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Epidemiology of New Psychoactive Substances in Relation to Traditional Drugs of Abuse in Clinical Oral Fluid Samples

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ABSTRACT

New psychoactive substances (NPS) are health-hazardous through unpredictable toxicity and effects and largely unknown epidemiology, motivating studies of the latter.

Up to 138 NPS were retrospectively identified using liquid chromatography-high resolution mass spectrometry data from all 34 183 oral fluid drug samples collected in one Swedish health care region 2019–2020 representing 9468 psychiatric and addiction care patients. In total, 618 findings representing 58 NPS were detected in 481 samples from 201 patients. Male gender and age ≥25 years correlated positively with NPS use. Ketamine correlated positively with all NPS classes except cannabinoids; additionally, fentanyl, methadone, tapentadol and clonazepam correlated with multiple NPS classes. More numerous traditional drugs of abuse (DoA) correlated positively with sedative/hypnotic NPS, indicating that these are used in broader patient groups than other NPS. Mitragynine correlated negatively with other NPS in general and with several traditional DoA, but positively with the potential opioid abstinence remedies buprenorphine, loperamide and tapentadol aside from ketamine. In conclusion, NPS use is infrequent but occur also at higher ages, certain traditional DoA and particularly ketamine could have clinical value as NPS use signals, and mitragynine exhibited an atypical NPS consumption pattern indicating significant use as an opioid abstinence remedy.

1 | Introduction

New psychoactive substances (NPS) are often defined as narcotic or psychotropic drugs that are not controlled by the United Nations drug conventions but which pose a public health threat comparable to substances listed in these conventions [1]. However, in the more clinical sense, they can be described as 'recreational drug substances newly designed or revived for the purpose of being legal, avoiding analytical

Abbreviations: DoA, drugs of abuse; EU EWS, European Union Early Warning System on NPS; LC-HRMS, liquid chromatography-high resolution mass spectrometry; NPS, new psychoactive substances.

Plain English Summary

New psychoactive substances (NPS), especially in the sense "designer drugs" or "internet drugs", could be extremely dangerous due to lack of user experience, unpredictable toxicity and undetected use. Therefore, to provide clinical guidance, we herein present uniquely large data on NPS epidemiology including information about which traditional drugs and other patient characteristics that are associated with NPS use. Among traditional drugs, especially ketamine but also others such as fentanyl, methadone, tapentadol and clonazepam could serve as NPS use signals. Suspected opioid abstinence could be a mitragynine use signal, as this NPS appeared to be used as an opioid abstinence remedy.

detection and/or offering interesting pharmacological effects', and may actually pose an even worse threat to life and health than the UN controlled substances due to limited user experience and unknown toxicology [2–4]. Striking examples are extremely potent and potentially lethal opioids such as fentanyl and nitazene derivatives [5–9]. The lack of clinically available routine laboratory analyses for NPS may aggravate this danger by limiting the knowledge of NPS consumption at both the individual and population level. However, given the analytical challenges associated with the rapid turnover of NPS on the market, a comprehensive picture of NPS use at every patient consultation will be difficult to achieve in the foreseeable future. Thus, knowledge about NPS epidemiology is of vital interest, not least in relation to traditional drugs since these could serve as indicators for NPS use. Currently, such epidemiological knowledge is very limited [10, 11] presumably due to low NPS prevalence making epidemiological studies difficult. We have previously presented a concept for retrospective identification of NPS in raw data from liquid chromatography-high resolution mass spectrometry (LC-HRMS) based multidrug panel analysis on clinical samples [12]. Although retrospective HRMS analysis of NPS is not unique *per se* [13–19], the large size of our data set allows, to our knowledge, unique epidemiological possibilities. With the aim to provide guidance in clinical situations, we herein present new epidemiological insights into the consumer profiles of NPS-users after retrospectively having identified NPS in LC-HRMS data from 34 183 clinical oral fluid samples.

2 | Methods

The retrospective identification of NPS was performed as previously described [12]. In brief, all 34 183 clinical oral fluid drug samples collected 2019–2020 in the Swedish health care region Västra Götalandsregionen were included; these were from 9468 patients and health care providers as detailed in Table 1. The samples had been routinely analysed using a high through-put LC-HRMS method [20] and stored data were subjected to retrospective analysis of NPS either (i) notified for the first time in 2019–2020 by the European Union Early Warning System on NPS (EU EWS), or (ii) notified earlier but deemed to still be on the market [12]. NPS already in the clinical routine method [20] were also included in the study. Ninety-three NPS were sought for in the data from 2019, whereas 44 NPS notified for the first time by EU EWS in 2020 and one in 2019 (5F-A-P7AICA) were added to the search list for 2020, yielding a total of 138 NPS sought for in data from 2020 (Supplemental Table 1). Traditional DoA were detected (as parent substances and/or metabolites) when the samples were routinely analysed. Substances ever classified as NPS were regarded NPS even if later included in (updates of) the United Nations drug conventions. Registered pharmaceuticals in Sweden (*e.g.* gabapentin, ketamine, loperamide, modafinil, pregabalin, tapentadol, tramadol, zolpidem, zopiclone) were considered traditional DoA (even though some are or have formerly been classified as NPS) as they are frequently detected, may be a prescribed medication, and would be atypical NPS in the sense that their safety profile is well known. Association between traditional DoA and NPS per pharmacological class was investigated per sample only and not per patient (as the goal was to investigate simultaneous drug use and as assessment of individuals is complicated by highly varying sample numbers and sampling frequencies). It was also limited to samples positive for traditional DoA (as there is a general association between traditional DoA and NPS, discussed in the 'Results and Discussion' section and presumably driven by control sampling of individuals free of substance use, that would otherwise make associations meaninglessly statistically significant and indiscriminative). Statistical analyses were performed in SPSS, version 23.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA) using Fisher's exact test for contingency tables and Pearson correlation test for correlations. Significance levels were adjusted for multiple testing using Bonferroni correction. Odds ratios with confidence intervals for the occurrence of NPS in the presence or absence of traditional DoA in drug-positive samples were calculated using Microsoft Excel 365. The confidence intervals for odds ratios were adjusted to 99.98% for multiple testing ($N = 280$) corresponding to an adjusted significance level of 1.8×10^{-4} by using a critical z-value of 3.74. Ethics approval was obtained from the Swedish Ethical Review Authority (Etikprövningsmyndigheten; Dnr: 2019-05469); informed consent was not required. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [21].

3 | Results and Discussion

3.1 | Sample Set and Drug Findings

We analysed 34 183 samples from 9468 patients. Table 1 shows basic sample characteristics (data per patient were not considered reportable as patients often visited several caregivers). In total, 618 findings representing at least 58 NPS substances (some positional isomers could not be analytically distinguished) were detected in 481 samples from 201 patients. A maximum of nine NPS were detected in one sample; 10 samples contained ≥ 5 NPS and 66 samples ≥ 2 NPS. The NPS prevalence did not appear to differ drastically between samples from major types of caregivers (Table 1); hence, given the low NPS frequency, the following statistical analyses herein were performed on the whole dataset without subgrouping for caregiver type. The similar NPs frequencies in the different major types of caregivers contrast to differences between distinct populations (perhaps

TABLE 1 | Basic characteristics of samples.

Type of caregiver	Samples (*n*)					Findings				
	From male patients	From female patients	From patients < 25 years[a]	From patients ≥ 25 years[a]	Total	Traditional DoA (*n*)	Traditional DoA per sample	NPS (*n*)	NPS per sample	NPS per traditional DoA
General psychiatry[b]	1256	985	611	1630	2241	2277	1.02	27	0.012	0.012
General psychiatry excluding psychosis	2921	2518	1501	3937	5439	6159	1.13	47	0.009	0.008
Affective disorders[b]	338	208	93	453	546	528	0.97	13	0.024	0.025
Psychosis	1308	241	330	1219	1549	2417	1.56	20	0.013	0.008
Forensic psychiatry (care units)	1669	148	119	1698	1817	1892	1.04	62	0.034	0.033
Neuropsychiatry	521	459	317	663	980	635	0.65	15	0.015	0.024
SIB/PTSD[b]	410	153	73	490	563	1778	3.16	24	0.043	0.013
Personality disorders[b]	83	53	21	115	136	230	1.69	3	0.022	0.013
Psychiatric emergency room[b]	25	8	10	23	33	88	2.67	4	0.121	0.045
Child and adolescent psychiatry[c]	102	126	228	0	228	93	0.41	1	0.004	0.011
Subtotal psychiatric care	**8633**	**4899**	**3303**	**10228**	**13532**	**16097**	**1.19**	**216**	**0.016**	**0.013**
General outpatient addiction care	5962	2177	3748	4386	8139	11167	1.37	184	0.023	0.016
Opioid agonist therapy (substitution)[b]	7426	2357	174	9609	9783	19076	1.95	180	0.018	0.009
Withdrawal treatment	423	195	358	260	618	1353	2.19	15	0.024	0.011
Alcohol dependence[b]	91	16	1	106	107	110	1.03	5	0.047	0.045
Gambling addiction[b]	20	10	3	27	30	16	0.53	0	0	0
Subtotal addiction care	**13922**	**4755**	**4284**	**14388**	**18677**	**31722**	**1.70**	**384**	**0.021**	**0.012**
Outreach health and social care[b,d]	489	429	60	858	918	3109	3.39	8	0.009	0.003
Maternal health care[b]	0	410	136	274	410	251	0.61	0	0	0
Primary health care	197	77	70	204	274	210	0.77	4	0.015	0.019
Specifically somatic caregivers	88	35	14	109	123	134	1.09	1	0.008	0.007

(Continues)

TABLE 1 | (Continued)

Type of caregiver	Samples (*n*)				Findings				
	From male patients	From female patients	From patients < 25 years[a]	From patients ≥ 25 years[a]	Total	Traditional DoA (*n*)	Traditional DoA per sample	NPS (*n*)	NPS per sample	NPS per traditional DoA
Social services	83	143	126	100	226	213	0.94	5	0.022	0.023
Other	16	7	14	9	23	19	0.83	0	0	0
Total	**23 428**	**10 755**	**8007**	**26 170**	**34 183**	**51 755**	**1,51**	**618**	**0.018**	**0.012**
Whereof outpatient care	21 113	10 126	7329	23 904	31 239	45 740	1.46	519	**0.017**	0.011
Whereof inpatient care	2315	629	678	2266	2944	6015	2.04	99	0.034	0.016

Abbreviations: DoA indicates drugs of abuse; SIB, self-injurious behaviour; PTSD, post-traumatic stress disorder.

[a]Information about age is missing in six samples.

[b]Caregiver for adult patients only (> 18–21 years of age).

[c]Patients < 18 years of age.

[d]Largely patients suffering from psychiatric and addiction comorbidity.

confounded by different sampling practices and sampling years) reported in the literature. For example, 2.4% and 11% NPS positive oral fluid samples have been reported in French and Belgian drivers, respectively, whereas in French drivers that were at the same time music festival entrants 16% of the samples were NPS positive [22–24].

Outreach care was an exception from similar NPS frequencies showing high frequency of traditional DoA but few NPS. This may reflect lack of incentives to try to avoid analytical detection by switching to NPS in this stigmatized patient group, and, additionally, practical difficulties to obtain "internet drugs" in these, often homeless, patients. If so, this observation may argue against NPS largely being adulterants or impurities of traditional DoA and rather something that is acquired intentionally.

3.2 | Temporal Aspects of NPS Intake

The appearance of NPS findings per calendar month during the investigated period (2019–2020) is shown in Figure 1. No clear indications of replacement of older NPS with novel ones within the same pharmacological NPS class were seen, and many substances appeared to be relatively long lived. Thirty-eight of 165 (23%) findings of substances notified by EU EWS in 2019–2020 ($n = 22$; indistinguishable isomeric groups excluded) appeared prior to the notification date. In 2019, one patient contributed with 11 of 16 findings that appeared before the notification date; however, when analysing both 2019 and 2020, 17 patients contributed to the 38 findings. Consumption of non-notified NPS was temporally limited to three months or less before notification in all but one individual (data not shown), which may give a measure of the delay time between appearance on the market and formal notification.

3.3 | NPS Consumption Related to Gender and Age

The number of findings and patients, per gender and age, is shown for NPS classes in Table 2. In support of numerous previous works [12, 25–29], NPS use was more common among males than females, a difference that was statistically significant for total NPS but also for several NPS classes.

NPS frequency was higher in samples from patients ≥25 years compared to younger ones (Table 2). This contrasts to most data reported in the literature. In several studies, most NPS were observed in or self-reported by persons < 25 years [25, 29–31], although reported median ages of NPS users in the range 25–30 years are also frequent [27, 32, 33]. However, we are not aware of any studies designed to investigate NPS use frequency as a function of age, and data often emanate from case series based to various degree on cohorts such as festival or party visitors or online community members [30, 34], or events such as acute intoxications [29, 32], where young age is likely to be overrepresented. Indeed, varying patient characteristics in different cohorts of NPS-users significantly affect the median age [30], and, accordingly, one study specifically looking at general psychiatry patients reported a mean age of 35 years for NPS-users [26]. Furthermore, data

NPS	EU EWS	2019												2020										Total (n)
Cannabinoid	year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
5F-MDMB-Pica	2016	1	1		1																					3
5F-MDMB-Pinaca	2015		1																							1
4F-MDMB-Binaca	2018				1		2	4	1	1		1		1						1	1	1	1	2		17
ADB-BUTINACA	2019									★1	1				1	1	2				1	1				8
CUMYL-CBMINACA	2020														1		★									1
4F-ABINACA	2020																			1	2	1	★	1	1	6
5F-EMB-PICA/5F-MDMB-Pica	2020/2016																		★				1	8		9
MDMB-4en-Pinaca	2018																							1	2	3
Total (n)		**1**	**2**		**2**		**2**	**4**	**1**	**2**	**1**	**1**		**1**	**2**	**1**	**2**			**2**	**4**	**3**	**2**	**12**	**3**	**48**
Dissociative/Hallucinogenic		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
3-Methoxy PCP	2012										1	1	1	1			1		1							6
BOH-2C-B	2020													1					★							1
Methoxpropamine	2020													1★								1		1		3
MALT	2020																1						★			1
1-Cp-LSD	2019										★									1						1
3F-PCP	2020																				1	1		★		2
Total (n)											**1**	**1**	**1**	**3**			**2**		**1**	**1**	**1**	**2**		**1**		**14**
Opioid		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
4F-Furanylfentanyl	2019				★	1				1																2
Furanylfentanyl	2015					1																				1
Isotonitazene	2019					1			1★	3		3		1												9
Acrylfentanyl	2016							1																		1
4F-isobuturylfentanyl	2016								1																	1
Metonitazene	2020																				1	1★1		1	1	5
Nortilidine	2020																				★		1			1
Total (n)						**3**		**1**	**2**	**4**		**3**		**1**							**1**	**2**	**1**	**1**	**1**	**20**
Sedative/Hypnotic		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
Flualprazolam	2018	1	2	2		1	4	3	2	8	3	1		1					3	3	2	2	3			41
Norfludiazepam	2017	1	2																							3
Clonazolam	2015					1																				1
Etizolam	2011					1		2		3	2	2	2	4	2		2	7	5	2	4	2				40
Flubromazolam	2014					1				2								1	1					5		10
SL-164	2019									★				1												1
Total (n)		**2**	**4**	**2**		**4**	**4**	**5**	**2**	**13**	**5**	**3**	**2**	**6**	**2**		**2**	**8**	**9**	**5**	**6**	**4**	**3**	**5**		**96**
Stimulant		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
3F/4F-alpha-PiHP/PHP	2015-2020	1		1			1	4	1	3	3	1	2	1★	4	2	1	1			2					28
4-Methyl pentedrone	2014	2																								2
Ethylphenidate	2011	1								1																2
Isohexedrone	2019	2	2	3	★								1							1						9
N-Ethylhexedrone	2015	1								1						1		1	2	1	2	6	8	2		25
4′-Methylhexedrone	2019		2	1			1		★																	4
α-Pyrrolidinovalerophenone	2011		3	3																						6
Methylone	2005				1														1	1						3
N-Ethylpentedrone	2014				2	1	3	1	1	2						1	1	2	2	1	1	4		5		27
Alpha-PHP/PiHP	2014/2016					1		1										1		2	5	5	1		1	17
Eutylone	2014					1	1		2	1																5
3/4-MMC	2012/2008						1	1		1				1		1										5
MDPEP	2019									3★		1	1					1				1	3	12	2	24
3F-Phenmetrazine	2014									1																1
BMDP	2010											1														1
alpha-PCYP	2020													★1	2	5	1	5								14
3F-Methamphetamine	2009													1												1
3-Chloromethcathinone	2014														1						1					2
M-alpha-HCMA	2020														1									★		1
4-Chloromethcathinone	2014															1	2	1								4
4F-3-methyl-alpha-PVP	2020															1	2★	1	14	2	3	2	1	1	2	29
BOH-PHP	2020														★			1		3	6	5	1		1	17
3F-N-ethylhexedrone	2020																		2		1		★	1		4
MDPHiP	2020																			1	1★			3		5
N-Methylephedrine	2018																		1							1
Mephedrene	2020																				★		1	2	2	5
MDPV	2008																							2		2
Total (n)		**7**	**7**	**8**	**3**	**3**	**7**	**7**	**4**	**13**	**3**	**3**	**4**	**4**	**8**	**12**	**7**	**14**	**22**	**12**	**22**	**23**	**15**	**28**	**8**	**244**
Other		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	
Cyproheptadine	2019	1	2★1	1	1				1	1	1	1														10
Mitragynine	2008	6	3	5	4	6	1	2	1	6	2	12	11	7	7	10	2	8	10	10	10	14	17	12	10	176
Tianeptine	2015						3	3		1												1				8
Nefiracetam	2020															1★		1								2
Total (n)		**7**	**6**	**6**	**5**	**6**	**4**	**5**	**2**	**8**	**3**	**13**	**11**	**7**	**7**	**11**	**2**	**9**	**10**	**10**	**10**	**15**	**17**	**12**	**10**	**196**
Total NPS (n)		**17**	**19**	**16**	**10**	**16**	**17**	**22**	**11**	**40**	**13**	**24**	**18**	**22**	**19**	**24**	**15**	**31**	**42**	**30**	**44**	**49**	**38**	**59**	**22**	**618**
Total no. of samples per month		882	988	1064	1045	1174	1015	1070	1076	1498	1757	1671	1323	1675	1793	1335	1141	1516	1886	1350	1725	1992	1941	1782	1407	**34106***
Percent of samples pos. for NPS		1,9	1,9	1,5	1,0	1,4	1,7	2,1	1,0	2,7	0,7	1,4	1,4	1,3	1,1	1,8	1,3	2,0	2,2	2,2	2,6	2,5	2,0	3,3	1,6	**1,812**

FIGURE 1 | Appearance of NPS per calendar month during 2019–2020 illustrated as a heat map. Stars indicate the EU EWS notification date when occurring 2019–2020. Grey fields denote periods when the NPS was not sought for. * Data on sampling month is missing in 77 samples.

is often based on patient self-reports through interviews or questionnaires [25–27, 30, 31] where bias due to age is difficult to control but where adolescence could perhaps be associated with sensationalistic reporting. Possibly supporting the need for objective monitoring methods, one study based on hair analysis reported 33 years as mean age of NPS users [28]. Taken together, given the possible biasing factors mentioned, our objective laboratory findings from relatively broad patient groups are worth considering although contrasting to most other data, suggesting that caregivers should consider NPS also in older patients. Obviously, our data may also be biased, for instance by factors such as different sampling practices at different ages, and further studies on NPS and age could be clinically motivated.

TABLE 2 | Number of findings of, and patients positive for, NPS classes and substances in relation to gender and age.

	Findings							Positive patients						
	Total	**In male patients (*n*)**	**In female patients (*n*)**	***p*[a]**	**In patients <25 years (*n*)**	**In patients ≥25 years (*n*)**	***p*[a]**	**Total**	**Male**	**Female**	***p*[b]**	**<25 years**	**≥25 years**	***p*[b]**
Total number of samples/ patients	**34,183**[c]	23 428	10 755		8,007[c]	26,170[c]		**9468**	5571	3897		3,033[d]	6,430[d]	
Cannabinoid NPS	**48**	43	5	0.012	10	38	n/s	**17**	14	3	0.049	3	14	n/s
Dissociative/ Hallucinogenic NPS	**14**	14	0	0.019	9	5	0.0043	**6**	6	0	0.040	2	4	n/s
Opioid NPS	**20**	11	9	n/s	1	19	n/s	**7**	5	2	n/s	1	6	n/s
Sedative/ hypnotic NPS	**96**	81	15	**9.4E-04**	6	90	**1.5E-04**	**58**	48	10	**2.0E-04**	6	52	**3.8E-04**
Stimulant NPS	**244**	216	28	**1.2E-07**	25	219	**3.1E-06**	**60**	50	10	**1.1E-04**	4	56	**2.5E-05**
Other NPS	**196**	165	31	**2.2E-06**	9	157	**n/s**	**82**	70	12	**9.4E-07**	18	64	0.049
All NPS	**618**	530	88	**9.3E-15**	90	528	**6.9E-05**	**201**	167	34	**1.6E-12**	32	169	**6.9E-07**
Percent of samples/ patients positive for NPS	**1.4%**	1.7%	0.7%		0.9%	1.5%		**2.1%**	3.0%	0.9%		1.1%	2.6%	

Notes: n/s indicates not significant at 0.05 level or calculation not possible due to few cases.

[a]Fisher's Exact Test based on findings per sample. Bold figures denote significance at 1.8×10^{-3}-level, the latter calculated as 0.05/28 in accordance with Bonferroni correction for 28 analyses.

[b]Fisher's Exact Test based on findings per patient. Bold figures as above.

[c]Information about age is missing in six samples.

[d]Information about age is missing in five patients.

3.4 | Association Between Traditional DoA and NPS

We found a mean of 3.0 traditional DoA in samples ($n = 312$) positive for non-mitragynine NPS as compared to 1.5 traditional DoA in samples ($n = 33\,702$) negative for NPS ($p = 1.8 \times 10^{-52}$, Pearson correlation test) confirming a general association between traditional DoA as a whole and NPS shown also by others [10, 35, 36]. Table 3 shows associations between traditional DoA and NPS classes; associations that were significant after Bonferroni correction for multiple testing are highlighted (bold), but all associations significant at $p < 0.05$ are shown for discussion on trends. As mitragynine was found to have a different epidemiology (see below) compared to other NPS, it was excluded in the analysis of overall association between NPS and traditional DoA. To give an indication of strength of the association, odds ratios and confidence intervals were calculated for occurrence of the NPS class in samples positive versus negative for the traditional DoA (Figure 2). These calculations do not account for the number of NPS representing the class in the samples, which may contribute to discrepancies between statistical significance and confidence intervals not including the value 1. No odds ratio could be calculated for comparisons where one of the groups contained no findings.

3.4.1 | Cannabis vs. NPS Classes

Cannabis correlated with sedative/hypnotic NPS but no other NPS group. All cases involved etizolam and flualprazolam, substance names presumably not perceived as NPS by drug consumers, suggesting that cannabis is not a suitable indicator for intentional NPS use. When narrowing the statistical analysis to samples from patients at least once positive for NPS (2979 samples, 201 patients; data not shown) no correlation of cannabis with other NPS classes were found; the lack of temporal correlation in these patients further argues against an important role of NPS in relation to cannabis. An explanation could be that cannabis is often part of a less advanced consumption pattern involving only this drug, for example in young consumers [37].

3.4.2 | Ketamine vs. NPS Classes

Ketamine correlated positively with five of the six NPS classes and was the only traditional DoA correlating positively with mitragynine. Additionally, it showed a trend to correlation with cannabinoid NPS (Table 3). Of the 238 ketamine positive samples, 33 (14%) contained NPS, where the latter contained a mean of 1.8 NPS as compared to 1.2

TABLE 3 | Associations between NPS and traditional DoA.

		All NPS except for mitragynine ($n = 442$)			Cannabinoid NPS ($n = 48$)			Dissociative /Hallucinogenic NPS ($n = 14$)			Opioid NPS ($n = 20$)			Sedative/Hypnotic NPS ($n = 96$)			Stimulant NPS ($n = 244$)			Mitragynine ($n = 176$)		
	Traditional DoA[a]	Co-occurrence (n)[b] (expected; n)[c]	Patients involved (n)	*p*-Value[d]	Co-occurrence (n)[b] (expected; n)[c]	Patients involved (n)	*p*-Value[d]	Co-occurrence (n)[b] (expected; n)[c]	Patients involved (n)	*p*-Value[d]	Co-occurrence (n)[b] (expected; n)[c]	Patients involved (n)	*p*-Value[d]	Co-occurrence (n)[b] (expected; n)[c]	Patients involved (n)	*p*-value[d]	Co-occurrence (n)[b] (expected; n)[c]	Patients involved (n)	*p*-value[d]	Co-occurrence (n)[b] (expected; n)[c]	Patients involved (n)	*p*-Value[d]
	Cannabis ($n = 1673$)		n/s			n/s			n/s			n/s		18 (11)	11	**1.0E-04**		n/s		4 (13)	4	*0.0082*
	Ketamine ($n = 238$)	54 (5)	10	**8.9E-52**	3 (0.5)	1	0.0043	5 (0.1)	2	**4.0E-26**	3 (0.2)	2	**2.9E-07**	10 (2)	5	**1.3E-16**	33 (3)	5	**2.6E-37**	7 (2)	6	**1.6E-04**
Opioids	Buprenorphine ($n = 1391$)		n/s			n/s			n/s			n/s			n/s			n/s		22 (11)	5	0.00056
	Fentanyl ($n = 56$)	9 (1)	3	**6.9E-07**		n/s			n/s		3 (0.1)	2	**6.4E-29**		n/s		5 (1)	2	**1.6E-04**		n/s	
	Heroin ($n = 2381$)		n/s		11 (5)	3	0.025		n/s			n/s		31 (10)	22	**1.9E-10**		n/s		2 (19)	2	***3.9E-05***
	Loperamide ($n = 425$)		n/s			n/s			n/s			n/s			n/s			n/s		9 (3)	5	0.0018
	Methadone ($n = 148$)	26 (3)	3	**3.5E-19**	3 (0.3)	1	**9.8E-05**		n/s		6 (0.1)	1	**1.1E-42**	6 (0.6)	2	**3.9E-10**	11 (2)	2	**6.4E-07**		n/s	
	Morphine ($n = 283$)		n/s			n/s			n/s			n/s		4 (1)	3	0.019		n/s			n/s	
	Oxycodone ($n = 861$)		n/s			n/s			n/s		3 (0.8)	3	0.029		n/s			n/s			n/s	
	Tapentadol ($n = 222$)	32 (4)	6	**1.9E-18**		n/s		2 (0.1)	1	**2.7E-05**	9 (0.2)	2	**1.9E-63**	4 (1)	2	0.0037	16 (2)	3	**3.9E-09**	6 (2)	3	0.0012
Sedatives	Alprazolam ($n = 6033$)	158 (120)	72	0.0064		n/s		9 (4)	3	0.0086		n/s		61 (26)	41	**7.9E-14**		n/s		33 (48)	18	*0.013*
	Bromazepam ($n = 21$)	4 (0.4)	2	0.00023		n/s			n/s			n/s		1 (0.1)	1	0.0050	3 (0.2)	2	**1.0E-04**		n/s	
	Clonazepam ($n = 980$)	61 (19)	18	**1.7E-10**		n/s			n/s		9 (0.9)	4	**6.6E-14**	16 (4)	10	**5.2E-08**	34 (11)	7	**9.9E-07**	15 (8)	10	0.0073
	Lorazepam ($n = 103$)		n/s			n/s			n/s		1 (0.1	1	0.011		n/s			n/s			n/s	
	Midazolam ($n = 21$)		n/s			n/s		1 (0.0)	1	**6.0E-13**		n/s			n/s			n/s			n/s	
	Gabapentin (n =1903)	60 (38)	22	0.012		n/s		5 (1)	2	0.0023	10 (2)	2	**2.0E-08**	15 (8)	11	0.021		n/s			n/s	
	Pregabalin ($n = 2390$)	79 (47)	24	0.0013		n/s			n/s			n/s			n/s		54 (26)	14	**1.0E-04**		n/s	
	Zopiclone ($n = 4653$)		n/s			n/s			n/s			n/s		10 (20)	9	*0.020*	39 (51)	19	*0.033*	25 (37)	19	*0.029*
Stimulants	Amphetamine ($n = 8049$)		n/s			n/s			n/s		2 (7)	2	*0.040*	52 (35)	34	0.00062		n/s		40 (63)	29	*0.00021*
	Cocaine ($n = 4282$)		n/s			n/s			n/s			n/s		39 (18)	26	**7.5E-07**		n/s			n/s	
	MDMA ($n = 765$)	29 (15)	22	0.017		n/s			n/s			n/s		15 (3)	11	**1.1E-09**		n/s			n/s	
	Methamphetamine ($n = 669$)		n/s			n/s			n/s			n/s		8 (3)	8	0.0045		n/s		0 (5)	0	*0.019*
	Methylphenidate ($n = 3124$)		n/s			n/s			n/s			n/s			n/s			n/s		4 (25)	4	***6.7E-06***

Note: n/s indicates not significant at 0.05 level.

[a]Traditional DoA not found during the study period (mescaline, pethidine, phencyclidine, triazolam), not occurring together with any NPS (cathinone [$n = 15$], flunitrazepam [$n = 49$], ketobemidon [n = 8], lysergic acid diethylamide [LSD; n = 21], modafinil [$n = 4$], oxymorphone [n = 7], psilocin [$n = 3$]), or not correlating significantly with any NPS class (codeine [$n = 453$], diazepam [$n = 6144$], ephedrine [$n = 91$], ethylmorphine [$n = 58$], hydrocodone [$n = 94$], metorphan [$n = 83$], nitrazepam [$n = 192$], oxazepam [$n = 464$], tramadol [$n = 1936$], zolpidem [$n = 1422$]) are not shown in the table.

[b]N-values refer to number of NPS occurring together with the traditional DoA (and not number of samples where they co-exist).

[c]Expected numbers of NPS occurring together with traditional drug assuming lack of correlation between the two, calculated as: (number of NPS × number of traditional drug)/22311, where the latter is the total number of drug positive samples in this study.

[d]Significance calculations using Pearson correlation are based on drug positive samples only (n = 22 311). Bold figures denote significance at 1.8×10^{-4}-level, the latter calculated as 0.05/280 in accordance with Bonferroni correction for 280 analyses. Italics denote negative correlation.

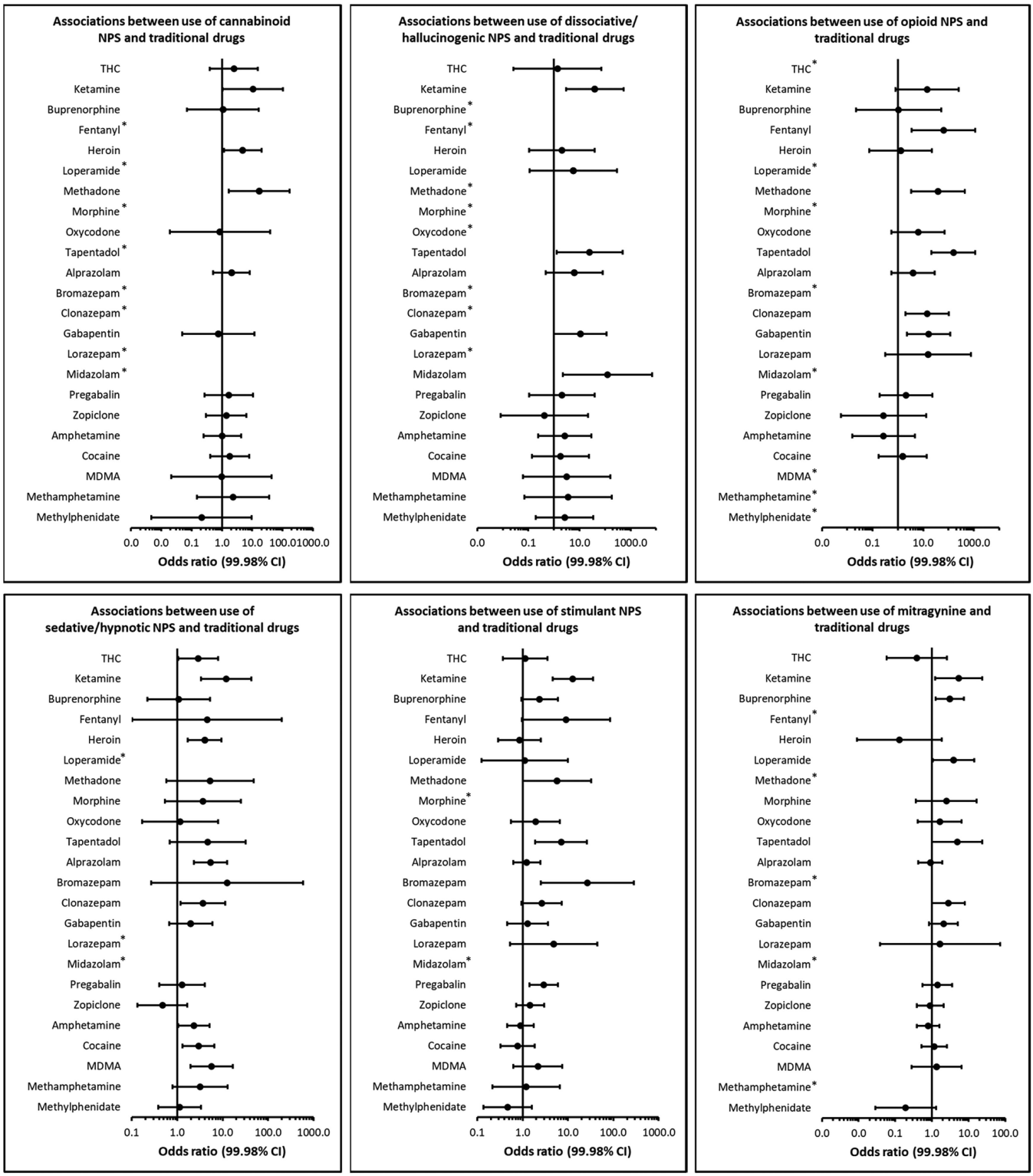

FIGURE 2 | Associations between use of NPS groups and traditional DoA expressed as odds ratios with confidence intervals adjusted for multiple testing. No odds ratio was calculated for starred substances as one of the groups contained no findings. CI, confidence intervals.

in NPS positive but ketamine negative samples ($n = 448$); $p = 2.9 \times 10^{-4}$; Pearson correlation test. These findings might not be surprising given previous reports on an association between NPS and ketamine [28, 36] or "psychedelics" in general [10], possibly reflecting a general willingness to experiment with unpredictable drugs in certain individuals. Hope to avoid analytic detection could also be a rationale for these combinations as ketamine is often not included in routine DoA testing in urine. Awareness of this drug combination could be of clinical value, as combining a drug affecting perception of reality and an NPS with unpredictable toxicity appears particularly dangerous.

3.4.3 | Traditional Opioids vs. NPS Classes

Fentanyl, methadone and tapentadol correlated positively with non-mitragynine NPS, with 8, 5, and 11% of positive samples being NPS positive, respectively. For all three, the correlation was significant with opioid NPS and stimulant NPS; for methadone also with cannabinoid and sedative/hypnotic NPS, and for tapentadol also with dissociative/hallucinogenic NPS (Table 3). A common feature of fentanyl, methadone and tapentadol is that they are relatively rarely used traditional opioids (totally 56, 148 and 222 findings, respectively; Table 3), giving the impression that NPS (except for sedative/hypnotic NPS; discussed below) covaries with unusual traditional DoA rather than more commonly found ones such as amphetamine, alprazolam, zopiclone and cocaine. Reasons for this may include a general interest in adventurous or "sophisticated" substances, and, at least in patients used to the limited DoA testing in urine, a patient's desire to avoid analytic detection. Additionally, correlation between fentanyl and opioid NPS may reflect that fentanyl and fentanyl derivatives are not always distinguished by consumers and therefore used in parallel [6].

The correlation between methadone and four NPS classes was based on three patients only (Table 3) but may illustrate an interesting contrast to buprenorphine pharmacologically explainable by the latter being a partial opioid antagonist. This explanation could be true even if we did not manage to fully exclude prescribed methadone and buprenorphine (opioid agonist therapy) from our dataset as intended (in our healthcare region buprenorphine is rarely combined with the full opioid antagonist naloxone which is not detected in our analysis), but a confounding explanation regarding opioid agonist therapy could be that methadone is used in clinically more severe cases than buprenorphine [38].

An association between heroin and sedative/hypnotic NPS was observed, and all except for five of the 31 samples involved also contained classical benzodiazepines. This may, as discussed elsewhere, suggest that sedative NPS represent a general need for benzodiazepines rather than a specific interest in NPS, presumably to complete the heroin effect or manage heroin abstinence [39]. If so, heroin, like cannabis, may not be a suitable indicator of intentional NPS use.

3.4.4 | Traditional Sedatives vs. NPS Classes

A positive correlation between the frequently observed benzodiazepines alprazolam and clonazepam and sedative/hypnotic NPS was observed (Table 3). Since NPS benzodiazepines (which constitute 95 of the 96 sedative/hypnotic NPS findings) are generally established and available since several years and have names resembling traditional benzodiazepines, one may speculate that they are regarded equally "normal" as traditional benzodiazepines and therefore not perceived as NPS by consumers. Indeed, sedative/hypnotic NPS correlated with a broader range of traditional DoA than the other NPS classes, presumably for the same reason. Thus, as discussed, their association with cannabis and heroin may represent a general need for benzodiazepines rather than a wish for NPS specifically. The lack of correlation between sedative/hypnotic NPS and the frequently observed benzodiazepine diazepam ($n = 6144$; data not shown) may reflect that diazepam is more often prescribed than alprazolam and clonazepam [40] and may therefore more seldom represent misuse.

Clonazepam correlated with opioid NPS use, possibly illustrating a subjective need for adding benzodiazepines to opioids as discussed above for heroin [39]. Indeed, the opioid findings in these samples were considerable, encompassing 4F-furanylfentanyl, acrylfentanyl, furanylfentanyl and isotonitazene, (1–3 NPS simultaneously), together with ≥ 1 traditional opioid. Associations of bromazepam, clonazepam and pregabalin with stimulant NPS may reflect a need to balance out the stimulant effect (see below). The association of midazolam with dissociative NPS is based on one finding and may therefore be disregarded.

The traditional non-benzodiazepine sedatives gabapentin, pregabalin and zopiclone appear less associated with sedative/hypnotic NPS compared to alprazolam and clonazepam (Table 3), perhaps because they are distinguished from traditional/NPS benzodiazepines by consumers. Association of gabapentin and pregabalin with opioid and sedative NPS, respectively, could reflect an intention to avoid analytical detection, as gabapentin and pregabalin are seldom included in routine immunochemical DoA testing of urine.

3.4.5 | Traditional Stimulants vs. NPS Classes

The traditional stimulants cocaine and MDMA correlated with sedative NPS; more than 90% of the samples also contained traditional benzodiazepines, again suggesting that traditional and NPS benzodiazepines are not discriminated by consumers. The role of the benzodiazepine in combination with stimulants could be to balance out the stimulant effect and relieve anxiety occasionally caused by stimulants [41, 42].

In contrast to benzodiazepines, traditional and NPS stimulants do not seem to appear together, possibly because stimulant NPS add little effect to, the often potent, traditional stimulants. Only 204 out of 8049 amphetamine findings were from neuropsychiatric patients, ruling out prescribed (lis)dexamphetamine as a major explanation for lack of significant association between amphetamine and stimulant NPS. Associations between MDMA and stimulant NPS would have been possible in the light of interview data [43] and reports of MDMA tablets adulterated with stimulant NPS [44] but were absent here.

3.4.6 | Mitragynine – Kratom

Mitragynine (an active substance in kratom) exhibited an atypical epidemiology compared to the other NPS (Table 3). It occurred together with other NPS only in seven samples where all the other NPS ($n = 8$) were stimulants. The mitragynine positive samples ($n = 176$) contained 1.05 NPS including mitragynine (mean) as compared to 1.4 NPS in samples positive for other NPS but negative for mitragynine (305 samples, 434 NPS findings); $p = 1.6 \times 10^{-5}$; Pearson correlation test. Mitragynine showed trends to negative correlations with several frequent traditional DoA (Table 3), and mitragynine

positive samples contained 2.0 traditional DoA (mean) as compared to 3.0 in samples positive for other NPS but negative for mitragynine ($p = 1.9 \times 10^{-7}$ vs mitragynine positive samples; Pearson correlation test) and 2.3 in samples negative for all NPS but positive for traditional DoA ($p = 3.1 \times 10^{-3}$ vs mitragynine positive samples; Pearson correlation test). This may illustrate that kratom adds limited recreational value when combined with other drugs. While traditional DoA are illegal and routinely analysed, kratom leaves can be obtained legally in Sweden and mitragynine or other kratom components are not analysed by most clinical laboratories. These aspects may define an important niche for kratom contributing to its negative association with several traditional DoA.

Kratom has significant opioid effects at higher doses [45], and is therefore sometimes self-administered as a remedy against opioid abstinence [46]. This may explain its negative correlation with heroin, and a trend for positive correlation with loperamide, which is used (at supra-pharmacological doses) as a legal self-medication for opioid abstinence [47]. The strong trend to positive correlation of kratom with buprenorphine could reflect a patient's desire to gain additional opioid like effect or better opioid abstinence treatment when using the partial opioid antagonist buprenorphine. Possibly, if we did not manage to fully exclude prescribed buprenorphine from our dataset as intended, it could also reflect buprenorphine-based opioid agonist therapy primarily against kratom use.

Taken together, use of kratom could be hard to predict from consumption patterns of traditional DoA (although ketamine correlates positively). This could merit intensified efforts in making clinical routine analysis available, as kratom at high doses appears to be highly addictive and have serious toxicity including lethal cases [48]. Additionally, patients using kratom as a self-administered opioid abstinence remedy could be especially motivated to quit opioid misuse and therefore worth identifying from a health care perspective.

3.5 | Strengths and Limitations of This Study

Strengths are the naturalistic setting, consecutive inclusion of all 34 183 clinical samples over two years, analytical coverage of over 180 substances, high analytical sensitivity and specificity, and use of oral fluid to enable detection of parent substances rather than metabolites which are often unknown for NPS. Additionally, the multidrug panel concept limits bias due to clinicians ordering analysis directed to specific drugs or drug classes.

A limitation could be that clinical routine samples have limited generalizability to the whole population. This may, however, be an academic rather than practical/clinical problem as our cohort is probably more representative than the whole population of most addiction patients and particularly regarding those with advanced polydrug use in which NPS use could be especially dangerous. In any case, an adequately powered laboratory analysis study based on a random sample of the whole population appears utopian for several reasons, not the least as NPS occur in ≥1 sample in only 2.1% of patients in our selected cohort. More realistic would be further observational studies based on other populations and selection criteria to test the external validity of our findings.

Other limitations are the low numbers for some drugs, the inability to identify possibly unintentional NPS intake (NPS as adulterants or impurities), and the retrospective analysis not allowing for optimization of analytical conditions to, for instance, separate isomers. Although oral fluid has advantages over urine detecting parent substance rather than metabolites, this matrix could have limitations compared to blood as for knowledge regarding for example concentrations as a function of dose and duration of detectability (in cases where such parameters are known for blood).

4 | Conclusions

The use of NPS in our population is limited with only 2.1% of the patients at least once positive for an NPS. However, these findings constitute 58 different compounds, which were commonly combined with traditional drugs probably increasing the risk for severe adverse effects. NPS use was more common in the age-group ≥25 years; rather the opposite has often been reported, meriting further studies. Ketamine could be useful as an indicator for NPS use, correlating positively with all NPS classes except for cannabinoid NPS, but also fentanyl, methadone, tapentadol, and clonazepam correlated with several NPS classes. Sedative/hypnotic NPS correlate positively with a large number of traditional DoA indicating that they are used within larger patient groups than other NPS. Mitragynine (kratom), unlike other NPS, had a negative correlation with several traditional DoA and positive correlation with the potential opioid abstinence remedies buprenorphine, loperamide and tapentadol, indicating a specific type of use potentially as a self-administered abstinence treatment. Taken together, the use of NPS is low but present, and new drugs are continuously emerging. Correlations of NPS use with traditional drugs reveal specific drug use patterns that can provide guidance in clinical situations.

Author Contributions

Magnus A. B. Axelsson: conceptualization (lead); data curation (equal); formal analysis (lead); funding acquisition (equal); investigation (equal); methodology (lead); project administration (equal); resources (equal); visualization (lead); writing – original draft (lead). **Hanna Lövgren**: data curation (equal); formal analysis (supporting); investigation (lead); methodology (equal); writing – review and editing (equal). **Robert Kronstrand**: conceptualization (equal); formal analysis (supporting); methodology (supporting); writing – review and editing (supporting). **Henrik Green**: conceptualization (equal); formal analysis (supporting); funding acquisition (equal); methodology (supporting); supervision (lead); writing – review and editing (equal). **Moa Andresen Bergström**: conceptualization (lead); data curation (equal); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (equal); writing – review and editing (equal).

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Ethics Statement

Ethics approval was obtained from the Swedish Ethical Review Authority (Etikprövningsmyndigheten; Dnr: 2019-05469).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

This study was based on individual-level data. The ethical approval of this research project does not include permission to publicly share the raw data.

References

1. *New psychoactive substances (NPS). Overview* (Lisbon, Portugal: European Union Drugs Agency (EUDA), 2024) Accessed November 1, 2024. https://www.euda.europa.eu/topics/nps_en.

2. A. Peacock, R. Bruno, N. Gisev, et al., "New Psychoactive Substances: Challenges for Drug Surveillance, Control, and Public Health Responses," *Lancet* 394 (2019): 1668–1684.

3. A. Shafi, A. J. Berry, H. Sumnall, D. M. Wood, and D. K. Tracy, "New Psychoactive Substances: A Review and Updates," *Therapeutic Advances in Psychopharmacology* 10 (2020): 2045125320967197.

4. A. Y. Simao, M. Antunes, E. Cabral, et al., "An Update on the Implications of New Psychoactive Substances in Public Health," *International Journal of Environmental Research and Public Health* 19 (2022): 4869.

5. D. Guerrieri, E. Rapp, M. Roman, H. Druid, and R. Kronstrand, "Postmortem and Toxicological Findings in a Series of Furanylfentanyl-Related Deaths," *Journal of Analytical Toxicology* 41 (2017): 242–249.

6. D. Guerrieri, E. Rapp, M. Roman, G. Thelander, and R. Kronstrand, "Acrylfentanyl: Another New Psychoactive Drug With Fatal Consequences," *Forensic Science International* 277 (2017): e21–e29.

7. R. Kronstrand, A. Åstrand, S. Watanabe, H. Green, and S. Vikingsson, "Circumstances, Postmortem Findings, Blood Concentrations and Metabolism in a Series of Methoxyacetylfentanyl-Related Deaths," *Journal of Analytical Toxicology* 45 (2021): 760–771.

8. U. Rauf, M. Ali, I. Dehele, V. Paudyal, M. H. Elnaem, and E. Cheema, "Causes, Nature and Toxicology of Fentanyl-Analogues Associated Fatalities: A Systematic Review of Case Reports and Case Series," *Journal of Pain Research* 14 (2021): 2601–2614.

9. J. Pergolizzi, Jr., R. Raffa, J. A. K. LeQuang, F. Breve, and G. Varrassi, "Old Drugs and New Challenges: A Narrative Review of Nitazenes," *Cureus* 15 (2023): e40736.

10. F. Fernandez-Calderon, C. M. Cleland, and J. J. Palamar, "Polysubstance Use Profiles Among Electronic Dance Music Party Attendees in new York City and Their Relation to use of New Psychoactive Substances," *Addictive Behaviors* 78 (2018): 85–93.

11. L. Elliott, C. K. Haddock, S. Campos, and E. Benoit, "Polysubstance Use Patterns and Novel Synthetics: A Cluster Analysis From Three U.S. Cities," *PLoS ONE* 14 (2019): e0225273.

12. M. A. B. Axelsson, H. Lövgren, R. Kronstrand, H. Green, and M. A. Bergström, "Retrospective Identification of New Psychoactive Substances in Patient Samples Submitted for Clinical Drug Analysis," *Basic & Clinical Pharmacology & Toxicology* 131 (2022): 420–434.

13. C. Noble, P. Weihe Dalsgaard, S. Stybe Johansen, and K. Linnet, "Application of a Screening Method for Fentanyl and Its Analogues Using UHPLC-QTOF-MS With Data-Independent Acquisition (DIA) in MS(E) Mode and Retrospective Analysis of Authentic Forensic Blood Samples," *Drug Testing and Analysis* 10 (2018): 651–662.

14. P. Kriikku, A. Pelander, I. Rasanen, and I. Ojanperä, "Toxic Lifespan of the Synthetic Opioid U-47,700 in Finland Verified by re-Analysis of UPLC-TOF-MS Data," *Forensic Science International* 300 (2019): 85–88.

15. M. C. Campos-Mañas, I. Ferrer, E. M. Thurman, J. A. S. Pérez, and A. Agüera, "Identification of Opioids in Surface and Wastewaters by LC/QTOF-MS Using Retrospective Data Analysis," *Science of the Total Environment* 664 (2019): 874–884.

16. P. O. M. Gundersen, S. Broecker, L. Slordal, O. Spigset, and M. Josefsson, "Retrospective Screening of Synthetic Cannabinoids, Synthetic Opioids and Designer Benzodiazepines in Data Files From Forensic Post Mortem Samples Analysed by UHPLC-QTOF-MS From 2014 to 2018," *Forensic Science International* 311 (2020): 110274.

17. J. Klingberg, B. Keen, A. Cawley, D. Pasin, and S. Fu, "Developments in High-Resolution Mass Spectrometric Analyses of New Psychoactive Substances," *Archives of Toxicology* 96 (2022): 949–967.

18. A. J. Krotulski, S. J. Varnum, and B. K. Logan, "Sample Mining and Data Mining: Combined Real-Time and Retrospective Approaches for the Identification of Emerging Novel Psychoactive Substances," *Journal of Forensic Sciences* 65 (2020): 550–562.

19. M. Pan, B. S. Rasmussen, P. W. Dalsgaard, et al., "A New Strategy for Efficient Retrospective Data Analyses for Designer Benzodiazepines in Large LC-HRMS Datasets," *Frontiers in Chemistry* 10 (2022): 868532.

20. M. A. Bergström, H. Lövgren, A. Abrahamsson, et al., "Rethinking Drug Analysis in Health Care: High-Throughput Analysis of 71 Drugs of Abuse in Oral Fluid Using Ion Mobility—High-Resolution Mass Spectrometry," *Journal of Analytical Toxicology* 46 (2022): 765–775.

21. P. Tveden-Nyborg, T. K. Bergmann, N. Jessen, U. Simonsen, and J. Lykkesfeldt, "BCPT 2023 Policy for Experimental and Clinical Studies," *Basic & Clinical Pharmacology & Toxicology* 133 (2023): 391–396.

22. C. Richeval, A. Gish, F. Hakim, et al., "Prevalence of New Psychoactive Substances in Oral Fluid Samples From French Drivers: A Longitudinal Survey (2016–2020)," *Journal of Analytical Toxicology* 45 (2021): e20–e21.

23. S. M. R. Wille, C. Richeval, M. Nachon-Phanithavong, et al., "Prevalence of New Psychoactive Substances and Prescription Drugs in the Belgian Driving Under the Influence of Drugs Population," *Drug Testing and Analysis* 10 (2018): 539–547.

24. A. Gish, V. Dumestre-Toulet, C. Richeval, et al., "Trends in the Pharmaceutical Design of New Psychoactive Substances Detected in Oral Fluid OF Drivers Around a Music Festival in South-West France: Comparison 2019/2017," *Current Pharmaceutical Design* 28 (2022): 1245–1249.

25. J. J. Palamar, M. J. Barratt, J. A. Ferris, and A. R. Winstock, "Correlates of New Psychoactive Substance Use Among a Self-Selected Sample of Nightclub Attendees in the United States," *American Journal on Addictions* 25 (2016): 400–407.

26. K. H. Bennett, H. M. Hare, R. M. Waller, H. L. Alderson, and S. Lawrie, "Characteristics of NPS use in Patients Admitted to Acute Psychiatric Services in Southeast Scotland: A Retrospective Cross-Sectional Analysis Following Public Health Interventions," *BMJ Open* 7 (2017): e015716.

27. P. Engelgardt, M. Krzyzanowski, P. Piotrowski, M. Borkowska-Sztachanska, A. Wasilewska, and T. Kowalkowski, "Characteristics of Psychiatric Inpatients Diagnosed With Mental and Behavioral Disorders Caused by Psychoactive Substances (F11–19 Block), with a Focus on NPS and Psychiatric Co-Morbidities," *International Journal of Occupational Medicine and Environmental Health* 33 (2020): 125–136.

28. I. A. Larabi, N. Fabresse, I. Etting, et al., "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)," *Drug and Alcohol Dependence* 204 (2019): 107508.

29. A. Helander, M. Bäckberg, and O. Beck, "Drug Trends and Harm Related to new Psychoactive Substances (NPS) in Sweden From 2010 to 2016: Experiences From the STRIDA Project," *PLoS ONE* 15 (2020): e0232038.

30. A. Benschop, R. Urban, M. Kapitany-Foveny, et al., "Why Do People use New Psychoactive Substances? Development of a New Measurement Tool in Six European Countries," *Journal of Psychopharmacology* 34 (2020): 600–611.

31. D. Dal Farra, A. Valdesalici, G. Zecchinato, et al., "Knowledge and Use of Novel Psychoactive Substances in an Italian Sample With Substance Use Disorders," *International Journal of Environmental Research and Public Health* 19 (2022): 915.

32. B. Crulli, A. M. Dines, G. Blanco, et al., "Novel Psychoactive Substances-Related Presentations to the Emergency Departments of the European Drug Emergencies Network Plus (Euro-DEN Plus) Over the Six-Year Period 2014–2019," *Clinical Toxicology (Philadelphia, Pa.)* 60 (2022): 1318–1327.

33. P. Engelgardt, M. Krzyzanowski, P. Piotrowski, M. Borkowska-Sztachanska, and A. Wasilewska, "Analytically Confirmed Presence of Psychoactive Substances, Especially New Psychoactive Substances in a Group of Patients Hospitalized With Mental and Behavioural Disorders Due to the Use of Psychoactive Substances Diagnosis," *International Journal of Occupational Medicine and Environmental Health* 35 (2022): 485–495.

34. K. F. da Cunha, K. D. Oliveira, M. S. Cardoso, et al., "Prevalence of New Psychoactive Substances (NPS) in Brazil Based on Oral Fluid Analysis of Samples Collected at Electronic Music Festivals and Parties," *Drug and Alcohol Dependence* 227 (2021): 108962.

35. P. Heikman, M. Sundström, A. Pelander, and I. Ojanperä, "New Psychoactive Substances as Part of Polydrug Abuse Within Opioid Maintenance Treatment Revealed by Comprehensive High-Resolution Mass Spectrometric Urine Drug Screening," *Human Psychopharmacology* 31 (2016): 44–52.

36. A. Niebel, F. Pragst, F. Krumbiegel, and S. Hartwig, "Prevalence of Cathinones and Other New Psychoactive Substances in Hair of Parents and Children of Families With Known or Suspected Parental Abuse of Conventional Illegal Drugs," *Forensic Science International* 331 (2022): 111148.

37. *ESPAD Report 2019 — Results from the European School Survey Project on Alcohol and Other Drugs* (Lisbon, Portugal: European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2020) Accessed November 1, 2024. https://www.euda.europa.eu/publications/joint-publications/espad-report-2019_en.

38. I. Makarenko, A. Mazhnaya, R. Marcus, et al., "Concurrent Drug Injection During Opioid Agonist Treatment Among People Who Inject Drugs in Ukraine," *Journal of Substance Abuse Treatment* 87 (2018): 1–8.

39. M. Vogel, B. Knopfli, O. Schmid, et al., "Treatment or "High": Benzodiazepine use in Patients on Injectable Heroin or Oral Opioids," *Addictive Behaviors* 38 (2013): 2477–2484.

40. *Statistical Database, Pharmaceuticals* (Swedish National Board of Health and Welfare (Socialstyrelsen)) Accessed February 27, 2024. https://sdb.socialstyrelsen.se/if_lak/val_eng.aspx.

41. G. Høiseth, H. Andås, L. Bachs, and J. Mørland, "Impairment Due to Amphetamines and Benzodiazepines, Alone and in Combination," *Drug and Alcohol Dependence* 145 (2014): 174–179.

42. P. A. Zarkowski, A. R. Van-Den-Ende, and J. A. Groen, "Prevalence and Socioeconomic Factors in the Prescription of Concurrent Amphetamine and Alprazolam," *International Journal of Psychiatry in Medicine* 56 (2021): 116–127.

43. R. Sutherland, A. Peacock, E. Whittaker, et al., "New Psychoactive Substance Use Among Regular Psychostimulant Users in Australia, 2010–2015," *Drug and Alcohol Dependence* 161 (2016): 110–118.

44. C. V. Gine, I. F. Espinosa, and M. V. Vilamala, "New Psychoactive Substances as Adulterants of Controlled Drugs. A Worrying Phenomenon?" *Drug Testing and Analysis* 6 (2014): 819–824.

45. C. Hartley, 2nd, M. Bulloch, and S. R. Penzak, "Clinical Pharmacology of the Dietary Supplement Kratom (Mitragyna speciosa)," *Journal of Clinical Pharmacology* 62 (2022): 577–593.

46. A. Garcia-Romeu, D. J. Cox, K. E. Smith, K. E. Dunn, and R. R. Griffiths, "Kratom (Mitragyna Speciosa): User Demographics, Use Patterns, and Implications for the Opioid Epidemic," *Drug and Alcohol Dependence* 208 (2020): 107849.

47. F. Schifano, S. Chiappini, J. M. Corkery, and A. Guirguis, "Abuse of Prescription Drugs in the Context of Novel Psychoactive Substances (NPS): A Systematic Review," *Brain Sciences* 8 (2018): 8.

48. C. Stanciu, S. Ahmed, S. Gnanasegaram, et al., "Kratom as an Opioid Alternative: Harm, or Harm Reduction? A Systematic Review of Literature," *American Journal of Drug and Alcohol Abuse* 48 (2022): 509–528.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.