



Review

The effects and risks associated to mephedrone and methylone in humans: A review of the preliminary evidences



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ABSTRACT

New psychoactive substances have drastically modified the world drug scene. An increasingly popular class comprises synthetic or substituted cathinones (legal highs, research chemicals, bath salts). Among the most common psychoactive constituents of bath salts are mephedrone and methylone. Recent reports on the abuse of novel synthetic cathinone derivatives call attention to the serious physical and psychological risks resulting from their consumption, thereby emphasizing the growing use of these drugs might constitute an important public health issue.

In this paper, we will review the available data regarding the use and effects of mephedrone and methylone in humans in order to highlight their impact on public health. To reach this objective, a literature search was performed on two representative databases (Pubmed, Google Scholar), the Erowid Center website (a US non-profit educational organization that provides information about psychoactive plants and chemicals), and various governmental websites. The terms used for the database search were “mephedrone”, “methylone”, “new psychoactive substances”, “synthetic cathinones”, “substituted cathinones”, “substance abuse”, “substance use disorder”, “adverse effects”, “fatalities”. The literature search was limited to years 2005–2015 and led to the identification of 71 potentially relevant articles.

To date, the actual prevalence rates of their use remains difficult to estimate. Important health-related issues have emerged in relation to the somatic, psychiatric, and addictive consequences of their use. The potential chronic health effects of their prolonged use remain to date unknown (e.g., reproductive toxicity, genotoxicity and carcinogenic potential). Treatment for patients with prolonged exposure to synthetic cathinones should ideally include a drug management plan coupled with psychotherapy taking place in a structured program of care.

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1. Introduction

New psychoactive substances have drastically modified the world drug scene (EMCDDA, 2014). A increasingly popular class comprises synthetic or substituted cathinones. These β -keto amphetamine analogues are also known as legal highs, research chemicals, bath salts, plant food or glass cleaner and labeled “not for human use” or “not tested for hazards or toxicity” (Cottencin et al., 2014). The overwhelming majority of synthetic cathinones is produced in China and South East Asian countries (Cottencin et al., 2014). Although all synthetic cathinones are inhibitors of monoamines reuptake, only some of them, e.g. mephedrone and methylone, act as substrates for transporter proteins and evoke neurotransmitters release (Simmler et al., 2013). They have psychostimulant and hallucinogenic effects, similar to those of amphetamines, 3,4-methylenedioxy-methamphetamine (MDMA), methamphetamine and cocaine (Karila et al., 2015). Recent reports on the abuse of novel synthetic cathinone derivatives call attention to the serious physical and psychological risks resulting from their consumption, thereby emphasizing the growing use of these drugs might constitute an important public health issue. There is a lack of epidemiological data concerning the new psychoactive substances. The main sources providing information for the study of these drugs are the European Monitoring Center for Drugs and Drug Abuse (EMCDDA), the European Union Early Warning System (EU-EWS) reports, the National Reitox reports, the *Internet* underground and governmental websites and the discussion groups (i.e. e-trip reports) (EMCDDA, 2014). The EU-EWS has identified more than 70 new cathinones in Europe. In 2013, over 10 000 seizures of synthetic cathinones were reported.

Among the most common psychoactive constituents of bath salts are mephedrone and methylone. These synthetic products are indeed not used as bath water additive. They are most frequently used as white powder or crystalline mixtures but also taken orally as tablets (Wood et al., 2012). The intravenous route for cathinones or “slamming”, including mephedrone, represents a major health concern (AIDES/Sidaction/AMG/Inserm., 2013).

Clinical effects of mephedrone and methylone, as other new psychoactive substances, are individual-, dose- and route of administration-dependent (Prosser and Nelson, 2012; Petit et al., 2013). The primary effects sought by users include euphoria, openness in communication, talkativeness, increased alertness, empathy, intensification of sensory experiences, reduced appetite, insomnia, increased sexual performance, and increased sociability (Rosenbaum et al., 2012).

In 2010, mephedrone became the first substituted cathinone to benefit from a formal risk assessment. It has served as a model and was evaluated according to the new operational guidelines for risk assessment, which allow an evidence-based, timely assessment when there is a lack of information (EMCDDA, 2010c). In October 2011, mephedrone and methylone were temporarily clas-

sified in the US as Schedule I controlled substances (Doj, 2011). Furthermore, in July 2012, a permanent Schedule I distinction was attributed to mephedrone and further in 2013 to methylone (U.S., 2013; Centers, 2013). In July 2012, synthetic cathinones and derivatives were classified as illicit substances by the *Agence Nationale de Sécurité du Médicament* in France (Journal Officiel, 2012). Since the legislative ban on mephedrone (in August 2011 in United Kingdom (UK)), a number of second-generation analogs have appeared in the street drug marketplace, including e.g. the 4-methyl-N-ethylcathinone (4-MEC).

In this paper, we will review the available data regarding the use and effects of mephedrone and methylone in humans in order to highlight their impact on public health. To reach this objective, a literature search was performed on two representative databases (Pubmed, Google Scholar), the Erowid Center website (a US non-profit educational organization that provides information about psychoactive plants and chemicals), and various governmental websites. The terms used for the database search were: “mephedrone”, “methylone”, “new psychoactive substances”, “synthetic cathinones”, “substituted cathinones”, “substance abuse”, “substance use disorder”, “adverse effects”, “fatalities”. The search was limited to years 2005–2015. The literature search conducted led to the identification of 71 potentially relevant articles. All articles were screened from their abstracts to determine their relevance in the framework of the current review.

2. Mephedrone (4-methylmethcathinone)

2.1. Description of the substituted cathinone

Mephedrone (4-methylmethcathinone, 4-MMC or MMC) was first described in 1929 in the *Bulletin de la Société Chimique de France* (Sanchez, 1929). First synthesized as a homologue of ephedrine, mephedrone appeared 12 months later (Green et al., 2014). Mephedrone is a synthetic ring-substituted cathinone closely related to the phenethylamine family, differing only by a keto functional group at the beta carbon, and forming a structure similar to methamphetamine (Fig. 1). Its main precursor, 4-methylpropiofenone, can be obtained relatively easily via specialized Internet websites (Karila et al., 2015).

Mephedrone (hydrochloride salt) is a water soluble white, yellowish, beige or brown powder/crystals. Tablets or pills sold throughout Europe containing mephedrone are marketed as *Meow Meow*, *Bubbles*, *Mef...* This drug has also other street names (see Table 1). Mephedrone is available for purchase on the Internet, from head shops or from established street dealers. On the Internet, mephedrone is often marketed as plant food, bath salt or research chemical (Cottencin et al., 2014). Powder can be sold in retail and in bulk quantities. By 2010, the average price ranges from 9 to 17 euros per gram but it has increased with its official ban in Europe (EMCDDA, 2010a).

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