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Prevalence of New Psychoactive Substances (NPS) and conventional drugs of abuse (DOA) in high risk populations from Paris (France) and its suburbs A cross sectional study by hair testing (2012–2017)

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ABSTRACT

Background: The aim of the present study is to describe the prevalence of NPS and conventional DOA in Paris and its suburbs over a six-year period using hair testing approach.
Method: Hair was sampled in patients admitted to different departments of Paris hospitals between 2012 and 2017. Two high-risk populations were mainly considered: *1)* drug-dependent and *2)* acutely intoxicated patients. Segmental hair analysis was performed by validated LC–MS/MS method to screen for DOA and 83 NPS.
Results: 480 patients (280 M/200 F, 15–70 years) were included. 141 patients tested positive for NPS (99 M/42 F; median age: 33). NPS prevalence was 29%, that of amphetamines, cocaine and opioids were 32%, 38.5% and 52%, respectively. 27 NPS were identified, 4-MEC and mephedrone (number of cases n = 24 each) were the most detected cathinones. JWH-122 (n = 1) was the only detected synthetic cannabinoid while ketamine (n = 104) was present in numerous NPS users (67%). 3-fluorofentanyl (n = 1), furanylfentanyl (n = 1), N-ethylpentylone (n = 2), pentedrone (n = 2), mexedrone (n = 1), methcathinone (n = 3), 6-APDB (n = 2), TFMPP (n = 2), 2-CE (n = 1), 3,4-MD-αPHP (n = 1) and dextromethorphan (n = 27) were identified for the first time in hair. Users were found to have more than one NPS in 53% of cases, mostly in combination with conventional DOA. The number of detected NPS rose from 5 in 2012 to 42 in 2017. A broad range of hair concentrations (0.001–318 ng/mg) was found, but the low median concentrations seem to show an occasional exposure more than chronic use.
Conclusion: NPS screening should be assessed in routine clinical practice, especially in high-risk populations.

1. Introduction

New psychoactive substances (NPS) are derived from regulated drugs of abuse (DOA) such as amphetamines, cocaine, ketamine or fentanyl after slight chemical alteration, and are ambiguously labeled as bath salts, research chemical (RCs) or legal highs to circumvent the legislation surrounding narcotics. They are increasingly available over the internet and widespread use is of concern. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2019) is actually monitoring more than 670 NPS with about one additional NPS being reported every week in Europe, illustrating how complex this market has become (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2018). NPS include several groups of drugs belonging to 4 major classes: synthetic cannabinoids (SC), synthetic cathinones and other synthetic stimulants, new synthetic opioids (NSO), and synthetic benzodiazepines. The increased number of recorded NPS has led several countries to adopt different strategies either by targeting the producers and retailers, or by applying generic bans to a wide number of structurally similar compounds. Part of the problem in controlling the proliferation of these substances lies in their variety, their ease of synthesis and purchase, low cost, and the fact that most are undetectable by standard toxicology screening (Khaled et al., 2016). Cases of severe toxicity and deaths caused by NPS are increasingly reported in the scientific literature (Gaillard et al., 2013; Gerace et al.,

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2014; Poklis et al., 2016; Papaseit et al., 2017; Rojek et al., 2014; Wikström et al., 2010; Wyman et al., 2013) but we note that self-reported use or case reports provide most of the current data (Bretteville-Jensen et al., 2013; Kelly et al., 2013; Kikura-Hanajiri et al., 2013; Simonato et al., 2013; Palamar et al., 2015, 2016).

The identification of NPS in biological or seized materials requires reliable analytical methods based either on gas or liquid chromatography coupled with mass spectrometry detection (GC–MS and LC–MS/MS). This requires expensive reference standards (RS) that are often unavailable and difficult to obtain. Consequently, due to the limited number of NPS screened by forensic laboratories, it is likely that the number of reported cases is underestimated. Recently, a new approach based on liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS), with the use of a shared MS spectra database and without a need for RS has emerged (Concheiro et al., 2015; Fabresse et al., 2019; Maurer and Meyer, 2016; Pleil and Isaacs, 2016; Scheidweiler et al., 2015), allowing qualitative determination of these compounds which can be secondarily confirmed and quantified by targeted screening using LC–MS/MS.

The usefulness of hair as a complementary matrix to blood or urine to study the exposure to many substances is well known: most substances are incorporated into hair mainly from the bloodstream, remain stable and can be detected from a few weeks up to months or years depending on hair length. Moreover, hair sampling is non-invasive, easy and does not require any medical training.

In the last decade, different strategies have emerged in order to study the prevalence of DOA. Some are based on wastewater analysis to estimate the consumption of drugs by the measurement of residues in sewage while other approaches evaluate specific population like the analysis of residual content of used syringes in injection drugs users (Karolak et al., 2010; Néfau et al., 2015). Both of these strategies provide an indirect link between drugs consumption and the population of consumers itself.

Besides that, the study of NPS prevalence using biological materials and especially alternative matrices as hair allow direct evaluation of drug exposure of an individual or a population by analyzing their own samples. Despite their great interest, this kind of approaches remain scarce (Adamowicz et al., 2016; Rust et al., 2012; Salomone et al., 2014, 2017).

The aim of this study is to evaluate the prevalence of NPS in high risk populations from Paris and its suburbs over a six-year period using hair testing, and to compare it with that of conventional DOA within the same populations.

2. Material and methods

2.1. Inclusion criteria

Adult patients (age ≥ 15 years) successively admitted from January 2012 through December 2017 to Paris hospitals and its suburbs were included in this study. Four groups were identified according to the department to which they were admitted: addiction departments (AD), emergency departments (ED), forensic departments (FD) and other departments (OD).

No consent from patients was needed as hair testing is part of a routine clinical investigation in France, and was asked by practitioners in order to have more information about patients' use of DOA.

2.2. Analytical method

The analysis was performed by a liquid chromatography tandem mass spectrometry technique (LC–MS/MS) derived from a previously published methods (Alvarez et al., 2016a; Larabi et al., 2018a).

2.2.1. Chemical and reagents

Reference and certified standards were purchased from 3 suppliers: LGC Standards (Molsheim, France), Sigma–Aldrich (Paris, France) and Lipomed AG (Arlesheim, Switzerland) in 1 mg/mL vials or as a powder to be reconstituted with a convenient solvent (e.g. methanol or acetonitrile). Acetonitrile, dichloromethane, hexane, ethyl acetate, formic acid and methanol were supplied by Sigma–Aldrich (Paris, France) in mass spectrometry or high-performance liquid chromatography (HPLC) grade. Sodium carbonate and sodium hydrogenocarbonate were from Prolabo (Paris, France). Ultra-pure water (18 MV) was obtained by ultrafiltration using a Direct-Q UV3 apparatus (Millipore Corp., Molsheim, France). Formate buffer (containing 2 mM ammonium formate in 0.1% formic acid) was prepared in ultra-pure water and stored after each analysis at +4 °C away from light for a maximum of one week.

2.2.2. Calibration standard and quality control

Eight calibration standards (CS) containing a mixture of all screened compounds at 1, 2.5, 5, 10, 50, 100, 500, and 1000 pg/mg of hair were prepared by spiking stock solutions of reference standards with appropriate volume into a 20-mg blank human hair. Quality controls (QC) were prepared by the same way at concentrations of 5, 20, 250 and 750 pg/mg.

Blank human hair was obtained from children who are not medically treated, after having requested a signature of the consent to their parents, and were stored at room temperature away from light until the analysis.

2.2.3. Hair sample preparation

Hair was decontaminated twice using dichloromethane and washed once with warm water (immersion for 2 min in each step). It was then grinded into a fine and homogeneous powder using a ball mill (MM200, FicherScientific, Illkrich, France). Each 20 mg were incubated in 1 mL of phosphate buffer at pH 5.0 at 95 °C for 10 min, in the presence of an appropriate amount of deuterated internal standards (IS). After spiking the corresponding volume of CS or QC working solutions, liquid–liquid extraction was performed by 4 mL of a mixture of hexane/ethyl acetate (v/v: 1/1) after addition of 2 mL of carbonate buffer at pH 9.7. After agitation and centrifugation for 20 min, the organic phase was recovered and evaporated to dryness. The residue was reconstituted in 80 µL of mobile phase and 10 µL were injected in the chromatographic system.

2.2.4. LC–MS/MS conditions

Chromatography was performed on Accela liquid chromatography pump (Thermofisher, Les Ulis, France) coupled with a CTC auto sampler (Thermofisher), using a Hypersil GOLD PFP column (100 x 2.1 mm, 1,9 µm) preheated at 30 °C. The column is preceded by a javelin filter (2.1 mm i.d.). The mobile phase is a gradient of acetonitrile and 2 mM formate buffer in 0.1% formic acid starting from 20% of acetonitrile to 90% in 10 min at a flow rate of 300 mL/min. The total run time was 12 min. Compounds were detected by a TSQ Vantage triple-quadrupole mass spectrometer (Thermofisher) equipped with an electrospray ionization (ESI) source set in a positive mode. An ion-spray voltage of +3.5 kV was applied. The heated capillary temperature was set at 350 °C. Nitrogen (Nitrox UHPLCMS 18, nitrogen generator, Domnick Hunter, Villefranche sur Saone, France) was employed as sheath and auxiliary gas at a pressure of 50 and 20 arbitrary units, respectively. The argon gas collision-induced dissociation was used with a pressure of 1.5 mTorr. Data were collected in selected reaction monitoring (SRM) mode, with two *m/z* transitions per analyte. Chromatographic data acquisition was performed using Xcalibur software (v2.0.7 SP1, Thermofisher), and quantification was carried out by using LCquan software v2.5.

MRM transitions with corresponding collision energies for the screened compounds are shown in supplementary material 1.

Table 1
validation parameters of some detected NPS in hair according to the EMA guideline on bioanalytical method validation.

Validation settings of some NPS	4-MEC	Mephedrone	MDPV	Butylone	DXM
1. Linearity (pg/mg)	1–1000	1–1000	1–1000	1–1000	1–1000
R^2	> 0.99	> 0.99	> 0.99	> 0.99	> 0.99
2. LOD (pg/mg)	0.5	0.5	0.5	0.5	0.5
3. LOQ (pg/mg)	1	1	1	1	1
4. Matrix Effect (%)	< 5	< 5	< 5	< 5	62
5. Extraction recovery (%)	66	70.1	87	81.9	85.8
6. Accuracy: trueness bias (B %) + precision (CV %)					
	QC 5 pg/mg				
Intraday CV (%)	5.4	14.4	7.0	8.8	9
Interday CV (%)	10.8	7.6	4.0	9.3	14.4
Trueness B (%)	100.3	101.2	104.6	103.4	102.0
	QC 20 pg/mg				
Intraday CV (%)	7.0	7.9	7.5	6.4	8.6
Interday CV (%)	4.5	8.2	11.7	11.8	3.2
Trueness B (%)	100	96.8	98.2	103.5	104.0
	QC 250 pg/mg				
Intraday CV (%)	9.9	8.1	9.2	8.7	9.2
Interday CV (%)	12.5	14.3	2.0	9.9	2.3
Trueness B (%)	99.3	96.4	96.2	102.6	99.2
	QC 750 pg/mg				
Intraday CV (%)	12.9	3.2	5.1	5.9	8.6
Interday CV (%)	5.7	6.7	8.3	14.6	10.4
Trueness B (%)	104.8	107.5	106.8	99.8	105.8

2.3. Hair analysis

Non-cosmetically treated hair was sampled within 24 h of hospitalization and systematic toxicological analysis (STA) was performed to screen conventional DOA and 83 NPS, as shown in supplementary material 1. As natural cannabinoids (THC, cannabidiol and cannabinol) are acidic compounds, their screening requests the use of a different extraction procedure on a second strand of hair, which was not available. Thus, their research was not performed in the present study. Whenever possible, hair was cut into 3 segments of 2 cm to explore user's exposure profiles in the last 6 months based on hair growth of 1 cm/month. Short hair (< 2 cm) was analyzed in bulk. Each segment was considered separately as it reflected a different timeframe.

2.4. Method validation and statistics

The method was validated according to the European Medicines Agency (EMA) guideline, in terms of *linearity*, *limits of detection* and *quantification* (LOD and LOQ), *specificity*, *matrix effect*, *extraction recovery*, within-day and between-day *accuracy* (bias) and *precision* (coefficient of variation).

Statistics and illustrations were performed using "Tableau Publique" 10.5.3 and GraphPad Prism 5.01 softwares.

3. Results

3.1. Method validation

No interferences were observed from constituents of drug free human hair at the retention times and the MRM (Multi Reaction Monitoring) transitions of the detected compounds. The calibration curves were linear from 1 to 5 pg/mg to 1000 pg/mg. They exhibited a good linearity (coefficient of determination $R^2 > 0.99$). Different weighting strategies were tested and 1/x was found to be the most appropriate to achieve the best response function. The LOD and LOQ were between 0.5 and 2 pg/mg, and 1 and 5 pg/mg, respectively. All CVs were < 15%. The data indicated satisfactory criteria regarding method accuracy (Bias and CV < 15%). Matrix effects were insignificant (< 5%) and the extraction recovery was adequate and enabled to achieve good accuracy and sensitivity. Carry over was less than 0.05% for each analyte when we injected a blank sample after the highest calibration standard (1000 pg/mg). Table 1 summarizes validation parameters of some detected NPS.

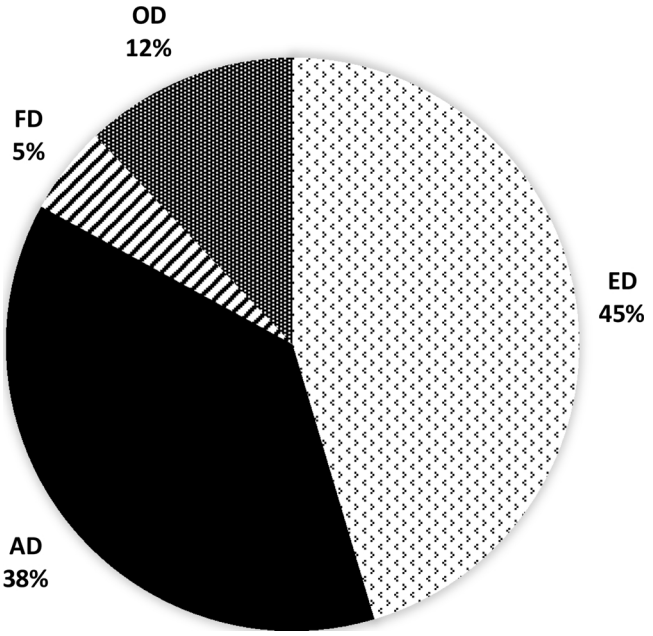

Fig. 1. Frequency of NPS detection according to the admission department (AD: addiction departments, ED: emergency departments, FD: forensic departments, OD: others departments).

3.2. Demographics

3.2.1. Overall studied population

Four hundred eighty patients (280 M, 200 F) were included. Most were admitted either to ED (n = 238; 143 M, 95 F) or to AD (n = 86; 65 M, 21 F). FD group represents 14% of patients (n = 69; 21 M, 48 F) while the remaining 18% of patients were admitted to OD (n = 87,

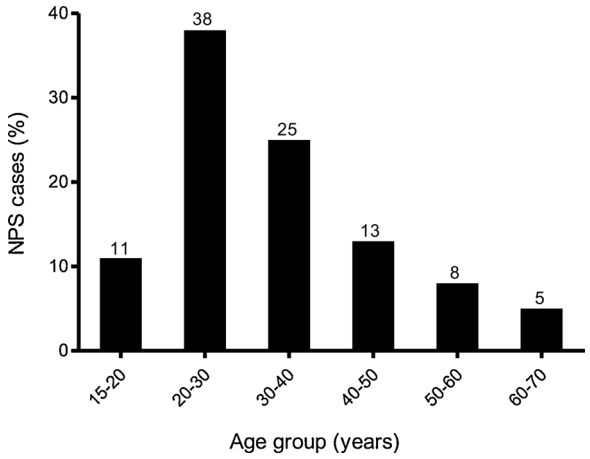

Fig. 2. Age distribution of NPS users.

58 M, 42 F). The mean age was 39 years [range: 15–70 years; median: 36 years].

3.2.2. Population of NPS users

141 patients tested positive for NPS corresponding to 99 M and 42 F (sex ratio = 2.35). When adjusting positive results according to gender, one in four female (42/200) and one third of male patients (99/280) tested positive for NPS. 64 cases (45%, 42 M, 22 F) were recorded in ED and 53 cases (38%, 43 M, 10 F) in AD. FD and OD recorded 7 (5%, 2 M, 5 F) and 17 cases (12%, 12 M, 5 F), respectively (Fig. 1).

The mean age of NPS users was 33 years [range: 17–70 years; median: 33 years] and the highest number of positive cases (n = 50, 35%) was observed in the 20–30 age group (Fig. 2). In comparison, the median age of cocaine, amphetamines and opioids users within the same populations were 36, 38 and 40 years old, respectively.

3.3. Prevalence of NPS

The prevalence of NPS was 29% (141/480): AD 11%, ED 13%, FD 1.5%, OD 3.5%. Prevalence of conventional DOA were: amphetamines: 32% (152/480: AD 12%, ED 13%, FD 3%, OD 3%), cocaine: 38.5% (185/480: AD 13%, ED 18%, FD 3%, OD 4%), licit and illicit opioids: 52% (248/480: AD 11%, ED 25%, FD 7%, OD 9%). 54% of NPS users had been exposed to more than one NPS in the same period (at least 2 detected NPS in the same segment), mostly in combination with cocaine (66%), amphetamines (65%) or opioids (64%). NPS alone were found in 32% of patients.

27 different NPS were identified (AD: 23, ED: 12, FD 2, OD: 8) (Fig. 3). Mephedrone: [range: 0.005–169 ng/mg hair, 24 cases (C), 56 positive segments (S)] and 4-MEC (0.001–97.3 ng/mg hair, 24C, 47S) were the most detected cathinones, followed by methylone (0.008–21.7 ng/mg hair, 15C, 35S) and MDPV (0.001–1.5 ng/mg hair, 7C, 16S). In the piperazine group, TFMPP (0.003-0.03 ng/mg hair, 2C, 5S), and m-CPP (0.07 ng/mg hair, 1C, 1S) were found. JWH-122 (0.2-0.43 ng/mg hair, 1C, 3S) was the only synthetic cannabinoid detected during this study. Other NPS were detected, some for the first time: 3-fluorofentanyl (0.06-0.15 ng/mg hair, 1C, 3S), furanylfentanyl (FU-F: 0.015-0.04 ng/mg hair, 1C, 3S), N-ethylpentylone (NEP: 0.015-0.64 ng/mg hair, 2C, 4S), pentedrone (0.018-0.65 ng/mg hair, 3C, 6S), 2-CE (0.07-0.25 ng/mg hair, 1C, 3S), mexedrone (0.03-0.05 ng/mg hair, 1C, 3S), methcathinone (0.011-0.485 ng/mg hair, 3C, 6S), 6-APDB (0.05-0.18 ng/mg hair, 2C, 5S), TFMPP (0.003-0.03 ng/mg hair, 2C, 5S), and 3,4-MD-αPHP (qualitative analysis, 1C, 3S). Table 2 summarizes the quantitative results for all detected NPS in comparison with hair concentrations found in the literature.

KET was found in 104C, most cases in the ED and AD groups (48C and 40C, respectively). In 10C, treatment with KET during the hospitalization was recorded. DXM was identified in 27C, mostly (71%) in ED and AD (10C each) in combination with DOA (70%), and with no recorded prescription.

The number of detected NPS increased from 2012 (9% of total

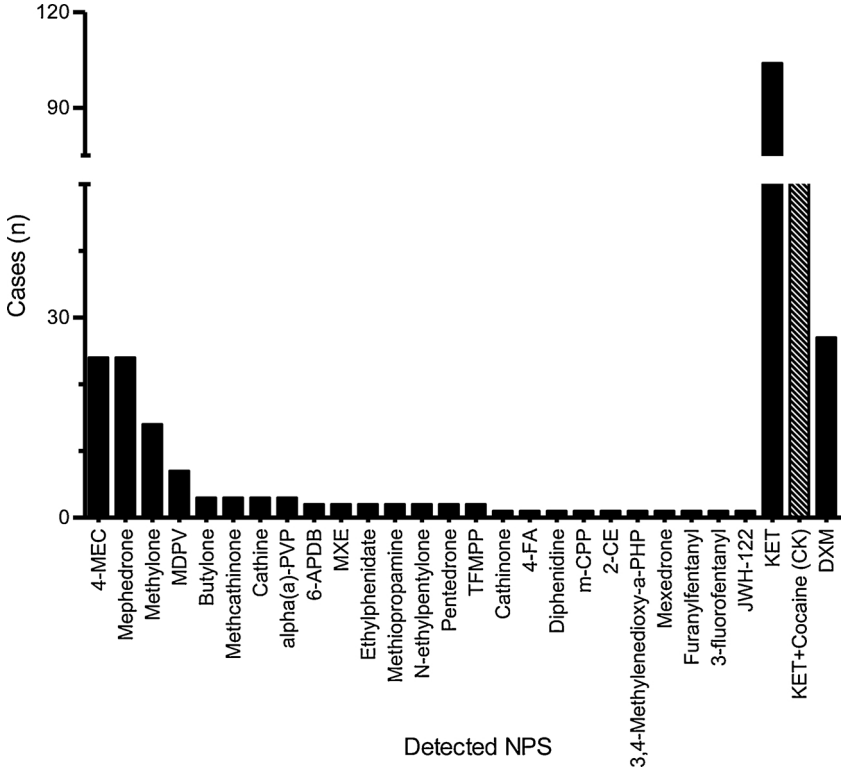

Fig. 3. Number of detected NPS in hair (abbreviations are reported in Supplementary material 1).

Table 2
Concentration range of the detected NPS (mean, median), number of hair positive segments and reported concentrations from the current literature (N1: number of cases, S: number of positive segments, N2: number of hair samples, ng/mg: nanograms per milligram of hair, NQ: not quantified, NA: not applicable, (*): concentrations found under trazodone treatment).

Substance	NPS and related compounds								
	Cases (N1)	Positive Segments (S)	LOQ [ng/mg]	Concentrations range [ng/mg]	Mean [ng/mg]	Median [ng/mg]	Reported hair concentrations [ng/mg]	Hair samples (N2)	References
KET	104	245	0.001	0.001–318	6.24	0.040	0.6–489	51	Leong et al., 2005
							0.11–11.4	6	Salomone et al., 2015
NKET	48	116	0.001	0.001–35	1.94	0.036	0.8–196.3	51	Leong et al., 2005
							0.02–0.71	6	Salomone et al., 2015
4-MEC	24	47	0.001	0.001–97.3	9.97	0.23	30	1	Alvarez et al., 2016a
							0.003	1	Larabi et al., 2018a
Mephedrone	24	56	0.001	0.005–169	6.05	0.08	0.1–87	24	Kintz, 2017
							0.2–213.2	13	Martin et al., 2012
Methylone	14	35	0.001	0.008–21.7	0.99	0.06	< 0.006–0.098	5	Salomone et al., 2017
MDPV	7	16	0.001	0.001–1.5	0.38	0.22	0.005	1	Larabi et al., 2018a
							0.12	1	Alvarez et al., 2016a
							1	1	Salomone et al., 2016
							1–22	1	Namera et al., 2013b
α-PVP	3	7	0.001	0.001–0.14	0.049	0.018	0.2–1.2	1	Namera et al., 2013b
							7.5–9.4	4	Namera et al., 2013a
Butylone	3	6	0.001	0.001–0.17	0.041	0.026	0.007–4.9	25	Salomone et al., 2017
Cathine	3	7	0.001	0.012–1.57	0.500	0.040	0.57 to 23.9	23	Sporkert et al., 2003
Ethylphenidate	2	6	0.0025	0.11–0.485	0.240	0.200	3.06	1	Lelong et al., 2018
MPA	2	6	0.001	0.19–0.91	0.550	0.550	0.38	1	Lelong et al., 2018
MXE	2	6	0.1	0.13–2.93	0.880	0.290	0.007–0.027	3	Salomone et al., 2016
Diphenidine	1	5	0.0025	0.02–0.12	0.066	0.079	0.079–0.12	1	Alvarez et al., 2016b
JWH-122	1	3	0.001	0.2–0.43	0.29	0.25	0.007–2.8	8	Salomone et al., 2014
4-FA	1	2	0.005	7.5–7.8	7.64	7.64	0.055	1	Salomone et al., 2016
Cathinone	1	1	0.01	0.13	NA	NA	0.11–22.7	23	Sporkert et al., 2003
m-CPP	1	1	0.05	0.07	NA	NA	0.34– > 4 (*)	10	Lendoiro et al., 2017
	NPS detected for the first time in real hair samples								
DXM	27	77	0.001	0.001–8.37	0.81	0.11	NR	—	—
Methcathinone	3	6	0.001	0.011–3.7	0.710	0.040	NR	—	—
6-APDB	2	5	0.0025	0.05–0.18	0.097	0.083	NR	—	—
TFMPP	2	5	0.0025	0.003–0.03	0.015	0.017	NR	—	—
N-ethylpentylone	2	4	0.001	0.015–0.64	0.033	0.027	NR	—	—
Pentedrone	2	3	0.001	0.018–0.65	0.310	0.275	NR	—	—
Mexedrone	1	3	0.0025	0.03–0.05	0.04	0.036	NR	—	—
2-CE	1	3	0.001	0.07–0.25	0.173	0.200	NR	—	—
Furanylfentanyl	1	3	0.005	0.015–0.04	0.025	0.020	NR	—	Larabi et al., 2018b
3-fluorofentanyl	1	3	0.0025	0.060–0.15	0.097	0.08	NR	—	Larabi et al., 2018b
3,4-MD-αPHP	1	3	0.0025	NQ	NQ	NQ	NR	—	—

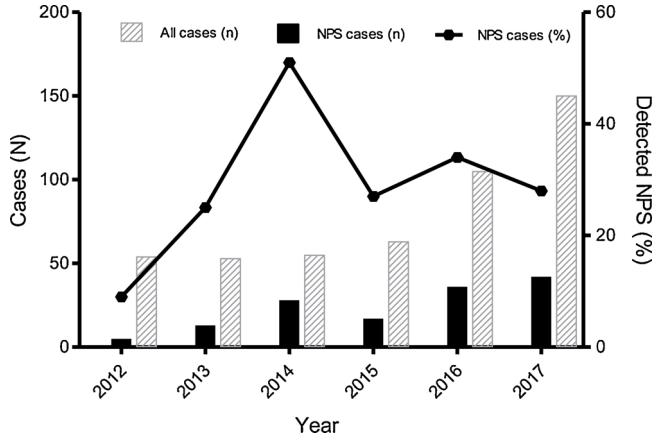

Fig. 4. Trend of NPS detection in Paris between 2012 and 2017.

cases) to 2017 (28%) with a peak of detection in 2015 where more than half of analyzed cases (51%) were positive to designer drugs. (Fig. 4).

4. Discussion

Hair is found to be a suitable matrix to study the prevalence of NPS. Indeed, hair offers a wide detection window (from months to years depending on hair length), is easy to sample and difficult to alter, so it can be kept for a long time and retrospectively analyzed (Kintz, 2015). Hair analysis has clear clinical and forensic applications. In emergency cases, hair is not used to diagnose intoxications, but rather to retrospectively study the exposure profile of poisoned persons. Hair testing has also gained an interesting role in the harm reduction process, which is often employed as a therapeutic approach in drug addiction. The results of hair analysis can be used to show drug users discrepancies that might exist between the compounds they bought, and those really consumed through the analysis of their hair (Larabi et al., 2018b). Finally, hair samples may be of use in forensic cases, notably in drug facilitated sexual assault (DFSA) where the use of some NPS has recently been reported (Hagan and Reidy, 2015; Larabi et al., 2018a). One hundred forty-one patients tested positive for at least one NPS. Men are twice as likely to be tested positive for NPS as women. NPS prevalence ranges from 0.3% in Hong Kong (Tang et al., 2015) to 37% in Switzerland (Rust et al., 2012) (Table 3).

The prevalence we found in Paris especially from high risk populations (29%) was as high as that recently observed by Salomone et al. (2017) in the US (32.5%) in a population of nightclubs attendees or by Rust et al. (2012) in Switzerland (37%) from amphetamines users. In Hong Kong, NPS were surprisingly not predominant (prevalence: 0.3%), despite the proximity to China, the country with the highest number of laboratories manufacturing NPS. (United Nations Office on Drugs and Crime [UNODC], 2017). Even though inclusion criteria are

Table 3
Comparison of major prevalence studies conducted by hair analysis (N1: number of included patients or volunteers, N2: number of NPS positive cases, N3: number of detected NPS, M: male, F: female, UKN: unknown, NR: not reported).

Countries / Authors / Publication Year	(N1)	Population Characteristics					NPS cases (N2)	Detected NPS (N3)	Top 3 of detected NPS	Prevalence (%)	References
		Sex (%)			Age (range, mean)	Type of population					
		M	F	UKN							
France Larabi et al., 2019	480	70	30	0	[16–70] m = 39	Addict follow-up Intoxications DFSA Clinical investigations	141	27	Ketamine 4-MEC Mephedrone (± 3-MMC)	29	—
USA Salomone et al., 2017	80	NR	NR	NR	[18–25] m = NR	Nightclubs attendees	26 (14M + 12F)	6	Butylone Methylone MXE	32.5	Salomone et al., 2017
Poland Adamowicz et al., 2016	NR	91	9	0	[16–50] m = 24.5	DUID, road accidents, drugs possession or use, violence, theft, rape, kidnapping, suicide, intoxications	112	21	3-MMC α-PVP Pentedrone	10.6	Adamowicz et al., 2016
Italy Salomone et al., 2016	77	> 70	NR	NR	[26–56] m = 36.3	MDMA and KET abusers (A) or subjects tested negative (B)	6 (4M + 2F)	8	MXE Mephedrone Methylone	7.8	Salomone et al., 2016
Hong Kong Tang et al., 2015	1036	74	26	0	[18–74] m = 35	Abuse clinics, Emergency department	3	2	PMMA Ketamine	0.3	Tang et al., 2015
Switzerland Rust et al., 2012	325	90	8	2	[18- up to 55] m : NR	Amphetamines users	120	7	Ketamine mCPP 4-FA	37	Rust et al., 2012

broadly different, especially with regard to the studied populations, the prevalence in all reported studies were high compared to conventional DOA. This is despite the fact that NPS are not routinely analyzed by all laboratories. It is likely that prevalence is underestimated.

According to the European School Survey Project on Alcohol and Other Drugs use (ESPAD) conducted in 2015 among 15- to 16-year-old students from 35 European countries, lifetime use of NPS averages 4% (range: 1% in Belgium to 10% in Estonia and Poland) (EMCDDA, 2018). In our study, we found that 11% of NPS users were under 20 years-old, which confirms the use of designer drugs in a young population in Paris. More than a half of NPS users had experienced more than one NPS in the same period (within two-months), more often in combination with conventional DOA (cocaine, amphetamines or opioids). It is important to stress that the use of NPS by opioid abusers is frequent in the studied populations and thus, screening of NPS should be considered in all DOA users and not be kept for patients abusing only stimulant drugs. NPS may be used in isolation: in our study 32% of NPS users had not used any conventional DOA. These consumers would not be detected if only routine drug analysis, which does not include NPS screening, is performed.

As observed in the previously published studies (Table 2), cathinones are the most prevalent group of NPS. However, differences can be seen with regard to substances dominating each local market. This could be related to different policies adopted by each country. Some have adopted an individual ban strategy of new emerging drugs (e.g. Poland), while others work on generic control regrouping a wide number of isomers and structurally similar compounds (e.g. France).

In our study, 4-MEC and mephedrone (4-MMC) are the most detected cathinones, followed by methylone and MDPV. 4-MEC was first notified as a recreational drug in Europe in 2010, but was only scheduled in table III of the 1971 United Nation (UN) Convention on psychoactive substances in 2016, due to many fatal cases and its abuse potential (Expert Committee on Drug Dependence [ECDD], 2016). In our study, 4-MEC was detected from 2013 (n = 2) through 2017 (n = 6) with a peak detection in 2016 (n = 9). In a study conducted by Néfau et al. (2015) in Paris area, 3489 used syringes were collected from injection drug users and analyzed by LC-MSMS for 23 DOA. 4-MEC was present in 23% of analyzed syringes (n = 2016), showing the appearance of this designer drug between the summer and winter of 2012 (Néfau et al., 2015).

Reports of mephedrone use emerged in different countries and regions of middle-east and Europe since 2007 (Kelly, 2011). Up to 2010, it was identified as the most common cathinone used in Europe (EMCDDA, 2019). Due to the choice of LC–MS/MS as reference screening method, we could not distinguish between mephedrone (4-MMC) and its isomer, 3-MMC, another designer drug that appeared later in the market. The two isomers have the same retention time and MRM transitions. Ideally, to distinguish between them, GC–MS analysis should be performed to achieve chromatographic separation (Gerace et al., 2014; Power et al., 2011). Another approach may consist of researching both metabolites of 3-MMC (eg. 3-methylephedrine or 3-methylnorephedrine) and of 4-MMC (eg. normephedrone) (Frison et al., 2016). Due to the absence of 3-MMC metabolites from our library, we used mephedrone for the validation process, even though we could not discriminate the isomers in positive samples. Thus, the presence of 3-MMC should not be excluded in mephedrone positive cases.

According to the EMCDDA 2018 report, synthetic cannabinoids (SCs) are the largest group of new substances seized and monitored in Europe. Surprisingly, this group was not dominant in most of the described studies conducted by hair analysis. Adamowicz et al. (2016) have reported the presence of only 7 cases of UR-144 use among 112 NPS positive cases (6.25%). Other studies have reported low prevalence of SCs, ranging from 1.29% (n = 232) (Cirimele et al., 2014) to 7.82% (n = 179) (Salomone et al., 2012) in different groups of drugs abusers. Concentrations of SCs ranged from 0.1 pg/mg for JWH-122, JWH-122 N-5 − OH and JWH-173 (Kim et al., 2015) to 13,000 pg/mg for MAM-2201 (Schaefer et al., 2013). From 2015, we introduced screening for 18 SCs (LOD and LOQ: 0.5 and 1 pg/mg, respectively), but JWH-122 was the only detected compound so far (range: 200–430 pg/mg), in accordance with the concentrations found in the literature (range: 7–2800 pg/mg) (Salomone et al., 2014). The low reporting of SCs from these studies could be explained in part by their high potency and thus their use at very low doses, which reduces their detectability in hair. Their low reporting could also be explained by their rapid metabolism leading to lower integration of parent drug into hair. In similar studies, the authors set the limit of detection as the minimum criterion to

establish the use of NPS. The results from positive samples with very low hair levels should be interpreted with caution because they do not exclude external contamination by passive smoking or handling materials containing SCs.

The high amount of seized SCs recorded by the EMCDDA and the low prevalence of SCs in hair samples could also show the effectiveness of regulation to control use as soon as there is enough scientific evidence demonstrating harmful effects.

KET and DXM are at the boundary between conventional DOA and NPS. These molecules have been abused for a long time but their use is still growing among NPS consumers. At the international level, ketamine was subject to a series of risk assessments and has found its place among clubbers, and is especially valued for its dissociative experiences like the "K-hole" with "near death" and "out of body" experiences (Dillon et al., 2003; UNODC, 2013). However, its use is often associated with cocaine: we found cocaine in over 70% of KET cases (n = 67), a combination so-called CK (Cocaine-KET), that has already been described in the literature (Rofael and Abdel-Rahman, 2002). DXM is a cough suppressant drug, but is also used recreationally, especially by teenagers. In recent years, it has appeared in MDMA-like (Ecstasy) tablets. When exceeding the maximum dosage, it acts as a dissociative hallucinogen with similar effects to those of ketamine and phencyclidine (PCP). DXM is not listed in the 1961 UN Convention on Narcotics, but several countries like France in 2017 have placed it under control due to its use in a harmful way (Cold and Cough Medicines, 2015; ECDD, 2012; Johnston et al., 2007).

Segmental hair analysis applied in 80% of cases (n = 384) showed a wide range of concentrations of NPS (Table 2). For the most detected NPS, low median values of hair concentrations differentiated two populations: occasional users with hair concentrations in the pg/mg range, and regular consumers with hair concentrations in the ng/mg range. Overall, hair concentrations are similar to those already described in the literature (Alvarez et al., 2016a, 2016b; Kintz, 2017; Larabi et al., 2018a, 2018b; Lelong et al., 2018; Lendoiro et al., 2017; Leong et al., 2005; Martin et al., 2012; Namera et al., 2013a, 2013b; Salomone et al., 2014, 2015, 2016, 2017; Sporkert et al., 2003). Finally, we report the presence of some NSO, like 3-fluorofentanyl (range: 0.06-0.15 ng/mg hair, 1C, 3S), and furanylfentanyl (range: 0.015–0.04 ng/mg hair, 1C, 3S). To our knowledge, this is the first time these fentanyls have been detected and quantified in hair. This is also the case for many other NPS such as N-ethylpentylone (0.015–0.64 ng/mg hair, 2C, 4S), pentedrone (0.018–0.65 ng/mg hair, 2C, 3S), mexedrone (0.03–0.05 ng/mg hair, 1C, 3S), methcathinone (0.011–0.485 ng/mg hair, 3C, 6S), 2-CE (0.07–0.25 ng/mg hair, 1C, 3S), 6-APDB (0.05-0.18 ng/mg hair, 2C, 5S), TFMPP (0.003–0.03 ng/mg hair, 2C, 5S), 3,4-MD-αPHP (not quantified), and dextromethorphan (0.001–8.37 ng/mg hair, 27C, 77S). These data are still difficult to interpret but remain important for future monitoring of NPS concentrations in hair.

5. Conclusion

This study addresses the issue of NPS spread through the identification of the most detected compounds in high risk populations from Paris and its suburbs over a six-year period, and allows the description of demographic characteristics of NPS users. In contrast to self-reported data, that often include reporting biases related to users' ignorance about the products they really consume, hair analysis brings objective data to the prevalence of designer drugs. This study shows that NPS prevalence is as high as that of conventional DOA in the studied populations. Thus, screening for NPS should be performed in clinical practice, especially in high-risk populations.

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Contributors

All authors are responsible for this reported research. I.A- LARABI designed the study, and conducted the statistical analyses. J.C ALVAREZ critically reviewed and revised the study and the manuscript. N. Fabresse and I. Etting performed analytical method development and analysis. L. Nadour managed the database on "Tableau publique" software. G. Pfau, JH Raphalen, P. Philippe and Y. Edel organized hair sampling and provided clinical information regarding included patients. All authors approved the final manuscript as submitted.

Declaration of Competing Interest

No conflict declared.

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Appendix A. Supplementary data

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