover in the middle of the week.

The differences in terms of effects between the different amphetaminic derivatives may be due to the higher or lower action and selectivity of each of them on one or several of the neurotransmitters involved and their effect on their respective receptors. Psychostimulating amphetamines seem to have higher action on dopamine and

noradrenaline and lower action on serotonin. Entactogenic amphetamines have a higher serotonergic selectivity although the highest serotonergic selectivity is shown by hallucinogenic amphetamines. Mephedrone has a mixed action profile, releasing both serotonin and dopamine in a similar way to MDMA and amphetamine, respectively.

Pharmacological effects

The effects caused by amphetaminic derivatives are mainly due to their action on the central nervous system and the peripheral nervous system, the cardiovascular system and the endocrine system.

The effects aimed by the users of this group of substances are different depending on the type of substance considered:

- Psychostimulating (typical of amphetamine): euphoria, increased energy, reduced sleepiness and appetite, reduced fatigue and improved level of alert and performance.

- Entactogenic (such as MDMA and derivatives): euphoria, positive state of mind and increased empathy and capacity to become close to others, communicate and for interpersonal relationships.

- Perceptive or hallucinogenic (typical of products related to methoxyamphetamines): change in the perception of the context and own image, which can range from subtle changes to real hallucinations.

The effects on cardiovascular, vegetative and endocrine systems are the following: increase in blood pressure and heart frequency (although the use of amphetamines may initially cause vagal reflex bradycardia), mydriasis, photosensitivity, blurred vision, bruxism, lockjaw, muscular tension, shivering, dry mouth, thirst and perspiration. There is also an increase in the concentrations of adrenocorticotropine (ACTH), cortisol, prolactin and vasopressin; the increase of the latter may lead to a syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Body temperature may also increase and it may be worsened by the extra temperature increase because of dancing, moving, etc., in people consuming these substances in crowded places with poor ventilation.

The effects caused by amphetaminic derivatives usually start 45 min-1 hour after their consumption, they reach their peak within 1 or 2 hours and can last for 4-6 hours (when talking about MDMA) and even 8-12 hours (if talking about amphetamine). When the effects are over, or the day after their consumption, the user feels some kind of slump (*crash*) that may last for 2 or 3 days.[30,31,32,33] Some derivatives, such as the *bromo-dragon-fly*, may start acting late (even six hours after their consumption) and their effects can last for up to 2-3 days.

Pharmacokinetics

Regarding their physical-chemical qualities, amphetaminic derivatives are weak bases (pKa 9.9), liposoluble and go through biological membranes very easily. They are well absorbed orally, reaching their maximum concentration 1-2 hours after being consumed. They show a good distribution, and it is possible to find considerable concentrations in saliva and perspiration.

They are mainly metabolized in the liver by the enzymes of the cytochrome P450 (CYP). Methamphetamine is metabolized into amphetamine (20%), i.e. out of each dose of methamphetamine, 20% turns into amphetamine. Likewise, MDMA turns into MDA (5%). MDMA and methamphetamine undergo demethylation partly by the cytochrome CYP2D6. In theory, there are 5-10% of slow metabolizers that would find it difficult to metabolize some amphetamines, although the clinical relevance of this peculiarity is unknown. MDMA shows a non-linear pharmacokinetics (i.e. the concentration increase or the administration of repeated doses do not entail proportional variations, as expected in a linear pharmacokinetics, regarding parameters such as distribution, metabolism or excretion). Many studies[34] suggest that this may be due to the inhibition of the MDMA metabolism by the MDMA itself or by any of its metabolites, by forming an inhibiting complex with the CYP2D6. Something similar seems to happen with methamphetamine.

This fact is significantly relevant because it explains why the repeated doses of MDMA may considerably increase its toxicity in the organism: since the substance cannot be metabolized at the same speed as with the first dose (because of the inhibiting effect on its own metabolic channel) the blood concentration of the MDMA increases and, therefore, its effects

may be greater. Nevertheless, some studies[35] under controlled conditions and atmosphere (other than the real atmosphere where the substances are consumed) seem to indicate that the repeated use of MDMA among healthy people would not imply a considerable increase in damages to the organism and would show a tolerance effect regarding most of the MDMA pharmacological effects.

Some of the derivatives included in the group of amphetamines (selegiline, fenproporex, mefenorex, clobenzorex or mesocarb) are prodrugs that are biotransformed into amphetamine or methamphetamine in the liver.

These products are excreted through the kidney and their excretion may increase when the urinary pH is acidified. The elimination half-life of the amphetamine and methamphetamine is 12 hours, 8 hours for MDMA, 7 hours for MDE, 8 hours for ephedrine and 6 hours for methylphenidate. Regarding cathine and cathinone (contained in *khat* or as single substances), the elimination half-life is 5 and 2 hours respectively. There is almost no information, particularly for human beings, on the remaining amphetaminic derivatives[32,33,36].

Pharmacological interactions

Interactions with medicines

As mentioned above, methamphetamine and MDMA inhibit the activity of CYP2D6, therefore they may have an impact on the metabolism of many medicines that use this channel for their transformation in the organism (codeine, tramadol, dextromethorphan, etc.). There are other medicines that can also inhibit the CYP2D6 (paroxetine, fluoxetine or others) and reduce the metabolism of some amphetamines (methamphetamine and MDMA).

Amphetamines increase the effects of metilxantines and sympathomimetics (nasal vasoconstrictors for example) and reduce the anti-hypertensive effect of beta blockers.

Combining amphetaminic derivatives with several types of antidepressants (MAO inhibitors, tricyclics or selective inhibitors of serotonin re-uptaking) may favour the appearance of a serotonergic

syndrome that, in mild cases, shows the following clinical signs: restlessness, tiredness, shivering, insomnia, tachycardia, hypotension or hypertension and face redness; and in more serious cases, mydriasis, muscular stiffness and difficulty in coordinating movements, perspiration, fever and even loss of consciousness.

The selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, fluoxetine or citalopram) reduce the euphoric effects of MDMA. This type of medicines and the MDMA compete for the membrane carrier that reuptakes the serotonin (SERT), so the SSRIs partially mitigate the MDMA effects. The reboxetine, a selective noradrenaline reuptake inhibitor, also reduces the MDMA's euphoric effects and its impact on vital signs.

Haloperidol (a classical antypsychotic) reduces the positive effects (euphoria, well being, etc.) and the mania induced by amphetamines. Ketanserine, an antagonist of serotonin 5-HT2 receptors, reduces the perceptive changes caused by MDMA.

Interactions with drugs of abuse

Alcohol increases the concentrations of methamphetamine and MDMA in blood by 10%. Amphetamine, methamphetamine and MDMA can reduce the feeling of alcoholic intoxication and sedation, but they barely modify the deleterious effects of alcohol on the psychomotor performance and the capacity to drive vehicles. Alcohol can increase euphoria and the cardiovascular effects of amphetamines and, of course, the combination can increase the risk of developing aggressive or high-risk behaviours.

Combining cannabis and dextroamphetamine or MDMA increases the feeling of intoxication and the intensity of the subjective effects of both amphetaminic derivatives, but it does not modify, i.e it does not reduce or counteract, the sedation or the psychomotor deterioration of cannabis. Moreover, the combination leads to a higher increase in heart frequency than the use of amphetamine only[37,38].

4.5. Clinical signs

Clinical signs result mainly from the stimulation of the cardiovascular and sympathetic nervous systems[39]. Among others, the use of amphetamines causes the following alterations:

1. Neurological and psychiatric

Although the effects are different depending on each person and the consumption conditions, there is usually an initial disorientation followed by changes in the state of mind (euphoria, disphoria), feeling of energy increase, alert, stimulation, improved attention, intellectual performance and carrying out of manual tasks and reduced tiredness, sleepiness and hunger.

The use increases talkativeness and improves the capacity to communicate; it also results in mental hyper-sharpness and increased self-confidence.

It may cause slight shivering, migraines, insomnia, tiredness, anxiety, irritability, fits of anger and aggressive behaviours with altered feelings and emotions. Psychotic episodes (even with therapeutic doses) and Gilles de la Tourette syndrome[40] have also been described. Psychotic signs can occur up to 36-48 hours after taking a single overdose and can last up to one week[41].

High doses can lead to disorientation, psychic depression, hallucinations, delirium, catatonia, convulsions or coma. Hallucinations are characterized by very real visions and they are usually auditory or tactile. Their use can also cause panic atacks, paranoid ideation, psychomotor agitation, mental deterioration, amnesiac disorders and incoherence[15,42] and emotional changes.

MDMA has been associated to irreversible or long-lasting neurotoxic effects in serotonergic neurones both in animals and human beings. The neurotoxic effects depend on the dose and frequency of administration, as well as on the concomitant use of other drugs. A higher prevalence of mental disorders and memory alteration has been observed in users even months or years after giving up the substance. Methamphetamine is neurotoxic for dopaminergic neurones.

2. Cardiovascular

The MDMA can lead to an increase in heart frequency, arterial hypertension, ventricular fibrillation and even death.

Research carried out in cell cultures, financed by the National Institute on Drug Abuse (NIDA, USA), concluded that MDMA and fenfluramine[43,44] can cause left ventricular hypertrophy by activating the 5-HT2b serotonin receptor that stimulates ventricular growth and heart valve hypertrophy and leads, over time, to valvular failure and heart failure.

Furthermore, there is an increased incidence of stroke in young people associated to the use of cocaine, amphetamine and other sympathetical-mimetic substances[45]. The mechanisms involved may be the increase in blood pressure, brainvascular vasoconstriction, some vasculitic phenomenons and higher platelet aggregability. In this case, death is mainly due to hemorrhagic phenomenons (subarachnoid hemorrhage or spontaneous intraparenchymal hemorrhage), which are usually associated to an underlying vascular malformation. There are also brain infarctions, generally in the white matter, that are often asymptomatic, thus underdiagnosed.

3. Digestive

There may be nausea and vomiting. The use of these substances may cause liver toxicity in form of hepatitis or severe liver failure and is characterized by the presence of jaundice, increase of serum transaminases and decrease of protrombine activity. Although most of the times the liver damages caused by the MDMA are not severe and are spontaneously solved, they can be fatal.

4. Blood

Cases of MDMA-related aplastic anemia have been described. However, most of these cases tend to improve spontaneously within 7-9 weeks.

5. Others

Muscular tension, bruxism, higher sensitivity to cold, suffocation, increased perspiration and thirst and malignant hyperthermia. Mydriasis, blurred vision and alterations in colour perception may occur as well. MDMA can increase the secretion of vasopressin and cause hyponatremia and brain edema.

6. Pregnancy

Experimental studies have shown effects on the weight of the fetus[46] as well as further problems in memory and learning processes.

4.6. Intoxication, addiction and withdrawal symptoms

Intoxication due to amphetamines and, in general, due to most stimulating psychoactive substances, results in behavioural changes and perceptive alterations among which the following are included:

- Euphoria and feeling of increased energy
- Hypervigilance
- Beliefs or acts of grandeur
- Aggressive behaviour
- Verbal beligerence
- Labile mood
- Repeated and stereotyped behaviours
- Auditory, visual or tactile illusions
- Hallucinations (generally keeping orientation)
- Paranoid ideation

All this is usually accompanied by the following signs: increased heart frequency, arrhythmia, hypertension/hypotension, perspiration, shivers, nausea, vomiting, mydriasis, etc[1].

Amphetamines present a high potential of abuse and may cause **addiction**[47]. In experimentation animals, they lead to increased locomotive activity (dose-dependant) and, with high doses, they cause stereotypy. It has been suggested that in human food binges may be a reflection of animals' stereotyped behaviours.

The chronic use of amphetamines causes neurochemical and neuroanatomic changes. Addiction is accompanied by increased tolerance and can entail deficits in memory processes, decision-making

processes and verbal reasoning. Sometimes the symptoms are similar to those of paranoid schizophrenia. These effects can remain through time although they are generally solved.

Interrupting or reducing the use of amphetamines, after a long period of consumption or in great amounts, causes **withdrawal symptoms** that, although usually lasting for some hours or several days after the interruption, may last for weeks or months, depending on the length of the previous period of consumption. These symptoms are:

- Depressive mood
- Fatigue
- Sleep disorders (feeling of vivid dreams and unpleasant nightmares; insomnia or excessive drowsiness)
- Irritability
- Increased appetite
- Motor agitation

Regarding MDMA, although users may present addiction criteria at some points, they usually reduce their consumption spontaneously or replace it with alcohol or cocaine. No specific withdrawal symptoms have been proven.

4.7. Therapeutic intervention

Severe intoxication

For all the substances included in this section, the treatment is mainly symptomatic and supporting:

- Control of vital signs (heart frequency, breathing, blood pressure).
- Stomach-pumping, which is only effective within the first two-three hours.
- Rehydration with saline solutions or isotonic drinks.

- In serious cases, urine acidification in order to try and reinforce the elimination of the toxic, but this procedure must be carried out in specialized units and by trained personnel.
- Hyperthermia control.
- Usual treatment of complications with specific measures.

It is advisable to treat severe intoxications related to any of these substances in a hospital equipped with an intensive care unit.

Abuse and addiction

The treatment of disorders resulting from the use of this group of substances has made considerable progress during the last decade. Nevertheless, there is not any specific pharmacological treatment yet, and psychological interventions are today the basis of its approach. Despite this, further clinical analysis are required in order to determine the psychosocial needs and improve the treatment of people addicted to amphetamines[48] and other psychostimulants.

There are some therapeutic alternatives to treat methamphetamine-related disorders that have shown good results, although the relevance of this substance is limited regarding the total number of drug-related treatment demands in Spain.

Among these alternatives, we find behavioural therapies (cognitive-behavioural interventions) and contingency management[48,49]. Particularly, a special type of programme called "Modelo Matrix" that was successfully developed to treat cocaine abuse in the 80s. It was used to treat more than 3,000 users of this substance[50] and later on it has also proven effective to treat methamphetamine abuse and addiction, with an increase in abstinence periods and in the continuance of users in treatment[50,51].

The Matrix model is a behavioural therapy with a comprehensive approach looking at (intensively and for 4 months/16 weeks) aspects regarding the prevention of relapses, behavioural changes, learning coping skills, family communication and others that are relevant to maintain abstinence. By means of individual sessions, group therapy, joint educational groups for patients and families, 12-step meetings and drug detection urine tests, a therapist-patient motivational relationship is

set up aiming to attain abstinence or, at least, control the consumption of substances.[53]

In Spain, the "Matrix Model" was recently adapted and piloted for 24 months in a group of people addicted to cocaine and alcohol, by using the methodology established by the Matrix Institute (US). Its evaluation showed results consistent with those obtained in the United States, with a considerable reduction in the use of alcohol and cocaine and high retention in the treatment (82%) after the four months.[54]

The interventions of "contingency management plus incentive therapy"[55] have also proven effective: patients are given low-cost tangible incentives in exchange for maintaining abstinence and continuing in treatment. The incentives used are generally vouchers to exchange for food or personal-use items and tickets for the cinema.

12-step meetings help maintain the recovery attained and consolidate abstinence.

Furthermore, harm reduction strategies must be always considered to be an alternative that minimizes the negative consequences of the methamphetamine use and abuse[56].

As to pharmacological treatments, although there is no specific medicine to treat methamphetamine addiction, recent studies carried out by the US National Institute on Drug Abuse (NIDA) indicate that:

- Bupropion, antidepressant inhibiting the reception of dopamine and norepinephrine, reduces the stimulating subjective effect of the methamphetamine as well as the *craving* (or consumption desire) associated to the drug itself or consumption-related environmental triggers.

- Topiramate does not seem to entail any safety problems resulting from the interaction of this medicine (in 200 mg doses) with methamphetamine, although it does lead to a slight increase in the subjective effects caused by the latter[57].

Other lines of research that are currently under experimentation in animals are conceived to design medicines based on monoclonal

antibodies in order to reverse the severe effects of methamphetamine and be used in emergency services, thus preventing medical complications in the medium and long term.

Finally, there are combined approaches joining the above-mentioned cognitive-behavioural techniques and the use of medicines aiming to recover the cognitive deficits and restore emotional aspects back to normal. Modafinil, used to treat narcolepsy, can have a positive impact on executive functions and impulsivity, thus improving the prevention of relapses[57].

In general terms, despite the existence of different effective treatments, the main challenge continues to be attaining a sustained recovery.

There is not any specific treatment either for the MDMA (ecstasy) abuse or addiction. The most effective therapeutic alternatives are also the cognitive-behavioural interventions, aiming to modify the drug use-related thought process, expectations and behaviours of the patient as well as to improve his/her capacity to deal with stress factors in daily life. Support groups, together with behavioural therapies, can be helpful to foster a long-term recovery without any relapse[52].

As to MDMA (ecstasy), when thinking about a non-pharmacological therapeutic intervention, it is vital to take into account the typical characteristicis of this type of consumption in our country: polydrug, abuse during the weekend, poor impact on care centres for drug addicts and treatment requests from families mainly[58].

Harm reduction strategies, used to control the use of ecstasy rather than for therapeutic purposes, would correspond to the prevention field, aiming, among other goals, to reduce the MDMA toxic potential regarding its capacity to cause neurocognitive changes and neuropsychological harm[59].

For the time being there are no specific pharmacological treatments for addiction to MDMA or similar substances. The use of benzodiacepines, antidepressants and/or atypical antipsychotics[60] is recommended to treat acute, subacute and chronic psychiatric complications that may arise.

4.8. Mephedrone and other synthetic cathinones

Mephedrone (4-methylmethcathinone; 4-MMC; MMCAT) is a chemical synthesis product whose structure and effects are somehow similar to other stimulating psychoactive substances such as amphetamine, MDMA ("ecstasy") and cocaine. Among the cathinone-derived substances (mephedrone, methylone, flephedrone and butylone), mephedrone is the most popular one as a legal alternative (until December 2010) to other stimulants such as cocaine and MDMA.

Until recently, mephedrone could be considered to be included within the group of the so-called research chemicals and legal highs, chemical compounds that have proven to have psychoactive qualities to a greater or lesser extent, even if initially they were not supposed to be used as products of abuse; therefore, they are legally marketed and there are not subject to the national and international controls and legislation applicable to the rest of psychotropic substances and narcotics. Abusing these substances for psychoactive purposes entails considerable risks since their effects, interactions with other substances of abuse, short and long-terms risks and consequences are barely known and in any case what is known is much less than the information available regarding other substances whose long history of abuse has enabled to establishe more defined risks (cannabis, cocaine, amphetamines, etc.).

Mephedrone can be purchased relatively easily on the Internet (different websites or social networks such as Facebook or Twitter) in powder, crystal or tablets or as a "fertilizer", "bath salts", or as a substance "not for human consumption", including detailed instructions suggesting its legitimate use as such. However, instructions usually suggest also how to use the product as a drug implicitly. This type of marketing is used to avoid the legislation and regulations controlling the sale of medicines and other legal substances not indicated for human consumption.

Nevertheless, as a result of the EU Council Decision of 2nd December 2010 (2010/759/EU) whereby the 4-methylmethcathinone (mephedrone) was put under control (OJEU 8/12/2010), the EU Member States had one year to modify their national legislations to include mephedrone in the group of substances controlled in accordance with the obligations established by the UN Convention on Psychotropic Substances of 1971.

The most frequent way of administration among mephedrone users is orally, which causes effects within 30-60 minutes and last for 2-3 hours. Another way of administration is sniffed powder, but it causes considerable irritation of the nasal mucus and even pain, which makes users prefer the oral use. The injected use is very infrequent.

Its use causes euphoria, increased sociability, improved musical appreciation and sexual arousal. Mephedrone users say that they have a softer feeling of "rush" and "slump" than with MDMA and less or even no "hangover" at all the following day.

Its use causes immediate effects similar to those of other stimulants such as ecstasy and cocaine: mydriasis, agitation, increased heart frequency and hypertension. In some cases there has been severe pheripheral vasoconstriction in hands and feet, arrhythmia, strokes and convulsions. Hallucinations and psychotic symptoms are frequent. These may depend on the dose and may be modulated and mixed with the effects caused by the simultaneous consumption of other substances (alcohol, cannabis or other stimulants, ketamine, etc.). The short duration of the effects caused by mephedrone favours the use of repeated doses, which increases the risk of intoxication.

Until the end of 2010 there were two deaths registered (UK and Sweden) as having a causal relation with the use of mephedrone. Moreover this substance was detected in the toxicological analysis of other 37 deceased people in the UK and Ireland but in these cases no clear causal relation has been established due to the co-existence of other reasons (traumatisms or use of other substances).

Mephedrone entails tolerance towards the effects of the substance after a long period of consumption and, although those using it sporadically deny the existence of withdrawal symptoms, usual consumers do admit to have these symptoms. Actually there have been some addiction cases in users that have decided to attend treatment centres. The possible neurotoxic effects of this substance, which do exist in MDMA or methamphetamine, are still ignored.

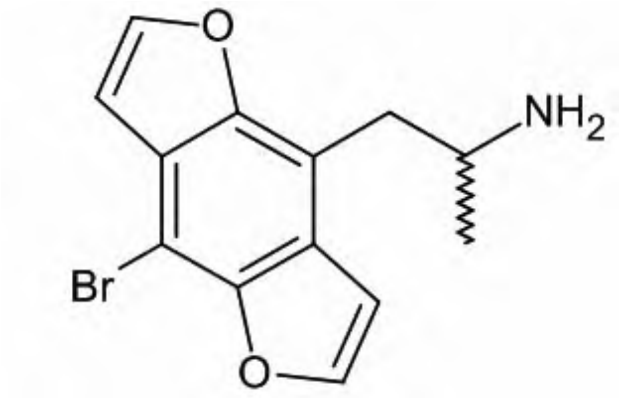
The little information available on toxicity, the long-term effects and the possible carcinogen or teratogen potential during pregnancy, together with the reports on the presence of impurities and differences in terms of

colour, smell, etc. in the products available in the market have made users themselves to regard mephedrone as a "dirty drug".

4.9. Bromo-*Dragonfly*

Bromo-Dragonfly (1-(8-bromobenzo [1,2-b; 4,5-b']difuran-4-yl)-2-aminopropane) is a powerful hallucinogen, active in very low doses (from 200 µg). Although it is chemically related to phenethylamines, its structure is different and belongs to the type of substances called benzodifurans (Figure 20). Its name (*dragonfly)* stems from the similarity of its structure to an insect due to the presence of the two furan rings on both sides of the benzene ring, like wings.

Figure 20. Bromo-Dragonfly chemical structure



www.drugs-forum.com

The first cases of recreational use of this substance were registered in 2001 and it has different names: "DOB-*Dragonfly*", "*Dragonfly*", "BrDF" or just "B-*fly*".

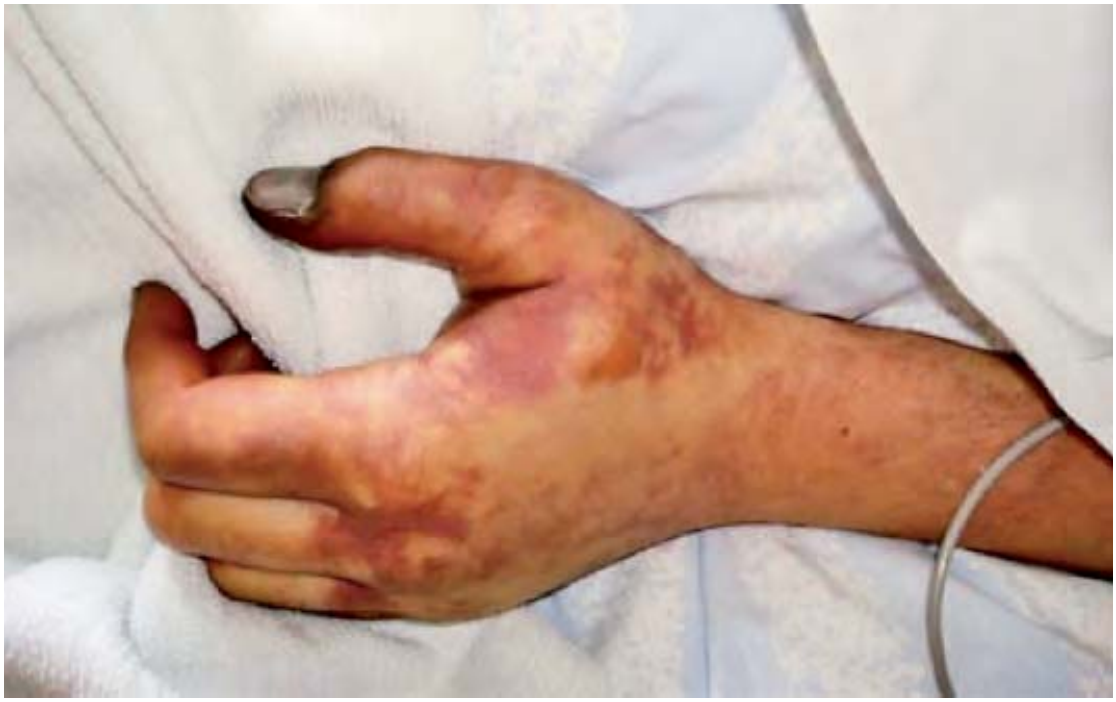
It is available on the Internet, in different ways of presentation: powder, suspensions in liquid, "blotting paper" and, less often, tablets. The most frequent way of adminstration is orally.

Bromo-*Dragonfly* is a non-selective agonist of 5HT2 serotoninergic receptors, through which it causes its psychodelic effects. Moreover, it leads to a sustained activation of peripheral alpha-1-adrenergic receptors, which is, to a great extent, responsible for its stimulating effects.

Its effects are very similar to those of LSD but longer (2-3 days) in addition to the stimulating effects. After its consumption, the first psychoactive effects are perceived from 30 minutes on and may appear up to 6 hours later. This delay and the oscilating character of its effects lead to the use of repeated doses of the product thinking that the first dose was not enough to get the desired effects and/or the use of other drugs while waiting for the first psychoactive effects to turn up.

Bromo-*Dragonfly* causes an initial feeling of euphoria, increased energy and pleasant alterations in terms of perception, but undesired effects have also been described, such as nausea and vomiting, migraine, hypertension, tachycardia, lung collapse, gastrointestinal problems, muscular tension, shivering, body temperature variations, anxiety, panic attacks with depersonalization, paranoid ideation, arrythmia, mydriasis, convulsions, hallucinations, flashbacks and memory alterations. In some cases there is an intense peripheral vasoconstriction that may appear up to several days after the use and cause colour changes in acral parts or even necrosis and as a result of this, amputation of the fingers and/or toes (Figure 21).

Figure 21. Necrosis related to the use of Bromo-*Dragonfly*



www.drugs-forum.com/forum/showwiki.php?title=Bromo-Dragonþy

B-*fly* is a very toxic powerful substance with a small safety margin, therefore the overdose risk is very high.

Several cases requiring hospitalizacion and even deaths have been described in different countries (Sweden, Denmark, the UK and the US) since 2007.

V. Piperazines

Piperazines emerged in the Northamerican market in the 90s. Ten years later they arrived in Europe and New Zealand and their use increased dramatically in 2004-2005[61]. In New Zealand, until they were banned, this group of substances was sold legally and in containers similar to those used to sell medicines (Figure 22).

Figure 22. Container with BZP capsules.

www.erowid.org/chemicals/bzp

The emergence of serious cases of intoxication in Europe made Europol and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) register alerts and carry out a risk-assessment report in accordance with the EU Council Decision of 10th May 2005, regarding information exchange, risk assessment and control of new psychotropic substances[62,63,64]. As a result of this report, on the European Commission's initiative, the EU Council decided to implement control measures to BZP (Council Decision 2008/206/JHA of 3rd March 2008).

5.1. Classification

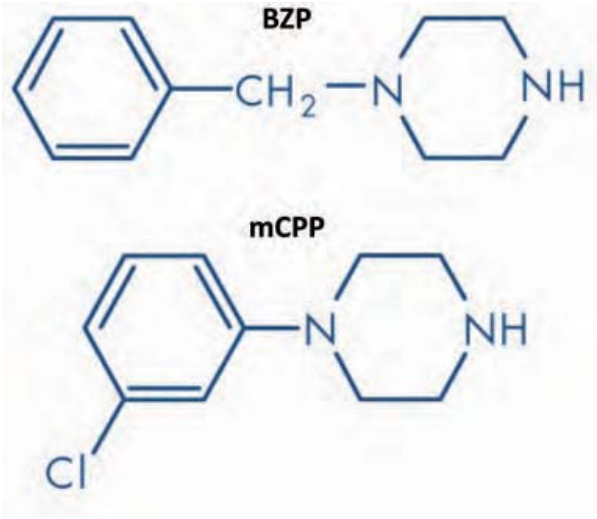
Piperazines can be classified into two groups:

- *Benzylpiperazines*, which include 1-benzylpiperazine (BZP) and an analogous substance 1-(3,4-methylenedioxybenzyl) piperazine (MDBP) and
- *Phenylpiperazines*, such as 1-(3-chlorophenyl)piperazine (mCPP), 1-(3-trifluoromethylphenyl)piperazine (TFMPP) and 1-(4-methoxyphenyl)piperazine (MeOPP).

BZP was tested as an anthelmintic but it was never marketed as such. Figure 23 shows its chemical structure. MCPP is an active metabolite of trazodone and nefazodone, both with antidepressive effects, and it is used as an activator of the central serotoninergic system for psychopharmacological research purposes[65].

They are generically known as herbal highs, herbal tonics, herbal ecstasy or party pills.

Figure 23. Chemical structure of BZP and mCPP



www.emcdda.europa.eu/publications/drug-profiles/bzp

5.2. Ways of administration and use

They are usually used orally. They are presented in form of tablets or capsules. BZP capsules contain from 50 to 200 mg and are sold with names such as Legal X, Frenzy, Charge, Rapture or A2. MCPP was introduced in the market as a legal alternative to ecstasy (MDMA). In recent years the so-called "white sharks" have been very popular as well as several types of pills of different coulours and composition with very popular logos that contained different types of piperazines and/or ecstasy. MCPP is often sold as ecstasy or mixed with MDMA in some tablets. Tablets often contain several types of different piperazines (mixtures of mCPP, TFMMP, oMPP and/or pCPP). They can be found on the Internet, particularly the derivatives that are not subject to legal restrictions (Figure 24).

Figure 24. Several formats of pills in which BZP was detected

www.justice.gov

www.watoday.com.au

www.scoop.co.nz

5.3. Pharmacology

Piperazines have stimulating effects on the central nervous system, similar to those of some amphetamines[66].

BZP favours the release and inhibits the reuptake of neuronal noradrenaline, dopamine and serotonin. It also has a direct impact, i.e. as an agonist, on the 5HT-1 serotoninergic receptors and as an antagonist on alpha-2 adrenergic peripheral receptors[67].

MCPP seems to be relatively selective on serotonergic neurones. It favours the release of serotonin because of its impact on the serotonin carrier (SERT) and it is agonist of several serotoninergic receptors (such as 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2C}) and antagonist of others (5-HT_{2B}).

The TFMPP's mechanism of action is similar to that of mCPP, stimulating the serotonin receptors of the type 5-HT-2C, 5-HT-1A and 5-HT-1B and favouring the release of serotonin[68,69].

Some studies suggest that combining several piperazines imitates the neurochemical mechanism of ecstasy (specifically BZP+TFMPP). Others

state that MBDP may inhibit the neurotoxicity caused by the MDMA in animal models.

Regarding its pharmacokinetics, they are absorbed orally and show maximum plasma concentrations between 0,5 and 3 hours after their administration. BZP, mCPP and TFMPP are metabolized in the liver, partly by the cytochrome (CYP2D6) and they may be expected to interact with other drugs of abuse and/or medicines that use this metabolic pathway. The elimination half-life of BZP, TFMPP and mCPP ranges from 5 to 6 hours.

5.4. Clinical signs

The effects are the same as for the rest of psychostimulating substances: euphoria, disinhibition, improved sociability, feeling of increased energy, etc. There is little information on the adverse effects of this type of drugs althoug they are very similar to those of dexamphetamine.

In recent years there has been an increase in the recreational use (clubs, rave parties, etc.) of this type of substances, due to their euphoric effects. It has been observed that when going to the emergency services after having used these substances, users show considerable interindividual variability regarding side effects and the different amount of drug that causes these effects depending on each person. This drug is metabolized by the cytochrome P450 and, therefore, it presents many interactions with other drugs and/or medicines, depending on genetic variability as well.

The most usual unwanted effects are similar to those of a sympathomimetic syndrome:

1. Cardiovascular
Tachycardia and hypertension. No significant changes have been observed in the QTc interval.

2. Digestive
Nausea, vomiting, epigastric pain.

3. Respiratory
It does not usually cause respiratory depression but it hampers the expulsion of mucus through the ciliary system.

4. Neurological and psychiatric
It may cause headache, dizziness and drowsiness in a small proportion of users. When they are used in high doses, there may be neurotoxic reactions together with motor incoordination, ataxia, paresthesias, vertigo, migraines, excessive heaviness, difficulty in talking, muscular weakness, myoclonus, visual disorders and nystagmus[70].

Some users of BZP (with or without a previous epileptic disease) have had convulsions. Some observations may suggest that taking this together with ethanol reduces the number of convulsions although it increases confusion, agitation and palpitations[71].

It may also cause anxiety, insomnia, weird thoughts, changes in the state of mind, etc.

5. Urinary
Urinary retention[72], severe kidney failure (related to severe rhabdomyolysis)[73].

6. Others
Hyponatremia, malignant hypertermia with multiorgan failure and severe metabolic acidosis.

Severe intoxication

There is not a set of clinical signs and symptoms to be specifically ascribed to the use of piperazines although the characteristics of the intoxication due to this group of substances are very similar to those of the rest of psychostimulants and interchangeable, for practical purposes, to those described regarding the use of amphetamines and MDMA.

Moreover, as mentioned in the pharmacology section, there is great interindividual variability regarding the effects caused by these substances due to the characteristics of the metabolic pathway they use.

Finally, piperazines are not usually the main substance of abuse, but they accompany (voluntarily or fortuitously) the use of other substances (ecstasy, alcohol, amphetamines, cocaine, etc.), therefore it is difficult to try and ascribe the symptoms to a single substance.

Abuse and addiction
There is not enough information on the potential of abuse and addiction of piperazines, although it is considered to be quite similar to that of amphetamines.

Withdrawal symptoms
No withdrawal symptoms have been determined after the use of these compounds.

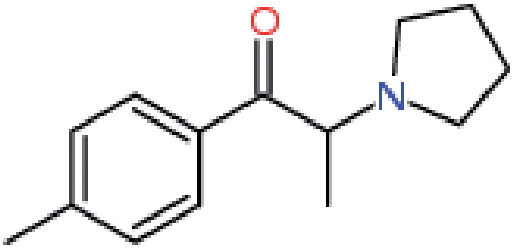
5.5. Therapeutic intervention

There is not enough experience in this type of consumption, therefore the pharmacological and psychosocial interventions are similar to those used to treat amphetamine-derived disorders.

VI. Pyrrodilinophenones

These drugs were introduced in the German black market at the beginning of 2000. This group includes: α-pyrrolidinopropiophenone (PPP), 4′-methoxy-α- pyrrolidinopropiophenone (MOPPP), 3′,4′-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP), 4′-methyl-α-pyrrolidinopropiophenone (MPPP), 4′-methyl-α-pyrrolidinohexiophenone (MPHP), 4′-methyl-α-pyrrolidinobutyrophenone (MPBP) and α-pyrrolidinovalerophenone (PVP). Figure 25 shows their chemical structure.

Figure 25. MOPPP chemical structure.



isomerdesign.com

They are sold in form of tablets, capsules or powder and are administered orally, preferably. The usual doses are unknown and are not normally included in drugs analysis.

There are few studies on pharmacological aspects of this group of substances in animals and there are hardly any studies published in human beings. According to the few descriptions of their effects on users, they seem to have psychostimulating effects similar to those of amphetamines, due to their similarity to some medicines containing α-amino-propiophenone in their structure (amfepramone, cathinone, methcathinone or ephedrine, pyrovalerone and bupropion). Most of these substances are metabolized in the liver by the cytochrome CYP2D6, therefore they may be expected to show pharmacological interactions[74] with other drugs of abuse and/or medicines.

VII. Ketamine

Ketamine (IC-581) is a general dissociative, non barbituric and non narcotic anesthetic described by Domino and his collaborators in 1965[75,76]. The anesthesia produced by this substance is different from that of classical anesthetics since it causes a particular state of unconsciousness in which the individual is not asleep or anesthetized, but disconnected from his/her body and context. It causes a functional dissociation of two brain areas: the thalamus-neocortex and the limbic system. Ketamine was introduced in the anesthetic clinical exercise to replace phencyclidine, which caused the above-mentioned dissociative effects observed later on with ketamine too.

US soldiers injured during the Vietnam war were anesthetized with ketamine due to its wide safety margin and young people started to use it for recreational purposes and as part of the protests against the Vietnam war at that time. Ketamine has been widely used in veterinary medicine and sterile vials for this purpose continue to be diverted for recreational purposes.

7.1. Nomenclature

Names given to ketamine include the following: Anesthetic for horses, Bump, K, Ket, Kit- Kat, Kizzo, Special K, Vitamine K, Mono Mix, or Business Monkey, Keta, Ketamine, Keller, Super K, Super Acid, etc. Curiously enough, in the UK is also known as Horse and Cat Valium (valium for cats) since it is an anesthetic used in these animals. In the US it is also called L.A. Coke. The combination of ketamine and cocaine is known as CK or Calvin Klein and when it is used mixed in marihuana joints it is called Mary-Kay.

To refer to the particular state caused by this substance, users talk about the K state, they say that they have visited K-land or K-zone. In the UK they also say to have gone through the K-Hole. In the UK and the US ketamine users are called K-Heads or K-Holers.

7.2. Ways of administration

Ketamine is characterized by its versatility in terms of possible ways of administration. When it is used for recreational purposes, almost every way is possible although sniffing dried ketamine powder is the most used one.

- **Intravenously and intramuscularly:** In liquid form, intravenously or intramuscularly. They are used by "psychonauts" and people addicted to ketamine.

- **Through the rectum:** Introducing the subsance in liquid form.

- **Nasally:** Sniffed in powder, as if it was cocaine or amphetamine.

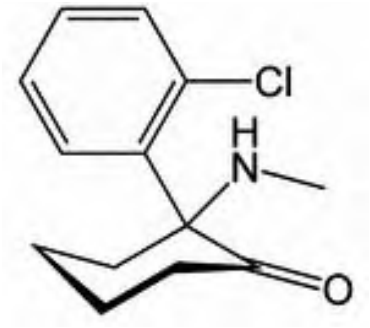
- **Smoked:** A little powder can be added when making marihuana or hashish joints or by impregnating a cigarette previously wet by the tongue with the powder. Users can also impregnate cigarettes with ketamine in liquid form and wait until they dry, but in this case the concentration of the active principle would be much lower.

- **Orally:** Both in powder and in liquid form although it has an unpleasant flavour (like salty aspirine in powder). It can be consumed directly or mixed with juices or soda drinks. When in tablets, pills or capsules it is usually mixed with MDMA ("ecstasy").

7.3. Pharmacology

Ketamine is a cyclohexylamine, (R,S)-2-(O-chlorophenyl)-2-methylamino-cyclohexan-1-one. It belongs to the family of dissociative anesthetics together with phencyclidine (PCP, "angel powder"). (Figure 26). It is partially water-soluble (1:4) and alcohol-soluble (1:14), and very liposoluble, therefore, it goes through the blood-brain barrier very easily, reaching the central nervous system.

Figure 26. Ketamine's chemical structure.



www.esacademic.com

The comercial product in Spain (Ketolar) is presented in vials in a slightly acid solution (pH 3,5-5,5) with a concentration of 50 mg of base ketamine per mililitre of solution (Figure 27). This preparation contains a 50% racemic mixture of the two optical isomers or enantiomers that exist: isomer S(+) ketamine (1-ketamine, levorotatory isomer) and R(-) ketamine (d-ketamine, dextro isomer)[77,78].

Figure 27. Comercial presentation of Ketamine on sale in Spain.

www.pfizer.es

When administered intravenously, both isomers differ in their pharmacokinetics and their effects. In analgesic and anesthetic terms, the S(+)K is more powerful than R(-)K. It also has quicker anesthetic recovery and elimination, as compared to the racemic mixture and the enantiomer R(-)K[79]. Nevertheless, the R(-) K has hallucinogenic effects and in equipotent anesthetic doses, it causes more psychomimetic reactions than the S(+)K and the racemic mixture.

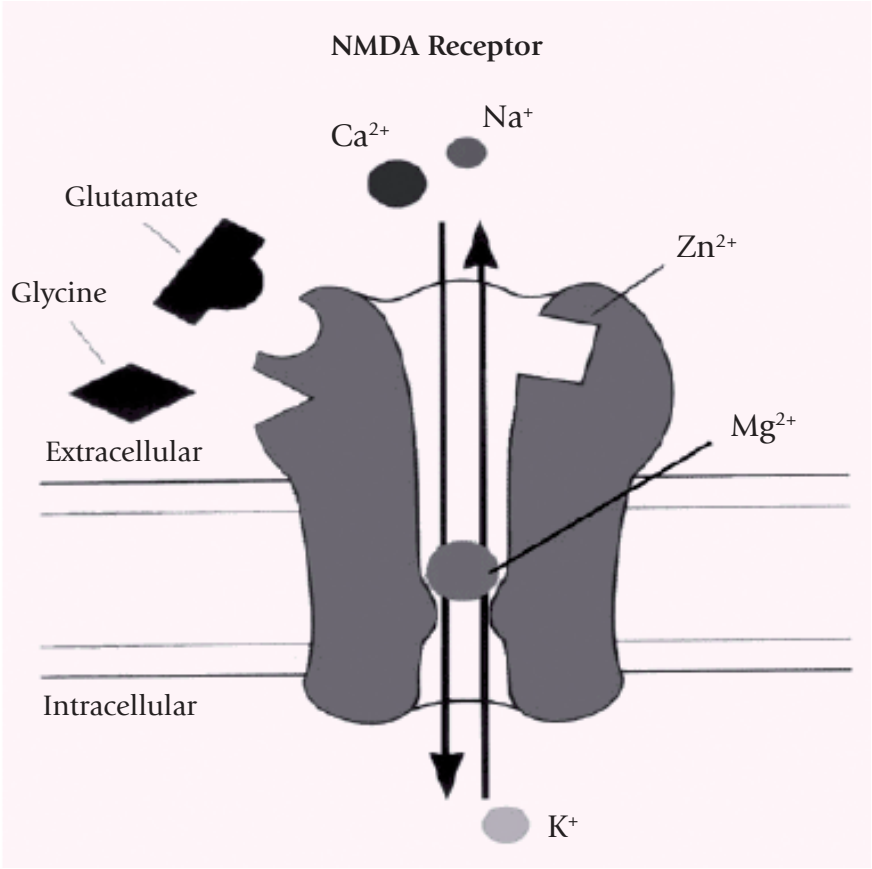
Regarding its pharmacokinetics, ketamine, intravenously administered, shows moderate protein-binding activity (12%-27%)[80]. It is quickly distributed within vascularized tissues (brain, heart, lungs) and then it is redistributed to muscular and adipose tissue, in which part of the product may stay and contribute to its accumulation when it is administered in repeated doses or in constant perfusion.

The concomitant administration of benzodiacepines, usual practice in the clinical application, extends the ketamine's effect. The presence of hepatorenal failure does not modify the ketamine's pharmacokinetics significantly.

Ketamine is metabolized by the hepatic enzymatic systems, mainly through cytochrome CYP3A4, and produces two metabolites: norketamine (metabolite I), which is less active, and hydroxynorketamine (metabolite II)[79,80]. It is not usual to find, in urine or faeces, metabolites or the ketamine itself in a not combined way. The elimination half-life of the ketamine is 2-3 hours. The bioavailability of the ketamine administered orally or through the rectum is limited due to the high first-step metabolism and/or its low absorption.

Regarding neurobiological aspects, the anesthetic action of ketamine is associated to the blocking or antagonism of the NMDA receptor, which is given this name because of its main agonist (N-methyl-D-aspartate). The NMDA receptor (Figure 28) belongs to the family of receptors of the glutamate, it is made up of, at least, two subunits (NMDAR1 and NMDAR2A-2D), has neuronal excitatory effects and it has been involved in the analgesia, anesthesia and neurotoxicity mediated by those neurotransmitters. Ketamine blocks the channel of the NMDA receptor in a use-dependent way, i.e. it only happens when the ionic channel connected has been opened[81].

Figure 28. The NMDA receptor



www.monografias.com/trabajos30/receptor-nmda/receptor-nmda.shtml

A great number of studies have proven that the ketamine's analgesic effects are mediated by its antagonist action on the NMDA receptors. There are high concentrations of these at the bone-narrow level and in areas of the central nervous system related to pain channels. Moreover, this same antagonist action on the NMDA receptors is responsible for the relaxing effect of ketamine on the bronchial smooth muscle[82].

Ketamine also acts on the opioid receptors and this is related to its capacity to produce analgesia in the central nervous system and at the spinal level, acting as an agonist in k receptors and as an antagonist in μ receptors, although the specificity of the interaction ketamine-opiate receptor is yet to be completely clarified.

It has been suggested that the ketamine has also a local anesthetic effect.

7.4. Clinical signs

1. Neurological and psychiatric

Ketamine administered intravenously causes dose-dependent unconsciousness and analgesia. As a single agent, in its regulated use as an anesthetic, it causes a "cataleptic" state, in which the patient remains with his/her eyes open, his/her pupils slightly dilated and slow nistagmus, with intact corneal reflexes and positive reaction to light. It can cause vocalization, intentional movements not related to surgical stimulation and muscular hypertonia. In subanesthetic doses (≥100 ng/ml) it has great analgesic power leading to a long postoperative analgesia period[83].

After an isolated administration, the duration of a general anesthetic dose (2 mg/kg intravenous) is 10-15 minutes and the spatiotemporal orientation is recovered in 15-30 minutes, although all this is influenced by the joint use of other anesthetics.

In the electroencephalogram (EEG), ketamine is able to reduce the activity of waves α, whereas waves β, δ, and τ increase[76]. The activity τ indicates the analgesic activity of ketamine and waves α indicate its absence[84].

Ketamine causes unwanted pyschological reactions when waking up from the anesthesia and are called emergency reactions. The usual signs are vivid dreams, delirium, hallucinations, feeling of floating and, sometimes, dissociative or out-of-body experiences that have been related to experiences close to death[75,76]. Agitation, moaning, crying, screaming and irrational verbalization have also been described.

These effects happen during the first hour, they usually disappear after one or several hours and can affect, approximately, 10-30% of adult patients receiving ketamine as only or main part of the anesthetic technique. Several factors, such as age, dose, sex, pyschological susceptibility and medicines administered concomitantly have an impact on the incidence of this type of reactions.

Ketamine has been used to treat different types of pain (post-herpetic neuralgia, oncologic, phantom limb, post-amputation pain, post-

laminectomy and lumbar pain, sympathetic reflex dystrophy, fibromyalgia, etc.), and it has been proven that it reduces the amount of morphine necessary to relieve the pain and reduce or prevents tolerance to morphine[85]. Nevertheless, due to its risks if it is taken over a long period, the use of ketamine as an analgesic is limited to really selected cases.

The usual consumption of ketamine, as a drug of abuse, has been associated to the emergence of panic and anxiety attacks, memory problems, concentration difficulties and flashbacks. Its use in big or constant doses is very likely to cause selective brain damage in the long term. These effects of chronic consumption may remain for months and up to even two years after quitting using ketamine.

Under its effects, the user can lose control of his/her acts for several hours, and even lose consciousness and memory. This may lead to extremely dangerous situations, particularly if we take into account the analgesic qualities of this drug, since if the user is seriously injured, he/she may not notice it, which could have serious consequences for the user or third parties.

Ketamine can make people with depressive syndrome think about suicide or to try and kill themselves; it can also make agitated people become violent and aggressive. This effect is similar to that of many other drugs (alcohol for example) but, under the effects of ketamine, death is represented in quite a peculiar way, differently from other substances, and this may entail very different consequences. A number of scientific works associate suicide with the combined use of alcohol and ketamine[86].

Moreover, using ketamine in rave parties and discotheques increases the possibility of having a "bad trip" due to the intensity of the stimula (light, sound, people…). Besides that, the possibility of suffering physical damages increases due to the incapacity caused by this substance.

The use of image techniques has enabled to observe that, after taking ketamine over a long period of time, there is a decrease in the volume of white matter in both frontal lobes and in the left temporary region of the cerebral cortex, although the exact mechanism of these actions is still unknown[87].

Finally, ketamine has antidepressive effects that were fortuitously discovered in 1994[88]. Later on, some studies have confirmed the antidepressive effects of ketamine, particularly, in patients with serious depression and that have become resistant to usual treatments[89,90,91]. This effect does not seem to be associated to the effect of ketamine on NMDA receptors[92,93].

2. Respiratory

Ketamine does not have any depressing effect over ventilation[94] but it can cause apnea if administered in very high doses[83]. Nevertheless, respiratory depression can be caused by the concomitant use of sedatives.

Ketamine relaxes the bronchial smooth muscle and when it is administered to patients with bronchial hyperreactivity and bronchospasm, it improves lung compliance.

3. Cardiovascular

Unlike other intravenous anesthetics, ketamine (0.5-2 mg/kg) is associated with an increase in heart frequency and blood pressure both at the systemic and lung level. Regarding patients with ischemic cardiomyopathy the consumption of myocardial oxygen may increase[95].

Although the mechanism by means of which ketamine stimulates the cardiovascular system is still unkown, it seems to be related to the direct stimulation of the central nervous sytem, and also, to the inhibition of the reuptake of catecholamines.

4. Others

Other effects related to the use of ketamine have been described: anorexia, nausea, vomiting, skin rashes, malignant hyperthermia, variations in intraocular pressure[83], apnea, laryngospasm or lung edema[96].

Urinary symptoms (urgency to urinate, painful urination), associated to severe ulcerative cystitis, have been described as a result of the chronic use of ketamine[97,98] among recreational users.

There is no information available on the excretion of ketamine through breast milk, so no effects on the newborn baby can be ruled out.

Severe intoxication

The emergence of severe intoxication depends both on the dose and the route of administration used and the simultaneous or consecutive presence of other drugs of abuse (alcohol or other depressants, stimulants, etc.) and, like with other psychoactive substances, on the specific characteristics of each person.

Severe intoxication[99] usually goes with tachycardia, pupillary dilation (mydriasis), perspiration, vomiting, shivering, hyperreflexia or convulsions. Less frequently, bronchospasm and laryngospasm, nistagmus and even rhabdomyolysis. Moreover, users may suffer from anxiety, depressive symptoms, paranoid ideas and reference ideas, hallucinations, depersonalization, alteration in the course of thought and derealization. Altered perception of colours and of the own body, feeling of being suspended in the air and synesthesias (mixed perception through the senses, such as hearing colours, seeing sounds, etc.) are frequent.

Although some people have died from an overdose of ketamine[100], most of the times it is difficult to ascribe the death to the presence of ketamine only, since, with some exceptions[101], polydrug is the pattern found in toxicological reports. In Spain, for the time being, there has not been any report on deaths directly related to the abuse of ketamine, although it usually accompanies other substances according to a small proportion of toxicological reports on people that passed away because of a severe reaction to a non-medical use of psychoactive substances.

Abuse and addiction

Its constant use causes tolerance and addiction, besides memory and learning difficulties. Psychiatric alterations include panic attacks, depression, night terrors, paranoid deliria, persistent hallucinations and suicidal ideas.

Withdrawal symptoms

If it is used sporadically and in not very high doses, withdrawal symptoms rarely occur when the use is interrumpted. However, if it is used often

and in high doses, clear withdrawal symptoms appear and are characterized by intense migraine, articular pain and nausea, accompanied by anxiety and irritability and flashbacks.

7.5. Therapeutic intervention

Treatment for severe overdose or intoxication

Ketamine has not any antidote, therefore treatment in the case of intoxication will be symptomatic and of general support.

It is recommended to stimulate urination through acidification with ascorbic acide and ammonium chloride as long as the existence of myoglobinuria (which could cause severe kidney failure) has been previously ruled out. This procedure should be carried out in experienced medical services[99].

Patients in a coma wake up few hours later, although the sedation may last for 24 hours. If there is anxiety or hallucinations, it may be necessary to use benzodiacepines and even antipsychotics if there are psychotic symptoms.

The abuse and addiction to ketamine will require a multidisciplinary approach, combining medical, psychological and social support aspects.

7.6. Legal situation

Ketamine is not included in the lists of substances controled by the UN Convention on Psychotropic Substances of 1971. Nevertheless, in March 2007 the Commission on Narcotic Drugs (UN Office on Drugs and Crime) passed the Resolution 50/3 "Responding to the threat posed by the abuse and diversion of ketamine", which suggested the Member States to consider the possibility of implementing a system of measures to be used by government bodies in order to facilitate the appropriate detection of the diversion of this substance.

Moreover, the above-mentioned Commission on Narcotic Drugs, in its 53rd period of sessions in March 2010, approved the resolution E/CN.7/2010/L.9 "International cooperation in countering the covert

administration of psychoactive substances related to sexual assault and other criminal acts", which, among other recommendations, urges the Member States to consider the possibility of including (in their national legislation or in the relevant guidelines) aggravating circumstances whenever psychoactive substances are surreptitiously administered to commit a sexual assault; it is the case of the ketamine, among others (GHB, flunitrazepam, etc.).

For this reason, and by means of the Order SAS/2712/2010, of 13th October, Spain decided to include ketamine (as well as its stereochemical variations, racemates and salts) in the list IV of the Appendix I of the Royal Decree 2829/1977, of 6th October, which regulates the production, distribution, prescription and dispensation of psychotropic substances and preparations and which transposes the international measures set in the Convention on Psychotropic Substances of 1971 signed by Spain on 21st February 1971.

Other countries like the US, Canada and the UK, had already legal measures in place in order to control ketamine although at that time this substance was not subject to international control measures by the UN. Ketamine is included in the List III of the United States Controlled Substance Act since 1999; in the UK list of Class C drugs since 2006; and in the List I of narcotics of Canada since 2005.

Regarding its possible involvement in drug-related sexual crimes, in the US ketamine is considered in a very similar way to GHB and flunitrazepam (Rohipnol), both of which are subject to a specific legislation: The Drug-Induced Rape Prevention and Punishment Act, October 12, 1996.

In Spain ketamine is a medicine for hospital use only, i.e. it is only dispensed on prescription in hospital chemists. The illegal supply uses preparations for veterinary use obtained in Spain or in other countries. Regarding its licit medical use as an anesthetic in human beings and animals, ketamine is subject to the Act 29/2006, of 26th July, of Guarantees and Rational Use of Medicines and Health-Care Products. Its illicit sale and distribution (dealing and illegal trafficking) are forbidden and have direct legal consequences (both under the Act 29/2006, of 26th July, of Guarantees and Rational Use of Medicines and Health-Care Products and the Penal Code in its section "Offences against public health").

VIII. Spice drugs

Although products similar to the ones called "spice" today were already sold in the 70s and 80s of the 20th century, in the last decade of the century different products started to emerge under attractive names such as Natural Herbal Ext (or XTC), Green XTC, Green Smoke, High-Incense, etc., which were theoretically promoted to be burnt in cauldrons or devices similar to those used to perfume the air with incense bars, in the shape of a pyramide or conic tablets for slow combustion.

At that time already, it was explicitly written that these products were not fit for human consumption. Despite this, they were smoked, inhaled and drunk in infusion or cooked. At that time their basic composition was ephedra as a basic plant, to which different mixtures of other aromatic plants, not always psychoactive plants, were added.

The international legislation, increasingly strict not only with forbidden substances, but also with those necessary to obtain and produce them (precursors), made its availability in the market decrease and led to an increase in the price of the products, which was not worth for users. The effective international control over the cultivation, production, sale and purchase and trafficking of ephedra and ephedrine forced the modification of the raw materials used to elaborate these products.

Since 2004 there are many alternative products to those, with a new format and composition that manage to avoid the current legislation.

8.1. Nomenclature

Spice drugs is the name given to a wide variety of products allegedly containing mixtures of exotic, aromatic and psychoactive plants not subject to international traffic restrictions applied to psychotropic substances or narcotics.

Most of them are offered and sold on the Internet[4,102], but they can also be found in many shops open to the public: Smart shops, which distribute Smart drugs, today known as spice drugs.

There are different names given to these products: spice silver, gold and diamond, gorillaz, tropical sinergy, egypt, K2, solar flear, earth impact, moon rocks, lotus bleue, etc (Figure 29).

Figure 29. ***Spice drugs***

www.guardian.co.uk/society/2009/may/07/spice-gold-herbal-high-drugs
(Picture by Alicia Canter)

They are offered and sold as coadjuvant elements for aromatherapy, meditation, yoga or other oriental disciplines. They are "incenses", not substances for human consumption, but their possibilities for human consumption were announced some time ago in specialized distribution lists, forums and blogs.

8.2. Composition

In many cases, although not in all of them, some of their contents in plants are explicitly stated: *Rosa canina, Pedicularis densiflora, Leonotis, Nymphea, Althaea, Canavalia marítima, Zornia, etc.*

The analysis of the composition of the products on sale has enabled to draw a number of conclusions:

1. The plants allegedly declared as part of their composition are not always detected.

2. On the contrary, products not declared in the composition, most of them synthetic cannabinoids, are detected.

3. They usually contain high amounts of Vitamin E, which hampers the physical-chemical analysis of other components.

The analysis of the non declared components of spice drugs became widespread since 2007, with the participation of several European specialized groups (THC-PHARM and AGES PharmMED, among others), and contributions from the US Drug Enforcement Administration (DEA) and the Health Science Institute of Japan. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) carried out a first thorough research that led to a technical report in 2009[103]. The most frequently found cannabinoid compounds were JWH-018, JWH-073, CP47497 and HU-210.

8.3. Ways of administration. Ways of use

Regarding the usual doses and ways of use, we do not know much but the information available on the Internet forums and blogs. Some of the plants that are part of the composition of these products have been sometimes used to replace marihuana and their psychoactive effects are well known, as well as the fact that they do not prove positive in the usual urine test used to detect tetrahydrocannabinol (THC). They can be used alone, smoked in combination with cannabis and tobacco or as an infusion.

The number of sales and the scope of use of these products have not been estimated yet. However, the secondary school survey on drugs in 2010 (ESTUDES), carried out by the Government Delegation for the National Plan on Drugs, in collaboration with the Autonomous Regions and Cities, has included, for the first time in Europe, a module on the prevalence of use of new substances in which spice has been included. Results have been included in this report, in the section regarding the current situation of consumption. In short, and with regard to their use, 1.1%, 0.8% and 0.5% of Spanish students between 14 and 18 years old used spice sometime in life, during the last 12 months and during the last 30 days respectively.

8.4. Pharmacology

The pharmacology of cannabis derivatives and its relation to the human endocannabinoid system has already a scientific record of near fifty years. Spain has taken a very active part in this specific area of basic research.

Two cellular receptors for cannabinoids have been identifid (CB1 and CB2) and there is a good understanding of the relation between physical-chemical structure and activity. The research carried out with animals has provided experimental models of high capacity to predict the psychoactivity of cannabinoids. Around 70 natural cannabinoids have been identified. The most popular one, which serves as a reference, is THC. Hundreds of synthetic derivatives have been synthetized from them.

Table 5 shows a simplified classification of synthetic cannabinoids:

Table 5. Classifications of synthetic cannabinoids.

AGONIST CANNABINOIDS:	**- Dibenzopyrans (or classical)** Tricyclic structure similar to that of THC Synthetic THC or dronabinol, HU-210, HU-211 **- Bi or tricyclic analogs (non classical)** CP 55940, CP47497 **- Amino alkiyindoles** Win 55212-2, JWH-015, JWH-018, JWH-073
ANTAGONIST CANNABINOIDS:	**-Endocannabinoids (eicosanoids),** synthetized from phospholipid precursors of cellular membranes **- Diarylpyrazoles** SR 141716 (Rimonabant) , SR 144528 **- Others (under analysis)**

Source: Clinical Committee of the Government Delegation for the National Plan on Drugs.

Antagonist synthetic cannabinoids have been object of an extensive research in animal and human models, particularly regarding diarylpyrazoles. One of them, "Rimonabant", was even authorized as a

prescription medicine to treat obesity. Nevertheless, less than two years later, the European Medicines Agency decided to revoke its authorization after objectifying psychological and psychiatric disorders related to its use[104].

Very few agonist synthetic cannabinoids have managed to meet the requirements needed to be authorized as a prescription medicine: Nabilone and Dronabinol (synthetic THC). They have been used to mitigate the side effects of some antineoplastic chemotherapies, specifically nausea, vomiting and pain. At present, this line of work is still open for alimentary behaviour disorders, demyelinating diseases, neuropathic pain, chaxesias stemming from different causes and terminal state of different diseases, AIDS among others[105].

8.5. Clinical signs

Initial alerts on spice drugs started in Europe after some hospital emergencies related to their use in Italy, Germany and Austria[106]. Since 2008, the alarm became widespread and made this group to be included in the Early Warning System (EWS) of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), which has published three documents on these substances[13,107].

There is almost no information available on the specific effects of their use. In any case, their profile is very similar to that of cannabis, although the psychodysleptic activity starts faster.

Severe intoxication

Effects of severe intoxications observed in hospital emergency services are the following: tachycardia, agitation, slight mental confusion, fluctuating level of consciousness and recovery within a few hours. However, the routine toxicological tests could not identify the substances responsible for those effects. Fast urine tests detect THC derivatives but they do not prove positive with synthetic cannabinoid derivatives such as spice drugs.

Withdrawal symptoms

There is not any final information on the existence of withdrawal symptoms after interrupting frequent use, use in high doses or constant use over time, althoug some isolated cases have been described. In spite of that, the withdrawal symptoms, if any, are likely to be similar to those of cannabis, since the psychoactive effects of spice drugs are similar to those caused by cannabis.

Abuse and addiction

Again there is little information on the matter, but frequent use or constant use over time, as well as use in high doses, are likely to entail addiction, like cannabis. The relatively short evolution of the "spice phenomenon" may be hampering the visibility of its possible effects in the long term.

8.6. Therapeutic intervention

Treatment in the case of intoxication will be symptomatic and of general support. It must be always taken into account that although spice products contain cannabic derivatives mainly, they can be mixed with other types of substances with similar effects to those of cannabis.

Treatment of abuse and addiction of spice-type products will require a multidisciplinary approach, combining medical, psychological and social support aspects.

8.7. Legal situation

On the time of publication of this report, no spice-type product, neither the plants part of their composition, nor synthetic cannabinoids, are considered to be, at the international level, illicit substances under control of the UN Conventions of 1961 and 1971.

At the EU level, representatives of the EMCDDA and Europol concluded in 2009, after going through all the available information on the subject, that the compounds JWH-018, CP 47497 and their equivalents did not

meet, at that time, the criteria set by the Early Warning System (EWS) in order to be regarded as substances that could be put under international control. Of course, the EWS considers the possibility of revising this conclusion in accordance with the information provided by the different Member States over time.

However, some EU countries such as Denmark, Germany, Estonia, France, Ireland, Italy, Latvia, Lithuania, Luxembourg, Austria, Poland, Rumania, Sweden and the UK have implemented, during 2009 and 2010, control measures regarding some or all spice products available in the market[107]. Spain has not implemented any legal measure yet.

IX. GHB/GBL

The gamma-hydroxybutyric acid (GHB, 4-hydroxybutanoic acid, gamma-hydroxybutyrate, hydroxybutyrate or sodium oxybate) was synthetized by H. Laborit in the 60s when he was trying to find a medicine that could cause brain effects similar to those of the gamma-aminobutyric acid (GABA) and that could cross the blood-brain barrier, unlike GABA aministered exogenously. Later on, GABA was found out to be an endogenous substance working as a neurotransmitter and whose main location is the Central Nervous System, but also other body tissues.

GHB is a depressant although, depending on the dose, it can cause a mixture of sedative and exciting effects. It has some approved uses as a medicine (anesthetic, treatment of sleeping disorders, treatment of alcoholism and its withdrawal symptoms, treatment of narcolepsy, etc.). However, because of its effects, it also has a high potential of abuse that has been confirmed since 1990 to nowadays.

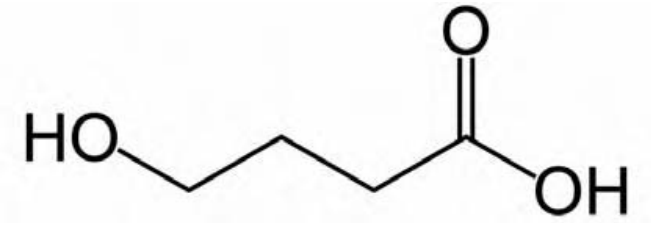
9.1. Composition

The GHB can be synthetized from succinate semialdehyde (SSA) and GABA, but it can also metabolize again into SSA and GABA. GHB can also be synthetized from two precursors: gamma-butyrolactone (GBL) or 1.4-butanediol (BD). Both substances are industrial products used as a solvent, stain remover or rust remover (GBL) or as a raw material to produce other organic chemical products (BD) and they are misused in order to turn into GHB in the organism.

GHB, just like GBL, can also be formed during fermentation processes; this is why they can be found in some beers and wines, but these amounts are insignificant and are not able to cause any biological effect[108].

GHB is a substance with a very simple molecule of low molecular weight (Figure 30).

Figure 30. GHB



www.psicofarmacos.info

9.2. Nomenclature

It is equivocally named "liquid ecstasy" (not having anything to do with MDMA or ecstasy) and also baby's bottles, liquid X, liquid G or just G, liquid E, drinkable gold, Easy Lay, Scoop, Fantasy or Cherry Meth.

9.3. Ways of administration. Ways of use

GHB is a colourlesses odorless and almost insipid substance (its flavour is slightly salty sometimes). It is used intravenously for anesthetic purposes, but when used as a drug of abuse it is usually presented as a white powder dissolved in water inside small glass bottles ("tins, pots or baby's bottles") from which people drink, or in all kinds of bottles (often bottles of water). It is mixed with other drinks. It is part of the so-called club drugs or dance drugs usually used in parties.

Despite being a sedative and having depressant effects, the use of GHB causes (initially) a feeling of inebriation, euphoria, reduced anxiety, increased libido, intensified tactile perception and social disinhibition; this is followed by drowsiness and loss of motor control. These last two effects may appear just after the use if this substance is used in high doses.

Usual doses stand between 500 mg and 2-3 g, higher doses cause intense sedation and severe intoxication[27]. The user starts to feel the GHB effects around 10-20 minutes after the use; the effects usually last from one hour and a half to three hours and end within 3 or 4 hours[42,109] or even more if used in a high dose or mixed with alcohol[110].

Its impact on libido and the fact that it favours sexual disinhibition explain its use as an aphrodisiac in gay atmospheres and in high-risk sexual relations.

Moreover, GHB increases the production of the growth hormone and, although the mechanism behind this increase is yet to be clarified, it is known that some athletes and bodybuilders legally used (until 1992 in the US) and still use GHB as a dietary complement to increase the concentrations of the growth hormone, and therefore their muscle mass.

It is also used as a drug to facilitate sexual assaults or as a method to force others to do something that they are not willing to do voluntarily (signing documents, etc.) since it causes sedation, loss of consciousness and anterograde amnesia (impossibility to remember events occurred just after taking the substance).

GHB, as a medicine, is marketed as an intravenous anesthetic in several countries (*Somsanit* in Germany and *Gamma OH* in France), as a therapeutic option to treat alcoholism (*Alcover* in Italy) and as a treatment for cataplectic crisis and excessive daytime sleep in narcolepsy, in the US, Canada, Switzerland and the EU.

9.4. Pharmacology

The GHB mechanism of action is not fully known. The endogenous GHB acts as an agonist of the GHB own receptors, which are coupled with proteine G. The GHB that is exogenously administered does not show this selectivity for the GHB receptors and acts on GABA-B receptors.

The main pharmacological effects, as already mentioned, are sedation and hypnosis, leading to sleep very similar to physiological sleep (REM-Rapid Eye Movement and slow wave stage) but waking up three or four hours later. It is also an anxiolytic weak analgesic that stimulates the secretion of the growth hormone (GH). Low concentrations of GHB lead to the release of dopamine. GHB also causes immunosuppression after its administration, although the relevance of this fact is ignored[111].

The combination of GHB with any other substance depressing the central nervous system (alcohol, benzodiazepines, opioids, ketamine or others)

intensifies the effects of both substances and increases the possibilities of suffering intense sedation and loss of consciousness, as well as serious intoxication.

Regarding its pharmacokinetics, after its oral administration, GHB is quickly absorbed and reaches its plasma peak after 20-45 minutes. It is widely distributed and, unlike other neurotransmitters, it goes through the blood-brain barrier reaching high concentrations in the brain.

Its plasma elimination half-life is short, 20-50 minutes. 6 hours after its administration, its presence in blood is no longer detected and only 5% is found in urine. 12 hours after its administration, it cannot be detected in urine. As a result of this, it is very difficult to detect GHB with the quick methods normally used in emergency services; therefore, it is not easy to document either those cases in which there are suspicions about the use of GHB or those in which the users themselves admit to have used it. In high doses, it shows a non-linear kinetics that may be involved in the extension of its effects when there is an intoxication[112].

9.5. Clinical signs

Besides the effects sought, both as a medicine and as a drug of abuse, already mentioned, it can entail the following clinical signs[113,114]:

1. Neurological and psychiatric
States of confusion and agitation, respiratory depression with phases of apnea, hypothermia, mydriasis, shivering, myoclonus (very typical), ataxia, decreased muscle tone and difficulty in concentrating.

2. Cardiovascular
Hypertension and tachycardia due to action on GABA- B receptors. If there is severe intoxication, it could cause bradycardia and death.

2. Respiratory
Respiratory depression and respiratory distress with non-cardiogenic lung edema.

3. Gastrointestinal
Decreased gastrointestinal motility, constipation and feeling of abdominal swelling.

4. Kidney
Polyuria due to activation of the kidney sympathetic system.

5. Sexual
It increases sexual prowess initially, but its chronic use reduces libido and causes impotence.

6. Others
Somnambulism and alteration of the sleep cycle. As to pregnant women, it increases the intensity of contractions and cervix dilation.

Severe intoxication

The most important consequence of an overdose is the decrease in the level of consciousness, which can range from drowsiness to a coma, with hypotonia and hyporeflexia[115], mydriasis, bradycardia and even death. The patient often recovers quickly (1-2 hours), even being in a coma, and without any neurological after-effects, unless there are other related complications (hypoxia, head trauma, etc.).

If the coma lasts for over 3 hours, there may have been a simultaneous use of other toxic substances depressing the central nervous system (alcohol, opioids, etc.). Apnea or bronchial complications may cause death[116].

Withdrawal symptoms

Interrupting the use of GHB, if it is frequent or in high doses, may cause withdrawal symptoms. Some cases have been documented, particularly among recreational users, rather than among those using it for therapeutic purposes (treatment of narcolepsy, etc.). Symptoms include insomnia, anxiety, nausea, shivering, tachycardia, cramps and perspiration, and they usually subside in 3-10 days.

There can be serious withdrawal reactions in patients with overdose of GHB or related compounds, particularly if they have also used other drugs or alcohol[116].

Abuse and addiction

The use of GHB can cause tolerance and addiction. Some studies carried out with sodium oxybate (Xyrem) for the treatment of narcolepsy suggest the existence of crossed tolerance with alcohol[117]. This must be taken into account, particularly in cases of recreational use, given the frequency of use of GHB together with other substances of abuse, especially alcohol.

9.6. Therapeutic intervention

Treatment of severe intoxication

Treatment will be symptomatic and of general support. It must be always taken into account that the patient may have used other substances of abuse that can aggravate or hide the symptoms. There are no standardized tests to detect GHB that can be used in hospital emergency services, and, as few doctors are familiar with this drug, many cases of GHB may go unnoticed[118].

The bradycardia related to the GHB overdose responds well to intravenous atropine. However, the depressant effects caused by GHB do not respond to the treatment with Naloxone or Flumazenil, although its use is frequent to rule out the co-participation of other substances (opioids or benzodiacepines, for example) in the intoxication.

Treatment of abuse and addiction

In general terms, the abuse and addiction to GHB and related products (GBL and BD) will require a multidisciplinary approach, combining medical, psychological and social support aspects.

However, for the time being, there is almost no information available to endorse specific recommendations to treat the abuse or addiction to gammahydroxybutyrate (GHB) and gammabutyrolactone (GBL).

The treatment of withdrawal symptoms is also symptomatic and includes the use of anticonvulsants in order to reduce agitation and the risk of convulsions. Intubation is not usually needed, and appropriate hydration, oxygentherapy and atropine if there is bradycardia are usually

enough. Some serious cases have required the use of barbiturates, very high doses of short-action benzodiacepines and antipsychotics[119]. Stomach-pumping and the use of activated charcoal have not proven effective and physostigmine must not be used.

9.7. Legal situation

In the EU, representatives of the EMCDDA and Europol concluded in 2000, after going through all the information available on the subject, that the Member States should assess the possibility of implementing control measures on GHB[120].

The National Commission on Narcotic Drugs of the UN Office on Drugs and Crime introduced the GHB in the Schedule IV of the Convention on Psychotropic Substances of 1971 in March 2001 since, until that moment, it was not considered to be an illicit or controled substance at the international level.

Spain, through the Order SCO/469/2002 of 19th February 2002 (RCL 2002,676), included GHB (and the salts, esters or ethers resulting from GHB) in the List IV of Appendix I of the Royal Decree 2829/1977, of 6th October, which regulates the production, distribution, prescription and dispensation of pyschotropic substances and preparations and transposes into the Spanish legislation the international measures set in the Convention on Psychotropic Substances of 1971, signed by Spain on 21st February 1971.

Nowadays, the vast majority of the rest of EU Member States have GHB control measures in place[121]. In the UK, for example, GHB was included as a Class C drug in June 2003.

GHB was included in the List I of the US Controlled Substances Act since March 2000 (before its inclusion in the UN Convention on Psychotropic Substances of 1971) although, since the use of GHB was authorized to treat narcolepsy (*Xyrem*) by the Food and Drug Administration (FDA), this medicine (only if it is used for therapeutic pruposes) is included in the List III of the above-mentioned regulations.

Regarding GHB permitted uses, for therapeutic purposes:

- It is marketed as an intravenous anesthetic in several countries (*Somsanit* in Germany and *Gamma OH* in France).

- It is used as a therapeutic option to treat alcoholism (*Alcover* in Italy).

- In 2002 it was approved as an orphan medicine under the name of sodium oxybate by the FDA (US), for the treatment of narcolepsy cataplectic crisis (*Xyrem*).

- In 2005, the *Xyrem* was approved by the FDA for the treatment of excessive daytime sleep in narcolepsy.

- Also in 2005, the *Xyrem* was approved for the treatment of narcolepsy cataplectic crisis by the European Medicines Agency and by the Swiss and Canadian relevant authorities.

- In 2010, the FDA rejected the request to include fibromyalgia as one of the indications in which the use of *Xyrem* may be permitted.

In Spain, GHB is regulated as a medicine for hospital use, which implies that it can only be obtained on prescription of hospital specialists and it is only dispensed in hospital chemists[122] for the treatment of narcolepsy.

Regarding GBL and BD, at the time of publication of this report, their sale is legal, they are lawfully used for industrial purposes and they are not subject to any control or monitoring (either as substances of abuse or as their precursors). Nevertheless, it is known that these products (GBL and BD) are directly used for psychoactive purposes and they are also used for the clandestine synthesis of GHB in small domestic laboratories.

Finally, as to the possible involvement of GHB in the so-called "drug-related sexual assaults", some countries include this substance in their legislations on the matter. In the US, GHB is included in the Drug-Induced Rape Prevention and Punishment Act, October 12, 1996. Since it is colourless, odorless and its flavour is mild, GHB can be easily mixed with any drink, normally alcoholic, which strengthens its effects. The aim of the sexual offender is to sedate the victim in order to reduce his/her resistance or to cause an overdose to make the victim lose his/her consciousness completely[1]. It is difficult to determine the causality

ascribable to GHB as well as the exact frequency of the sexual offences committed due to the difficulty, because of its quick elimination from the organism, in detecting GHB in blood or urine more than 12-24 hours after its use[110].

X. Other plant-derived substances of abuse

There is a great number of plants whose use is, or has been in the past, part of a ritual of initiation, transition to or expression of belonging to a certain religion. We know of some of them through the chronicles of seafarers and conquerors that met groups of believers. Others went unnoticed and have been recently discovered or rediscovered[123].

This monograph addresses the most popular ones, some of which have gone out of their traditional boundaries, which has led to a conflict between those that defend religious freedom and those responsible for implementing supply restrictions on substances dangerous to health. Sometimes the plants are forbidden because they contain substances controlled by international agreements or regulations of some particular countries. Generally speaking, their traditional use has been independent from the later knowledge of their chemical contents. Those members involved in the religious practice claim that their use should be accepted because they are part of a sacred ritual, regardless their eventual psychotropic contents (Table 6).

10.1. Ayahuasca

It is not a substance but the liquid resulting from processing two plants at a low temperature. The proportion of each of them and the type of plants mixed may change. In the Amazonic area, the most traditional formula is mixing lianas of *Banisteriopsis caapi*, a plant containing harmine and harmaline, reversible inhibitors of monoaminooxidase (IMAO) considered to be the real sacred plants by shamans, with others containing dimethyltryptamine (DMT), especially the leaves of *Psychotria viridis* (Figure 31). The latter, despite containing the base of the hallucinogenic psychoactive agent, does not cause any effect without the first one. This mixture is called "vine" or "rope of the dead", AYA-HUASCA[124]. It is prepared to be used in a group by a man initiated in the knowledge, a shaman, so that those that take it can enter into contact with the "totality", getting feelings of extracorporeal or astral travel[125].

Figure 31. Characteristics of the leaves, flowers, fruits and seeds of the species Banisteriopsis caapi and Psychotria viridis.

www.santodaime.be/en_history_ayahuasca.html

Although the ceremonies were known to exist since the beginning of the 19th century, they spread from Brazil in the mid-20th century by means of a booming syncretic Christian-Amazonian church, the Santo Daime Church, named by one of its most popular hymns, DAI ME or GIVE ME (love). It was founded by Raimundo Irineu, a bleeder of the rubber tree (latex) that had the ocassion to have a deep knowledge of the traditions of tribes that were not completely "civilized" at that time.

Due to the psychotropic substances that it contains, ayahuasca is subject to a number of restrictions regarding its international trade, trafficking and use, although in Brazil it is totally accepted by the Federal State. In 2009, after many lawsuits, the US Supreme Court granted Santo Daime the status of church and accepted the use of ayahuasca in its rites. Its legalization is still unaccepted in Europe.

Its use, for ritual purposes in communities, does not seem to be highly dangerous to health. Its effects are slightly sedative, visual and auditory hallucinatory, favouring the contact with the universe and distorting time

and space. Sometimes the experience seems to change the whole sense of life of some people[126].

Finally some people ascribe to ayahuasca some therapeutic power against cancer, which, for the time being, is far from having been verified.

10.2. Iboga

Ibogaine is the common name of 12-methoxybogamine, a psychodelic and halluginogenic active contained in the roots of some plants, particularly the *Tabernanthe iboga*. They are a magic product used in initiation ceremonies and rites of passage in religious practices of some tribal groups in Western Africa (Figure 32). The most popular participants call themselves "bwiti" and are found in several countries in the Gulf of Guinea, Equatorial Guinea included[126].

The fact that Equatorial Guinea was a Spanish colony favoured very interesting anthropological studies and even today there are researchers with studies on this substance yet to be published[1].

[1] Unpublished conversations with Professor Dr. Juan Aranzadi, Full Professor of Social Anthropology, UNED .

Figure 32. Characteristics of the leaves, flowers, fruits and seeds of the species *Tabernanthe iboga*.

www.erowid.org/library/books_online/golden_guide/g51-60.shtml

Ibogaine is a powerful and long lasting psychotropic whose action may last for more than 48 hours. It initially causes confusion, agitation and panic; therefore it is advisable to contain the individual until his/her body calms down and the hallucinatory activity and the film revision of the own life begin. The length of these effects was attractive, for recreational purposes, in the 80s, but its use has decreased considerably due to its side effects and its difficult extraction[125].

By chance, its recreational use by people addicted to morphine and heroin enabled to obtain data on some therapeutic potential that was object of an experimental study in France and the US, although the

decrease in the heroin epidemic made it difficult to draw conclusions on the matter. Ibogaine seems to reduce the opioids' withdrawal symptoms, although its effectiveness and its benefit-risk ratio are yet to be confirmed. Prior tests were carried out with little success in order to assess its use as an antidepressant (Lambarene).

Ibogaine is classified as a dangerous substance and its use, trafficking and sale are forbidden by the national legislations of many countries. Nevertheless regulations are very unspecific sometimes and it is not clear whether they also affect unprocessed root powder.

10.3. Sage

Salvia divinorum is a plant belonging to the *Lamiaceae* family coming from the region of Oaxaca in Mexico. It was directly consumed by Mazatecs by chewing its fresh leaves or as an infusion, for ritual or medical purposes. The species was characterized in Europe in 1962 by Epling and Játiva (Figure 33).

It is given different names: ska pastora, ska Maria, herb Maria or herb of the Gods, Sally D, Diviner´S Sage, Lady Salvia, Magic Mint, etc.

Figure 33. ***Salvia divinorum***

www.elicriso.it/es/plantas_alucinogenas/salvia_divinorum/

The active principle responsible for its psychoactive effects is found is Salvinorine A, which is found in the leaves and was identified by Ortega and Valdés in the 80s. Salvinorine A is a diterpene, not an alkaloid like classical halluginogens, therefore its molecule does not contain nitrogen and it is insoluble in water.

Sage psychoactive effects result from the fact that Salvinorine A is a powerful agonist of Kappa opioid receptors and, unlike what happens with the rest of hallucinogenic substances, it has no effect on the serotoninergic receptors that are the main cause of hallucinogenic effects in most substances of this type, or on NMDA receptors.

Although sage leaves are traditionally consumed chewed or as an infusion, the usual way of consumption for recreational purposes is by smoking its leaves (dry and crushed) or extracts – prepared with different power- in small pipes or water pipes (water bongs); the effects begin in 1-2 minutes and last for approximately 15-20 minutes. Salvinorine A is degraded in the gastrointestinal tract, therefore the use of sage as an infusion is little effective if looking for psychoactive effects.

Its effects are the following: loss of control over body movements, mixed or film visual hallucinations, feeling of dreaming awake, alteration in spacial-temporal limits, uncontrollable laugh, and even psychotic alterations in vulnerable users. Dizziness, amnesia and intense migraine have been described after the end of the rest of effects. There is no information available on the long-term effects of the use of sage or on its possible addictive potential.

Most information on the effects caused by the use of sage comes from the information provided by users on the Internet (Figure 34). They warn about the possibility of having a "bad trip" and they give extensive information on methods and specific websites where this substance can be acquired, on its specific legal situation in different countries and also on the fact that the above-mentioned psychoactive effects make this plant become a substance used mostly by experienced psychonauts or users looking for new experiences, rather than by recreational users of other drugs such as cannabis or alcohol.

Figure 34. Commercial presentation of *Salvia divinorum* announced on the Internet.

www.salviafacts.com

The information available today on the prevalence of use of sage comes from different groups of population, different sources and different countries and for the time being it does not enable to make appropiate comparisons.

Regarding sage legal situation, neither the plant nor its active principle (Salvinorine A) are under the UN international control. However, recently, Belgium, Denmark, Italy, Lithuania, Latvia, Rumania, Sweden, Australia, Japan and several states in the US have included sage and Salvinorine A among the substances controlled by drug regulations. Other countries apply the legislation on medicines and medicinal products. In Spain its sale to the public for medicinal purposes is forbidden since 2004; however it is accepted for ornamental purposes (ORDER SCO/190/2004, 28th January, which establishes the list of plants whose sale to the public is forbidden or restricted due to their toxicity).

10.4. Hallucinogenic mushrooms

There are between 70 and 100 mushrooms containing active psychotropic alkaloids. Most of them belong to two families: agarics (*Amanita muscaria* and *panterina*) and psilocybes (*cubensis* and *mexicana*, the most common ones) (Figure 35). When they are used as an hallucinogen they are used raw or after being dried. Any of them can be found in many wooded areas

of conifers in the Northern Hemisphere and in high meadows. Psilocybes also grow in tropical areas such as Mesoamerica. Unfortunately, it is easy to mistake them for other similar species of serious or fatal toxicity, so its cultivation by experienced people is safer[124].

There are doubts regarding the religious use of *amanitas* in druid rituals or rituals of the Indo-European Irminsul, but there is no doubt regarding the use of psilocybes in most Mesoamerican pre-Columbian cultures. They were known as *"Teonanacatil"* and mixed, after a long and slow process, with other substances, mainly honey and *"txocoatl"* (chocolate), made up the potion of the daily ritual conceived to beg the sun rise in the morning by addressing the father of the *Huitzilopotxli* gods and making human sacrifices. There are very detailed chronicles of some missionaries after the Discovery, Fray Bernardino de Sahagún among them[125].

turbinaweb.blogspot.com/2008/01/micologa-en-riaza.html;
bemarmon.wordpress.com/2007/11/07/jornadas-micologicas/;
paradojadelareinaroja.blogspot.com/2008/12/venenos-y-ponzoas-ii-cultivando-hongos.html;
miradelotrolado.blogspot.com/2008/07/exp-psicoactivas-6-psilohuasca.html

The hallucinogenic compounds of psylocibes are psilocine (4-hydroxymethyltryptamine, 4-OH-DMT) and psilocybin (phosphoryl-4-hydroxydimethyltryptamine, 4-PO-DMT), similar to the serotonin neurotransmitter (5-HT) structurally speaking. Actually, psilocybin is a prodrug of psilocine since, in vivo, psilocybin turns into psilocine after dephosphorylation.

Generally speaking, its effect is similar to a "trip" with LSD-25 but it changes depending on the dose, the atmosphere in which it is used and the user's idiosyncrasy. Although most of the effects are related to the central nervous system, they also stimulate the cardiovascular system (tachycardia, increased blood pressure, etc.) due to the presence of phenylethylamines in many of these mushrooms. Users refer to a pleasant feeling of relax and well-being, alteration in visual perception and in the perception of time and space, but sometimes, also anxiety, panic reactions, feeling of depersonalization and paranoid psychosis of subacute and chronic course. These subjective effects can be accompanied by mydriasis (pupillary dilation), shivering, nausea, abdominal pain, diarrhea and muscular pain.

Artificial cultivation techniques of some mushrooms with culinary value such as *champignons* or sitaki have been successfully used to produce hallucinogenic mushrooms such as psilocybes, in some damp and dark habitats with controlled bioclimate. They are sold and used fresh, dried, treated (boiled or cooked together with other products) or even in form of capsules. Users buy the products directly from the place in which they are produced, on the Internet or in specialized establishments (smartshops).

The hallucinogenic power varies depending on the species, the type of cultivation, the way of preparation, etc. but, in general, the percentage of active ingredients in the dried product is 10 times that of the fresh product due to the fact that 90% of the weight of the fresh product is water. The effects usually begin 30 minutes after the use and last for approximately 4-6 hours.

Regarding the prevalence of use, hallucinogenic mushrooms are preferably used by young people. In 2009, the EMCDDA[5], on the basis of data from the population surveys carried out in the EU Member States, estimated that between 0.3% and 8.3% of young people between 15 and

24 years old had used hallucinogenic mushrooms sometime in their lives and between 0.2% and 2.8% had done it during the year previous to the survey. In Spain, the data obtained in the survey ESTUDES 2010 show that the yearly prevalence of use (last year) of hallucinogenic mushrooms among Spanish students between 14 and 18 years old stood at 1.6%.

At present, no medical use of hallucinogenic mushrooms is known. Although in general terms they are not considered to be very dangerous, psilocine and psilocybin are included in Schedule I of the Convention on Psychotropic Substances of 1971. Nevertheless, the control over these substances is interpreted and carried out very differently in the different Member States.

Amanitas are very different. Their use is usually regarded as much more dangerous and it is accompanied by nausea, shivering, vomiting, diarhea and unpleasant hallucinatory-delirous feelings. Their artificial cultivation has not been possible yet and their use as a recreational drug is not very frequent. The amanitas active alkaloids are muscimol and ibotenic acid (which turns into muscimol), which causes a peculiar state of inebriation. Their identification is easier on the ground. Intoxications, sometimes very serious, are accidental and result from a mistake in the harvest. Poisoning from recreational use is exceptional.

As a curiosity, there is a microscopic purple mushroom named *Claviceps purpurea* that sometimes infects the rye and and spoils it as bread, especially in damp climates. This fungus contains several alkaloids of type ergotamine and ergotoxine and small amounts of lysergic acid amide, LSA, a precursor of lysergic acid diethylamide (LSD-25). In the Middle Ages the contamination of the bread by this fungus caused ergotism, called "Saint Anthony's fire", accompanied with intense vasoconstriction of extremities that could cause gangrene and hallucinations. It has been speculated, on solid foundations, about its deliberate cultivation to cause hallucinatory-delirous intoxication in the Viking culture[126].

10.5. Peyote

In the *nahuatl* lenguage, *peyotl*, *Lophophora williamsii*, is a cactaceae of yearly madurative growth able to resist big droughts that begins to run

short in its usual habitat because of furtive overexploitation (Figure 36). The are well documented records on it since it is an important part of the religious rituals of many tribes *huicholes* or *arawak of the South*, such as *apaches, sioux, pies-negros (black feet), chirikawas and mescaleros.* At present, there is still the tradition of the religious worship through the Native American Church, specifically authorized by the Drug Enforcement Administration (DEA) for the harvest and ritual use of the cactus.

The annual harvest takes place in a long and complex rite that lasts for several days, with intense conversations and public confessions, mainly at night, although today it can also be discreetly cultivated in flowerpots and protected terraced fields. Unfortunately, the "classical" ritual has become, on many ocassions, a form of exotic narcotourism offer[125].

Its hallucinogenic psychotropic agent is mescaline or trimethoxyphenylethylamine, which produces euphoria and facilitates introspection, with a considerable stimulating effect on the body and the esoteric imagery, with intense spiritual content. It causes visual hallucinations that remain when closing the eyes, increases tactile and proprioceptive sensitivity and provides some conviction of being in contact with the transcendent totality. It regularly becomes a substance for recreational use but not in a stable way[124].

Figure 36. ***Lophophora williamsii.***

www.erowid.org/plants/peyote/peyote.shtml

Peyote, which contains mescaline, must not be mistaken for a drink resulting from the distillation of maguey pulp. The maguey is a cactus of the *agaves* family called "mescal" in Mexico and that, together with the pulque, fermented alcoholic drink of the same pulp, were the most popular drinks in Mexico until recently. Tequila, also a distilled drink from the *blue Agave*, is the most popular one at the international level.

10.6. Khat

Catha edulis is an evergreen shrubby plant very resistent to dry climates (Figure 37). It comes originally from northeastern Africa (Ethiopia, Somalia, Eritrea and Kenya) and from the Asian coast of southern Arabia (Yemen, Aden). Its leaves are traditionally harvested and chewed. It contains two active psychotropics derived from phenyl-ethylamine: cathinone and cathine, both subject to international control and included in the schedules of the UN Convention on Psychotropic Substances of 1971.

Cathinone is not stable and oxidizes in ten days. Therefore, it is a dangerous plant from the toxicological point of view only when it is fresh. It is not frequent to find it in the black market. It can be planted in gardens and flowerpots far from its place of origin, but its quality gets worse as the weather gets damper. Consignments of rolled up leaves (bunches) sent regularly from Kenia to the UK and the US have been exceptionally detected. They were sent addressed to citizens and companies of Somali or Ethiopian origin. In some countries, such as the UK, the possession of the plant itself is not pursuited since 2006.

Cathinone serves as a basis to easily obtain methcathinone, a very powerful phenylethyl-amine, similar to methamphetamine, which is also under international control. There is a controversy about its carcinogenic potential in the mouth.

Chewing *khat* leads to a state of euphoria, feeling of mental sharpness and excitment. The user also experiments an increase of blood pressure and heart frequency. The effects begin to decrease after one hour and a half to three hours, but can last for up to 24 hours. At the end of the use of *khat*, there can be irritability, loss of appetite, depressive state of mind and difficulty in sleeping.

Figure 37. ***Catha edulis.***

www.fkog.uu.se/course/essays/catha_edulis/Pics/Catha_edulis_Specimen.jpg

The intense or long-term use of *khat* has been associated with several adverse effects such as dental alterations and gum diseases, gastrointestinal disorders (constipation, ulcers, gastritis and increased risk of tumours in the upper part of the digestive system) and cardiovascular disorders such as arrhythmia and ischemic cardiopathy. A weak association between the chronic use of *khat* and the emergence of mental disorders has also been described. Although there is no clear causal evidence, the symptoms of people with pre-existing psychiatric problems may get worse as a result of the use of *khat*.

It is not clear whether *khat* causes tolerance, physical dependence, addiction or withdrawal symptoms, but nightmares and slight shivering a few days after having chewed it have been described.

An estimated number of 10 million people chew *khat* all over the world. It is commonly found in the south-western part of the Arabian Peninsula and in eastern Africa, where it has been used for centuries because of its stimulating effects as part of a well established cultural tradition. According to a research carried out in Yemen, 82% of men and 43% of women admitted to have used *khat* sometime in their lives. At present, its

use among some immigrant communities in the US and Europe has caused alarm in the field of Public Health[127].

10.7. Betel

It is a cultivated palm tree called *Areca catechu* (Figure 38). Its seed (areca walnut) is masticable and its use is widespread in India and southeastern Asia. It is very popular in the Philippines, former Indo-China and the islands near Indonesia and Papua New Guinea. Betel walnuts have been traditionally used in several ritual ceremonies. However, at present, they have become stimulating and satiety-inducing appetizers.

At the end of the 19th century, betel was object of thorough researches carried out by Louis Lewin. Mastication is possible by combining pieces of walnut, leaves and a piece of clay in a small vegetable bag. It is sometimes mixed with tobacco and cadamomo, in a similar way to cocaine leave and lime. The leaves are not always from the plant itself but from a wild pepper (*Piper betel)*.

Figure 38. *Areca catechu.*

www.gastrosoler.com/pagina_nueva_65.htm

Its psychotropic active principles are piperazine derivatives: arecoline, arecaidine and its acids, resulting from alkaline hydrolysis because of salivation and mastication. The walnut has also many tannins and flavonoids. Betel leaves give carbachol-type aromatic oils. The effect is slightly stimulating, to a degree similar to tobacco or coffee. It colours teeth red and, in the long term, black. It has been traditionally used as a medicine in its context of consumption.

A number of studies have been carried out to assess its therapeutic potential to treat cognitive deterioration with no final results yet and its potential as a carcinogen in the oral mucosae has been proven. Its compulsive use and addiction have not been described, unlike

withdrawal symptoms, which have been proven. Betel is not subject to any restriction regarding cultivation, trafficking or use.

10.8. Kawa kawa

Piper methysticum is an evergreen bush of heart-shaped leaves that grows in the tropics, in habitats of damp forests up to 100 metres above sea level (Figure 39). The part that is used is the most superficial root, which is crushed until getting a whitish powder that is diluted in water or boiled in a tepid or cold infusion. It has sedative long-lasting effects (although it does not affect the level of consciousness excessively).

Piper methysticum played an important role in the social life of the natives of the Pacific islands when the Europeans arrived in the 18th century. Rhizome was taken, chewed or fermented in water to produce a brownish-gray potion with psychotropic effects.

Figure 39. ***Piper methysticum.***

http://commons.wikimedia.org/wiki/File:Starr_070515-7054_Piper_methysticum.jpg

Kavalactones are the active components of *Piper methysticum*, which is considered to be an anxiolytic, anti-depressant and mild sleep inducer. Contrasted double-blind studies have proven that it is an effective and safe substance (by using a standardized pure kawa extract as a reference). Nevertheless, its considerable liver toxicity has curbed its sale in Europe and the US.

No abuse or addiction have been described. Its use as an anxiolytic and antidepressant is very widespread in Micronesia.

10.9. Ololiuqui

Among the most recent rediscoveries in etnobotanic anthropology we can highlight the finding and recovery of the allegedly ancient ceremonies of the Mazateca mountains, in southeastern Mexico, which suggests the identification of the pre-Columbian term "Ololiuqui" with the flower of a climbing plant belonging to the family of *Convulvuláceas*. The flower is known as white, tricolour or purplish *Ipomea* in common botanics and as *Morning glory* or *Don Diego by day* (Figure 40). In its cultural context, it is the sacred material in a syncretic Christian-Toltec ceremony that has been known of through many studies.

This flower is also called Mary's Cloak, but it is not clear enough whether it refers to the Virgin Mary or María Sabina, the last great priestess of the Mazateca mountains, made quite popular by Albert Hoffmann, the man who discovered the LSD-25, in the 50s. This Swiss pharmacologist typified and identified the lysergic acid amide (LSA) in its seeds, very difficult to harvest, and in those of many other similar varieties, such as *Corymbas*. The active substance of ololiuqui is thus the lysergic acid amide (ergine), related to LSD and one of its precursors. The effect is mainly sedative, although it can cause mild hallucinations[128].

Figure 40. Purplish *Ipomea*.

www.erowid.org/plants/morning_glory/

The rational basis of its historical coincidence with the ancient rite is found in the documents of Francisco Hernández, protophysician of His Majesty the King Felipe II, who returned from his journey to the Indies in 1651 with the thorough harvest and description of 1,300 plants, unknown in Europe at that time, with details on their medicinal and magic-religious use. His work was forgotten until the beginning of the 20th century. The recent interest results from finding out that it was used in other rites of different areas in the Mexican mountains when there was psilocybe mushrooms shortage[124].

Ipomea's seeds are coffee colour, chestnut colour, and are appropriate for women. Those of *Corymba* are black and are considered to be the appropriate ones for men. The liquid resulting from crushing the seeds is drunk diluted in several drinks, mescal included. It is neither heated nor boiled or drunk as an infusion.

10.10. Solanaceous

Burundanga is the linguistic variant of African yoruba origin giving name to a well-known bush: the white beleno. In the popular language of *nahuatl* origin it is called *toloache* and in Spanish *"burladora"* or *"borrachero"*. It is one of the more than fifty plants, bushes or trees of the *solanaceae* family, which contain, among others, alkaloids with a structure similar to atropine (Figure 41). They can be found all over the world, except for desert or very cold steppe areas. Some of them are the following:

- *Brugmansia alba arborea*. (Angel's trumpets). It is the biggest one.
- *Datura stramonium*. It is also known as "devil's fig tree" and it is very common in Europe.
- *Belenos* or *Hyoscyamus, albus and niger*.
- *Atropa belladona*. Used as a cosmetic in the Roman Empire due to the extreme mydriasis it causes. It has also been used as an antispasmodic agent.
- *Mandragora* or *Mandragora officinarum*.

The alkaloids contained in this group of plants have been known and used, for different purposes (social or pharmacological) for more than thirty centuries. The most used ones are atropine (racemic form of hyoscyamine, combination of D and L isomers), escopolamine (or hyoscine) and hyosciamine (atropine L-isomer). These three compounds have antagonist effects on the colinergic receptor of muscarinic type, by reducing the activity of the parasympathetic system. Hyoscine butylbromide is the antispasmodic component of some popular medicines such as Buscapine or Cibalgine.

Hyoscyamus albus (Beleño blanco) http://waste.ideal.es/plantasvenenosas.htm
Mandragora http://waste.ideal.es/mandragora.htm
Datura stramonium http://waste.ideal.es/plantasvenenosas.htm
Atropa belladona http://waste.ideal.es/plantasvenenosas.htm

None of them are usually associated with chronic use, voluntary abuse or addiction and no specific withdrawal symptoms have been described as

a result of interrupting its consumption. Nevertheless, its use may cause severe intoxication, sometimes with potentially fatal effects. Actually, in the languages of pre-Romanesque origin the terms "beleño", "beleno" and "veneno" (poison) have almost the same meaning[129].

Burundanga is included in a publication on drugs of abuse because it is used, for criminal purposes, as a toxic, diluted in alcoholic drinks or inhaled in cigarettes to sedate victims of kidnapping, sexual assault or theft.

According to some hypothesis, this substance may even act through the skin contact or the inhalation of clothes or papers impregnated, although the data coming from the police and medical emergencies have not confirmed this hypothesis. It is true that it is absorbed through the skin, which explains its use in the form of skin patches against travel-sickness, but there has not been any registered case of will suppresion or amnesia through this way, not even in the most vulnerable groups, such as children and the elderly.

However, there are many literary references mentioning this substance as either one of the components of "magical" love potions used in the Middle Ages or as "ring poisons" during the Roman Empire.

Severe intoxication is accompanied with symptoms such as dry skin, hypertermia, dry mouth, lack of saliva and sweat, mydriasis, blurred vision, tachycardia, intestinal ilea and urinary retention because of its antimuscarinic effects. There can be mood swings, ataxia, inattention, distractions and memory deterioration. High doses cause disorientation, fabulations, slight euphoria and hallucinations, delirium, coma and even death.

The abuse for recreational purposes of some medicines with antimuscarinic effects such as trihexyphenidyl (Artane) (because of its slightly euphoric and hallucinogenic effects when administered in high doses) has been described.

Table 6. Plant-derived substances of abuse.

	AYAHUASCA	IBOGA	SAGE	HALLUCINOGENIC MUSHROOMS	PEYOTE	KHAT	BETEL	KAWA KAWA	OLOLIUQUI	BURUNDANGA
Origin	Amazon basin	Eastern Africa (Gulf of Guinea)	Region of Oaxaca, Mexico	Wooded areas of conifers in the Northern Hemisphere	Middle America	Northeastern Africa and Asian coast of Southern Arabia	India and Southeastern Asia	Oceania. Polynesia and Micronesia	Southwestern Mexico	Universal distribution except for desert areas or very cold steppe areas
Vegetable species	*Banisteriopsis caapi* + *Psychotria viridis*	*Thabernanthe iboga*	*Salvia divinorum*	*Amanita muscaria* *Amanita panterina* *Psilocybes cubensis* *Psylocibes mexicana*	*Lophophora williamsii*	*Catha edulis*	*Areca catechu*	*Piper methysticum*	*Convulvulaceas (Ipomea violacea)*	*Datura stramonium* *Hyoscyamus albus* *o niger* *Atropa belladona* *Mandragora*
Active principles	Harmine and harmaline and DMT (dioxy-dimethyl tryptamine)	Ibogaine	Salvinorin A	Amanitas: Muscimol and butenoic acid Psylocibes: Psilocin and psilocybine	Mescaline	Cathinone and cathine	Arecoline and arecaidine	Kavalactones	LSA (lysergic acid amide)	Atropines
Effects	Enteogenic, sedative, hallucinatory (visual and auditory)	Twilight consciousness states, confusion, agitation, panic, visual hallucinations	Loss of control over body movements, visual hallucinations, psychotic alterations, dizziness, amnesia and migraine	Psylocibes: panic states, visual hallucinations, paranoid psychosis Amanitas: nausea, shivering, vomiting, diarrheas, hallucinations and delirium	Stimulant. Talkativeness, visual hallucinations, increased tactile and proprioceptive sensitivity	Mild stimulant. Irritability, agitation, loss of appetite and difficulty in sleeping. Mental and gastrointestinal disorders	Stimulant. It colours teeth red and, in the long term, black. It may be carcinogenic for oral mucosae	Anxiolytic, mild antidepressant and mild sleep inducer. Liver toxicity	Stupefaction and mild sedation. Mixed hallucinatory effects	Dry skin, dizziness, low blood pressure and tachycardia
Further info	Shamanic product par excellence. Currently legally used by Saint Daime Church in Brazil and the USA	Magic product for initiation religious ceremonies in some tribal groups in western Africa	Used by Mazatecs for ritual or medical purposes	Used mainly by young people. Intoxication in Viking culture (rye ergot containing LSD-25 precursor)	It used to be part of the religious rituals of huichole or arawak tribes of the south It is still used in the Native American Church	Around 10 million people all over the world chew khat	Traditional use in celebrations. It has become a kind of stimulating and satiety-inducing appetizer. Hundreds of millions of people use it for social purposes	Significant role in the social life of the natives of the Pacific islands when the Europeans arrived in the 18th century. It is still moderately used for social and medical purposes	Aztecs and other tribes have used it in religious ceremonies and magic medical practices since pre-Hispanic times	It has been used as a component of witch or magic love potions in the Middle Ages as well as "ring poisons" in the Roman Empire period and other periods

Source: Drawn up by the Clinical Committee of the Government Delegation for the National Plan on Drugs.

XI. Therapeutic intervention

The addiction to any psychoactive substance is a complex disease that affects both the brain function and the person's behaviour and that can be accompanied, simultaneously or later on, by other mental disorders, as well as different infectious diseases related to high-risk behaviours developed during the use of drugs. From this point of view, the second edition (revised in 2010) of the publication "Principles of drug addiction treatment. A research based guide" of the National Institute on Drug Abuse (NIDA) suggests an update of the research on the different effective approaches to the treatment of addiction to different drugs[130].

The therapeutic intervention in disorders related to the use of emerging drugs should not ignore the key principles detailed in this report and these must be present in any treatment programme if we want it to be effective[130]. Therefore, we think it is advisable to use the edition of this monograph to support the consideration of these principles when planning and conceiving a therapeutic plan. They are the following[2]:

1. The addiction is a complex disease that can be treated and affects the brain function and the person's behaviour, which causes changes that may remain even after quitting drugs. This explains why people that have had drug addiction problems in the past are likely to relapse, even after long periods of abstinence and despite being aware of its potentially harmful consequences.

2. There is not an only treatment appropriate for everybody. The final objective for each patient is being productive again in the family, at work and in society.

3. Access to the treatment must be easy. Just like other chronic diseases, the sooner the treatment is offered, the higher possibility of being succesful.

4. An effective treatment must tackle both the abuse of drugs and the different related problems (physical, psychological, social and legal) and must adapt to the age, sex, ethnic group and culture of each patient.

---

[2] Modified by the Clinical Committe of the Government Delegation for the National Plan on Drugs.

5. Continuing the treatment during an adequate period of time is vital for it to be effective. Clinical research shows that most of the patients require at least three months of treatment in order to significantly reduce or interrupt the use of drugs, although the best results are usually obtained with longer treatments. Recovering from the addiction is a long-term process and it often requires several cycles of treatment.

Given the fact that many people usually quit the treatment prematurely, therapeutic problems must include strategies fostering the patient's attachment to the treatment.

6. Individual and group therapies, besides other types of behaviour therapy, are the most common methods of treament for drug abuse. Behaviour treatments favour the commitment of people to the treatment and, depending on their approach, can be oriented to increase the patient's motivation to change, give incentives for abstinence, develop skills to reject the use of drugs, replace activities in which drugs are used by constructive and rewarding activities, improve aptitudes to solve problems and foster better interpersonal relationships. Participating in group therapies and other support programmes during and after the treament can help to maintain abstinence.

7. To many patients, medicines are an important element of the treatment, particularly when combined with psychological orientation and other types of behaviour therapy. For example, methadone and buprenorfine are effective to help people addicted to heroin and other opioids to settle down and reduce the use of illicit drugs. Naltrexone is also an effective medicine for some people addicted to opioid substances or alcohol. Other medicines for the treatment of alcohol addiction include acamprosate and disulfiram. Regarding nicotine addicts, products replacing nicotine (such as patches, chewing gums or lozenges) or an oral medicine (such as bupropion or varenicline) can be effective components when they are part of a comprehensive programme of behaviour treatment.

8. Treatment and any other kind of intervention received by each patient must be regularly evaluated and modified if appropriate. The patient may require different combinations of resources and procedures during the treatment and recovery.

9. Many people with drug addiction problems have also mental disorders. Addicted patients must be evaluated to detect whether they have some type of mental disorder. When both types of disorders coexist, the treatment must be oriented to both (or more) problems and include the use of medicines, if necessary.

10. Medical desintoxication is just the first stage of the addiction treatment, and it is not enough to modify the abuse of drugs in the long term by itself. Although severe physical withdrawal symptoms can be safely tackled through medical desintoxication, which sometimes can smooth the path to an effective long-term treatment, desintoxication itself is not usually enough to help patients to attain long-lasting abstinence. For this reason, patients must be explained the need of the treatment and motivated to continue with it after the desintoxication stage.

11. Treatment does not need to be voluntary in order to be effective. Penalties or rewards from family, work or the penal legal system can significantly increase the number of patients joining treatment programmes. The same applies to the continuance rate and the final success of drug addiction therapeutic interventions.

12. The use of drugs during treatment must be constantly monitored since there may be relapses during the treatment. The fact of knowing that the use of drugs is monitored may be a great incentive for patients and may help them resist the impulse of using drugs. Monitoring also serves as an early indicator of a relapse in the use of drugs, which can indicate that it is necessary to modify the treatment plan for it to meet to the patient's needs better.

13. Treatment programmes must include analysis for HIV/AIDS, hepatitis B and C, tuberculosis and other infectious diseases, besides providing a therapy specifically oriented to help patients change those behaviours that increase the risk of contracting or transmitting infectious diseases.

The treatment for drug abuse typically tackles some of the drug-related behaviours that put people at risk of infectious diseases. Health education and psychological counselling specifically oriented to reduce the risk of infectious diseases can help patients to reduce or avoid behaviours associated to the use of substances. Moreover, psychological counselling

can help those already infected to deal with their disease in a better way. Complying with the treatment for the abuse of substances may facilitate compliance with other medical treatments. It is important for medical professionals to promote and support tests to detect HIV and hepatitis B and C and inform the patients that the highly active antiretroviral therapy (HAART) has proven effective to fight HIV, even in people with drug addiction problems.

Risk and harm reduction

Risk and harm reduction are intervention strategies conceived for people that do activities entailing health risks and that, understanding the difficulty in quitting, aim to reduce the associated risk and harm.

Risk reduction and harm reduction are similar but not identical concepts. Risk reduction is more similar to prevention (like in programmes conceived to avoid driving vehicles under the effects of alcohol or any other drug in order to prevent traffic accidents), whereas harm reduction rather relates to care and assistance (for example, maintenance programmes with opioid derivatives or assisted venipuncture rooms).

Both the EU Drugs Strategy (2005-2012) and the Spanish National Strategy on Drugs (2009-2016) aim to prevent experimental consumption and sporadic use from becoming constant use and especially, to reduce or limit health damages among people using drugs and, in general, the unwanted social and health effects related to their use[131,132].

The use of drugs, emerging or not, for recreational purposes is usually accompanied by the concomitant use of other substances that can strengthen the effects. Polydrug is, therefore, usual among the users of these psychoactive substances. It is vital to implement a number of measures in order to reduce the risks stemming from the use of drugs. Among these measures, some of them have to do with the substance, pattern and way of consumption, and others depend on other variables such as personality, mental and organic state of the user or context of consumption.

Please find below some recommendations on the matter:

- The use of substances of abuse is more likely during the weekend and "party" occasions. It must be previously decided whether to use drugs or not and in what amount. Setting a previous limit will help to be aware of what is being consumed.

- Previous information on how to use each type of substance should be available: whether it is recommendable to eat before or not, interactions with other substances, medicines, etc.

- Purchasing this type of drugs on the street, discotheques, parties or on the Internet is associated to risks of adulteration by other unspecified accompanying substances. Upon consumption, you never know their exact composition or concentration of the active principle that is to be taken. It is recommended to get information on the origin and purity of the substance to be used.

- Substance mixtures should be avoided. Mixing different substances may have unpredictable effects and in general, intensifies and aggravates unwanted effects.

- If it is the first time using a particular substance, the use must begin with low doses and if the user decides to increase the dose, the increase must be gradual.

- It is recommendable to use them in the appropriate atmosphere to each substance. It is not the same taking stimulants or depressants. If someone decides to use stimulants, the place to do it should be a relaxed comfortable atmosphere that does not intensify the agitation caused by this type of substances. It is never appropriate to use drugs alone, it is advisable to have someone else present that does not take the drug at the same time and can control the emergence of adverse effects or intoxication and ask for help if necessary.

- Whenever someone does not feel well or starts feeling something weird, it is appropriate to take him/her to a quiet place, interrupt consumption and take some fresh air. If after a while the problems continue, it will be necessary to go to an emergency service.

- After the initial feeling of euphoria and well-being, some substances cause a state of agitation that may lead to aggressive and/or violent

behaviours. It is advisable to have someone that has not taken drugs near.

- For any substance, after using a dose, it is appropriate to wait for the effects and then not to use it until several days later, in order to recover the normal level of activity. Sometimes users do not get the desired effects, so they repeat the dose, which entails the risk of accumulating effects as well as physical and psychological complications, increasing the risk of overdose or intoxication.

- It is advisable for the user to tell a close friend that he/she intends to use drugs since, if any problem arise, the friend could inform the health-care services.

- It is recommended not to drive vehicles, use machines or do activities that, under normal conditions, are high-risk activities, during the next 24 hours after the use so that the organism can take its time to recover. If the driver has taken substances to "get high" he/she must not drive and nobody should accept to be taken in the vehicle.

- Regarding sexual relations, using drugs may favour high-risk behaviours. Preventive measures must be considered.

- If you are with someone that has decided not to use drugs or that is fighting not to do it, you must not offer him/her the possibility of using drugs. Nobody must be encouraged to use drugs.

- It is not recommended to use drugs when you are in a low state of mind or with high levels of anxiety or stress. The use of drugs is not recommended either in people with previous personal or family history of mental problems. Due to their high psychotropic effects, these substances may trigger mental disorders that may not arise if drugs were not taken.

- The use of drugs is not recommended either in people with a history of physical alterations such as arrhythmias, etc.; in people being treated with medicines that may interact with the drugs used (tranquilizers, antidepressants, antipsychotics, antiepileptics, etc.); in pregnant women or while breastfeeding; in minors (period of physical and psychological development in which people is

particularly vulnerable to the effects caused by the use of legal and illegal drugs).

There are working platforms and nonprofit organizations that carry out a very valuable task in reducing risk and harm drug-associated effects, with a focus on recreational uses and leisure contexts (macrodiscotheques with techno music, night clubs with techno, house and trance music, rave parties, after-hour clubs, etc.).

The aim is not to promote the use of drugs, but to improve the information available to users or those thinking about beginning to use drugs in order to prevent problematic uses, minimize associated harm and favour responsible decision-making processes.

These resources serve as a complement to others offered by institutional bodies (central, regional and local administrations), scientific societies, etc. and include practical information on the different types of substances of abuse, specific resources for the different types of use and, in some cases, a substance analysis service (tests carried out on site) as an effective tool to contact users and provide orientation for a safer and less risky use.

Many of these platforms and organizations have a website whose contents on the matter are accessible to everybody: www.energycontrol.org, www.hazkunde.com, www.somnit.org, www.harmreduction.org, www.ailaket.com, www.grd.red2002.org.es, www.controlaclub.org., etc.

XII. Social aspects

Emerging drugs are a wide group of substances of very heterogenous chemical structure, effects and origin; their patterns of consumption are also very different, all of which determine their consequences and social impact. Amphetamines and their derivatives, ketamine, the different preparations of alkyl-nitrile (called *popper* in slang), different hallucinogenic mushrooms, or preparations made with plants (herbal extracts or plant extracts), make up an illicit market of substances with a versatile and dynamic structure, which makes it very difficult to control it and to predict its medium-term development. To have an idea of its variability, it may be noted that since 1997, when the EU Early Warning System (EWS) was set up, over 110 substances have been notified to the EMCDDA and Europol[13].

Their relevance as a criminogenic factor is very varied and is modulated by the conditions of use, social context, marginality situations, leisure activities associated to their use, etc. One of the most frequent problems is the associated use of other substances that intensify the capacity of modifying the behaviour by increasing the risk of committing offences or the incidence of accidents.

A less known aspect of this group of emerging drugs is their role as substances facilitating sexual assaults (Drug Facilitated Sexual Assault, DFSA). Epidemiological studies show limits to know the exact prevalence of use of this type of substances. Moreover, there are many difficulties in obtaining a biological sample for the toxicological analysis early enough to be able to detect their presence and establish causalities. Finally, this type of offences is not always reported and sometimes, although they are reported, they are not typified as such because of the above-mentioned reasons.

Most of these uses are voluntary[133,134], the most used substances for these purposes are ethanol, flunitrazepam, gamma-hydroxybutyrate (GHB) and ketamine[135].

GHB and its precursors are transparent and they have almost no flavour, therefore they can be mixed without any suspicions from the victim. They are usually mixed with alcohol, which intensifies the decrease in the level of consciousness. These features make GHB one of the most used

substances for this purpose in the US[133,136]. Similar data exist for Germany and other European countries[137,138]. However, a wide review carried out by Németh, Kun and Demetrovics (2010)[139] has only proven the presence of these substances in 0.2-4.4% of sexual assaults.

In a research on sexual aggressors and victims carried out in Poland in 2000-2004, the substances most frequently detected were amphetamines and THC, followed by alcohol, MDMA, and benzodiacepines (oxazepam, nordazepam, estazolam)[140]. In a review of 1,014 cases of drug facilitated sexual assaults in London,[141] the presence of alcohol (alone or with other substances) was detected in 470 cases (46%), illegal drugs were detected in 344 cases (34%), with cannabis being the most frequently found (26%), followed by cocaine (11%). In 21 cases (2%) a sedative substance or a substance favouring dishinbition was detected (MDMA, GHB and benzodiacepines). In a research on 1,806 women that admitted to have suffered a sexual assault in Sweden[142], ethanol and/or other drugs were not detected in 559 cases only (31%). The most frequent illicit substances were amphetamines and cannabis derivatives.

In a recent study carried out in Ontario (Canada)[143] on 182 cases of sexual assault, urine tests detected several substances in 44% of the cases (alcohol in 12.9%, and alcohol together with other drugs in 18.0%). The substances found together with alcohol were cannabinoids (40.2%), cocaine (3.2%), amphetamines (13.8%), MDMA (9.2%), ketamine (2.3%), and GHB (1.1%). The striking fact was that the victims ignored to have used drugs in 87 cases, which suggests that they may have been drugged in order to facilite the sexual assault.

The facilitating role of the use of methamphetamines has also been described in relation to violent behaviours[144,145].

A case-control study carried out in 2009 proves the correlation between the use of this substance and committing a homicide[146]. In 2006 Cartier, Farabee and Prendergast published a research that concluded that there was a statistically significant relation between the use of this substance and the criminal recidivism and violent behaviours[147]. However, a prospective study carried out on 478 young people in Vancouver in 2009 found a relation between the use of alcohol and violent behaviours, but the relation with the use of methamphetamine was not proven[148]. Other

studies suggest that the use of methamphetamine plays a facilitating role in domestic violence[149,150].

Several studies have detected a higher risk of death in drivers that had used amphetamines as compared to the general population[151]. These and other studies enable to state that the use of these substances increases the risk of accidents and violent death[152,153,154].

Modifications in reaction speed, concentration, perception capacity, psychomotor responses, etc. depend on the effects of the substances used (related to the dose, mechanism of action, associated consumption of other substances, etc.). The effect of the use of these substances on driving is very negative as it significantly increases the risk of an accident.

The presence of these substances in traffic accidents shows and is in line with the spread of their use in neighbouring countries, much below substances like alcohol, cannabis or cocaine. In a research carried out in Swizerland in 2010[155], in 4,794 drivers suspected of using drugs (4,243 men and 543 women), the substances most frequently found were cannabinoids (48%), ethanol (35%), cocaine (25%), opioids (10%), amphetamines (7%), benzodiacepines (6%) and methadone (5%).

In a research carried out on people suspected of driving under the effects of drugs in Sweden in 2008, GHB was detected in 215 cases (39%)[156]. Another study on the same group of drivers published by the same authors in 2008 identified the presence of amphetamines (alone or with other substances) in 15,898 out of the 26,556 cases of drivers analysed (60%), being the only substances present in 6,094 cases[157]. In Sweden, the illegal drug most frequently used by people killed in a car accident are amphetamines[158]. These results differ from those obtained by Norwegian authors (Gjerde, Normann, Pettersen and cols) in 2008[159]. They detected zopiclone (1.4%), benzodiacepines (1.4%), codeine (0.8%), tetrahydrocannabinol (0.6%) and amphetamines (0.3%). Two or more drugs were detected in 0.6% of the cases (15% of the drivers that tested positive in drugs).

XIII. Legal aspects

The use of new substances for recreational purposes and their inclusion in human consumption raise the need for a normative system able to adapt to the dynamism and versatility of the market and to involve the different countries in an integrated and lively solution. From the point of view of legal regulations, their effectiveness depends on their capacity to solve problems in a positive risks/benefits balance. Unappropriate regulations may cause more problems than those aiming to solve initially. An example of the adaptation of regulations in terms of effectiveness is not penalizing the use, as it is the case in Spain, and damage reduction policies. The proportionality principle requires sensible laws, leaving the criminal code as a last resort, with the basic principle of minimum penal intervention.

Declaring a particular substance illegal is the final result of a process that starts with the existence of social or health problems resulting from its use. Many debates on the legalization or not of a particular substance forget this point. Substances do not emerge as illegal substances, they are declared illegal after a process that shows the objective risk of its use. There is different sensitivity when talking about food additives, medicines or pesticides, regarding which everybody accepts the strict application of the so-called "principle of precaution", according to which a substance can only be used once its harmlessness has been completely proven, unlike the drugs used for recreational purposes, which are declared illegal when they are proven to be harmful.

As to the substances included in international treaties, their production, distribution and marketing would fall under the offences classified in our Criminal Code, in Chapter III, offences against public health (Articles 359,360,361,361 bis, 362, 363, 364, 365,366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378).

The voluntary use of any of the substances known today as emerging drugs is incompatible with driving motor vehicles, and, depending on the intensity of their effects, it may be considered to be an offence classified in article 379 (chapter IV of offences against road safety) of our Criminal Code:

"1. Driving a motor vehicle or a motorbike sixty kilometres per hour on an urban road or eighty kilometres per hour on an intercity road faster

than permitted in the relevant regulations will be punished with a prison penalty from three to six months or with a fine from six to twelve months or with works for the community from thirty one to ninety days, and in any case, deprivation of the right to drive motor vehicles and motorbikes for more than one year and up to four years.

2. *The same sentences will be applied to people driving a motor vehicle or motorbike under the effects of toxic drugs, narcotics, psychotropic substances or alcoholic drinks*. In any case these sentences will be applied to those driving with an alcohol rate in breath above 0.60 milligrams per litre or with an alcohol rate in blood above 1.2 grams per litre."

For this norm to be applicable it is necessary to have the psychoactive substances included in the appropriate list of monitored substances, and, besides, their use must affect the driver's psychomotor functions that enable to meet driving requirements.

The history of the internationalization of regulations on marketing, distribution and use of drugs starts in 1909, when thirteen nations held a meeting in Shanghai and set up a Commission that led to the first treaty on drug monitoring in 1912 (the "Hague Opium Convention"). After a number of Conventions (1920, 1925, 1931, 1936) in 1946 the United Nations (UN) set up the Commission on Narcotic Drugs under its authority. The UN drew up the Single Convention on Narcotic Drugs of 1961. Two bodies were set up: the Permanent Central Committee on Narcotic Drugs and the Monitoring Body on Narcotic Drugs; their fields of responsibility were integrated into the International Narcotics Control Board (INCB) on 2nd March 1968.

The INCB functions are contained in the following treaties: the Single Convention on Narcotic Drugs of 1961, modified by the Protocol of 1972; the Convention on Psychotropic Substances of 1971, and the UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988. In general terms, the INCB is responsible for:

a. Regarding the production, trade and licit use of drugs, the INCB in cooperation with governments, tries to guarantee appropriate drug supplies for medical and scientific purposes, as well as to prevent the diversion of drugs from licit sources to illicit channels. The INCB also monitors the control implemented by governments over the chemical

products used for the illicit production of drugs and assists governments to prevent the diversion of these chemical products towards illicit traffic.

b. Regarding the production, traffic and illicit use of drugs, the INCB determines the deficits in national and international monitoring systems and helps to correct these situations. The INCB is also responsible for the evaluation of the chemical products used in the illicit production of drugs in order to determine whether they must be subject to international control or not.

In order to comply with these obligations, the INCB:

a. Manages a system to predict the needs of narcotic drugs and a system to voluntarily present predictions on the needs of psychotropic substances, and monitors licit activities through a statistical information system in order to help governments to reach a balance between supply and demand.

b. Monitors and promotes measures taken by governments to prevent the diversion of substances frequently used in the illicit production of narcotic drugs and psychotropic substances, and evaluates these substances in order to determine whether it is necessary to modify the scope of the control implemented in accordance with Charts I and II of the Convention of 1988.

c. Analyses the information provided by governments, UN bodies, especialized institutions or other relevant international organizations in order to guarantee that governments observe the provisions of the international monitoring treaties and recommend the necessary corrective measures.

d. Maintains a permanent dialogue with governments in order to help them comply with the obligations contained in the international monitoring treaties and recommends, if appropriate, the provision of technical or financial assistance for that purpose.

The INCB must ask for explanations if the treaties have been violated, in order to suggest the appropriate corrective measures to those governments that are not fully implementing the provisions contained in

the treaties or that are having difficulties in implementing them and, if necessary, assists governments to overcome those difficulties. Nevertheless, if the INCB considers that the necessary measures to correct a serious situation have not been taken, it can notify the matter to the stakeholders, the Commission on Narcotic Drugs and the Economic and Social Council. The treaties enable the INCB, as a last resort, to recommend the parties to stop importing drugs from or/and exporting drugs to the offending country. In all cases the INCB acts in close cooperation with governments.

The INCB assists national administrations to comply with their obligations in accordance with the different Conventions. For that purpose, it suggests the organization of regional training seminars and programmes for people responsible for the drugs control, and takes part in them.

Most of these substances known as emerging drugs are contained in the green list (list of pyschotropic substances subject to international control). This list is regularly updated with the inclusion of new substances detected and identified as substances whose use entails serious risks to human health, restricting or forbidding (depending on the particular case) their production, trade and distribution.

The INCB publishes a list of psychotropic substances subject to international control every year. It is known as "green list" and contains the reference information on all substances. The green list is made up of four parts and is updated every year to include the decisions made by the Commission on Narcotic Drugs and all the new related data provided to the INCB.

We can define as monitored substance all those substances included in the green list and thus subject to international control and restriction. A similar term is controlled substance. It is defined as controlled substance any chemical substance or chemical precursor whose production, possession, trade, distribution or use are regulated by law. The Controlled Substances Act was approved in the US in 1970 (Controlled Substances Act, CSA; Title II of the general act for the prevention and control of the abuse of substances of 1970, 21 USC Sec. 812), which listed the substances that should be included as "controlled substances", and that should be subject to strict regulations. Given the fact that the US have

signed the international agreements, the list of substances contained in the INCB green list is applicable.

It should be taken into account the use for recreational purposes of some psychodrugs regulated in the medicines act. In this case all the regulations on prescription and dispensation of these products are applicable.

No matter how lively the regulatory capacity is, it will always come after the problems raised and our obligation is to have a legislative system able to solve problems as effectively and early as possible, but it must be understood as part of the solution, and as a means, not as the magical solution to all problems. In a globalized world, regulations must be integrated into supranational structures facilitating their effectiveness.

In Spain there are the following regulations on this matter at the state level:

International treaties ratified by Spain for narcotic drugs and psychotropic substances:

- Single Convention on Narcotic Drugs of 1961, amended by the 1972 Protocol amending the Single Convention on Narcotic Drugs.
- Yellow list: list of narcotic drugs subject to international control.
- Convention on Psychotropic Substances of 1971.
- Green list: list of psychotropic substances subject to international control.
- UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.
- Red list: list of precursors and chemical substances frequently used in the illicit production of drugs.

National Legislation for narcotic drugs and psychotropic substances:

- Act 4/2009, of 15th June, of control over drugs precursors (Official State Gazette [BOE in Spanish] no. 145, 16th June).
- Act 17/1967, of 8th April, on narcotic drugs (BOE 86, 11th April) and updated lists in appendix.

- Royal Decree 641/2009, 17th April, regulating drug taking control processes and authorized analysis laboratories and setting complementary measures of drug taking prevention and health protection in sports (BOE no. 112, 8th May).
- Royal Decree 1573/1993, 10th September, of restrictions to the distribution of psychotropic products and narcotic drugs (BOE no. 235, 1st October).
- Royal Decree 2829/1977, 6th October, of regulation of psychotropic medicinal preparations and substances (BOE no. 274, 16th November) and updated lists in appendix.
- Order SAS/2712/2010, of 13th October, whereby Ketamine is included in the Appendix I of the Royal Decree 2829/1977, of 6th October, of regulation of psychotropic preparations and substances. (BOE no. 255, 21st October).
- Order SCO/1870/2008, of 17th June, whereby oripavine is included in the list I attached to the Single Convention on Narcotic Drugs of 1961. (BOE no. 156, 28th June).
- Order SCO 2359/2004, of 2nd July, that modifies the Appendix I of the Royal Decree 2829/1997, of 6th October, of regulation of psychotropic products and substances.
- Order SCO 3685/2003, of 22nd December, whereby amineptine is included in the list II of Appendix I of the Royal Decree 2829/1997.
- Order SCO 1906/2002, of 15th July, whereby paramethoxymethylamphetamine is included in the list of the appendix I of the RD 2829/1977, of 6th October, of regulation of psychotropic products and substances.
- Order SCO 469/2002, of 19th February, whereby certain active principles are included in appendix I of the RD 2829/1977, of 6th October, of regulation of psychotropic products and substances.
- Order SCO 2004/2006, of 19th June, amending the Order SCO/469/2002, of 19th February, whereby certain active principles are included in Appendix I of the Royal Decree 2829/1997, of 6th October, of regulation of psychotropic products and substances.
- Order of 7th February 2000, whereby certain active principles are included in list I attached to the Single Convention on Narcotic Drugs of 1961. (BOE no. 42, 18th February).

- Order of 31st January 2000, whereby 4-methylthioamphetamine (4-MTA) is included in list I of the Royal Decree 2829/1977, of 6th October, of regulation of psychotropic preparations and substances. (BOE no. 33, 8th February).
- Order of 27th December 1995, whereby some active principles are included in appendix I of the Royal Decree 2829/1977, of 6th October, of regulation of pyschotropic preparations and substances. (BOE no. 26, 30th January).
- Order 25th April 1994, of regulation of prescriptions and special requirements for the prescription and dispensation of narcotic drugs and medicines for human use purposes (BOE no. 105, 3rd May).
- Order of 18th February 1982, whereby preparations containing Dextropropoxyphene are included in list II attached to the Single Convention on Narcotic Drugs of 1961. (BOE no. 48, 25th February).
- Order of 14th January 1981, of development of RD 2829/1997, of 6th October, of regulation of psychotropic preparations and substances and of complementary control regulations regarding the production, commercialization and distribution of psychotropic substances (BOE no. 25, 29th January).

XIV. Conclusions

1. According to the UN Office on Drugs and Crime (UNODC), in 2009 an estimated number between 149 and 272 million people all over the world (3.3% to 6.1% of population between 15 and 64 years old) used illegal drugs sometime during the previous year. Cannabis users are the main group of users, followed, in terms of volume of use, by amphetamines, opioids and cocaine. In the EU, the prevalence of use of amphetamines in the last year, among people between 15 and 64 years old, ranges from 0.0% and 1.7 % depending on the country.

2. The patterns of use of psychostimulants in Europe are heterogenous. Some studies suggest that the different types of stimulants (amphetamines vs cocaine) may play the same role or have a relatively stable position within the specific patterns of use of substances in each country. Actually in some countries (Spain and most of southern and western European countries) cocaine would be the prevailing stimulating substance, whereas in other countries (northern and central European countries), amphetamines and their derivatives prevail.

3. In Spain, in 2009 3.7% of the population between 15 and 64 years old had tried amphetamines sometime in their lives, 0.6% had used them during the last year and 0.3% had done it during the month previous to the survey. The trends of use are stable although, since 2005, a downwards trend can be observed. Among students between 14 and 18 years old, in 2010 2.6% had tried amphetamines (in any of their forms of presentation) sometime in their lives, 1.6% had used them during the last year and 0.9% had done it during the last month.

4. In Spain, in 2009 4.9% of the population between 15 and 64 years old had tried ecstasy sometime in their lives, 0.8% had used it during the last year and 0.4% during the last month. The use patterns during the last year and last month remain stable since 2003, although there is an upward trend in terms of experimental use since 1999. Among students between 14 and 18 years old, in 2010 2.5% had used ecstasy (or what is sold as ecstasy) sometime in their lives, 1.7% had tried it during the last year and 1.0% had done it during the last month. The prevalence of use of ecstasy in this group of population has decreased down to less than half since 2000. Its use is mainly sporadic.

5. In Spain, in 2009 3.7% of the population between 15 and 64 years old had tried hallucinogens sometime in their lives, 0.5% had used them during the last year and 0.2% during the last month. Among students between 14 and 18 years old, in 2010 3.5% had used hallucinogens sometime in their lives, 2.1% had tried them during the last year and 1% had done it during the last month. Nevertheless, their use shows a decreasing trend.

6. Emerging drugs are a wide changing varied group of substances, natural, semisynthetic or synthetic, known or unknown, and used for different purposes, that have emerged or re-emerged in the market of psychoactive substances as an alternative and/or complement to traditional drugs (heroin, cocaine, cannabis, ecstasy, etc..), whose effects imitate, but without being subject, many of them, to legal restrictions in national and international contexts.

7. The use of emerging drugs shows higher prevalence among young people (between 15 and 34 years old) and may be associated to night leisure contexts, especially to some particular types of music and dance. Nevertheless, there has been a recent increase in the number of people that take these drugs on their own looking for new experiences and feelings.

8. According to the data obtained in the National Survey on the Use of Drugs among Secondary-School Students between 14 and 18 years old in Spain (ESTUDES 2010), 3.5% of those surveyed had used one or more of the drugs included in the module on emerging drugs sometime in their lives. Those substances with higher prevalence of use were magic mushrooms, ketamine and spice, although the spread of their use does not seem to indicate (for the time being and regarding this group of age) that emerging drugs are a major problem in the field of use of drugs in Spain.

9. The effects caused by emerging drugs are as varied as their origin and composition. A vast majority of them can be considered to be psychostimulating, thus causing hyperactivation of the central nervous system with cardiovascular implications, which may be aggravated by the increase in body temperature resulting from physical activity (dancing and other factors related to the characteristics of leisure contexts). Nevertheless, many other substances included in this group have

depressing effects on the central nervous system or a mixture of both, and others have hallucinogenic effects.

10. Part of the risk associated to the use of emerging drugs lies in the fact that users ignore their exact composition and effects, which cannot be generalized to all the substances classified as emerging drugs. Moreover, the frequent association of their use with other drugs of abuse (legal and illegal) increases the risk of unwanted and unexpectable effects and makes the therapeutic approach difficult.

11. Many of the substances included in the group of emerging drugs have proven to have abuse and addiction potential. Experience in the care and assistance field is limited, therefore priority should be given to those preventive interventions making potential users aware of this risk, and to those training professionals in prevention, early detection and treatment of drugs use.

12. Generally speaking, under the effects of any of these substances, it is likely to develop aggressive and high-risk behaviours, such as reckless driving or unprotected sexual relations. In some countries some substances, such as GHB or ketamine, are considered to be used to facilitate sexual offences.

13. It is necessary to keep on going deeper in the understanding of the effects of the use of many of these emerging drugs in all the fields of scientific research in order to optimize the interventions focusing on prevention and appropriate treatment of the associated harm among potential users.

14. The collaboration of all the sectors involved is essential to reinforce the mechanisms guaranteeing the notification (to the national and international warning systems) of new substances that may be used as drugs of abuse, as well as their health effects, risks and consequences. This would aim to conceive preventive interventions increasing the risk perception, both among users and among professionals, as well as in society in general.

15. The Internet plays a central role in the promotion, distribution, sale and accessibility of many of the substances included in the group of emerging drugs. Priority must be given to the detection and control

over these activities by the relevant authorities and to those other measures aiming to protect public health and to use the Internet as a platform to raise awareness and provide potential users with truthful information.

16. In Spain the impact of the use of psychostimulants other than cocaine on treatment demands related to the abuse of psychoactive substances is relatively small as compared to other substances of higher prevalence of use and, in 2009, they only accounted for 1.2% of admissions. The temporal trend shows a slight increase in the number of amphetamine-related treatments and a decrease in ecstasy-related treatments in 2009. Hallucinogen-related treatments account for a low percentage among those admitted to treatment, although they saw a slight increase in 2009.

17. In Spain, the percentage of times on which amphetamines were mentioned in the clinical records of those that went to an emergency service because of a reason related to the use of drugs has remained stable, at around 5% during the period 2004-2009. Regarding ecstasy, this percentage (3.2%) decreased in 2009 as compared to 2008 (5%), although it is still higher than some years ago (1.6% in 1996). The proportion of mentions to hallucinogens remains stable and at low levels (at around 2%) since 2005, although a slight increase was observed in 2009 (3.2%).

18. In Spain, the toxicological analysis carried out in 2009 to people whose direct cause of death had been a severe adverse reaction after the non-medical intentional use of pyschoactive substances (legal drugs excluded) showed presence of amphetamines in 3.5% of cases and ecstasy in 1.1% of cases. However, it cannot be concluded that there was a causal relation between the use of these substances and the decease due to the prevalence of a polydrug pattern among the deceased people.

19. The ilicit use of ketamine shows limited spread in Spain and has a poor impact on the indicators of drug-related problems. Nevertheless, during the period 2006-2009 there has been an increase in the number of admissions to treatment in which ketamine was the main drug or one of the secondary use drugs. There has also been an increasing presence of ketamine in hospital emergencies during that same period.

20. For the time being, there is not any effective specific pharmacological treatment for the abuse and addiction to amphetaminic stimulants; therefore, the appropriate approach to the addiction must be combined: symptomatic pharmacological and psychosocial.

XV. Bibliography

(1) Bobes J and Saiz P. Editors. Monograph *Drogas Recreativas*. Journal Adicciones. Vol.5, Supplement 2. 2003.

(2) Morgan JP. Designer Drugs, in Substance Abuse, pages 264-269. 3rd Ed. Williams & Wilkins 1997.

(3) Grob C and Poland R. MDMA, in Substance Abuse, pages 269-276. 3rd Ed. Williams & Wilkins 1997.

(4) Mustata C, Torrens M et al. *Spice drugs: los cannabinoides como nuevas drogas de diseño. Adicciones*.2009;21(3):181-186.

(5) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2009 Annual report on the state of the drugs problem in Europe. EMCDDA. 2009, Lisbon. Available on www.emcdda.europa.eu/publications/annual-report/2009

(6) DGPNSD (Government Delegation for the National Plan on Drugs). *Drogas de Síntesis en España: Patrones y tendencias de adquisición y consumo*. 1997. Ministry of Health, Social Policy and Equality. Available on: www.pnsd.mspsi.es/Categoria2/publica/publicaciones/drogas.htm

(7) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2001 Selected Issue. Synthetic Drugs. EMCDDA. Available on: www.emcdda.europa.eu/attachements.cfm/att_37256_ES_sel2001_3es.pdf

(8) Shulgin AT, Shulgin A. TIHKAL the continuation. Berkeley: Transform Press. 1997.

(9) Shulgin AT, Shulgin A. PIHKAL a chemical love story. The continuation. Berkeley: Transform Press. 1991.

(10) European Early Warning System–EWS. Available on: www.emcdda.europa.eu/themes/new-drugs/early-warning

(11) EMCDDA–Europol 2010 Annual Report on the implementation of Council Decision 2005/387/JHA. Available on: www.emcdda.europa.eu/publications/implementation-reports/2010.

(12) United Nations Organization. UN Office on Drugs and Crime (UNODC). World Drug Report 2011. Vienna. Available on www.unodc.org/unodc/en/data-and-analysis/WDR-2011.html

(13) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2010 Annual report on the state of the drugs problem in Europe. 2010, Lisbon. Available on: www.emcdda.europa.eu/publications/annual-report/2010

(14) EMCDDA–Europol 2010 Annual Report on the implementation of Council Decision 2005/387/JHA. Available on: www.emcdda.europa.eu/publications

(15) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). Selected Issue 2010. Problem amphetamine and methamphetamine use in Europe. 2010, Lisbon. Available on www.emcdda.europa.eu/publications/selected-issues/problem-amphetamine.

(16) INCB (International Narcotics Control Board). 2010 Report. Available on ww.incb.org/incb/es/annual_report.html

(17) www.mixmag.net

(18) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). Khat use in Europe: implications for European policy. Available on www.emcdda.europa.eu/attachements.cfm/att_137392_EN_TDAD11001ESC_WEB.pdf

(19) DGPNSD (Government Delegation for the National Plan on Drugs). Spanish Drug Observatory. Household Survey on alcohol and drugs in Spain, EDADES 2009. Available on: www.mspsi.gob.es/gabinetePrensa/notaPrensa/pdf/presentacionEdades200910.ppt

(20) Flash Eurobarometer. Youth attitudes on Drugs. European Comission. Available on: ec.europa.eu/public_opinion/flash/fl_330_en.pdf

(21) DGPNSD (Government Delegation for the National Plan on Drugs). Spanish Drug Observatory. Treatment Indicator 1996-

2009. Available on: www.pnsd.msc.es/Categoria2/observa/pdf/AdmisionesTratamiento.pdf

(22) DGPNSD (Government Delegation for the National Plan on Drugs). Spanish Drug Observatory. Mortality Indicator 1990-2009. Available on: www.pnsd.msc.es/Categoria2/observa/pdf/MortalidadDrogas.pdf

(23) DGPNSD (Government Delegation for the National Plan on Drugs). Spanish Drug Observatory. Emergencies Indicator 1996-2009. Available on: www.pnsd.msc.es/Categoria2/observa/pdf/UrgenciasHospitalarias.pdf

(24) CICO (Intelligence Centre against Organised Crime). *Informe Estratégico del Tráfico Ilícito de Drogas*. December 2010, Madrid. State Department of Security. Spanish Home Office.

(25) Camí J, Farré M. *Éxtasis, la droga de la ruta del bakalao*. Med Clin (Barc). 1996;106:711-6.

(26) Farré M. *Manejo del paciente con adicción. Sustancias de abuso más habituales*. In: Castaño J, Castillo J, Escolano F, Montes A, Samsó E, editors. *Analgesia perioperatoria: nuevas implicaciones para el anestesiólogo*. Madrid: Grupo Editorial Entheos; 2006. p. 127-136.

(27) Farré M. *Intoxicación aguda por drogas de abuso*. In: Rozman C, editor. *Medicina Interna*. 16ª ed. Madrid: Elsevier; 2009. p. 2642-2645.

(28) Schifano F., Deluca P, Baldacchino A, Peltoniemi T, Scherbaum N, Torrens M, Farré M, Flores I, Rossi M, Eastwood D, Guionnet G, Rawaf S, Agosti L, Di Furia L, Brigada R, Majava A, Siemann H, Leoni M, Tomasin A, Rovetto F, Hamid Ghodse A on behalf of the Psychonaut 2002 research group. Drugs on the web; the Psychonaut 2002 EU project. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:640-6.

(29) Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O, Davey Z, Corkery J, Siemann H, Scherbaum N, Farre M, Torrens M, Demetrovics Z, Ghodse AH, Psychonaut Web Mapping and ReDNet Research Groups. Mephedrone (4-methylmethcathinone;

'meow meow'): chemical, pharmacological and clinical issues. Psychopharmacology (Berlin). 2010 Nov 12. [Epub ahead of print].).

(30) Mas M, Farré M, de la Torre R, Roset PN, Ortuño J, Segura J, Camí J. Cardiovascular and neuroendocrine effects, and pharmacokinetics of MDMA in humans. J Pharmacol Exp Ther. 1999;290:136-45.

(31) Camí J, Farré M, Mas M, Roset PN, Poudevida S, Mas A, San L, de la Torre R. Human pharmacology of 3,4-Methylenedioxymethamphetamine («Ecstasy»): Psychomotor performance and subjective effects. J Clin Psychopharmacol. 2000;20:455-66.

(32) de la Torre R, Farré M, Navarro M, Pacifici R, Zuccaro P, Pichini S. Clinical pharmacokinetics of amphetamine and related substances monitoring in conventional and non-conventional matrices. Clin Pharmacokinet. 2004;43:157-85.

(33) de la Torre R, Farré M, Roset PN, Pizarro N, Abanades S, Segura M, Segura J, Camí J. Human pharmacology of MDMA: Pharmacokinetics, metabolism and disposition. Ther Drug Monit. 2004;26:137-44.

(34) de la Torre R, Farré M, Ortuño J, Mas M, Brenneisen R, Roset PN, Segura J, Camí J. Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. Br J Clin Pharmacol. 2000;49:104-109.

(35) Tomillero Alemany, Ángels. *Farmacología clínica de la metilenodioxianfetamina (MDMA, éxtasis) tras su administración a dosis repetidas*. Departament of Pharmacology and Therapeutics. UAB. www.tdx.cat/TDX-0925101-163333.

(36) Marchei E, Farré M, Pardo R, Garcia-Algar O, Pellegrini M, Pacifici R, Pichini S. Measurement of Methylphenidate and Ritalinic Acid in oral fluid: Correlation with Plasma Drug Concentrations. Clin Chem. 2010; 56: 585-592.

(37) Farré M, Abanades S, Roset PN, Peiró AM, Torrens M, Ó' Mathúna B, Segura M, de la Torre R. Pharmacological Interaction Between

3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and Paroxetine: Pharmacological effects and pharmacokinetics. J Pharmacol Exp Ther. 2007;323:954-62.

(38) Hernández-López C, Farré M, Roset PN, Menoyo E, Pizarro N, Ortuño J, Torrens M, Camí J, de la Torre R. 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and alcohol interactions in humans: Psychomotor performance, subjective effects, and pharmacokinetics. J Pharmacology Exp Ther. 2002;300:236-44.

(39) Robledo P. *Las anfetaminas. Trastornos Adictivos*. 2008;10 (3):166-74.

(40) Díez Tejedor E, Tejada J, Caminero AB, Vivancos F. *Alteraciones neurológicas relacionadas con simpaticomiméticos y el consumo de cocaína*. In: JF Martí-Massó, B Anciones (Eds). *Alteraciones neurológicas inducidas por fármacos*. Ediciones Argón. Barcelona, 1993; pp. 489-506.

(41) Ramos MJ, Frank A, Díez Tejedor E. *Encefalopatías, alteraciones cognitivas y de conducta producidas por fármacos.* En: JF Martí-Massó, B Anciones (Eds). *Alteraciones neurológicas inducidas por fármacos*. Ediciones Ergón. Barcelona, 1993; pp. 33-48.

(42) Lorenzo P, Moreno A, Lizasoain, Leza JC, Moro MA, Portolés A. Velázquez *Farmacología Básica y Clínica.* 18th Ed. Panamericana, Madrid, 2008.

(43) Setola V, Hufeisen SJ, Grande-Allen KJ, Vesely I, Glennon RA, Blough B, Rothman RB, and Roth BL. 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. Molecular Pharmacology. 2003;63(6):1223-1229.

(44) Rothman, R.B.; Baumann, M.H.; Savage, J.E.; Rauser, L.; McBride, A.; Hufisein, S.; and Roth, B.L. Evidence for possible involvement of 5-HT2B receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation 2000;102(23):2836-2841.

(45) Díez Tejedor E, Tejada J, Frank A. *Complicaciones neurológicas debidas al consumo de cocaína, anfetaminas y simpaticomiméticos*. In: E. Díez Tejedor y P. Martínez (Eds.). *Complicaciones Neurológicas de la infección por V.I.H. y de las toxicomanías*. Arch. Neurobiol. 1989; 52 (Supl. 1): 162-182.

(46) Broening HW, Morford LL, Inman-Wood SL, Fukumura M and Vorhees CV. 3,4-methylenedioxymethamphetamine (ecstasy)-induced learning and memory impairments depend on the age of exposure during early development. Journal of Neuroscience 2001; 21(9):3228-3235.

(47) World Health Organization. *Clasificación de los trastornos mentales y del comportamiento CIE-10* (The ICD-10 Classification of Mental and Behavioural Disorders). Editorial Médica Panamericana, Madrid, 2000.

(48) Vocci FJ, Montoya ID. Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. Friends Research Institute, Baltimore, USA. Current Opinion in Psychiatry. 2009; 22(3):263-8.

(49) NIDA (National Institute on Drug Abuse). Methamphetamine Abuse & Addiction. Research Report Series. NCADI, September 2006. NIH Publication Number 06-4210.

(50) Rawson RA, Shoptaw SJ, Obert JL, McCann MJ, Hassson AL, Marinelli-Casey PJ, Brethen PR & Ling W. (1995). An intensive outpatient approach for cocaine abuse treatment: The Matrix model. Journal of Substance Abuse Treatment, 12: 117-127.

(51) Rawson RA, Huber A, Brethen PR, Obert JL, Gulati V, Shoptaw SJ, & Ling W. Status of methamphetamine users 2-5 years after outpatient treatment. Journal of Addictive Diseases 2001; 21 (1): 107-119.

(52) NIDA National Institute on Drug Abuse. Info Facts: Methamphetamine. Revised in March 2010. (access 15th September 2010). Available on www.drugabuse.gov/infofacts/methamphetamine.html

(53) Obert JL, McCann MJ, Marinelli-Casey P, Weiner A, Minsky S, Brethen P, & Rawson R. The Matrix Model of Outpatient Stimulant Abuse Treatment: History and Description. Journal of Psychoactive Drugs 2000;32(2): 157-164.

(54) Sánchez Máñez A, Palau Muñoz C, Zarza González MJ, Obert JL, Rawson RA, Cortell Cortell C, Perelló del Río M. *Resultados del pilotaje y adaptación del Modelo MATRIX en España*. In: *Socidrogalcohol. Libro de Ponencias de las XXXVII Jornadas Nacionales de Socidrogalcohol*; Oviedo, Spain. 2010 April 22-24:85-86.

(55) Roll JM, Petry NM, Stitzer ML, et al. Contingency management for the treatment of methamphetamine use disorders. Am J Psychiatry 2006;163(11):1993–1999.

(56) Tatarsky A. Harm reduction psychotherapy: extending the reach of traditional substance use treatment. Journal of Substance Abuse Treatment 2003;25:249-256.

(57) Vocci FJ, Elkashef A, Appel NM. Pharmacological treatment of methamphetamine addiction. In: Roll J.M.; ed. lit.,Ling W.; ed. lit.,Rawson R.A.; ed. lit.,Shoptaw S.; de. lit. Methamphetamine addiction: from basic science to treatment.- New York: Guilford. 2009; p. 202-229.

(58) Sáiz PA, González M, Martínez S, Bascarán MT, Bousoño M, Bobes J. *Aproximación terapéutica del uso-abuso de MDMA (Extasis)*. Adicciones 2000; 12(2): 167-175.

(59) Echeverry JJ, Nettles CD. Club drugs: an overview. En: Cohen L.M.; ed. lit., Collins F.L.; ed. lit., Young A.M.; ed. lit. ,McChargue D.E.; ed. lit., Leffingwell T.R. Cook K.L. Pharmacology and treatment of substance abuse : evidence and outcome based perspectives.- New York: Routledge. 2009; p. 419-438.

(60) Landabaso Vazquez MA, Gutierrez Fraile M. *Aproximación terapéutica al uso y abuso de drogas recreativas*. Adicciones 2003; 15 (2):347-352.

(61) de Boer D, Bosman IJ, Hidvegi E, Manzoni C, Benko AA, dos Reys LJ et al. Piperazine-like compounds: a new group of designer

drugs-of-abuse on the European market. Forensic Sci Int 2001;121:47-56.

(62) Europol – EMCDDA: Joint Report on a new psychoactive substance: 1-benzylpiperazine (BZP). Disponible en: www:emcdda.europa.eu/attachements.cfm/att_33251_EN_Final_Joint_Report_BZP.pdf

(63) Europol – EMCDDA: Active Monitoring Report on a new psychoactive substance:1-(3-chlorophenyl) piperazine (mCPP). Available on: www.emcdda.europa.eu/attachements.cfm/att_33256_EN_Final_Europol-EMCDDA_Active_Monitoring_Report_mCPP_290307.pdf

(64) EMCDDA. (European Monitoring Centre for Drugs and Drug Addiction). Report on the risk assessment of BZP in the framework of the Council decision on new psychoactive substances. Lisbon, February 2009. Available on www.emcdda.europa.eu/publications/risk-assessments/bzp

(65) Rajkumar R, Pandey DK, Mahesh R y Radha R. 1-(m-chlorophenyl)piperazine induces depressogenic-like behaviour in rodents by stimulating the neuronal 5-HT(2A) receptors: proposal of a modified rodent antidepressant assay. Eur J Pharmacol. 2009; 608(1-3):32-41.

(66) Maurer HH, Kraemer T, Springer D, Staack RF. Chemistry, pharmacology, toxicology, and hepatic metabolism of designer drugs of the amphetamine (ecstasy), piperazine, and pyrrolidinophenone types: a synopsis. Ther Drug Monit 2004;26:127-31.

(67) Johnstone CA, Lea RA, Brennan KA, Schenk S, Kennedy MA, Fitzmaurice PS. Benzylpiperazine: a drug of abuse?.J Psychopharmacol 2007;21:888-94.

(68) Bossong MG, Brunt TM, Van Dijk JP, Rigter SM, Hoek J, Goldschmidt HM, Niesink RJ. mCPP: an undesired addition to the ecstasy market. J Psychopharmacol. 2010;24:1395-401.

(69) Gijsman HJ, Cohen AF, van Gerven JM. The application of the principles of clinical drug development to pharmacological

challenge tests of the serotoninergic system. J Psychopharmacol 2004;18:7-13.

(70) Jeffrey K. Aronson. Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and interactions, 2006. Pages 2840-2841.

(71) Gee P, Gilbert M, Richardson S, Moore G, Paterson S, Graham P. Toxicity from the recreational use of 1-benzylpiperazine.Clin Toxicol (Phila). 2008; 46(9):802-7.

(72) Gee P, Richardson S, Woltersdorf W, Moore G. Toxic effects of BZP-based herbal party pills in humans: a prospective study in Christchurch, New Zealand. N Z Med J. 2005;118(1227):U1784.

(73) Gee P, Jerram T, Bowie D. Multiorgan failure from 1-benzylpiperazine ingestion—legal high or lethal high?. Clin Toxicol (Phila). 2010;48(3):230-3.

(74) Staack RF, Maurer HH. Metabolism of designer drugs of abuse. Current Drug Metabolism 2005;6:259-74.

(75) Domino EF, Chodoff P, Corsenn G. Pharmacological effects of CI-581, A New Dissociative Anesthesic, in Man.Cli.Pharmacol Ther. 1965; 6:279-91.

(76) Domino, EF. Taming the Ketamine Tiger. Anesthesiology 2010; 113: 678-684.

(77) White PF. Ketamine update: its clinical uses in anestesia. Domino EF. Status of ketamine in anaesthesiology. Ann Arbor: NPP Books, 1990; 343-66.

(78) White PF, Way WL, Trevor AJ. Ketamine- its pharmacology and terapeutic uses. Anesthesiology 1982; 56: 119-36.

(79) Kharasch ED, Labroo R. Metabolism of ketamine stereoisomers by human liver microsomes. Anesthesiology 1992; 77:1201-7.

(80) Dayton PG, Stiller RL, Cook DR, Perel JM. The binding of ketamine to plasma proteins: emphasis on human plasma. Eur J Pharmacol 1983; 24: 824-31.

(81) López Gil, J. *Efectos de los antagonistas NMDA sobre la neurotransmisión serotoninérgica y glutaminérgica en la corteza prefrontal. Mecanismo de acción de los fármacos antipsicóticos.* Doctoral Thesis. Departament of Cellular Biology, Immunology and Neuroscience. University of Barcelona. 2009.

(82) Arcusa Mon MJ. *Estudio de toxicidad aguda S(+)-Ketamina y RS-Ketamina administrada por vía subaracnoidea en conejos. Comparación con Lidocaína.* Doctoral Thesis. Departament of Physiology. University of Valencia 2005.

(83) Reboso JA, González F. *Ketamina*. Rev Esp Anestesiol Reanim.1999; 46: 111-122.

(84) Reves JG, Glass PS, Lubarski DA. *Anestésicos intravenosos no barbitúricos*. Miller RD. *Anestesia*. 4th edition. Vol. 1. Madrid: Harcourt Brace, 1998: 239-80.

(85) López Millán JM, Sánchez-Blanco C. *Utilización de la Ketamina en el tratamiento del dolor agudo y crónico*. Rev Soc Esp Dolor 2007; 1: 45-65.

(86) Dinis-Oliveira RJ, Carvalho F, Duarte JA, Dias R, Magalhaes T, Santos, A. Suicide by hanging under the influence of ketamine and ethanol. Forensic Sci Int. 2010 Oct 10;202(1-3):e23-7. Epub 2010 May 26.

(87) Liao Y, Tang J, Ma M, Wu Z, Yang M, Liu T, Chen X, Fletcher PC, Hao W. Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. Brain 2010; 133: 2115-22.

(88) Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremmer JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiat 1994; 51: 199-214.

(89) Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiat 2000; 47: 351-4.

(90) Zárate CA, Sing JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh SA, Charney DS, Manji HK. A randomized trial of an N-methyl-Daspartate antagonist in treatment-resistant depression. Arh Gen Psyquiat 2006; 63: 856-64.

(91) Goforth HW, Holsinger T. Rapid relief of severe major depressive disorder by use of preoperative ketamine and electroconvulsive therapy. J Ect 2007; 23, 23-5.

(92) Martin DE, Hall Mn. The expanding TOR signalling network. Curr Opin Cell Biol 2005; 17: 158-166.

(93) Stern PR. Antidepressant Action of Ketamine. Sci Signal 2010; ec 259.

(94) Hamza J, Malit LA, Gross JB. Ventilatory response to CO_2 following intravenous ketamine in children. Anesthesiology 1989; 70:422-5.

(95) Munro HM, Sleigh JW, Paxton LD. The cardiovascular response to ketamine: the effects of clonidine and lignocaine. Acta Anaesthesiol Scand.1993; 37:75-78.

(96) Pandey cK, Mathur N, Singh N. Fulminant pulmonary edema after intramuscular ketamine. Can J Anesth 2000; 47: 894-896.

(97) Shahani R, Streutker C, Dickson B y Stewart RJ. Ketamine-Associated Ulcerative Cistitis: A New Clinical Entity. Urology 2007; 69: 810-2.

(98) Azurmendi-Arína I, García-Escudero López A, Infante-Riañoa R, Padilla-Nieva J, Martín-Bazacoa J y Arruza-Echevarría A. Ketamine-induced cystopathy. *Diálisis y Transplante* 2010; 31(1): 3-6.

(99) Galanter M, Kebler HB. Texbook of Substance Abuse Treatment. American Psychiatric Pub 2008; Fourth.

(100) Gill JR, Stajic M. Ketamine in non-hospital and hospital deaths in New York City. J Forensic Sci. 2000; 45:655-658.

(101) Lalonde BR, Wallage HR. Postmortem blood ketamine distribution in two fatalities. J Anal Toxicol.2004;28(1):71-4.

(102) Psyconaut Web Mapping Research Group (2009). Spice report Institute of Psychiatry. King's College London. UK.

(103) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction): Action on new drugs briefing paper: Understanding the Spice phenomenon. 2009. Available on: www.emcdda.europa.eu/attachements.cfm/att_80086_EN_Spice%20Thematic%20paper%20%E2%80%94%20final%20version.pdf

(104) European Medicines Agency EMA. London 23 October 2008. Press Release. Ref. EMEA/CHMP/537777/2008. Available on: www.ema.europa.eu

(105) Ben Amar M. Cannabinoids in Medicine: a Review of their potential. J. of Ethnopharmacology. 2006;105:1-25.

(106) Auwärter V, Dressen S, et al. Spice and other herbal blends: harmless incense or cannabinoid designer drugs? J of Mass Spectrometry. 2009;44:832-837.

(107) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). Drug Profile: Synthetic Cannabinoids and Spice. Available on www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids.

(108) Abanades S, Peiró AM, Farré M. *Club drugs: los viejos fármacos son las nuevas drogas de la fiesta.* Med Clin (Barc). 2004;123:305-11.

(109) Maxwell JC, Spence RT. Profiles of club drug users in treatment. Subst Use Misuse 2005;40(9–10):1409–1426.

(110) García FB, Pedraza C, Navarro JF. *Actualización del ácido gamma-hidroxibuitírico.* Rev. Neurología 2006; 43 (1): 39-48.

(111) Pichini S, Farré M, Abanades S, Pacifici R, Zuccaro P, Langohr K, de la Torre R. Immunomodulating properties of Gamma-hydroxybutyrate (GHB), flunitrazepam and ethanol in "Club Drugs" users. Addict Biol. 2010; 15:336-45.

(112) Abanades S, Farré M, Barral D, Torrens M, Closas N, Langohr K, de la Torre R. Relative abuse liability of gamma-hydroxybutyric acid (GHB), flunitrazepam and ethanol in "Club Drugs" users. J Clin Psychopharmacology 2007;27:625-638.

(113) Snead OC 3rd, Gibson KM. Gamma-hydroxybutyric acid. N Engl J Med. 2005;352(26):2721-32.

(114) Galicia M, Nogué S, To-Figueras J, Echarte JL, Iglesias ML, Miróa O. *Intoxicaciones por éxtasis líquido atendidas en servicios de urgencias hospitalarios de la ciudad de Barcelona durante 2 años*. Med Clin (Barc). 2008;130:254-8.

(115) Nogué S, Galicia M, Amigó M, Miró O. *Brotes epidémicos de sobredosis de éxtasis líquido (GHB)*. *Emergencias 2007*;19:234-235.

(116) World Health Organization (Geneva, Switzerland). WHO Expert Committee on drug dependence: 34 Report. Published by the World Health Organization WHO, 2007; pages 14-15.

(117) www.drugs.com/pro/xyrem.html

(118) NIDA (National Institute on Drug Abuse). InfoFacts: *Las Drogas de Club (GHB, ketamina y Rohipnol)*. Revised in June 2009. Available on URL: www.drugabuse.gov/infofacts/ClubDrugs-Sp.html.

(119) Degenhardt L. *GHB: Un análisis*. Adicciones 2003; 15 (2): 167-177.

(120) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). Report on the risk assessment of GHB in the framework of the joint action of new sinthetyc drugs. Available on: www.emcdda.europa.eu/attachements.cfm/att_33346_EN_Risk4.pdf

(121) www.emcdda.europa.eu/attachements.cfm/att_65482_EN_Substances%20and%20classifications%20Nov08.xls

(122) Abanades S, Farré M. Frontera entre medicamentos y drogas: El ejemplo de las Club Drugs. In: Baños JE, Bigorra J, editors. La

proyección social del medicamento. Monographs Dr. Antonio Esteve 33. Barcelona: Fundación Dr. Antonio Esteve; 2007. p. 9-15.

(123) Lewin L, M.D. Phantastica. Park Street Press.1998.

(124) www.mind-surf.net/drogas

(125) www.Erowid.org

(126) Schultes RE. Hallucinogenic Plants. Golden Press.1976.

(127) NIDA (National Institute on Drug Abuse). Info Facts. Khat. December 2007. Available on: www.nida.nih.gov/PDF/Infofacts/khat-Sp07.pdf

(128) MedlinePlus. Kava. Available on: www.nlm.nih.gov/medlineplus/spanish/druginfo/natural/872.html

(129) MedlinePlus. Belladona. Available on: www.nlm.nih.gov/medlineplus/spanish/druginfo/natural/531.html

(130) NIDA (National Institute on Drug Abuse). Departament of Health and Human Services. Principles of Drug Addiction Treatment: A Research-Based Guide. USA, July 2010. NIH Publication No. 10–4180(S).

(131) EU Council. The EU Drugs Strategy (2005-2012). Brussels, 22nd November 2004. Available on: europa.eu/legislation_summaries/justice_freedom_security/combating_drugs/c22569_es.htm

(132) DGPNSD (Government Delegation for the National Plan on Drugs). National Drugs Strategy 2009-2016. Ministry of Health, Social Policy and Equality. Available on: www.pnsd.msc.es/novedades/pdf/EstrategiaPNSD2009-2016.pdf

(133) ElSohly MA, Salmone SJ. Prevalence of drugs used in cases of alleged sexual assault. J Anal Toxicol. 1999;23:141–146.

(134) Slaughter L. Involvement of drugs in sexual assault. J Reprod Med. 2000;45:425–430.

(135) Juhascik MP, Negrusz A, Faugno D, Ledray L, Greene P, Lindner A, Haner B, Gaensslen RE. An estimate of the proportion of drug-facilitation of sexual assault in four U.S. localities. J Forensic Sci. 2007;52(6):1396-400.

(136) LeBeau MA, Andollo W, Hearn W, et al. Recommendation for toxicological investigations of drug-facilitated sexual assaults. J Forensic Sci. 1999;44:227–230.

(137) Andresen H, Stimpfl T, Sprys N, Schnitgerhans T, Müller A. Liquid ecstasy - a significant drug problem. Dtsch Arztebl Int. 2008;105(36):599-603.

(138) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction. EMCDDA Technical Datasheets - Sexual assaults facilitated by drugs or alcohol. 2008 Available on: www.emcdda.europa.eu/html.cfm/index50537EN.html

(139) Németh Z, Kun B, Demetrovics Z. The involvement of gamma-hydroxybutyrate in reported sexual assaults: a systematic review. J Psychopharmacology. 2010;24(9):1281-7.

(140) Adamowicz P, Kała M. Date-rape drugs scene in Poland. Przegl Lek. 2005;62(6):572-5.

(141) Scott-Ham M, Burton FC. Toxicological findings in cases of alleged drug-facilitated sexual assault in the United Kingdom over a 3-year period. J Clin Forensic Med. 2005 ;12(4):175-86.

(142) Jones AW, Kugelberg FC, Holmgren A, Ahlner J.Occurrence of ethanol and other drugs in blood and urine specimens from female victims of alleged sexual assault. Forensic Sci Int. 2008;181(1-3):40-6.

(143) Du Mont J, Macdonald S, Rotbard N, Bainbridge D, Asllani E, Smith N, Cohen MM. Drug-facilitated sexual assault in Ontario, Canada: toxicological and DNA findings. J Forensic Leg Med. 2010;17(6):333-8. Epub 2010 Jun 15.

(144) Watanabe-Galloway S, Ryan S, Hansen K, Hullsiek B, Muli V, Malone AC. Effects of methamphetamine abuse beyond individual users. J Psychoactive Drugs. 2009;41(3):241-8.

(145) Sexton RL, Carlson RG, Leukefeld CG, Booth BM. An ethnographic exploration of self-reported violence among rural methamphetamine users. J Ethn Subst Abuse. 2009;8(1):35-53.

(146) Stretesky PB. National case-control study of homicide offending and methamphetamine use. J Interpers Violence. 2009;24(6):911-24.

(147) Cartier J, Farabee D, Prendergast ML. Methamphetamine use, self-reported violent crime, and recidivism among offenders in California who abuse substances. J Interpers Violence. 2006;21(4):435-45.

(148) Martin I, Palepu A, Wood E, Li K, Montaner J, Kerr T. Violence among street-involved youth: the role of methamphetamine. Eur Addict Res. 2009;15(1):32-8.

(149) Sommers I, Baskin D, Baskin-Sommers A. Methamphetamine use among young adults: health and social consequences. Addict Behav. 2006 ;31(8):1469-76.

(150) Stuart GL, Temple JR, Follansbee KW, Bucossi MM, Hellmuth JC, Moore TM. The role of drug use in a conceptual model of intimate partner violence in men and women arrested for domestic violence. Psychol Addict Behav. 2008;22(1):12-24.

(151) Karjalainen K, Lintonen T, Impinen A, Mäkelä P, Rahkonen O, Lillsunde P, Ostamo A. Mortality and causes of death among drugged drivers. J Epidemiol Community Health. 2010;64(6):506-12.

(152) De Letter EA, Piette MH, Lambert WE, Cordonnier J. Amphetamines as potential inducers of fatalities: a review in the district of Ghent from 1976-2004. Med Sci Law. 2006;46(1):37-65.

(153) Verschraagen M, Maes A, Ruiter B, Bosman IJ, Smink BE, Lusthof KJ. Post-mortem cases involving amphetamine-based drugs in The Netherlands. Comparison with driving under the influence cases. Forensic Sci Int. 2007;170(2-3):163-70.

(154) Schifano F, Corkery J, Naidoo V, Oyefeso A, Ghodse H. Overview of amphetamine-type stimulant mortality data—UK, 1997-2007. Neuropsychobiology. 2010;61(3):122-30.

(155) Senna MC, Augsburger M, Aebi B, Briellmann TA, Donzé N, Dubugnon JL, Iten PX, Staub C, Sturm W, Sutter K. First nationwide study on driving under the influence of drugs in Switzerland. Forensic Sci Int. 2010;198(1-3):11-6.

(156) Jones AW, Holmgren A, Kugelberg FC. Driving under the influence of gamma-hydroxybutyrate (GHB). Forensic Sci Med Pathol. 2008;4(4):205-11.

(157) Jones AW, Holmgren A, Kugelberg FC. Driving under the influence of central stimulant amines: age and gender differences in concentrations of amphetamine, methamphetamine, and ecstasy in blood. J Stud Alcohol Drugs. 2008;69(2):202-8.

(158) Jones AW, Kugelberg FC, Holmgren A, Ahlner J. Five-year update on the occurrence of alcohol and other drugs in blood samples from drivers killed in road-traffic crashes in Sweden. Forensic Sci Int. 2009;186(1-3):56-62.

(159) Gjerde H, Normann PT, Pettersen BS, Assum T, Aldrin M, Johansen U, Kristoffersen L, Øiestad EL, Christophersen AS, Mørland J. Prevalence of alcohol and drugs among Norwegian motor vehicle drivers: a roadside survey. Accid Anal Prev. 2008 ;40(5):1765-72.

pnsd

GOBIERNO
DE ESPAÑA

MINISTERIO
DE SANIDAD, POLÍTICA SOCIAL
E IGUALDAD