

SPECIAL ISSUE ON NOVEL PSYCHOACTIVE SUBSTANCES

Patterns of use and toxicity of new para-halogenated substituted cathinones: 4-CMC (clephedrone), 4-CEC (4-chloroethcathinone) and 4-BMC (brephepedrone)

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Abstract

Objective: This paper aims to present results of the analysis of clephedrone (4-CMC), 4-chloroethcathinone (4-CEC), and brephedrone (4-BMC) on recreational drug markets and a systematic review of all the available information concerning these substances.

Material and methods: Samples collected by the drug checking service of the Spanish harm reduction NGO—Energy Control were analyzed and systematic research was conducted. Between June 2014 and October 2016, 1,471 samples with at least one NPS were analyzed, 397 of which contained cathinones.

Results: Clephedrone was found in 29 samples, brephedrone in 8, and both were present in 2 samples. 4-Chloroethcathinone was detected in 5 samples. Eleven out of the 47 purchased samples (23.4%) were tested to contain the substance the user expected. Samples received were mainly sold as 3-MMC, MDMA, ketamine, and other cathinones. No literature on the effects or toxicity of these substances was found; the only information available was on internet fora. On many posts, users exhibit concerns about potential toxicity and side effects of using these substances.

Conclusion: Since the emergence of these substances could prove to be the next step to the cat-and-mouse game existing between drug producers and legislation, further clinical and epidemiological research should be carried out in order to build evidence to support policy for public health issues.

KEYWORDS

4-BMC, 4-CEC, 4-CMC, cathinones, new psychoactive substances, NPS

Abbreviations: 3-CMC, 1-(3-chlorophenyl)-2-(methylamino)-1-propanone; 3-MMC, 2-(Methylamino)-1-(3-methylphenyl)-1-propanone; 4-BMC, brephedrone, 4-bromomethcathinone. 1-(4-bromophenyl)-2-methylaminopropan-1-one; 4-CEC, 4-chloroethylcathinone. 1-(4-Chloro-phenyl)-2-ethylamino-propan-1-one; 4-CMC, clephedrone, 4-chloromethcathinone 1-(4-chlorophenyl)-2-(methylamino)-1-propanone; 4-MEC, 2-ethylamino-1-(4-methylphenyl)propan-1-one; 5-APB, 5-(2-Aminopropyl)benzofuran; 5-MAPB, 1-(Benzofuran-5-yl)-N-methylpropan-2-amine; 5-methyl-ethylone, 2-(Ethylamino)-1-(7-methyl-1,3-benzodioxol-5-yl)-1-propanone; Bupropion, 3-chloro-N-tert-butyl-β-keto-amphetamine; Butylone, 1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one; Cathine, 2-amino-1-phenylpropan-1-ol; Cathinone, 2-Amino-1-phenyl-1-propanone; Diethylpropion, 2-diethylamino-1-phenylpropan-1-one; Ephedrine, 2-(methylamino)-1-phenylpropan-1-ol; Ethylone, 1-(1,3-benzodioxol-5-yl)-2-(ethylamino)propan-1-one; GHB, γ-hydroxybutyrate; Ketamine, 2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone; LSD, (6aR,9R)-N,N-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-fg]quinoline-9-carboxamide; MDMA, 3,4-metilendioximetamphetamine; MDPV, 1-(Benzo[d][1,3]dioxol-5-yl)-2-(pirrolidin-1-yl)pentan-1-one; Mephedrone, 2-Methylamino-1-(4-methylphenyl)propan-1-one; PCP, 1-(1-phenylcyclohexyl)piperidine

1 | INTRODUCTION

New psychoactive substances (NPS) are becoming a major issue as their consumption rises and their number increases yearly. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) of the European Union, more than 560 NPS are currently being monitored, and 98 of these substances were reported for the first time in 2015 (EMCDDA|European Drug Report 2016). The number of patients arriving yearly at a British emergency department with self-reported NPS use and drug-related toxicity rose from seven to 98 between 2006 and 2011 (David M Wood, Greene, & Dargan, 2013). This signifies a 14-fold increase in 5 years, but this may only reflect an increase in the number of users that are consuming these substances knowingly. In fact, a considerable number of users are not aware they are ingesting NPS, as the adulteration of traditional drugs with NPS presenting similar effects has become a common strategy for dealers (Karila, Megarbane, Cottencin, & Lejoyeux, 2015).

NPS can be categorized into different groups such as synthetic cannabinoids (e.g., the JWH family), indolamides (LSD and tryptamine derivatives), arylcyclohexylamines (PCP and ketamine derivatives), and phenethylamines (amphetamine and cathinone derivatives) among others (Liechti, 2015; Papaseit, Farré, Schifano, & Torrens, 2014). Synthetic cathinones and cannabinoids represent more than two thirds of the NPS available on this emerging drug market (Karila et al., 2015) and both constitute a higher risk than similar traditional drugs (van Amsterdam, Nutt, Phillips, & van den Brink, 2015).

Cathinone (Figure 1) is a stimulant alkaloid found in the leaves of the khat plant primarily used in the Arabian Peninsula and the Horn of Africa. It produces psychostimulatory effects, including euphoria, alertness, and psychomotor hyperactivity, similar to amphetamine (Figure 1) but less potent (Kalix, Geissshusler, Brenneisen, Koelbing, & Fisch, 1990; Krikorian, 1984). Structurally, cathinone is a β -ketoamphetamine that provides the base structure for synthetic cathinones and their amphetamine analogues. Both amphetamines and most cathinones release dopamine, serotonin, and norepinephrine and inhibit monoamine transporters (Baumann et al., 2012; Liechti, 2015; Rickli, Hoener, & Liechti, 2015; Simmler et al., 2013; Simmler, Rickli, Hoener, & Liechti, 2014). Despite their similarities, cathinones seem

to present higher selectivity for the Dopamine Transporter (DAT) than the Serotonin Transporter (SERT), resulting in a higher DAT/SERT inhibition ratio (Kehr et al., 2011; Simmler et al., 2014). They also present lower TAAR1 affinity, resulting in more dopaminergic stimulation. Synthetic cathinones are abused not only for their hedonistic and euphoric effects but as a replacement for other stimulants that are tightly regulated (e.g., cocaine, MDMA, and other amphetamines) and that are more expensive, more difficult to obtain, or considered less pure (German, Fleckenstein, & Hanson, 2015).

Some cathinone derivatives, however, are marketed as clinically useful drugs. Bupropion (Figure 1) is a cathinone approved as an antidepressant in 1989 and also used for smoking cessation and attention-deficit disorder with hyperactivity. Bupropion offers the same efficacy as selective serotonin reuptake inhibitors (Maneeton, Maneeton, Eurviriyankul, & Srisurapanont, 2013) and venlafaxine for major depression disorder (Hewett et al., 2010). It possesses, however, a valuable side effect profile: less sexual and cognitive dysfunction, and no weight gain. Nevertheless, anxiety, insomnia, convulsion risk, and the possibility of abuse limit its clinical applications to a subgroup of depressed patients. Diethylpropion (amfepramone—Figure 1) is another cathinone marketed as an appetite suppressant in some countries although it has been withdrawn from others (Soto-Molina et al., 2015).

Mephedrone (4-methylmethcathinone, 4-MMC) was one of the first legal highs in Europe and is considered a typical cathinone derivative (Gibbons & Zloh, 2010). It has been widely used to mimic the effects of MDMA, despite its being considered by experts as a more harmful drug (van Amsterdam et al., 2015). Due to the increasing abuse of mephedrone throughout Europe, most governments reacted by banning the substance (EMCDDA, 2010; EMCDDA, 2011). As a consequence, the drug market was swamped by other psychoactive cathinone derivatives designed to circumvent the law. These derivatives resemble the structure of better known cathinones, with discrete changes in their backbone structure. One simple way of generating mephedrone derivatives is by adding other substitutions to the fourth position of the phenyl ring. The resulting substances are known as para-substituted cathinones. Adding halogens such as fluorine, bromine, or chlorine to this position has led to the emergence of flephedrone, brephedrone, and clephedrone, respectively, which have recently been detected on the drug market (Taschwer, Weiß, Kunert, & Schmid, 2014). Substitution of the methyl for an ethyl group in clephedrone results in 4-chloroethcathinone.

Brephedrone (4-bromomethcathinone, 4-BMC, Figure 1) acts as a serotonin, dopamine, and norepinephrine transport inhibitor and releases dopamine and norepinephrine, similar to amphetamine. (Cozzi & Foley, 1999; K. F. Foley & Cozzi, 2002; Rickli et al., 2015). The molecule was studied as a bupropion (Figure 1) derivative under the name 4-BMAP in 2002, with apparently no further research in this line.

In 2014, clephedrone (4-chloromethcathinone, 4-CMC), a chlorine-substituted derivative of cathinone (Figure 1) was mentioned in the scientific literature for the first time (Klavz, Gorenajk & Marinsek, 2016; Taschwer et al., 2014).

The first and only scientific publication about 4-CEC (4-chloroethcathinone) is from 2017. There is a report on Erowid from April 2016 and almost no more information available (Kuś, Kusz, Książek, Pieprzyca, & Rojkiewicz, 2017).

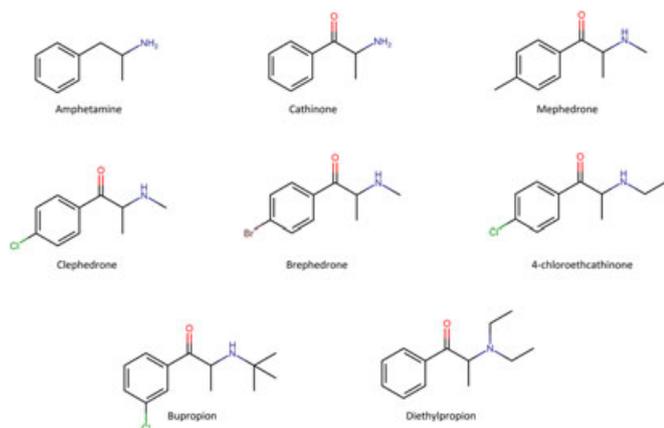


FIGURE 1 Chemical structure of amphetamine, cathinone, mephedrone, clephedrone, brephedrone, 4-chloroethcathinone, bupropion and diethylpropion

To the best of our knowledge, no studies have been published focused on the effects or patterns of use of brephedrone, 4-chloroethcathinone, or clephedrone.

The objective of this paper is to study the presence of clephedrone, brephedrone, and 4-chloroethcathinone in recreational settings. These three substances have been selected because they lack of an academic description of their toxicity and effects in humans, and due to the high toxicity of their amphetamine analogues, they could be a threat for drug users.

2 | MATERIALS AND METHODS

2.1 | Sample collection

Drug specimens collected between June 2014 and October 2016 were handled by Energy Control, a harm reduction project within the Spanish NGO "Asociación Bienestar y Desarrollo." The aim of Energy Control is to provide information and counseling to people who intend to consume drugs. It offers a free and anonymous drug checking service to Spanish nationals and charges a fee for international analysis. Spanish nationals can personally take their samples to one of the four Energy Control headquarters (Madrid, Catalonia, Balearic Islands, and Andalucía), send them by mail, or hand them in during outreach work in nightlife settings, such as music festivals, clubs, and underground raves. The drug checking service of Energy Control has a threefold purpose: (a) to make contact with drug users who would not normally approach drug programs and who are concerned how the consumption, adulteration, and purity of their products might affect their health; (b) to employ this service as an educational and harm/risk reduction tool by making contact with consumers and providing them with individual and personalized information about the substance they may consume; and (c) to monitor the illegal market by detecting new trends of drugs and drug use and make this information available to all the stakeholders involved.

Since 2000, Energy Control has analyzed almost 25,000 samples, both from Spain and, since 2014, from abroad. Although it may not be an exact reflection of the market, it contributes to our understanding of what is happening at street level.

2.2 | Laboratory analysis

Preliminary identification of samples was performed by GC/MS at the IMIM facilities using an Agilent 7890B gas chromatograph, coupled to a 5977A quadrupole mass spectrometer detector (Agilent; Santa Clara, CA, USA). The gas chromatograph was fitted with G4513A autosampler injector. Insert liners packed with silanized glasswool were used, and the injector and the interface were operated at 280 °C. Samples were injected in split mode into a 30 m 0.25 mm i.d., 0.25 µm film thickness 5% phenylmethylsilicone column (HP-5MS, Agilent Technologies). Helium was used as carrier gas at a flow rate of 1 ml/min. The oven temperature was initially maintained at 90 °C for 2 min and programmed to reach 320 °C at 20 °C per minute. It was finally maintained at 320 °C for 9.5 min (total run time was 21.5 min). The mass spectrometer was operated in electron impact ionization mode at 70 eV. In order to confirm the mass spectra, four libraries were used: the Searchable Mass Spectral Library NIST/EPA/NIH

Mass Spectral Library, Data Version: NIST 14; Searchable Mass Spectral Library Version 2.3 (<http://www.swgdrug.org/ms.htm>); Searchable Mass Spectral Library Cayman Spectral Library (<https://www.caymanchem.com/app/template/SpectralLibrary.vm>); and the Energy Control's Mass Spectral library for internal use.

2.3 | Literature and forum research

Systematic internet searches were conducted in October of 2016 on Google using "4-CMC," "clephedrone," "4-CEC," "4-BMC," and "brephedrone" in combination with the terms "experience," "report," "forum," and "trip." The search yielded 8810, 264, 1940, 6250, and 561 hits, respectively, to the four main search criteria when combined with the additional terms mentioned and filtered by verbatim. The sites that provided relevant information were bluelight, drugs-forum, reddit, drugs.tripsit.me, vice (vol.17n³6), flashback, hyperreal, and dopalator. Google Trends were also employed to look for "4-CMC," "4-CEC," "clephedrone," "4-BMC," and "brephedrone." A systematic search was also conducted in PubMed and Google Scholar in September 2015 using the same four main search terms and the IUPAC nomenclature (4-Bromomethcathinone 1-(4-bromophenyl)-2-methylaminopropan-1-one and 4-Chloromethcathinone 1-(4-chlorophenyl)-2-(methylamino)-1-propanone, and 4-Chloroethcathinone 1-(4-chlorophenyl)-2-(ethylamino)-1-propanone). Of the results obtained, only reports that were concise, relevant, and mentioned previous experience with cathinones were chosen.

3 | RESULTS

3.1 | Results and effects described of samples collected

From August 2009 to May 2014, we analyzed 13,621 samples without finding any containing brephedrone, clephedrone, or 4-chloroethcathinone. The first sample of any of these substances was detected in June 2014. From then to October 2016, 12,965 samples were analyzed at Energy Control's facilities. From those, 1,471 (11.34%) contained at least one NPS and only 910 of those (61.86%) were purchased as NPS. NPS delivered at Energy Control drug checking service were mainly phenethylamines and cathinones. Use of other types of NPS such as synthetic cannabinoids is not common in Spanish drug users.

Forty-seven samples contained, or were suspected to be, 4-chloroethcathinone, brephedrone, and/or clephedrone, representing 11.8% of the 397 analyzed cathinones. Clephedrone was found in 29 samples, brephedrone in eight, and 4-chloroethcathinone in five. In two specimens, both clephedrone and brephedrone were detected (see Figure 2).

Only 11 out of the 47 purchased samples (23.4%) were tested to contain the substance the user expected. The samples were handled as shown in Table 1 and Figure 2.

In relation to users ($n = 34$), some socio-demographic information was obtained: 91.7% were male and they were aged between 26 and 46 years. Of the purchased samples, 17.4% had been previously consumed prior to testing, and 56.5% of the received samples were in the form of crystal rocks whereas the others were powder. The

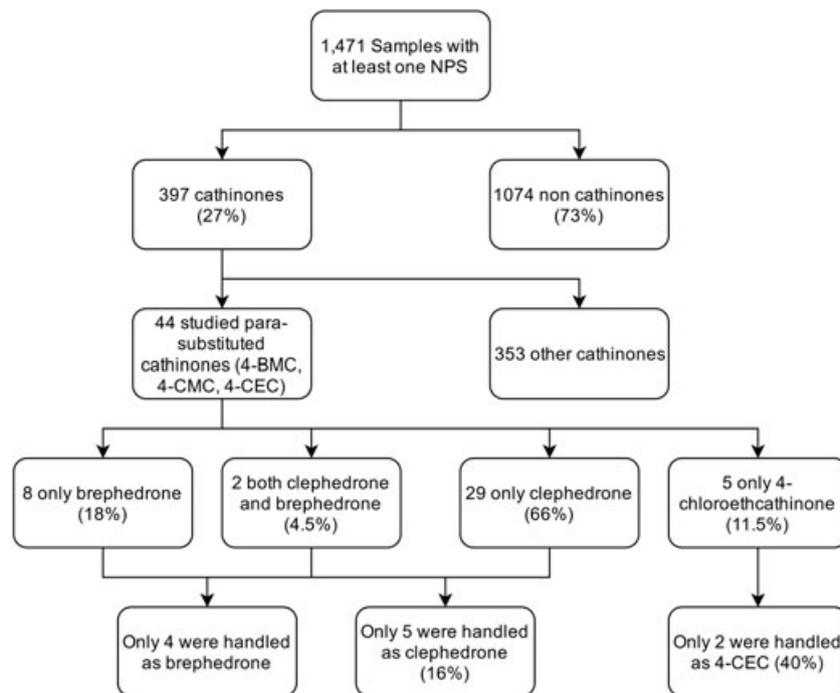


FIGURE 2 Distribution of collected samples containing new psychoactive substances and users' expected result

TABLE 1 Substance expected in samples containing 4-CEC, 4-CMC, or 4-BMC

Sample result	Samples handled as									Total
	4-CMC	4-BMC	4-CEC	3-MMC	3-CMC	Ketamine	MDMA	Unknown	Other cathinones	
4-CMC	5	0	0	1	1	2	6	11	3	29
4-BMC	3	4	0	1	0	0	0	0	0	8
4-BMC & 4-CMC	0	1	0	0	0	0	0	1	0	2
4-CEC	0	0	2	0	0	0	0	1	2	5
Unknown	0	0	3	0	0	0	0	0	0	3

cathinones were mainly taken orally (75% of users) and 25% snorted them. One of the contacted users stated that he had previously used these substances intravenously in private sex parties that could last from several hours to days. Fifty percent of the users reported mixing the cathinones with other drugs, mainly with cocaine but also with ketamine and GHB. Consumers described euphoric effects similar to MDMA: "It (4-BMC) feels like MDMA but the effects disappear very quickly" and "Many hours of euphoria, you're going 100 miles per hour. Endogenous drug (4-BMC) with brain superpowers."

With regard to side effects, only one user reported insomnia.

3.2 | Effects described on fora

Data about the effects of 4-CMC, 4-CEC, and 4-BMC in humans are limited to self-reported experiences on user websites of recreational drugs. Information on these websites does not include analytical or biochemical confirmation of the substances consumed.

The 4-BMC users reported that it was common to mix the substance with other stimulants such as methylenedioxypropylvalerone. (MDVP) One consumer reported rectal consumption with very strong side effects of nausea, dysthermia, feeling cold, and insomnia. The same individual described a psychotic episode lasting 6 months that was

characterized by delusions of parasitosis. Most 4-CMC and 4-CEC users reported being sent a free sample with a purchase of other NPS. Only one consumer described an analytical confirmation of the substance. Searching for a legal alternative to mephedrone and having the substance available at home played a role in the decision to ingest it. Although there is no proven link, many users report concerns over possible neurotoxicity due to structural similarity to 4-chloroamphetamine, a well-studied neurotoxin. Many of the forum threads are littered with warnings and advice not to consume this substance. The following is an example of the kind of comments in such fora:

"There is not a link because there is no research on the subject (or none that I'm aware of). This belief is derived from the high neurotoxicity of chlorinated amphetamines in comparison to other amphetamines and the assumption that this high neurotoxicity of chlorinated amphetamines due specifically to the chlorination would cause chlorinated cathinones to be neurotoxic as well." (Reddit, 2016).

In several reports, other users followed the recommendation to throw it away. Further information collected from the Internet is summarized in Table 2.

TABLE 2 Shows a comparison of the trends, dosages, effects, and legal status between 4-BMC, 4-CMC, and 4-CEC

	4-BMC	4-CMC	4-CEC
Online trends	There has been forum activity regarding buphedrone since at least 2011; reaching a peak in Google searches in September 2015 and then decreasing. ¹	The term "4-CMC" had no significant amount of Google searches before July 2014 when it peaked. Several users reported receiving free samples from suppliers in 2015.	The term "4-CEC" had no significant amount of google searches until October 2015, shortly after the China ban on 116 NPS, including 4-CMC. ²
Dosages reported	50–400 mg ⁴	50–1,000 mg tolerance varies wildly, as many users speak of past experiences and abuse of other cathinones alongside 4-CMC.	15–300 mg user reports are few and far between. Users prefer 4-CMC over 4-CEC ⁵
Duration	50 mg in the 2-hr experience and 100 mg in the 9-hr one.	Duration 2–4 hr. ⁶	Around 1–3 hr ⁸
Searched effects	Described as a ready available alternative to MDMA and mephedrone, despite seeming a weaker stimulant. Rated as less exciting than 5-MAPB and 3-MMC. 50 mg, snorted: Enhanced mood, feeling close to others, extroversion, and well-being. 100 mg, snorted: Higher mood than before, strong empathy, relaxation, and pleasant sensation. 200–250 mg, orally and snorted: Clear euphoria, de-realization, enhanced music perception, and entactogenic feeling comparable to MDMA. 400 mg, intense restlessness and easy distraction, insomnia, tension, palpitations, stabbing pain, and headache. ⁹ 50 mg, snorted: Actively reported lack of adverse effects or changes in pupils or blood pressure. 100 mg, snorted: Urge to redose. 200–250 mg orally and snorted: Face numbness and sensation such as "being drunk." 100 mg insufflated: User reports subtle but present effects: Stimulation, euphoria. ¹⁰ 100–150 mg: User reports smooth stimulation and euphoria, and greatly increased sociability, no notable mydriasis, and an increase in concentration. ¹¹	Up to 20 mg users describe no clear effects, called underthreshold dose. 50 mg , comparable to 75–90 mg of MDMA, experimenting euphoria, increased energy, sociability and sexuality, visual and auditory hallucinations, and strong empathogenic feelings. ¹² User did 1 gram over 24 hr, in combination with MDPPP and MDPHP, reports intense tremor, bruxism, and nearly blacking out. Describes it as a stimulating empathogen, weaker than 3-MMC. Recommends 150 mg as a dose for "an experienced ketone user" (sic) ¹³ User reports dose for a first-time user as 100 to 200 mg orally and 50 to 100 mg nasally, and warns of pain upon insufflation ¹⁴ Upon insufflation of 80 mg, user reports light-headedness, dizziness, and feelings of warmth. ¹⁵ Injection of 80 and 250 mg 20 min later: User describes increase in body heat, nystagmus, euphoria, and extreme feelings of ecstasy for about 30 min, and then a gradual decrease of effects. ¹⁶	15 mg: "felt great" with an unpleasant crash after 3 hr ¹⁷ 66 mg: Stimulation, sociability, euphoria, slight perceptual changes. ¹⁸ 100 mg: Half-hour peak, weaker than 3-MMC. 150 mg: Effects begin after 5–10 min. Stimulated, talkative 150 mg: No notable effects 200 mg divided into 50–66 mg doses: Sharp focus, euphoria, after peaking for 10 min, visual changes. Lights look more intense, flashing colors. About 1-hr duration with 300 mg: Feels like a poor analogue of 4-CMC, sensation of a good come-up that falls short ¹⁹ 200 mg no noticeable effects beyond placebo, 4-CMC is better ²⁰ Do not hold your breath man. My friends, the report is concise and clear; after about 100 mg x3, I seemed to feel some heat gain in the wear lobes, this could well be attributed to the cup of coffee I have recently taken. Conclusion: this substance seems just as ineffective as any other new RC's I have tried in the past month. 300 mg split into 3 doses seems to be inactive. (not analytically confirmed) ²¹
Adverse effects	Adverse effects reported have been sweating, angina, tachycardia and psychotic symptoms (when mixed with MDPV), nausea, diathermia, insomnia (when taken rectally).	Extreme pain when snorted, this results as a limiting factor in this route of administration. Most users describe headaches the following day. Users also reported psychic and somatic anxiety, apathy, jaw tension and involuntary eye movements. ²² One user reported consuming 1gr of 4-CMC iv. By mistake and surviving, explaining he needed assistance in an emergency department and received beta blockers as treatment. He also reported an intense MDMA-like hangover lasting at least 1 week.	Extreme pain when snorted, very bad-tasting nasal drip after insufflation, nausea. "crash" that lasts several hours after effects have faded Users express concern over possible neurotoxicity due to similarities in structure to 4-CA, a known neurotoxin ²³
Legal status	Scheduled in China, ²⁴ Virginia, United States, ²⁵ Sweden ²⁶ And U.K. ²⁷	Scheduled in Germany ²⁸ ; U.K. ²⁹ China ³⁰ ; Sweden ³¹ ; Virginia, United States ³² ;	Only controlled in countries with analogue acts or blanket bans such as the U.K. ³³ .

4 | DISCUSSION

Our study confirms the presence of para-substituted cathinones, such as 4-BMC, 4-CMC, 4-CEC, and others on the recreational market (Rickli et al., 2015; Simmler et al., 2014). In addition, these substances have been detected on Internet fora, and clephedrone was mentioned in an EMCDDA report in September 2011. Buphedrone and clephedrone have been included as controlled substances in several

countries (see Table 2), which suggests their presence on the international recreational markets. The first detection of 4-CEC was in January by our drug checking service, and it remains unscheduled in all countries except those with analogue laws. In addition, they show indicators of popularization, peaking for the first time in Google Trends in September 2015. It is worth mentioning the trend exhibited specifically by 4-CEC and 4-CMC: Around October, shortly after 4-CMC is prohibited in China, there is a sharp decrease in the

number of searches for 4-CMC just as the number of searches for 4-CEC increases.

The patterns of use of these para-substituted cathinones are consistent with those that were previously described for other substituted synthetic cathinones. In a similar manner, 4-BMC, 4-CMC, and 4-CEC are snorted, ingested orally, and injected intravenously (German et al., 2015). Moreover, the use of cathinones combined with methamphetamine and GHB has also been reported in male sex parties (McCall, Adams, Mason, & Willis, 2015).

The effects described on the fora are also like those reported by regular mephedrone users who refer to feelings of intense euphoria, increased concentration, talkativeness, empathy, and an "urge to move" (Winstock et al., 2011).

To the best of our knowledge, we present data for the first time from both experiences on Internet and from users handling samples with analytically confirmed results. It should be noted, however, that this study has major limitations due to the clear selection bias of the samples managed at the Energy Control facilities: The user profile could overrepresent the prevalence of NPS consumption. Despite this clear limitation, our study integrates data from Energy Control and forum research. It is the only one describing the effects of 4-BMC, 4-CMC, and 4-CEC and one of the few studies reporting the effects of NPS with analytical confirmation.

Only 23.4% of the 4-chloroethcathinone, brephedrone, and clephedrone samples handed were analyzed to be the substance that the user expected. It is worth mentioning that this trend was particularly high in samples purchased as 4-CMC after China's ban. Furthermore, it was observed that 17.8% of the analyzed samples were being sold as MDMA and ketamine. These numbers are in coherence with the ones detected by the same authors between 2010 and 2012. In this previous study in 11.4% of samples sold as controlled drugs, cathinones were replacing its presence (Caudevilla-Gálligo et al., 2013). The adulteration of ketamine samples concurred with a lack of availability of ketamine on the Spanish market as detected by Energy Control. This is not the first time that NPS have been found as adulterants in established illicit drugs when there is a shortage of precursors: It has previously occurred in The Netherlands and Spain (Brunt, Poortman, Niesink, & van den Brink, 2011; Caudevilla-Gálligo et al., 2012; Giné, Espinosa, & Vilamala, 2014). Neither is it the first time that 4-CMC has been found being sold as MDMA. Since August 2016, this adulteration was detected in Austria, Switzerland, and United States (Ecstasy data.org 2016). Such a situation is in contrast to NPS being sold through websites as alternatives for established illicit drugs as has been largely the case in the United Kingdom or the United States (Brandt, Sumnall, Measham, & Cole, 2010; Miotto, Striebel, Cho, & Wang, 2013; D M Wood et al., 2014). The apparition of these new para-substituted cathinones on the market could be the next move in the ongoing cat-and-mouse game between legislation and clandestine laboratories. As soon as legislation passes, a new designer stimulant replaces the outlawed substance (Brandt, Freeman, Sumnall, Measham, & Cole, 2011). Evidence suggests that the production and consumption of mephedrone have declined because it was controlled and scheduled. Nevertheless, new groups of synthetic cathinones, which are not controlled by current legislation, are already being distributed and abused. Therefore, it

is important to monitor the use, effects, and side effects of these new para-substituted cathinones if major health issues are to be avoided.

It is also important to highlight the need to introduce harm reduction strategies inside these experimental drug users' fora and be in contact with them. After analyzing these fora, it was clear that there is a considerable number of people asking for evidence of these compounds' toxicity and safety in order to take informed decisions. Moreover, samples are being sent free of charge to NPS users who are being used as guinea pigs.

Data regarding the toxicity of the three most commonly encountered cathinones (mephedrone, methylone, and methylenedioxypropylvalerone) have already been published. The most common symptoms are psychosis and even fatal excited delirium. Such reactions seem to be dose related and more likely to occur in chronic drug abusers (Karch, 2015). Excessive consumption may lead to toxicity with severe neurologic and peripheral symptoms, including death (German et al., 2015). However, little is known about the toxicity of para-substituted cathinones. It is possible that the 4-halogenated cathinones share the selective serotonergic neurotoxicity of their corresponding amphetamines (Karch, 2015; Rickli et al., 2015; Simmler et al., 2014). Our study has found several cases of intoxications with these para-substituted cathinones. None, however, displayed the hyperthermia-rhabdomyolysis syndrome reminiscent of serotonin syndrome and, presumably, the cause of death following intoxication with PMMA (EMCDDA, 2003), a highly toxic para-substituted amphetamine. From the information on fora, it appears that brephedrone and clephedrone at low doses do not lead to hyperthermia. The same pattern has been observed for mephedrone in which doses of up to 10 mg/kg do not cause substantial or life-threatening hyperthermia (Aarde et al., 2013; Miller et al., 2013; Wright, Vandewater, Angrish, Dickerson, & Taffe, 2012). This could be explained by the higher DAT/SERT inhibition ratio cathinones have in relation to their amphetamine counterparts (Liechti, 2015).

Although concerns regarding the neurotoxicity of para-halogenated cathinones due to their structural similarities to para-halogenated amphetamines (Fuller & Snodder, 1974) lack evidence, it is possible that MDMA-like cathinones are less neurotoxic in VMAT2-related toxicity. Although this mechanism is but one of the many that can contribute to the toxicity of a substance, in regards to amphetamine and cathinone analogues, it is one of the few that has sufficient evidence to make a comparison. As an example, methylone is significantly less potent at VMAT2 inhibition than its amphetamine counterpart, MDMA (Cozzi et al., 1999). Nevertheless, there is great variability within the cathinones themselves, with, for example, mephedrone having an IC50 of 3.40 nM and butylone having an IC50 of 81.83 nM at VMAT2 (López-Arnau et al., 2012). This mechanism of neurotoxicity could be further studied in regards to para-halogenated cathinones to determine their selectivity at these receptors.

It is also important to note that 4-CMC has been referred to by several users as addictive and they advised controlling frequency of use. Our findings are in line with the ones detected in *in vitro* studies that demonstrate that cathinones exhibit higher DAT/SERT inhibition ratio and lower affinity to TAAR₁ receptors. Such a lack of affinity

may contribute to more stimulant-like and addictive properties compared with traditional amphetamines (Simmler et al., 2014).

In addition, clinical effects are influenced by the concomitant consumption of these synthetic cathinones with other drugs. In our study, the simultaneous use of 4-CMC with cocaine, ketamine, and GHB has been reported. The concurrent use of synthetic cathinones with other stimulants leads to significantly greater monoamine toxicity (Angoa-Pérez et al., 2013), which may point to the high frequency of polydrug use fatality associated with synthetic cathinones (Aromatario, Bottoni, Santoni, & Ciallella, 2012; Busardò, Kyriakou, Napoletano, Marinelli, & Zaami, 2015; Marinetti & Antonides, 2013). It is, therefore, mandatory to develop clinical research and gather information about toxicity, risks, and treatment from addiction and emergency departments to establish patterns of abuse and toxicity, and clarify the role of hyperthermia (Levine, Levitan, & Skolnik, 2013; Liechti, 2015).

Because of the similar pharmacology, cathinone derivatives may be a useful alternative to amphetamines in treating disorders such as attention deficit hyperactivity disorder, smoking cessation, and depression (Carroll et al., 2010; German et al., 2015; Rickli et al., 2015; Simmler et al., 2014). In particular, brephedrone (4-BMC) showed promising results in a preclinical trial as an antidepressant with rats (K. Foley & Cozzi, 2003). As the heterogeneous nature of depression makes it unlikely that the quest for the ideal antidepressant will ever be resolved, each new addition to the armamentarium of antidepressants will be welcome despite its limitations (Pacher & Kecskemeti, 2004). Other authors have already described the potential utility of some legal highs in central nervous system disorders (Davidson & Schifano, 2016), which warrant further research before drug policy can hinder development (Nutt, 2014; Sessa & Nutt, 2015).

Due to very different niche uses in society, structural differences, and significantly varied effects, 4-CMC, 4-CEC, and 4-BMC are perceived as being wholly separate from medically used cathinones such as Bupropion. It is obvious that these substances are all different, but it is debatable how much of this is due to how their use is framed in society and how much of it is due to their structure and effects. With the right research, it is very possible that other gems such as Bupropion could be discovered in the cathinone family. Nevertheless, indiscriminate prohibition of cathinone analogues, without providing an accessible way of researching them, could severely stunt the discovery of new pharmaceutical substances related to this diverse family.

CONFLICT OF INTEREST

No conflict of interests reported.

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NOTES

- ¹ <https://www.flashback.org/t1220728p2>
- ² https://www.erowid.org/psychoactives/law/countries/china/china_law_2015_09_27_list_of_newly_controlled_chemicals.pdf; <https://www.google.com/trends/explore?q=4-CEC>
- ³ <https://www.google.com/trends/explore?q=4-CEC,4-CMC>
- ⁴ <https://drugsforum.com/forum/showthread.php?t=161321>
- ⁵ <https://www.reddit.com/r/askdrugs/comments/48l27y/4cec/>; <https://www.erowid.org/experiences/exp.php?ID=108163>; <https://hyperreal.info/talk/4-cec-t45620-20.html?sid=3b34829d76ccb2ea838de9fa16c9c8>
- ⁶ https://www.reddit.com/r/researchchemicals/comments/35wgn5/any_experiences_with_4cmc/
- ⁷ <https://drugs-forum.com/forum/showthread.php?t=63250#ixzz34G8N5Dpz>
- ⁸ <https://www.reddit.com/r/askdrugs/comments/48l27y/4cec/>; <https://hyperreal.info/talk/4-cec-t45620-20.html?sid=3b34829d76ccb2ea838de9fa16c9c8>
- ⁹ <https://www.reddit.com/r/askdrugs/comments/48l27y/4cec/>
- ¹⁰ <http://www.bluelight.org/vb/threads/722014-4-CMC-quot-Clephedrone-quot>
- ¹¹ <https://www.erowid.org/experiences/exp.php?ID=108163>
- ¹² <https://drugs-forum.com/forum/showthread.php?t=161321>
- ¹³ <http://www.bluelight.org/vb/threads/722014-4-CMC-quot-Clephedrone-quot?page2>
- ¹⁴ <https://hyperreal.info/talk/4-cec-t45620-20.html?sid=3b34829d76ccb2ea838de9fa16c9c8>
- ¹⁵ <https://drugs-forum.com/forum/showthread.php?t=63250#ixzz34G8N5Dpz>
- ¹⁶ <https://dopalator.info/Thread-4-CMC-4-klormetkation-Klefedron-opinie-dzia%C5%82anie-opis?page=3>
- ¹⁷ <https://hyperreal.info/talk/cmc-klfedron-t42440-10.html?sid=333e4df44f60accd6bd4e6b74b0694f8>
- ¹⁸ <https://www.flashback.org/t1220728p7>
- ¹⁹ <https://www.flashback.org/t1220728p10>
- ²⁰ <https://hyperreal.info/talk/4-cec-t45620-20.html?sid=3b34829d76ccb2ea838de9fa16c9c8>
- ²¹ <https://www.flashback.org/t2681512p3>
- ²² <http://www.bluelight.org/vb/threads/722014-4-CMC-quot-Clephedrone-quot?page2>
- ²³ http://www.bluelight.org/vb/threads/745806-4-CEC-4-chloroethcathinonehttps://www.reddit.com/r/researchchemicals/comments/4u28oc/4cec_experienceopinions/
- ²⁴ <http://www.sfda.gov.cn/WS01/CL0056/130753.html>
- ²⁵ <http://law.lis.virginia.gov/admincode/title18/agency110/chapter20/section322/>
- ²⁶ <https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2015/juni/23-nya-amnen-kan-klassas-som-narkotika-eller-halsofarlig-vara/>
- ²⁷ https://www.gesetze-im-internet.de/btmg_1981/anlage_i.html
- ²⁸ <http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted/data.htm>
- ²⁹ <http://www.sfda.gov.cn/WS01/CL0056/130753.html>
- ³⁰ <https://www.folkhalsomyndigheten.se/nyheter-och-press/nyhetsarkiv/2015/juni/23-nya-amnen-kan-klassas-som-narkotika-eller-halsofarlig-vara/>
- ³¹ <http://law.lis.virginia.gov/admincode/title18/agency110/chapter20/section322/>

- ³² <http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted/data.htm>
- ³³ <http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted/data.htm>

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