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Research report

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.

Contents

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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 classified 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-methylpropiophenone, can be obtained relatively easily via specialized Internet websites (Karila et al., 2015).

Mephedrone (hydrochloride salt) is a water soluble white, yellowith, 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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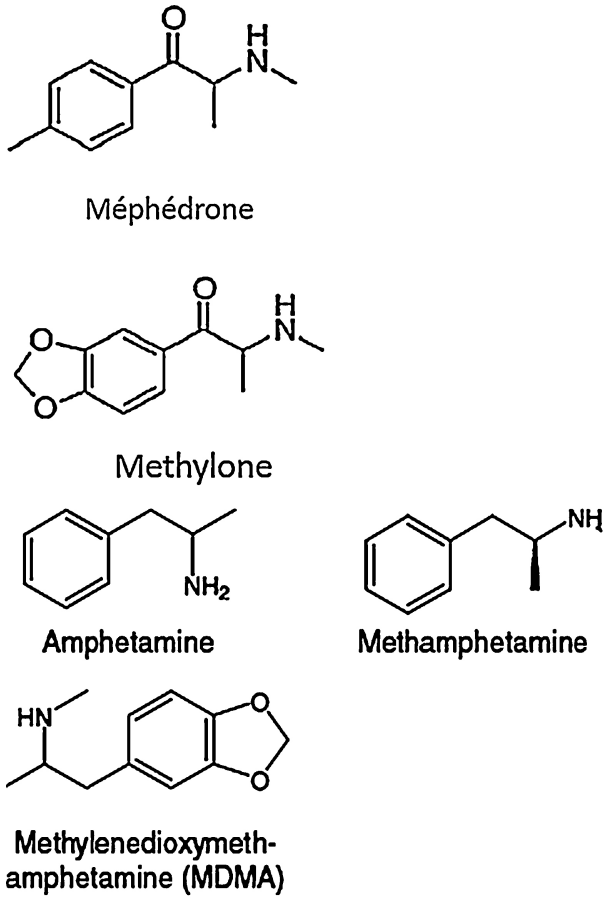

Fig. 1. Chemical structures of mephedrone, methylone, amphetamine, methamphetaminbe and MDMA.

Table 1
Street names of Mephedrone and Methylone.

Mephedrone	Methylone
Meow, Meow Meow, Miaow, Miaow Miaow (UK, USA)	Ease
Miaou miaou, Meph (France)	Explosion
Bubble(s), Bounce, Drone, Subcoca (UK, USA)	Inpact
Rush (Belgium)	Mdmcat
MMC Hammer (Germany)	bk-MDMA
Hurricane Charlie, Ketones, Dove (Ireland)	M1
Mef (Slovenia, Sweden)	Neocor
Mefi, Mephisto, Moonshine (Hungary)	Room Odorizer
Flower Magic Powder, Special Diamond, Special Gold (Romania)	

2.2. Route of administration

Oral (ingesting powder rolled up in cigarette paper or "bombing"), intranasal, intramuscular, intravenous ("slamming"), or rectal routes have been reported (Zawilska and Wojcieszak, 2013). Mixing mephedrone with heroin ("speedball") was also documented (Glennon, 2014). Binge consumption of mephedrone is frequently described, based over a 9 h period and 30 min to 2 h between doses, in social contexts (e.g., friends' homes, rave parties, night clubs, music festival), and its use is frequently associated with other drugs (e.g., alcohol, cocaine, ecstasy, cannabis) (EMCDDA, 2010c).

2.3. Epidemiological data

Mephedrone has been the first substituted cathinone identified by European authorities in November 2007 and notified via the EU-EWS 4 months later (EMCDDA, 2010a, 2010c). This drug was detected and seized in 28 European countries by 2010 (EMCDDA, 2012a). Mephedrone use rapidly increased to reach the level of ecstasy use (1.4%) and cocaine use (4.4%) in the festive scene (EMCDDA, 2012a). For example, prevalence of mephedrone and synthetic cathinones used in Northern Ireland was estimated at 2% during lifetime and at 1% during the previous year. In Europe, lifetime use was reported to be higher among the 15 to 24-year aged group (6%). A 2011 survey on a sample of UK gay nightclubbers found a lifetime use of mephedrone of 63.8% (EMCDDA, 2012b). Another survey conducted in UK regular clubbers however showed a decrease in the use of mephedrone in the previous year (from 19.5% in 2011 to 13.8% in 2012). In years 2012–2013, past year reported use of mephedrone among European adults (16–59 years old) was estimated at 0.5% (see EMCDDA, 2014).

According to the Europol–EMCDDA Joint Report, mephedrone is usually used with other synthetic cathinones (i.e. methylone, butylone, ethylcathinone) (EMCDDA, 2012a). In addition, other associated substances were identified, including lactose, caffeine, MDMA, or *meta*-Chlorophenylpiperazine (mCPP) (EMCDDA, 2010a).

Various populations of psychoactive drug users have been shown to consume new psychoactive substances (Karila et al., 2015). However, mephedrone is predominantly used by teenagers and young adults (Vardakou et al., 2011). The association between binge-drinking habits and new psychoactive substances use was highlighted as very common in a community sample of 3011 individuals, aged between 16 and 24 years and recruited in urban, intermediate and rural areas of Italy (Martinotti et al., 2015). Furthermore, associated risky sexual behaviors have been described and constituted a growing concern in men having sex with men in the framework of "Chem Sex Parties" (McCall et al., 2015), in which sexual activities are associated with the use of mephedrone, Gamma-Butyrolactone (GBL), methamphetamine, cocaine and/or sildenafil (Karila and Reynaud, 2011; Bourne et al., 2014, 2015).

2.4. Consumption and desired effects

Mephedrone is often used as an alternative to illicit drugs. It can be an attractive substance for individuals seeking stimulant psychoactive effects for recreational purposes or for substance addicted individuals who want to avoid being involved in illegal actions. Furthermore, this synthetic cathinone appears to substitute MDMA in many tablets sold as ecstasy (Brunt et al., 2011). It is to date well known that mephedrone has its own very specific pharmacology that is distinct from MDMA and also other amphetamines (Kelly, 2011). The reasons given by users are that mephedrone, in comparison to cocaine, MDMA or methamphetamine is a safer and less expensive product (Karila and Reynaud, 2010, 2011).

Mephedrone used intranasally elicits rapid and short lasting effects which appear within minutes, reach the peak in less than 30 min, and last for less than an hour. Orally ingested mephedrone (both in the form of powder and tablet) exerts its psychoactive effects after 45 min to 2 h which then last for 2–4 h. Noteworthy, several consumers first snort and then ingest the drug in order to achieve both fast and long lasting effects (Zawilska and Wojcieszak, 2013; Schifano et al., 2011).

The main effects of mephedrone are an elevated mood, feelings of intense euphoria, a sense of well-being, an increased self-esteem, tachypsychia, motor excitation, a reduced perception of tiredness, an increased concentration, alertness, talkativeness, empathy, dis-

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inhibition, a sense of being sped up, and mild sexual stimulation (Karila et al., 2015; Wood and Dargan, 2012).

2.5. Adverse effects

Numerous negative physical and psychiatric effects have been associated to high dosage and/or prolonged used of mephedrone. Cardiovascular, gastrointestinal and several neurological adverse effects do not necessary require high dosage or prolonged use of mephedrone (Cottencin et al., 2014; Karila and Reynaud, 2011). Documented effects includes jaw clenching, reduced appetite, increased body temperature, increased sweating ("mephedrone sweat"), abnormal vision, dilated pupils, headaches, tachycardia, palpitations, significant hypertension, arrhythmias, chest pain, seizures nausea, bruxism, teeth grinding, rhabdomyolysis and renal failure (German et al., 2014). Significant hyponatremia has been documented, similar to that displayed by MDMA users, which is likely due to a combination of sweating, electrolyte loss, and antidiuretic hormone secretion (German et al., 2014). Mephedrone inhalation has also been found to cause pneumomediastinum (Graham et al., 2014), uvulitis (Murphy and Haughey, 2014) and urinary retention (Conway et al., 2013).

Intranasal route of mephedrone is linked with significant nasal irritation and pain which leads some users switching to oral use of mephedrone. Debruyne et al. also reported diminished libido in regular users (Debruyne et al., 2010).

Intravenous mephedrone use is more often associated to addictive symptoms and was also found to be associated with increased risk for other drug uses (e.g., more than 35% reported being opiate users) and more elevated comorbid psychopathology (Kapitany-Foveny et al., 2015). It also produces an intense burning sensation on injection. Furthermore, repeated injections often result in vein blockages, leading to serious pathological changes, including, among others, localized infections, blisters, abscesses, scabs, lumps, gangrenous tissue, blood clots and large holes at the injection site. Thus, they are limited to two-three per site (Van Hout and Bingham, 2012).

Other related medical risks comprise human immunodeficiency virus (HIV) or Sexual Transmitted Diseases, especially when the drug is consumed in "Chem Sex Parties" (Bourne et al., 2015).

The main psychiatric effects associated to mephedrone use include agitation, anxiety, dysphoria, depression, insomnia, hallucinations, paranoia, cognitive disorders (e.g., impaired short term memory and attentional capacities), delusions, aggressive behavior, suicidal ideations, suicidal actions (Chan et al., 2015; Wood et al., 2011). Psychotic disturbances were reported mainly after high mephedrone doses, multiple dosages of the drug consumed during one session and in users with underlying psychobiological vulnerability (John et al., 2014; Dragogna et al., 2014; Bajaj et al., 2010).

The potential chronic health effects of mephedrone use, including reproductive toxicity, genotoxicity and carcinogenic potential, remain to date unknown (EMCDDA, 2010c).

2.6. Addictive potential

Initial cases of mephedrone abuse was reported in the early 21st century, following claims circulated via the Internet that it could provide in a legal alternative to MDMA (Morris, 2010). Yet, the addictive potential of mephedrone is real (Karila and Reynaud, 2011; Winder et al., 2013). Mephedrone taken intranasally could have a potential for abuse comparable to that of cocaine or methamphetamine (Karila and Reynaud, 2011). Indeed, a survey conducted on 1500 mephedrone users found that over 50% reported being addicted to the drug (Carhart-Harris et al., 2011). In another study, 25% of users reported experiencing mephedrone-related cravings (Winstock et al., 2011). Central addiction symptoms have been described in mephedrone users, including loss of control, craving, and tolerance, similar to those generally observed in cocaine or amphetamines misuse (EMCDDA, 2010c). A stimulant withdrawal syndrome has also been described in heavier users. Withdrawal effects documented to include tiredness, insomnia, impaired concentration, irritability, nasal congestion, tremor, shivers, increased or decreased temperature, palpitations, headache with "brainzap" (similar sensation to electric shocks), depression, anxiety, or paranoia (EMCDDA, 2010c; Karila et al., 2015; Winder et al., 2013).

2.7. Fatalities

Mephedrone was reported to be implicated in several fatalities across the world (Weaver et al., 2015; Loi et al., 2015). The first documented death case attributable to mephedrone use was a Swedish deceased from the consequences of hyponatremia and brain edema (Gustavsson and Escher, 2009). By 2012, 128 mephedrone-associated fatalities have been reported (Schifano et al., 2012). Studies have not determined the minimum lethal dose of mephedrone (EMCDDA, 2010c). Eighteen fatal cases were confirmed post-mortem with mephedrone in biological samples of the deceased. The death was attributed to mephedrone intoxication in 9 cases, whereas multiple drug toxicity (including mephedrone) (Busardo et al., 2015) was considered as the cause of death in 6 cases. Several additional cases were attributed to mephedrone, at least as the adjunctive causative agent (for a review, see Prosser and Nelson, 2012).

3. Methylone

3.1. Description of the substituted cathinone

Methylone (3,4-methylenedioxymethcathinone) is methylated on the amine group and α carbon of this β-ketophenethylamine backbone (Fig. 1). It has a methylenedioxy ring attached to the aromatic ring, forming a structure similar to MDMA (Meyer and Maurer, 2010). The substituted cathinone was first synthesized in 1996 as a potenital antidepressant and anti-Parkinsonian agent (Jacob and Shulgin, 1996). It however never resulted in a commercialized pharmaceutical product. Methylone is also named M1, MDMC and bk-MDMA (Karila and Reynaud, 2011).

Methylone was initially described in 2004 as a liquid solution, sold as a vanilla-scented room odorizer (Erowid). This drug can be purchased via the Internet and in headshops (Meyer et al., 2010). The compound mainly exists in powder form and in tablets (EMCDDA, 2010b). Street names of this drug are summarized in Table 1. Methylone was first seized in The Netherlands in 2005 (Bossong et al., 2005). Methylone became illegal in Sweden since 2007, in the UK since april 2010 and in France since 2012 (EMCDDA, 2010b). Use and abuse have been reported in several countries, including the U.S., Japan and Europe (WHO, 2014).

3.2. Route of administration

Methylone is administered through a variety of different routes, including oral, intranasal, intravenous, sublingual, or rectal. Oral use is the most popular route of administration. This drug can be used with a larger first dose ("boosting") and then smaller doses ("bumps") to maintain the effects for a longer period (WHO, 2014; De Felice et al., 2014).

3.3. Epidemiological data

According to U.S. Drug Enforcement Administration in 2012, methylone was reported to be the 11th most common hal-

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Table 2
Adverse effects of methylone use.

Somatic adverse effects	Psychiatric adverse effects (EMCDDA, 2010b)
• Cardiovascular system: tachycardia, palpitations, hypertension • Gastro-intestinal system: nausea, vomiting • Central nervous system: mydriasis, nystagmus, confusion, seizures, hyperthermia • Musculoskeletal system: involuntarily bodily shakes, bruxism, jaw clenching, trismus, extreme unsteadiness of the hands and a general lack of motor control • Other: sweating, dry mouth, dehydration, difficulty urinating	• Anxiety • Anorexia • Derealization/depersonalization • Impaired short term memory • Psychosis • Hallucinations • Suicidal ideations

lucinogens within the United States (US Drug Enforcement Administration, 2012). Cases where new psychoactive substances have been detected in biological material are published (Rust et al., 2012; Adamowicz et al., 2016). An online UK survey of clubbers found that 10% had used methylone (Winstock et al., 2011). A study conducted in Ireland which analyzed the urine collected from attendees at a methadone maintenance clinic found that 3% were positive for methylone (McNamara et al., 2010). A 2011 study realized with Irish prisoners showed that this population reported injecting cathinones, with a past year prevalence of injection of methylone of 7% among females and 1% among males (Drummond et al., 2014).

The National Forensic Laboratory Information System identified confiscated drugs throughout the United States, and emphasized that among the 25 most frequently confiscated drugs in 2014, three were synthetic cathinones, including 4768 reports involving methylone (US Drug Enforcement Administration, 2015).

3.4. Consumption and desired effects

Methylone-related psychoactive effects last from 3 to 5 h. Onset of desired effects is typically seen within 15–60 min post oral ingestion. Desired effects last approximately 30–45 min (WHO, 2014).

The effects of methylone range from amphetamine-like stimulation (such as a calm euphoria, happiness, thought acceleration, alertness, restlessness, reduced fatigue, increased locomotor activity) to entactogenic effects resembling those produced by MDMA (e.g. strong sense of empathy, reduced fear) (Shimizu et al., 2007). The high of methylone can be described as a moderate to extreme euphoric tingling sensation (WHO, 2014).

3.5. Adverse effects

Methylone shares many of the risks generally associated to MDMA (WHO, 2014). Known adverse effects of methylone use (Prosser and Nelson, 2012) are summarized in Table 2.

The seizures and hyponatremia induced by methylone might be due to similar causes than those produce by the consumption of MDMA. A potential explanation might be that methylone may favor the release of inappropriate secretion of antidiuretic hormone mediated via the serotonin system (Boulanger-Gobeil et al., 2012). Methylone also induces hyperthermia, which is thought to contribute toward the lethal consequences of its overdose (Piao et al., 2015).

3.6. Addictive potential

Abuse of methylone has been reported worldwide (WHO, 2014). Methylone is highly susceptible to have an addictive potential, probably comparable to the one of MDMA, but the related evidence are to date lacking in the literature (EROWID).

3.7. Fatalities

A number of fatal intoxications involving methylone use have been reported. For example, Pearson et al. presented three cases of fatal intoxications caused by methylone. Metabolic acidosis, rhabdomyolysis, acute renal failure and disseminated intravascular coagulation were identified as causal lethal factors in these cases (Pearson et al., 2012). Warrick et al. reported a case of a 24-year-old female who died following the ingestion of a capsule containing methylone and butylone sold as ecstasy (Warrick et al., 2012). Acute methylone intoxication was also reported to be involved in an accidental drowning (McIntyre et al., 2013). Sudden cardiac death associated with methylone use was reported (Carbone et al., 2013). The first lethal case documented in France concerns a 21-year-old man who died following the ingestion of methylone during an evening with friends (Barrios et al., 2015).

4. Conclusion

The addiction landscape has indubitably been modified by the appearance of substituted cathinones, such as mephedrone or methylone. To date, and in a similar way that for other drugs, the actual prevalence rates of their use remained 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 is primarily symptomatic. Treatment option should ideally include a drug management plan coupled with psychotherapy taking place in a structured program of care. Based on the initial evidence reviewed here, it appears that developing clinical research and improving management of addiction and poisonings attributed to new psychoactive substances should be considered a public health priority.

Conflict of interest

- Dr Laurent Karila receives consulting fees from BMS Otsuka, Lundbeck, Gillead, Shering Plough, Eutherapie, Merck/Serono, Astra Zeneca, Janssen-Cilag, Bouchara Recordati Pharmaceuticals.
- Pr Amine Benyamina receives consulting fees from Bristol-Myers-Squibb, Euthérapie, Lundbeck and Merck-Serono Pharmaceuticals. He is clinical investigator for Euthérapie Pharmaceuticals and member of Reckitt-Benckiser Board.
- Pr Christophe Lançon receives consulting fees from Lundbeck, Janssen-Cilag, Roche Pharmaceuticals.
- Pr Olivier Cottencin receives consulting fees from Lundbeck, Shire, Indivior, Bouchara Recordati Pharmaceuticals.
- Pr. Joël Billieux reports no conflict of interest.

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