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ORIGINAL ARTICLE

The Correlation between NPS and Polysubstance Use in High-Risk Population: a Five-year Longitudinal Study in Taiwan

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Abstract

The emergence of new synthetic substances (NPS) leads to rapid changes in substance prevalence. Here urine analysis and questionnaires were employed to construct a landscape of substance abuse. 3,064 urine samples were randomly selected from suspected substance abusers (N = 6,335) from 2014 to 2018 in Taiwan. Demographic information was self-reported. Principal component analysis (PCA) were used to explore the substance pattern. The positive detection of NPS reached 19.6%. The highest links of polysubstance use were the use of phenethylamines with the co-use of amphetamines (aOR = 4.33), benzodiazepines (aOR = 2.09), and synthetic cathinones (aOR = 5.01) and the use of synthetic cathinones with the co-use of ketamine (aOR = 6.72) and benzodiazepines (aOR = 2.62). No evidence indicating an increase in the use of NPS/other substances as a replacement for traditional substances. The presence of polysubstance patterns may be due to similarities in the effects of the various substances or users undergoing a transition in their substance abuse patterns.

Keywords NPS · Polysubstance use · High risk population · Urinalysis · Demographic factors

Taiwan plays a major role in substance smuggling; (Lo, 2009; UNODC, 2020a) however, strict substance control measures have largely prevented substance abuse. Nonetheless,

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social issues related to traditional substance have seldom been addressed, and the emergence of a wide range of synthetic substances continually alters the usage landscape. (Das & Horton, 2019) In the 1990s, substance use expanded from opioids and (meth)amphetamine to barbital, sniffing glue, and flunitrazapine. Since that time, barbitals and sniffing glue have been replaced by ecstasy and even more so ketamine, particularly among young adults. (Liu et al., 2005) Since, 2005, ketamine has been one of the top three substances with amphetamines and opioids. This prompted amendments to the Narcotics Hazard Prevention Act 2009 dictating higher criminal charges for the use or possession of ketamine in amounts less than or equal to 5 g; however, the abuse of this substance remains high. Note that the surge in ketamine abuse occurred within a six-year period. Recently, synthetic substances, such as synthetic cathinones, are becoming mainstream in Taiwan despite a decrease of synthetic cathinones in the global substance profile. (Investigation Bureau, 2018; UNODC, 2020b) This discrepancy indicates that patterns of new psychoactive substances (NPS) vary from region to region, due to differences in lifestyle and/or social-cultural conditions. It is important to monitor these changes to maintain the effectiveness of substance control measures.

Self-reported substance use via interviews or questionnaires is a common approach to investigating substance prevalence. (Palamar & Acosta, 2015; Piro et al., 2019) Note however that the results can be skewed by the rapid emergence or disappearance of specific substances. Illicit substances with labels camouflaging them as normal products often contain multiple substances. (Chiang et al., 2019) In many cases, it is this misleading information on product packaging that makes substance users lack of awareness of the contents, leading to incorrect estimates of substance use in interviews and surveys. (Johnson & Fendrich, 2005; Piro et al., 2019) Accurate assessments can only be achieved when sensitive analytical instruments are used to analyse biological samples. Numerous studies have expounded the use of liquid chromatography-mass spectrometry (LC–MS) in the detection of substances in urine, blood, or seized materials; (Bertol et al., 2017; Chiang et al., 2019) however, there is little information about a survey of detecting numbers of traditional/emerging substances at the same time, and combining data both from substance abusers to provide a more realistic indication of the substance usage landscape.

Efforts to bridge this gap prompted a substance survey in Taiwan between 2014 and 2018. This included the collection of urine samples from high-risk populations (i.e., suspected substance abusers apprehended by law enforcement). Analysis focused on substances, including common substances and emerging substances recently. Demographic factors of the high-risk population were obtained from self-reported questionnaires. In the current study, we employed this substance survey, and information from abusers to unravel trends in substance abuse and corresponding demographic profiles.

Methods

Study design and participants

Specimens and demographic data were obtained under authorization from the Taiwan Food and Drug Administration (TFDA). Suspected substance abusers apprehended by law enforcement were considered a high-risk population. Urine samples were delivered to 14 local toxicology laboratories authorized by the TFDA for routine substance analysis, which included opioids, (meth)amphetamines, cocaine, cannabis, and ketamine. To obtain a representative sample of the high-risk population, we employed a systematic sampling method involving the selection of urine samples with the last two digits 11 and 61 between August 2014 to July 2018. The samples were further analyzed for polysubstance use by LC–MS/MS in this study.

Measures for outcome indicators

All urine samples from substance abusers were stored at -20℃ until analysis and prepared as described in the supplementary (appendix p1). The 66 substances were detected including five common substances (i.e., opioids, (meth)amphetamine derivatives, ketamine, cocaine, and cannabis). The remaining substances were selected according to their prevalence in seizures by law enforcement during the 10 years prior to 2014. Note that we also analyzed substances that had been detected in countries other than in Taiwan as well as derivatives of substances recently seized in Taiwan (appendix p2-4). In LC–MS/MS analysis, commercial artificial urine was used as a blank sample to establish calibration curves (nine levels). Substance levels were quantified via interpolation from calibration curves using a ratio of the peak area of a substance to that of internal standards. The correlation coefficients of linear regression lines were > 0.995 in all cases (appendix p2-4). Two concentrations (5 and 50 ng mL^{-1}) for control samples were respectively selected as low- and high-concentrations. Acceptable accuracy for a positive control result was ± 20%. Substance concentrations greater than the limit of detection were reported as positive results. Samples were reported positive when the relative retention time between each substance and its corresponding reference material was < 2%.

Measures for independent variables

Valid questionnaires were those in which all questions were answered. A total of 3,064 urine samples and valid questionnaires were collected from high-risk individuals between August 2014 and July 2018 (805 in 2014, 504 in 2015, 487 in 2016, 607 in 2017, and 660 in 2018). Note that we excluded 3,271 invalid questionnaires (415 in 2014, 834 in 2015, 678 in 2016, 583 in 2017, and 761 in 2018). The questionnaire was divided into two parts. The first part was self-completed by the individual, including year of birth, age, gender, highest level of education (illiterate, elementary school, junior high school, senior high school, university, or graduate school), occupation (government employee, student, blue-collar workers, farmer, service industry, merchant, unemployed, retiree, or homemaker), frequency of being arrested (first offender or recidivist), and history of methadone treatment (yes or no). The second part included the date, city, and place of arrest (including random checkpoint on road, nightclub entertainment, accommodation), and the means of investigation (routine spot-check, extended or due-to-case investigation, self-confession by substance abuser, or acting on tip-off).

Statistical analysis

Statistical analysis exploring patterns in substance use was performed in four stages. First, we calculated the positive detection rates of all substances and their metabolites between 2014 and 2018 and plotted the results in a line graph. Note that a similar process was also conducted for NPS only. Second, all compounds were categorized into eight substance types (amphetamine derivatives (AMP): amphetamine, methamphetamine, MDA, MDMA, MDEA, and PMA; opioids (OPI): morphine, codeine, 6-acetylmorphine, 6-acetylcodeine, heroin, methadone, oxycodone, fentanyl, and U-47700; cannabis (CB): THCA; cocaine (COC): cocaine; ketamine (KET): ketamine; NPS, benzodiazepines (BZD) and other-type) (appendix p2-4). Raw concentration data were respectively recoded into scores of 1, 2, 3, and 4 according to their original distributions of 25th, 50th, 75th, and 100th percentiles, whereupon we individually assessed the sums of the scores of the eight substance types (appendix p5-6). Principal component analysis (PCA) was used to re-organize the data of the eight substance types into three principal components (PC1, PC2, and PC3) with the largest source of variation and data were presented into 3-D scatter plots. Note that PCs are linear combinations of initial variable S with coefficients referred to as loadings to be solves using eigenvalues of the covariance matrix. Third, multiple logistic regression was used to identify risk factors by calculating the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) pertaining to the relationship between demographic information and the various substance types. Fourth, regression models were constructed to assess patterns in polysubstance use. Statistical significance was defined as a P-value < 0.05, whereas $0.05 < P$-value < 0.1 was considered a borderline significant trend. Furthermore, Bonferroni correction for multiple testing was used and the logistic regression results which had reached the adjusted significant level ($\alpha = 0.05/$ number of testing, such as $\alpha = 0.05/5$ in Table 1 and $\alpha = 0.05/3$ in Table 2) were bolded. All statistical analysis was conducted using SPSS® Subscription (IBM Corporation., Armonk, NY, USA). Charts were produced by SigmaPlot 14.0, and the optimal visual angle was determined using R-3.6.2 with 'rgl' package.

Results

Positive rates and five-year trends of illicit substance

Between 1 August 2014 and 31 July 2018, 6,335 urine samples collected in Taiwan were sent to us by local toxicology laboratories. Out of these samples, 3,271 cases were excluded because the corresponding self-reported questionnaires were incomplete. A total of 3,064 samples and questionnaires were deemed valid for analysis. As shown in Fig. 1, at least 1 substance was detected in 2,863 of the samples and up to 16 substances were detected in a single sample. The substances were categorized into eight types. Concentrations and positive detection rates varied widely among substance types and individuals. Median concentrations as follows: 5.9–2,798.0 ng mL^{-1} for AMP, 10.0–742.7 ng mL^{-1} for OPI, 9.0–10.9 ng mL^{-1} for CB, 2.4–2.5 ng mL^{-1} for COC, 260.0–428.9 ng mL^{-1} for KET, 1.8–2,804.9 ng mL^{-1} for NPS, 5.5–234.1 ng mL^{-1} for BZD, and 2.5–93.4 ng mL^{-1} for other-type (appendix p7-8). Figure 2 (A)-(C) respectively illustrate the top 11 positive detection rates of all substances, NPS alone, and the quantity of each substance as a percentage of all substances seized by law enforcement in Taiwan. Among the 2,863 samples, the lowest positive detection rates were cannabis (n = 21, 0.73%) and cocaine (n = 24, 0.84%), and the positive detection rates for NPS were between 7.4% and 19.6%. We also observed subtle changes on a smaller scale. Positive detection rates for mephedrone (6.77%), 5-MeO-DiPT (4.09%), PMMA (2.20%), and 2C-B (1.57%) reached their peak in 2017. Note that the positive detection rates 4-MEAPP and 4-chloroethcathinone (added in 2018) were 2.36% and 1.73%, respectively. Thus, they were ranked as the second and third most common substances

Table 1 Polysubstance use of NPS[a] with traditional substance or between NPS based on binary logistic regression model

Variables[b, c]	N	PEA ± aOR[d] (95%CI)	PZ ± aOR[d] (95%CI)	sCAT ± aOR[d] (95%CI)	sCB ± aOR[d] (95%CI)	TRY ± aOR[d] (95%CI)
Traditional substance[e]						
AMP ±	2190	**4.33 (1.91–9.81)** ***	1.09 (0.60–1.99)	0.82 (0.61–1.12)	2.38 (0.23–24.28)	1.12 (0.34–3.69)
OPI ±	828	0.75 (0.40–1.41)	0.91 (0.53–1.58)	0.79 (0.54–1.18)	0.45 (0.07–2.79)	1.34 (0.45–3.96)
KET ±	1262	1.40 (0.77–2.53)	0.74 (0.42–1.31)	**6.72 (4.58–9.88)** ***	1.03 (0.17–6.15)	0.41 (0.13–1.33)
OTHER ±	292	1.92 (0.93–3.95)	0.93 (0.44–1.96)	0.92 (0.54–1.56)	2.40 (0.37–15.53)	2.56 (0.82–8.02)
BZD ±	513	**2.09 (1.22–3.60)****	**2.26 (1.37–3.72)****	**2.64 (1.93–3.62)*****	1.07 (0.16–7.12)	0.73 (0.22–2.38)
NPS[a]						
PEA ±	20	-	1.31 (0.45–3.78)	**4.92 (2.71–8.92)** ***	2.48 (0.11–57.46)	4.48 (1.19–16.93) *[f]
PZ ±	77	1.18 (0.40–3.45)	-	**3.36 (1.79–6.30)** ***	8.20 (1.30–51.61) *[f]	**6.96 (1.91–25.39)** **[f]
sCAT ±	248	**5.01 (2.72–9.23)** ***	**3.22 (1.71–6.10)** ***	-	0.42 (0.01–12.14)	**8.57 (2.57–28.51)** ***[f]
sCB ±	8	3.29 (0.30–36.05)	8.33 (1.49–46.45) *[f]	1.07 (0.12–9.97)	-	11.67 (1.14–118.99) *[f]
TRY ±	70	3.88 (0.98–15.43) [# f]	**5.69 (1.63–19.85)****[f]	**6.68 (2.12–21.07)****[f]	12.44 (0.74–210.62)	-
Gender						
Male	2390	reference	reference	reference	reference	reference
Female	474	0.85 (0.44–1.65)	1.32 (0.74–2.36)	**1.66 (1.18–2.33)** **	1.24 (0.14–10.69)	1.00 (0.31–3.25)
Age						
< 17	82	1.54 (0.29–8.16)	0.29 (0.04–2.35)	0.96 (0.38–2.39)	-	11.07 (1.22–100.69) *[f]
18–34	1553	1.61 (0.69–3.76)	0.64 (0.34–1.21)	1.18 (0.71–1.96)	0.19 (0.03–1.15)	2.05 (0.38–11.09)
35–44	820	0.67 (0.25–1.81)	0.67 (0.34–1.33)	0.98 (0.56–1.73)	0.30 (0.05–1.90)	1.81 (0.31–10.58)
> 45	409	reference	reference	reference	reference	reference
Mean of investigation						
Routine spot-check	1839	reference	reference	reference	reference	reference
Extended or due-to-case investigation	437	0.27 (0.08–0.88)*	1.02 (0.51–2.02)	0.86 (0.55–1.36)	-	0.28 (0.04–2.16)
Self-confession by substance user	415	1.11 (0.56–2.20)	1.50 (0.82–2.76)	1.13 (0.75–1.69)	0.55 (0.06–4.77)	0.20 (0.03–1.58)

Table 1 (continued)

Variables[b, c]	N	PEA ± aOR[d] (95%CI)	PZ ± aOR[d] (95%CI)	sCAT ± aOR[d] (95%CI)	sCB ± aOR[d] (95%CI)	TRY ± aOR[d] (95%CI)
Acting on tip-off	173	1.06 (0.39–2.83)	0.81 (0.28–2.34)	0.80 (0.43–1.48)	-	0.65 (0.08–5.34)

[a] NPS are grouped as aminoindanes (AI), phencyclidine-type substances (PCP), phenethylamines (PEA), piperazines (PZ), plant-based substances (PLANT), synthetic cannabinoids (sCB), synthetic cathinones (sCAT), tryptamines (TRY), and other substances (NPS_OTHER). The substance list in this study include PEA (PMMA, 2C-B, 2C-C, 2C-I, PMEA, 4-chloroamphetamine, and 4-chloromethamphetamine), PZ (zolpidem, phenazepam, and TFMPP), sCAT (mephedrone, methylone, MDPV, butylone, ethylone, 4-methylethcathinone, 4-chloromethcathinone, DMBDB, 4-MEAPP, 4-chloroethcathinone, and α-PVP), sCB (JWH-250 and XLR-11), TRY (5-MeO-MiPT and 5-MeO-DiPT) only

[b] Subject is marked as "substance use" if at least one substance in specific category is positively detected

[c] Due to results of Table S3, demographic factors with significant coefficient (gender, age, and means of investigation) are introduced in this model

[d] Odds ratio with 95% confidence interval adjusted for all demographic factors (variables)

[e] The substance type "COC" and "CB" are excluded from this model because of small sample size

[f] Although the coefficient differed from 0 significantly, its 95% confidence interval is over-ranged, indicating low accuracy resulted from insufficient positively detected samples or multicollinearity between variables; therefore, the data is not considered significance

[#] P-value < 0·06

*P-value < 0·05

**P-value < 0·01

*** P-value < 0·001

Table 2 Association between demographic factors of study subjects and COC, KET, or BZD use[a] based on binary logistic regression model

Variable	N	COC ±		KET ±		BZD ±	
		OR (95%CI)	aOR (95%CI)[b]	OR (95%CI)	aOR (95%CI)[b]	OR (95%CI)	aOR (95%CI)[b]
Gender							
Male	2390	reference	reference	reference	reference	reference	reference
Female	473	0.95 (0.39–2.27)	1.14 (0.45–2.91)	1.10 (0.90–1.34)	0.91 (0.73–1.14)	1.34 (1.05–1.71) *	1.34 (1.03–1.74) *
Occupation							
Government employee or student	144	-	-	**2.39 (1.68–3.39)** ***	1.30 (0.86–1.96)	0.65 (0.38–1.12)	0.72 (0.39–1.31)
Blue-collar worker or farmer	1197	reference	reference	reference	reference	reference	reference
Service industry or merchant	622	1.08 (0.48–2.47)	1.13 (0.46–2.75)	**1.45 (1.20–1.77)** ***	1.10 (0.89–1.38)	1.19 (0.92–1.53)	1.16 (0.88–1.53)
Unemployed, retiree or homemaker	900	1.08 (0.52–2.26)	1.15 (0.54–2.48)	**1.37 (1.15–1.63)** ***	**1.35 (1.11–1.63)** **	**1.40 (1.12–1.75)** **	1.30 (1.03–1.64) *
Education							
Illiterate or elementary school	79	1.86 (0.41–8.38)	1.61 (0.34–7.55)	0.87 (0.53–1.41)	1.19 (0.72–1.99)	0.99 (0.55–1.77)	0.83 (0.46–1.52)
Junior high school	943	reference	reference	reference	reference	reference	reference
Senior high school	1657	0.96 (0.48–1.92)	0.93 (0.44–1.93)	**1.62 (1.38–1.91)** ***	1.26 (1.05–1.50) *	0.87 (0.71–1.07)	0.92 (0.74–1.14)
University or graduate school	184	0.39 (0.05–3.01)	0.39 (0.05–3.11)	**2.20 (1.60–3.02)** ***	1.31 (0.92–1.85)	0.95 (0.64–1.43)	1.09 (0.70–1.67)
Age							
< 17	82	-	-	**4.15 (2.54–6.79)** ***	**3.35 (1.91–5.86)** ***	0.35 (0.16–0.76)	0.43 (0.19–1.00) *
18–34	1552	0.55 (0.26–1.17)	0.49 (0.21–1.14)	**4.00 (3.12–5.12)** ***	**3.24 (2.49–4.23)** ***	0.68 (0.53–0.89)	0.70 (0.53–0.94) *
35–44	820	0.34 (0.13–0.91) *	0.32 (0.12–0.88) *	1.27 (0.97–1.67)	1.16 (0.88–1.54)	0.67 (0.50–0.90)	**0.67 (0.50–0.91)** **
> 45	409	reference	reference	reference	reference	reference	reference
Place of arrest							
Road (random checkpoint)	1485	reference	reference	reference	reference	reference	reference
Nightclub entertainment	189	0.71 (0.17–3.05)	0.68 (0.16–3.01)	1.42 (1.05–1.93)*	1.13 (0.82–1.56)	0.86 (0.56–1.31)	0.85 (0.55–1.32)
Party venue or accommodation	1025	0.66 (0.31–1.39)	0.98 (0.44–2.18)	**0.75 (0.64–0.88)** ***	0.97 (0.80–1.17)	1.28 (1.04–1.56) *	1.14 (0.90–1.43)
Detention center or the others	164	1.66 (0.57–4.89)	3.06 (0.83–11.22)	0.85 (0.61–1.17)	1.10 (0.76–1.60)	0.80 (0.51–1.27)	0.78 (0.48–1.29)
Mean of investigation							
Routine spot-check	1838	reference	reference	reference	reference	reference	reference

Table 2 (continued)

Variable	N	COC ±		KET ±		BZD ±	
		OR (95%CI)	aOR (95%CI)[b]	OR (95%CI)	aOR (95%CI)[b]	OR (95%CI)	aOR (95%CI)[b]
Extended or due-to-case investigation	437	0.14 (0.02–1.02) #	0.11 (0.01–0.87) *	**0.51 (0.41–0.63)** ***	**0.54 (0.42–0.70)** ***	1.30 (1.00–1.69) *	1.20 (0.89–1.60)
Self-confession by substance user	415	0.89 (0.37–2.14)	0.58 (0.20–1.66)	0.71 (0.57–0.88) **	0.77 (0.60–0.99) *	0.97 (0.73–1.29)	0.98 (0.72–1.34)
Acting on tip-off	173	0.35 (0.05–2.59)	0.33 (0.04–2.60)	0.75 (0.55–1.03)	0.82 (0.58–1.17)	1.42 (0.97–2.07)	1.23 (0.83–1.84)
Frequency of being arrested							
First offender	1754	reference	reference	reference	reference	reference	reference
Recidivist	1109	0.56 (0.27–1.16)	0.46 (0.22–0.99) *	**0.55 (0.47–0.64)** ***	**0.74 (0.62–0.87)** ***	1.14 (0.94–1.39)	1.04 (0.84–1.27)

[a] Subject is marked as "substance use" if at least one substance in specific category is positively detected

[b] Odds ratio with 95% confidence interval adjusted for all demographic factors (variables)

P-value < 0·06

* P-value < 0·05

** P-value < 0·01

*** P-value < 0·001

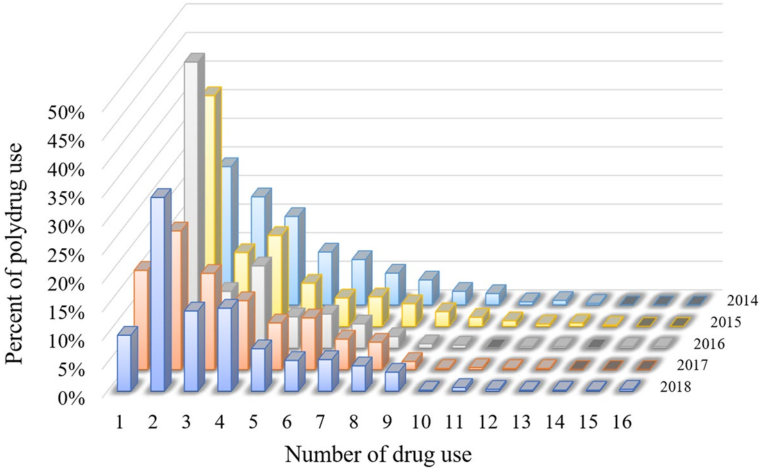

Fig. 1 The polydrug use in the high-risk population within 2014–2018

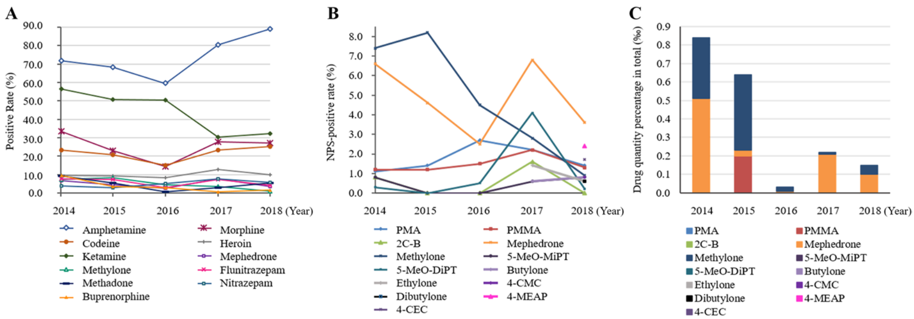

Fig. 2 The positive rates of drugs. (**A**) The top 11 drugs; (**B**) NPS in this study; (**C**) The quantity percentage of drug from (**B**) seized by border/law enforcement force in Taiwan

in 2018 and eighth and tenth in terms of the total cases of NPS over the five-year study period. Some substances (most of which were NPS) were found in fewer than 10 samples, whereas other substances widely used in other regions (e.g., as fentanyl, oxycodone, and 2C-C) were not detected at all. Note that 19 of the 22 substances that were rarely detected or not detected were NPS.

As shown in Fig. 3 (A) to (F), the variance explained by PC 1, PC 2, and PC 3 was 55.68%, 18.30%, and 10.22%, respectively. After data recasting, PC 1 was interpreted as OPI use (i.e., the frequency of OPI use as well as an estimation for its dependency). PC 2 was interpreted as the amount of KET (towards positive direction) or AMP use (towards negative direction), which implies that there was an inverse relationship between KET and AMP dependence. PC 3 was used as a measurement of polysubstance use (mainly AMP, KET, NPS, and BZD). The loadings of S(CB) and S(COC) were negligible in PCs; therefore, the positions of both were very close to the origin within a 3-D space.

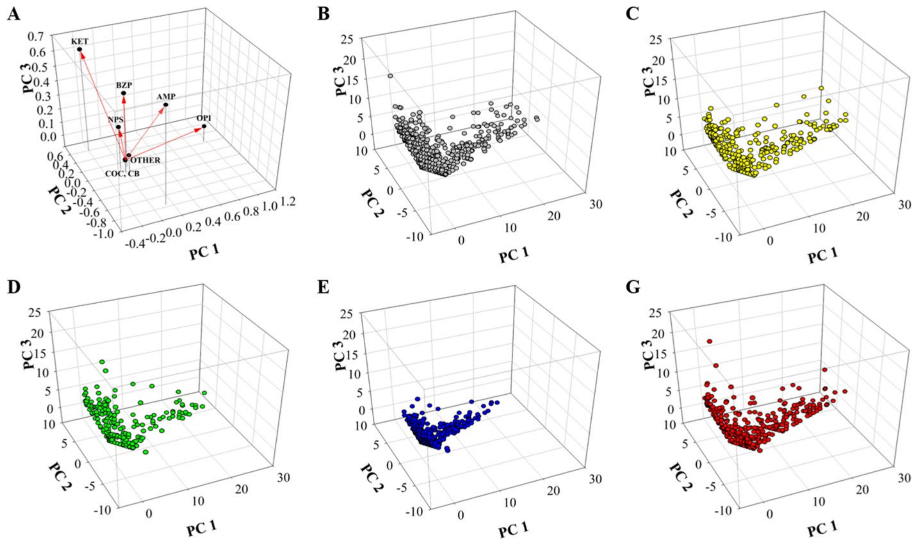

Fig. 3 The 3-D scatter graph for five-year distribution of substance use among high-risk population based on PCA. (**A**) Loading plot of eight drug types, (**B**) 2014, (**C**) 2015, (**D**) 2016, (**E**) 2017, and (**F**) 2018

Polysubstance use of NPS

Table 1 lists the correlations of NPS use with that if traditional substances and other NPS after controlling for possible confounders. NPS were categorized as aminoindanes (AI), phencyclidine-type substances (PCP), phenethylamines (PEA), piperazines (PZ), plant-based substances (PLANT), synthetic cannabinoids (sCB), synthetic cathinones (sCAT), tryptamines (TRY), and other substances (NPS_OTHER), in accordance with the definitions by The United Nations Office on Drugs and Crime. PEA was commonly used with AMP (aOR 4.33), BZD (aOR 2.09), or sCAT (aOR 5.01). PEA use was associated with means of investigation (aOR 0.27 for extended or due-to-case investigation). PZ was commonly used with BZD (aOR 2.26) or sCAT (aOR 3.22). sCAT was commonly used with KET (aOR 6.72), BZD (aOR 2.62), PEA (aOR 4.92), or PZ (aOR 3.36).

Demographic factors for substance use

AMP use was associated with occupation (aOR 0.49 for government employee or student; aOR 0.81 for unemployed, retiree, or homemaker), education (aOR 0.56 for illiterate or elementary school), age (aOR 0.53 for subjects aged 17 or under; aOR 0.52 for subjects aged 18–34), place of arrest (aOR 0.70 for nightclub entertainment), and frequency of being arrested (aOR 1.48 for recidivist). OPI use was associated with gender (aOR 1.42 for female), occupation (aOR 0.73 for service industry or merchant), age (aOR 0.22 for subjects aged 17 or under; aOR 0.37 for subjects aged 18–34), place of arrest (aOR 0.63 for detention center or the others), means of investigation (aOR 1.42 for extended or due-to-case investigation), and frequency of being arrested (aOR 1.35 for recidivist). These results are shown in appendix p9-10. We found no significant associations with the use of CB, due perhaps to its low positive detection rate (0.73%). As in Table 2, we also observed a small positive detection rate for COC (0.84%); however, three factors were associated with COC use: age (aOR 0.32 for subjects aged 35–44 relative to subjects aged 45 or over), means of investigation (aOR 0.11 for extended or due-to-case investigation relative to spot-check), and frequency of being arrested (aOR 0.46 for recidivist relative to first offender). KET use was associated with occupation (aOR 1.35 for unemployed, retiree, or homemaker), education (aOR 1.26 for senior high), age (aOR 3.35 for subjects aged 17 or under; aOR 3.24 for subjects aged 18–34), means of investigation (aOR 0.54 for extended or due-to-case investigation; aOR 0.77 for self-confession), and frequency of being arrested (aOR 0.74 for recidivist). BZD use was associated with gender (aOR 1.34 for female versus male), occupation (aOR 1.34 for unemployed, retiree, or homemaker), and age (aOR 0.43 for subjects aged 17 or under, aOR 0.70 for subjects aged 18–34, and aOR 0.67 for subjects aged 34–55).

Screening for substances identified as NPS began later than that for other substances. Thus, we classified two groups were classified as follows: NPS 2014 ~, NPS 2017 ~, NPS 2018 ~, other-type 2014 ~, or other-type 2017 ~ (appendix p11-14). NPS 2014 ~ was associated with gender (aOR 1.68 for female), age (aOR 1.47 for subjects aged 18–34), and means of investigation (aOR 0.63 for extended or due-to-case investigation). Other-type 2014 ~ was associated with occupation (aOR 1.42 for unemployed, retiree, or homemaker), age (aOR 0.60 for subjects aged 18–34), place of arrest (aOR 0.49 for detention center or others), and means of investigation (aOR 1.70 for extended or due-to-case investigation; aOR 1.56 for self-confession). Other-type 2018 ~ was associated with education (aOR 0.48 for senior high) and place of arrest (aOR 4.36 for nightclub entertainment) (appendix p13-14).

Discussion

National surveillance is used to track substance prevalence in real-time in high-risk populations. This study used LC–MS/MS to analyze urine samples to confirm the types of substances that were being abused. The limits of detection (LODs), ranging from 0.05 to 0.5 ng mL^{-1}, were established as the cut-off for the analytes. The dilute-and-shoot method employed in this study demonstrated LODs that were compatible with other dilute-and-shoot systems utilizing LC–MS/MS. (Alcántara-Durán et al., 2018; Dahlin et al., 2019; Fan et al., 2021; Kwok et al., 2016; Lawson et al., 2016; Malaca et al., 2019) (appendix p15) Note that this was the first study to analyze such results with the context of self-reported questionnaires. Combining the data provided a complete profile of a substance survey for control policy and offered effective strategies for public health authorities. Our findings revealed that the substances with the highest positive detection rates during the 5-year study period were (meth)amphetamine, ketamine, and opioids. These findings are consistent with the substance quantities seized in Taiwan between 2006 and 2018 (appendix p16-21). (TFDA annual report, 2021) Note the 20 substances most commonly detected in urine analysis were also the 20 most commonly used (in terms of quantity). Among the less common substances (ranked below position 20), the positive detection rates in urine and the quantities seized remained low and stable between 2014 and 2018. We found no evidence of an abrupt increase in the use of substances during the study period. However, several NPS have emerged recently in Taiwan. It should be noted that ketamine (also categorized as an NPS) has dominated the Taiwanese market for decades. Based on previous patterns in ketamine use, we monitored other NPS, and particularly those seized in Taiwan between 2009 and 2013. The urinary positive detection rate of NPS was between 7.4 to 19.6% (not as high as those of ketamine), which is similar to the rates reported in other countries. (EMCDDA, 2020; Peacock et al., 2019; UNODC, 2020b) We were alarmed to discover a surge in the seized quantities of various synthetic cathinones since 2010. Since 2013, mephedrone has been the second most prevalent NPS behind ketamine. Based on a review of the literature and other substance warning systems, we also monitored 16 substances identified as derivatives, metabolites, or substances which have emerged in other countries but have yet to arrive in Taiwan (e.g., 4-chloromethamphetamine, dibutylone, 5-MeO-DiPT, U47700, oxycodone, and JWH-018). The near absence of synthetic opioids in urinary analysis corresponds to the very low quantities seized by law enforcement. (TFDA annual report, 2021) The results may be due to a geographical and cultural disparity of abused substances. We observed significant increases in the prevalence of derivatives from amphetamine and synthetic cathinones, the development of which was likely prompted by a need to circumvent regulations. Analysis of the corresponding metabolites, which are often stable in the human body, is an effective approach to tracing substance abuse in situations where the active substance is quickly converted. However, there is a lack of relevant information pertaining to the plethora of emerging substances. The regular updating of substance lists in real-time is crucial to the effective monitoring of changes in substance prevalence. (EMCDDA, 2020; Peacock et al., 2019).

AMP or OPI were used especially for those over the age of 45. This is supported by a 2014 national survey in Taiwan, which reported that abusers of traditional substances only (i.e., heroin, (meth)amphetamine, or methadone) were older than users of club substances only (e.g., ketamine, GHB, or mephedrone). Similar observations have been reported in western countries. (Arndt et al., 2011; Maree et al., 2016) Those who initiate substance use and become addicted at a younger age face an elevated risk of social problems when they are older (e.g., social isolation, lack support, and poverty) and health issues (e.g., depression, cognitive impairment, chronic pain, and ill-health conditions). These difficulties increase the probability of exposure to illicit substances later in life, which renders them vulnerable to substance dependency. (Gossop & Moos, 2008) In contrast, KET abuse were mostly first-time offenders and comprised a younger population, with the majority aged less than 17 or between 18 and 34 years old. It has been argued that due to peer pressure, ketamine use in adolescents is associated with having friends who use ketamine. (Chang et al., 2019; Cole et al., 2023; Lee et al., 2012; Muetzelfeldt et al., 2008) Accessibility to ketamine as well as the lower expectations of negative outcomes and unstable emotions of adolescents may play important roles in early-onset substance use. (Evans, 2023; Lee et al., 2012; Robinson, 2014).

The rate of positive detection for cannabis was very low (0.73%), and did not correspond to the quantities seized in Taiwan. This can perhaps be attributed to differences in sampling method and study population. In this study, subjects were drawn from a pool of suspected substance abusers arrested by law enforcement; however, it is possible that cannabis users are younger, without criminal records, and/or having few encounters with the law enforcement. (Liao et al., 2017) Due to the legalization of cannabis in many areas, many young people underestimate the damage caused by cannabis abuse (Jeffers et al., 2021; Knaappila et al., 2020; Legleye et al., 2012). Furthermore, cannabis is regarded by many researchers as a gateway substance. (Hall & Lynskey, 2005) It is important therefore to recruit subjects from schools or outpatient chemical dependency services or to use non-probability sampling (e.g., snowball or judgmental) to estimate the prevalence of cannabis use. There is a pressing need to clarify these results because other variables have not been greatly discussed in previous studies. It is also possible that some of the factors for which we were unable to control (e.g., socioeconomic status and habits of law enforcement) affected such variables and thus made them difficult to extract and identify. (Jeffers et al., 2021) A French study (Legleye et al., 2012) indicated that adolescents from affluent families were more prone to experimenting with cannabis, using it at low levels and with less frequency or problematic use. Similarly, a Finnish study (Knaappila et al., 2020) found that the prevalence of adolescent cannabis use significantly increased due to socioeconomic adversities, including parental unemployment in the past year, low parental education, and not living with both parents. Additionally, a US national study (Jeffers et al., 2021) reported that higher-frequency cannabis use was more common among young individuals and racial minorities with low socioeconomic status. These socioeconomic disparities contribute to increased individual suffering levels and place a heavy burden on public health and economy. (Koskinen S & Nykyiset, 2007; Legleye et al., 2012) Apart from socioeconomic factors, the practices of law enforcement also play a role. In Canada, law enforcement is allowed to use roadside oral fluid drug screeners to address cannabis impaired driving, which is a serious public issue requiring immediate action and strengthened legislation to ensure social safety. (McLellan et al., 2016) Adolescent substance users are a challenging population to engage with. (Liao et al., 2017) Law enforcement is a significant factor in identifying adolescent substance abuse and influencing the environment to reduce substance use and related crime through drug-specific interventions, such as drug policies and law enforcement efforts. (El-Khatib et al., 2021) The number of law enforcement raids and the duration of interventions have been shown to significantly suppress levels of drug dealing and related crime in targeted areas and their surroundings. However, the effects tend to diminish significantly when interventions are withdrawn. (Cohen, 2003).

PCA results revealed that subjects who used KET more tended to use AMP less. Additionally, OPI users (mainly heroin) were almost not to use KET, AMP, NPS, or BZD. In previous studies conducted in Taiwan, the demographics of subjects and their reason for using club substances (e.g., ketamine, cannabis, or ecstasy) differed from the factors motivating the use of traditional substances (e.g., (meth)amphetamine and heroin). (Chen et al., 2017) Ketamine and (meth)amphetamine both intensify the efficiency of synaptic transmission, leading to psychosis-like behaviors, and in animal testing, ketamine was shown to function faster and more efficiently than did amphetamine. (Kessal et al., 2005) Due to the similar effects of KET and AMP, substance users appear to choose only one, rather than taking them simultaneously. For example, party participants prefer KET for its rapid onset. (Cole et al., 2016; Green et al., 2011) This explains the antagonistic relationship between AMP usage and KET usage in the PCA results. In this study, OPI was not used in conjunction with other substances, however, this is inconsistent with results in the US, where (meth)amphetamine is often co-injected with heroin. (Farrell et al., 2019) In 2015, 50% of a sample in Colorado had either co-injected or injected separate substances in the previous 12 months. There are two possible reasons for this disparity: (1) the specific mechanism(s) of opioids and (2) the unique pathway to opioid dependence. The pain manipulation of opioids appears to be activated through opiate receptors, which are also responsible for powerful opioid dependence. (Bodnar & Klein, 2005) Given that the loadings from PCA partly expressed substance dependence, the non-coplanarity of the loading of OPI with the other substances may indicate a difference between OPI and other substances in terms of the effect (mechanism) and the means by which dependence develops. Growing evidence has indicated that the use of prescribed opioids often leads to heroin abuse and may explain the opioid epidemic in the US. (Carlson et al., 2016) Unlike ketamine, MDMA, and (meth) amphetamine (used primarily for recreation), substances for medical purposes (e.g., as painkillers) often lead to opioid abuse and/or addiction. (Volkow & McLellan, 2016; Zhao et al., 2019) Nonetheless, we did not observe this situation in the current study, due perhaps to the very low or zero positive detection rates for prescribed opioids. Note that higher concentrations of substances and metabolites in urine correspond to more intense and/or more frequent substance use, perhaps implying a relative high level of substance dependence. (Naranjo & Busto, 1989) Our PCA results revealed the quantity of substances being used, annual distribution patterns, and the dependence levels for specific substance types. Most of the substance use was evenly distributed among OPI, AMP, and KET, which indicates that these substances may be associated with relatively severe dependence. Pan et al. reported that recidivism within 3 years of quitting was 33.85% for ketamine and 39.52% for other substances. (Pan et al., 2021) It appears that governmental agencies should consider continuous monitoring for populations with a history of reverting to substance use.

Our analysis revealed that unlike ketamine, which is generally in the form of a tablet, NPS (containing mephedrone and methylone with nitrazepam and nimetazepam) are often disguised as coffee/milk tea bags, beverage powder, snacks, or famous Taiwanese pastries. (Ministry of Justice Taiwan, 2020) Substance dealers pitch these products using terms, such as coffee or tea, to make them more attractive to substance-naïve people. This practice is frequently used for synthetic cannabinoids and phenethylamines. (Madras, 2017) The deliberate misbranding of substance mixtures means that many individuals are unconsciously and unintentionally consuming multiple substances at one time, and are not aware what they have actually used. Only analytical instruments can provide an accurate understanding of polysubstance use. Our PCA results revealed that the co-use of PEA-AMP, PEA-sCAT, KET-sCAT, and BZD-sCAT was very common in our high-risk population. This is consistent with previous reports conducted in Taiwan detailing the use of NPS (sCAT and PEA), wherein KET and AMP were the most common ingredients in substance mixture packs. Note that adulterated BZD and LSD have also been reported. (Ministry of Justice Taiwan, 2020; Yang et al., 2020) The co-use of NPS and traditional substances has also been reported in many studies, wherein most of the individuals who abused NPS had also tried traditional substances. (Dal Farra et al., 2022; Higgins et al., 2021; Kurcevic & Lines, 2020) In other words, there appears to be a connection between NPS and traditional substances and polysubstance use. (Palamar & Acosta, 2015) Previous studies have reported that sCAT use could be attributed to its use in adulterating common party substances, such as ecstasy. (Oliver et al., 2018) Considering that PEA and sCAT are major components in many of the substance packs seized in Taiwan, the heterogenous pattern of polysubstance use may be due to the inclination of subjects to use a combination of substances to achieve specific effects. Similarities in the chemical structures of substances often results in similar effects and efficacy, which means that they are treated as interchangeable. For example, PEA has a structure and mechanism similar to those of AMP and sCAT (so-called beta-keto amphetamines), while acts on the monoamine neurotransmitter system by enlarging presynaptic release and hampering re-uptake. (German et al., 2014) Likewise, the chemical structures of PZ and BZD are similar, such that PZ also generates antidepressant and antipsychotic effects via the modulation of GABAergic and serotoninergic activity. (Brito et al., 2019) In fact, many NPS that mimic the psychoactive effects of traditional substances are more accessible than traditional substances and cost significantly less. (Davey et al., 2012) This may partially explain the frequent co-use of PEA-AMP, PEA-sCAT, or PZ-BZD. Note that the demographic characteristics of users, including gender, occupation, and education are discussed in (appendix p22-23).

The project has been carried out in collaboration with TFDA since 2013. The data has been regularly shared with the authorities to enhance the monitoring of both traditional substance/NPS abuse and substance prevalence on an annual basis. Through the analysis of emerging NPS and multiple updates to the list between 2013 and 2018, valuable information has been uncovered. This information, combined with data from various sources such as seizures at borders, law enforcement agencies, and contributions from different ministries, has collectively prompted the Taiwan government to implement further official measures in response. To strengthen substance control, the Taiwan government has launched various inter-ministerial efforts. For example, in 2013, TFDA introduced the Regulation on Reporting and Rewards for Drug Abuse. (Taiwan Food and Drug Administration, 2013) In 2015, the Ministry of Justice implemented the Anti-Drug Mobilization Policy. (Ministry of Justice Taiwan, 2015) Additionally, the Ministry of Justice has developed the New Generation Anti-Drug Strategy, while the Ministry of Health and Welfare has established the Medical Surveillance Mechanism for Emerging Illicit Drug Use. (Ministry of Health & Welfare, 2021) Furthermore, in 2020, the Executive Yuan introduced the New Generation Anti-Drug Strategy (Anti-Drug 2.0). (Ministry of Justice Taiwan, 2020) These initiatives represent direct or horizontal collaborations between Taiwan government ministries and councils, working collectively to promote substance prevention and curb the proliferation of substances.

This study has a number of limitations, which should be considered in the evaluation of our results. First, this study focused exclusively on a high-risk population, which prevented inclusion of specific populations of interest (e.g., cannabis users). These omissions may have led to incomplete results, an underestimation of the prevalence, or the skewing of substance use patterns. Second, this study focused on substance use in Taiwan, such that the structure/pattern of substance abuse may have been affected by the availability and legal status of substances, which can vary considerably among regions. Thus, our findings are not necessarily generalizable to all populations. Another limitation was the questionnaire used in this study, which did not address potential confounders, such as lifetime substance use, alcohol/cigarette use, sexual orientation, cognitive status, or economic status. Thus, some of the factors that were correlated with substance use may appear perplexing or invalid. Finally, it is very likely that we were unable to detect the latest NPS smuggled into Taiwan, due to the rapid proliferation of new compounds. Future research in public health will require constant revisions and continuous updating.

In conclusion, we observed slight changes in the prevalence and substance abuse patterns over the five-year study period. The positive detection rates of NPS in this pollution ranged from 7.4% to 19.6%, which corresponds to the rates reported around the world. We found no evidence of an increase in NPS or other substances to replace traditional substances. Our use of LC–MS enabled us to address the issue of polysubstance use, which tends to be obscure and complicated. Our results revealed that PEA, sCAT, and sCB (major ingredients substance packs) were frequently co-used with traditional substances. The use of these compounds may be attributed to the similar effects of PEA, sCAT, and sCB or the fact that users are undergoing a transition in their substance use. Our estimates of substance prevalence based on urine analysis corresponded well to the quantities reported in substance seizures except cannabis. Urinalysis and substance seizure are method complementarity. Updating substance lists for urinalysis as well as adding major metabolites of substances to urinalysis could facilitate the monitoring of substance prevalence, providing rapid intelligence for public health authorities.

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Author Contribution DPY, TTT, and PSC contributed to the study conception, statistical analysis of data, interpretation of results, and drafting of the manuscript. DPY, HWC, YNK, JHC, HTL, JYC, YCJ, MCL, and YHH contributed to instrumental method validation, sample analysis, literature review, and data analysis. DPY, HWC, YNK, JHC, HTL, JYC, YCJ, MCL, WRC, and YHH were responsible for the organization and integrity of data. DPY, TTT, HWC, YNK, WRC, and PSC contributed to the revision and approval of the manuscript. DPY and TTT contributed equally as first authors. PSC obtained funding for the study and was responsible for supervision.

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Data Availability The present data would be available on request.

Declarations

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Conflict of Interest The authors declare no competing interests.

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