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Synthetic cathinones in drug-facilitated sexual assault: A case report involving the novel generation substituted cathinone N-ethylpentedrone and a review of the literature

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ABSTRACT

The use of 3,4-methylenedioxymethamphetamine (MDMA) in drug-facilitated sexual assault (DFSA) is not uncommon. Indeed, the effects associated with the use of this substance may lead to disinhibition. Several synthetic cathinones, such as mephedrone or methylone, also possess marked entactogenic properties. This manuscript aims to (i) report a DFSA case involving a novel cathinone derivative, namely *N*-ethyl-pentedrone (NEPD) and (ii) review previously reported DFSA cases involving synthetic cathinones. Using liquid chromatography-high-resolution mass spectrometry (LC-HRMS), NEPD was detected in both plasma and urine collected from a 36-year-old male who had been victim of DFSA. Furthermore, an exhaustive, non-period-specific English-language literature search was performed using several different electronic databases to identify DFSA cases involving synthetic cathinones. Overall, five synthetic cathinones have been associated with DFSA:methyl-enedioxypyrovalerone, 4-methylethcathinone, α -pyrrolidinopentiophenone, mephedrone, α –pyrrolidinohexiophenone, and methylone, which appears to be the most frequently reported. Methylone is the β-keto analog of MDMA, with which it shares substantial pharmacological similarities. Indeed, the pharmacological effects of methylone are similar to those associated with MDMA. By contrast, little is known regarding NEPD's pharmacological effects in humans. Based on subjective reports, NEPD can produce both positive and negative effects in human. Unlike what is reported in the case of methylone or mephedrone, only a small minority of NEPD users report slightly entactogenics effects. Such properties theoretically make NEPD more suitable for use in a chemsex context than in DFSA context; even though, the boundary between these two specific forms of sexualized drug use can sometimes appear tenuous.

1. Introduction

Drug-facilitated sexual assault (DFSA) is defined as a sexual assault in which the victim is incapacitated and/or unable to provide consent to the sexual act due to the consumption and/or administration of xenobiotics. Two types of DFSA can be distinguished using classification criteria: i) proactive DFSA or DFSA-Involuntary Ingestion (DFSA-I), in which the attacker surreptitiously administers an incapacitating or disinhibiting substance to the victim with the aim of assaulting him/her; ii) opportunistic DFSA or DFSA-Voluntary Ingestion (DFSA-V), in which the perpetrator engages in sexual activity with a victim who is deeply intoxicated as a result of his/her own actions [1,2]. According to these two forms of DFSA can be distinguished using classification criteria. Stimulants are not uncommon in cases of DFSA [3,4]. Indeed, the use of amphtemanine-type stimulants especially 3,4-methylenedioxymethamphetamine (MDMA) has been previously reported [5,6]. MDMA is an entactogenic substance. According to Nichols, entactogens are defined as a class of psychoactive drugs that "allow or promote a touching within

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or reaching inside to retrieve repressed memories" [5,6]. This class includes MDMA but also other substances with similar pharmacological effects such as 3,4-methylenedioxy-N-ethylamphetamine (MDEA), 1, 3-benzodioxolyl-N-methylbutanamine (MBDB), paramethoxyamphetamine (PMA) and several synthetic cathinones [5,6]. The effects associated with the use of these substances may lead to disinhibition resulting in inappropriate or riskier acquiescence in sexual activity. As a result, their use in DFSA cases appears consistent, even in the absence of any sedative effects or anterograde amnesia-inducing properties [5]. Indeed, as postulated by Abondo et al., a distinction between consciousness and awareness must be made in DFSA cases, as a victim may consent and actively participate in a sexual act that he/she would not normally assent to [7].

Synthetic cathinones are derivatives of the naturally occurring compound cathinone, the main psychoactive component of the plant *Catha edulis*. Synthetic cathinones appeared in drug markets in the mid-2000 s and have since emerged as a persistent and evolving issue worldwide [8]. Thus, at the end of 2022, the European Centre for Drugs and Drug Addiction was monitoring 167 synthetic cathinones, making them the second largest category of new psychoactive substances monitored by the European Union Early Warning System, after synthetic cannabinoids [9]. Synthetic cathinones are designed to mimic effects similar to those produced by more common drugs of abuse such as cocaine, methamphetamine or MDMA [8]. Like MDMA, some synthetic cathinones possess marked entactogenic properties such as sensorial intensification, increased sociability, disinhibition and sexual arousal [8,10]. These properties have been particularly well described for mephedrone and methylone [10,11]. In this context, this manuscript aims to (i) report a DFSA case involving a novel cathinone derivative, namely *N*-ethyl-pentedrone (NEPD) and (ii) review previously reported DFSA cases involving synthetic cathinones.

2. Materials and methods

2.1. Case report

A 36-year-old male was discovered naked wandering on a public highway. At the emergency department, he appeared disoriented and confused. The patient asserted to have been drugged and sexually assaulted by three men. He also reported losing consciousness and not remembering everything. His medical history was unremarkable except for occasional cannabis consumption, and he had not taken any medication regularly in the past. The clinical examination did not reveal any specific finding, and there were no signs of sexual violence noted. Given the circumstances, plasma and urine samples were collected (about 6 hours after the alleged facts) for toxicological analyses, including detection and quantification of gamma-hydroxybutyrate (GHB). Aliquots of both matrices (plasma and urine) were also sent to the French reference center at Lille for the identification of new psychoactive substances (NPS). It is important to note that the patient refused any hair sampling.

3. Toxicological investigations

3.1. Chemicals, solvents, and reagents

The different drug standards and internal standards (IS) were purchased from Sigma-Aldrich (Saint-Quentin-Fallavier, France), LGC standards (Molsheim, France), Bertin Bioreagent (Montigny-le-Bretonneux, France) and/or INTERCHIM SAS (Montluçon, France). All solvents and reagents were HPLC grade or analytical grade. Milli-Q water was used throughout the analysis.

3.2. Systematical toxicological investigations

Toxicological analyses were performed in both plasma and urine. Ethanol concentration determination was carried out using gas chromatography with flame ionization detection [12]. Determination and quantification of GHB and drugs of abuse (DOAs)were yielded using previously described validated methods [12,13]. DOA included tetrahydrocannabinol (THC) and metabolites (11-hydroxy-delta9-tetrahydrocannabinol [11-OH-THC], 11-nor-9-carboxy-delta9-tetrahydrocannabinol [THC-COOH]), amphetamine, methamphetamine, MDEA, MDMA, 3,4-methylenedioxyamphetamine, cocaine and metabolites (benzoylecgonine, methylecgonine, cocathylene), fentanyl, norfentanyl, morphine, codeine, 6-monoacetylmorphine, oxycodone, noroxycodone, oxymorphone, methadone and its metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), buprenorphine, norbuprenorphine, etc. Specific investigation of new psychoactive substances (NPSs) was also performed using a previously described method [13]. This dedicated method has been previously published and allows the identification and quantification of approximately twenty synthetic cathinones including methcathinone, mephedrone, 3-methylmethcathinone (3-MMC), flephedrone, pentredone, 4-methylethcathinone (4-MEC), 4-fluoroethcathinone (4-FEC), α -pyrrolidinopentiophenone (α -PVP), methylenedioxypyrovalerone (MDPV), methylone, mexedrone, etc [13]. Finally, a comprehensive non-targeted screening was performed using liquid chromatography and high resolution mass spectrometry (LC-HRMS). This method allows the detection of several compounds including prescription drugs, DOAs, NPSs, and other toxicants. Samples preparation was achieved by protein precipitation 100 µL of a methanol solution contining ZnSO4 and several IS were added to 50 µL of sample. IS included dihydrocodeine-d3 (50 µg/L), lopinavir-d8 (50 µg/L), prazepam (50 µg/L), gamma-hydroxybutyrate-d6 (10 mg/L), and metformin-d6 (100 µg/L). Chromatographic analysis was carried out using a shimadzu LC-40B X3 CL pump (Shimadzu Corporation, Marne-la-Vallée, France). Separation was achieved using a Kinetex Phenyl-Hexyl column (4.6 ×50 mm); 2.6 µm (Phenomenex SAS, Le Pecq, France). Mobile phase A was composed of ammonium formate buffer (10 mM in 0.05% formic acid) and deionized water while mobile phase B included methanol (in 0.05% formic acid). Chromatographic separation was performed at a column temperature of 30°C and a flow rate of 0.7 mL/min. The injection volume was 10 µL and the total run time was 11 min. The elution gradient of the mobile phase was as follow: phase A 90%/phase B 10% a at time 0 min, phase A 2%/phase B 98% at time 7.5 min, and phase A 90%/phase B 10% at time 9.1 min. The UHPLC system was coupled to a Sciex X500R quadrupole time-of-flight (QqTOF) mass spectrometer system (ABSciex, Les Ulis, France) equipped with a Turbo V ™ Ion Source with electrospray ionization (ESI) interface. MS and MS/MS data were collected by Information-dependent-acquisition (IDA)-MS/MS and SWATH® acquisition using both ionization modes. SCIEX OS 2.1 software was used for instrument control and data evaluation.

3.3. Specific investigation for synthetic cathinone identification

Comprehensive toxicological screenings for drugs and toxic compounds based on LC-HRMS were performed in the blood and urine samples using a previously published [14]. Briefly, after internal standards (methyl-clonazepam and β-OH-ethyltheophyllin) addition, a liquid extraction was performed using an OASIS HLB on-line column (Waters, Manchester, UK) and chromatographic separation occurred using an ACQUITY HSS C18 column (Waters, Manchester, UK). Mass spectrometric detection was performed using a XEVO G2-XS QTOF (Waters, Manchester, UK) instrument controlled with MassLynx 4.1 software. Data process was performed using ChromaLynx, TargetLynx, MassFragment and MetaboLynx associated softwares (Waters) using a homemade database of more than 1.700 substances including more than 700 NPS or metabolites (august 2023) [15]. Criteria used for identification of the targeted compounds included 3 mDA as exact mass error of the precursor ion as well as product ions, and +/- 0.25 min as tolerance in retention time for the precursor ion. Regarding NEPD, this cathinone derivative was identified in October 2022 in the blood and urine of a 36-year-old chemsex addict after a documented intoxication, when he

was admitted to an emergency care unit in North of France [14]. On this occasion, NEPD's analytical data were recorded into the database: retention time: 4.29 min; *m/z* of the precursor ion ($[M^+H^+]$): 206.1540; main observed MS/MS product ions (*m/z*): 188.1434, 130.0651 and 146.0964.

3.4. Literature review

An exhaustive literature search was performed using several electronic databases: PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, without limiting findings to any specific period. The search was carried out using the terms: "drug-facilitated assault", "drug-facilitated crime", "DFSA", "sexual assault", and "synthetic cathinones", combining them in an appropriate manner. The results were limited to English language publications. The resulting articles were then screened for appropriate content. Bibliographic references within the articles were also reviewed in order to gather additional DFSA cases involving synthetic cathinones.

4. Results and discussion

The novel generation substituted cathinone NEPD was identified in both urine and plasma by LC-HRMS. Unfortunately, NEPD was not quantified in plasma due to the absence of the certified reference material. Ethanol concentration was < 0.10 g/L in both plasma and urine. GHB was < 10 mg/L in urine and < 5 mg/L in plasma. No other substance was detected in plasma or urine. Further, the review of the literature showed that six articles describing DFSA cases involving synthetic cathinones were published between 2014 and 2023 [16–21]. Taken as a whole, these articles report a total of 16 DFSA cases involving synthetic cathinones. Their characteristics are detailed in Table 1**.** When reported (in 9 cases), mean age was 32.4 years [17–38]. When reported (in 11 cases), the male/female ratio was of 0.6 (male: 4; female: 7). Reported synthetic cathinones included MDPV (in 3 cases), 4-MEC (in 2 cases), methylone (in 9 cases), α-PVP (in 1 case), mephedrone (in 2 cases), and α -pyrrolidinohexiophenone (α-PHP) (in 1 case). Other identified substances included H1-antihistamine (diphenhydramine, doxylamine, hydroxyzine, etc.), ethanol, benzodiazepines, phosphodiesterase inhibitors, and DOA (cannabis, cocaine, amphetamine, methamphetamine, MDMA).

While the use of synthetic cathinones has been particularly documented in the context of chemsex, its occurrence in DFSA remains rare. To the authors' knowledge, their use in this context was first documented by Vieira et al. who reported two DFSA cases in which synthetic cathinones were analytically detected. The first case involved MDPV in combination with diphenhydramine, a first-generation H1-antihistamine known for its sedative properties and medically used to treat allergies or insomnia. The second case involved 4-MEC in combination with several other substances including common DOAs (cannabis, cocaine) and medications (benzodiazepines, doxylamine and hydroxyzine) [16]. Hagan & Riedy likewise reported six further cases in which only methylone was analytically identified either on its own or in combination with other substances including stimulants (amphetamine, methamphetamine, MDMA) [17]. More recently, Larabi *et al.* reported the case of a 44-year-old man who was sexually assaulted under the influence of synthetic cathinones. In this case, both 4-MEC and MDPV were identified using segmental hair analysis in combination with doxylamine [18]. In the same year, Ballesteros *et al.* reported another similar case involving α-PVP [19]. The medical examiner defined this case as DFSA within the context of committing a robbery [19]. Furthermore, in a retrospective study conducted by Lee *et al.* at the Kaohsiung Medical University Hospital in Taiwan, over a four-year period: methylone was identified in the urine samples of three out of 126 (2.4%) sexual assault victims and mephedrone in two out of 126 (1.6%) [20]. Finally, Magny *et al.* reported a case involving a 28-year-old man with α-PHP identification in both urine and plasma, in combination with other stimulants (cocaine, methamphetamine, and amphetamine) and sildenafil [21]. Overall, five synthetic cathinones have been associated with DFSA, namely MDPV, 4-MEC, α-PVP, α-PHP, mephedrone and methylone, which appears as the most frequently reported.

Methylone, or 3,4-methylenedioxymethcathinone, is a ring-substituted cathinone that first emerged on the illicit drug market in 2009 [22]. It is the β-keto analog of MDMA. Regarding its mechanism of action, methylone inhibits the reuptake of norepinephrine, dopamine and serotonin and increases concentrations of these monoamines into the synaptic cleft [23]. There are substantial pharmacological similarities between methylone and MDMA. Indeed, several studies suggest that the pharmacological effects of methylone are similar to the psychostimulant and entactogenic profile associated with MDMA, including euphoria, stimulation, altered perception, and an increase in sociability [24,25]. A similar profile has also been described for mephedrone, 4-MEC and α-PHP, three of the other synthetic cathinones mentioned above, which could explain why they are used as chemical weapons to facilitate sexual assaults [26–28]. By contrast, MDPV and α-PVP present low serotonin to dopamine reuptake and/or release ratios, with their effects appearing closer to those of pure psychostimulants than those of MDMA [28,29].

According to the classification criteria established by Fields et al., the present case was considered as a proactive DFSA. Indeed, the patient

Table1
DFSA cases involving synthetic cathinones.

	Cases	Reported year	Age (year)	Gender	Synthetic cathinones	Other identified substances
Vieira et *al.* [16]	1	2014	46	female	MDPV	diphenhydramine
	2		40	male	4-MEC, MDPV	Cannabis, cocaine, benzodiazepines, doxylamine, hydroxyzine, cetirizine
Hagan & Reidy [17]	3	2015	*not reported*	female	methylone	none
	4		24	female	methylone	Ethanol, cannabis
	5		22	female	methylone	Cannabis, methamphetamine, amphetamine, MDMA
	6		17	female	methylone	Cannabis, naproxen, dextromethorphan
	7		18	female	methylone	none
	8		*not reported*	female	methylone	Cannabis, cocaine, alprazolam
Larabi et *al.* [18]	9	2018	44	male	4-MEC, MDPV	doxylamine
Ballesteros et *al.* [19]	10	2018	53	male	α-PVP	nordiazepam
Lee et *al.* [20]	11	2018	*not reported*	*not reported*	methylone	*not reported*
	12				methylone	
	13				methylone	
	14				mephedrone	
	15				mephedrone	
Magny et *al.* [21]	16	2023	28	male	α-PHP	Cocaine, methamphetamine, amphetamine, sildenafil
Case study	17	2023	36	male	NEPD	none

claimed that he had been given substance against his will and presented with incapacitation symptoms including partial amnesia and loss of consciousness. Furthermore, sNEPD alone was identified, in both plasma and urine. NEPD is a short-acting novel generation substituted cathinone that entered the illicit drug market in the mid-2010 s [29]. It is also known as alpha-ethylaminopentiophenone, alpha-ethyl-aminovalerophenone and *N*-ethynorpentedrone. As described by Espinosa-Velasco et al., NEPD's structure is very similar to that of its parent molecule, pentedrone, differing only in the presence of an *N*-terminal ethyl group instead of a methyl group [30]. Furthermore, NEPD also shares similarities with *N*-ethylpentylone, from which it differs in the absence of the methylenedioxy group in the aromatic ring [30]. To date, only little is now regarding NEPD's pharmacological effects on human subjects, even though some cases of intoxicationhave been reported [31]. Indeed, most of the discussion regarding its pharmacology is based upon its chemical structure and/or related to animals' studies [30,32,33]. In mice, NEPD acts as a potent norepinephrine-dopamine reuptake inhibitor with very poor affinity for serotonin transporters, inducing psychostimulant and anxiolytic-like effects when acute administered [33]. Repeated exposure to NEPD in mice also appears to induce mild hyperthermia and impede weight gain during the treatment phase, while producing increased aggression during weaning [30]. More recently, with an experimental model using human liver microsomes, Barcia de Godoi et al. documented NEPD's preliminary pharmacokinetic parameters including: an elimination half-life of 770 minutes, an in vitro intrinsic clearance of 3.6 μL/min/mg, and an in vivo intrinsic clearance of 3.7 mL/min/kg [34]. Furthermore, twelve metabolites were identified following phase I and phase II reactions [34]. Based on subjective reports, NEPD can produce both positive and negative effects in humans including wakefulness, euphoria, mood enhancement, increased motivation, anxiety, paranoia, muscle tension, bruxism, and restlessness [35]. However, unlike methylone or mephedrone, only a small minority of users report slightly entactogenics effects [35]. The experience that is usually reported includes greater talkativeness but not in a caring or empathetic way. NEPD, by contrast, appears to increase sexual arousal, with some user reporting that it enhances sex with partners [35]. Such properties theoretically make NEPD more suitable for use in a chemsex context than in DFSA context; even though, in fact, the boundary between these two specific forms of sexualized drug use (and more specifically between chemsex and opportunistic DFSA) can sometimes appear tenuous like in the case reported by Magny et al. [21]. Indeed, technically, chemsex involves consensual sexual activity while under the influence of drugs (which is not the case in DFSA). However, in any situation where drugs or alcohol are present, it seems easy for people to lose the capacity to consent. If someone is asleep, unconscious or so dizzy that they cannot make a decision for themselves, they cannot consent. In these cases, having sexual relationship may be considered as being sexual assaulted (and so considered as an opportunistic DFSA) [36,37].

5. Conclusion

While the use of synthetic cathinones has been particularly documented in the context of chemsex, its occurrence in DFSA remains rare. The authors report here on a case of NEPD, a new-generation synthetic substituted cathinone whose pharmacology is poorly documented in humans. Among similar published cases, methylone appears to be over represented compared to other synthetic cathinones. This could be attributed to its marked entactogenic properties. Indeed, methylone, the β-keto analog of MDMA, is considered to be the prototypical entactogen.

Compliance with ethical standards

None

Ethical approval

This article does not contain any studies with human participants or animals that were performed by any of the authors.

CRediT authorship contribution statement

Guillaume Drevin: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Jean-Michel Gaulier:** Writing – review & editing, Writing – original draft, Investigation. **Florian Hakim**: Writing – review & editing, Writing – original draft, Investigation. **Alexandr Gish:** Writing – review & editing, Writing – original draft, Investigation. **Séverine Ferec**: Investigation. **Laura Renard**: Resources. **Stéphane Malbranque**: Writing – review & editing, Writing – original draft, Resources. **Marie Briet**: Writing – review & editing, Writing – original draft. **Chadi Abbara**: Writing – review & editing, Writing – original draft, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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