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New Synthetic Drugs in Addictovigilance

François Chavant[1], *Alexandra Boucher*[2], *Reynald Le Boisselier*[3], *Sylvie Deheul*[4] *and Danièle Debruyne*[3]

1 Centre d'Addictovigilance de Poitiers, CHU, Poitiers, France
2 Centre d'Addictovigilance de Lyon, CHU, Lyon, France
3 Centre d'Addictovigilance de Caen, CHU, Caen, France
4 Centre d'Addictovigilance de Lille, Faculté de médecine, Lille, France

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Abstract – New substances, also known as "designer drugs" or "legal highs" are increasingly available to drug users. Two hundred and fifteen hitherto unlisted substances have been notified by European Union member states since 2005. These synthetic drugs, which have been developed to side-step the legislation on drugs, are analogues or derivatives of existing drugs and medications. The availability of these "legal highs", sold on Internet under various denominations such as bath salt, plant fertilizer, chemical not intended for human use, or spice, is unlimited. The effects felt by users vary, and the substances may be stimulant, entactogenic, hallucinogenic, psychedelic or dissociative. The pharmacological targets also vary, and may be either the increase of extracellular levels of neurotransmitters *via* different mechanisms (reuptake inhibition, stimulation of intracellular release) or else fixation on specific receptors. Several chemical classes, themselves divided into sub-classes, are involved: phenethylamines, tryptamines, piperazines, cathinones, cannabinoids etc. The toxicity of the main members of these categories is increasingly well known, the most deleterious being behavioural effects, physical manifestations, and cardiovascular consequences. However, small variations in their chemical structure can generate effects that are quantitatively different, thus enhancing their toxicity or addictive potential, and much remains to be achieved in terms of knowledge about these new drugs. These substances are indeed present on the French territory, as shown by data provided by the *Observatoire Français des Drogues et Toxicomanies*, and notifications by the French Addictovigilance network. Screening in clinical toxicology laboratories is not widespread, since these molecules are not detected by the standard screening tests, so that there is probably an under-estimation of the use of these new drugs. The legislation on these substances changes regularly, with more and more countries classifying them as "narcotics" or illegal psychotropic drugs so as to restrict their use, applying a generic classification when possible.

Abbreviations: see end of article.

1. Introduction

In the last decade, new synthetic substances with psychoactive effects have appeared on the drugs market, for different reasons, among which firstly the reduced availability or poorer quality of the "classic" drugs like heroin, cocaine or ecstasy, secondly the appearance and development of "free parties", thirdly the quest for stimulants and entactogens that mimic the effects of ecstasy or cocaine and are designed for these festive venues (party pills, funk pills), and fourthly the spectacular development of information and sales websites. These synthetic "designer drugs" have been created to side-step existing legislation, and are thus known as "legal highs". They are most often analogues, or are derived from existing drugs and medications, obtained by variously altering their chemical structure (and termed "research chemicals"). These new drugs are related to numerous different chemical classes: phenethylamines, tryptamines, piperazines, cathinones, cannabinoids etc, which are in turn divided into subclasses each comprising numerous items. Indeed, the general mode of development of these substances consists in starting from the basic structure of a group, often natural, and exploring all the possible additions of radicals so as to create a host of derived substances. These substances are nevertheless not necessarily new, as a number of these synthetics have been described, for instance by Alexander and Anne Shulgin in the books "PiHKAL"[1] and "TiHKAL"[2] published in 1991 and 1992 respectively, or by John

William Huffman whose research in the 1980s was centred on the identification of endo-cannabinoid receptors.[3] These drugs can be obtained *via* commercial websites under various appellations, such as "bath salts" or "plant fertilizer", which have no real relationship with the actual purpose of the substance, and under more generic commercial names like "herbal essences", "Ivory Wave", "NRG" etc, or again under the international nonproprietary names (INN) for chemical substances with the proviso "not intended for human use". These drugs are now part of the range of substances offered by street dealers. None of these different appellations, however precise, guarantees the nature of the substances purchased or its exact composition, and mixes are frequently observed in samples analysed.

In vitro, the pharmacological targets are varied 1) mostly aiming to enhance the synaptic concentration of monoamines by way of different mechanisms of reuptake or release from storage sites (concentrations of these catecholamines, among which dopamine, serotonin, or norepinephrine, affect the hallucinogenic, toxic or addictive potential of the drug in different ways), and 2) also contributing to the activation of specific receptors, such as the central cannabinoid receptors type 1 (CBI) that are liable to the euphoric effects of cannabinoid drugs.

In vivo, in animals, with the exception of cannabinoids the new drugs usually enhance locomotor activity to a variable degree and for variable durations. They are also involved in the regulation of motor coordination, memory and thermo-regulation. The greatest risk is cardiovascular.

In humans, the felt effects vary, and include stimulant/relaxant, entactogenic, hallucinogenic, psychedelic and dissociative effects. The toxicity of these substances is increasingly well mapped-out, and entails behavioural effects (anxiety, psychosis, violence) and physical manifestations (hyperthermia, rhabdomylosis, cardio-vascular accidents). The care provision for these patients is above all symptomatic, which is reinforced by the fact that diagnosis of poisoning by one or other of these new drugs is not easy to establish. Their screening is not usual in ordinary analysis laboratories, because these molecules do not fit into classic screening tests. In clinical or forensic laboratories, the ability to obtain reference solutions from highly reactive suppliers has enabled a rapid updating of the analysis libraries, and the documentation of medical or forensic cases. However the fairly unspecific mass spectra and frequently low concentrations in biological fluids, entailing the need for sophisticated equipment, as well as the constant arrivals of new substances, make analysis difficult and time-consuming.[4,5]

Two hundred and fifteen new substances have been notified *via* the EU member states Early Warning System since 2005, of which 46 in 2011 and 73 in 2012, so that they have become a key phenomenon in drug use in Europe.[6] Likewise, in the French Addictovigilance networks and Poison Control centres, as well as in forensic toxicology laboratories, since the first instances of use of these drugs in the years following 2010, other notifications have corroborated the use of these substances on French national territory.

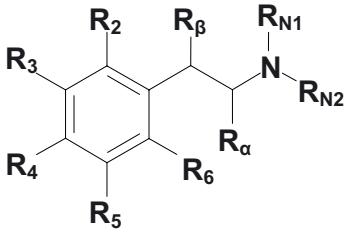

Fig. 1. Structure of substituted phenethylamines.

The majority of EU states, aware of the public health issues raised by the arrival of these new drugs, have taken energetic measures to assess and contain the propagation of this phenomenon. The legislation concerning these substances has consequently evolved, with more and more countries deciding to monitor and limit their use in their territories. Thus in France, the health and sports Minister decided to classify the following as "narcotics": several cannabinoids in 2009, mephedrone in 2010, 4-fluoroamphetamine in 2011, the cathinone family and 4-methylamphetamine in 2012, methoxetamine in 2013 and 5-IT in 2014.

The aim of this paper is to set out present knowledge about the substances that have most concerned health authorities in recent years, with particular emphasis on the specific features of each new drug or group of drugs.

2. Substituted amphetamines type 4-FA (4-fluoroamphetamine) and 4-MA (4-methylamphetamine)

Substituted phenethylamines (figure 1) include a wide range of drug and medication classes, among which amphetamines and methamphetamines are certainly the most popular. In chemical terms, 4-fluoroamphetamine (4-FA) and 4-methylamphetamine (4-MA) only differ from amphetamine by the presence, in the para position (position 4) of the aromatic ring, of a fluorine ion for the former and a methyl group for the latter. 4-FA and 4-MA are therefore phenethylamines that are structurally close, but present different pharmacological profiles, thus exemplifying the variability of the structure/activity relationship of substituted amphetamines.